A prospective vaccination approach to combat obesity

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Abstract: Obesity, a pan-global disease has risks to health and significant contribution to morbidity and mortality. Its associated pathological abnormalities are important health hazards contributing to illnesses. An immediate cost effective primary prevention must reach out to the global community. In this article, I argue that exclusive breastfeeding with cellular, immunological, genetic, hormonal and bioactive components has potential to prevent obesity. The argument is strengthened by some evidence that in the absence of breastfeeding, and by the substitution of artificial formula in early life, fundamental cellular pathways that are best mediated by substances in breastmilk may be adversely affected and this can result in both obesity and its associated diseases. The integration of the unique protection from infection without much inflammation obtained by breastfeeding, and its capacity for early genetic programming add to its protection in this area. The genetics within breastmilk and their influence to its constituents, if modulated, are opportunities for primary prevention. Additionally, if the genes through breastfeeding with beneficial epigenetic change to the nursling, are inherited, individuals, communities and generations can be protected. Both the social care worker and the scientist may do well to consider how, despite only modest statistical evidence of the role of breastfeeding in obesity protection, there is wealth of knowledge within its protective potentials. The areas highlighted in this article, if further explored, could make an impactful difference towards reducing the burden of today’s escalating health cost and social care all over the world.

Key words: breastfeeding, obesity, health, primary, prevention

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Introduction

Global statistics of childhood overweight and obesity show increasing trends (Onis, Blossner and Borghi 2010). The World Health Organization (WHO) estimates 43 million overweight children under the age of 5 and by 2020 in excess of two thirds of global disease burden to be soon linked to obesity related problems (Onis, Blossner and Borghi 2010). Trends indicate a disturbing increase in the prevalence of overweight and obesity worldwide and its prevalence is projected to reach a ssignificant 9% or 60 million people in 2020 (Wang and Lim 2012). The global prevalence of childhood overweight and obesity increased from 4.2% in 1990 to 6.7% in 2010, a pattern projected to reach 9.1% estimated to be around 60 million, in 2020 (Onis , Blossner and Borghi 2010). In growing economies of the South East Asian region, Malaysia recorded a significant increase in obesity prevalence among adults, from 4.4 % in 1996 to 14 % in 2006. (Khor, 2012). In Vietnam, prevalence of overweight and obesity in adults increased considerably from 1992 to 2002. (Tuan, Tuong and Popkin 2007). Of note is the suggestion that Asians are more likely to develop central obesity which is adversely linked to many obesity- related comorbid states. (Thomas, Ho, Lam et al. 2004).
Paediatric obesity has variable distribution in parts of the globe. In areas such as in Africa, the prevalence of childhood overweight and obesity in 2010 is estimated at 8.5% and predicted to reach 12.7% in 2020 (Onis, Blossner and Borghi 2010). A study reported the prevalence of overweight and obesity as 12.6% and 6.2% in junior school students and 11.5% and 4.3% in high school students, respectively (Ahmadi, Gharipour, Nouri et al 2014). The global impact of obesity and the effect it has on health resources is further appreciated when one notes that of the 43 million children overweight or obese referred to earlier, a large proportion were in developing countries (Wang and Lim 2012). Thus, the prevention of obesity is a crucial health and social issue and an effective international obesity-related health cost appraisal is needed (Tremmel, Gerdtham, Nilsson et al 2017). Health programmes must universally emphasise the early prevention of both short term effects of obesity to all but specifically in children because of the enduring impact to society and plan cost effective strategies to entirely overcome its long term health consequences.

1. Multifactorial causes of obesity

There are multifactorial causes of obesity (Jou, 2014; Sahoo et al 2015). Both endogenous and exogenous factors contribute (Jou 2014; Sahoo et al, 2015) (Figure 1) and psychosocial aspects of obesity (Beck 2016) can occur either as a part of obesity or as a result of it. Many causes overlap making distinction of mechanisms of obesity sometimes difficult.

**Figure 1: Multifactorial causes of obesity**

Simple obesity is mainly predisposed to by eating habits and lifestyle factors (Weker, 2006), risk factors for familial ‘clustering’ of obesity are the interaction of both genes and environment (Li, Lou, Du et al 2014) while hormonal obesity is a feature of specific endocrinopathies (Jou, 2014; Sahoo et al 2015; Lugo, Pina and Cordido 2012). A child with an obesity syndrome may also have a history of familial obesity. Syndromes are linked to obese phenotypes and in the majority of morbid obese cases there is involvement of a genetic mutation implicating the function of hypothalamic regions controlling food intake (O’Rahilly and Farooqi 2006). The genetic causes of inheritance patterns in monogenic and polygeneic obesity (Hinney, Vogel and Hebebrand 2010) are well documented. The overarching importance of obesity is its link to potentially dangerous health conditions. In children as in adults, a spectrum of disorders is linked to obesity such as hypertension, dyslipidaemia, impaired glucose metabolism, nonalcoholic steatohepatitis, obstructive sleep apnea, orthopaedic complications and psychosocial problems (Jarolimova, Tagoni and Stern 2013). Paediatric hypertension is a predictor of adult hypertension, and this precedes cardiovascular mortality risk in adults (Raj 2012). Cardiovascular disease manifests as heart failure, acute coronary syndrome, and premature sudden death (Rosiek and Lekowskii 2016). Of note is obesity-related left ventricular hypertrophy (LVH) and its dysfunction in children (Attar, Safdar, Ghoneim et al 2016). It merits mention that obesity is also a risk factor for the development and progression of cancer with poor prognosis in specific types of tumours (Hopkins, Goncalves and Cantley 2016). The aetiopathogenesis of the underlying influences predisposing to, a consequence of, or a complication due to obesity are not fully elucidated. However, certain fundamental mechanisms are suggested (Figure 2). A chronic low-grade inflammatory state accompanies obesity, pathologically explained by elevated systemic inflammatory markers in serum and inflammatory cell infiltration of tissues (Lee, Lee and Choue 2013). Inflammation is activated early in adipose tissue expansion and in chronic obesity with an overall tendency for the immune system towards proinflammatory responses (Bull and Plummer 2014; Houghteling and Walker 2015). Dyslipidaemias, muscle hypertrophy, hormonal abnormalities and deranged end organ responses to hormonal action are sometimes recognised in obesity and contribute to a variety of associated diseases (O’Rahilly and Farooqi 2006; Jarolimova, Tagoni and Stern 2013; Attar, Safdar, Ghoneim et al 2016).
‘Dysgenesis’ or abnormalities of commensal gut microbial flora in the human gut is now known to impact an individual’s health (Dietert and Dietert 2012). As postulated by Dietert, R and Dietert, J (Dietert, Dietert 2012) failure to adequately incorporate commensal microbes in the neonatal period is a crucial component that potentially deters “holistic health”. The pathogenesis of many metabolic diseases including obesity has been related to the gut microbiota which, with the host, are involved in dynamic homeostatic mechanisms (Lee, Lee and Choue 2013; Bull and Plummer 2014; Houghteling and Walker 2015). Altered gut microbial composition together with predisposing factors, could cause or exacerbate the aetiopathogeneses of underlying obesity (Dietert and Dietert 2012). Additionally, the gut microbial milieu is also influenced by in utero events, postnatal contact and exposure.

Figure 2: Known and possible aetiopathogeneses of obesity-linked disorders and comorbid conditions. Can breastfeeding reduce health care costs and social care burden that result from at least some of these links?

2. The placental – amniotic fluid- maternal -foetal tetrad

In utero the growing foetus is nourished both by the placenta and also by maternal, foetal and amniotic fluid factors (Mor and Cardenas 2010; Neu 2015). The placental – amniotic fluid- maternal–foetal symbiotic tetrad influences growth and maturation by hormonal, bioactive and immunological factors (Mor and Cardenas 2010; Neu 2015). It is noteworthy that constituents of the tetrad skew immunological factors uniquely to one of immune modulation (Neu 2015; Floris Kraft and Altosaar 2016) Microbial colonisation of the foetal gut occurs in utero by substances from the amniotic fluid (Neu 2015; Floris, Kraft and Altosaar 2016). The permeable foetal gut absorbs swallowed amniotic fluid and has nutritive and regulatory roles (Neu 2015; Floris, Kraft and Altosaar 2016). This modulates intestinal inflammation and affects bacterial colonization of the foetal gut and gut inflammatory responses, impacting the weight of the newborn (Mor and Cardenas 2010; Neu 2015; Floris, Kraft and Altosaar 2016). In pregnancy human placental lactogen (hPL) is secreted into maternal and foetal circulations, activating maternal production of insulin-like growth factor (IGF) further influencing foetal metabolism (Handwerger and Freemark 2000). In the foetus, receptor mediated action of hPL occurs with production of IGFs, insulin and lung maturational factors, vital for foetal survival (Handwerger and Freemark 2000). Protection from foetal infection is by placental trophoblasts with their anti-microbial peptides such as human beta defensins (Mor and Cardenas 2010), secretory leukocyte protease inhibitor (SLPI) (Mor and Cardenas 2010; King, Critchley and Kelly 2000;) and beta interferon (IFN-β) (Mor and Cardenas 2010).

From the moment of conception, throughout pregnancy and at birth, the mother and infant are involved in cellular signals, which are probably bidirectional (Floris, Kraft and Altosaar 2016). For these signal mediators to function physiologically, they are protected from biological degradation and although not yet fully elucidated, their signals control growth and development in the prenatal and postnatal phases (Floris, Kraft and Altosaar 2016). With potentials for diverse action, they are impacted by many extrinsic factors, such as maternal diet, mode of delivery, microbes in the maternal gut, and the type of milk feeds postnatally (Floris, Kraft and...
3. Breastfeeding, obesity and associated conditions

i. Breastfeeding transfers maternal genomic information, influences development and function of tissues in the nursling

An infant is born with a set of genes, its expression and regulation determining many states of health and disease. The early postnatal period is crucial with environment and nutrition potentially influencing genetic expression. DNA methylation and imprinting, histone modification by acetylation and methylation and RNA associated silencing are epigenetic influences (Simmons 2008); these, with other postnatal experiences modify, alter or impact gene expression without alteration of the DNA sequence (Simmons 2008). At birth, fetal swallowing of maternal flora influences the infant’s gut milieu, directly and indirectly influencing growth and maturation of the gastrointestinal tract and other organ systems (Neu 2015). Postnatally, nutrition by the lactating mammary gland is an influential exposure both because it is continuous and repeated, and by the nature of its constituents (McGuire and McGuire 2015). Mammary stem cells can differentiate into adipocytes and epithelial cells (Zhu and Nelson 2013). The mammary gland consists of glands, ducts, connective tissue and adipose tissues. Adipose tissue principally makes up the volume of the breast consisting of adipocytes, fibroblasts and macrophages (Zhu and Nelson, 2013; Kajimura and Saito, 2014). Adipose tissue exists in two forms, and evidence suggests that both forms can undergo transdifferentiation (Kajimura and Saito, 2014). White adipose tissue (WAT) is for energy storage as triglycerides, brown adipose tissue (BAT) is responsible for thermogenesis via uncoupling protein-1 and its sympathetic innervation, predominantly a mechanism utilised by the newborn (Kajimura and Saito, 2014). In adipose tissue, hyperplasia, a primarily irreversible process, denotes the increase in number of adipocytes and is determined from childhood to adolescence remaining constant during adulthood, in both lean and obese individuals (Spalding, Arner, Westermark et al 2008 et al); in an adult about 10% of fat cells are renewed annually (Spalding, Arner, Westermark et al 2008). Hypertrophy involves the accumulation of triglycerides which are able to take up, store, and release free fatty acids depending on systemic nutritional status, and are uniquely capable of tolerating high concentrations of lipids without lipotoxicity (Rutkowski, Stern and Scherer 2015). The mammary epithelial cell (MEC) embedded in the mammary fat pad, constitutes the functional unit of the mammary gland and together with adipose tissue influence its growth and milk production (Zhu and Nelson 2013). While the infant suckles at the nipple, ducts that link lobules, lobes and glands allow milk to flow through them. Breastmilk, the nutrition of the mammary gland, is a rich source of early stem cell progenitors and differentiated cells (Witkowska-Zimny and Kaminska-El-Hassan 2017). Milk microvesicles are formed from the apical parts of the MECs or from the milk fat globules (MFG) (Bourlieu and Michalski 2015), which during secretion into milk envelop their cell contents and contain abundant mammary cell ribonucleic acid (RNA) (Lemay, Ballard, Hughes et al 2013). The genes in breastmilk represent different cell populations and show great variation in expression (Lemay, Ballard, Hughes et al 2013). Although the activators of these events are not well defined, it is possible that both incorporation of maternal genomic information into tissues and control over how tissues of the nursling develop and function occur by breastfeeding (Irmak, Oztas and Oztas 2012). It is proposed that breastfeeding is capable of transfer of messenger RNAs (mRNAs) transcripts from mother to nursling (Irmak, Oztas and Oztas 2012). These are coding RNA molecules that transmit genetic information from maternal deoxyribonucleic acid (DNA) to the ribosome as a template for protein synthesis. It is also suggested that microvesicles containing mRNA transcripts possess reverse transcriptase activity and that they are transferred to cells of the nursling by endocytosis (Irmak, Oztas and Oztas 2012). mRNA, acted upon by reverse transcriptas, termed ‘retrotransposoons’, are integrated into the tissues of the nursling (Irmak, Oztas and Oztas 2012).

Maternal genetic influence does not cease here. Micro RNAs (miRNAs), noncoding RNAs which can also affect genes are found in breastmilk mainly from synthesis in the MEC (Alsaweed, Lai, Hartmann, Geddes et al 2016; Gigli and Maizon 2013). There seems to be different pathways by which miRNAs are formed (Shabalina and Koonin 2008; Chong, Zhang, Cheloufi, et al 2010); one biosynthetic pathway requires two RNaseII
enzymes. Initial transcription is by RNA polymerase II generating primary miRNA (pri-miRNA), these are acted upon by the enzyme Drosha to form pre-miRNA (pre-MiRNA) which is then transported to the cytoplasm and is enzymatically cleaved by Dicer which is loaded onto an argonaute (Ago) protein which primarily forms the RNA-induced silencing complex (RISC) (Shabalina and Koonin 2008).

An array of different miRNAs are synthesised in the MEC (Alsaweed, Lai, Hartmann et al 2016) with dynamic action. In the lactating mammary gland, the cell content is known to increase post-feeding (Alsaweed, Lai, Hartmann, et al 2016), suggesting that MECs synthesise miRNAs as the infant suckles from the breast, underscoring the importance of demand feeding for the nursling to obtain the full spectrum of miRNAs. In this context, there are a few issues to be considered. How far is the range of miRNAs that direct gene expression entering the milk feed responsive to infant suckling? Mother to infant communication seems to occur during breastfeeding – variables such as the health status of the lactating breast as well as of the “mother and infant dyad” are suggested (Hassiotou, Hepworth, Metzger et al 2013). Similarly, in the setting of this discussion, could an infant by the nature of suckling in hunger or in satiety, trigger or suppress the expression of genes for appetite impacting factors in breastmilk? Is it conceivable that the weight of an infant triggers cellular messages to modify synthesis of genes that produce pro-obesity proteins? Are maternal genes within the “intelligence” of breastmilk destined for some form of communication educating the infant’s course of “bio-geno-immuno-nutritive” (Kutty, 2016) pathways provided through her breastmilk? By post-transcriptional gene modification, in a myriad tissues of the breastfed, genetic information is assimilated into tissues (Melnik and Schmitz 2017); these potentially confer epigenetic modification to the expression of genes in the nursling (Melnik and Schmitz 2017). The unfolding of genetics in breastmilk seems fundamental to health, metabolism and disease (Dietert and Dietert 2012; Melnik and Schmitz 2017).

ii Breastmilk proteins, the enteromammary axis and gut bacteria

Unique proteins in breastmilk influence both the metabolism and weight of the nursling. These macronutrients consist of milk fat globule membrane (MFGM) proteins, caseins and whey (Lönnerdal, Erdmann, Thakkar et al 2017). The mother produces them despite her diet as milk macronutrient composition is not notably affected by fasting (Rakicioğlu Samur, Topçu et al 2006). Milk proteins are bioactive, biologically affecting tissues, some with features that optimise in vivo action, resisting digestion in the gastrointestinal tract for purposeful physiological functions (Lönnerdal, Erdmann, Thakkar et al 2017; Davidson and Lönnerdal 1987). The metabolism of the nursling is affected by the milk feeds and the microbes in the gut (Davidson, Lönnerdal 1987; Jost, Lacroix, Braegger, et al 2013). Tangibly breastfeeding establishes the maternal – to infant bond via the enteromammary axis, linking the mother’s gut to her lactating mammary gland, influencing factors in the milk feed (Jost, Lacroix, Braegger, et al 2013). Through this bond, many potential influences of the mother’s gut which are under novel stimuli, are factually and at present, hypothetically, directly or indirectly transmitted to her nursling (Obata and Pachnis 2016; Jost, Lacroix, Braegger, et al 2013). The immature neonatal immune system is thus under maternal influence and in some ways there is “immune education” because breastmilk stimulates useful gut bacteria such as Bifidobacterium, Clostridiales and Lactobacillus which positively influence homeostasis for optimal growth and metabolism (Jost, Lacroix, Braegger et al 2013). Different microbial patterns induced by artificial feeding will not provide the nature and extent of homeostasis or influence metabolism in the same manner, and this is supported by the suggestion that such microbial flora is potential nidus for abnormalities of metabolic maturation and homeostasis, predisposing to immediate and long term metabolic derangements (Risser 2015; Jost, Lacroix, Braegger et al 2013).

iii Breastmilk proteins, adiposity and organ effects- do they save a nation’s health resources in the long term?

Breastmilk is dynamic during phases of lactation and at different times within a feed with variation in its proteins, cells, fats and other constituents. Early in lactation, whey concentrations are high, compared to casein, comprising beta and kappa caseins (Lönnerdal 2013). The median whey-to-casein ratio, nearly 80:20 in colostrum falls to 60:40 by the second week (Lönnerdal 2013). Colostrum, the first
‘vaccination’ of a breastfed infant has immunoglobulins and other whey proteins for early protection, with \(\alpha\)-lactalbumin having highest concentrations (Lonnerdal 2013). Other bioactive proteins are lactoferrin, lysozyme, secretory immunoglobulin A(sIgA), haptocorrin, lactoperoxidase, bile salt stimulated lipase and tumour growth factor- beta (Lonnerdal 2013). Breastmilk is a source of iron with high bioavailability and in term infants protects against iron deficiency anæmia, the commonest micronutrient deficiency worldwide (Qasem and Friél 2015); this deficiency impacting growth and development and predisposing to infections. Metabolic effects of lactoferrin, a bioprotein with immunological activity are evident by its ability to increase insulin sensitivity and lower blood sugar levels(Ono, Murakoshi, Suzuki et al 2015), with a possible beneficial role in decreasing visceral fat and the metabolic syndrome (Navarrete, Ortega, Bassols et al 2009) - in vivo actions are therapeutic approaches to explore in obesity linked conditions.

Differences by feeding mode in the amount and content of proteins and their amino acids ingested at different periods of lactation and their influence on hormones and growth factors may explain varied growth patterns observed in the breastfed compared to the formula fed infant (Csap and Salamon 2009). Casein forms 30% of the total protein in breastmilk and 80% in cow’s milk. Caseins have a high content of proline, and form micelles of calcium and phosphorus (Csap and Salamon 2009). In breastmilk the content of glutamic acid is highest and methionine lowest, whilst, of the essential amino acids, leucine and lysine are the highest, followed by those of isoleucine, valine, threonine and histidine (Csap and Salamon 2009). Compared to the protein intake of breastfed infants which declines with age in tandem with requirements for protein during the early months of life for growth and development, the protein intake of formula fed infants is more or less static and tends to exceed metabolic requirements after the first 1-2 months of life (Ziegler 2006).

Insulin synthesis and secretion are stimulated in infants fed formula with high levels of protein, as indicated by increased urinary C-peptide compared to breastfed infants (Luque, Monasterolo, Escribano et al 2015; Socha, Grote, Gruszfeld et al. 2011). The actions of insulin influenced by the variations in protein supply affect adipose tissue and other organs. (Dimitriadis, Mitrou, Lambadiari et al 2011). Insulin enhances active transport of amino acids into muscle and stimulates protein synthesis. It decreases lipolysis in adipose tissue, stimulating fatty acid and triglycerol synthesis, enhances uptake of triglycerides into adipose tissue and muscle and reduces fatty acid oxidation in muscle and liver (Dimitriadis, Mitrou, Lambadiari et al 2011). Insulin is primarily involved in metabolic activities but its growth factors, such as IGF, control growth and differentiation of many cells and tissues. There is possible “cross-talk between the various ligands and receptors of the IGF family” (Werner, Weinstein and Bentov 2008). Based on postnatal differences in growth and development of organs, target tissues are differently sensitive to actions of IGF-1 in infants (Luque, Monasterolo, Escribano and Ferré 2015; Dimitriadis, Mitrou, et al 2011; Werner, Weinstein, Bentov 2008). There are modulation and dynamic levels of these factors, their binding proteins and specific proteases in breastmilk with a decline of their levels over the course of lactation (Milsom, Blum and Gunn 2008). The insulin like growth factor-1 (IGF-1) axis is possibly influenced differently by formula feeding compared to breastmilk, contributing to higher body weight in formula fed infants (Socha, Janas, Dobrzafiska et al 2005). IGF influences local and systemic cell growth and differentiation by autocrine and paracrine signals of organs including the musculoskeletal and endocrine systems (Wang, Bikle and Chang 2013). The early protein hypothesis denotes the protein-induced growth of organs as possibly due to IGF-1 (Luque, Monasterolo, Escribano et al 2015; Laron 2001).

Reiterating the importance of physiological levels of IGF-1, its deficiency is associated with Laron Syndrome, such infants being short at birth (Laron 1999); with abnormalities involving the brain (Laron 1984), musculoskeletal system and heart (Brat, Ziv, Klinger et al 1997; Feinberg, Scheinowitz and Laron 2000).

Amino acids of digested milk proteins are regulatory nutrients in breastmilk. In the absence of breastfeeding and with replacement by artificial feeding, quantitative or qualitative differences in the amino acids in cow milk-based infant formula is postulated to be a cause of obesity. (Melnik 2012). The mammalian target of rapamycin (mTOR), is recognised to be “a master regulator of cellular, developmental and metabolic processes” (Jaina, Arauzc, Aggarwala et al 2014) and, nutrition, influencing growth and development, coordinates this link (Melnik 2012, Laplante and Sabatini 2012). mTOR controls the expression of miRNA (Laplante
and Sabatini 2012). mTOR is assembled into two distinct complexes, mTORC1 and mTORC2 with suggestion that there may be a link between the two (Jaina, Arauzc, Aggarwala, et al 2011). Nutrients can modulate signalling of miRNA and leucine, an essential amino acid and a precursor of fatty acid and cholesterol synthesis—is found to activate mTORC1 (Jewell, Flores and Guan 2015). Additionally obesity related comorbidities that burden health and social support systems in the long term; these maybe partly explained by the suggestion that consumption of cow milk- based formula is not species specific, dissimilar in its leucine content from human breastmilk (Melnik, John and Schmitz 2013; Melnik and Schmitz 2017), as a result, it may be argued that uncontrolled stimulation of hormonal and cellular pathways results in abnormalities and disease(Jewell, Flores and Guan 2015 Melnik and Schmitz 2017) A nation’s health resources could be affected by these diseases with a dismal statistical impact- if indeed the higher quantity of leucine in infant formula signals mTORC1 differently than that of breastmilk, increasing adipogenesis and irreversible adipocyte hyperplasia ( Melnik, 2012; Melnik, John and Schmitz 2013; Melnik and Schmitz 2017) , predisposing to obesity and its associated conditions. mTORC1 signalling by leucine also increases blood flow and arterial pressure (Harlan, Guo, Morgan et al 2013) and mTOR activation has been linked to murine cardiac hypertrophy (Lollo, Batista, Moura et al 2013)

The proteins in breastmilk also constitute the active components of the membrane proteins of the milk fat globule and include lactadherin, butyrophilin, xanthine oxidase, human milk mucins and membrane mucins on the fat globule (Lonnerdal 2013), with much potential for immune modulation (Zanabria, Tellez, Griffiths et al 2014). The milk fat globule (MFG) per se is rich in RNAs, and supplies energy as nutrients via triacylglycerol (TAG) (Zanabria, Tellez, Griffiths et al 2014). Its bioactive constituents influence the metabolism of lipids TAG has a role in determining microbiota of the gut that modulate immune responses (Zanabria, Tellez, Griffiths et al 2014). Specific micronutrients are protected and cholesterol absorption is lowered by MFG (Fernandez-Hernando, Suarez, Rayner et al 2011), rapidly clearing chylomicrons from plasma (Fernandez-Hernando, Suarez, Rayner et al 2011) miRNAs, functioning at the post-transcriptional level of gene synthesis regulate genes associated with lipid metabolism (Fernandez-Hernando, Suarez, Rayner, Moore 2011). miRNA precursors may influence cholesterol homeostasis, fatty acid oxidation, and lipogenesis (Rayner, Suarez, Davalos et al 2010). The abundance of miRNAs in breastmilk may reflect the extent and influence on growth and metabolism provided by the genetics of breastfeeding.

At six months of age an infant who is exclusively breastfed must start complementary feeding. Undigested substances in infant weaning diets such as fibre are fermented in the colon to produce Short Chain Fatty Acids (SCFA); SCFAs are sources of energy requirements for the colonic epithelium (Schwiertz, Taras, Schäfer et al 2010; Byrne, Chambers and Morrison 2015). Gut microbes via SCFAs may stimulate Glucagon-like Peptide -1 ( GLP-1) a neuropeptide from the transcription of the proglucagon gene, influencing satiety, gut transit times and insulin secretions (Byrne, Chambers and Morrison 2015).

### iii Breastmilk hormones and obesity

Hormones in breastmilk play a role in metabolism and physiologically balance states of energy deficit with excesses (Savino, Liguori Fissore and Oggero 2009; Savino, Fissore, Liguori, Oggero 2009). Some hormones are inversely related to obese states while others more directly prevent obesity. During energy deficit, ghrelin in breastmilk, a peptide hormone and a stimulator of growth hormone secretion is released from the stomach and the mammary gland by signals from the arcuate nucleus for appetite stimulation (Savino, Fissore, Liguori Fissore et al 2005). The active form of ghrelin increases during a lactational period and decreases over time (Savino, Fissore, Liguori Fissore et al 2005). Formula fed infants, receive a higher amount of ghrelin, with greater feeding impetus compared to breastfed infants leading to increases in weight and growth rates (Savino, Petrucci, Lupica et al 2011). A correlation between ghrelin in breastmilk of obese and non obese infants suggests its regulatory effect acting together with other hormones (Savino, Petrucci, Lupica et al 2011; Savino, Liguori, Fissore et al 2009). Levels of satiety and food preferences exert early stimulus, influenced by the type of milk feeds (Brown and Lee 2012). Plausible basis for cultural and ethnic differences in cuisine prenatally is the recognition of taste and odours as the fetus swallows amniotic fluid flavoured by the mother’s diet (Mennella, Jagnew and Beauchamp 2001). Flavours of maternal diet through breastmilk
continue to influence the breastfed infant (DeCosmi, Scaglioni and Agostoni 2017). This, complemented by the interplay of breastmilk hormones seem important in weight control. Excessive intake of food has a link to “polymorphisms in the fat mass and obesity-associated gene (FTO)” (Karra, O’Daly, Choudhury et al 2013) FTO may cause epigenetic change via a potential regulatory RNA modification, predisposing to human obesity (Karra, O’Daly, Choudhury et al 2013).

Adipopectin is reactive to energy deficits, released from adipocytes in the fasting state, decreasing in obesity. Its effective levels in breastmilk favour its penetration of the intestinal barrier to modify infant metabolism (Khodabakhshi, Ghayour-Mobarhan, Roo ki, et al 2015). In breastmilk adiponectin is inversely linked to infant weight and body mass index (BMI) protecting against overweight and obesity in later life (Ballard and Morrow 2013). The adipokine, Ne sfatin-1, in breastmilk with a role in obesity might be expressed by nigral dopaminergic neurons (Shen, Song, Du, Yong et al 2017). Hormones in breastmilk that inhibit appetite and increase energy disbursement by central action, such as leptin, derived from the adipocyte, as well as by interaction with CCK and pancreatic insulin intestinal peptide YY, impact weight control (Perry and Wang 2012). As in utero, postnatally, leptin in colostrum and breastmilk correlates with body mass index (BMI) in infants (Casabiell, Piñeiro, Tomé et al 1997). It acts through the Ob-receptor (s-Ob) and reduces food intake while increasing energy expenditure (Catli, Dunda and Dundar 2014; Savino, Liguori and Lupica, 2010). Either from maternal plasma or by active production in the MEC, (Bonnet, Delavaud, Laud et al 2002) leptin acts on specific neurons in the hypothalamus and upregulates anorectic α-melanocyte-stimulating hormone (α-MSH) and downregulates orexigenic neuropeptides (Zhou and Rui 2013). Leptin also has specific effects on T-lymphocytes such as enhancing proliferation of naive and memory T-cells, increasing interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) (Riejos, Najib, Alvarez et al 2010; Ouchi, Parker, Jesse et al 2011); a single component in breastmilk having a number of useful functions.

iv Adipose tissue inflammation, infections and breastmilk protection
Integration of knowledge on the causes and pathogenesis of obesity and how the potentials by breastfeeding can counter mechanisms that cause obesity may clarify its role in prevention.

A nutrition linked epigenetic mechanism that is inheritable has been proposed (Kaati, Bygren and Edvinsson 2002). It was earlier mentioned that chronic inflammation is an obesity linked aetiopathogenetic mechanism. Hypertrophy and hyperplasia of adipocytes occur during lipogenesis (Jung and Choi 2014; Ghigliotti, Barisone, Garibaldi et al 2014). Accumulation of triglyceride inside white adipocytes causes hypertrophy (Jung and Choi 2014; Ghigliotti, Barisone, Garibaldi et al 2014), an increase in the size of adipocytes. Adipocyte hypertrophy is not a limitless process hence when excessive, large hypertrophied adipocytes experience hypoxia and may not be able to perform the physiological functions associated with this tissue. (Rutkowski, Stern, Scherer 2015; Schwartz, Woods, Porte et al 2000). In obesity, adipose tissue is infiltrated by a large number of macrophages, and this is related to systemic inflammation and insulin resistance (Weisberg, Mc Cann and Desai 2003; Ouchi, Parker, Jesse et al 2011). Being an active endocrine organ, adipose tissue- derived adipokines have proinflammatory effects contributing to the complications of obesity. (Weisberg, Mc Cann, Desai, et al 2003). There is also interrelationship between adipose tissue and infections where pathogens maybe postulated to cause, exacerbate or modify immune responses in obesity. (Hedge and Dhurander, 2013) Hence, responses in breastfeeding that shield from early and recurrent infections together with its predominant antiinflammatory action may be viewed as general antiobesity protection.

In the acute protection against respiratory infections in early life, there is immunomodulation, with breast milk immunoglobulin G (IgG) significantly absorbed by the breastfeeding infant (Li, Liu, Jiang, et al 2017). It has been shown that high levels of IgG on the nasal mucosa are able to protect against respiratory syncytial virus (RSV) infections (Vissers, Ahout, de Jonge et al 2016). In cases of previous infections, memory cells produced in breastmilk potentially ameliorate infections; the absence of such immunological memory favours recurrent infections and chronic inflammation, heightening the proinflammatory scenario alluded to earlier, already present in obesity.
Immunological memory in breastmilk involves both arms of immunity and disease- causing microbes gain access to the body mainly through mucosal portals. In breastmilk, CD8+ T cells have intestinal and mucosal homing receptor and memory cells (Sabbaj, Ghosh, Edwards et al 2005). Its B cells, are switched memory cells primed to secrete antibodies(Tuaillon, Valea, Becquart et al 2009). To emphasise the role of breastmilk as an anti-inflammatory agent, breastfeeding from allergic mothers with intact B cell immunity, successfully protect offspring from allergic airway disease (Matson, Thral, Rafit et al 2009). At the cellular level, miRNAs have a role in immunity and may link inflammation, immunity and obesity (Ge, Brichard, Yi and Li 2014).

If chronic inflammation is a pathogenetic mechanism of obesity, secretory immunoglobulin A also (sIgA) is deemed to have antiobesity function. In defence and protection against local and systemic infections without inflammation, sIgA , at mucosal sites block attachment of pathogens to epithelial cells (Mantis, Rol and Corthésy 2011). As is already well established, in the airways, sIgA functions efficiently to shield mucosae from injury without inflammatory responses (Mantis Rol and Corthésy 2011), and, pertinent to this discussion in reducing the pathogenetic mechanisms in obesity . It directly reduces pathogen induced proinflammatory responses and prevents pathogens binding to intestinal cells for transepithelial transport which may otherwise stimulate systemic immune responses (Mantis Rol and Corthésy 2011). Moreover, potent antiinflammatory effect by sIgA per se is its ability to interact with dendritic cells (DC) through the specific intercellular adhesion molecule (ICAM)-3 grabbing non-integrin receptor 1 (SIGNR1) (Monteiro 2014). Gut intestinal microbes are important again here- as part of the mucosa associated immune system (MALT), sIgA, influences gut intestinal microbiota by both Fab-dependent and Fab- independent mechanisms (Mantis Rol and Corthésy 2011), downregulating proinflammatory pathogens and allergen induced responses (Mantis Rol and Corthésy2011). Furthermore, microbial colonization itself can generate antibodies in the gut shaping composition of beneficial gut microbiota through “antibody-mediated immunoselection” (AMIS) (Kubinak and Round 2016). The absence of breastfeeding and replacement by artificial formula has been known to cause more diverse bacterial flora such as coliforms, C. difficile and Bacteroides fragilis. (Mueller, Bakacs, Combellick et al 2015) which can cause infections and diseases. Lipopolysaccharides, (LPS), the outer membrane constituent of coliforms regulate expression of cannabinoid receptors via the LPS receptor, triggering systemic sepsis (Csóka, Németh, Mukhopadhyay, et al 2009)- this could potentially enhance adipose tissue inflammation through infection, stimulating aetiopathogenetic mechanisms associated with obesity.

iv Antioxidants in breastmilk and obesity

The antioxidant enzymes in breastmilk namely superoxide dismutase (SOD), catalase and glutathione peroxidase (GSHPx) together with bioactive nutrients protect from oxidative stress. (Živković, Sunarić, Trutić, et al 2015). Obesity results in conditions that stress the endoplasmic reticulum (ER) by the unfolded- protein response (UPR) (Zhang and Kaufman 2008 ). ER stress and the UPR lead to obesity-induced inflammation, triggering activator proteins, kinases, acute-phase responses and reactive oxygen species (ROS) (Rains and Jain 2011). Chronic exposure to ROS affects glucose transporters, impairs insulin-stimulated glucose uptake (Marseglia, Manti, D’Angelo et al 2015) and may predispose to specific cancers (Wang, Li, Ye et al 2016). The enhanced antioxidant capacity of human milk compared to the reduced levels in commercial formula (Mehta and Petrova 2014) is a general advantage in breastmilk against many causes of oxidative stress. It is possible that the antioxidant capacity of breastmilk may be protective in obesity-induced inflammation in adipose tissue.

Conclusion

The impact of obesity on immediate and long term health is of great concern both for the individual as well as for the community. Primary prevention is mandatory because of the mechanical stressors of obesity and its important comorbidities. Breastmilk has potential action against obesity, because of its interactive constituents of “bio-genno-immuno-nutrition” (Kutty 2016), and can positively influence or counteract some aetiopathogenetic mechanisms. By epigenetics and by the inherent nature of its constituents, breastmilk can potentially alter the expression of diseases (Verduci, Banderali, Barberi et al 2014), including obesity. Although, with time there may be a weakening effect of the benefits of
breastmilk (Horta and Victoria, WHO 2013) contributed to by the influence of other dietary and lifestyle factors, the impact by multifunctional miRNAs in breastmilk may be different. Through the capacity to change genetic expression, the influence of breastfeeding may be more enduring then presently surmised, endowing the lactating mammary gland with substantial potential for broad but important metabolic protection. Furthermore, if epigenetic expressions can be inherited (Kaati, Bygren and Edvinsson 2002) the epigenetic influence of genes through breastfeeding could endow natural feeding as a necessary vaccine that can be modulated in an individual and across communities and generations (Figure 3), the absence of which detrimental to overall health.

**Figure 3:** The public health and social care impact of obesity protection by breastfeeding.

In other words, in the absence of breastfeeding, miRNAs in formula feeding can increase the risk of “diseases of civilization” (Melnik 2017) such as obesity, type 2 diabetes mellitus and so on (Melnik 2017) – these, if inherited, have a negative impact on the health burden of a population, but on the other hand, inheritance of potential protective action against these diseases by optimal physiological growth and function of organs by breastfeeding may be holistically viewed as a generational public health tool to reduce morbidity and mortality risk. Early prevention of adipose tissue hyperplasia and hypertrophy by breastfeeding may reduce the later difficulties encountered with weight control and the problems linked to overweight.

When discussing more specific protection through breastmilk, a number of interventions to the breastfeeding mother may be possible (Alasil and Kutty 2015). Just as maternal immunisation can give focused protection to the nursling against specific infectious diseases, (Alasil and Kutty 2015) could targeted obesity-related modulation transmitted through breastmilk be feasible through intervention in high-risk families?

This idea must clearly be further developed. Research on cellular mother-to-infant signal activators may take the lead in the therapeutics of obesity-comorbidity states. Milk industries could benefit from knowledge of the dynamic action of breastmilk proteins in bionutrition, immunology and genetics.

The epigenetics of breastmilk nutrition enhanced by modulation must be considered advancements in health care. With more in-depth research in the areas highlighted in this article, exclusive breastfeeding could be priceless primary vaccination against obesity across the global community reducing health care cost and social care burden.

**References**


Alasil, SM. and Kutty, PK (2015) Breastfeeding as a Tool that Empowers Infant immunity through maternal vaccination J Vaccines Vaccin .6: p271

Alsaweed, M Lai, CT. Hartmann ,PE.Geddes ,DT. and Kakulas, F . (2016) Human milk miRNAs primarily originate from the mammary gland resulting in unique miRNA profiles of fractionated milk Scientific Reports 6 Article 20680


Ge, Q. Brichard, S. Yi, X. and Li, QF. (2014) microRNAs as a New Mechanism Regulating Adipose Tissue Inflammation in Obesity and as a Novel Therapeutic Strategy in the Metabolic Syndrome. *Journal of Immunology Research* Volume 2014, Article ID 987285, 10 pages http://dx.doi.org/10.1155/2014/987285


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