Milk and Growth in Children: Effects of Whey and Casein

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Abstract

Consumption of cow’s milk is recommended in many countries. Observational and intervention studies show that cow’s milk most likely has a positive influence on growth in children. The strongest evidence comes from observational studies and intervention studies in low-income countries, but there are also observational studies from high-income countries showing positive associations between milk intake and growth. Milk seems thus to have a specific stimulating effect on linear growth, not only in developing countries with high rates of malnutrition, but also in industrialized countries. However, it is not known which components in milk stimulate growth. Possible components are proteins, minerals, vitamins or combinations of these. Cow’s milk proteins have a high protein quality, and whey has a slightly higher quality than casein, according to some indices based on amino acid composition. Studies, mainly from sport medicine, have suggested that whey protein also has the potential to increase muscle mass. Whether whey improves body composition to a larger extent than other milk proteins is not clear. The mechanism behind a possible growth-stimulating effect of milk and milk components is likely to be through a stimulation of insulin-like growth factor-I synthesis and maybe insulin secretion. In conclusion, there is strong evidence that milk stimulates linear growth. The mechanism is not yet clear, and more intervention studies are needed to understand which components in milk are responsible for the growth stimulation. The effects of milk on linear growth and adult height may have both positive and negative long-term implications.

During the last half century, the consumption of cow’s milk has changed considerably worldwide. In some countries like China, there has been a huge increase in the intake of milk products [1]. Many countries recommend cow’s milk during childhood because it is believed that it is healthy and has a
positive influence on bone mineralization and growth. Due to the changes in milk consumption, there is a need to improve our understanding about both possible positive and negative effects of milk and milk products in different age groups.

Milk is designed by nature to stimulate and support growth in offspring, whether it is animals or humans. Milk is species specific and, for example, cow’s milk is designed by nature to support the high growth rate in calves. Cow’s milk is therefore also different from human milk which is designed to support the slower growth of infants (table 1) [2]. Cow’s milk has a content of protein and minerals needed for the high growth rate which is several times as high as the content in human breast milk [2]. Furthermore, the ratio between the milk proteins whey and casein is very different. Cow’s milk protein contains about 20% of whey and 80% of casein, while human milk contains about 60 and 40%, respectively. In infant formula based on cow’s milk, the amount of whey and casein have been adjusted to be close to the composition in human milk, because it is believed that the composition of human milk is optimal for healthy growth in infants. However, the type and content of specific proteins in the whey and casein fractions are also different in cow’s milk, compared to human milk. The principal fractions of caseins in cow’s milk are α-s1- and α-s2-caseins, β-casein and κ-casein [3]. These casein proteins are conjugated mainly with phosphate groups and bind large amounts of calcium phosphate.

Table 1. Content of energy and selected nutrients in cow’s milk, infant formula and breast milk (per 100 ml)

<table>
<thead>
<tr>
<th></th>
<th>Breast milk</th>
<th>Formula</th>
<th>Full-fat milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kJ</td>
<td>270–290</td>
<td>280–290</td>
<td>270</td>
</tr>
<tr>
<td>Energy, kcal</td>
<td>65–70</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Protein, g</td>
<td>0.9</td>
<td>1.2–1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>6.7</td>
<td>7–8</td>
<td>4.4</td>
</tr>
<tr>
<td>Oligosaccharides, g</td>
<td>1.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fat, g</td>
<td>3.5</td>
<td>3.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>20–25</td>
<td>42</td>
<td>116</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>12–14</td>
<td>21</td>
<td>93</td>
</tr>
<tr>
<td>Sodium, mg</td>
<td>12–25</td>
<td>16</td>
<td>45</td>
</tr>
<tr>
<td>Potassium, mg</td>
<td>40–55</td>
<td>55</td>
<td>144</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>0.03–0.09</td>
<td>0.4–0.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Zinc, mg</td>
<td>0.1–0.3</td>
<td>0.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Vitamin A, µg</td>
<td>30–60</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>Vitamin C, µg</td>
<td>10</td>
<td>7–9</td>
<td>1.2</td>
</tr>
<tr>
<td>Vitamin D, µg</td>
<td>0.03</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Vitamin K, µg</td>
<td>0.2–0.5</td>
<td>2.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Folic acid, µg</td>
<td>80–140</td>
<td>6.5</td>
<td>11</td>
</tr>
</tbody>
</table>

From Michaelsen et al. [2].
The major proteins in whey from cow's milk are β-lactoglobulin, α-lactalbumin, serum albumin, immunoglobulins and glycomacropeptide, while some of the minor proteins are lactoferrin, β-microglobulin, insulin-like growth factor (IGF) and γ-globulin [3]. β-Lactoglobulin is absent in human milk where α-lactalbumin is a major protein [4]. In addition to high-quality protein containing all essential amino acids, many other nutrients in milk may be related to growth (table 1) [2, 5, 6], such as calcium, magnesium, and phosphorus. Whole milk is also a good source of energy (266 kJ/100 g) and has a good balance between energy and protein, which is important for the optimal utilization of protein [4, 7].

Regulation of linear growth is complicated and not fully understood. The regulation may be different in different age groups as indicated by Karlberg's Infancy, Childhood and Puberty Growth Model (fig. 1). It discriminates between infant growth, where growth hormone is less important than during childhood growth, and the puberty growth spurt with an additional effect of sex hormones [8]. The role of nutrients may also differ in different growth periods. Several studies have shown that in low-income countries addition of animal source foods to the diet in infancy, childhood and adolescence stimulates growth. The reason could be that animal foods add components such as micronutrients and quality protein to a food with a marginal content of these
nutrients [5]. Milk contains many nutrients which may increase the nutritional value of the diet in a marginal situation [2, 5].

**Milk and Growth**

Several studies have shown that formula-fed infants have a higher growth velocity than breastfed infants especially during second half of infancy. But these studies are not randomized, and the mechanisms causing the higher growth velocity are not clear. One explanation could be the higher protein content in cow’s milk formula (1.2–1.8 g/100 ml) compared to breast milk (0.9 g/100 ml) [2].

In preschool children, only few studies are available. An intervention study from Guatemala found that energy intake and not protein intake was the most important factor for linear growth [9]. In well-nourished children, only few studies exist. In 2.5-year-old Danish children, a positive association was found between height and animal protein and milk intake [10].

There are more studies in school age children. One of the most famous is the Boyd Orr study conducted in Scotland about 80 years ago [11, 12]. The effect of whole milk, skimmed milk and biscuits with the same energy content was studied in school children aged 5–6, 8–9 and 13–14 years by comparing them with control children receiving no intervention. The growth in the two milk groups was 20% higher during the 7-month intervention period compared to controls. The biscuit group did not grow more than the control group. Furthermore, those who got a supplement of milk for an additional year continued to grow at a higher rate compared to those who did not get extra milk. As the study was conducted in the 1920s, it is likely that the children had some degree of malnutrition.

In another study from New Guinea with 7- to 13-year-old children, many of them being stunted and having a low protein intake, Lampl et al. [13] also found an effect of skimmed milk supplementation on linear growth compared to children getting margarine with similar energy content.

Older studies from the US reviewed by Hoppe et al. [5] from 1925 and 1945 also found an effect of extra milk on linear growth in deaf and blind children or children with growth failure. Similarly, a randomized intervention study with British schoolchildren aged 7–8 years also found an effect on height gain of 190 ml milk supplementation daily [14]. These children were classified as ‘disadvantaged’. In contrast, a number of other studies with school age children have found no effect of milk supplementation on height. Grillenberger et al. [15] found no difference in growth between schoolchildren supplemented with milk compared to meat in a Kenyan study. In a study with 6- to 7-year-old children conducted in England and Scotland, Cook et al. [16] found that children with free access to milk did not grow more than those with no access.
Some intervention studies have examined the effect of dairy products on bone growth [17]. Cadogan et al. [18] found an effect on bone size of one pint of milk given for 18 months to 12-year-old girls with low habitual milk intake. However, no significant effect was found on height. Similarly, Chan et al. [19] found an effect on bone mineral density of dairy products given for 12 months. However, height gain was not different between the dairy group and the control group.

The association between dairy intake and height has also been examined in observational studies. Several but not all studies have shown that milk avoiders due to, e.g., milk allergy or lactose intolerance are shorter than children drinking milk [20]. Pastoralists in Africa and Asia are normally taller than agriculturalists. An explanation could be the higher intake of milk and milk products [5]. In a newly published cohort study with young girls aged 9–14 years at baseline from throughout the US, it was examined how dairy consumption influences growth in height. The girls were followed up to year 2003. When analyzing the effect of different types of macronutrients such as non-dairy animal protein, vegetable protein, dairy fat, non-dairy animal fat and vegetable fat, the growth in height was strongest associated with dairy protein [21]. However, the effect of milk on growth may not be the same in all age groups [22]. In a study using data from NHANES 1999–2002, milk consumption was a predictor of height in age group 12–18 years but not in age group 5–11 years [22]. It was not clear why there was no effect in the 5–11 years.

A recent review from our group summarizing observational and intervention studies concluded that cow’s milk most likely has a positive influence on growth in children [5]. The strongest evidence comes from observational studies and intervention studies in low-income countries, but there are also observational studies from high-income countries showing an association between milk intake and growth. Milk seems thus to have a specific stimulating effect on linear growth, not only in developing countries with high rates of malnutrition, but also in industrialized countries.

**Whey and Casein**

It is not known which components in milk may have the growth-stimulating effects. Possible components are proteins/peptides, minerals (like calcium [23], phosphor and magnesium), vitamins or combinations of these (table 1). Bioactive peptides may be present in milk or formed during digestion of the protein. Concerning protein, the quality of various proteins is defined based on the proteins’ ability to support maximal growth. Factors like amino acid profiles, digestibility of the protein and components with biologically active or inhibiting properties may be important [24]. In relation to protein and growth, several indexes for protein quality based on the amino acid composition have been used [24]. The preferred method in human nutrition is Protein
Digestibility-Corrected Amino Acid Score [7, 24]. This index reflects the first limiting essential amino acid in relation to a reference pattern of essential amino acids. According to most of these different indices, whey has a slightly higher quality than casein. But to our knowledge it is not known to what extent this in practice influences the growth-stimulating effects of whey and casein. In a study comparing short- and long-term effects of feeding hydrolyzed protein formulas, there was no difference in linear growth up to age 6 years between children fed with whey or casein-based formulas for the first 16 weeks of life [25]. Regarding the functions of whey or casein in children, attention has been paid to the effect on gastric emptying. In clinical nutrition, faster gastric emptying when giving high amounts of whey may reduce emesis [26]. It is not clear whether the intake of so called fast (whey) or slow (casein) proteins have a different influence on linear growth. The potential differences in stimulation of IGF-I are discussed below in the section on mechanism.

**Body Composition**

Studies have suggested that whey protein has the potential to increase muscle mass [24], which may be beneficial for a healthy body composition in children. One of the hypotheses is that whey contains amino acids with a pattern very similar to muscle proteins and especially a high amount of branched-chain amino acids, which may promote protein synthesis in the muscle. Whey seems to stimulate insulin and thereby protein synthesis. Furthermore, whey has high content of arginine and lysine, which both stimulate the anabolic hormone growth hormone [24]. It is, however, not clear whether whey, casein or whole milk have the strongest effect on body composition. Most studies are from sports medicine, and have only shown an effect if the protein is taken immediately in relation to endurance training [27]. A study comparing the net leucine balance over 7 h after intake of fast (whey) or slow (casein) protein found a higher leucine balance after casein, though whey intake resulted in a much higher but shorter increase in plasma amino acids [28]. In general, the fast protein whey results in a higher whole body protein synthesis than casein, while casein reduces the proteolysis, and the total result is a higher protein retention with casein compared to whey [27]. To our knowledge, no studies have compared the effects of whey and casein on body composition in children. The constituents in whey from cow's milk also have a number of other potential beneficial functions, e.g. immune stimulation [24] which in some cases could be positive for growth.

**Mechanism**

The mechanism behind a possible growth-stimulating effect of milk is likely to be through a stimulation of IGF-I synthesis (fig. 2) [29, 30]. IGF-I has
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a central role in regulation of growth, and the secretion can be influenced by protein, energy and certain micronutrients. The effects on insulin and IGF-I were investigated in an intervention study, where 8-year-old boys were randomized to a high intake of protein either in form of meat or skimmed milk for 1 week. It was shown that milk in contrast to meat stimulate IGF-I [29] and insulin secretion [31]. For children in this age group, stimulation of insulin secretion may be positive in relation to growth as insulin is an anabolic hormone inhibiting proteolysis. It has been shown that type 1 diabetic children aged 14 (±3) years increase their growth considerably when changed from conventional to more intensive insulin therapy [32]. To further examine which fractions in milk are responsible for stimulating these growth factors, 8-year-old boys were randomized to a diet with milk-based drinks containing either whey or casein and with a high or low content of minerals (P and Ca) for 1 week. The casein fraction resulted in a 15% increase in the IGF-I concentration, but there was no effect on fasting insulin, whereas the group receiving whey had 21% increase in fasting insulin concentration but no change in IGF-I concentration. There were no interactions with or independent effects of the milk minerals [33]. It seems therefore that the natural combination of whey and casein found in milk may be better to stimulate both IGF-I and insulin. The insulinotropic effect of whey has also been found in a test meal study with healthy young adults, where the postprandial insulin response was increased after a whey meal [34]. Likewise, supplementation of meals with a high glycemic index with whey resulted in higher postprandial insulin secretion than without whey in subjects with diet-treated type 2 diabetes in the age range 27–69 years [35].

Fig. 2. Possible associations between ingestion of milk, growth and health. Modified from Hoppe et al. [5].
In conclusion, there is strong evidence that milk stimulates linear growth. The mechanism is not yet clear, and more intervention studies are needed to understand which components in milk are responsible for the growth stimulation. The effects of milk on linear growth and adult height may have both positive and negative long-term effects, as discussed in other chapters of this book.

References

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Discussion

Dr. De Beer: You gave a very elegant presentation on the use of milk and its effect on height. I would like to hear your thought about milk consumption and weight because there are a couple of publications about milk consumption and overweight, especially in the preadolescent child. Perhaps you have some comments on that?

Dr. Mølgaard: I think there are some studies saying that a higher milk intake is related to a better body composition and thereby a lower risk of obesity, but still it’s a discussion at what time you consume it. There are studies that relate early protein intake and late increase in obesity to IGF-I stimulation. Still, I am not sure the evidence is so strong for this; this was discussed earlier, and there is also an intervention study from Koletzko’s group in Munich where they compared different levels of protein related to IGF-I but also related to body composition. In this study, they found a higher BMI after 2 years, but maybe we cannot translate BMI to obesity [1].

Dr. Anderson: As was presented on Friday, whey is not as insulinotropic as perhaps came out in your presentation. When you compared meat with milk, you had the milk in that study at 1.5 l, so that’s about 55 g of protein spread out over the day. Was meat intake spread out in the same way as milk intake?

Dr. Mølgaard: I agree that this is not only a question about protein, it’s also a question about other things in milk, for example calcium, but we decided that the protein content should be the same in the two. It was an intervention where we asked the
participants to drink 1.5 l of milk or to eat 250 g of meat, and the other part of the diet was free [2]. So, in this way it’s not a strong control study, it’s very difficult to make this in small children, I think.

Dr. Anderson: My point is that they would probably drink the milk with the meals over the day and maybe just eat the meat in the evening. That would make a huge difference in insulin, depending on when the samples were taken.

Dr. Mølgaard: The samples were taken in the morning.

Dr. Giavi: Most of the hypoallergenic formulas are based on the whey protein hydrolysate. Why do we choose to exclude the casein fraction in most of the hydrolysate formulas, especially in the extensively hydrolyzed formulas?

Dr. Mølgaard: I don’t know that, there could be technical reasons.

Dr. Haschke: The reason for choosing either whey or casein has to do with cow’s milk protein allergy. Allergic reactions against the casein and the whey fraction have been described. Therefore, some producers of high-degree hydrolysates have chosen to have either hydrolyzed casein or whey as the protein source.

Dr. Melnik: I think it’s very important for us to see that the insulinotropic effect of milk resides in the whey fraction. Have you gone a step further and looked into fractionation of whey to discriminate which proteins or which fractions within the whey fraction are most insulinotropic?

Dr. Mølgaard: At the moment, we have no studies on this, but as I told you earlier we have another study with obese 12- to 15-year-old boys and girls where we compare the same amount of whey, casein, skimmed milk or water in a 3-month intervention study. We plan to include 200 children, and in this study we will look at the metabolic profile of lipids, insulin, etc.

Dr. Martin: The gene-environment interaction on the slide you showed is very interesting because if something is known about the function of those variants, that knowledge could provide insights into the biology of IGFs or IGF receptors. Can you provide insights into why there was an interaction?

Dr. Mølgaard: I don’t know why there was an interaction, but I think IGF-II is important for early growth and also for fetal growth [3].

Dr. Martin: If that IGF-2 variant is associated with IGF-II, then that doesn’t explain the postnatal growth effects. It could be that there are other functional effects of that gene or that it has something to do with the receptor.

Dr. Mølgaard: But also maybe it could be interesting to look at IGF-I receptors.

Dr. Martin: Yes.

Dr. Prentice: It is fascinating how the human body as it is growing manages to synchronize the growth of the lean tissue and the growth of the skeleton. Many years ago, Prof. MacIntyre in London postulated that amylin amide was cosecreted with insulin and was one of the factors that promoted the deposition of calcium into bone after a meal, such that after a meal, insulin would rise because of the energy and protein, and amylin amide would rise because of the bone-forming minerals [4]. I haven’t been able to find any information on that more recently, but I wondered if the high calcium content of whey may be part of the reason why you are seeing increases in insulin which may in fact be a proxy for other secretions that are happening at the same time?

Dr. Mølgaard: But the calcium content of whey, is not so high, it’s much higher in casein.

Dr. Prentice: But it would be soluble casein?

Dr. Mølgaard: I think it would be interesting to look more into the interaction between protein and minerals, especially calcium and phosphate.

Dr. Sankaranarayanan: Are there any comparative studies on cow’s milk and buffalo milk with reference to IGF and insulin response?

Dr. Mølgaard: I have not seen these studies.
**Dr. Sankaranarayanan:** Why shouldn't we introduce a treatment with buffalo milk? It is supposed to be better than goat milk.

**Dr. Mølgaard:** It could be important to also make studies with milk from other species.

**Dr. Klassen:** Just a small comment on that, I do not know all published data, but I do know from internal analyses that there are some differences in the amino acid profile between buffalo and cow's milk, but I am not sure that it would explain any differences in the effects compared to cow's milk. As far as I know, it is a practice in India to mix cow's milk with buffalo milk, so I wonder if consequently one would see any marked differences compared to cow's milk.

**Dr. Boukari:** You said that milk with whey or casein showed an effect in children aged 12–18 years but not in children aged 5–11 years. Do you have an explanation for this?

**Dr. Mølgaard:** No, it was the study from the US, and I don’t think they themselves have any explanation. Still, it was interesting that the main determinant of height in this group was energy intake [5].

**Dr. Boukari:** Do you think we can extrapolate the conclusions of 1-week intervention studies, such as the one you did, to real life?

**Dr. Mølgaard:** I am not sure because to be honest it would be very nice if we had enough money and enough children who agree to drink a certain amount of milk for a longer period. In our new study now with 12-year-olds, we give these different milk products for 3 months and hope to see more lasting effects. Still, 3 months is a very short period in a whole life. I agree with you, I don’t think we can say that if you consume whey for a long period you will have very high insulin.

**Dr. Michaelsen:** The effect we saw on insulin with milk compared to meat might be a semi-acute effect because we don’t see it in cross-sectional studies when comparing milk and meat intake with fasting insulin. We did not want to give high amounts of milk for a long period for ethical reasons, but wanted to study the mechanisms short-term.

**Dr. De Beer:** My question relates to the previous speaker’s comment. You saw insulin’s trophic effect after consumption of high volumes of milk (1.5 l a day). In real life, we recommend maybe 2 glasses or 500 ml of milk a day to children. Do you expect to see the same trophic effect of insulin or some of the positive effects that you saw with the high consumption over a short period?

**Dr. Mølgaard:** I think that it could be an effect of a very high intake. I would not expect to see it with half a liter a day for a long period because I think there would be some mechanism to regulate it.

**Dr. Sankaranarayanan:** In the study you showed, you gave 1.5 l of milk per day or 250 g of meat to 8-year-old children. It’s a high intake of milk that never happens in real life.

**Dr. Mølgaard:** We wanted to test the biology behind this, and therefore we gave them a high dose of milk to see whether we could stimulate it. I know that it’s not a realistic intake in a normal everyday situation. It was a research study.

**Dr. Sankaranarayanan:** Are there any studies that state what milk consumption is optimal?

**Dr. Mølgaard:** I don’t think that there is a single answer for this. In our society, we recommend half a liter a day because we think that it’s a good source of calcium and also for protein, but we are also afraid that the children increase their intake to a much higher level because as we heard from Iceland the iron intake is too low and you can have anemia. We would not recommend a very high intake of milk, but in our society we recommend around half a liter a day. We don’t have strong scientific evidence that it should be exactly half a liter.
**Dr. Melnik:** I think, to answer this question, we have to differentiate between protein intake from dairy products with and without insulinotropic effects, and we also have to consider the frequent intake of yogurt as well. If you look at normal daily uptake of dairy products of young adults or adolescents, they have corn flakes in the morning with 300 ml of milk and may have a cacao drink with 100 or 200 ml, and they may consume 1 or 2 yogurts a day. So people of western civilization have an accumulated intake of insulinotropic milk proteins during the day. We observe a strong acne-promoting effect of insulinotropic milk products and high glycemic carbohydrates in adolescents, which is linked to the pathogenesis of acne [6–8].

**Dr. Mølgaard:** Our recommendation is half a liter, including all the other things.

**Dr. Martin:** I just wanted to go back to the comments about milk intake raising insulin levels and the effects of that in the long-term. Elwood et al. [9] published a systematic review of prospective studies looking at milk intake in relation to a number of outcomes. Milk intake in adulthood was inversely associated with metabolic syndrome in which insulin resistance is a component. Thus, the observational evidence suggests there is an inverse relationship in the long-term, not a positive relationship as your data would suggest.

**References**