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Understanding the role of milk in regulating human homeostasis in the context of the COVID-19 global pandemic

Guangxu Ren, Guangyan Cheng, Jiaqi Wang *

Institute of Food and Nutrition Development, Ministry of Agriculture and Rural Affairs of the People's Republic of China, Beijing, China

ABSTRACT

Although data from clinical observation have directly shown that children aged 0–14 years are less susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than those who are between 15 and 64 years old, due to a lack of biological evidence of differences in cell entry receptors between age groups, it remains debatable whether children are actually less susceptible than adults. To date, studies on COVID-19 have consistently shown that pediatric patients generally have relatively milder cytokine release syndrome and lower mortality rates than adults. Interestingly, similar phenomena of relatively mild symptoms in children have been observed in previous outbreaks of coronaviruses, including SARS-CoV and MERS-CoV. In fact, in the early stage of life, there are many mechanisms that spontaneously regulate excessive inflammatory responses. Milk, as the main food of infants, not only provides necessary energy and nutrients but also plays an important role in regulating homeostasis related to the immune system, gut microecology and nutrition balance. This review discusses some roles of milk in regulating human homeostasis, especially in the disease states. These clues provide new insight and references for personal care at home and/or in the hospital during the global COVID-19 pandemic.

1. Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has reached pandemic status. As of August 02, 2020, coronavirus disease 2019 (COVID-19) had been confirmed in 17,660,523 people and caused 680,894 deaths worldwide according to the World Health Organization (WHO). Clinical data indicate that people of different ages infected with SARS-CoV-2 exhibit different symptoms. Some evidence indicates that nutritional derangements should be systematically and urgently managed in patients affected by COVID-19, it should also be considered that symptoms of COVID-19 may be exacerbated by malnutrition (Caccialanzaet al., 2020).

Existing epidemiological evidence shows that consumption of cow's milk and/or breast milk in early life is associated with a lower prevalence of allergies, respiratory tract infections, and asthma (Perdijk et al., 2018). Milk not only provides the energy and nutrients necessary for life but also plays an important role in maintaining health by regulating the balance of the immune system and intestinal microbial ecosystem. Here, we discuss some potential roles of milk in regulating human homeostasis to provide new insight and references for personal care at home and/or in the hospital during the global COVID-19 pandemic.

2. Homeostasis in COVID-19 patients

2.1. *Cytokine storm: the straw that broke the camel's back*

The symptoms of patients infected with SARS-CoV-2 range from minimal symptoms to severe respiratory failure with multiple organ damage. Patients with severe disease have been reported to have increased plasma concentrations of proinflammatory cytokines, including interleukin (IL)-6, IL-7, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP) 1α, and tumor necrosis factor (TNF)-α (Chenet al., 2020a). These findings suggest that cytokine storms correlate positively with COVID-19 severity. This type of cytokine storm was also observed in previous outbreaks of coronaviruses, including severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) (Moore & June 2020). Therefore, effectively inhibiting or alleviating cytokine release syndrome (CRS) is very important to reduce mortality among SARS-CoV-2-infected patients.

Are adults truly more susceptible to SARS-CoV-2 than children?

Recently, data from Wuhan and Shanghai obtained via questionnaires directly report that children aged 0–14 years are less susceptible to SARS-CoV-2 infection than those are aged 15–64 years (odds ratio 0.34, 95% CI 0.24–0.49) (Zhanget al., 2020). Although the results are

* Corresponding author. No. 12 ZhongGuanCun South Street, Haidian, Beijing, 100081, China.
E-mail address: wangjiaqi@caas.cn (J. Wang).

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significant, epidemiological differences between age profiles and the consequent differences in infection do not necessarily reflect differences in biologically causal mechanisms. Furthermore, given their relatively narrow social scope and the additional care they receive, children are less likely to be exposed to the virus than adults. It is known that SARS-CoV-2, similar to SARS-CoV, uses the angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptor to gain entry into cells. This receptor is widely expressed in cardiopulmonary tissues but also in some hematopoietic cells. Due to a lack of biological evidence for differences in entry receptor expression among different age groups, it is still debatable whether children are less susceptible than adults. Another important issue is whether COVID-19 can spread vertically and pose a risk to a fetus and newborn. A small group of cases reported by The Lancet indicate that there is currently no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy (Chenet al., 2020b).

Notably, studies to date on COVID-19 have consistently shown that pediatric patients generally have relatively milder symptoms and lower mortality rates than adults (Chenet al., 2020c; Onder et al., 2020; Zhouet al., 2020). As mentioned above, similar phenomena of mild symptoms in children were observed in previous outbreaks of coronaviruses, including SARS-CoV and MERS-CoV (Memish et al., 2020). Based on these clues, we speculate that the cytokine storm caused by infection with coronaviruses, including MERS-CoV, SARS-CoV and SARS-CoV-2, might be spontaneously regulated by children to some extent.

2.2. Humans have evolved to deal with excessive inflammation in the early stages of life

According to the sterile-womb hypothesis, the fetus is conceived in a sterile environment. Although this traditional concept is currently challenged, there is no doubt that the environment of the uterus is relatively sterile compared with that of the outside world (Willyard, 2018). Early life is commonly characterized by high vulnerability to infection and inflammation-mediated tissue injury. If the body is unable to control the excessive inflammatory response induced by infection after birth, it may lead to neonatal necrotizing enterocolitis, a common and serious condition. Thus, for newborns, the first issue after birth is not nutrition but rather sudden exposure to microbes in the extrauterine environment.

An excessive inflammatory reaction after birth is partially controlled by the consumption of breast milk, the composition of which is tailored to contribute to the need for immunity and nutrition in early life. In addition to directly providing immune proteins (i.e., antibodies and lysozyme), breast milk can also regulate the immune system via bioactives, such as lactoferrin. As a natural modulator of immune homeostasis, lactoferrin is a cell-secreted mediator that bridges innate and adaptive immune functions in mammals (Actor et al., 2009). Recent evidence shows that lactoferrin can bind to the low-density lipoprotein receptor-related protein 2 (LRP-2) receptor, which is expressed on the surface of myeloid cells, including neutrophils and monocytes. The binding of lactoferrin to LRP-2 causes activation of myeloid cells and subsequent initiation of the NF-κB-mediated cascades that convert myeloid cells into myeloid-derived suppressor cells (MDSCs) (Heet al., 2018; Liuet al., 2019). Lactoferrin-induced MDSCs are important regulators of immune homeostasis and can attenuate excessive inflammation via direct secretion of regulatory cytokines, including reactive oxygen species (ROS), nitric oxide (NO), arginase, prostaglandin E_2 and IL-10, or by indirectly coordinating other immune cells, including dendritic cells, T regulatory cells, macrophages, natural killer T cells, $CD4^+$ T cells and $CD8^+$ T cells (Ostrand-Rosenberg & Sinha, 2009). Interestingly, LRP-2 receptor expression decreases with age. According to recent research, lactoferrin obviously inhibits TLR-4/NF-κB/TNF-α/IL-1β pathway components induced by oxygen and glucose deprivation and cerebral ischemic reperfusion (Yanget al., 2020). Lactoferrin is present in human/bovine breast milk and other dairy products. Furthermore, as children consume the most dairy products of any age group in the world, from the perspective of human evolution, children can maximumly cope with the threat of excessive inflammation by consuming milk (see Fig. 1A).

2.3. Milk is a natural food that benefits to maintan homeostasis

The neonatal period is an exceptionally vulnerable period of life, during which preterm infants are at high risk for morbidity and mortality. According to data from the WHO, 2.6 million neonates died globally in 2016 alone (Telang, 2018). Newborns adjust to the extrauterine environment through the development of intestinal homeostasis. On the one hand, the excessive inflammatory response caused by sudden microbial exposure needs to be alleviated, and breast milk has been shown to exhibit substantial anti-infective properties that serve to bolster neonatal defenses against multiple infections. Lactoferrin is the dominant whey protein in human milk, and it has been demonstrated to perform a wide array of antimicrobial and immunomodulatory functions and play a critical role in protecting newborn infants from infection (Telang, 2018). On the other hand, appropriate microbes are needed to train the immune system. As the initial food of mammals, milk contains a wide array of bioactive proteins, growth factors, cells, and other constituents that modulate the development of a competent immune system and intestinal microecology. Importantly, milk can perfectly balance this contradiction (see Fig. 1B). Indeed, milk stimulates the proliferation of a well-balanced and diverse microbiota, which initially influences the switch from an intrauterine Th2-predominant response to a Th1/Th2 balanced response, with the activation of T regulatory cells by specific breast milk-stimulated organisms (*Bifidobacterium*, *Lactobacillus*, and *Bacteroides*) (Walker & Iyengar, 2015). Short-chain fatty acids (SCFAs) in breast milk activate receptors on regulatory T cells and bacterial genes, which preferentially mediate intestinal tight junction expression and anti-inflammation (Walker & Iyengar, 2015). Other components of breast milk (defensins, lactoferrin, glycopeptides, caseinomacropeptide, etc.) can inhibit pathogens and further contribute to the composition of the microbiotal community (Cacho & Lawrence, 2017; Maga et al., 2013).

For elderly COVID-19 patients, there are several factors, including the disease itself, treatments and stress, that might disrupt intestinal homeostasis during the infection. In fact, diarrhea, a sign of intestinal imbalance, can be a presenting symptom in patients with SARS-CoV-2 infection. Aging is associated with significant shifts in microbiome diversity and proinflammatory states. Thus, intestinal homeostasis in elderly COVID-19 patients is likely seriously damaged. Furthermore, in elderly patients, imbalance of the intestinal microecology will aggravate malnutrition and inflammation. On the one hand, milk proteins have been shown to promote growth and maturation of the small intestine by stimulating glucagon-like peptide (GLP)-2 secretion (Izumiet al., 2009). On the other hand, milk can shape a healthy gut microbiota. (see Fig.1B) Lactose, for instance, is the main source of nutritive carbohydrates in maternal milk and can be used for energy by some bacteria, particularly *Bifidobacterium* spp. And *Lactobacillus* spp. (Forsgard, 2019). Bifidobacteria are able to prevent or alleviate infectious diarrhea through effects on the immune system and resistance to colonization by pathogens (Picardet al., 2005). Lactobacilli ferment carbohydrates into SCFAs, which can be used as biomarkers of the health of the microbiota (Belkaid & Hand, 2014).

2.4. Nutritional deficiency may aggravate symptoms in older COVID-19 patients

As the immune system attempts to eliminate SARS-CoV-2, a large amount of nutrients will be needed to support the proliferation of immune cells and the synthesis of antiviral cytokines (Laaret al., 2018). Unfortunately, a high body temperature suppresses appetite and

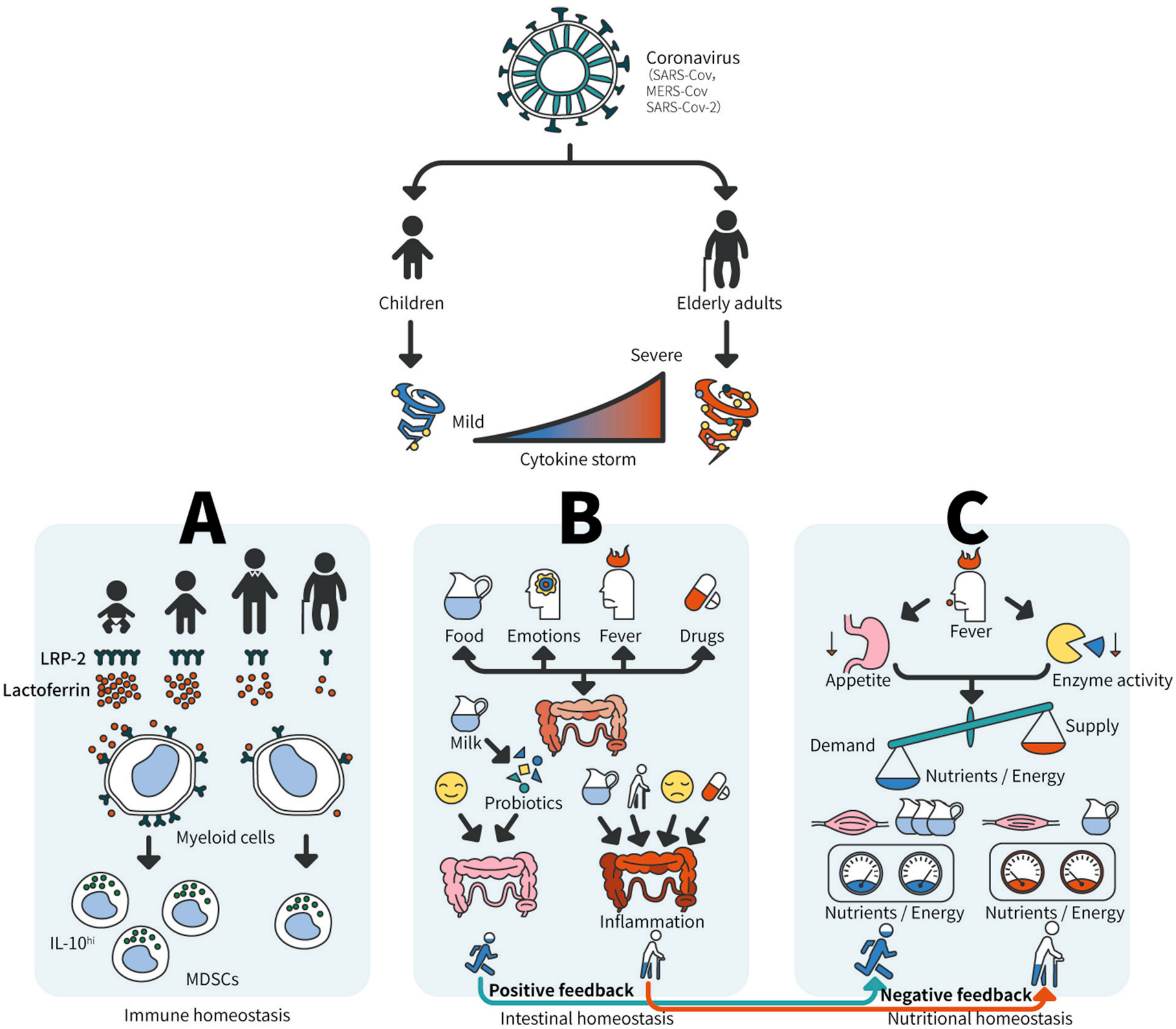

Fig. 1. Homeostasis orchestrated by milk in COVID-19 patients.
Phenomena: 1, Mild symptoms in children were observed in outbreaks of SARS-CoV-2; 2, cytokine storms correlate positively with COVID-19 severity;
View points: children regulate homeostasis in the disease state through a series of mechanisms, which is conducive to alleviation of the disease; 2. milk plays a very important role in the maintenance of homeostasis.
A: Immune homeostasis: Milk and its nutrients can regulate excessive inflammation. For example, myeloid cells can differentiate into MDSCs and attenuate excessive inflammation by using LRP-2 to sense lactoferrin from milk.
B: Intestinal homeostasis: Aging, anxiety, medication and fever disrupt homeostasis in the gut. Imbalance of the intestinal microbiota can aggravate the development of disease by reducing food digestibility, producing harmful metabolites and inflammatory cytokines. Milk is rich in prebiotics, which can reverse the imbalance of gut microbiota and promote intestinal health.
C: Nutritional homeostasis: Fever symptoms can cause loss of appetite and digestive enzyme activity, leading to malnutrition during illness. At this time, a large number of immune cells proliferate, and the demand for nutrition increases. Milk can provide essential nutrients for patients with new crown disease to support immune cells against SARS-CoV-2.

digestive enzyme activity. Both of these factors lead to a shortage of nutrients. If nutrients cannot be supplemented in time, the muscle tissue will be degraded first to compensate for the lack of protein. Malnutrition will be aggravated in elderly people with sarcopenia and imbalance of the intestinal microecology.

Given that milk can provide the majority of nutrients necessary for life, especially in disease states, including high-quality protein, thiamine, riboflavin, folate, choline, iron, copper, zinc, calcium, phosphorus, magnesium, iodine, selenium, lipids, carbohydrates, and vitamins A, C, D, E, K, B6, and B12 (Haug et al., 2007), milk intake may be the best choice for COVID-19 patients without lactose intolerance (see Fig. 1C).

3. Conclusions

In the early stage of human life, an excessive immune response can be effectively regulated by milk and its bioactive components. Milk can both provide nutrition for life activities under special conditions and maintain a healthy intestinal microenvironment through milk components (see Fig. 1) This evidence provides new insight and references for personal care in families and/or hospitals during the global covid-19 pandemic.

Declaration of competing interest

All authors are employees of the government research institute and have no potential conflicts of interest.

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