Review

Relevance of Milk Composition to Human Linear Growth from Infancy Through Puberty: Facts and Controversies

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Review

Relevance of Milk Composition to Human Linear Growth from Infancy Through Puberty: Facts and Controversies

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Abstract: Milk is the principal nutrient of newborn humans and a diagnostic feature of the order mammalia. Its release is elicited reflexly by infant sucking under the control of hormone oxytocin. While it is recognized that breast milk optimally promotes infant longitudinal growth and development, this review explores facts and controversies regarding the extent to which the milks of several domesticated animals and formula milk approximate special properties and bioactivities of breast milk. The review provides evidence that early exposure to undernutrition during pregnancy and infancy predominantly and permanently stunts longitudinal growth in both animals and humans, but is often accompanied later in life by obesity and metabolic dysfunction, and sometimes also by altered timing of sexual maturation. There is insufficient understanding of the relationship between critical periods of nutritional vulnerability and the control of longitudinal growth in humans this growth is characterized by a relatively prolonged period of slow childhood growth bracketed by two rapid neonatal and pubertal growth phases. It is not known whether there are additional critical nutritional periods during the extended and variable phases of human growth beyond the intrauterine and the early postnatal ones. It also is not clear how long the qualitative and quantitative characteristics of infant milk intake can influence subsequent periods of childhood and pubertal growth and development. Metabolic consequences of the macronutrient and hormonal composition of human milk during the critical early under- or over-nutrition will be better understood in studies linking the interactions of nutrient properties to controls of linear growth and body composition over the extended period of human growth from infancy through the end of puberty.

Keywords: breast milk; domesticated animal milk; formula milk; milk composition. milk bioactivities; longitudinal growth; obesity; metabolic dysfunction; critical nutritional periods

1. Introduction

Milk is an evolutionary innovation refined by natural selection for optimal nutrition of newborn mammals including human infants. The order Mammalia, to which humans and other mammals belong, developed during the Jurassic Mesozoic period, about 160 million years ago. The evolution of milk provided a more effective nutrient mix and mode of delivery for newborns than the older system of providing the nutrition within extruded shelled eggs, estimated to have started 320 million years ago, which was used by dinosaurs and persists to the present in birds, and crocodilians [1]. Two genetically programmed reflexes facilitate non-competitive availability of milk for infant for several months after birth. Milk ejection reflex is mediated by the anterior pituitary hormone oxytocin triggered from one group of hypothalamic neurons in response to infant sucking on the breast nipple [2]. Milk letdown can be conditioned to mother hearing infant crying or even thinking about nursing [3]. The same hormone promotes bonding between mother and infant [4]. Breast feeding interferes with pregnancy for up to 6 months following parturition provided the infant is nursing intensively [5]. This reserves access to ample milk supply to the newborn infant for the first 6 months of its life. Several health organizations acknowledge the presence of these reflexes and advocate breast-feeding benefit to the infant during the 6 to 12 months after birth [6–8]. In addition, a wealth of data attests to

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the benefits of breast milk in promoting growth and development during infancy [9] and childhood [10].

The next development regarding human milk consumption took place about 10,500 years ago, in Anatolia (Asian portion of present-day Turkey), and possibly simultaneously in other parts of the world when humans domesticated cattle, goats, sheep, and camelids [11,12] and started fermenting kefir and yogurt, as well as producing and using cream, butter, and cheese.

Despite the abundance of research on the capacity of milk to stimulate growth and healthy development in breast-fed infants, it is not clear to what extent milk produced by cattle, sheep, goats, and camels, or synthetic formula milk, can match the composition and bioactivity of human milk. The purpose of this literature review is to address the facts and controversies regarding this question.

2. How Does Milk Produced by Cows, Sheep, Goats, and Camels Compare to Human Milk and Infant Formula in Stimulating Infant Linear Growth and Affecting Body Composition ?

2.1.1. Comparison of Human Breast Milk Composition to that from Domesticated Mammals and to Synthetic Milk Formula

Properties of milk of different species of lactating mammals have evolved to support the specific growth and development of their young. Accurate measurements and comparisons of milk properties are challenging because the composition of milk changes in response to the times relative to the onset of lactation, to the phase of individual nursing bout, and to the intervals between feedings [13]. Characteristics of the mother such as her age, diet, and BMI also play a role [14], as well as infant's gender [15] and its needs as they change with age. Data also are affected by different measurement methods. With respect to stage of lactation, breast milk composition changes from colostrum released immediately after infant's birth to transitional milk, and then to mature milk [16]. During the transition to mature milk, lactose peaks by seventh month, and the concentration of lipids progressively increases, while high concentrations of growth factors found in the colostrum decline [14]. In the course of a single nursing bout, fat content increases, and lactose decreases between the foremilk and the hindmilk [17]. In young mothers between 20 to 30 years, breast milk contains the highest concentration of protein but does not affect lipid and lactose. Maternal dietary fatty acids (6-omega vs 3-omega) appear in breast milk within 2 to 3 days [18], while breast tissue can synthesize medium-chain fatty acids (MCFAs) of between 10 and 14 carbons.

Breast milk contains about 87% water, 4% fat, 1% protein, and 7% lactose. It is a complex medium that also contains additional constituents many of which interact with each other and confer to breast milk special bioactivities. Major components of breast milk are broadly comparable in the five species of domestic animals with some differences in the concentrations of protein and fat. Human and donkey milk contain the least protein, sheep contains the most, and cow, camel, and goat have intermediate amounts. Sheep milk is richest in fat and in the ratio of whey protein to casein. Concentrations of lactose and most other components are less variable (Table 1).

Table 1. Composition of human breast milk (Guo 2014) relative to cow (Guo 2014), camel [19–23], donkey [24], goat [26,27], and sheep milks [27].

Milk components	Human	Cow	Camel	Donkey	Goat	Sheep
Protein	1.0	3.4	3.4	1.7	3.6	5.6
Casein	0.4	2.7	2.4	0.9	2.1	4.2
α_{s1}-casein	0	1.0	0.5	0.2	0.1	0.5
α_{s2}-casein	0	0.3	0.2		0.4	0.4
ß-casein	0.3	1.0	1.6	0.4	1.2	3.2
κ-casein	0.1	0.4	0.1		0.4	0.1

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Whey proteins	0.7	0.6	0.7	0.6	0.6	1.1
Fat	4	4.4	3.3	2.5	4.5	7.5
Saturated fatty acids (SFA)	2	3.2	2.4	1.4	2.7	4.6
Monosaturated (MUFA)	1.7	1.1	0.8	0.9	1.1	1.7
Polyunsaturated (PUFA)	0.5	0.2	0.1	0.6	0.2	0.3
Cholesterol (mg/100 ml)	13	13	6	9	11	22
Emulsified fat globules (μm)	2.5	4	3		3	4
Carbohydrates: lactose	6.7	5.5	4.3	6.6	4.3	4.6

2.1.2. Colostrum

Colostrum is the first milk delivered to the sucking newborn. It contains very high concentrations of whey protein rich in immunoglobulin IgA, has little fat and lactose, and an almost undetectable concentration of casein compared to mature milk. The absence of casein, but high concentrations of immunoglobulins, and double the concentrations of oligosaccharides (OLIs) compared to mature milk, suggest that the principal function of colostrum is for immunologic protection of the baby outside mother's sterile uterine environment. [14,28]. In addition to its nutritional and immunologic role, colostrum strongly promotes growth as it is richer in growth factors such as epidermal growth factor, TGF-β, and colony stimulating factor than the mature milk [14].

2.1.3. Milk protein [29]

Human breast milk contains approximately one third the amount of protein found in cow, camel and goat milk, and even less compared to sheep milk. Breast milk proteins include caseins, whey, and mucins. Whey proteins are in the soluble phase of milk. Their concentration in breast milk is 30% higher than that of casein. In the cow, camel, and goat milk, casein concentration is between 3.5 and 4.5 times higher than whey protein [12]. Caseins form suspended micelles. They include enzymes, immunoglobulins like IgA, and proteins alpha-lactalbumin, lactoglobulin, lactoferrin, serum albumin, lysozyme, and carbohydrate- and triglyceride-digesting enzymes [14,29]. A number of these proteins have special bioactive functions [30]. Alpha-lactalbumin controls lactose synthesis and binds Ca and Zn ions. Casein micelles bind calcium and phosphorus. Lactoferrin and lysozyme have antibacterial functions, while the immunoglobulin IgA destroys bacteria and protects infant's intestinal mucosa. Milk proteins provide the building blocks for infant growth. Breast milk also contains growth factors and hormones imported from maternal blood, molecules derived from maternal and infant gastrointestinal microbiome, vitamins, minerals, and immune and stem cells [30].

2.1.4. Milk Fat

Lipids contribute between 40 and 55% of the total breast milk energy [14]. Milk fat exists in the form of an emulsion. Over 95% of lipids exist as triglycerides which, along diglycerides, monoglycerides, free fatty acids (FAAs), phospholipids, and cholesterol, are packaged into milk fat globules. The sphingomyelins in the coating of fat globules support development of infant lungs and brain myelinization. Some FAs (with 8 to 12 carbon chains) are synthesized de novo in the mammary cells. Others, both short-chain (up to 6 carbons), and longer chain FAs, are formed from circulating metabolites including those produced by fermentation of carbohydrate by rumen bacteria. Others are produced in some organs, and all are carried to mammary gland in lipoproteins. Most plentiful FAs in breast milk are monounsaturated oleic (18 carbons, 36% of FAs), saturated 16-carbon palmitic (27%), and 18-carbon polyunsaturated linoleic (15%) acids. Two 18-carbon FAs, alpha linolenic (omega 3) and linoleic (omega 6) are essential and must be obtained from the maternal diet. They are converted to a 20-carbon arachidonic acid (AA, omega 6) and eicosapentaenoic acid (EPA, omega 3),

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while the latter is converted to a 22-carbon docosahexaenoic acid (DHA, omega 3). AA, EPA, and DHA are important for supporting infant growth and immune system. They mediate inflammatory responses and support infant neuromotor and sensory development [30].

2.1.5. Milk Carbohydrates

Lactose is the main milk carbohydrate in human breast milk and in the milk of all examined mammals. It is a disaccharide composed of glucose and galactose produced by lactose synthetase in the mammary gland. Lactase enzyme produced by the infant small intestine frees up contained monosaccharides. In populations where the expression of this enzyme gene is deficient, lactose malabsorption and intolerance syndromes are observed. The stability of lactose concentration relative to changes in concentrations of fat and protein in the course of single nursing episode, or in stages of infant development (Martin) assures the stability of milk osmotic pressure. Besides the lactose, milk carbohydrates include several hundred of different OLIs comprising about 1.3% of mature milk and about 2% of it at day 4 after birth [14]. Over 200 characterized OLIs consist of different combinations 5 different sugars (D-glucose, D-galactose, L-fucose, sialic acid, and N-acetylglucosamine) in addition to lactose [14]. OLIs act as probiotics facilitating growth of beneficial bacteria (bifidobacteria and lactobacilli) and help establish infant intestinal microbiota [14]. OLIs defend infants against the pathogen *Campilobacter diarrheae* and respiratory tract infection. This antibacterial role involves their acting as decoys preventing binding of pathogenic bacteria like *Streptococcus pneumoniae* and *Escherichia coli* to infant's intestinal wall.

2.1.6. Milk Vitamins and Minerals

Human breast milk contains all metabolically important water-soluble vitamins including the C and nine B vitamins. It also has the fat-soluble A and E vitamins, but is relatively low-to-deficient in K and D vitamins [29]. At concentrations of 0.15, 0.37. 2.1, and 0.1 mg/L vitamins B1 (thiamin), B2 (riboflavin), B5 (pantothenic acid), and B6 (pyridoxine), are 35, 22, 58, and 21% lower, respectively, in human breast milk than in cow's milk. However, breast milk has 85% of B3 (niacin,1.7 mg/L), and twice as much of B8 (inositol, 300 mg/L) than cow's milk, while concentrations of B12 (cobalamin) and biotin are very low in both (< 0.005 mg/L). Of the fat-soluble vitamins, human breast milk has 43% more of A (0.53 mg/L), about the same amount of its precursor carotene (0.24 mg/L), and about 5 times more of E (tocopherol, 5.4 mg/L) than cow's milk, while the concentrations of vitamin K (phyllo quinone) and of vitamin D (cholecalciferol) are low in both (0.02 and <0.001 mg/DL.). Near absence of vitamin D in human and cow's milk is of concern because of its importance in calcium absorption, bone mineralization, and neuromuscular and immune defense functions. Its deficiency can cause rickets in infants. During pregnancy, vitamin D appears to perform primarily its immune function rather than regulate skeletal homeostasis. It is speculated that the human behavioral change of wearing clothing and using sunscreens has reduced exposure to solar energy which normally stimulates vitamin D formation. This change has occurred too recently to trigger an evolutionary compensatory adaptation. To prevent rickets, supplementation with 400 IU daily for the first year of infant's life is recommended [31].

Minerals in human milk are an essential part of many important enzymes and contribute to structural components of infant body [29]. Five of the macrominerals are present at lower concentrations in human breast milk than in the cow's milk. Phosphorus (130 mg/L) is 13% of the concentration in the cow's milk. Calcium and magnesium at 300 and 30 mg/L, respectively, are 25% in human relative to cow's milk, while potassium and chloride at 600 and 430 mg/L are respectively 40 and 45% in human compared to cow's milk. The trace minerals iron, zinc, copper, manganese, fluoride, selenium, cobalt, chromium, and molybdenum are represented in similar concentrations of between 1 μg to 1.6 mg in human and cow's milk with the exception of iodine which is present at 27% (70 μg) in human relative to cow's milk.

2.1.7. Breast Milk Hormones

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The foremost involvement of hormones in breast feeding is that milk secretion is initiated by the exclusively mammalian hormone oxytocin (OXY). Milk let-down reflex is mediated by supraoptic and paraventricular hypothalamic neurons which release OXY from the posterior pituitary into systemic circulation in response to infant sucking stimulation [2,32]. This triggers rhythmic contractions of mammary ducts in both breasts as long as infant sucks [33]. Besides its control of milk ejection, OXY also assists parturition through elicitation of uterine contractions during childbirth [2]. A second set of OXY projections terminates in the bed nucleus of stria terminalis in medial basal forebrain and in the ventromedial hypothalamus, brain regions responsive to sex steroids [34]. When activated by OXY, these neurons facilitate social and prosocial behaviors such as attachment and bonding of infants with mother, between animals [34] and humans [35]. The role of OXY in bond formation and pro-social behaviors, appear to be, like sucking behavior in milk ejection, mediated by body touch [4].

Sucking behavior after infant's birth also suppresses pregnancy. The hormonal effect appears to be mediated by the intensity and duration of sucking episodes which alter the pattern of gonadotropin, and increase prolactin, secretion. This blocks menstruation by interfering with follicle development and ovulation. The effect lasts up to 6 months provided that suckling episodes last greater than 60 minutes and take place more than 5 times per day [5]. This endocrine reflex encourages breast feeding up to 6 months, the duration recommended by several health agencies [6–8], but it appears to be secondary to sucking stimulation rather than a direct effect of oxytocin.

There also is intense interest in the hormonal composition of breast milk obtained from maternal circulation and its possible influence of on infant growth and development. However, it should be emphasized that studies reporting concentrations of individual hormones can only establish associations with infant growth and changes in body composition rather than a causal relationship. Famine studies reported that fetal intrauterine growth retardation increases the risk of obesity and metabolic disabilities in adulthood [36], but also, excess fetal nutrient availability and intake [37], or accelerated catch-up growth during neonatal period following intrauterine growth retardation, [38,39], also can produce this effect.

A number of hormones and cytokines have been detected in human breast milk. They include apelin, beta-endorphin, cholecystokinin, cortisol, estrogen, ghrelin, glucagon-like peptide 1 (GLP-1), insulin, insulin-like growth factor 1 (IGF-1), irisin, leptin, melatonin, motilin, neuropeptide Y, obestatin, peptide YY, progesterone, resistin, thyroid hormones (and more) [14,40–48]. Significance of most of these hormones in breast milk to infant milk intake, growth, and body composition, if any, is not as yet fully understood. Beta endorphin was associated with infant crying, colic, and maternal disturbed sleep [41]. Progesterone, but not estrogen, concentration was negatively related to maternal protein intake [45]. Melatonin rhythm in maternal circulation and in breast milk were synchronized suggesting that circadian timing of breast feeding may be important [42]. Triiodothyronine (T3), but not thyroxin (T4), was detected in breast milk [46]. Myokine irisin concentration did not vary between different stages of milk secretion [47], while early morning circadian elevations, and midnight nadir of cortisol, had no apparent effect on infant behavior [48].

Adipokines leptin, adiponectin, obestatin and resistin in human breast milk attracted research because these cytokines are released from the adipose tissue and are therefore assumed to potentially influence body composition and development in later life [40,44]. Adipokine leptin and hormone insulin attracted most attention as key hormones affecting body composition and thought to affect appetite in adulthood. The working hypothesis behind studies seeking associations between human breast milk hormones and infant growth and body composition is that these hormones may cause developmental programing of infant's appetite and weight gain toward, or away, from obesity in later life. Justification for interest in leptin was a demonstration that humans who are genetically unable to produce leptin experience intense hunger and display a high level of obesity, manifestations that can be abolished with leptin administration [49,50]. In addition, extensive research has documented that leptin can suppress appetite by inhibiting orexigenic neurons in the hypothalamus. It also increases lipolysis and fat utilization, and facilitates hunger when its

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concentrations decline during energy restriction [51]. Insulin is the key hormone ruling the control of nutrient intake and their storage in the form of inert molecules of glycogen, fat, and structural proteins [52]. The two messengers actually form a counterregulatory team in adulthood [53] in that meal-induced insulin secretion facilitates leptin secretion from the subcutaneous adipose tissue, and leptin, in turn, suppresses insulin secretion and actions while promoting lipolysis.

There is a good deal of controversy regarding the working hypothesis that adipokines and insulin and leptin in the milk have the capacity to reprogram linear growth or body composition during infancy and laterlife. Two reviews present contrasting evidence with one mostly listing the inconsistencies and contradictions [54] and the other presenting supportive evidence [55] for the hypothesis. In a recent systematic review [56], concentrations of adipokines were compared to several parameters of infant growth. The results, usually measured over less than a year of infant's life, were mostly inconsistent, and at times contradictory. Adiponectin was inversely proportional to infant fat in three studies, positively related to fat in one, inversely related to linear growth in one, and not associated with any change in three studies. Leptin in human breast milk did not affect body composition in four studies of which one had a 3 and 5 year follow-up, but was also associated with four studies reporting increases in fat mass or body weight and in three that reported the reverse outcome. Ghrelin and insulin were both associated with infant weight and weight-to height gain in five studies, and not associated with any body composition variable in two.

The final issue is a relative silence in breast milk literature regarding the potential role of hormones of growth on perinatal infant growth, as growth hormone (GH) regulates linear growth in childhood and adolescence through the mediation of the hormone IGF-1 and its binding proteins [57]. Absence of GH measurements in the milk-hormone studies may partially reflect the inconvenience of nocturnal circadian timing of most of GH secretion, and difficulty of frequent blood or breast milk sampling to capture the defining mechanism of stimulation of growth through the changes in GH pulsatility [58]. IGF-1 has been detected in breast milk [43] where its concentration, and that of leptin, was correlated with rapid infant growth at 3 months. IGF-1 concentrations and its binding proteins were higher in preterm than in term infant milk [59]. Higher IGF-1 concentrations were observed during the first week of life than in later weeks [60] when they are postulated to be stimulating maturation of infant gut. None of these studies evaluated the relevance of the measurements on infant linear growth or body composition.

2.1.8. Comparison of Infant Formula to Breast Milk

In 2016, only 38% or 1.5 million of infants were breast fed globally, and the remaining 62% or 2.4 million relied on infant formulas (IFs) for nutrition. In the United States, 75%, or 3 million infants, initiated breast feeding, but this declined to 67% or 2.7 million by the third month [30]. Industrial production and sales of infant formula generated 38.2 billion dollars in 2021, and a few companies (Nestle, Danone, Abbott, FrieslandCampina, and Heinz) controlled about 60% of global market [61]. Besides the general acknowledgment [6–8] that breast milk is ideal food for infants for at least 18 months, formula feeding to the vast majority of world newborns led to a global cost of production and its overall environmental impact at 300 billion [61].

The purpose of IF feeding is not to closely duplicate human milk, which is qualitatively incomparable and highly complex, but to approximate the nutritional characteristics that human milk offers. In the US, Food and Drug Administration does not proscribe a specific IF composition but approves manufacturer proposals and insures their adherence to the acceptable ranges according to Code of Federal Regulations Title 21 [62]. The concentrations of nutrients in this code track concentrations of macronutrients, vitamins and minerals per 100 kilocalories of IF in whatever form is prepared for consumption. Concentrations and doses listed are close to the breast milk values expressed in grams/100 ml milk shown in Table 1 and discussed in the human breast milk text. In particular, milk protein, fat, and carbohydrate aim to conform to 1:2:4 proportions; polyunsaturated 18-carbon fatty acid with two unsaturated sites like linoleic omega 6 acid to be 2 to 3% of total energy; and casein to whey ratio to be 40:60. Minerals and vitamins are fortified as needed, osmolarity

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adjusted to 270 milliosmoles per liter to support infant's kidney function, and bioactive ingredients such as omega 3 and essential fatty acids, carnitine, taurine, polyamines, nucleotides, oligosaccharides, folates, prebiotics, and probiotics are supplemented to approximate human milk or according to results of studies indicating their benefits to infant growth and development [29].

In attempts to match human breast milk composition of 1% protein 3.8% fat, 7% lactose in 87 to 88% of water, companies [29,30,61] use purified whey and casein from cow's, or occasionally another domestic animal's, milk for protein. With soy milk as the starter, fat often is provided by a blend of vegetable oils, vitamins, and minerals matched to human breast milk values. Probiotics and prebiotics isolated from fecal or food microbiota may also be substituted in IF milk.

The major unresolved issues and controversies are the extent to which IF captures the bioactivity of human breast milk. Several reviews compare chemical composition of IF to breast milk and summarize the extent to which different versions of IF succeed, or still need improvement, in meeting this goal [29,30,61,63].

Notably, **bioactive components** need to be adjusted or substituted when the low-fat cow milk is used to produce IF, as its composition of some of these molecules differs from human breast milk [63]. Total protein content and casein to whey ratio has to be adjusted to 1% and a 40:60 ratio, respectively, because these two variables are about 3.5 and 7.5 higher in cow's milk compared to breast milk (Table1). This requires lowering the casein proportion of cow's milk, and increasing the proportion of whey proteins. Alpha-lactalbumin (αLA), an important whey protein, accounts for 28% of total human breast milk protein, and only 3% of cow's milk protein [63]. αLA provides tryptophan, cysteine, lysine, and branched-chain amino acids (leucine, isoleucine, and valine) for infant nutrition and facilitates lactose synthesis, absorption of minerals, and blocks adhesion to infant's intestinal wall of the pathogen *Helicobacter pylori* . Supplementation of αLA to IF improves infant sleep (due to tryptrophan) and immune system function (due to cysteine). αLA has antimicrobial action against *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococci, and Candida albicans*. Other whey proteins such as lactoferrin and lysozyme are being tested for supplementation benefits. As to immunoglobulins, human breast milk has secretory IgA, IgM, IgD, and IgE, but cow's milk has mostly IgD, so sIgA is supplemented to IF when cow's milk is used in IF milk.Taurine is the most abundant free amino acid in human breast milk at the concentration of 4.7 mg/100 kcal and higher than in cow's milk. It is considered essential because it is obtained from maternal diet. This bioactive molecule is essential for perinatal central nervous system development and for neuroprotection. Synthetic taurine is mostly being added to IF for premature infants. Folates also are bioactive molecules. Folic acid is an essential water-soluble B vitamin (B9) obtained from maternal diet. Folates stimulate erythropoiesis in bone marrow. Its deficiency causes congenital anomalies, neural tube defects during embryogenesis, deficient brain development, neurological diseases, and deficits in vitamin B12. Folate concentration in human breast milk is 12.3 μg/100 mL, and in cow's milk only 5–10 μg/100 mL. Infant folate intake of 65 μg DFE (dietary folate equivalents)/-day or 80 μg DFEs/day of folic acid are required for infants at age 6 to 12 months. All infant formulas must be supplemented to a minimum of 10 μg/100 mL and a maximum of 50 μg/100 mL folic acid. Polyamines are organic molecules that contain more than two amino groups. Their important bioactivity entails interactions with DNA and RNA leading to synthesis, maintenance, and stability of nucleic acids. They can be imported through maternal diet, but breast makes high levels of polyamines, mainly spermine (173.4 nmol/dL) and spermidine (457.5 nmol/dL), with a lower amount of putrescine (82.4 nmol/dL). Polyamines are required for the formation of infant liver and pancreas, immune system's development, proliferation and maturation of the GI tract epithelium and formation of intestinal microbiome. They prevent food allergies by decreasing mucosal permeability to antigenic proteins. However their concentrations in breast milk are variable and differ from those in IF, so their supplementation is controversial. Milk fat globule membrane (MFGM) is a bioactive organelle in breast milk secreted by the human alveolar epithelial cells and bound to lipolytic enzymes. It is composed mainly of lipids and proteins and their diameter at 1 month is 0.2 to 15 μm. Their nucleus consists of triglycerides, and their membrane has three layers constituted of

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phosphatidylcholine, sphingolipids, cholesterol, cerebrosides. and glycoproteins. MFGM produces bioactive molecules important in immune and gastrointestinal health, brain development, and cognitive function. Although substitution of MFGMs in IFs is considered desirable, it is absent from standard IFs when cow's milkfat is replaced by vegetable oils such as oleo, coconut, soy, palm, sunflower, and safflower oils because their use in the manufacture of IFs with vegetable oils is not feasible.

Bioactive fatty acids include some that humans can synthesize. These include saturated (SFAs) and MUFAs, the monounsaturated fatty acids. Humans cannot synthesize two18-carbon fatty acids PUFAs, the polyunsaturated fatty acids, like α-linolenic acid (ALA, 3 omega) and linoleic acid (LA, 6 omega) These are essential as they have to be obtained from the diet and are precursors of long-chain poly-unsaturated fatty acids (LC-PUFAs). ALA is converted to eicosapentaenoic acid (EPA, 20 carbons), and then to docosahexaenoic acid (DHA, 22 carbons, 3 omega), whereas LA is converted to arachidonic acid (ARA, 20 carbons, 6 omega). DHA and ARA are transferred from mother to fetus in the third trimester through the placenta. Mean DHA and ARA levels in breast milk worldwide are 0.32% and 0.47% of total fatty acids, respectively. The bioactive significance of DHA and ARA is that they play a critical role in infant brain development where they account for approximately 25% of the fatty acids in brain cells and in retina. DHA constitutes 40%–50% of PUFAs in the two organs. EPA contributes also to cardiovascular and immunological health. Since infants cannot synthesize LC-PUFAs, the enrichment of IF with DHA and ARA is desirable and has been shown to improve development of the visual system. Current supplementation of IF with fatty acids recommends the range of between 3 and 6 g/100 kcal. Allowable LA range is 300 to1,200 mg/100 kcal or 7%–20% of total fatty acids, similar to the amount found in breast milk. When plant oil are used in IFs, supplementation with palm oils isnecessary to increase the level of butyrate to that comparable to breast milk. LC-PUFA supplementation limits are optional in USA . They specify 2% of ARA relative to total fatty acids, 1% for DHA (not to exceed the concentration of EPA), and DHA not to exceed 0.5%. In Europe addition of DHA (20–50 mg/100 mL) is mandatory.

Finally, prebiotics and probiotics are also considered as bioactive molecules. The former are non-digestible carbohydrates (di- oligo- and polysaccharides composed of glucose, fructose, galactose and other sugars), that reach the colon intact, where they are fermented by a specific group of bacteria. Almost 200 out of estimated 1000 Breast milk oligosaccharides (BMOs) have been found in breast milk and they decline in the course of lactation from 20.9–23.0 mg/mL to 7.0–12.9 mg/mL. Their functions are to modulate beneficial intestinal bacteria *Bifidobacterium* and *Lactobacillus* and block pathogenic bacteria by acting as their competitive ligands on infant intestinal cells. BMOs are practically nonexistent in the cow's milk. Production of BMOs is expensive and challenging so IFs based on cow's milk are supplemented with nondigestible carbohydrates, such as galacto-oligosaccharides (GOS) and/or fructo-oligosaccharides (FOS) and/or polydextrose (PDX) which approximate the concentration of human breast milk BMOs. Probiotics are living bacteria that adjust intestinal microbial balance and resist intestinal colonization by pathogenic bacteria. Breast milk-fed intestinal flora is richer in beneficial and more varied bacteria than the flora of FI-fed infants. To approximate the two involves requires either supplementing IF milk with prebiotics, or adding cultures of bacteria and lactobacilli, to mimic infant gastrointestinal colonization.

2.1.9. Summary of Breast Milk Effect on Infant Growth and Health: Facts and Controversies

The facts and controversies regarding the contribution of different sources of milk to infant growth and health can be reduced to three key issues: (1) What features of breast milk intake conveys special benefits to infants and how well does formula milk match it? (2) In what ways does the research seeking answers to this question focus on relevant issues and where it misses the mark? And, (3) Which controversial areas would provide better understanding of determining factors in growth and development from infancy to adulthood?

2.1.9.1. Special Benefits of Breast Milk in Comparison to Infant Formula Milk

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A wealth of evidence-based research attests to the benefits of breast milk in promoting growth of newborn infants and their physical development and health [9,10]. Relevant health organizations [6–8] recommend exclusive breast feeding for between 6 and 12 months of infant's life. Sections 2.1.2 through 2.1.7 list the chemical properties of breast milk, section 2.1.1. compares human milk to that of five other domesticated species, and section 2.1.8 compares the remarkable extent to which infant formula (IF) milk approaches the properties of breast milk. Efforts to define the relative importance of breast milk chemistry, and to apply the findings to improvements of IF milk, continues.

Two insufficiently explored issues are whether the method of milk delivery to infants, and a potential difference in the calorie density of breast milk and IF milk, affect differently infant linear growth and body composition in the short term and in later life. Breast milk is delivered on demand when infant wants to suck, and the quality of milk changes during individual feeding episodes from higher protein and fructose concentration to an increase in fat content toward the end of the feeding bout [17]. Formula milk delivery is to an important extent under maternal control where its provision may be inappropriately responding to infant fussing for reasons other than hunger. In addition, IF composition of protein, fructose, and fat does not change (section 2.1.8) and produces different caloric delivery of the three nutrients as a function of time. This issue has been studied infrequently [64,65] as it is inconvenient to measure changes in infant weight after individual feedings as well as the changes in the major breast milk nutrients during feeding bouts. The concern regarding whether the actual energy intake, rather than specific nutrient intake, in breast-fed and IF-fed infants differs may shed more light on the linear growth and body composition outcomes during infancy and in later life.

2.1.9.2. In What Ways Does the Research Regarding the Factors Influencing Infant Nutrition, Growth, and Health, Focus on Relevant Issues and Where It Misses the Mark?

A large number of studies hypothesize that hormones ghrelin and insulin, and adipokines leptin and adiponectin influence infant appetite, growth, and body composition. They have likely been influenced by controversial interpretations of research on the control of hunger and satiation in adult humans. Of the usual four gut peptides associated either with hunger (ghrelin) or satiation (cholecystokinin-CCK, glucagon-like peptide 1-GLP-1, and peptide YY-PYY), and another one, GIP-glucose-dependent insulinotropic peptide that is not associated with either, only the GLP-1 has demonstrated the capacity to suppress hunger, as shown by the commercial success of its analog semaglutide in reducing hunger and causing weight loss in overweight and obese individuals [66]. Even the appetite-suppressing effect of GLP-1 effect may be indirect, as its secretion [67], together with that of PYY [68], suppresses gastric emptying in the capacity of an "ileal break" when unabsorbed nutrients from large meals reach ileum and colon. Regardless of the actual cause of the appetite suppressing effect, the relevant finding is that the effect is produced by a gut hormone which plays a role in usual gastro-intestinal processing of eaten food. In a direct comparison of the endogenous secretion of ghrelin assumed to signal hunger and of postprandial hormones GIP, GLP-1, PYY, and CCK that have been associated with the ratings of satiation, there was no relationship between ratings of appetite and the pattern of these hormones during a meal that preceded or followed energy expending exercise. Secretion of all five hormones simply followed the time course of nutrient transit through the GI tract [69]. In addition, attributing a direct role of leptin and insulin in the control of hunger is contradicted by findings that human appetite responds to these messengers only when nutrients are taken by mouth and processed by the gatro-intestinal (GI) tract [70]. If they are introduced parenterally, that is by intravenous infusion, they have no effect on either hunger or satiation. Instead, leptin increases hunger when its concentration declines with energy deprivation and its inhibitory control of hypothalamic orexigenic centers wanes [71]. Both leptin and insulin exert physiological effects, leptin by stimulating lipolysis and lipid utilization, and insulin by storing the energy as glycogen, fat, and tissue proteins regardless of the method of intragastric access of nutrients that elicit their release. Similarly, the assertion that ghrelin causes hunger as it was observed to coincide with the onset of meals [72] is contradicted by a lack of any relationship between the appetite

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ratings and the time course of endogenous ghrelin secretion when humans are challenged with different timing of energy expenditure before or after a meal [69].

So, in view of the inconsistent associations between leptin, ghrelin, adiponectin, and insulin in breast milk and infant body mass and composition (section 2.1.7) and the very short duration of most of these studies, two additional research strategies would be desirable. One, to extend the examination of neonatal endocrine or adipokine influences in the breast milk relative to infant formula over the longer-term periods of growth during childhood through pubertal periods of human growth. And the second one, to focus on the potential differences in milk energy content and timing of breast milk and IF consumption or the timing of milk macronutrients during infancy on the rate of linear growth and body composition as a function of nutrient processing by infant's GI, as there is substantial evidence that gut to a large extent controls appetite and body weight in adult humans [73].

2.1.9.3. The Need for a Better Understanding of Critical Periods of Nutritional Vulnerability in Humans

The evidence that abundance of early nutrition has dramatic and lasting effects both in humans and in animals is incontrovertible. What is unclear or inadequately explored are three issues: (1) Which stages of human and animal life represent the critical periods of dietary vulnerability? (2) Are these critical periods related to the phases of linear skeletal growth? And, (3) How are these critical periods related to the mechanism of energy regulation following cessation of linear growth after puberty, when food intake appropriately matches energy expenditure to achieve stable adult body mass? One generalization that applies to all three issues is that energy restriction causes more profound and lasting physiological changes than food overabundance, and that defenses against body mass loss, be it against body fat or structure, are more vigorous than defenses against accretion of either variable [74]. Both set of facts make evolutionary sense in that they represent adaptations that protect human and animal survival.

Several lines of evidence support the existence of nutritional critical periods affecting human growth. The first line of evidence was a consequence of Dutch famine of 1944 to1945 during World War 2. Exposure to famine during the first two trimesters of gestation, but not during the third trimester (), or possibly energy deprivation even during the time of conception [76], produced profound metabolic disruptions. Early intrauterine energy deficiency led to increased risks of obesity, type 2 diabetes [77], cardiovascular disease, and visual and auditory deficits throughout adult life [78]. Observed metabolic dysregulations were associated with epigenetic changes in histone methylation of particular genes detected even 60 years after the maternal exposure to famine [76].

Another line of evidence for acritical period of nutritional vulnerability comes from examination of global childhood stunting of linear growth. Severe undernutrition between 6 and 24-months after birth was critical as it reduced linear growth by 2 standard deviations (SDs) below the WHO Child Growth Standards [79], and the stunting was largely irreversible. The process is particularly severe in cases of maternal undernutrition during pregnancy where infant length is usually 0.5 SD below WHO standard at birth, and it declines to almost 2 SDs below the WHO standard by the end of 2nd year [80]. While in this situation, weight for length Z score remains relatively unchanged over 58 postnatal months (suggesting that weight tracks linear stunting), weight for age Z score declines to half, and height for age Z score to 25 % of the starting score during the same period [80].

The third line of evidence for the critical period of neonatal nutritional vulnerability was described in the altricial rat. After matching the rat pups for weight at birth, neonatal nutrient abundance was increased by reducing the newborn litter size to 2 or 3 pups to be suckled by a single dam, and was reduced by having a dam suckle 15 to 20 pups. The rate of weight gain and the body mass of small-litter (SL) pups diverged from day 1 after birth. It was 2.4 times greater by week 3, the date of weaning, 2.2 times greater by sixth week, and between 1.3 and 1.5 times greater at 3 and 6 months of measurement, at which time the large-litter (LL) rats weighed about 280 grams, and SL ones up to 425 grams [81–83]. These studies revealed the following facts: (1) Undernutrition between

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birth and weaning on day 21 produced different weight-gain trajectories in the male rats for as long as they were studied; (2) The nutritionally critical period was between birth and weaning at day 21 because reducing access to food of SL pups to the amount of LL pups between weeks 3 and 6 or 3 and 9 weeks did not affect the growth-rate trajectories except for an initial 8% downward deflection. When the same was done between 9 and 12 weeks, food-restricted SL pups, again, maintained the weight trajectory of the unrestricted group and even overreached it by 8% by week 40 [84]. (2) This early postnatal 3-week critical period of nutritional vulnerability reprogrammed the rate of growth of body length, kidneys, brain, heart, liver, and testes to make them proportional to the growth of body mass in both SL and LL regardless of their different postnatal body weights [81]. There were three exceptions. Growth of the intestine was proportional to body mass in both groups until the weight of 100 g. Thereafter, growth of the intestine decreased significantly in LL rats to attain 6,2 g at 280 g, while it increased to 8.6 g in SL rats at the weight of 400g . The second divergence was in disproportionate accumulation of body fat which in SL pups between birth and the weight of150 g. Beyond 150 grams, the proportion of body fat in SL declined to become to body mass up to the 400 g final study measurement [81]. The third divergence was in the growth rate of testes [81] and the body mass and age at the time of female rat vaginal opening [83]. Testes grew in in SL pups disproportionately faster than in the LL pups from birth. By 90 days hen testes size stabilized in both groups, SL testes were 10% larger [81]. Puberty in female rats occurs about day 42 of life, but the vagina opened in SL pups at 30 days and weight of 70g. In LL rats, this event occurred at 46 days and 65 grams, indicating that puberty is achieved with attainment of greater body mass [83]. (3) Between weeks 2 and 4, rat pup food intake (estimated from mid-week changes in body weight) was 45 kcal/100 g, maximal that rats are capable of [82]. Both the appropriate weekly increase in weight and the appetite were a simple function of body weight. This relationship was not affected by increasing protein concentration in rat pellets to 30%.

Thus the answer to the first question is that there is strong evidence for critical periods of nutritional vulnerabilities in both animals and humans, but that human critical periods are inadequately defines or studied. The answer to the second question is that the critical periods of nutritional vulnerabilities are in some inadequately understood way dependent on the control of linear growth. The dietary deficiency appears to reprograms linear growth and the growth of several other organs and total body mass is in most case adjusted to altered linear growth rate.

The answer to the third question of how the nutritional critical periods are related to the mechanism of energy regulation after the cessation of linear growth in adulthood where food intake appropriately matches energy expenditure to achieve stable adult body mass, is also poorly understood. Here the evidence from rat research indicates that food intake is quantitatively adjusted to the rate of growth, or when growth ceases, to body size. Thus food consumption is maximal when the linear growth is fast, and is quantitatively adjusted to the body mass when the linear growth declines and ceases. The area of the brain that matches food intake to body mass in post-pubertal, non-growing humans is likely to be in the area of the ventromedial hypothalamus by analogy to the rat experiments done by Gordon Kennedy (Ken 1). Lesioning this brain area increases the amount of food intake to the rat maximum of 45 kcal/100 body weight leading to significant obesity. The same level of hyperphagia is observed in neonatal SL rat pups during postnatal weeks 2 and 3, the period of their fastest rate of linear growth. The anatomical and functional neural circuits controlling linear growth and those matching food consumption to body mass as different, as obesifying lesions do not affect linear growth. As the growth rate of lesioned animals, and infant rats declines, the amount of food consumption gradually declines to match an obesity plateau in lesioned rats and a stable adult size in rats whose liner growth has dramatically eclined. slowed down.

The experimental search for a better understanding interactions between critical nutritional periods and the rates of growth in human infants, children and adolescents would require cooperation between nutritionists and pediatricians. The pattern of human growth is discontinuous and varies at different stages of development [85] compared to a steadily decelerating rate in other mammals like rats until adult body mass and sexual maturity are achieved. The fastest human growth

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rate of 2.5 cm/week is during the gestational weeks 20 and 24 mostly mediated by nutrient-induced IGF-1 and several other growth factors. That is why maternal starvation during this period is so metabolically and physically damaging [75,77,78]. During the first year of life, infants grow 25 cm/year, but during second year, growth declines by half. Between second and 8th year, height velocity of both girls and boys iseven slower, usually 6 to 8 cm/year with a transient increase at the onset of adrenarche (increased production of androgens by the adrenal gland) at that time. During childhood growth hormone (GH) assumes a key role in the control of linear growth [57] assisted by insulin, leptin. and thyroid T4 hormone. GH stimulates the release of IGF-1 from liver. Then, between ages 10 and 11 in girls, and 12 and 13 in boys, a pubertal growth spurt occurs with an average peak height velocity (PHV) of about 8 cm/year in girls and 9.5 cm/year in boys. This is achieved through activation of hypothalamic-pituitary adrenal axis initiated by changes in pulsatility of gonadotrophic hormone which activates secretion of sex steroid hormones estradiol and testosterone. The site where both circulating and local hormones achieve linear growth is the epiphyseal growth zone (EGZ) at the ends of long bones. Elongation of long bones responds both to circulating hormones and to direct local activation of chondrocyte growth by GH, IGF-1, leptin, and sex steroids. After PHV, the growth rate steeply declines as females attain menarche, and boys complete gonadarche, and over the next 2 to 3 years, epiphyseal growth zones in long bones close in response to high titers of estradiol. The protracted slow childhood period of human growth is hypothesized to have evolutionarily evolved to allow acculturation, socialization, and learning of children.

To increase our understanding of the identity and timing of human nutritional critical periods and link them to different rates of human linear growth, several new lines of experiments would be desirable, preferably studying epiugenetic markers which were shown to persist decades after the nutritional interventions [76]:

1. Establish whether variations in energy content of breast milk relative to IF milk has the capacity to reprogram birth weight, the rate of linear growth, and body composition from infancy, through childhood and puberty.
2. Assess the relevance of maternal insulin resistance as a function of obesity [86] during pregnancy and breast feeding to fetal and neonatal overexposure to high insulin and leptin concentrations in breast milk on the birth weight, the rate of linear growth, and body composition from infancy, through childhood and puberty.
3. Analyze the mechanism through which nutrition during vulnerable critical periods affects the onset of adrenarche and menarche and the extent that they affect linear growth and body composition from infancy, through childhood and puberty. This line of investigation is prompted by evidence that both alterations in the rate of linear growth in response to early energy deprivation and accelerated childhood growth at ages of 6 to 9 and 9 to 11 years display earlier adrenarche and onset of puberty [87].

Defining the critical periods of human nutritional or hormonal vulnerabilities and their relationship to linear growth and sexual maturation could extend our understanding of the interactions between nutrition, linear growth, and metabolic health.

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