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Nutrition

A pilot study of synbiotic supplementation on breast milk mineral concentrations and growth of exclusively breast fed infants

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ABSTRACT

Despite the crucial role of breast milk mineral contents for health and growth of the infants, they decrease with the duration of lactation. So, this pilot study aimed to determine the effects of synbiotic supplementation on breast milk mineral composition and infants' growth. In this pilot, randomized, double-blind, placebo-controlled trial, 57 lactating mothers were randomly divided into two groups to receive a daily supplement of synbiotic ($n=30$) or a placebo ($n=27$) for 30 days. Breast milk zinc, copper, Iron, magnesium and, calcium concentrations were determined by flame atomic absorption spectrometry. Weight for age *Z*-score (WAZ) and height for age *Z*-score (HAZ) were assessed for infants. Dietary intake was collected from lactating women using the 24-h recall method. Data analyses were carried out using nutritionist IV, Epi Info and SPSS soft wares. Synbiotic supplementation led to an insignificant increase of the mean breast milk levels of zinc (from 2.44 ± 0.65 to $2.55\pm0.55\,mg\,L^{-1}$), copper (from 0.35 ± 0.24 to $0.40\pm0.26\,mg\,L^{-1}$), iron (from 0.28 ± 0.42 to $0.31\pm0.38\,mg\,L^{-1}$), magnesium (from 17.14 ± 1.35 to $17.17\pm1.09\,mg\,L^{-1}$), and calcium (from 189 ± 25.3 to $189.9\pm21.7\,mg\,L^{-1}$); whilst in the placebo group, these variables decreased significantly ($P=0.001$). The observed changes between two groups were statistically significant ($P<0.05$). Although WAZ and HAZ of infants increased slightly in the supplemented group (from 1.19 ± 0.79 to 1.20 ± 0.69 and 0.36 ± 0.86 to 0.37 ± 0.85 respectively), these two parameters decreased in the placebo group which was significant only for WAZ ($P=0.01$). Moreover, no significant association was found between mineral intake and breast milk mineral contents. It seems, synbiotic supplementation may have positive effects on breast milk mineral contents.

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Introduction

Human milk is a complex mixture of nutrients that is recommended by world health organization as the ideal food for growth of infants [1,2].

Breast milk composition including minerals can be affected by numerous factors such as maternal health and nutritional status, lactation phase and probably dietary and supplements intake [1]. Among these factors, the influence of maternal dietary and supplements intake on milk composition is of interest for maternal health and infant nutrition [3]. It has been reported that some supplements intake during lactation not only improve maternal health, but also increase milk quality and infant's growth. One of these supplements that is becoming increasingly popular for pregnant or lactating women is probiotics or synbiotics [3–5].

Probiotics are defined as: "Live microorganisms, which when administered in adequate amounts confer a health benefit on the host". The term "synbiotic" is used sometimes to describe products that contain both probiotics and prebiotics [6,7]. Over the past years, the evaluation of the positive effects of probiotics and synbiotics has become an area of increasing interest [3]. Based on previous animal and human studies, supplementations of these dietary components during lactation have improved breast milk composition, infants' health and growth [3,4]. Several animal studies in the past 10 years reported the beneficial effects of these supplements on mineral absorption in the intestine and serum

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mineral content [6,7]. It is supposed that supplementation during lactation may have positive effects on breast milk mineral content and infants' growth.

Considering the importance of breast milk mineral content in infants' growth and the widespread deficiency reported in Iran and the most of other developing countries [1,8,9], this study aimed to evaluate the effect of synbiotic supplementation on breast milk mineral composition and infants' growth.

Materials and methods

In this randomized clinical double-blind, placebo-controlled trial, seventy lactating women were selected from urban areas of Tabriz, Iran who exclusively breast-fed their infants aged 90–120 days, in April 2014. The research sample included all mothers in a defined population of urban health centers who were admitted for their infants' vaccination.

Mothers were included if they had child who was full term with a normal birth weight between 2500 and 4000 g and exclusively breastfed for 3 months. The exclusion criteria for mothers and infants were having clinical evidence of chronic illness or gastrointestinal disorders or if they had received trace elements, antioxidants, probiotic or synbiotic supplements, antibiotics and corticosteroids in the month preceding the recruitment.

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Science and registered in the registration center for clinical trials in Iran (code: IRCT201110181197N12). All subjects were informed about the content of the study and a written informed consent was obtained.

The volunteer mothers were randomly divided into two groups to receive a daily supplement of synbiotic or a placebo (rice starch). The synbiotic supplement contained the freeze-dried *Lactobacillus acidophilus* PXN 35, *Lactobacillus casei* PXN 37, *Lactobacillus bulgaricus* PXN 39, *Lactobacillus rhamnosus* PXN 54, *Streptococcus thermophilus* PXN 66, *Bifidobacterium breve* PXN 25, *Bifidobacterium longum* PXN 30 and fructooligosaccharide (as documented by the manufacturer, Protexin, Probiotics International Ltd, Somerset, UK).

During the intervention period, the experimental group was supplemented with two synbiotic capsules/day, which contained different probiotic strains (2.0×10^8 CFU) and fructooligosaccharide (394 mg) 30 min after dinner for 30 days. As a measure of agreement compliance, unused supplements were counted by an independent investigator. A computer-generated random sequence mentioned to the random allocation of subjects to study groups was kept in a remote secure situation and conducted by an independent third party, who was not involved with the clinical conduct of study until all study data were collected and certified. Lactating mothers and those involved in enrolling participants, administering interventions, evaluating outcomes, and analyzing data were blind to group assignments.

Data collection from mothers and infants

Demographic data (i.e. age), and clinical data (i.e. health status) were obtained through interview at the onset and end of the intervention. Information on food intake was collected by using a 24 h recall method for 2 days and food record questionnaire for 1 day before the supplementation and at the end of the study. Dietary intake of subjects was analyzed by nutritionist IV software program.

Maternal and infants anthropometric indices were measured at the onset and end of the study. Body weight of mothers was measured with barefoot and light clothing to the nearest 0.1 kg with a Seca scale. Height of subjects was measured with barefoot and using an amounted tape with the subject's arm hanging freely at their sides and recorded to the nearest 0.5 cm. The body mass index (BMI) for mothers was calculated as weight (kg) divided by height (m^2).

Infants' body weight, height and head circumference were measured by precisely calibrated instruments (body weight measurement by Soehnle electronic scales, max wt. 20 kg, accurate to 10 g; height measurement by a stadiometer from Schorr Industries; head circumference measurement by a plasticized non-elastic measuring tape accurate to 1 mm). Weight for age *Z*-score (WAZ) and Height for age *Z*-score (HAZ) were analyzed by EPIINFO (2007) software program.

Determination of trace elements in breast milk

Breast milk (15 ml) samples were collected into metal free tubes by self-expression early in the morning before the infants' first feeding after discarding the first 5 ccml. The samples were kept at 4 °C and then transferred to metal-free, screw-cap plastic tubes and frozen within 1 day at −80 °C before extraction. Breast milk samples were wet-ashed and analyzed according to Clegg et al. [10]. Samples were melted, mixed thoroughly, and digested in ultrapure concentrated nitric acid (Fisher, Los Angeles) at room temperature for 1 h and then at sub boiling temperature for 5–6 h. Zinc, copper, iron, magnesium and calcium concentrations were determined by flame atomic absorption spectrometry (Chem Tech Analytical-2000 A.A.A.).

Statistical analyses

Statistical analyses were performed with SPSS version 16 software. Results are presented as mean and SD or SEM values. Normal distribution of data was analyzed with the Kolmogorov–Smirnov test. The comparison between groups was made by independent sample *t*-test for quantitative data and χ^2 test for qualitative data. The changes between variables in each group before and after the intervention were compared by paired *t*-test for quantitative data and McNemar test for qualitative data. Multiple linear regressions were used to analyze association between different factors (age, BMI, energy, carbohydrate, protein, fat and minerals intake) and minerals status in milk. All of the tests were performed 2-sided and a P value < 0.05 was considered statistically significant.

Results

70 individuals were enrolled in the study. Eight mothers in the placebo group and 5 in the synbiotic group did not complete the study because of having the gastrointestinal problems, or antibiotic and mineral treatment of mothers or infants. Hence, the data were analyzed for total 57 subjects (synbiotic group: $n = 30$; placebo group: $n = 27$). As presented in Table 1, no significant differences in maternal age, type of delivery, infants' gender, and anthropometric measures (age, BMI, weight, and height) were observed at the baseline between the study groups ($P > 0.05$). Maternal BMI increased in the synbiotic group and decreased in the placebo group which was not significant ($P > 0.05$).

There were no significant differences at the baseline mean daily total energy, macronutrients, and minerals intake between the synbiotic and placebo groups ($P > 0.05$). As shown in Table 2, the mean intake of energy, carbohydrate, protein decreased in the placebo group, which was significant only for energy and carbohydrate at the end of the intervention; however, these variables increased slightly in the synbiotic group. Furthermore, the mean daily dietary intake of zinc, copper, iron, and magnesium increased in the synbiotic group and decreased in the placebo group at the end of the study which was not significant (Table 2).

Table 1
General and anthropometric characteristics at baseline in the study groups.

	Synbiotic group ($n=30$)	Placebo group ($n=27$)	*P*-value
Mothers' age (mean ± SD)	26.34 ± 5.3	27.52 ± 5.3	0.42[a]
Delivery, spontaneous/ cesarean, *n*	12/18	8/19	0.37/0.86[b]
Mothers' weight (kg)	72.09 ± 11.5	70.28 ± 10.5	0.55[a]
Mothers height (cm)	157.7 ± 5.6	158.5 ± 4.4	0.58[a]
BMI (kg/m^2)	28.67 ± 4.4	27.59 ± 3.7	0.33[a]
Infants' gender, male/female, *n*	14/16	16/11	0.57/0.25[b]
WAZ	1.19 ± 0.79	1.37 ± 0.75	0.61[a]
HAZ	0.36 ± 0.86	0.49 ± 0.85	0.08[a]
Head circumference (cm)	39.90 ± 2.31	40.53 ± 1.52	0.22[a]

[a] Independent *t*-test.
[b] χ^2 test.

No significant differences were observed in the baseline mean breast milk concentrations of zinc, copper, iron, magnesium and calcium between the synbiotic and placebo groups ($P>0.05$). The mean breast milk concentrations of minerals in both study groups are compared in Table 3. The total mean breast milk zinc, copper, iron, magnesium, and calcium levels were 2.39 ± 0.72 mg L^{-1}, 0.37 ± 0.33 mg L^{-1}, 0.32 ± 0.36 mg L^{-1}, 17.03 ± 1.05 mg L^{-1}, and 192 ± 21.3 mg L^{-1}; respectively. No significant correlation was observed in the baseline total mean breast milk minerals content and dietary intake. The mean breast milk levels of zinc, copper, iron, magnesium and calcium increased in the synbiotic group which was not significant; however, in the placebo group, the mean levels of minerals decreased significantly ($P=0.001$). As presented in Table 4, significant changes were observed in breast milk minerals between study groups after the intervention ($P<0.05$).

The baseline infants' anthropometric measures (WAZ, HAZ and head circumference), duration of breast milk and rate of diarrhea had no significant differences in both study groups. As shown in Table 5, the mean of WAZ and HAZ increased in the synbiotic group which was not significant; however, these variables decreased in the placebo group which was significant only for WAZ. The head circumference of infants increased significantly in both groups ($P=0.001$). Duration of breast milk intake decreased significantly in the placebo group ($P=0.01$), while it increased slightly in the synbiotic group. Although the rate of diarrhea decreased significantly in the synbiotic group, it did not change significantly in the placebo group. The comparison of changes in infants' duration of breast milk intake and rate of diarrhea showed a significant difference between the two study groups after the intervention; however, there were not significant changes in WAZ, HAZ and head circumference between groups after the intervention. After adjusting for maternal age, BMI and energy, carbohydrate, protein, and lipid intake, no significant association was found between mineral intake and breast milk mineral content.

Table 4
The comparison of changes in breast milk mineral content between the two study groups after the intervention.

	Synbiotic group ($n=30$)	Placebo group ($n=27$)	*P*-value*
Zn (mg L^{-1})	+0.11	−0.6	0.02
Cu (mg L^{-1})	+0.05	−0.16	0.00
Fe (mg L^{-1})	+0.03	−0.18	0.00
Mg (mg L^{-1})	+0.03	−0.17	0.00
Ca (mg L^{-1})	+0.9	−20.1	0.00

* Independent *t*-test.

Discussion

Lactating mothers are considered as a nutritionally vulnerable group especially in developing countries. The success of lactation and also health status of infant depends on the kind of diet consumed by women during pregnancy and lactation [11].

In our study, the mean copper (0.31 ± 0.26 mg L^{-1}) and iron (0.32 ± 0.36 mg L^{-1}) levels in breast milk were in the normal ranges (0.2–0.4 mg L^{-1} and 0.3–0.9 mg L^{-1}); however, the mean

Table 2
Mean daily intake of total energy, and minerals in both study groups before and after the intervention.

	Synbiotic group ($n=30$)		*P*-value*	Placebo group ($n=27$)		*P*-value*
	Before	After		Before	After	
Energy (kcal)	2135.8 ± 100	2196.9 ± 116.5	0.77	2241.1 ± 123	2071.8 ± 124.8	0.03
Carbohydrate (g)	329.4 ± 18	346.7 ± 22.4	0.69	330.4 ± 30.3	283.4 ± 22.6	0.02
% energy	60.57 ± 1.3	61.53 ± 1.1	0.80	61.74 ± 1.8	60.5 ± 1.9	0.76
Protein (g)	68.47 ± 5	75.33 ± 5.3	0.23	73.69 ± 5	66.67 ± 6.2	0.16
% energy	12.92 ± 0.6	13.80 ± 0.7	0.61	15.23 ± 1.2	14.52 ± 1.3	0.70
Lipid (g)	63.27 ± 3.6	60.09 ± 3.7	0.34	60.32 ± 5.1	51.83 ± 4.8	0.09
% energy	26.34 ± 1.3	24.57 ± 1	0.22	23.10 ± 1.6	24.78 ± 1.8	0.78
Zn (mg/d)	8.2 ± 0.6	9.8 ± 0.8	0.10	8.8 ± 0.9	8.49 ± 0.9	0.27
Cu (mg/d)	1.16 ± 0.08	1.33 ± 0.11	0.14	1.31 ± 0.10	1.02 ± 0.11	0.10
Fe (mg/d)	13.76 ± 1.9	13.87 ± 1.7	0.82	15.77 ± 2.3	15.28 ± 2.4	0.74
Mg (mg/d)	236.7 ± 26.2	263.1 ± 28.1	0.38	266.5 ± 21	216.1 ± 22.4	0.09
Ca (mg/d)	613.6 ± 72.3	713 ± 67.6	0.10	659.4 ± 76.8	559.9 ± 70.7	0.10

* Pair *t*-test.
Values are shown as mean ± SEM.

Table 3
Breast milk concentrations of zinc, copper, iron, magnesium, and calcium in both study groups before and after the intervention.

	Synbiotic group ($n=30$)			Placebo group ($n=27$)		
	Before	After	*P*-value*	Before	After	*P*-value*
Zn (mg L^{-1})	2.44 ± 0.65	2.55 ± 0.55	0.72	2.34 ± 0.79	1.74 ± 0.79	0.00
Cu (mg L^{-1})	0.35 ± 0.24	0.40 ± 0.26	0.19	0.39 ± 0.23	0.23 ± 0.27	0.00
Fe (mg L^{-1})	0.28 ± 0.42	0.31 ± 0.38	0.84	0.36 ± 0.28	0.18 ± 0.20	0.00
Mg (mg L^{-1})	17.14 ± 1.35	17.17 ± 1.09	0.93	16.92 ± 0.75	16.22 ± 0.71	0.00
Ca (mg L^{-1})	189 ± 25.3	189.9 ± 21.7	0.93	195 ± 17.4	174.9 ± 16.6	0.00

* Pair *t*-test.
Values are shown as mean ± SEM.

Table 5
Infants' anthropometric measures in both study groups before and after the intervention.

	Synbiotic group ($n=30$)		*P-value	Placebo group ($n=27$)		*P-value
	Before	After		Before	After	
WAZ	1.19 ± 0.79	1.20 ± 0.69	0.86	1.37 ± 0.75	1.17 ± 0.73	0.01
HAZ	0.36 ± 0.86	0.37 ± 0.85	0.90	0.49 ± 0.85	0.43 ± 0.82	0.68
Head circumference (cm)	39.90 ± 2.31	41.14 ± 1.22	0.00	40.53 ± 1.52	41.63 ± 1.50	0.00
[a]Rate of diarrhea (%)	12.90%	5.54%	0.00	27.27%	27.27%	0.99
Duration of breast milk intake (min/24 h)	169.4 ± 41.3	171 ± 52.5	0.83	195.9 ± 55.1	161.9 ± 54	0.01

[*] Pair *t*-test.
[a] MC Nemar.
Values are shown as mean ± SD.

zinc ($2.39 \pm 0.72\ mg\ L^{-1}$), magnesium ($17.03 \pm 1.05\ mg\ L^{-1}$), and calcium ($192 \pm 21.3\ mg\ L^{-1}$) concentration were lower than the normal ranges ($3–5\ mg\ L^{-1}$, $30–35\ mg\ L^{-1}$, and $250–350\ mg\ L^{-1}$) [12]. Also, they were lower than the reported values from developed countries such as Austria [13], California [14] and Japan [15].

Our findings showed that the mean daily energy, zinc, magnesium, and calcium intake in lactating mothers were less than RDA recommendations [12]. In general, there is controversy in the effect of dietary intake of some minerals on breast milk mineral contents. Several studies concluded that breast milk zinc, iron, copper, magnesium, and calcium concentration were not influenced by maternal intake [16,17], while some others have reported inconsistent results [18,19]. In line with most previous studies, no associations were observed between energy, macronutrients and minerals intake and breast milk mineral levels in this research.

To the authors' knowledge, there is no study investigating the effect of synbiotic supplementation on minerals content of human milk. In previous studies it has been reported that the mineral levels of breast milk decrease during lactation [20,21]. As a pilot study, our results also indicated the significant decrease in breast milk mineral levels in the placebo group, whereas in the synbiotic group, the supplementation led to an insignificant increase of the mineral levels ($P > 0.05$). Since, in this study, no correlation was observed between mineral intake and breast milk mineral levels, it can be assumed that these positive changes could be due to synbiotic supplementation. Some studies have reported the positive effects of the probiotics and prebiotics on the serum minerals content such as zinc, copper, iron, magnesium and, calcium [6]. The results of a pooled analyses of randomized controlled studies indicated that probiotics supplementation increased the serum levels of zinc, iron and calcium in monkeys and rats [22,23]. Also, the results of other studies in animals and humans demonstrated that zinc, copper, iron, magnesium and calcium levels increased in serum by prebiotic supplements [24,25]. Moreover, other studies showed that synbiotic supplementation in pigs and rats resulted in increased iron, magnesium and calcium serum levels [6,26,27]. Also, in another study in chickens, the addition of probiotic or synbiotic increased the villus height in duodenum and consequently increased digestive and absorptive function of the intestine, expression of brush border enzymes, and nutrient transport systems [28]. Different mechanisms of probiotic and prebiotic supplements in relation to the impact on the absorption of minerals are listed. Prebiotics are selectively fermented by probiotic bacteria in the intestine, which cause an increased production of short-chain fatty acids (SCFA) particularly butyrate, which is an important energy source for colonocytes. Also prebiotics fermentation resulted in a reduction in intestinal pH, which can in turn increase mineral solubility. Moreover, SCFA stimulate mucosa cell proliferation which results in enlargement of the absorptive surface area of the intestine. In addition, fermentation of prebiotic by probiotics may affect the expression of mineral transport proteins or regulatory genes involved in the absorptive process [6,7]. The previous studies have shown that in well-nourished lactating mothers both serum and breast milk minerals content were high [29]. Besides some studies have reported that the serum and breast milk mineral content could be affected by mineral supplements especially in poor nutritional status. It seems that, the mammary gland has remarkable homeostatic mechanisms to control breast milk minerals [18,19]. Furthermore, some microorganisms (Lactic acid bacteria, bifidobacteria, and yeast) could be considered as organic matrixes for incorporation of minerals [30,31]. Also it has been reported that the organic forms of trace elements are more bioavailable than the inorganic forms [32-34]. Therefore it could be assumed that, as another mechanism, the supplemented probiotic bacteria high in mineral content could reach the mammary glands from maternal gut through an endogenous route [35] and may affect the mineral content of breast milk.

The results of our study also showed that in contrast to synbiotic group, the WAZ and HAZ decreased in the placebo group which was significant only for WAZ ($P = 0.01$). Recent animal and human studies have shown the positive effect of probiotic or synbiotic on growth of off springs. The results of an animal study indicated that rats' off spring body weight gain during two weeks of lactation were higher in mice fed on probiotic diet [36]. Also, the other study showed that the body weight and average daily weight gain were significantly increased by the dietary synbiotic compared with the control and probiotic-fed broilers [28]. For the first time the results of our study showed that synbiotics may improve infant growth when they are supplemented indirectly. Preventing the reduction of mineral levels in breast milk and increasing the duration of breast milk intake are the two plausible mechanisms affecting the growth of infants in the synbiotic group.

This study had some limitations. The serum mineral levels, mineral absorption rate, and the rate of bacterial colonization in the intestine were not analyzed, which limit our findings to determine the exact effect of synbiotic supplementation on breast milk mineral levels.

Conclusion

This pilot study showed that the administration of synbiotics may prevent the reduction of mineral levels in breast milk and improve infants' growth in the fourth month of lactation. For concise conclusion, more human studies using different species of probiotic bacteria, prebiotics, and longer duration of supplementation are needed.

Conflict of interest

None of the authors had a conflict of interest with respect to this manuscript.

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