Re-thinking human milk for systematic anti-viral immunotherapy

ABSTRACT

Background Organized protection against novel mucosal pathogens, crucial during unpredictable circumstances such as the SARS-CoV-2 in the Covid19 pandemic is provided by exclusive human milk feeding.While systematic analysis comparing SARS-CoV-2 and its impact by natural feeding is useful, the number of studies presently available on this topic may not be ideal for complete or meaningful clinical conclusions.Attempting to overcome this challenge, analysis, synthesis and integration of human milk immune potentials against the immunopathogenesis of Covid19 highlight human milk as timely immune therapy. Uniquely,early nutrition, locally modulated by maternal mammary glands and possibly enhanced by systemic events such as maternal vaccination immunity, is also primary, secondary and tertiary disease prevention .**Methods** Articles were selected for three areas of investigation which included pathogenetic mechanisms of SARS- COV- 2 infection , immunological protection in human milk and the role of protection in relevant mucosal diseases. This information was synthesised with focus on pathogenetic mechanisms , early innate protection, specific and nonspecific anti-viral action and facets of mucosal immunity in human milk. These were integrated to functions in human milk specifically protective against mucosal infections in general, but focused to SARS CoV-2 infections. **Results** The cause of the disease can theoretically be reduced or mitigated by the effect of early immunity provided by human milk. Human milk can protect in a systematic manner against stages of SARS-CoV-2 infection establishment, invasion and immune dysregulation with hypothesis that systematic human milk protection in this context, benefits the individual and the community. Preventing infection, limiting clinical disease and offering lasting health benefits by reducing disease complications were theoretically possible through human milk feeds**. Limitations** Exact contribution to protection in Covid19 by human milk factors are largely hypothesised, although multiple interactive factors with redundant actions and adaptive capacity are undeniably present in human milk. The isolation of many more substances to explore individual action and to assess their actions against breastfeeding outcome are necessary. This must then be compared to statistical data of breastfed children who have possibly been protected from infection or complications during this pandemic. These steps will allow greater understanding of the impact of human milk against novel mucosal infections and in future pandemics**. Conclusion** Reviewing immune potentials in human milk for anti-viral defences during unpredictable circumstances indicates its usefulness as immunotherapy requiring further testing, but nevertheless present in its diverse constituents. The counselling of breastfeeding for these specific reasons, should further motivate all mothers to sustain exclusive breastfeeding to prevent unexpected diseases and complications. To add on, it is plausible that the anti-viral action through exclusive breastfeeding could contribute to the lesser number of infections observed in children compared to adults, in this pandemic. A re-think on this subject is mandatory to nutrition and therapy.

Keywords: human milk feeding, immunity, SARS-CoV-2, mucosal, immunotherapy

INTRODUCTION

The pathogenesis of Covid19 explains its clinical manifestations and highlights the importance of timely preventive therapy to prevent the infection or to reduce its impact.

Covid19 is primarily a mild disease of childhood but its pathogenesis can involve multiple organ systems, especially the respiratory system[1]. Its peak infectivity coincides with maximum SARS-CoV-2 load, just before or within the initial five days of symptom onset[1] . The acute disease spectrum includes acute asymptomatic, mild and severe disease. Amongst children who develop severe disease, there are often predisposing factors such as obesity and bronchial asthma and other immunosuppressive conditions[1]. There is a growing body of evidence that the virus is also temporally related to a post infective phenomena causing a novel disease now recognized to be a separate disease entity referred to as the Pediatric Multisystem Inflammatory disease which is temporally associated with Covid19[1].Its manifestations are often acute, severe abdominal pain or high grade, often unremitting fevers refractory to antibiotics [1]. Covid 19 may also impact long term health but while some children with Covid 19 continue to experience prolonged illness, most recover by day 56 of illness[2].The spectrum of psychological impact of Covid 19 in children is well supported [3]

Children have a different susceptibility to the illness compared to adults[1] and this is attributed due to a number of factors[4].Lower exposures to SARS-CoV-2 and differences in innate and adaptive immune responses in children may explain this. The presence of cross reactivity from other coronavirus infections due to previous exposures in children who have a greater frequency of upper respiratory infections may explain this. The differences noted in intestinal microbial colonization in children with a less inflammatory immune profile in the gut or the presence of higher blood levels of some factors such as melatonin have been suggested. Moreover, nonspecific, off target protection from live vaccination[4]may work independently or in combination with other factors to explain this difference.

Additionally, this article considers the possibility that the immunological benefits of human milk may also be a mechanistic explanation for the differences observed in children in this mucosal infection.

Human milk feeding allows every mother to provide immune defences innately present in her milk, even without infection exposure. This can potentially systematically hinder invasion of mucosal portals, prime targets of the SARS-CoV-2, and provide a multitude of anti-viral defences, protecting from early infections. At the same time, the adaptive immunity in human milk which develops after exposure to infection mainly by antibody formation, is ‘stimulated’ or bridged by powerful innate immune factors. Maternal vaccination against the infection may further sustain and modify useful mucosal protective immune potentials.

It is now appreciated that human milk does not transmit the SARS-CoV-2 to the nursing infant , instead, infected mothers produce specific antibodies in the milk[5], which are likely to protect. While SARS-CoV-2 ribonucleic acid (RNA)was detected on several breast swabs[5] it was not found in any breastmilk sample in women diagnosed with Covid-19. Moreover, SARS-CoV-2-specific antibodies of the immunoglobulin A (IgA) and immunoglobulin G (IgG) type were found correlating with SARS-CoV-2 neutralization activity [5] Of added importance is that the vaccination of breastfeeding women against SARS-CoV-2 produced specific IgA and IgG antibodies in breast milk for 6 weeks after

vaccination. IgA was detected 2 weeks after vaccination followed by a spike in IgG after 4 weeks coinciding with a week after the second given vaccine[6].

To prevent subsequent pathogenesis of Covid19 which is multi-fold but fuelled by a proinflammatory cytokine response, human milk can potentially modulate this by its predominant anti -inflammatory content and this has the potential to have impact on acute disease, tissue preservation and some of its sequalae.

2. MATERIAL AND METHODS

Articles included focused mainly but not exclusively on SARS-CoV-2 and coronaviruses. Articles describing pathogenesis of the SARS-CoV-2 were reviewed. In the primary search, clinical research articles, experimental work, expert and interim guides were used. In the second area, articles included searches on breastfeeding, innate immunity and breastmilk immunology related to SARS - COV 2 and other pathogens with focus on those that involve the mucosal systems of the respiratory and gastrointestinal tract. Only articles available in the English language were used.

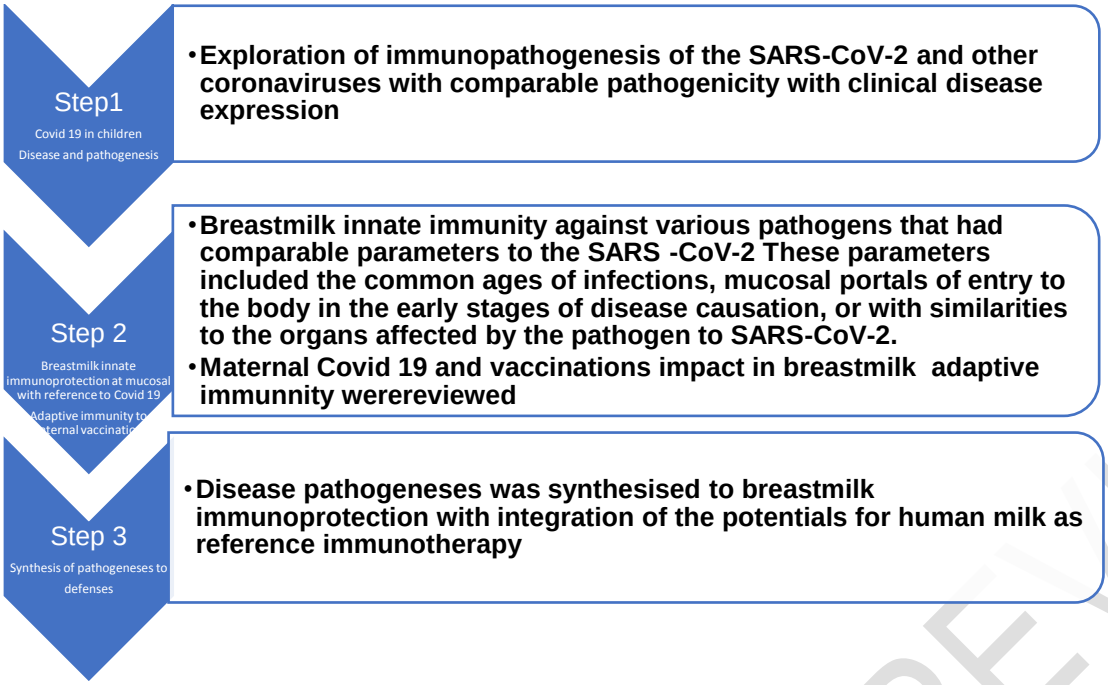
Articles exclusion criteria included Webpages which provide the public with questions and answers and media releases. Except for diabetes mellitus which was considered to significantly influence the unborn infant, specific immune impact on Covid19 on geriatric patients, influenced by specific chronic underlying disease, social habits or other dietary factors, were not considered in pathogenesis.

Data analysis and methods: Information from publications on the pathogenesis of Covid19 were analysed. The first step was to explore how the immunopathology of the novel virus impacts different stages of the disease. Immunopathogeneses was also often integrated to the expression of the clinical disease and outcome. Publications included were on human infections in the pandemic and other mucosal viruses with comparable pathogenicity.

The second step analysed actions of breastmilk on immunity against various pathogens that were comparable by different parameters to the SARS -CoV-2. These parameters included the common ages of infections, the mucosal portals of entry to the body in the early stages of disease causation, or with similarities to the organs affected by the pathogen to SARS-CoV-2. The unfolding impact of maternal Covid 19 vaccinations in breastmilk was reviwed. Publications in this section included case reports, meta-analyses, systematic reviews on humans and experimental observation in animal studies. The third step synthesised disease pathogeneses to breastmilk immune-protection.

Preventive mechanisms in human milk for primary, secondary and tertiary prevention of mucosal infections were integrated to the pathogenetic mechanisms of SARS-CoV-2.

Fig 1: Step wise analysis and synthesis of data



3 Results and discussion

3.1 SARS -COV-2 pathogenicity

SARS-CoV-2 is a large, spherical single stranded RNA virus. It is a mucosal pathogen and genetically similar to SARS-CoV, but with a higher reproductive rate (R 0)[5] .There are four main structural proteins , the nucleocapsid protein that contains the viral genome and three envelope proteins of which the spike protein, attaches to host cells through a receptor binding domain[7]

If timely clearance of the virus at the respiratory mucosae does not occur, the virus attaches itself to target receptors which are also found in many organs with hazards of widespread disease. SARS-CoV-2 binds to angiotensin converting enzyme -2 (ACE-2) receptors and fusion with a protein on host cell surfaces internalises the virus[8]. The virus is viable for days on smooth surfaces such as stainless steel, plastic or glass and at lower temperatures and humidity[8,9]. Of note is that cellular receptors of coronaviruses belong to the same protein family, and cellular entry occurs through the co-expression of other host peptidases which activate the coronavirus spike proteins [8]. The transmembrane serine proteases cleave and activate the coronavirus spike proteins during cell entry[8]. Spike protein dismantling releases infective viral genome, and with proofreading mechanisms in this RNA virus, a lower mutation rate[9] in the early stages of the pandemic was quickly followed by the occurance of many dangerous mutants[10].Droplets and contact with nasal ,oral or conjunctival mucosae propagate the virus[10,11].

Fever, myalgia, headache, respiratory symptoms and temporary anosmia with taste loss due to transient damage to olfactory cells may occur[11].Intracellular viral replication releases infective virions which stimulate host's innate immune responses [7,11] Viral recognition stimulates T lymphocytes and dendritic cells to the site of infection for early viral clearance. Host immunity is induced to produce inflammatory factors, macrophages, maturation of dendritic cells, and the synthesis of interferons (IFNs), all vital for eliminating the virus. Neutralising antibodies are produced in SARS-CoV-2, possibly useful, but their exact duration and impact are yet unclear. The viral load may also be a factor in recovery[7]. Immune suppression,viral evasion , high viral load and host variables influenced by underlying conditions may contribute to more severe disease with spread to

the lower airway[7,12]. Pneumonic lung involvement is associated with inflammation, confirmed by pathological findings[1,4]. Some develop septic shock, multi- organ dysfunction[6] which are important complications and Guo et al found that specific cytokines and serum markers were significantly higher in diabetic patients predisposing them to the inflammatory storm[12], and extensive tissue destruction is linked to hyperferritinemia[13]

In acute severe SARS-CoV2 many children had underlying predisposing factors such as obesity, bronchial asthma , sickle cell anemia and immunosuppression[1]. The other complication associated with the SARS -COV2 is multi-system inflammatory syndrome in children (MIS-C)[1]. Support of an immune phenomena in children who recovered from mild disease and who were relatively healthy. Clinical and laboratory observations suggest a number of hypotheses of the inflammatory state that occurs in the disease some 2-6 weeks following an acute illness or exposure to SARS-CoV-2. Immune dysregulation in the genesis of MIS-C resulting from exaggerated hyperimmune response is supported by positive serology and negative PCR testing, while antibody or T- cell recognition of self- antigens (molecular mimicry) leading to synthesis of autoantibodies and formation of circulating immune complexes has been proposed[14]. The role of genes in clinical expression is suggested by differences in disease incidence in the world [14].

3.1.1 Immunobiology in children against SARS COV2

Natural immunobiological mechanisms of children against the SARS COV 2 are more favourable than in adults and at least partially explain the relatively fewer mortalities amongst children in this disease compared to adults. The protective mechanisms include reduced expression of receptors that the virus utilizes to enter target cells, the differences in innate and adaptive immunity in this age group compared to adults which contribute to different immune dynamics, protective against pathogenesis of this virus. The differences in childhood immunity are suggested to also preserve the pulmonary endothelial barrier and prevent acute respiratory distress syndrome (ARDS)[14].

4. Importance of innate immunity in human milk

Early immune responses of innate immunity are critical to deter viral survival in the human \severe respiratory infections can occur with specific gene polymorphisms of innate immune responses [15] and such genetic polymorphisms can delay, diminish or exaggerate antiviral responses[16] resulting in severe , invasive disease. Adding to this challenge is that respiratory pathogens have evolved processes to suppress or evade these important innate responses.
Evolutionarily, human nutrition provides innate protection from novel infections and tissue damage as a result of it [17]. The mammary glands extract substances from maternal blood or may actively synthesise constituents with direct or indirect immune capacity . These substances are present in its cellular content, in the milk fat globule membrane found in milk, in its growth factors and in encrypted peptides within bioactive components. Many milk factors seem to have evolved for multiple functions with capacity to adapt to the mother infant dyad [17,18,19]. This makes human milk, on the whole, not reproducible in its immune potential, cost effective, and uniquely responsive in biological potential.
Human milk is empowered, through its innate immunity to fortify primary mucosal sites where infective agents gain entry [18,19], an early defence that is mandatory in the young with relative immunodeficiency. The infected mother can protect, by early innate immune responses[18,19], and further this by priming adaptive immune protection.
At chief sites of major antigenic challenge in the respiratory and gastrointestinal tract, innate defences strengthen the infant's developing immunity and in some situations give added individual protection as its immune content varies from mother to mother or with feeding time, in colostrum, transitional milk and mature milk[18,19], for such dynamic immune-protective potentials.

4.1 Enhancing physical and chemical barriers

The ciliated pseudostratified columnar epithelium which line most of the respiratory tract has special functions as barrier to pathogens and foreign antigens, preventing infections and tissue injury[20].Goblet cells secrete mucous , and form a vital layer of vigorous innate defense through mucociliary clearance[21].

Mucociliary clearance at the airway epithelium is augmented by the formation of mucous gel , the glycosylated mucin glycoproteins, with multiple defensive roles and transmembrane mucins such as MUC1 and MUC 4 as innate defences[21,22,23].Underlying the mucosal epithelia are leukocytes which secrete antibodies, defensins and lysozyme , for early immune defences[22].These substances provide a dual protection , acting as a physical barrier and providing direct antimicrobial activity, with capacity to opsonize microbes and clear them[22] .

Inefficient mucociliary clearance or absence of sufficient mucin glycoproteins in the airway disrupts this early and vital defense.Viruses can develop methods that interfere with early defences as in SARS- CoV -2 infections resulting in cell fusion , epithelial destruction , cilium shrinkage and other pathological changes to the epithelium[24], weakening its defense.

In the infant energy dependant processes must be conserved for growth and development and human milk is an investment towards this as nutrition is enriched by early defence ingredients.

For instance, mucosal tissues utilise energy to produce mucins, and increase their energy requirements to produce the important early defensive shield by mucin glycoproteins to fight off infections [22].However human milk nutrition has defensive mucous enriching factors that augment the amount of mucous in the respiratory tract or that step up early immunity by coating epithelial surfaces with mucous that prevents viral entry [25], and an effective step for primary infection prevention. Mucins in human milk add a layer to the developing immunity in the gastrointestinal and respiratory tracts by supporting the prevention of adhesion of pathogens to the cell surface[25]. MUC1 and MUC4 competitively inhibit receptor to virus interaction[25].Sialyated human milk mucin inhibits viral binding to the infant's cell surface glycan receptor and inhibits rotavirus in the gastrointestinal tract, blocking experimental adhesion of recombinant norovirus-like particles , possibly emulated in action for immunotherapy[25,26]

Human milk proteins impact at core of immune defences by stimulating gene expression. β-casein, for example, stimulates MUC2 gene expression for increased goblet cell numbers[27,28] Additionally mucous secretion is also enhanced by substances such as epidermal growth factor (EGF) increasing mucin production by goblet cells[28],enhancing synthesis and secretion of mucous.

Trefoil factors, are cellular products that produce mucin in breastmilk and step up immunity by activating intestinal epithelial cells and healing of mucosae[29],enhancing tissue repair and limiting tissue damage .Mucosal barriers remove the virus by agglutination and expulsion through muco-ciliary action in the respiratory tract or peristaltic movement in the gut[30].

Initial epithelial adherence and colonisation are steps to prevent infection and complications but also important to control infection transmission. Abundant in human milk, are human milk oligosaccharides (HMOs) which coat epithelial surfaces, and prevent pathogen contact and adherence to epithelia, an important mechanism which would otherwise permit viral replication[31].Soluble fucosylated and sialyated HMOs are bound by lectin receptors of fucose or sialyl-dependent pathogens, entrapping viruses so the host innate immune system cannot recognise them[31]. HMOs are also prebiotics for commensal microbes, which augment holistic health and fortify epithelia to prevent early steps of infection such as viral adherence [31].

4.2 Receptor blockage

Viral entry sabotages cellular machinery for viral replication. Blocking cellular entry by interrupting viral receptors, can prevent or reduce intracellular invasion and load. The SARS-COV-2 requires specific ACE-2 receptors [4]to enter cells while heparan sulfate proteoglycan (HSPG) receptors assist in SARS-COV-2 cell entry [32], establishing infection.

Human milk has ingredients that are tactful “receptor decoys” in early infection prevention[31]. Viruses utilise cell surface glycoconjugates as receptors to enter cells, while some human milk oligosaccharides (HMOs),abundant in early nutrition, express glycans that bind onto host cell surface lectins and prevent viral binding and invasion[33].Not all breastfeeding mothers can effectively provide protection through this route , as specific HMO glycosylation providing these receptors depends on factors such as the mother’s blood Lewis status[34].

Lactoferrin, a multifunctional glycoprotein, abundant in colostrum[35] fortifies human nutrition with direct and indirect anti -viral action. Its dynamic levels increase as lactation progresses to the second year[36], re-emphasising holistic importance of sustained breastfeeding. Lactoferrin is a versatile anti-viral agent against a gamut of non -enveloped and enveloped DNA and RNA viruses through numerous mechanisms; inhibiting cellular entry, by direct attachment to the virus or by blocking cellular receptors. Its action against human pathogens such as Herpes simplex virus, human papillomavirus, human immunodeficiency virus (HIV), and rotavirus from entering host cells[37] is notable at the step where these viruses enter cells utilising common cell surface receptors such as heparan sulfate glycosaminoglycan cell receptors (HSPG)[37]. Noteworthy, is that lactoferrin may also interrupt the vital step of cellular entry of SARS viruses as both the SARS- COV and SARS-CoV-2 utilise HSPG as cofactor, for cell anchor and entry[38].Lactoferrin blocks HSPG receptors , or could break the viral envelope by its interaction with viral hemagglutinin[39].

The anti-viral spectrum of lactoferrin includes fighting off infections that depend on iron. Lactoferrin deprives and interferes with iron utilisation of pathogens. Viruses may also electively infect iron-acquiring cells by binding to another human milk protein, transferrin receptors during cell entry. Other viruses alter proteins involved in iron homeostasis. In coronavirus infection and inflammation, lactoferrin has a preventive role in the respiratory and gastrointestinal tract[40]. Enhancing human milk defences at early disease barriers , lactoferrin respiratory and intestinal mucosae; possibly reverting iron disorders linked to viral colonization[38].

Human milk components of adaptive immunity, generally of importance later in the infection, also contribute to multifunctional early defences, and is an area for further study. While SARS-CoV-2 Secretory immunoglobulin A(SIgA) responses in human milk follow maternal recovery from COVID-19 [41], the protective mechanism by this tetrameric complex with secretory component (SC) primarily of mucosal adaptive immune functions in this scenario is not known. However, timely antimicrobial protection by SIgA at intestinal mucosal sites by blocking receptor binding, immune exclusion and interference with pathogen virulence determinants[42]has been demonstrated against other pathogens.

A more recent article comparing human milk mRNA vaccination responses to human milk responses to parental Covid 19 infections found that an IgG dominant response with neutralisation activity against live SARS-CoV-2 virus followed vaccination whereas IgA responses in human milk followed infection [43]. Human milk collected after infection and vaccination had microneutralization activity which increased throughout time in the vaccine group only but was higher in the infection group vs the vaccination group after the first-dose human milk samples (P = .002)[43]These variations in human milk responses after parental Covid 19 infection compared to vaccination highlight the potentials of modifying human milk protection through maternal vaccination for sustained anti-viral action[43].

4.3 Innate immune recognition

Timely, selective and regulated pathogen recognition must differentiate from the plentiful commensals in the human body. Anti-viral immune attack must cautiously minimise tissue destruction. Cells infected with viruses must be destroyed early by focused immune recognition and effective, regulated

anti-viral responses. At the same time, where dysregulated immunity can cause invasive disease and tissue destruction, as in the immunopathology of invasive SARS- CoV-2 infection, anti-viral action with capacity for anti- inflammation and immunomodulation is optimal.

The innate immune system recognises pathogens by pathogen-recognition receptors (PRRs) that sense distinct pathogen-associated molecular patterns (PAMP) [42]. Toll-like receptors (TLR) are activated and signalled by RNA viruses through RNA sensors [44]. Members of the TLR family detect viruses and induce the production of interferons through several signalling proteins[44].Reproducing this , TLR agonists are suggested therapy[44]. The anti-viral spectrum in human milk such as cytokines, monolaurin, Vitamin A , Tenascin C , lactadherrin and others [35] may be captured even where direct nursing is not feasible, through milk banks that collect milk with specific properties [35].

Innate immunity in human milk tightly regulates TLR recognition by a gamut of pro and anti - inflammatory bioactive components of human milk which modulate TLR pathways, by suppressing, dampening , attenuating or inhibiting TLR signalling [46] TLR2, TLR3, TLR5 as well as soluble cluster of differentiation (sCD)14, and human β-defensin-1 (hBD-1), function as pattern recognition receptors (PRRs) [18]

The SARS-CoV-2 activates TLR2 signalling, which results in the robust expression of proinflammatory cytokines [45]. PRRs in human milk and other bioactives in the intestine of the breastfed infant create an anti-inflammatory milieu [47], with TLR responses modified by soluble toll-like receptors (sTLRs) and (sCD)14[48]. The immunomodulation in human milk, explored further in the text, potentially fine tunes specific TLR mediated inflammatory responses, while focusing on defences against viruses by the interaction of sTLRs and sCD14 with a spectrum of bioactive factors. Furthermore, the intestinal microbial ecosystem unique in the infant fed human milk, adds on to human milk innate defenses[18].

4.4 Immune cells

Immune cells and their anti-viral products prevent or limit the infection.

Maternal blood leukocytes that home to the mammary gland go through epithelial cell spaces to be secreted into milk, whereas blood monocytes reaching the mammary gland become activated and function as motile macrophages, secreted into breastmilk for various immune functions [49]. Immune constituents are also guided into mother's milk by mucosal immunity [35]as the lactating mammary gland and its products are integral to this immune compartment. Holistic maternal health including the health of the mother's lactating mammary glands may be important for this.

Immune cells including the important motile macrophage, neutrophils, lymphocytes, innate lymphoid cells (ILCs), hematopoietic progenitor cells and stem cells exist in human nutrition. Human milk lymphocytes are CD3+ T cells, of CD4+ and CD8+ cell type, as well as Tγδ+ cells (11%), CD16+ NK cells (3-4%), and B cells (2%), for purposes of antiviral defences[50,51]. There are also specific modulatory responses on epithelial cells, monocytes, dendritic cells, and peripheral blood monocytic cells [48]. The immune cells in milk last in the infant for about 6 days[51] ; but human milk can continue to stimulate proliferation of immune cell colonies, through colony stimulating factors[51].In the mother who expresses milk, milk cells remain viable for a few hours after expression , and do not typically survive after freezing or pasteurisation[51], stressing advantages of direct breastfeeding.

Individually important protection is evident in the milk of mothers whose infants have severe bronchiolitis where there are increased number of live cells .Milk from mothers of infants who were hospitalized with bronchiolitis had increased viable cells compared to milk from mothers of healthy infants (1.3 ± 0.4 vs. 0.3 ± 0.03 × 106 cells/ml, mean ± s.e.m.; $p \leq 0.001$). [52].

Maternal milk cells from infants hospitalized with bronchiolitis produced a skewed cytokine profile *ex vivo* in response to stimulation by live RSV but not when cultured with a non-specific mitogen.[52]

Animal experiments indicate that pluripotent stem cells in human milk can replicate and differentiate outside the mammary cell lineage and can integrate to distant organs[53]. For instance,it is fascinating that human milk stem cells can reach the brain and differentiate into neuron and glial cells [53], with hypothesis that such cells can repair damaged or injured tissue in the aftermath of invasive viral infections.

4.5 Immune modulation

Human milk does not merely accelerate immune maturity but does so by immune modulation of the developing immune system. By providing an interactive network of bioactive substances which are often multifunctional, sometimes redundant, responsive and individualised, much effective protection is rendered. 'Micromanaged' via action of micro- messengers such as human milk microribonucleic acids (miRNAs), human milk confers diverse immediate and long term clinical impact, [35] with capacity to guide the proper development of immune maturity.

For instance, lactoferrin, a multifunctional substance, has direct and indirect anti -viral action by binding viruses, rerouting them from target cells or suppressing intracellular viral replication[54].Infected bronchial cells are protected from inflammation and cell necrosis by lactoferrin[54]which also immunomodulates BCG vaccine responses through gamma interferon[55] by attaching to a lipoprotein receptor related protein 2 (LRP-2) activating myeloid cells through a cascade of anti- inflammatory responses [54].

Extrapolation permits hypothesis that the action of the individual substance ex vivo may have similar impact in the nursing infant through the same substance found abundantly in human milk. Lactoferrin, in human milk, may similarly have immune dampening capacity against the immune dysregulation of the 'cytokine storm' recognised in SARS -CoV-2 , through net anti- inflammatory impact of human milk, reducing organ -induced pathogenesis of SARS-COV-2 in the lung.

Lactoferrin also transports iron and deprives iron from iron dependent microbes, reducing their infectivity, with possible role in the hyperferrinemia associated with Covid 19. Preventing thrombocytopenia, through platelet surface receptors may help in the hypercoagulable state, recognised in COVID-19[54]. Lactoferrin and other substances stimulate effective immune responses by recruiting antigen presenting cells to amplify specific adaptive immune responses[54,55]

Responsive immune-protection is evident during active infections. In nursing infants, mother's milk showed increased total number of white blood cells, specifically the number of macrophages, and TNFα levels [49], a regulation that helps accelerate recovery in the nursing infant. Individual protection through human milk occurs within the dynamics of a unique compartment distinct from maternal plasma, predominantly anti- inflammatory, differing amongst mammalian species, influenced by diet and stage of feeding, with notable differences in colostrum and mature milk [55,56].

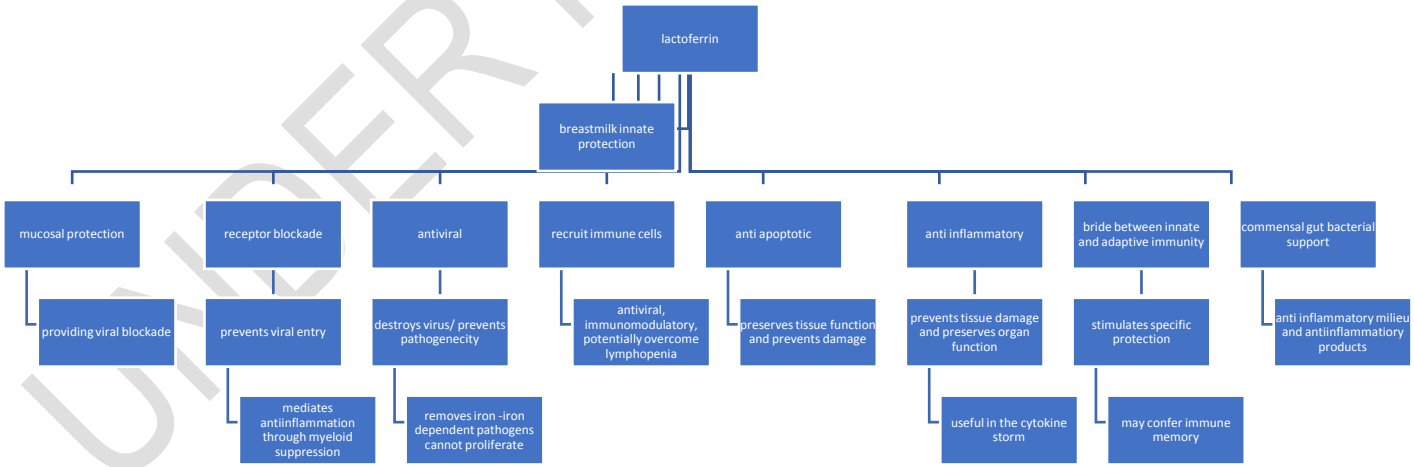
At the microlevel, the human milk compartment is also tightly immune regulated. Human milk microribonucleic acids (miRNAs) is mainly produced in the mammary gland, while small amounts are drawn from maternal blood with lactation-specific regulatory functions. Cells, exosomes and fat globules protect milk miRNA and transfer them to the infant's bloodstream [56]. Additionally, maternal diet can transfer subtypes of miRNAs codified by non-human genomes but still present in circulation into human milk [57], and some have been noted to have anti-viral immune activity such as the freely circulating xeno-miRNA (XenomiRs), against the Influenza A viruses (IAVs)[58].

Diverse pathways of immune modulation in human milk are supported by the reduction in different immune diseases such as allergies and immune-related diseases in breastfed infants[59]. Distinct microbial colonization of the breastfed infant's gastrointestinal tract, permits microbes and their metabolites to modulate local immune pathways .A fortified mucosal layer induced by human milk microbes, cytokines and immunomodulatory substances, prevents microbial penetration and antigenic components from entering into systemic circulation[60], preventing over stimulation of systemic immune responses.

The impact of microbes through a "mother-microbe-infant-microbe"[61]bond, consisting of microbes, their products and the support of the breastfed infant's intestine by human milk constituents , integrates to attenuate immune stimulation and unnecessary inflammatory responses resulting in reduced allergic diseases. This renders human milk as positive influence both for prevention of acute diseases and for long term health [59].

The framework of disease prevention by human milk feeding can be compared to that of vaccination . While vaccines work to prevent individual clinical expression of infection, could protect against asymptomatic infection or colonization, and reduce community transmission with some having the potency to stimulate immune responsiveness to infections with a variety of pathogens, probably through innate immune stimulation [62], human milk has an incomparable safety profile, with potentials to fulfill health targets of an excellent vaccine.

Fig 2: Postulation and facts: Multifunctional, dynamic innate defenses by human milk lactoferrin [35-40]



5. CONCLUSION

Analyses and integration of the pathogenesis of Covid19 to early human milk immune defenses, reiterate a systematic framework of protection in human milk feeding. Innate immune protection in

human milk not only interferes with establishment and invasion of viral mucosal pathogens at critical mucosal sites which are important in preventing disease to an individual, but also , by these actions , reduce onward transmission of the pathogen to the community.

The innate system in human milk provides powerful, multifunctional bioactivity enhanced in ways such as maternal vaccination. In addition, responsive immune forces between the mother- infant dyad, as seen in milk content during infant infections, reiterate that disease prevention is biologically dynamic in human milk, and deserves exploration for practical immunotherapy.

A re-think on these facets augments and develops both nutrition and therapy.

CONSENT

Not applicable

ETHICAL APPROVAL

This is a review and as such, this is not applicable. All work cited is referenced correctly to the best of my knowledge

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