Whole Cow’s Milk in Early Life

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Abstract
Cow’s milk is a major food for young children. Whole cow’s milk is known to be detrimental to infants, mainly due to its low iron content. The negative association with iron status led to recommending the introduction of formula feeding in infancy during the weaning period or when breastfeeding ceased. More recently, the literature suggests that consuming whole cow’s milk in infancy has unfortunate effects on growth, especially weight acceleration and development of overweight in childhood. These issues are discussed in the following chapter. Other suggested reasons for the avoidance of whole cow’s milk in infancy are touched upon, such as milk protein allergy and high renal solute load. The hypothesis about early cow’s milk introduction in the pathology of certain diseases, mainly through the peptide β-casomorphin-7, is briefly reviewed, showing that there is no clear evidence for the suggested associations. The chapter gives a recent example of introducing formula at 6 months of age instead of whole cow’s milk in infants’ diet in Iceland. Several aspects of consuming whole cow’s milk in infancy can be found in recent reviews.

Cow’s Milk in Infancy and Iron Deficiency

One of the most negative aspects of cow’s milk consumption in infancy is its association with diminished iron stores and increased probability of iron deficiency (ID). Iron has many important roles in the human body, and its deficiency can have a great impact. Among other things, iron plays a part in oxygen distribution, the body’s immune system and brain functions. ID in its most severe form presents as ID anemia (IDA). Chronic IDA in infancy can lead to long-term effects lasting into adolescence and adulthood [1]. Intervention early in life is therefore vital. This is especially important after the first months of life, to prevent worsening of iron status after the depletion
of iron stores from birth. Infants are born with sufficient iron stores to last for at least 4 months [2].

There has been an increased focus on the long-term effects of ID in later years. Most studies report that differences in behavior and developmental skills persist in the majority of iron-deficient anemic infants even after iron treatment [1, 3], even though it has been questioned whether social and other environmental factors may act as confounders.

Various factors control iron absorption; it can even vary considerably between individuals as it is regulated by iron status. A study of iron absorption in breastfed infants showed that children with serum ferritin <12 μg/l had significantly higher iron absorption than children with higher serum ferritin levels [4]. This is consistent with iron absorption regulation in adults [5]. Iron in food is divided into two groups, heme and non-heme iron. Heme iron is found in meat and animal-derived food. Heme iron is easily absorbed relatively independent of diet composition. Non-heme iron, on the other hand, is not so easily absorbed. Non-heme iron is influenced by several dietary factors, such as ascorbic acid (vitamin C) that enhances absorption and calcium that hinders its absorption. Several other factors like tannins, phytates, phosphates, soy protein products and various dietary fibers have been reported to inhibit non-heme iron absorption.

Protein-rich food can either increase or decrease iron absorption. The different kinds of amino acid combinations in protein are the reason for the various effects protein can have on iron absorption. Hurrel et al. [6] argued that cysteine is the only amino acid that has been demonstrated to increase iron absorption. Meat and fish are rich in cysteine, but cow’s milk is not. This suggests that cow’s milk consumption can hinder iron absorption in infants because of the amino acids in its protein construction. Additionally, whey proteins, which predominate in human milk, are more easily digested than casein protein from cow’s milk [6]. Cow’s milk proteins are also believed to induce blood loss through feces. However, this blood loss is not thought to be of clinical significance. Nevertheless, fecal blood loss is an aggravating factor of ID among infants fed cow’s milk, but not among breastfed infants [7].

**Infant Formula instead of Whole Cow’s Milk**

In the literature, unmodified cow’s milk is deemed to have great negative impact on infants’ iron status. The two relevant factors are the amount of cow’s milk consumed and the age when consumption begins. Cow’s milk and human milk are both low in iron (0.2-0.5 mg/I), but the bioavailability of iron from human milk is more favorable for an infant’s intestine than iron from cow’s milk. Human milk is a much better choice than cow’s milk for infants. Moreover, breastfeeding for 25 weeks or more has been shown to positively impact hemoglobin level [8]. However, prolonged exclusive breastfeeding (>6 months) has been associated with ID [9]. Others have concluded that ID is not of concern when cow’s milk is given to infants after 6 months of age if the complementary foods are rich in iron [10]. However, this matter is still under discussion, and the many factors associating cow’s milk with worse iron status in infancy have to be considered. Cow’s milk contains approximately four times more calcium than human milk [11], which in addition to the protein type and content of cow’s milk negatively influences iron absorption from food.

In the last century in Iceland, the custom was to give cow’s milk when breastfeeding decreased or stopped after 6 months of age. This was in accord with the official advice on infant feeding practices [12]. The study on nutrition in Icelandic infants that was carried out between 1995 and 1997 showed a high prevalence of ID, i.e. more than 40% of the children had serum ferritin values below reference (<12 μg/l), confirming an independent negative association with cow’s milk. The infants consuming more than 460 g/day of cow’s milk at 9 and 12 months were found to have lower iron status indices, indicative of deficiency [12]. An association between ID and cow’s milk consumption was still evident at 2 years of age, but when the velocity of weight growth from birth was included in the statistical model, it was the only significant predictor for ferritin [13]. Furthermore, low iron status at 1 and 2 years of age contributed to worse iron status at 6 years of age [14]. In the same children, who were longitudinally followed, worse fine motor development scores at 6 years of age were independently associated with ID at younger ages (fig. 1) [15, 16]. The observed association between lower iron stores values at 1 and 2 years of age and the children’s development scores at the age of starting school shows that the relation may be found even in populations of developed
countries with high rates of breastfeeding and, besides early whole cow's milk consumption, relatively good quality complementary feeding. Persistent effects on sleep and neurofunctions in children formerly with IDA have been suggested to contribute to reduced potential for optimal development [17].

Following this study, the recommendations for infant nutrition were modified, and from 2003 Icelandic iron-fortified follow-on milk was recommended from 6 months to 2 years of age instead of unmodified cow's milk (table 1). Since then, the iron status of Icelandic infants has improved enormously: 5.8 vs. 41% iron-depleted, 1.4 vs. 20% iron-deficient and 0 vs. 27% iron-deficient anemic [18]. This was observed in a recent study evaluating the effects of the new recommendations. The follow-on milk composition was according to the current Icelandic directive with higher iron and vitamin C content and lower calcium and protein concentrations than whole cow's milk (table 1), which led to increased intake of iron at 12 months and vitamin C at 9 months. This is therefore the most likely reason for the improvement in iron status of 12-month-old children.

**Whole Cow’s Milk and the Consequences of the High Protein Concentration**

More recently, another concern about early cow's milk consumption emerged as the high protein content of cow's milk may stimulate rapid growth in bodyweight and development of overweight. High protein intake early in life has been associated with higher body mass index (BMI) later in childhood. The study on nutrition in Icelandic infants carried out between 1995 and 1997 and the longitudinal follow-up at 6 years of age showed that boys in the highest quartile of protein intake as a percentage of energy intake at the age of 9–12 months had higher BMI (17.8 ± 2.4) at 6 years than the lowest (15.6 ± 1.0) and second lowest (15.3 ± 0.8, p = 0.01) quartiles [19]. The energy intake did not differ between the groups. In the recent Icelandic study on infant nutrition, the protein intake at 9 and 12 months of age had decreased compared to the one 10 years earlier. However, the protein intake (g/kg) at 9 months was positively related to weight growth velocity from 8 to 12 months (r = 0.20, p = 0.019) but not to length gain (r = 0.134, p = 0.124). Protein intake was still higher for non-breastfed infants, compared with a breastfed reference group (table 2). It has been suggested that the association between high protein intake early in life and adiposity later in childhood is mediated through increased IGF-I concentration [20]. Results from another study also suggest that high protein intake increases IGF-I concentrations in healthy infants who have no signs of malnutrition, and whose protein intakes far exceed requirements [21]. The increased IGF-I concentration can then increase muscle mass and adipose tissue and therefore lead to higher BMI. A large European study, European Childhood Obesity Project, indicated that feeding infants with formula with reduced protein content could normalize growth relative to a breastfed reference group and that modification of infant feeding practice has important potential for long-term health promotion [22].

Cow’s milk protein has been shown to have various negative effects on infants’ health. Besides the mentioned effects, i.e. that protein fractions in cow’s milk may have a negative effect on iron absorption [11] and may lead to overweight by a protein intake above optimal, it is a burden on several organs. Cow’s milk protein has been shown to be a significant etiological factor for constipation when consumed in high doses but also in lower doses in allergic infants and young children [23]. Furthermore, it has been shown that the high protein concentration in unmodified cow’s milk combined with an immature renal function can cause fluid losses and dehydration [24]. During illness, such as fever and diarrhea, water loss is greater through evaporation and fecal losses; therefore, water balance maintenance is of great importance to prevent dehydration. As whole cow’s milk has more protein and minerals than infants need, the excess is excreted in the urine. The high renal solute load increases the risk of negative water balance in febrile illness [25].

**Table 1.** Nutrient content of Icelandic follow-on milk and unmodified cow’s milk, and the minimum and maximum values allowed for follow-on milk composition according to Icelandic Regulation No. 735/1997 regarding follow-on milk (values are shown as a portion of 100 g).

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Icelandic follow-on milk</th>
<th>Whole milk</th>
<th>Min. for follow-on milk</th>
<th>Max. for follow-on milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kJ (kcal)</td>
<td>280 (67)</td>
<td>280 (67)</td>
<td>251 (60)</td>
<td>335 (80)</td>
</tr>
<tr>
<td>Protein, g</td>
<td>1.8</td>
<td>3.4</td>
<td>1.55</td>
<td>3.6</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>7.2</td>
<td>4.5</td>
<td>4.2</td>
<td>11.2</td>
</tr>
<tr>
<td>Fat, g</td>
<td>3.5</td>
<td>3.9</td>
<td>1.98</td>
<td>5.2</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>0.75</td>
<td></td>
<td>0.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>90</td>
<td>114</td>
<td>47.25</td>
<td>126</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>9</td>
<td></td>
<td>4.8</td>
<td>–</td>
</tr>
<tr>
<td>Vitamin D, µg</td>
<td>1.2</td>
<td></td>
<td>0.6</td>
<td>2.4</td>
</tr>
</tbody>
</table>

**Table 2.** Estimated protein intake in g/kg per day (mean ± SD) and the energy percentage (E%) from protein of breastfed and non-breastfed infants [18].

<table>
<thead>
<tr>
<th>Age</th>
<th>Breastfed E%</th>
<th>n</th>
<th>Non-breastfed E%</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months</td>
<td>2.33 ± 0.78</td>
<td>75</td>
<td>2.83 ± 0.80</td>
<td>75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 months</td>
<td>2.91 ± 1.21</td>
<td>29</td>
<td>3.30 ± 1.14</td>
<td>119</td>
<td>NS</td>
</tr>
</tbody>
</table>
Icelanders generally consume high levels of protein, and this also applies to infants.

The previous tradition of cow's milk consumption among Icelandic infants during the second half of infancy, along with the high initiation rate and long duration of breastfeeding among Icelandic mothers, made Iceland different from its neighboring countries. As mentioned, in 2003 the current recommendation on infant nutrition was launched, recommending Icelandic follow-on milk from 6 months to 2 years of age. The protein content of Icelandic follow-on milk is more similar to breast milk than unmodified cow's milk as it contains 1.8 g of protein per 100 g, as compared to an average 1.3 g of protein per 100 g in breast milk and 3.4 g per 100 g in Icelandic cow's milk (table 1).

Allergy and Cow's Milk Protein

Cow's milk protein is the most frequently encountered dietary allergen in infancy when the immune system is relatively immature and susceptible to sensitization from environmental antigens. The prevalence in early childhood is 2-5%, but decreases to 0.1-0.5% in adulthood. The majority of affected infants acquire natural tolerance to cow's milk protein before the age of 3 years. However, around 20% of patients will remain allergic for a longer period. The best prevention for cow's milk allergy is breastfeeding; however, exclusive breastfeeding does not completely eliminate the risk since traces of cow's milk protein can be transferred into the milk from the mother's diet. Allergies to milk can be classified into immunoglobulin E (IgE)-mediated allergy and non-IgE-mediated allergy. Non-IgE-mediated immune reactions are not as well defined as the former and more difficult to recognize. Correct diagnosis of cow's milk allergy is crucial since restricted diet can reduce the quality of life and lead to serious detrimental effects, especially in infants and young children [26]. β-Lactoglobulin is the major whey protein in cow's milk, but it is not expressed by the human mammary gland, and is one of the proteins involved in allergic reactions to cow's milk [27].

Cow's Milk and Less Evident Hypothesis on Diabetes Type 1 and Autism

Some studies have found a statistical association between type 1 diabetes and early introduction of cow's milk. However, such an association is not observed in all studies. The potential association was the issue of a scientific report by EFSA on the potential health impact of β-casomorphins and related peptides [28]. Several studies have investigated distinct cow's milk proteins to identify the possible diabetogenic factors in milk. The suggested milk antigens are, for example, bovine serum albumin (BSA), bovine insulin, β-lactoglobulin and β-casein and fractions thereof. The role of BSA in type 1 diabetes was questioned since several authors could not confirm specifically enhanced humoral or cellular responses to BSA in diabetic patients compared with controls. When genetic risk determinants were included, antibodies to BSA, β-lactoglobulin, whole cow's milk and islet cell antibodies were not independently associated with the risk of type 1 diabetes in a multivariate, logistic regression analysis. Elevated levels of antibodies to β-casein were demonstrated in some patients with type 1 diabetes, but not in others. The role of β-casein as a causative factor in diabetes development remains unclear. A diabetogenicity of β-casein A1, A2 and B has been suggested. Ecological studies have linked β-casomorphins, derived from β-casein A1 and B, with type 1 diabetes. Ecological studies have the shortcoming of being unable to establish cause-effect relationships, and they cannot adjust for possible confounding factors. They may indicate a hypothesis but do not demonstrate cause-effect relationships. The content of β-casein A1 + B in milk produced in the observed countries with high or low prevalence of type 1 diabetes does not explain differences in occurrence of type 1 diabetes. Based on the EFSA review of available scientific literature, a cause-effect relationship between the oral intake of β-casomorphins or related peptides and etiology of diabetes cannot of course be established.

Other dietary risk factors for type 1 diabetes include diet at a young age, i.e. use of soy milk formulas, consumption of wheat or gluten toxic chemicals and high growth rate have also been proposed as risk factors. Preschool day care has been suggested as protective. That theory has been linked to the age-dependent modifying influence of infections on the developing immune system. Dietary risk factors seem to be important in type 1 diabetes, but clear evidence is lacking.

A link between β-casomorphins and disorders of the central nervous system has also been suggested in the literature — autism, ventilation disorders and sudden infant death syndrome. The assumption is that β-casomorphins might be absorbed from the infant's gastrointestinal tract, and pass easily through the blood-brain barrier because of the infant's immature central nervous system. It has not been possible to prove these assumptions. The hypothesis is that in infants with abnormal respiratory control and vagal nerve development, opioid peptides derived from milk might induce depression of the brainstem respiratory centers, leading to apnea and sudden infant death. However, infants fed either formulas or human milk have a similar risk of developing sudden infant death syndrome, which does not support the hypothesis. Therefore, no evidence for such a relationship could be found during the review. Based on a hypothesis about genetically based peptidase deficiency and increased intestinal permeability, it has been suggested that casein-derived peptides are associated with autism. However, recent data do not provide any support for such a relationship.
Conclusions

The evidence for avoidance of whole cow's milk in infancy mainly involves the risk of iron insufficiency and its consequences among infants receiving high amounts of cow's milk. Additionally, there is discussion of whether children given whole cow's milk early in life have accelerated growth and are more likely to develop overweight and obesity in childhood than their peers. These theories seem to gain support from recent studies. High protein intake following milk consumption is thought to be the main reason for this association. The high protein and mineral concentration are also reasons for possible adverse effects on water balance among sick infants with fever. The evidence, if any linking cow's milk to diabetes and serious illness originating in the central nervous system are weak and should not be regarded as a public health concern. Well-established evidence-based guidance should be promoted and all possible research encouraged, increasing the value of infant nutrition recommendations. A recent review described the determinants for early introduction of cow's milk, i.e., mother's low education and socioeconomic status and not following the main guidelines for infant nutrition [29], indicating that research is needed to increase the likelihood of compliance with the recommendations.

References

18. Thorisdottir I, Thorisdottir AV, Palsson G: Improved iron status by revised recommendations in infant nutrition – prospective cross-national cohorts.

Discussion

Dr. Manage: I would like to know your view on giving diluted cow's milk to infants before the age of 6 months.

Dr. Thorisdottir: Before the age of 6 months, if the mother is not able to breastfeed her child, it's usually recommended to use infant formula, which has a lower protein content than cow's milk. Diluted cow's milk sweetened with sugar was used many years ago.

Dr. Sarwar Ferdaus: On the Asian subcontinent, most of the children develop lactose deficiency by the age of 3 years. So if children are fed milk right from the beginning and then again milk from the age of 6 months, these children will develop lactose deficiency and suffer from diarrheal disease or constipation if they continue to be fed with cow's milk. Moreover, they never develop proper food habits even after the age of 5 or 6 years and only consume milk. The other thing is that if the child consumes more than 400 or 500 ml a day, he/she will develop intestinal bleeding. Ultimately the
result is iron deficiency and a total change in the food habit. Could you make a comment on that?

Dr. Thorsdottir: You are correct of course that cow's milk is associated with iron deficiency. There are many reasons for that. It's both the low content and bioavailability of iron in cow's milk; also the high calcium content in cow's milk is related to bad absorption, so there are several reasons for the development of iron deficiency and iron deficiency anemia. Regarding allergy, if we are looking at various possibilities that iron given to those that already have adequate iron status has an adverse effect. This is the first study I have seen with iron fortification having an adverse effect on growth. We have to be aware that we need to subdivide these populations; virtually all studies on iron fortification or iron supplementation have been done in populations where iron status is relatively low, and therefore you can expect a positive outcome when giving iron. What you have to do is to subdivide your cohort into those who are iron replete from the beginning and those who are iron deficient, and then you can see if there is an adverse effect by giving iron to the iron-replete population. That is why we found it in Sweden as most infants were iron replete; however, in most cases, the proportion of iron replete infants is small, and if you put them together the overall outcome is likely to be positive.

Dr. Hague: My question concerns the protein content of milk, especially β-casein. You said that A1 β-casein is implicated in diabetes mellitus, so what is your suggestion for the consumption of unmodified cow's milk for the adult? The other question is, is A1 β-casein present in human milk, and if it is what is the concentration of A1 β-casein in human milk?

Dr. Thorsdottir: I think this is just an observation and we do not exactly know if there is a real association. Regarding your second question, I would guess that this has not been measured, that would be my honest answer. Casein in general is very low in human milk compared to cow's milk.

Dr. Hague: You mentioned that A1 β-casein is in some way related to the development of diabetes mellitus.

Dr. Thorsdottir: Yes, I mentioned it; I just showed it as an ecological observation. There is no evidence for a cause-effect relationship.

Dr. Saldana: In my country, we usually give infant formula until 1 year and then cow's milk from there on. Do you think there is enough economic and scientific evidence to continue providing children with follow-on formulas until 3 years of age?

Dr. Thorsdottir: I think this is a difficult question because in this particular population I was telling you about, we had a bad iron status also at the age of 2 years. Maybe it's remnant from the bad iron status around 1 year of age, and follow-on milk is prepared in a way that it could be recommended until the age of 2 years. The protein intake is not very low, it's 1.8 g per 100 g, and according to the general diet of the very young children at 1 year of age, you eat meat, fish, eggs and different kinds of dairy foods, so I think there is no reason to recommend the follow-on formula until the age of 2 years.

Dr. Herron: I was quite surprised to see the real good effect of the new recom- mended iron status in your country, when children have actually already had iron depletion at 12 months of age, and I think your figures are even better than we have in Sweden; we have at least a few percent using conventional criteria, which could be questioned during infancy. So my question is, do you think that the iron levels in the new follow-on formulas are too high?

Dr. Thorsdottir: According to the Codex, they are still low, but anyway it's different from the former status, and I think it was discussed a lot before this was decided. We had to be within the Codex regulation above the minimum, but of course I cannot really answer this question.
Thorsdottir/Thorisdottir

*Dr. Okai Brako:* If we talk about whole cow’s milk, are we talking about pasteurized cow’s milk or milk straight from the cow?

*Dr. Thorsdottir:* Pasteurized cow’s milk.

*Dr. Bhattacharya:* The first question from the gentleman from Bangladesh has actually raised a very important issue. I have some experience in working in Bangladesh, and there is a huge number of children who at present in that part of the world suffer from nutrition-related problems for various complex reasons. The question he has asked contains certain answers, but I am afraid those are very robust answers, so for this forum at some point if I am given the opportunity I might try to make some comments on those issues which I believe are very important for that part of the world.

*Dr. Thorsdottir:* Concerning malnutrition in children all around the world, I think the best would be if we had some local evidence from most of the places. It’s really hard to translate the research from Iceland to your country, and we really have to admit that we want true evidence-based scientific research for each and everyone. In my opinion, and we see it from the literature, when we come to public health guidelines for infant, child and family nutrition, it’s very important to have some local information.

*Dr. Kapur:* You haven’t talked about complementary feeding from 6 months onward. What is your view on the benefits of promoting complementary feeding vs. follow on milk?

*Dr. Thorsdottir:* I think especially in the developing countries it might be wise to breastfeed exclusively as WHO has recommended until the age of 6 months. We have also followed that recommendation in the Nordic countries, but I think it’s especially important in developing countries, and weaning food has to be added gradually and slowly. I think this applies to areas all over the world. I also think the circumstances, the hygienic procedures and so on have to be as good as possible, and it might be wise to try to continue breastfeeding beyond 1 year of age, up to 2 years, and even longer if that suits the family in question. The cultural differences are so large that we cannot give out any very hard laws or regulations about complementary feeding. In general, as recommended by the WHO, it should be formula after breastfeeding and then gradually increasing porridges, fruits, vegetables and other kinds of food. But I understand, and we have seen it in the surveys, that there are cultural differences which we have to take into consideration.

**References**
