

Regulation of Mineral and Trace Elements in Human Milk#58; Exogenous and Endogenous Factors [Lead Review Article]. Nnerdal, B. Nutrition Reviews. #169; August 2000 International Life Sciences Institute Vol 58(8): 223-229

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Abstract

Breast-fed infants are dependent on an adequate supply of minerals and trace elements for normal growth and development. For most of these elements, the mammary gland appears to have developed mechanisms to regulate their concentrations, even when the maternal diet varies considerably or maternal conditions are affected by different challenges. For some elements, however, there appears to be little or no such regulation. Increased knowledge about these mechanisms, or their absence, and to what extent they may compensate for adverse maternal

conditions, including poor nutrition, will help identify infants and women at risk for deficiencies of these nutrients.

Introduction

It is generally believed that breast-fed infants are protected against most nutrient deficiencies. Even poorly nourished women have been shown to produce milk of good nutritional quality,¹ although milk volumes in some instances may be reduced.² Even if the nutritional quality of breast milk usually is well maintained, however, the rapid growth of the infant puts high demands on the supply of nutrients, including minerals and trace elements. Most estimates of nutrient requirements of infants indicate that the intake of minerals and trace elements is low. Although high bioavailability of these nutrients in part compensates for this, it is evident that the concentrations of minerals and trace elements in breast milk need to be maintained at a certain level to meet infants' needs. This suggests that mechanisms are present in the mammary gland to assure an adequate supply to the infant. These mechanisms may be affected by various conditions in the mother, however, resulting in lower than normal concentrations of specific nutrients in her milk. Recently, there has been some concern that poor maternal nutritional status may impair normal mammary gland function, particularly the metabolic handling and/or secretion of other essential nutrients into milk.

Maternal conditions affecting breast milk mineral and trace element concentrations

can be studied by several approaches. First, the mineral and trace element status of lactating women can be assessed, and the possible correlation with breast milk mineral and trace element concentrations can be analyzed. This approach is practically possible for nutrients whose status can be accurately assessed, e.g., iron (hemoglobin, ferritin) and selenium (serum/plasma selenium, glutathione peroxidase), whereas it is difficult for elements whose status is difficult to assess, e.g., calcium, magnesium, zinc, and manganese. Second, the effect of maternal mineral and trace element intake on milk concentrations can be analyzed. Although it is often difficult to accurately assess the nutrient intake of pregnant/lactating women, it is possible to follow women with habitually low mineral or trace element intake who are given supplements. This approach has been used for calcium, iron, zinc, and selenium. Third, because the mammary gland acquires nutrients from serum for further export into milk, it is possible to study clinical conditions in women whose serum mineral or trace element concentrations are elevated or decreased. One example of this is infection, where serum copper concentrations increase and iron and zinc concentrations decrease. For each of the above-mentioned elements, this review will examine results of these approaches and discuss possible mechanisms involved in the transfer of minerals and trace elements from the mother to her breast milk.

Effect of Maternal Conditions on Minerals and Trace Elements in Human Milk

Calcium

Serum calcium is normally tightly controlled by homeostatic mechanisms, and most women would be expected to have very similar serum and milk calcium concentrations.

The concentration of calcium in human milk, however, does appear to be affected under some conditions. Whereas several studies have found no effect of maternal

calcium intake on milk calcium concentrations,^{1,3-5} a study by Greer et al.⁶ did report a positive correlation between calcium intake and milk calcium. There was no correlation between serum calcium and milk calcium, however, suggesting that factors other than circulating calcium concentrations determine milk calcium concentrations.

Interestingly, a few studies have found surprisingly low calcium concentrations in breast milk. In a study in New Guinea,⁷ poorly nourished women were found to have milk calcium concentrations of 154 mg/L, which is substantially lower than the normal level of approximately 260-340 mg/L. The women in this study had very low calcium intakes, and infants were shown to have poor skeletal calcification. Poorly nourished Pakistani women, however, were found to have milk calcium concentrations within the normal range, with a mean of 284 mg/L.⁸

For some time, it was considered likely that the study in New Guinea suffered from some methodologic problems, because milk magnesium concentrations were very low by comparison with most other studies (13.6 mg/L versus 30-40 mg/L in controls). Other studies in The Gambia⁹ and Zimbabwe,¹⁰ however, show that women indeed can have very low milk calcium concentrations. Laskey et al.⁹ showed that milk calcium in lactating rural Gambian women is considerably lower than in milk from women in the United Kingdom, 177 versus 254 mg/L at 7.5 months of lactation. Women from both The Gambia and Zimbabwe had an average of 15-20% lower breast milk calcium than British women. Interestingly, milk phosphorus concentration decreased in milk from women in the United Kingdom and Zimbabwe, whereas this was not the case in Gambian women.¹¹ As a consequence, Gambian women had a very low calcium:phosphorus ratio in their milk (1.1 at 6 months), whereas that of women in Zimbabwe (1.6 at 6 months) was intermediate between Gambian and British women (2.0 at 6 months).

Despite a low calcium intake of the Gambian women, long-term daily supplementation with generous amounts (mean of 714 mg/day) of calcium failed to affect milk calcium concentrations, even after 1.5 years of supplementation (Figure 1).¹² By contrast with these studies, women in Nepal were found to have breast milk calcium concentrations similar to those of U.S. women, despite an appreciably lower dietary intake of calcium.¹³ Thus, factors other than dietary intake of calcium are likely to cause these low concentrations. Strong conservation of bone calcium and/or hormonal regulation have been hypothesized as possible causative factors, but little is known yet about the underlying mechanisms.

Figure 1. Effect of calcium supplementation (~714 mg/day) of lactating Gambian women on milk calcium concentration. Values are means \pm SD. Source: adapted from reference 12.

Magnesium

Similar to calcium, serum magnesium concentrations are regulated by homeostatic mechanisms and most studies do not show an effect of maternal magnesium intake on milk magnesium.^{3,6} An exception to this may be women who are treated for pre-eclampsia with pharmacologic doses of magnesium.¹⁴ Such women were reported to have significantly higher milk magnesium concentrations than were control women, even though these higher levels were still within the normal range. The effect appeared to be transitory; 24 hours after termination of the treatment with magnesium sulfate, milk magnesium concentrations were similar to those of control women. The study from New Guinea⁷ was discussed above with respect to

calcium, but it should be mentioned that in contrast with calcium, dietary intake of magnesium was high. It is possible that the very low calcium intakes had an effect on whole-body and serum calcium:phosphorus ratios and that a secondary effect on magnesium in serum and milk was obtained. It is evident that more studies are needed on the interrelationship between calcium, magnesium, and phosphorus and its effect on milk levels of these nutrients.

Iron

Iron deficiency and iron deficiency anemia are very common worldwide, and the potential effect of low maternal iron status on breast milk iron concentration has been explored in lactating women. Maternal iron status assessed by hemoglobin, serum ferritin, and transferrin saturation was found not to be correlated with milk iron (Figures 2A and 2B) in a study of Swiss women.¹⁵ However, iron status of this group of women did not vary much, and none of them were anemic. Similar observations were made in a group of Nigerian women with considerably more variable iron status.¹⁶ The women were divided into three groups, "iron deficient" (Hb \leq 100 g/L), "normal," and "iron overloaded" (Hb \geq 120 g/L), but no difference in milk iron was found between groups. Transferrin saturation varied widely between groups: 6%, 27%, and 64%, respectively. A study on Malaysian women indicated that ethnicity affected milk iron, but there was no correlation between maternal iron status, as assessed by hemoglobin, serum iron, or total iron-binding capacity, and milk iron.¹⁷

Figure 2. Correlation between milk iron and (A) hemoglobin and (B) serum ferritin in lactating Swiss women. Source: adapted from reference 15.

In contrast with these studies, a study in India suggested a positive effect of maternal iron deficiency on milk iron.¹⁸ Severely anemic women (Hb \leq 80 g/L) had significantly higher milk iron concentrations than nonanemic women (Hb \geq 110 g/L). Concentrations of lactoferrin, the major iron-binding protein in human milk, were also higher in the anemic women. The number of subjects was very low, however, and samples were taken very soon after delivery (\leq 2 weeks postpartum), a period when milk iron changes dramatically depending on the volume of milk produced. It is not known whether the anemic women were given iron supplements when diagnosed, which may have increased circulating levels of iron even if it was too early to affect hemoglobin concentration.

In a study of Peruvian women, anemic women (Hb \leq 110 g/L) were found to have similar concentrations of iron and lactoferrin in colostrum (day 2 of lactation) to those of nonanemic women.¹⁹ The anemic women were given iron (100 mg daily) from day 2 to day 30 postpartum, which significantly increased their hemoglobin concentrations (from 92 to 105 g/L), but no effect on milk iron or lactoferrin was found (Table 1). Similarly, iron supplementation during pregnancy (60 mg daily) did not affect colostrum iron concentrations.²⁰ Several studies on maternal iron intake and milk iron concentration have found no correlation between these parameters.²¹

Table 1. Effect of Maternal Iron Status in Peruvian Women on Milk Iron and Lactoferrin

Although studies have investigated the potential correlation between hemoglobin or iron stores (ferritin) and milk iron, it is more likely that iron taken up by

the mammary gland is supplied by circulating iron, i.e., serum iron. We explored this possibility in women with acute infection during the early postpartum period or during established lactation (2-3 months postpartum).^{22,23} Although serum iron decreased during infection as an acute phase response, no effect on colostrum or mature milk iron concentrations was found (Table 2). Thus, it appears that milk iron is not affected by maternal iron intake or status or infection, suggesting the presence of a mechanism in the mammary gland that regulates milk iron concentrations.

Table 2. Effect of Maternal Infection on Serum and Milk Iron Concentration

Zinc

Several studies have investigated the correlation between maternal dietary intake of zinc and milk zinc but found no significant correlation.^{1,21} Because the concentration of zinc in breast milk decreases precipitously during lactation, it was believed that low maternal zinc status had a negative effect on milk zinc concentrations. However, lactating well-nourished women given daily supplements of zinc had milk zinc levels similar to unsupplemented women (Figures 3A and 3B) even though serum zinc concentrations increased significantly.^{24,25}

In a recent study of Peruvian women given zinc supplements 20,²⁶ daily during pregnancy and the first week of lactation, no effect was found on colostrum zinc or milk zinc at 1 or 3 months of lactation. The unsupplemented women had low plasma zinc concentrations, and even if no signs of zinc deficiency were observed, it is likely that their zinc status was low. This suggests that marginal maternal zinc status does not affect milk zinc concentrations.

Figure 3. Effect of zinc supplementation of lactating U.S. women on (A) serum zinc concentration and (B) milk zinc concentration. Source: adapted from reference 24.

The mammary gland is likely to acquire zinc from the plasma pool, and low plasma zinc may therefore affect milk zinc. In our study of Peruvian women with acute infection during early or established lactation,^{22,23} serum zinc concentrations decreased significantly as an acute phase response, but no effect on milk zinc concentration was found. Thus, similar to milk iron concentrations, there appears to be a mechanism that regulates breast milk zinc concentrations.

Copper, Manganese, and Chromium

There are very few studies on the effect of maternal copper, manganese, or chromium intake or status on milk concentrations of these elements. No effect of dietary intake of copper on milk copper has been observed.^{1,21} In one study, maternal dietary manganese intake was found to be correlated with breast milk manganese.²⁷ It should be noted, however, that human milk manganese concentrations

are very low (4-8 $\mu\text{g/L}$) and difficult to analyze accurately and that the database for the manganese content of various food items is limited. Further studies are needed on this potential correlation. There have been no studies on the effect of maternal copper or manganese supplementation on breast milk copper or manganese. The concentration of chromium in breast milk does not appear to be affected by maternal chromium intake.²⁸ In our study of Peruvian women with

acute infection during lactation,^{22,23} serum copper increased significantly, but there was no effect on milk copper. Thus, it appears that circulating copper concentrations do not affect milk copper and that a regulatory mechanism exists.

Selenium

Maternal selenium status has been shown to be closely correlated with milk selenium.^{29,30} Studies in areas with low selenium intake (e.g., Finland, New Zealand, and China) have shown that women in these regions have lower than normal concentrations of serum and milk selenium.²⁹ Dietary habits have also been shown to influence milk selenium concentrations.³¹ Studies in The Gambia showed that maternal nutrition affects breast milk selenium concentrations and that parity has an effect.³² It is known that soil selenium affects selenium concentrations in plants and animals raised on this soil and that selenium status of subjects will be strongly affected by dietary selenium.³³ Selenium supplementation by women in low-selenium areas has been shown to increase milk concentrations considerably.²⁹ Both inorganic (selenite) and organic (yeast) forms of selenium were effective, with the latter possibly being better utilized (Figures 4A and 4B). Because milk selenium concentrations are closely correlated with circulating levels of selenium, it is unlikely that there is a mechanism regulating mammary gland selenium uptake and its export into milk.

Figure 4. Effect of selenium supplementation of lactating Finnish women on (A) serum selenium concentration and (B) milk selenium concentration. Note: * p < 0.016; ** p < 0.003; and *** p < 0.0003. Source: adapted from reference 29.

Mechanisms Regulating Minerals and Trace Elements in Milk

It is evident that mechanisms exist in the mammary gland that can regulate concentrations of iron and zinc in milk. This regulation may occur at two different sites: either at the uptake of trace elements from serum by the mammary epithelial cell or at the synthesis and secretion of milk from the gland. Control at the uptake phase appears more plausible because the cell otherwise may increase/deplete its trace element content.

Iron

Because most cell types use transferrin receptors (TfRs) to regulate cellular iron concentrations, we explored the involvement of mammary gland TfRs in milk iron regulation in an animal model. We found a correlation between the declining trend in milk iron concentration during lactation and mammary gland TfR concentrations,³⁴ suggesting an involvement of TfRs in normal physiologic changes during lactation. We also studied the effect of maternal iron intake and status on milk iron and TfRs.³⁵ The results from this study are more complicated to interpret. Iron-deficient rats had lower milk iron concentrations compared with controls. This was accompanied by higher mammary TfR concentrations, suggesting up-regulation to compensate for the low iron content. Rats fed high-iron diets had even higher mammary TfR concentrations compared with controls, however, although milk iron concentrations were similar.

It should be mentioned that rats may not be an ideal model to study the effects of maternal iron status on milk iron because iron status in this species does affect milk iron concentration, which is not the case in humans. This is likely owing to the strong "drain" imposed on the dam by around-the-clock nursing of

12-16 pups ingesting milk high in iron. However, there is no reason to believe that the mechanisms underlying the acquisition of iron from serum and the secretion of iron into milk are fundamentally different between these species. Thus, it is likely that studies on the regulation of milk iron concentrations performed in rats are valid.

Zinc

The mechanism by which cells acquire zinc has not yet been established. Zinc in serum is transported by α_2 -macroglobulin (α_2 M) and serum albumin, although some (1-2%) zinc is loosely attached to amino acids. Serum albumin binds zinc nonspecifically, and to date there has been no evidence of this protein delivering zinc to the cell. Since α_2 M binds four atoms of zinc with high affinity, we hypothesized that this protein is involved in the delivery of zinc to the cell. We found that the binding of α_2 M to human mammary epithelial cells in culture is specific and saturable, which is indicative of a receptor-mediated mechanism.³⁶ We also found that the mRNA for the α_2 M receptor is expressed in the mammary cells, suggesting that this is a mechanism to deliver zinc to this cell type. The quantitative significance of this pathway for mammary cell acquisition of zinc is not yet known, nor do we yet have conclusive data on the effect of media or cellular zinc concentration on α_2 M receptor expression, which is important for an understanding of regulatory mechanisms. We have recently explored the regulation of milk zinc in a rat model. Rats were fed a low-zinc diet through lactation only or through pregnancy and lactation, or were fed a control diet throughout.³⁷ Although liver zinc concentration was significantly lower in dams fed the low-zinc diet, mammary gland zinc and milk zinc were not affected, suggesting that under conditions of maternal zinc deficiency/marginal zinc intake, milk zinc concentrations are maintained. It is possible that maternal α_2 M receptors are involved in this regulation.

Factors That May Adversely Affect Milk Mineral and Trace Element Concentrations

Very little is known about cases in which concentrations of trace elements in milk are abnormally low. We have, however, studied several cases of women who had significantly lower concentrations of breast milk zinc compared with women with normal concentrations at the same stage of lactation (Figure 5). Most of these cases were women delivering infants prematurely; however, cases have also been found in women delivering at term.³⁸ We analyzed the concentrations of protein, lipid, and carbohydrate, as well as other trace elements such as iron and copper, and found them all to be within the normal range. Further, concentrations of ligands binding zinc in milk were found to be normal. It is not yet known why milk zinc was specifically low in these women, but it is possible that a zinc transporter responsible for the secretion of zinc into milk may be defective. It is possible that similar defects may exist for other trace elements, but in the case of zinc, the infants suffering the consequences of zinc deficiency are easier to find and diagnose than those suffering from iron or copper deficiency, whose signs are less specific and take longer to manifest.

Figure 5. Zinc concentration of milk from control women and women with zinc-deficient infants. Note: various symbols represent different subjects with zinc-deficient infants; darkened circle with standard errors is mean \pm SD for milk from control women. Source: adapted from reference 38.

Effect of Maternal Mineral or Trace Element Deficiency or Excess on Normal

Mammary Gland Function

Although most of the concern about lactating women having suboptimal trace element status has been related to the concentration of the particular element in milk, the possibility of an effect on mammary gland function in general needs to be considered. Latulippe et al.³⁹ have shown that iron-deficient women produce milk that is low in folate. The mechanism behind this lesion is not yet known, but it is possible that one of the steps in mammary folate uptake and/or secretion is dependent on normal iron status. Bitter et al.⁴⁰ have shown that women with high selenium intake secrete milk that is low in zinc, suggesting that selenium intake above a certain level may impair normal zinc uptake or secretion by the mammary gland.

Conclusions

It is evident that mechanisms exist that regulate milk concentrations of trace elements such as iron and zinc, although the transfer of elements like selenium appears unregulated and may be explained by passive diffusion. Little is known about the mechanisms involved in the uptake of calcium and magnesium into milk and factors affecting these mechanisms. Increased knowledge of these mechanisms may help us not only to understand the transfer of minerals and trace elements into milk under normal conditions but also to investigate the lesions behind abnormal transfer of minerals and trace elements, as well as defects in mammary gland function induced by suboptimal nutrition.

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