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Review

Mechanisms of breast feeding actions on obesity prevention: a systematic review

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Summary. *Background/Objective:* The worldwide increasing prevalence of obesity necessitates research studies that focus on exploring the simple and inexpensive ways to prevent it. Breast feeding (BF) is one of the easiest methods that might protect against obesity. Given the lack of a review on the mechanisms of BF actions in the prevention of obesity this study aims to focus on the effects of BF on obesity prevention during infancy, childhood, adolescence, and adult life with emphasis on possible mechanisms. *Methods:* Databases of PubMed and Science direct were searched for terms: "breast milk" plus obesity, and "human milk" plus obesity from 2005 till March 2015. Searching was limited to articles with English language. Review articles, case reports, abstract in symposium and congress, studies on preterm infants and non-healthy babies, non-human studies, and unpublished studies were excluded. Based on critically appraise, eligibility of included articles were evaluated. *Results:* After applying the inclusion and exclusion criteria, 27 articles from 456 studies remained for further consideration. Eighteen studies on comparison of feeding type effects, 7 studies on hormones and bioactive compounds in breast milk, and 2 studies on macronutrient contents of breast milk were reviewed. Most of the studies showed positive effects of BF on obesity prevention during infancy, childhood, adolescence, and even adult life with aforementioned mechanisms. *Conclusion:* Evidence from recent studies suggests that BF may prevent not only childhood obesity, but also in other periods of life with various mechanisms including hormones, bioactive compounds, and macronutrient contents in breast milk. Further clinical trials about BF mechanisms of actions controlling for confounding variables, especially maternal pre-pregnancy overweight, is suggested.

Key words: breast feeding, human, milk, obesity

Introduction

Obesity is a complex issue related to lifestyle, environment, and genes. Environmental and genetic factors have a complex interaction with psychological, cultural, and physiologic influences. It is an energy metabolism disorder which is related to the excessive storage of fat and may also physical and psychological problems (1, 2). Currently, the prevalence of obesity is an issue in developed and also developing countries (3). Obesity affects both adults and children. Childhood obesity can have a harmful effect on the body in a variety of ways. Obesity is associated with an increasing prevalence of impaired glucose tolerance (4), metabolic syndrome (5, 6), and type 2 diabetes mellitus (7). Compared with children and adolescents with normal body weight, obese children and adolescents have been observed to have a more unsuitable lipid profile (8, 9). The initiation of atherosclerotic process in childhood is supported by a growing number of scientific data, which represents an increasing health problem in obese children and adolescents (10). Higher childhood body mass index (BMI) increases the risk of esophageal adenocarcinoma (11). Considering these health

problems with high worldwide prevalence of obesity indicate the need for preventive strategies.

Breast feeding (BF) can prevent childhood obesity (12). Several mechanisms suggested for BF actions on the prevention of obesity. Three appetite hormones including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and leptin (13) in addition to several peptide/protein hormones including adiponectin, resistin, obestatin, nesfatin, irisin, adropin, copeptin, ghrelin, pituitary adenylatecyclase-activating polypeptide, apelins, motilin and cholecystokinin were detected in breast milk (14, 15). Bioactive substances such as leptin, ghrelin, insulin, adiponectin, obestatin, resistin, epidermal growth factor (EGF), platelet-derived growth factor and insulin-like growth factor 1 (IGF-1) play roles in energy intake and regulation of body composition (16). These hormones may represent the link between BF and obesity prevention in later life (17).

The worldwide increasing prevalence of obesity necessitates research studies that focus on exploring the simple and inexpensive ways to prevent it. BF is one of the easiest methods that might protect against obesity. Given the lack of a review on the mechanisms of BF actions in the prevention of obesity this study aims to focus on the effects of BF on obesity prevention during infancy, childhood, adolescence, and adult life with emphasis on possible mechanisms.

Methods

Data bases of PubMed and Science direct were searched from 2005 till March 2015. Key words were: "breast milk" plus obesity, and "human milk" plus obesity. Literature search yielded 456 studies for further consideration. Title and abstract of each article were assessed to delete duplication data. Any irrelevant papers were excluded. The remaining articles were reviewed to determine compatibility with the inclusion criteria. Searching was limited to articles with English language. Review articles, case reports, abstracts in symposium and congress, articles about effects of BF on the other variables, studies on preterm infants and non-healthy babies, non-human studies, and unpublished studies were excluded. After critically appraise of articles, 27 articles were selected and classified in three groups: 1) Studies on comparison of feeding type effects, 2) Studies on hormones and bioactive compounds in breast milk, and 3) Studies on macronutrient contents of breast milk. Flow diagram of choosing articles for this review study was shown in Figure 1. Characteristic of studies have been summarized in Table 1.

Results and Discussion

From 27 chosen articles, 18 articles were found on comparison of infantile feeding type effects on body weight in later years of life, 7 articles were on assessment of the association between some hormones (e.g., GLP-1, PYY, leptin) and bioactive compounds in breast milk and infants or children weight gain, and 2 articles were on the association of some macronutrient contents of breast milk with body composition and weight. Discussion about outcomes of these articles classified in three parts as follow:

Feeding type effects on the obesity prevention

Effects of BF on obesity during 1 and 2 years of age

From 18 studies that investigated the effects of different feeding types and duration of BF on body weight, 5 studies assessed the effect of feeding type on

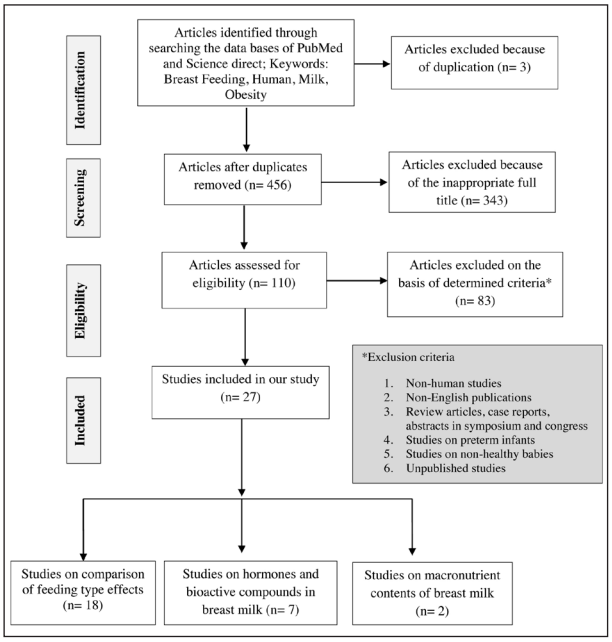

Figure 1. Flow Diagram of literature search and selection.

Table 1. Characteristics of included studies (Continued...)

Author (Date)	Source of data	Subjects age	Sample size	Groups	Obesity prevention effects
Studies on comparison of effects of feeding type					
Haisma et al. (2005)	Pelotas, Brazil; cross-sectional study	8 Mon	62 infants	2 groups (BM, n= 35; BCM, n= 27)	Yes ($p < 0.001$)
Burdette et al. (2006)	The Division of Gastroenterology and Nutrition, Children's Hospital of Philadelphia; cohort study	3-5 years	313 children	4 groups (never BF, BF but also FF < 4 Mon, BF > 4 Mon& FF after 4 Mon, BF > 12 Mon & never FF)	No ($p = 0.17$)
Li et al. (2008)	The Infant Feeding Practices Study II; prospective study	> 6 Mon	1896 infants	BF intensity: n= 1858 (3 groups); Frequency of infant-initiated bottle emptying: n= 1461 (3 groups)	Yes ($p < 0.01$)
O'Tierney et al. (2009)	Child-welfare clinics, Helsinki, Finland; cohort study	62 years	129 adults	4 groups [BF for <2 Mon (n= 22), for 3 to 4 Mon (n=30), for 5 to 7 Mon (n=38), for >8 Mon (n= 39)]	Yes ($p = 0.04$)
Li et al. (2010)	School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan; cohort study	Birth up to 18 Mon	15868 infants	3 groups (BF> 6 Mon, BF< 6 Mon, never BF)	Yes ($p < 0.001$)
Holmes et al. (2011)	The National Health and Nutrition Examination Survey, Department of Pediatrics of Concord Hospital, USA; cohort study	0-71 Mon	6788 children	2 groups (CBFF: 8%, Exclusively BF: 55%)	Yes ($p < 0.01$)
Crume et al. (2011)	Exploring Perinatal Outcomes among Children (EPOCH), Colorado; retrospective cohort study	6-13 years	468 (89 youth exposed to diabetes in utero, 379 youth unexposed to diabetes in utero)	2 groups (Unexposed to diabetes in utero, Exposed to diabetes in utero) Infant feeding: BF for < 6 Mon vs BF for > 6 Mon	Yes ($p = 0.02$)
Mandić et al. (2011)	Baranja, Croatia; retrospective study	Birth up to 12 Mon	203 infant-mother pairs	4 groups (exclusively BF, FF, mixed milk fed, cow's milk fed infants)	Yes ($p < 0.001$)
DiSantis et al.(2011)	The waiting area of a private pediatric primary care office located in suburban Philadelphia; retrospective cohort study	3-6 years	109 children	3 groups (directly BF (fed exclusively at the breast), bottle-fed human milk, bottle-fed formula)	Yes ($p \leq 0.01$)
Madsen et al. (2011)	The SKOT study, the Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen, Denmark; cohort study	9 Mon up to 18 Mon	252 infants	2 groups (BF, not BF)	Yes ($p = 0.007$)

(Continued...)

Table 1. Characteristics of included studies (Continued...)

Author (Date)	Source of data	Subjects age	Sample size	Groups	Obesity prevention effects
Crume et al. (2012)	Exploring Perinatal Outcomes among Children (EPOCH), Colorado; retrospective cohort study	6-13 years	442 children and adolescents	2 groups (BF for > 6 Mon, BF for < 6 Mon)	Yes ($p < 0.001$)
McCrory et al. (2012)	The Growing Up in Ireland study; retrospective study	9 years	7798 children	2 groups (BF for 13-25 weeks, BF for > 26 weeks)	Yes ($p < 0.01$)
Li et al. (2012)	The Infant Feeding Practices Study II; prospective study	Birth up to 12 Mon	1899 infants	6 groups (BF only, BF and HM by bottle, BF and non-HM by bottle, HM by bottle only, HM and non-HM by bottle, non-HM by bottle only)	Yes ($p < 0.001$)
Grossman et al. (2012)	A US Baby-Friendly hospital, Boston, MA, USA; prospective cohort study	Birth up to 1 week	121 infants	4 groups (exclusively BF, mainly BF, mainly FF, exclusively FF)	Yes ($p < 0.001$)
Oddy et al. (2014)	The Western Australian Pregnancy Cohort (Raine) Study in Perth, W.A., Australia Study in (1989-1991); retrospective study	1, 2, 3, 6, 8, 10, 14, 17, 20 years	2868	At 3 y: BF for < 4 Mon vs > 4 Mon, at 1-8 y: BF for < 4 Mon vs > 12 Mon, at 20 y: BF for < 6 Mon vs > 6 Mon	Yes ($p < 0.001$)
Gibbs et al. (2014)	Early Childhood Longitudinal Program (ECLS-B, 2009); longitudinal study	24 Mon	8030 infants	2 groups (Predominantly FF for the first 6 Mon, Predominantly BF for the first 6 Mon)	Yes ($p < 0.05$)
Rossiter et al. (2015)	2011 Children's Lifestyle and School-performance Study II (CLASS II); retrospective study	11 years	5560 children	4 groups [Only BF (BF for > 6 Mon), CF for > 6 Mon, CF for < 6 Mon, Only FF (BF for < 1 week or never)]	Yes ($p < 0.01$)
Park et al. (2015)	Department of Nursing, College of Medicine, Dongguk University, Gyeongju, South Korea; non-experimental retrospective study	3-6 years	528 children	2 groups [Predominantly BF (BF for the first 6.7 Mon), mixed feeding]	Yes (OR = 1.68, 95% CI = 1.07–2.63)
Studies on hormones and bioactive compounds in breast milk					
Miralles et al. (2006)	Biochemistry, Molecular Biology, Nutrition. and Biotechnology Nutrigenomics, Department of Fundamental Biology and Health Sciences, University of the Balearic Islands, Palma de Mallorca, Spain; prospective study	Women: 23-37 years Infants: Birth up to 2 years	28 non-obese mothers and their infants	-	Yes ($p < 0.01$)

(Continued...)

Table 1. Characteristics of included studies (Continued...)

Author (Date)	Source of data	Subjects age	Sample size	Groups	Obesity prevention effects
Weyermann et al. (2007)	The Department of Gynecology and Obstetrics at the University of Ulm, Germany; prospective study	Mothers: 18-45 years Infants: Birth up to 24 Mon	674 mother-infant pairs	-	No (Adjusted OR = 2.1; 95% CI = 1.1– 4.2)
Woo et al. (2009)	Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio and National Institute of Medical Sciences and Nutrition, Mexico City, Mexico; prospective study	Birth up to 6 Mon	322 mother-infant pairs	-	Yes ($p < 0.0001$)
Woo et al. (2012)	Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA and National Institute of Medical Sciences and Nutrition, Mexico City, Mexico; prospective study	Birth up to 2 years	192 mother-infant pairs	6 groups (high & low milk APN, high & low infant serum APN, high & low maternal serum APN)	During the first year: Yes ($p < 0.01$) During the second year: No
Fields et al. (2012)	The Children's Metabolic Research Center on the campus of the University of Oklahoma Health Sciences, Oklahoma City, USA;cross-sectional pilot study	Mothers: 18-45 years Infants: 1 Mon ± 5 day	19 mother-infant pairs	-	-
Savino et al. (2012)	Department of Paediatrics, University of Turin, Regina Margherita Children's Hospital, Italy; cross-sectional study	< 6 Mon	41 infants	2 groups (exclusively BF, FF)	Yes ($p = 0.02$)
Khodabakhshi et al. (2014)	Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; cross-sectional study	Infants: 2-5 Mon	80 mother-infant pairs	2 groups (40 mothers with overweight or obese infants, 40 age-matched mothers with normal-weight infants)	Yes = ($p < 0.0001$)
Studies on macronutrient contents of breast milk					
Koletzko et al. (2010)	European Childhood Obesity Project; double-blind, randomized clinical trial	Birth up to 2 years	1678 infants	3 groups (FF with high-protein formula, FF with low-protein formula, BF)	Yes ($p < 0.01$)
Pedersen et al. (2012)	Copenhagen Study on Asthma in Childhood; prospective study	Birth up to 9 years	281 mothers, 222 children	4 quartiles based on the breast milk DHA levels	Yes ($p = 0.02$)

BM, breast milk; BCM, breast and cows' milk; HM, human milk; BF, breast fed; FF, formula fed; CF, combination feeding; CBFF, combination breast milk and formula-feeding; Mon, Months; VS, versus; APN, adiponectin; DHA, docosahexaenoic acid; OR, odds ratio; CI, confidence interval.

body weight up to 1 year of age (18-22). All of these showed positive relation between BF and prevention of obesity during the first year of life. Haisma *et al.* (2005) concluded that cow's milk, as a complementary feeding, alters the sleeping metabolic rate in breast-fed infants. Li *et al.* (2008) showed that in comparison with infants with high (>80% of milk feeds being breast milk) BF intensity during the first half of infancy, infants with low (<20% of milk feeds being breast milk) or medium (20%-80%) BF intensity was at least 2 times more likely to have excess weight during the second half of infancy. In other study (20) Li *et al.* compared infants fed at the breast with infants fed only by bottle and suggested that in addition to type of milk consumed, mode of milk delivery may also affect infant's weight gain. They indicated that regardless of milk type in the bottle, bottle-feeding effect on infants' weight gain might be distinct from effect of feeding at the breast. Grossman *et al.* (2012) investigated normal newborn weight loss during the first week of life among infants born in a US Baby-Friendly hospital and found a significant association between maximum percent weight loss and feeding type. Mean and the range of time to nadir were 2.5 and 0-7 days after birth, respectively. The observed weight loss for exclusively and mainly breastfed infants was 5.5%, and for mainly formula-fed infants and exclusively formula-fed infants were 2.7% and 1.2%, respectively. In conclusion, they represented infant feeding pattern as a powerful predictor of newborn weight loss.

In the Taiwan Birth Cohort Study (23), Li *et al.* (2010) found no significant effect of BF duration on infant weight within the first 6 months, but after the 7th month, in comparison with infants who were not breastfed, infants who had been breastfed for ≥6 months were lighter.

Madsen *et al.* (2011) examined how IGF-1 concentration measured at age 9 months is related to diet and growth in infancy and found that median IGF-1 concentration in infants not being breastfed at 9 months of age was higher than breastfed infants (24). They showed a negative dose response effect of daily numbers of BFs on IGF-1 concentration. They found that between birth and 9 months of age IGF-1 concentration was positively related to increase in weight and BMI, but between 9 and 18 months of age it was negatively related to increase in BMI. They found a strong negative effect of BF on IGF-1 concentrations in late infancy. Despite negative association between IGF-1 concentrations at 9 months of age and change in BMI during the following 9 months occurrence of an early adiposity rebound and thereby an increased risk of obesity later in life were supposed.

Gibbs *et al.* (2014) examined the impact of infant feeding on child obesity and showed that the risk of obesity at 24 months of age in infants predominantly fed formula for the first 6 months was about 2.5 times more than infants predominantly fed breast milk. They also suggested that the probability of obesity was also increased by the early introduction of solid foods (<4 months) and putting the child to bed with a bottle.

Effects of BF on obesity prevention during preschool children

Four studies investigated the effect of feeding type on obesity during preschool children (25-28), but 1 study showed no effects of BF on childhood obesity prevention (25). Burdette *et al.* (2006) found no significant differences of fat mass between groups of children who had different combination of BF and formula feeding (FF) and children who were never breastfed. They concluded that there was no association between BF or the timing of the introduction of complementary foods and adiposity at age 5 years. Adjustment of analysis of their study for potentially confounding covariates such as maternal obesity, socioeconomic status, and maternal smoking may explain this difference by findings. The other 3 studies' results confirmed the effect of BF on childhood obesity prevention (26-28). Holmes *et al.* (2011) defined the combination breast milk and formula-feeding (CBFF) as daily BF and FF begun in the first week of life. They compared CBFF and FF with 4 months of exclusive BF and found that CBFF and FF increase the risk of overweight/obesity between ages 2 and 6 years. DiSantis *et al.* (2011) suggested that there is an association between direct BF during early infancy and greater appetite regulation later in childhood. Park *et al.* (2015) showed that the risk of obesity in children who had mixed feeding were 1.68 times more than those who were predominantly breast-fed.

Effects of BF on obesity prevention during school-aged children and adolescents

Four studies were conducted on this age group and all of them confirmed the positive association be-

tween BF and obesity prevention (29-32). Crume *et al.* (2011) showed the association of adequate (vs. low) BF status with significantly lower BMI at ages 6–13 years. They also found an association between exposure to diabetes in utero and a 1.7 kg/m^2 higher BMI among youth in the low BF category, but among those with adequate BF in infancy, there was no significant effect of prenatal exposure to diabetes on childhood adiposity outcomes. They suggested that adequate BF prevents childhood adiposity and results in a reduction in the increased adiposity levels associated with exposure to diabetes in utero. Mc Crory *et al.* (2012) found 38% and 51% reductions in the risk of obesity at 9 years of age in infants who were breastfed for 13-25 weeks and for >26 weeks, respectively.

Effects of BF on obesity prevention in adult life

Few studies investigated the effects of feeding type on adults (33, 34). The results of one cohort study didn't confirm the association between BF and obesity prevention in all later years of life (33). O'Tierney et al. (2009) found an association between longer period of BF and lower BMI at 1 year of age but by the age of 7 years this relation disappeared. They showed that BF for 5-7 months was associated with the lowest BMI at age 60 years, although this was not statistically significant. They also found that BF for < 2 months and >8 months increases BMI and percentage body fat in later life. They concluded that because of lack of exposure to protective factors in breast milk BF for < 2 months may be deleterious and since mother's hormones in breast milk reset the infant's hypothalamic-pituitary-thyroid axis BF for>8 months may be deleterious (33). But Oddy et al. (2014) found the positive association between longer BF and a reduction in risk of obesity during infancy, childhood, and adolescence. They also showed that introduction of milk other than breast milk before 6 months compared to at >6 months was associated with obesity at 20 years of age.

Studies on hormones and bioactive compounds in breast milk

As previously mentioned, the association between some hormones (e.g., GLP-1, PYY, leptin) and bioactive compounds in breast milk and infants or children weight gain was investigated in 7 studies. Four studies examined the relation between adipokines in human milk and risk of childhood obesity (35-38). Miralles *et al.* (2006) found a negative correlation between milk leptin concentration at 1 month of lactation and infant BMI at 18 and 24 months of age. They concluded that milk leptin concentration during the first stages of lactation may affect infant body weight during the first 2 years of age. Thus, it seems that moderate milk-borne maternal leptin can protect infants from an excess of weight gain moderately. These results indicate that the higher risk of obesity in formula-fed infants than breast-fed infants could be explained by milk leptin.

Weyermann *et al.* (2007) found a negative association between prevalence of overweight and duration of BF. They also assessed the risk of obesity in breast-fed children which the adiponectin and leptin contents of milk were different among them. They found higher risk of overweight for children in the 3 higher quartiles of adiponectin than children in the lowest quartile of adiponectin, but the risk of obesity was higher just for children in the upper quartile of leptin, compared with children breast-fed with milk containing the lowest quartile of leptin. They showed that the risk of obesity was not clearly associated with milk leptin levels but increasing breast milk adiponectin levels were positively associated with an increased risk for overweight at the age of the 2 years among children who were breast-fed for at least 6 months. They did not give any explanation for this unexpected result. Another study showed a negative association between milk adiponectin and infant weight-for-age Z-score and weight-for-length Z-score but not length-for-age Z-score, over the first 6 months (37). Woo *et al*. in other study found an association between median milk adiponectin and lower infant weight-for-age Z-scores at 0, 3, and 6 months. They showed that high milk adiponectin increased weight-for-age Z-score during the second year of life, while between 12 and 24 months of age change in weight-for-age Z-scores for infants exposed to lower milk adiponectin were little (38).

Fields *et al.* (2012) assessed the associations of appetite-regulating hormones and growth factors (leptin, insulin, glucose) and inflammatory factors including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in human breast-milk with infant size, adi-

posity, and lean tissue at 1-month of age. They found a negative association between milk leptin and BMI Z-score and a positive association between glucose and relative weight, and both fat and lean mass. Concentrations of milk insulin were negatively associated with infant weight, relative weight, and lean mass. They showed a negative association between milk IL-6 and relative weight, weight gain, percent fat, and fat mass. TNF-α was negatively associated with lean mass, but not measures of adiposity. Finally they concluded that in the first months of life, the accrual of fat and lean body mass could be affected by breast-milk concentrations of insulin, glucose, IL-6, TNF-α and leptin differentially.

Savino *et al.* (2012) assessed serum resistin and leptin concentrations and their proportions in infants and in breast milk. They found a positive correlation between serum resistin concentrations in breast-fed infants and breast milk resistin. They also have shown that resistin correlated positively with leptin in total group of infants, confirmed in breast-fed subjects. But serum hormones were not correlated with anthropometric parameters of infants.

Khodabakhshi *et al.* (2014) compared the concentrations of three hormones (ghrelin, leptin, adiponectin) and two growth factors (EGF and IGF-1) in the breast milk of mothers with obese and normal weight infants. They found that compared to mothers with obese infants, the mean breast milk concentrations of ghrelin and EGF were higher in mothers with normal-weight infants. They observed that the concentrations of leptin, adiponectin and IGF-1 were not significantly different between two groups. They also found that EGF was positively correlated with ghrelin in both groups. The results of this study suggested that EGF and ghrelin in breast milk may have a regulatory effect on breast fed infants' weight.

Studies on macronutrient contents of breast milk

As mentioned previously, we found 2 studies on the association of some macronutrient contents of breast milk with body composition and weight. One of these studies showed an association between protein contents of milk and infant weight gain (39). They randomized infants and fed them by the high-protein infant formula and follow-on formula with lower protein contents for the first year. The follow-up data obtained at age 2 years showed that feeding by formula with reduced protein content was associated with normal early growth and may have a significant preventive effect on later obesity. According to the results of this study and because the protein content of human milk is lower than usual infant formulas, feeding by breast milk is suggested during the first months of infant's life for protection against obesity.

Pedersen *et al.* (2012) found that the breast milk docosahexaenoic acid (DHA) is inversely associated with BMI from 2 to 7 years and fat mass. They showed that age at adiposity rebound for girls was positively associated with DHA level in breast milk, but they observed no association for boys.

Comparison with results of other review studies

Arenz *et al.* (2004) conducted a systematic review for assessment the BF effect on childhood obesity. Population-based cohort, cross-sectional or case-control studies with English, French, Italian, Spanish, or German languages were included in that study. They showed an association between BF and childhood obesity prevention but they indicated that this protective effect is small but consistent. Similar to some studies, the utilization of the regression method was a limitation of Arenz *et al*'s study because in meta-analyses of less than 20 studies the statistical power is low (40).

A systematic review, which published by the World Health Organization (WHO), covered studies published from 2006 till September 2011 (41). Observational and randomized studies with English, Spanish, or Portuguese languages were searched for that review. Studies on the BF effects on the blood pressure, total cholesterol, overweight/obesity, type-2 diabetes, and performance in intelligence tests were included. Since they evaluated the long-term effects of BF, studies on infants were excluded. They included studies with any type of categorization of BF and utilized funnel plots and Egger's test to assess the presence of publication bias. They also stratified the analysis according to study size, for assessing the effect of publication bias on the pooled estimate. They concluded that BF is associated with lower prevalence of later overweight or obesity.

In a recent systematic review Hornell *et al.* (2013) reviewed short- and long-term effects of BF and complementary feeding on health. They reviewed publications with English or Nordic language since January 2000 and only human studies in which the study population was relevant to the Nordic countries. In addition to prospective cohort studies, systematic literature reviews, meta-analysis, and reports from organizations and committees were included in that study. They just reviewed studies on BF duration and publications on breast milk hormones and bioactive substances were excluded. Due to the exclusion of studies that their population was irrelevant to the Nordic countries, the generalization of the results of that study may be controversial. In conclusion they confirmed the exclusive BF until 6 months of age which is recommended by Nordic Nutrition Recommendations (NNR) 2004, and to continue BF as part of the diet during the first year of life.

Suggestions for further studies

According to our review several cohort and cross-sectional studies examined the effect of infant feeding practices and duration of any feeding type on the risk of obesity in later periods of life and the selection of BF as exclusive feeding type for early months of life is suggested by most studies. But it seems that most of the conducted studies investigated this association during infancy and childhood and there are a few studies on BF effect on adulthood obesity prevention, so further well-designed prospective studies are needed to investigate the association between BF and the risk of obesity in adults.

Several hormones and bioactive substances exist in breast milk but just some of them had been investigated for their effect on the risk of obesity, thus for determining the mechanisms of BF actions in the prevention of obesity, the examination of the association between each of hormones and bioactive compounds in breast milk and the risk of obesity seems to be an important area of research.

Limitations and strengths

Most of the studies that included in our review had investigated a small population (<500 subjects), which can reduce the power of findings. In assessment of the association between infant feeding and later obesity it is difficult to discover whether the outcomes seen for BF or other confounding factors, it seems that this problem is more complicated for studies on BF effect on risk of obesity in later periods of life (childhood, adolescence, or adulthood), because of an increase in number of factors which may affect the body mass. In studies that the data on feeding practices during the early life were gathered retrospectively and through maternal questionnaires, the collected data may have insufficient accuracy because of the possible inability to recall the exact duration of any feeding type (e.g., BF, FF, etc.). Diverse definitions of BF in the included studies are also problematic. Inappropriate definition of exclusive BF, insufficient details about complementary feeding, and comparison only between breast fed and not breast fed infants are other methodological problems which exist in some of included studies in current review.

We assessed studies from 2005 till March 2015 and tried to collect the most recent obtained outcomes. In addition to assessment of the feeding type (e.g., BF, FF, etc.) effects on obesity prevention we reviewed studies which evaluated the effects of hormones, bioactive compounds, and some nutrients in breast milk on risk of obesity for investigation the mechanisms of BF actions in the prevention of obesity. No restriction on the age of subjects was applied in present study and we reviewed effects of BF on the risk of obesity during any periods of life (e.g., infancy, childhood, adolescence, and adulthood). We just searched data bases of PubMed and Science direct, so we found and reviewed part of studies on this topic. With searching more databases, more studies with various methods will obtain and so the conclusion will be more appropriate. According to inclusion criteria for this study we missed out non-English publications and animal studies.

Conclusion

Most of the reviewed studies revealed that selection of exclusive BF for feeding infant in early months of life can prevent obesity during infancy, childhood, adolescence, and even adult life with various mecha-

nisms. Most studies showed a positive association between hormones and bioactive compounds in breast milk and obesity prevention but in the case of breast milk adiponectin levels results were contradictory. Since few studies on macronutrient contents of breast milk were assessed in present study, it is difficult to conclude about the effectiveness of BF on obesity prevention regarding the breast milk macronutrient contents.

Despite positive effects of BF on obesity prevention, limited clinical trials evaluated exact mechanisms of BF effects. Additional well-designed studies, with larger sample size, focusing on different ethnicities and feeding types are now warranted to validate this finding.

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