Review Article

Maryam Soori, Younes Mohammadi, Mohammad Taghi Goodarzi* and Minoo Mahmoodi

Association between breast milk adipokines with growth in breast feeding infants, a systematic review and meta-analysis

[Anne sütü adipokinleri ile emziren bebeklerde büyüme Arasındaki İlişki, sistematik bir İnceleme ve meta-analiz]

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Abstract

Objectives: Breast milk adipokines are associated with growth, body mass index (BMI) and weight gain in infants. In this study, the effect of breastmilk adipokines (leptin and adiponectin) on the BMI and weight gain of breast-fed infants was evaluated using systematic review and meta-analysis.

Materials and methods: We used PRISMA checklist for carrying out this study. 752 articles were collected from the database searching and other sources from 1994 to April 2019. According to the criteria in the study, 25 articles remained for evaluation. Eight papers were related to the effect of breast milk leptin on weight gain and BMI of infants that were evaluated by meta-analyzing. The adiponectin articles were surveyed by systematic review.

Results: There was no significant publication bias in the meta-analysis study. The results of random-effect model indicated a reverse and significant correlation between breastmilk leptin with weight gain and BMI (r=−0.331). The adiponectin level in breast milk was associated with the BMI and weight gain of infants.

Conclusions: Meta-analysis indicated a significant inverse correlation between breastmilk leptin with weight gain and BMI in infants; furthermore, the systematic review study expressed significant correlation between breast milk adiponectin with growth (BMI and weight gain) in infants.

Keywords: adiponectin; body mass index (BMI); leptin; systematic review; weight gain.

Öz

Amaç: Anne sütü adipokinleri bebeklerde büyüme, vücut kitle indeksi (VKİ) ve kilo alımı ile ilişkilidir. Bu çalışmada anne sütü adipokinlerinin (leptin ve adiponektin) anne sütüyle beslenen bebeklerin vücut kitle indeksi ve kilo alımı üzerindeki etkisi sistematik derleme ve meta-analiz kullanılarak değerlendirildi.

Gereç ve Yöntemler: Bu çalışmayı gerçekleştirmek için PRISMA kontrol listesini kullandık. Veri tabanı taramasından ve diğer kaynaklardan 1994'ten Nisan 2019'a kadar 752 makale toplanmıştır. Çalışmadaki kriterlere göre değerlendirilmek üzere yirmi beş makale kalmıştır. Meta-analiz ile değerlendirilen sekiz makale, anne sütü leptininin bebeklerin kilo alımı ve BMI üzerindeki etkisi ile ilgilidir. Adiponektin makaleleri sistematik bir inceleme ile incelenmiştir.

***Corresponding author: Mohammad Taghi Goodarzi**, Department of Biochemistry, Shahrood Branch, Islamic Azad University, Shahrood, Islamic Republic of Iran, Phone: +98 9181115969, E-mail: mtgoodarzi@yahoo.com. https://orcid.org/0000-0002-5546-5812

Maryam Soori and Minoo Mahmoodi, Department of Biology, Hamedan Branch, Islamic Azad University, Hamedan, Islamic Republic of Iran. https://orcid.org/0000-0001-7831-6388 (M. Soori). https://orcid.org/0000-0002-3541-8832 (M. Mahmoodi)

Younes Mohammadi, Department of Epidemiology, Hamadan University of Medical Sciences, Hamadan, Islamic Republic of Iran. https://orcid.org/0000-0001-7521-4909

Bulgular: Meta-analiz çalışmasında önemli bir yayın yanlılığı yoktu. Rastgele etki modelinin sonuçları, anne sütü leptini ile kilo alımı ve VKİ arasında ters ve anlamlı bir korelasyon olduğunu gösterdi (r=−0.331). Anne sütündeki adiponektin düzeyi, bebeklerin vücut kitle indeksi ve kilo alımı ile ilişkiliydi.
Sonuç: Meta-analiz bebeklerde anne sütü leptini ile kilo alımı ve VKİ arasında anlamlı bir ters ilişki olduğunu gösterdi; ayrıca, sistematik gözden geçirme çalışması bebeklerde anne sütü adiponektini ile büyüme (VKİ ve kilo artışı) arasında önemli bir korelasyon olduğunu ortaya koymuştur.

Anahtar Kelimeler: adiponektin; kilo alımı; leptin; sistematik inceleme; vücut kitle indeksi (VKİ).

Introduction

The global epidemic of overweight has become a general issue in recent years. Overweight can lead to obesity that is associated with metabolic syndromes, cardiovascular, and mental diseases. The latest investigations show that the trend of overweight in children and adolescents is positively correlated with baby feeding. Naturally, breast milk is the first liquid for nutrition after the birth of the infants [1]. Several studies have shown a significant relationship between breastfeeding and overweight in childhood and later life [2]. Breast milk contains 87–90% water that is the main source of water for infants. In addition, there are hormones and proteins in breast milk including adipokines. Adipokines are hormones such as resistin, obestatin, nesfatin, ghrelin, leptin, adiponectin and TNF-α that are secreted from adipocytes [3]. The adipokine precise mechanism of breastfeeding is still equivocal. However, researchers suggest that the level of adipokines in the breastmilk is directly pertinent to blood adipokines in infants. Many studies reported the effect of adipokines on the regulation of glucose and lipid metabolism, homeostasis of energy, nutritional energy, insulin sensitivity, inflammation, immune system, fat tissue production, vascular function, coagulation, setting appetite, and body weight balance short- and long-term.

Moreover, breast milk comprises adiponectin and leptin. Some studies indicated a possible association between breast milk leptin and weight gain in infants. According to these studies, the level of body leptin is highly essential in regulating energy and body weight balance due to the suppression of fat storage by reducing appetite [4, 5]. Recent studies show that adiponectin level in human milk (HM) is 40 times higher than the level of other adipokines such as ghrelin and leptin [6]. Adiponectin is an insulin-sensitizing hormone that regulates lipid and glucose metabolism and stimulates food intake. This anti-inflammatory molecule participates in energy balance [3, 7, 8]. There is a negative association between adiponectin and weight gain in infancy and puberty [3, 9–12]. Moreover, there are different reports about the relationship between leptin and adiponectin hormones against weight gain, overweight and body composition in infants. Olga Mrilles's study showed a negative effect of breast milk leptin in weight gain and BMI in infants [13]; while the F. Savino´s study indicated a positive relationship among breast milk leptin and weight gain and BMI [14]. Due to the contradiction in studies, the present systematic review and meta-analysis aimed to determine whether human breastmilk leptin and adiponectin are associated with growth (weight gain and BMI) in infants.

Materials/subjects and methods

In this study, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was used. Two researchers participated in the performance of this meta-analysis, following standard guidelines. The electronic databases included Web of Science, PubMed, Scopus, Cochrane Library, and EMBASE. Papers were collected from 1994 to April 2019. The search mesh terms and text words were restricted by the following criteria individually or/and in multifarious combinations: infant, growth, breastmilk, adipokine, adiponectin, leptin, and weight gain. The characteristics of the studied papers were as follows: English published articles, studies in humans, and two-year-old age-group babies that were only breastfed. The reference lists of all published articles were also searched to find other published articles that were not identified in the database search.

Study selection

Three authors (S.M, G. MT, and M.Y) examined all qualifications, simultaneously. All the analyses were based on previously published papers. Thus, moral satisfaction or patient consent was not required. The papers incorporated mothers and children with normal weight and physical health. Infants were just breastfed from one month to one year. The methods of measuring hormones were enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA). A correlation coefficient (r) was considered for the relationship between breastmilk leptin and adiponectin with the growth (BMI and weight gain) of infants in studies.

Data extraction

Excel file was also designed. The following information was checked out from each study: first author's name, year of publication of the article, journal name, name of the country implementing the project, the name of the examined hormones, the number of patients, sexuality, and the mean concentration of the hormones studied in different months. The Newcastle-Ottawa Scale (NOS) checklist was used to evaluate the quality of the articles.

Results

The excel file was also designed. The following information was checked out from each study: first author's name, year of publication, journal name, the name of the country implementing the project, the name of the examined hormones, the number of patients, sexuality, and the mean concentration of the hormones studied in different months. The Newcastle-Ottawa Scale (NOS) checklist was used to evaluate the quality of the articles. The PRISMA checklist was used to evaluate the quality of the papers (Figure 1). The keywords were selected using the PICOTS (Patient, Intervention, Comparison, Outcome, Time, Study) method. The search results for the three keywords (infant, adipokines, and growth) are as follows. A summary of 752 papers was reviewed. Additional records were identified through other sources in eight papers. Table 1 is related to the Parisis checklist of the study. Forty-one text articles were thoroughly studied. Ultimately, 25 articles were extracted according to the criteria. Sixteen articles were deleted from the study for the mentioned reasons. Nine articles were designed to determine the level of adipokines in the infants' serum [5, 6, 11, 15–20]. Six articles had an intervention factor [4, 21–25]. Finally, one paper had been designed for the effect of breast milk adipokine in premature infants [20]. The present study was conducted to evaluate the effect of breastmilk adiponectin and leptin on infant growth (BMI, weight gain). The leptin papers were twenty (eight meta-analyses and 12 systematic reviews). In the case of adiponectin, 14 articles were reported in a systematic review, and seven papers were simultaneously evaluated for both leptin and adiponectin.

Study characteristics

All studies included statistical population, correlation coefficient, statistical indexes between the leptin or

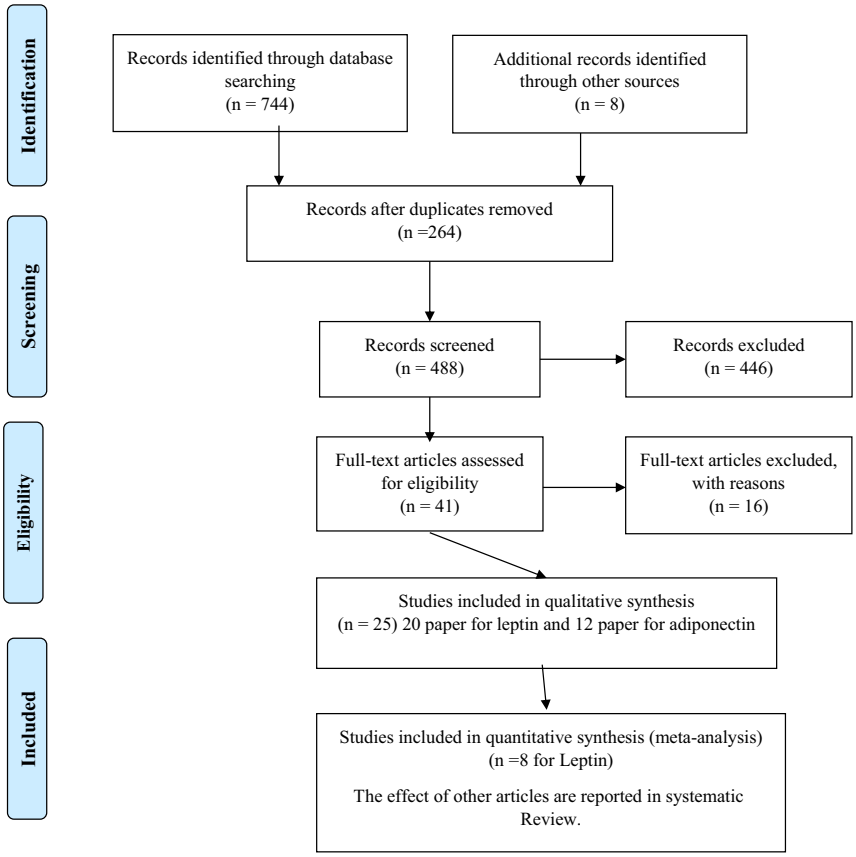

Figure 1: Process PRISMA flowchart of the study selection.

Table 1: Characteristics of the studies included in the meta-analysis and systematic review of leptin and adiponectin levels in breast milk with BMI and weight gain measures.

Study (published year)	Country	Adipokines	Method	Sample size	Mean of in breastmilk	Type of study	Statistical index	Association	NOS	Reference number, (Meta-analysis)*
Fields et al. (2012)	Oklahoma (United States)	Leptin	ELISA	19	91.8±47 pg/mL	Cross-sectional	Spearman correlation	Negative	7	36*
Doneray et al. (2009)	Turkey	Leptin	RIA	15	18.15±17.05 ng/mL	Cross-sectional	Spearman correlation	Negative	7	12*
Miralles et al. (2005)	Spain	Leptin	ELISA	28	0.156±0.09 ng/mL	Cross-sectional	Spearman correlation	Negative	7	13*
Savino et al. (2016)	Regina of Canada	Leptin	RIA	58	0.89 ng/mL	Cross-sectional	Spearman correlation	Positive	8	14*
Uysa et al. (2002)	Turkey	Leptin	RIA	50	0.37±0.4 ng/mL	Cross-sectional	Spearman correlation	NO	7	24*
Khodabakhshi et al. (2014)	Iran	Leptin	ELISA	80	1.81 ng/mL	Cross-sectional	Spearman correlation	Negative	7	35*
Schuster et al. (2011)	Leipzig (Germany)	Leptin	RIA	23	0.18±0.15 ng/mL	Cohort	Spearman correlation	Negative	7	33*
Dundar et al. (2005)	Turkey	Leptin	RIA	47	18.4±2 ng/mL	Cohort	Regression	Negative	8	32*
Chan et al. (2018)	Canada	Leptin	ELISA	430	361 pg/mL	Cohort	Covariate regression	Negative	9	26
Weyermann et al. (2007)	Germany	Leptin	ELISA	1066	174.5 pg/mL	Cohort	Logistic regression	Negative	8	9
Bronsky et al. (2011)	Prague	Leptin	ELISA	327	0.3±0.04 ng/mL	Cohort	Spearman correlation	NO	8	28
Quinn et al. (2015)	Philippines	Leptin	ELISA	113	300.7±293.6 pg/mL	Cohort	Spearman correlation	Negative	7	29
Savino et al. (2016)	Regina of Canada	Leptin	RIA	60	0.51 ng/mL	Cross-sectional	Spearman and Pearson correlation	NO	7	14
Karatos et al. (2011)	Turkey	Leptin	ELISA	62	0.26 (14.48) ng/mL	Cohort	Pearson correlation	It's related	6	30
Ucar et al. (2000)	Turkey	Leptin	RIA	18	3.036±1 ng/mL	Cross-sectional	Pearson correlation	NO	7	39
Gridneva et al. (2018)	Australia	Leptin	ELISA	20	–	Cross-sectional	Regression	NO	7	7
Larsson et al. (2018)	Australia	Leptin	ELISA	30	0.1 ng/mL in 9 month and 0.07 ng/mL in 5 month	Cohort	Regression	NO	7	31
Savino et al. (2012)	Italy	Leptin	RIA	41	2.34 (5.7) ng/mL	Cross-sectional	Spearman correlation	NO	7	6
Yesim et al. (2010)	Turkey	Leptin	IRMA	47	0.4±0.2 ng/ml	Cross-sectional	Spearman and Pearson correlation	NO	7	41
Kon et al. (2014)	Moscow (Russia)	Leptin	ELISA	103	3.29±0.7 ng/mL	Cohort	NA	It's related	8	27

Table 1: (continued)

Study (published year)	Country	Adipokines	Method	Sample size	Mean of in breastmilk	Type of study	Statistical index	Association	NOS	Reference number, (Meta-analysis)*
Chan et al. (2018)	Canada	Adiponectin	ELISA	430	19.4 (3.7–74.4) ng/mL	Cohort	Covariate regression	NO	9	26
Kon et al. (2014)	Moscow (Russia)	Adiponectin	ELISA	103	1.14±0.09 ng/mL	Cohort	NA	NO	8	27
Khodabakhshi et al. (2014)	Iran	Adiponectin	ELISA	80	323.48 ng/mL in lean infant and 330.05 ng/mL in obese infant	Cross-sectional	Spearman correlation	NO	7	35
Weyermann et al. (2007)	Germany	Adiponectin	ELISA	767	10.9 ng/mL	Cohort	Logistic regression	Positive	8	9
Bronsky et al. (2011)	Prague	Adiponectin	ELISA	327	22.8±0.8 ng/mL	Cohort	Spearman correlation	NO	8	28
Hamdy et al. (2017)	Egyptian	Adiponectin	ELISA	–	5.5–25 ng/d lit	Cross-sectional	Regression	Negative	7	42
Anderson et al. (2016)	Philippines	Adiponectin	ELISA	117	7.74±5.75 ng/mL	Cross-sectional	Regression	Negative	7	43
Woo et al. (2009)	Mexico	Adiponectin	RIA	162	22.63±0.95 ng/mL	Cohort	Spearman correlation	Negative	7	8
Woo et al. (2009)	Mexico and Cincinnati	Adiponectin	RIA	277	24±8.6 µg/mL	Cohort	Regression	Negative	8	8
Marhazlina et al. (2018)	Malaysia	Adiponectin	ELISA	155	11.53 ng/mL	Cohort	Regression	Negative	8	34
Gridneva et al. (2018)	Australia	Adiponectin	ELISA	20	–	Cross-sectional	Regression	NO	7	7
Larsson et al. (2018)	Australia	Adiponectin	ELISA	30	14.65 ng/mL in 9 month and 17.56 ng/mL in 5 month	Cohort	Regression	Positive	7	31

NOS, Newcastle-Ottawa Scale; NO, No correlation found.It's related: There is a correlation; however no correlation coefficient is mentioned.

adiponectin levels in breast milk and the growth of the infants. Body mass and weight gain were considered as the growth indices in infants. There was no disagreement on inclusion/ exclusion criteria of the specific studies. All articles were a cohort or cross-sectional studies. These studies were conducted in different countries and in both sexes. The period of lactation was not considered because of the difference in different studies. This study included 13 cohort papers [3, 8, 9, 14, 26–34] and 12 cross-sectional papers [7, 12, 13, 24, 25–43]. The methods for measurement of breastmilk leptin and adiponectin were as follow: ten studies conformed radio-immune assay (RIA) [3, 8, 12, 14, 24, 32, 33, 37–40], 13 studies used enzyme-linked immune sorbent assay (ELISA) [7, 9, 13, 26–31, 34, 35, 42, 43] and two studies used other methods of immunoassay [36, 41]. The correlation between breastmilk adipokines and infant growth (BMI or weight gain) was expressed with regression statistic index in eight papers [7, 8, 26, 31, 33, 34, 42, 43], Spearman correlation in ^{12} studies [3, 14, 24, 28, 29, 35–41] and Pearson correlation in three studies [13, 30, 32] and in one paper was logistic index [9]. In Ya Kon et al. study, the correlation was not mentioned [27].

Risk of bias within studies

Begg's funnel plot was used for detection the risk of bias within the studies.

Results of individual participant studies in the meta-analysis

The main characteristics of all studies participant in this meta-analysis and systematic review are summarized in Table 1. The results of quality assessment by the Newcastle-Ottawa Scale (NOS) confirmed that all cohort and cross sectional studies had high quality with a greater than six score. A correlation coefficient (r) was used to express any possible correlation in this meta-analysis.

Cochran´s test was performed for heterogeneity studies and Begg's funnel plot was used to detect publication bias of the selected papers (Figure 2). The survey indicated no significant publication bias in this meta-analysis.

According to Figure 3, heterogeneity was (I- squared) 80 and p-Value=00.00, therefore the random-effects was calculated for meta-analysis of eight study of leptin. The results of random-effect model indicated a reverse and significant correlation between breast milk leptin with the growth (BMI and weight gain) of infants (r=–0.331).

Meta-analysis of leptin

Eight papers are presented in the meta-analysis [12–14, 24, 32, 33, 35, 36]. According to meta-analysis, there was a reverse and significant correlation between breast milk leptin and the growth (BMI and weight gain) of infants.

Leptin systematic review

The results of other studies in correlation with the effect of leptin breast milk on weight gain and BMI of infants are described below. According to Table 1, two papers showed a negative correlation between infant´s weight gain with breast milk leptin levels [9, 26]. In one study, breast milk leptin was negatively correlated with body mass index [29]. In Karatas et al. study there was a correlation between breast milk leptin and weight gain and body mass index [30]. No significant correlation was found between weight

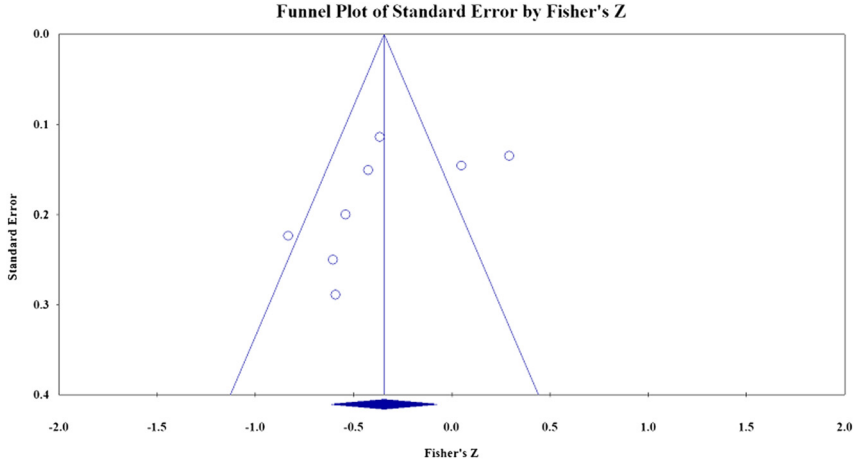

Figure 2: Publication bias of the effect of breast milk leptin on growth (weight gain and BMI) in infants.

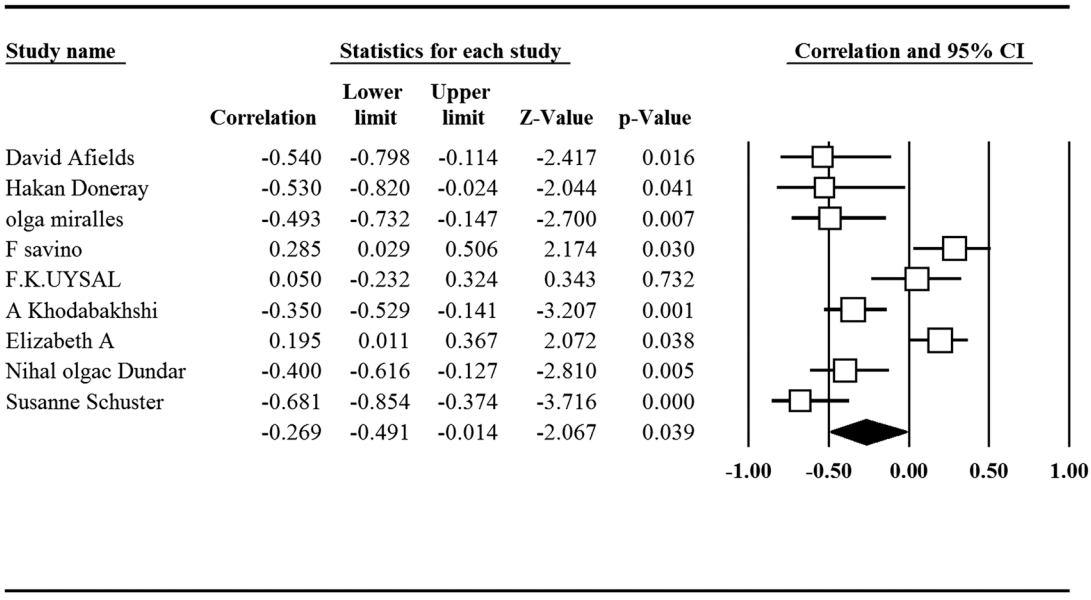

Figure 3: ORs and 95% CIs of individual studies of the effect of breastmilk leptin on growth (weight gain and BMI) in infants.

gain and breastmilk´s leptin in eight articles [7, 13, 28, 31, 37, 39–41].

Systematic review of adiponectin

According to the results of surveyed studies, the correlation of adiponectin breast milk with weight gain and BMI in infants were inconsistent; therefore, meta-analysis was failed; the related findings are presented as a systematic review.

Woo et al. (2012), in a study in Mexico City that was followed for two years, analyzed milk adiponectin in 192 infants. They showed that maternal serum adiponectin was correlated with milk adiponectin (r=0.37, p<0.0001) and infant serum adiponectin (r=0.29, p=0.01). In this study infants that received high milk adiponectin, had increased WFL Z-scores (weight-for-length) between age 1 and 2 years compared to other groups [3].

Another study by Woo et al. in 2009 showed the importance of adiponectin in breast milk in the growth of infants. They indicated an association between higher adiponectin concentration and lower weight and leaner body during the first six months of age in breast feed infants [8].

Chan et al. (2018) in a study in 430 infants and mothers showed that breast milk leptin and insulin concentrations were associated with lower infant WFL (weight-for length) in the first year of life; however, no significant association was found between breast milk adiponectin and growth in infants [26].

There is a report showing that increase in breastmilk adiponectin concentration was significantly associated with lower infant body weight at 6th months of age (r=–0.3) [34]. It is concluded that adiponectin concentration in maternal serum and milk is negatively associated with adiposity development in first year infants [34]. Similarly, Hamdy et al. (2017) reported that human milk adiponectin was significantly associated with lower infant WAZ score at six month (r=–0.480, p=0.002) [42].

Weyermann et al. in 2007 suggested that low level of breast milk adiponectin could have protective effects against childhood obesity [9].

Finally, the results of published articles can be summarized as below. According to Table 1, in six papers there was a negative correlation between weight gain and breastmilk adiponectin [3, 8, 9, 34, 42, 43]. In W. Larsson et al. study, at five-months age and one-year age there was no correlation between adiponectin and weight gain; but, there was a positive correlation between breast milk hormones and WAz (Weight for age z-scores) at four months of age [31]. In the two studies of the searched articles (Chan et al. and Bronsky et al.), there was no correlation between weight gain and BMI with breastmilk adiponectin [26, 28]. In three studies, the correlation was not mentioned [7, 27, 35].

From the survey of these publications, it can be indicated that milk adiponectin has important role in breast milk feeding infants; however, the knowledge about variation in milk adiponectin concentration and its physiological functions are incomplete to be able to approach an overall conclusion. Different nutritional status of infants,

different BMI of mothers, and different period of infants' age are important factors that cause different conclusion and must be considered carefully in future studies. Lastly as Weyermann et al. concluded in their study "breast-fed children may benefit most from prolonged breast-feeding with respect to prevention of obesity when milk contains low levels of adiponectin" [9].

Discussion

In this study, the effect of adiponectin and leptin on the growth of breastfed babies by meta-analysis and systematic review were discussed. Accordingly, in leptin meta-analysis, leptin has an inverse relationship with body weight gain and body mass index (BMI) in infants, also according to the systematic review, leptin and adiponectin of breast milk are significantly associated with body weight gain and body mass index (BMI) in infants. Adiponectin is a 30 kDa secretory protein having a sequence of collagen domain, a carboxyl-terminal domain, and a variable globular-head N-terminal [36]. Coded by the APM1 gene in the cell nucleus [44], adiponectin is found in full-length (fAd) and globular forms (gAd). After transcription, its mRNA enters the endoplasmic reticulum (ER) and adiponectin specific settings are made subsequently. Monomeric adiponectin (mAd) modified and further oligomerized to create LMW (low molecular weight, trimers), MMW (medium, hexamers), and HMW (high, oligomeric) forms [45, 46]. Adiponectin carries much of its cellular effect by joining two Adipo R1 and Adipo R2 receptors [47]. These two receptors have a seven-dominant structure. The Adipo R1 and R2 are expressed in the hypothalamus; moreover, the expression of Adipo R2 have been observed in the paranotrichular nucleus (PVT) [48]. Since Adipo R1 is predominantly expressed in skeletal muscle, yet Adipo R2 expressed primarily in the liver, gAd is more effective in insulin resistance and insulin-mimetic than fAd in skeletal muscle. Adiponectin activity depends on its molecular form, its receptor, and the target tissue [49]. Several adiponectin receptor proteins have been identified. The APPL1 mediated molecule is the only intermediate molecule that binds both Adipo R1 and R2 receptors [49–52]. It has recently been shown that APPL1 is quite essential in several metabolic reactions in the liver, muscle, and epithelial cells, which binds signals from the adiponectin receptor to specific pathways and activates adiponectin [48, 53]. Adiponectin plays a significant role in the metabolism of energy in the human body [54]. The concentration of both total adiponectin and HMW decreases in obesity and increases again due to weight loss. In addition, total adiponectin and HMW have an inverse correlation with BMI, glucose, insulin, triglycerides levels, IR degree, and visceral fat accumulation. Adiponectin in fatty tissues increases the absorption of glucose in the base. The absorption of glucose increases insulin production by activating AMPK [44]. In the pancreas, it also causes insulin secretion [49, 55, 56].

Leptin is mainly secreted from white adipose tissue and less in the bone marrow, ovary, placenta, stomachs, and lymphatic tissues. Since the level of leptin depends upon the storage of body fat, it will have little fluctuation in a short time [57]. Leptin reductions lead to obesity, reduced body growth, reproductive, and total metabolism of the body by slowing down the sympathetic pathway and thyroid function. Leptin reductions also increase the production of glucose in the liver and decrease the blood glucose levels, and some brain behaviors such as increased irritability, anxiety, shortness of breath, diabetes, and other types of intracerebral disorder. Leptin is produced by the ob gene. It is a 16 kDa polypeptide mainly produced in white adipose tissue [58]. Leptin expression is chiefly regulated by different hormones such as insulin and glucocorticoids [59, 60].The physiological function of leptin is largely unknown [59]. The biological activity of leptin is performed by the central nervous system (CNS), namely the hypothalamus. Leptin has a long receptor. The leptin receptor (Lep Rb) is scattered in many regions of the brain and tissues. The Lep Rb gene produces six leptin receptor isoforms (a, b, c, d, e, f) [61]. Leptin receptors are members of the interleukin-6 (IL-6) receptors family. They do not have enzymatic activity on their own. However, by binding to a cytoplasmic tyrosine kinase called JAK2 (Juns Kinas 2), it stimulates phosphorylation of the three tyrosine residues (Tyr 985, Tyr 1077, Tyr1138) on their own [59, 62]. The Src homology 2 (SH2) domains attach to phosphorylated tyrosine, which binds the downstream molecules to the Lep Rb-JAK2 complex. Then, MAPK, PL3K, STATE5, and STAT three pathways are activated. From these paths, STAT3 is vital because stopping this pathway causes obesity and a sharp decline in energy consumption. STAT3 increases the direct transfusion of pro-opiomelanocortin (POMC), which reduces appetite and increases energy consumption. The cytokine-3 (SOCS3) signaling suppressant on the JAK2 / STAT3 pathway is resistant to leptin and obesity [57, 61, 63–65].

For the limitations of this study, we can point out the small sample size used in the original articles. Small number of useful articles for meta-analysis presentation was another limitation of this project. Using only English articles was another problem because there may be reports in other languages. It is noteworthy the route of digestion

and absorption of adipokines in the body has not been fully elucidated, and this could qualitatively affect the results of reported research.

Due to the positive effects of adipokines such as leptin and adiponectin on regulating energy and metabolism of the body as well as the impact of these two proteins in the control of appetite and body weight, it is necessary to specifically investigate these proteins and their key roles in the body from the neonatal period. Considering the short-term and long-term effects of these proteins from neonatal period in the body, and the fact that the only source of these proteins during the neonatal period is breast milk, it can be suggested that these adipokines are added to formula milk used by infants fed with formula milk.

Conclusions

The present meta-analysis provides a reverse and significant correlation between breast milk leptin with the growth (BMI and weight gain) of infants. Also according to the systematic review´s results, the amount of adiponectin in breast milk is associated with the growth of infants.

In most of the published articles, a relationship between breast milk adipokines and infants growth has been pointed out; however, the findings about adiponectin is controversial. To find out more precise and the detailed of these relationships, the following studies are suggested. (a) survey of breast milk adipokines and determination of possible effects of genetic, nutritional and economic factors, (b) study the starting age of adipokines biosynthesis in infants adipocytes and (c) analyzing of other adipokines and micronutrients in breastmilk and their relationship with weight gain, growth and development in infants.

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Author contributions: MG and YM designed the research; MS collected articles from the database searching. MG, YM and MS check out the articles, interpreted the results, prepared and drafted the manuscript; MG and MM edited and revised the manuscript.

Competing interests: Authors state no conflict of interest.

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