Breast milk decreases the risk of obesity

A remarkable increase in the prevalence of obesity has been observed in several countries and in different age groups, including the pediatric population, in the last few years. This is a review of the literature on this topic, with an analysis of several epidemiological studies that investigated a possible relationship between breastfeeding and obesity, and of studies that demonstrate the biological plausibility of this relationship and seek to explain the mechanisms that may be involved. Articles published on this subject between 1980 and 2005 were searched in the Medline database using the keywords “breastfeeding”, “overweight”, “obesity”, “children” and “adolescents”. Several studies demonstrated an association, but found no relationship between breastfeeding and obesity. One study covering a small sample reported greater adiposity in breastfed children. Different definitions of exposure and outcome were used in the various studies, making comparison difficult.

Breastfeeding appears to have a protective effect against childhood obesity, but this issue still deserves further investigation.

1. Introduction

The increase in the prevalence of childhood obesity is alarming because of the increased risk of obese children becoming obese adults, and the existence of several obesity-related morbid conditions. In the United States, obesity affects 20% to 27% of children and adolescents. Serdula et al found a risk of at least twice as high for adult obesity in obese, compared to nonobese children. Around one third of obese preschool children and half of obese schoolchildren become obese adults.

The effects of childhood obesity may be observed in the short and the longer term. Short-term complications include orthopedic disorders, respiratory problems, diabetes mellitus, hypertension, and dyslipidemia, in addition to psychosocial disorders. In the long term, high mortality due to multiple causes and specifically to coronary heart disease has been reported for individuals who were obese in their childhood or adolescence.

Among the complications caused by obesity, an entity known as nonalcoholic steatohepatitis (NASH) has been described recently, initially in adults, but it has now been observed in children and adolescents. The prevalence of NASH has increased, probably due to the increase in the prevalence of obesity, and also because health professionals have become more alert to its diagnosis. This condition is characterized by its silent development—it may be diagnosed incidentally in asymptomatic children or in those with vague symptoms, such as intermittent abdominal pain—and by its wide variation in nature, ranging from benign cases to cirrhosis, which is potentially deadly.

The treatment options are limited; gradual weight loss appears to be the most effective measure.

As obesity is a chronic disease that is difficult to treat and is associated with various potentially fatal diseases, and as its prevalence has been increasing, special attention should be paid to preventive measures. Simple measures with no potential adverse effects and low cost are particularly appealing. In this regard, several authors have formulated the hypothesis that breastfeeding has a protective effect against obesity, but controversial results have also been reported.

The objective of this study was to review the literature concerning the hypothesis that breastfeeding has a protective effect against obesity. The biological plausibility of this hypothesis and the potential mechanisms involved are discussed.

2. Energy balance regulation

The body’s energy balance is regulated by a complex neuroendocrine system, not yet fully understood, which
consists of an afferent system, a processing unit in the central nervous system, located in the ventromedial hypothalamus, and an efferent system.\textsuperscript{15}

The afferent system conveys information on hunger versus satiety and on body energy stores. Afferent signals may be short or long-term and may be generated peripherally or centrally.\textsuperscript{15}

Among peripheral hunger signals are low blood glucose levels, cortisol, and grelin, a recently discovered hormone.\textsuperscript{15,16} Grelin is produced in the stomach and was identified in 1999, initially as a growth hormone stimulator and later as a regulator of the energy balance. Fasting causes an increase in grelin secretion, while eating reduces it.\textsuperscript{15,16} Grelin has already been found in umbilical cord blood, but its effects on the feeding behaviour of neonates is still to be clarified.\textsuperscript{17}

Peripheral satiety signals include gastric distension, the action of nutrients and several hormones, such as insulin, cholecystokinin and peptide YY\textsubscript{3,36} (PYY\textsubscript{3,36}), to cite a few.\textsuperscript{15,18} PYY\textsubscript{3,36}, an intestinal hormone, is released after eating, in proportion to the caloric content of the meal. The infusion of postprandial PYY\textsubscript{3,36} at normal levels significantly reduces the appetite and decreases food intake by approximately 33\% over 24 hours.\textsuperscript{18}

Identified in 1994, leptin acts as a long-term peripheral afferent signal. It is produced mainly by adipocytes and it informs the hypothalamus about the energy stores available in the adipose tissue.\textsuperscript{15,19,20} Leptin inhibits the appetite and metabolic pathways and stimulates the catabolic pathways.\textsuperscript{19,20} In addition to the adipose tissue, other sources of leptin have been described, e.g. liver, stomach, and placenta.\textsuperscript{20} Vatten et al\textsuperscript{21} found a positive association between leptin levels in umbilical cord blood and weight and length at birth. Sandoval and Davis,\textsuperscript{22} in their review article, reported an integrated regulation between leptin and insulin, suggesting that abnormal leptin levels might be implicated in the pathophysiology of diabetes.

Besides these peripheral signals, the ventromedial hypothalamus also receives information from other parts of the brain. Dopamine, gamma-amino butyric acid, neuropeptide and corticotropin-releasing hormone provide information on stress, the state of alertness and pain, with an inhibitory effect on appetite. Serotonin and norepinephrine appear to play a key role in inducing satiety. The effect of serotonin on the induction of satiety seems to have both a central and a peripheral component, with intestinal secretion of serotonin.\textsuperscript{23} Metenkephalin, orexins A and B, melanin-concentrating hormone and galanin stimulate food intake and energy storage.\textsuperscript{15}

Peripheral and central afferent signals reach the neurons of the ventromedial hypothalamus, where they are integrated by a “central processing unit” designed to promote or reduce food intake and energy expenditure. This central processing unit has an anorexigenic branch, which contains the neurons that express the proopiomelanocortin (POMC) peptide, with its alpha-melanocyte-stimulating hormone (alpha-MSH) cleavage product and the cocaine-amphetamine-regulated transcript (CART) peptide, and an orexigenic branch, which contains the neurons that express neuropeptide Y (NPY) and agouti gene-related protein (AgRP). These two branches compete for melanocortin receptors.\textsuperscript{15} Overfeeding and leptin infusions induce POMC and alpha-MSH synthesis. Alpha-MSH induces anorexia, binding to the melanocortin receptor. CART synthesis also is induced by leptin and reduced by fasting.\textsuperscript{15}

NPY is the major orexigenic peptide and has specific receptors. Fasting and weight loss stimulate NPY expression, whereas leptin inhibits it. The AgRP peptide is a competitive melanocortin receptor antagonist, which blocks the binding of alpha-MSH to the receptor, preventing it from inducing satiety.\textsuperscript{15}

According to Kalra et al,\textsuperscript{23} rhythmicity and synchronism in the secretion of leptin, grelin and NPY are important for the daily meal pattern, and subtle and progressive problems with this mechanism lead to a positive energy balance, resulting in excessive weight gain and obesity.

The efferent system is concerned with the balance between appetite and storage and energy expenditure. The sympathetic nervous system stimulates energy expenditure, whereas the parasympathetic nervous system stimulates storage.\textsuperscript{15} Total daily energy expenditure comprises three components: resting energy expenditure (usually representing 50% to 65% of total expenditure), thermogenesis (around 10\% of total expenditure) and voluntary energy expenditure (which ranges from 5\% to 50\% of total expenditure).\textsuperscript{15} Bachman et al\textsuperscript{24} showed that rats submitted to ablation of the three types of adrenergic receptors developed obesity, due to a food-induced deficiency in the thermogenic mechanism.

### 3. Obesity: Multicausality

Obesity is a multifactorial disease in which genetic and environmental factors are involved.\textsuperscript{1,25,26} A family trait is noted, which means that children whose parents are obese are at a greater risk of becoming obese.\textsuperscript{15} However, evaluating to what extent genetics and environmental factors are implicated is not an easy task, since parents and
children often have similar eating habits and patterns of physical activity.\textsuperscript{27–29} There is evidence that genetic factors can modulate the body's response to changes in environmental factors, such as diet and physical activity.\textsuperscript{25} It has been documented, for example, that there is a considerable variation between individuals as to alterations their serum fat levels in response to changes in the amount of fat and cholesterol in the diet. Some individuals are relatively insensitive to changes in their diet, while others have a greater sensitivity.\textsuperscript{26}

Interventional studies with monozygotic twins also demonstrate modulation of the genetic response to environmental changes.\textsuperscript{26} In a study of 12 pairs of monozygotic twins submitted to a hypercaloric diet, the response in terms of weight gain, increase in body fat and increase in visceral fat varied remarkably between individuals, but the between-pair was greater than the within-pair variation. A study of monozygotic twins submitted to negative energy balance, based on a programme of physical exercise, also revealed a greater within-pair agreement as far as variations in weight, body fat, subcutaneous fat and visceral fat were concerned.

Although there appears to be a genetic modulation of the response to changes in environmental factors, there is also evidence that certain environmental conditions acting during a critical period of development, can cause changes in the expression of certain genes.\textsuperscript{20} The first nutritional experiences of an individual are believed to influence the susceptibility to certain chronic diseases in adulthood, including obesity.\textsuperscript{20,21} Hoffman et al\textsuperscript{21} reported, for example, that children with a prior history of malnutrition, classified as stunted, exhibit a deficiency in lipid oxidation, and are therefore at higher risk for obesity when the nutritional intake is increased. These authors suggest that this could be one of the mechanisms explaining the increase in the prevalence of obesity in developing countries.

Increased energy intake and reduced energy expenditure have been described as the major causes of obesity.\textsuperscript{1,22,23} However, some authors have found no difference between the energy intake of obese and nonobese individuals, but information provided by the individual about energy intake might not be a valid evaluation parameter.\textsuperscript{1} The interaction between genetic and environmental factors is another plausible explanation.\textsuperscript{26} In addition to the total calorie content, the composition of the diet is also important, as a diet rich in simple carbohydrates and lipids is a risk factor for obesity.\textsuperscript{1,34}

Recently, the role of lipids in the etiology of obesity has been discussed. Willett,\textsuperscript{35} in a recent review article, argues that in the United States in the last 20 years there has been a considerable reduction in the amount of dietary energy consumed as fat, and that during this period, there has been a large increase in the prevalence of obesity. Willett maintains that there is no consistent evidence that a high content of lipids in the diet plays an important role in the etiology of obesity and suggests that the effect of confounding variables, including physical activity, might have been responsible for the discrepant results in the study of this association. Other authors, however, believe that there is enough scientific evidence for the recommendation of a low-fat diet. Astrup,\textsuperscript{36} for example, underscores the conclusions of the three meta-analyses of randomized clinical trials investigating this issue, namely that a 10% reduction in dietary fat causes a remarkable weight loss, sufficient to reduce the incidence of diabetes by approximately 50%.

With regard to energy expenditure, several studies have revealed that this tends to be lower in obese individuals, in whom any of its three components may be altered – resting metabolic rate, thermogenesis, or physical activity.\textsuperscript{1,37}

Obesity has been classified as endogenous (secondary to genetic syndromes and endocrinopathies, e.g. Prader-Willi syndrome, Down's syndrome, hypothyroidism, etc.) and exogenous (caused by excessive energy intake compared to energy expenditure). Currently, endogenous obesity is believed to account for only about 1% of cases.\textsuperscript{37} However, recent advancements in the understanding of the neuroendocrine regulation of energy balance, the genetics of obesity and the interactions between genetics and environment point to a future revision of this classification with a change in this rate, as this low prevalence of endogenous obesity may be due to poor understanding of these phenomena. As new hormones, neurotransmitters, receptors, and genes are discovered, the etiology of obesity assumes another dimension and patients formerly placed in a single obesity group (endogenous) may have the specific cause for their obesity determined at the endogenous level.

Cases of childhood obesity secondary to leptin deficiency have been described, but human obesity is more frequently associated with resistance to leptin than with its deficiency.\textsuperscript{38} MC4R mutations have been regarded as the most frequent genetic cause of obesity in humans.\textsuperscript{38} Children with syndromes have been described, characterized by obesity, adrenal insufficiency and red hair, attributed to proopiomelanocortin gene mutations, which inhibit the production of alpha-MSH. Alpha-MSH affects hair colour by binding to MC1R in the skin, and influences food intake.
and energy expenditure by binding to MC3R and MC4R in the hypothalamus; adrenal insufficiency in these children may be explained by the fact that alpha-MSH consists of the first 13 amino acids of adrenocorticotropic hormone. An association has been suggested between MC4R mutations and certain mental diseases characterized by eating disorders and obesity.

The identification of multiple causes of obesity may contribute to the future implementation of safer, efficient, and personalized treatments for obese individuals.

4. BREASTFEEDING AND OBESITY: EPIDEMIOLOGICAL STUDIES

The hypothesis that breastfeeding has a protective effect against obesity is not recent. Contradictory results have been found, and the issue is still topical, especially because of the increase that has been observed in the prevalence of obesity.

Different definitions of exposure and outcome hinder the comparison between several studies and in addition, outcome was assessed at different ages. Another aspect of the methodology, pointed out by Dewey, is that studies which present the outcome as prevalence of overweight and obesity should be more highly valued than those which show mean body mass index (BMI) only. Dewey emphasizes that breastfeeding possibly reduces both overweight and underweight, which would result in a lower prevalence of overweight, but not in a difference in mean BMI. Therefore, interpretations should concentrate on the right-hand end of the distribution curve and not the central point.

In 1981, Kramer published the result of two case-control studies conducted on adolescents aged 12 to 18 years in Canada. One of the studies included 639 patients from a clinic for adolescents and the other 533 students in a Canadian school; both studies reported a protective effect of breastfeeding against obesity. The adolescents were considered obese when their relative weight exceeded 120% and the measurement of one of the skinfold measurements (triceps or subscapular) exceeded the 95th percentile or both exceeded the 90th percentile. The breastfeeding period was considered to have ended when the child was bottle-fed more than once a day. In these studies, a long time elapsed between exposure and outcome, predisposing to a recall bias. In a subsample of approximately 10% of the adolescents, the authors compared the information provided by the mothers on their children’s feeding in the first months of life with information supplied by the physician who had followed the child, and the information matched in all cases. The protective effect of breastfeeding persisted even after the control of confounding variables, such as parental nutritional status, ethnicity and socioeconomic class.

In 1984, Fomon et al. in a cohort of 469 children, found no difference in adiposity parameters (BMI, triceps and subscapular skinfolds) or serum cholesterol levels, at the age of eight years, between breastfed and formula-fed children. It was claimed that some children were not exclusively breastfed, but there was no clear definition of the exposure variable, which is a limitation of this study.

Agras et al. reported that breastfeeding for longer than five months was associated with greater adiposity, determined by BMI at the age of six years. This result was obtained from a cohort study, in which the small sample size was reduced by losses to follow-up; of the 99 patients included in the study, only 54 concluded it.

Zive et al. found no association between the length of breastfeeding and adiposity at four years, determined by BMI and the sum of triceps and subscapular skinfold measurements, in a study of 331 children. Birthweight, ethnicity, socioeconomic class, and maternal adiposity (BMI and sum of skinfold measurements) were assessed. Maternal adiposity was the major determinant of adiposity in the children.

O’Callaghan et al. observed no association between the length of breastfeeding and the prevalence of obesity at five years, in a prospective cohort of 4,062 Australian children. Several variables were taken into consideration, such as BMI, educational level, family income, birthweight, and gestational age.

In a longitudinal study conducted in Sweden with 781 adolescents, Tulldahl et al. described lower prevalences of overweight, defined as BMI greater than or equal to the 85th percentile, among those children who had been breastfed for longer than three months.

In a cross-sectional study of 9,357 German children aged between five and six years, published in 1999, von Kries et al. found an obesity of 4.5% prevalence among children who had never been breastfed and a 2.8% prevalence among breastfed children. A dose-dependent effect was observed for the length of breastfeeding, with an obesity of 3.8% prevalence for those children on exclusive breastfeeding for two months, 2.3% for 3 to 5 months, 1.7% for 6 to 12 months and 0.8% for longer than 12 months. Similar results were observed as to the prevalence of overweight. After adjustment for possible confounding factors, breast-
feeding persisted as a protective factor against obesity and overweight. Obesity was defined as BMI above the 97th percentile and overweight as BMI above the 90th percentile.

The findings of the study conducted by Liese et al.\textsuperscript{47} corroborate those found by von Kries. In a cross-sectional cohort study of 2,108 children aged between nine and ten years from two German cities Lise et al.\textsuperscript{47} observed a lower prevalence of overweight (defined as BMI greater than or equal to the 90th percentile) among breastfed children, even after control for several confounding variables, such as nationality, number of siblings, and socioeconomic class.

Gillman et al.\textsuperscript{48} in a large study of 8,186 girls and 7,155 boys aged 9 to 14 years, found a lower risk for overweight in individuals who had been on exclusive or predominant breastfeeding in the first six months of life than in those who had been formula-fed. The protective effect of breastfeeding persisted after control for several confounding variables. These authors also described a dose-dependent effect, and observed a lower risk for overweight in individuals breastfed for at least seven months compared to those breastfed for three months or less. Overweight was defined as BMI above the 95th percentile.

In a cross-sectional cohort study of 2,565 American children aged between three and five years, Hediger et al.\textsuperscript{49} observed that children who had been breastfed showed a lower prevalence of "overweight risk"; defined as BMI between the 85th and 95th percentiles, compared to those who had never been breastfed, but no protective effect against obesity, defined as BMI equal to or greater than the 95th percentile. Confounding variables such as birthweight, ethnicity, and maternal BMI were taken into consideration.

Assessing 32,200 Scottish children aged 39 to 42 months, Armstrong et al.\textsuperscript{50} found a lower prevalence of obesity in those who had been exclusively breastfed in the first six to eight weeks of life than in those who had been exclusively formula-fed, after adjustment for socioeconomic class, birthweight and gender. Similar results were obtained with two different definitions of obesity (BMI greater than or equal to the 95th percentile and the 98th percentile).

Toschke et al.\textsuperscript{51} in a cross-sectional cohort study of 33,768 Czech children aged 6 to 14 years found lower prevalences of overweight (defined as BMI above the 90th percentile) and obesity (defined as BMI greater than the 97th percentile), among breastfed children. Parental educational level and obesity, birthweight, number of siblings, and physical activity were taken into consideration. The authors highlighted the homogeneity of socioeconomic conditions of the studied population, which was at that time a socialist society.

5. BREASTFEEDING: BEHAVIOURAL ASPECTS

Breastfeeding consists not only of biological aspects (e.g. composition of the breast milk), but also includes psychological and behavioural aspects of the mother-child relationship, which also applies to eating habit formation in children.

It is widely known that breastfeeding contributes towards strengthening the link between mother and child.\textsuperscript{52} The increase in oxytocin levels in the mother's brain during breastfeeding is believed to strengthen this link.\textsuperscript{52} An association has been reported between breastfeeding and a higher frequency of interactive behaviours between mother and child, as well as maternal perceptions of competence, greater flexibility in child care and seeing their children's temper as "easier".\textsuperscript{52} These positive behavioural aspects of breastfeeding may contribute to a smoother dietary transition and to the formation of healthier eating habits.

The development of eating habits is a complex process, which involves several factors. In general, children have an inborn predisposition for sweet and salty foods and reject acidic and bitter ones.\textsuperscript{53} Neophobia, the tendency to reject new foods, is also observed, and offering the new food repeatedly tends to increase its acceptance.\textsuperscript{53} The association with the context in which the food is eaten also influences the development of food preferences.\textsuperscript{54} Parents influence their children's development of food preferences through their own preferences and their attitudes to eating, and by regulating the availability of food.\textsuperscript{54}

Breastfed infants may possibly develop more efficient mechanisms for the regulation of their energy intake. It has been reported that in situations in which parents have a greater control over their children's diet the development of self-regulating mechanisms may be impaired, since external control mechanisms may subdue internal hunger and satiety signals.\textsuperscript{55} In this way bottle-feeding could favour the development of overweight by stimulating excessive milk intake or by impairing the development of self-regulating mechanisms.

It is common knowledge that the maternal diet affects the flavour of breastmilk and that various different tastes interfere with milk intake. There is evidence that experience with several flavours (tastes) during breastfeeding facilitates the acceptance of new and varied foods by the child in the future.\textsuperscript{56}
6. FINAL CONSIDERATIONS

In view of the several morbid conditions associated with obesity, as well as its increasing prevalence and the difficulty of its treatment, it is necessary that efficient preventive measures be applied. Simple measures, without potential adverse effects and a low cost, should be a priority.

The hypothesis that breastfeeding could have a protective effect against obesity is supported by epidemiological evidence, and is biologically plausible, but literature data are contradictory. If this hypothesis is confirmed, it will represent one more advantage of breastfeeding, as well as a “weapon” for fighting obesity.

Different definitions of exposure and outcome hinder the comparison between several of the reported studies. The long time between exposure and outcome measurement also interferes with the analysis of the possible association, by producing a recall bias or not allowing all confounding variables to be taken into consideration and it incurs elevated costs because of the long duration, and operational difficulties of longitudinal studies.

The potential mechanisms still need to be clarified. Breastfeeding involves several aspects, such as the amount of food intake, composition of the food (nutrients and bioactive factors), time of introduction of solid foods and development of regulatory eating mechanisms, as well as behavioural factors related to the mother-child relationship and formation of eating habits.

Obesity, with its multicausality and multiple consequences, is a challenge to pediatricians and other health professionals who work with children. Preventive measures have the potential for avoiding long-term adverse effects in the biological and psychosocial context.

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