Human Milk Microbiota on Maternal and Child Health

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Human milk (HM) is considered the most complete food for infants as its nutritional composition is specifically designed to meet infant nutritional requirements during early life. HM also provides numerous biologically active components, such as polyunsaturated fatty acids, milk fat globules, IgA, gangliosides or polyamines, among others; in addition, HM has a “bifidogenic effect”, a prebiotic effect, as a result of the low concentration of proteins and phosphates, as well as the presence of lactoferrin, lactose, nucleotides and oligosaccharides. Recently, has been a growing interest in HM as a potential source of probiotics and commensal bacteria to the infant gut, which might, in turn, influence both the gut colonization and maturation of infant immune system. Our review aims to address practical approaches to the detection of microbial communities in human breast milk samples, delving into their origin, composition and functions. Furthermore, we will summarize the current knowledge of how HM microbiota dysbiosis acts as a short- and long-term predictor of maternal and infant health. Finally, we also provide a critical view of the role of breast milk-related bacteria as a novel probiotic strategy in the prevention and treatment of maternal and offspring diseases.

Keywords: human milk ; microbiota ; health programming ; probiotics

1. Introduction

Human milk (HM) represents the gold standard, providing protective and functional nutrients for the newborn, ensuring healthy growth and development [1][2]. Accordingly, the World Health Organization (WHO) and other international organizations, such as the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), recommend that infants should be exclusively breastfed during their first 6 months of life, with breastfeeding continuing until two years of age, combined with complementary feeding [3][4]. However, it is necessary to point out that exclusively breastfed infants present a particular risk of vitamin D deficiency, due to its low concentration in breast milk [5], low maternal vitamin D levels and daily intake, as well as the lack of exposure of newborns and suckling infants to sunlight [6]. Therefore, associations such as the American Academy of Pediatrics and ESPGHAN recommend vitamin D supplementation at doses of 400 IU/day in infants who are exclusively or partially breastfed [7][8].

Unlike its traditional consideration as a sterile fluid, HM is now recognized as an interesting source of potentially probiotic and commensal bacteria such as *Bifidobacterium* spp., *Lactobacillus* spp., *Clostridiales* spp., viral organisms, among others, which may lead to healthy infant gastrointestinal (GI) microbiota and immune system maturation [9][10][11]. Although studies provide strong evidence of the existence of microbes in human milk, their origin and potential role in breastfed infants’ health need to be studied in greater depth, particularly concerning the contribution of HM microbes to the growth and development of infant gut microbiota. In fact, some authors reported that HM microbiota contributes less than previously expected to gut microbiota composition during early life, and virtually nothing at 6 months of age [12][13]. Nevertheless, as human microbiota is essential for optimal host physiology, there is currently great interest in better understanding how HM microbiota dysbiosis could be related to the development of non-communicable diseases in both mother and child [14]. Consequently, methodological advances and more consistent findings are still needed to better understand the uncertain aspects related to HM microbiota origin, composition and function [15], and its potential interaction with other bioactive components.

2. Short- and Long-Term Implications of HM Microbiota on Maternal and Child Health

Regardless of its origin, the existence of commensal microbes in HM might have a beneficial role in the health of mothers and their newborn infants. In fact, research carried to date points to a potential influence of HM microbiota on health outcomes [16][17]. However, further studies are still needed to obtain stronger scientific evidence, particularly considering that HM not only contains commensal bacteria, but also many other immune, nutritional and bioactive factors that may influence maternal and child health.

2.1. Maternal Pathologies and Human Milk Microbiota Dysbiosis

It is established that breastfeeding provides short- and long-term positive effects on maternal health, including better postpartum recovery, lower risk of breast and ovarian cancer, and a reduced incidence of cardiovascular and autoimmune diseases [18][19]. Interestingly, clinical and scientific evidence also suggests a bidirectional interaction through which maternal health can modify HM microbiota composition.

Mastitis is a common inflammatory condition that affects 33% of lactating women and causes pain during lactation, redness of the breast and fever, ultimately leading to decreased milk production and subsequent early suppression of breastfeeding [20]. There is evidence suggesting an association between this inflammatory condition and HM microbiota dysbiosis in terms of low microbial diversity, decreased relative abundances of commensal bacteria (*Lactococcus* and *Lactobacillus*) and the establishment of opportunistic pathogens such as *Staphylococcus*, *Streptococcus* and *Corynebacterium* [21][22]. In fact, acute mastitis is widely caused by *S. aureus*, reaching concentrations of 4.0 $\log_{10}$ colony-forming cells (cfu)/mL in milk of acute mastitis-suffering women compared to concentrations from 1.5 to 3 $\log_{10}$ cfu/mL reported in the milk of healthy women. However, other potentially pathogenic strains, including coagulase-negative *Staphylococci*, *S. epidermidis* and *Corynebacterium*, also lead to subacute, chronic or granulomatous mastitis in lactating women, respectively [23][24]. As these bacteria are often resistant to antibiotic therapy, promising strategies for mastitis treatment are currently based on the use of *Lactobacillus* strains isolated from the human milk of healthy women. Clinical trials published to date indicate that oral intake of different *Lactobacillus* strains isolated from human milk, either alone, such as *L. fermentum* CECT5716 and *L. salivarius* CECT5713 [25], or combined (*L. salivarius* CECT5713 plus *L. gasseri* CECT5714) [26], reduces the counts of pathogenic bacteria and improves mastitis symptoms after 14–21 days of treatment, thereby emerging as promising treatment for lactational infectious mastitis when antibiotic treatment fails. Interestingly, both *L. fermentum* CECT5716 and *L. salivarius* CECT5713 were also found in HM samples of treated women, suggesting that both strains are able to recolonize the mammary gland to reduce and reverse mastitis-associated dysbiosis [25]. Further studies have been performed to better understand the key biomarkers and potential mechanisms involved in this probiotic effect. Overall, these studies showed that *Lactobacillus*-based probiotic treatment did not affect milk macronutrient composition, but was associated with specific microbiological, immunological and metabolomic markers related to the improved integrity of mammary gland epithelia [27][28]. Moreover, a recent study also suggest that probiotic treatment might act on specific genes involved in inflammatory and cell-growth signaling pathways, thus opening new avenues for research based on specific responsive molecular targets [29]. Finally, daily oral intake of HM-related *L. salivarius* PS2 between week 30 of gestation and delivery, significantly reduced the incidence of mastitis in women who suffered this pathology in previous pregnancies, compared to those who received a placebo during the same period [21].

The potential protective role of HM microbiota in breast health is also indirectly suggested by the close link between the microbial communities present in mammary tissues and risk of breast cancer. In this line, Urbaniak et al. [30] reported cancer-related dysbiosis characterized by a significantly lower abundance of LAB, but increased abundance of *Bacillus* spp., *Staphylococcus epidermidis*, family *Comamonadaceae* and Enterobacteria such as *Escherichia coli*. However, the potential mechanisms through which microbiota dysbiosis could contribute to breast cancer are still unknown. On the one hand, this effect could be explained due to the ability of *S. epidermidis* and *E. coli* to induce DNA damage by double-strand breaks [30]. Moreover, breast-cancer-associated microbial dysbiosis could downregulate the host immune system, which, in turn, leads to a permissive environment for breast tumorigenesis [31]. Xuan et al. [32] found a lower abundance of *Sphingomonas yanoikuyae* in breast tumor tissue, a gram-negative bacteria involved in immune cell activation and the inhibition of tumor growth. In a similar study, nipple aspirate fluid from breast cancer women was rich in genus *Alistipes* and other bacteria with β-glucuronidase enzymatic activity, which is associated with profound changes in estrogen metabolism and an increased risk of breast cancer [33]. It is also important to note that the use of chemotherapy to treat breast cancer might alter the bacterial communities present in HM and mammary tissues, reducing these potentially beneficial bacteria for mother and infant health [34]. Despite this evidence, further studies are still needed to clarify whether these bacteria strains could grow into a tumorigenic environment or whether they are a direct cause of breast cancer.

Other maternal pathologies also seem to be accompanied by HM microbiota dysbiosis. For instance, González et al. [35] showed that breast milk of human immunodeficiency virus (HIV)-infected women presented increased bacterial diversity and *Lactobacilllus* spp. frequency, but its content in *S. hominis* and *S. aureus* was lower compared to breast milk of healthy women. Nevertheless, no evidence for HIV-related microbial dysbiosis was found in other studies [36]. These contradictory findings may be explained by methodological and population differences between studies, making it difficult to identify whether changes in HM microbiota composition were a response to maternal disease or vice versa. Similar conclusions have been obtained in studies that analyzed HM microbiota composition in women who suffer from allergies or celiac disease. In both cases, lower relative levels of *Bifidobacterium* and *Bacteroides* were found in breast milk samples, but there were significant differences in dietary habits between healthy and unhealthy women [37][38].

Special mention should be made to the potential relationship between HM and coronavirus disease 2019 (COVID-19). Although HM microbiota dysbiosis has not yet been found in women positive for SARS-CoV-2, recent evidence suggest that GI microbiota is profoundly altered in COVID-19 patients, particularly in terms of reduced bacterial diversity and lower levels of commensal bacteria with immunomodulatory role (*Faecalibacterium prausnitzii*, *Eubacterium rectale* and *Bifidobacterium*), as well as increased growth of potentially pathogenic *Enterococcus* strains [39][40]. These changes in GI microbiota composition seem to be positively related to cytokine storm intensity and subsequent disease severity [40], and preliminary results suggest that therapeutic strategies focused on GI microbiota modulation using pro- and synbiotics (mainly *Lactobacillus* spp. and *Bifidobacterium* spp.) could be effective in the prevention and treatment of severe COVID-19 [41]. Interestingly, noting the entero-mammary origin, it is plausible that COVID-19 disease also involves dynamic changes in HM microbiota composition. Moreover, due to the hypothetical role of HM microbiota in the establishment of infant GI microbiota, breastfeeding could have a potential protective effect on severe COVID-19-related dysbiosis in infants. While both assumptions require further research, there are different approaches, emphasizing that mothers infected by SARS-CoV-2 can breastfeed their infants, with the necessary precautions, in order to transmit HM's protective properties against COVID-19 disease [42][43][44][45]. In fact, unlike other viruses- such as HIV and human cytomegalovirus, which can be transmitted to infants via breast milk, Bäuer et al. reported that HM samples obtained from mothers with SARS-CoV-2 infection and/or those who have recovered from COVID-19, showed no presence of SARS-CoV-2 RNA [46]. Interestingly, these authors also observed that HM could provide passive immunity to breastfed infants via the transfer of SARS-CoV-2 spike-protein-specific antibodies. Similarly, Demers-Mathieu et al. found a positive correlation between antigens and secretory antibodies in breast milk samples from mothers with confirmed COVID-19 PCR, characterized by higher levels of S2 subunit SARS-CoV-2-specific IgG, while SIgA and SIgM were polyreactive and cross-reactive to S1 or S2 subunit SARS-CoV-2 [47]. In conclusion, the data discussed here seem not only to support the breastfeeding recommendations during the COVID-19 pandemic, but also its potential beneficial role for mothers and their offspring in the prevention of severe COVID-19 disease [48]. However, as mentioned above, further studies are required to better understand the role of both HM and GI microbiota in the physiopathology and management of COVID-19.

Lastly, there is growing interest in evaluating the effects of maternal metabolic conditions during pregnancy on the composition and activity of HM microbiota, as well as its potential associations with later maternal and child health status. In this regard, it is now established that maternal obesity and gestational diabetes mellitus (GDM) involve gut microbiota dysbiosis which, if we consider the entero-mammary pathway as a potential origin of HM microbiota, might result in HM microbiota dysbiosis. Thus, the gut microbiota of obese women is characterized by their lower diversity and higher *Firmicutes*:*Bacteroidetes* ratio with respect to lean women [49]. Similar changes were also found in gut microbiota composition in women affected with GDM, including lower α-diversity, changes in β-diversity, higher *Firmicutes*:*Bacteriodetes* ratio, increased prevalence of gram-negative bacteria, and reduced levels of potential probiotic bacteria [50]. Therefore, these dynamic changes might not only alter HM microbiota composition, but also generate an "obesogenic" environment in infant gut, thus increasing infant obesity risk [49][50]. However, there is limited knowledge about the possible effects of maternal metabolic conditions on HM microbiota composition. Studies conducted to date seem to indicate that both maternal pre-pregnancy obesity and excessive gestational weight gain were related to lower diversity and *Bifidobacterium* abundance, but increased counts of *Lactobacillus* and *Staphylococcus* in milk samples [51] [52]. These characteristics in HM microbiota composition were also related to changes in immunological biomarkers [52], which may further explain the plausible link between higher risk of child and maternal obesity and HM microbiota dysbiosis. Recent studies have focused on analyzing the combined impact of both maternal metabolic conditions on HM composition. LeMay-Nedjelski et al. [53] found that milk samples obtained from obese mothers with GDM or impaired glucose tolerance contained higher levels of *Gemella*, compared to normal-weight mothers. Moreover, the colostrum samples of obese mothers with GDM showed higher microbial diversity and increased levels of amino acid and carbohydrate metabolism-related bacteria [54]. However, the HM microbiota composition reported in these studies was also affected by other confounders, including type of delivery, use of antibiotics, ethnicity and infant sex [53][54]. Consequently, further studies are required to better evaluate potential mechanisms by which HM microbiota from mothers suffering obesity and GDM may influence later health and development.

2.2. Role of Human Milk Microbiota on Child Health

Several clinical trials have described the potential benefits of HM in infants who suffer from necrotizing enterocolitis (NEC), gastrointestinal disorders, celiac disease, obesity, dermatitis, asthma, and infection-related processes such as surgical procedures and chemotherapy [55][56]. These health effects are largely due to HM's composition, which is rich in nutritional, immune and bioactive compounds. Furthermore, the presence of commensal and potentially probiotics bacteria could also be an important factor in explaining the protective effects of HM on infant health. For instance, some authors suggest that *Bifidobacterium breve*, a common member of the microbiota of breastfed infants, could be key to promoting healthy GI microbial colonization due to its ability to use HMOs, thus possibly protecting against infection and

modulating immune system maturation [57][58]. However, it is important to point out that further studies are still needed to accurately understand the potential implication of HM microbiota on infant health, as well as the possible biological mechanisms and interactions with other bioactive compounds through which HM microbiota could exert these potential protective effects on child health.

NEC is a major cause of acquired intestinal morbidity and neonatal death, especially in preterm infants [59]. Although a clear dysbiosis pattern has not yet been reported, the obtained findings suggest that preterm infants suffering from NEC or nosocomial sepsis showed dynamic changes in gut microbiota composition (mainly decreased bacteria diversity and high levels of potentially pathogenic bacteria such as *Proteobacteria* and *Clostridium perfringes*), compared to healthy infants [60][61]. Due to its possible ability to modulate infant gut microbiota, human milk feeding has emerged as promising strategy to reduce the risk of NEC [62]. In addition to its high nutritional, the preventive role of HM could be explained by its high content of commensal beneficial bacteria, including *Bifidobacteria*, *Lactobacillus*, and *Streptococcus*. Interestingly, these bacteria strains showed both species-specific probiotics effects and wider preventive effects when combined [62][63]. Breastfeeding should be also encouraged in preterm infants due to its high HMO concentration, which favors commensal bacteria growth in the gastrointestinal tract. This would explain why breastfed infants respond better to probiotic treatment than formula-fed infants [54]. For mothers unable to produce sufficient breast milk to meet the nutritional needs of their premature infants, pasteurized donor milk supplemented with the mother´s own milk is highly recommended to support optimal gut microbiota maturation, thus improving premature infant health [64]. In combination with this modulatory role in infant GI microbiota, HM can also decrease the risk of neonatal NEC through anti-inflammatory mechanisms related to the inhibition of the NF-κB signaling pathway. In fact, HM reduces IL-1β-induced activation of the IL-8 gene, an NF- κB-dependent, pro-inflammatory cytokine that is crucial for NEC pathophysiology. This anti-inflammatory effect seems to be related not only to increased IκBα synthesis, a key inhibitor of the NF-κB pathway, but also to a decrease in its 26S proteosome-dependent degradation [65]. Taken together, these results suggest that breastfeeding, due to its complete nutritional composition, should be taken into account as a protective and therapeutic strategy to reduce the risk of NEC and other inflammatory bowel diseases.

Human-milk-related beneficial bacteria also seem to have a protective effect on minor gastrointestinal disorders in healthy infants; as an example, the intake of infant formula enriched with *L. fermentum* CECT5716 Lc40 or *B. breve* CECT7263, both previously identified in breast milk, reduced both the frequency and recovery time of GI infection-associated diarrhea and infant colic-associated crying, respectively [66]. However, other HM compounds such as HMOs are also implicated in the prevention of infant gastrointestinal disorder. Thus, 2′-fucosyllactose (2′-FL), a HMOs related to Secretor gene *fut2* [67], plays a protective role in diarrhea caused by *Campilobacter jejuni* [68]. Similarly, fucosyltransferase enzyme (FUT3), associated with the Lewis-Secretor gene [67], is involved in the synthesis of different types of HMOs with potent in vitro antimicrobial activity against Group B Streptococcus (GBS), potentially reducing the risk of neonatal infection [69].

The protective role of breastfeeding on the incidence and severity of infant atopic disorders (AD) and asthma has gained a lot of research interest as the prevalence of both pathologies is increasing globally [70][71]. However, the results obtained to date are controversial. In this respect, Orivuori et al. reported that soluble IgA (sIgA) levels in breast milk were associated with microbial-load-related environmental factors but not with breastfeeding duration. Interestingly, sIgA levels during the first year of life were related to lower risk of AD up to between 2 and 4 years, but associations between sIgA levels and risk of AD or asthma were not found at 6 years [72]. On the other hand, the results obtained from exhaustive review and meta-analysis showed that children who were breastfed longer had a lower risk of developing asthma and eczema up to 2 years of age, although this risk increased with infant's age [73]. Conversely, Kong et al., using non-targeted metabolic analysis in mouse model, identified the long-chain saturated fatty acids (LCSFA) present in breast milk as damage-associated molecular patterns (DAMPs); thus, breast milk intake was related to increased levels of inflammatory Group 3 innate lymphoid cells (ILC3) in gut, with increases in the production of IL-17 and IL-22, which may migrate to the skin and increase the risk of AD [74].

Based on its immunomodulatory role, human-milk-related LAB could have a promising therapeutic effect on infant allergic conditions [75]. According to this assumption, in vitro studies suggest that *L. salivarius* CECT5713 and *L. fermentum* CECT5716 isolated from breast milk are potent activators of NK cells, but their effects seem to be moderate on CD4+, CD8+ and regulatory T cells, and seriously limited on T cells activation. Moreover, both potentially probiotic strains could modulate the cytokine patterns, favoring Th1 immunity response and enhancing both innate and acquired immune responses [76]. Interestingly, the plausible protective role of HM in allergic conditions could be related to the low contents of *Bifidobacteria* found in breast milk from allergic women [77]. Thus, maternal probiotic treatment with *Lactobacillus* spp. and/or *Bifidobacterium* spp. aiming to modulate HM microbiota should be considered a useful tool for the prevention or treatment of allergic conditions, although questions about species-specific and dose-dependent effects, time of administration and treatment duration remain unsolved [77].

Finally, Gough et al. [78] found a lower bacterial diversity and high concentrations of *Acidaminococcus* genus in gut microbiota from infants who suffer from severe linear growth retardation. Considering its potential role in healthy infant gut colonization, these findings might suggest that the beneficial features of HM microbiota could determine optimal infant growth and development, although direct evidence has been not reported to date.

Overall, the findings discussed here suggest that the complex modulation of infant gut microbiota through breast milk could have beneficial effects on infant health. These benefits are especially important in preterm infants since their GI microbiota are rich in potentially pathogenic bacteria. However, the available evidence is sparse, and further studies should be carried out to better understand the role of HM microbiota in infant health, which would allow us to identify novel HM-related beneficial strains as promising therapeutic tools for the treatment of microbiota-dysbiosis-related disorders.

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