



Dietary protein intake and quality in early life: impact on growth and obesity

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Purpose of review

Obesity is an increasing problem and high-protein intake early in life seems to increase later risk of obesity. This review summarizes recent publications in the area including observational and intervention studies and publications on underlying mechanisms.

Recent findings

Recent observational and randomized controlled trials confirmed that high-protein intake in early life seems to increase early weight gain and the risk of later overweight and obesity. Recent studies have looked at the effect of different sources of protein, and especially high-animal protein intake seems to have an effect on obesity. Specific amino acids, such as leucine, have also been implicated in increasing later obesity risk maybe via specific actions on insulin-like growth factor I. Furthermore, additional underlying mechanisms including epigenetics have been linked to long-term obesogenic programming. Finally, infants with catch-up growth or specific genotypes might be particularly vulnerable to high-protein intake.

Summary

Recent studies confirm the associations between high-protein intake during the first 2 years and later obesity. Furthermore, knowledge of the mechanisms involved and the role of different dietary protein sources and amino acids has increased, but intervention studies are needed to confirm the mechanisms. Avoiding high-protein intake in early life holds promise as a preventive strategy for childhood obesity.

Keywords

complementary feeding, growth, infancy, obesity, protein sources

INTRODUCTION

Obesity is an increasing problem worldwide and effective strategies for prevention are much needed. Early life is a period wherein potential long-term programming of health occurs [1]. There is a strong evidence that childhood obesity increases the risk of adult obesity, and thereby increases the burden of noncommunicable diseases [2]. Preventive strategies during this period might have pronounced effects on later health, and one nutritional factor that has been much examined in this period is the amount and quality of ingested protein [3–7]. Protein amount and especially quality is important for optimal growth during early life, and low-quality protein is a major cause of stunting in low-income countries. Much controversy, however, is found when looking at the levels of optimal intakes of protein. This review will focus on recent human studies (published between January 2014 and June 2016) including observational and intervention studies and articles focusing on the mechanisms behind the effects on later obesity.

PROTEIN INTAKE IN EARLY LIFE AND LATER OBESITY: RECENT EVIDENCE FROM COHORT STUDIES AND RANDOMIZED CONTROL TRIALS

Three recently published systematic reviews have focused on early life interventions and the risk of obesity with two focusing on protein content in infant formula [4,6] and one on a broad range of interventions [3]. All of them point out that the evidence seems to support avoiding high-protein formula in early life as it does support a higher growth velocity and thereby might result in an increased risk of later obesity. In the meta-analysis

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KEY POINTS

- Recent evidence support that early life nutritional interventions, especially avoiding high-protein intake might be an effective preventive strategy for childhood obesity.
- Some subgroups might be particularly sensitive to high-protein intake in early life, but more research is needed to identify this.
- Multiple mechanisms may be involved in the long-term programming of high-protein intake in early life including IGF-I signaling and epigenetic regulation.

by Patro-Golab *et al.* [6[■]] they found that infants fed a lower protein formula (range 1.1–2.1 g/100 ml) from 6 to 12 months of age had lower mean weight and weight for age z-score (WAZ) in that period compared with the higher protein formula (range 1.5–3.2 g/100 ml). Abrams *et al.* [4] also concluded that lower protein formulas (range 1.7–2.2 g/100 kcal) provided adequate protein to support normal growth, and thus using high-protein formulas (range 1.9–4.4 g/100 kcal) on the basis of supporting normal growth does not seem to be warranted. In addition, the studies with large differences in the high-protein and low-protein formulas showed the clearest differences in anthropometric outcomes compared with studies with smaller differences, suggesting that there is a dose–response effect [4]. The systematic review on randomized interventions early in life to prevent overweight and obesity [3] identified only one study comparing different levels of protein in formula, which was the Childhood Obesity Programme (CHOP) study described below. It also identified two intervention studies showing that those randomized to formula with hydrolyzed protein had a weight gain closer to the recommended than those receiving formula with intact protein. However, they concluded that it was not advisable to use hydrolyzed protein if there is not a medical reason because of the special taste and the potential adverse implications. All the meta-analysis concluded that there was limited available evidence from randomized controlled trials (RCTs) and further that there was a lack of long-term follow-up studies [3,4,6[■]].

A major study contributing to these results is the European Union CHOP study. On the basis of this study, Weber *et al.* [8[■]] showed that lower protein content of infant formula reduces BMI (0.51 BMI units increase in high protein) and obesity risk at 6 years of age (2.43 times higher risk in the high-protein group). An earlier adiposity rebound in the

high-protein group and a clear increase in the upper BMI percentiles (90th and 95th) were seen from 42 months of age [8[■]]. Compared with breastfed infants, the BMI curves were comparable in the low-protein group and no significant differences were found in mean BMI and obesity risk between these groups [even though the nominal risk was still lower among breastfed (5.2 vs. 3.6%)]. To be noticed is the high-protein content of the high-protein group (2.94 vs. 1.79 g/100 kcal in infant formula, and 4.4 vs. 2.2 g/100 kcal in follow-up formula), especially in follow-up formula. The concentration in the follow-up formula was about 80% of the concentration in cow's milk (3.5% fat). At the time of the study this was within the recommended range, but later the upper limit has been reduced to 2.5 g/100 kcal by the European Food Safety Authority (EFSA) [9].

Other intervention studies have compared formulas with lower protein content. Ziegler *et al.* [10[■]] fed a low-protein formula (1.61 g protein/100 kcal) or a control formula (2.15 g protein/100 kcal) between 3 and 12 months of age and compared with a breastfed group. A higher weight gain was found in the control formula compared with the low-protein formula (14.9 vs. 14.2 g/day); however, both groups had a higher weight gain than the breastfed group (12.6 g/day). At 12 months both formula groups had a higher weight for age than the breastfed group (WAZ = –0.06) and the low-protein formula (WAZ = 0.52) had a significantly lower WAZ than the control formula (WAZ = 0.59) [10[■]]. In addition, they found lower odds (0.40 [0.18–0.89]) of being greater than 85th percentile of WAZ score with low-protein formula compared with high protein [10[■]]. Similarly, a study including infants of overweight and obese mothers showed that low-protein formula (1.65 g protein/100 kcal) decreased weight gain (–1.34 to –0.86 difference in g/day) and BMI-z-score (1.23 vs. 1.38) compared with control formula (2.7 g protein/100 kcal) at 12 and 24 months [11[■]]. This was especially pronounced in the subgroup of obese mothers with a BMI >30 kg/m². Interestingly, the degree to which the low-protein formula decreased weight gain and BMI, made the low-protein group weight gain comparable to breastfed control infants [11[■]]. No differences in body composition [dual-energy X-ray absorptiometry (DXA)] at 12 months were found between the three groups [11[■]]. Thus, it seems important to measure body composition in future research to elucidate further details regarding early protein intake and the increased obesity risk.

A recent large observational study including twins examined the role of protein intake during the second year of life and risk of obesity at age

5 years [12²²]. They found that protein intake at 21 months of age was associated with higher BMI (0.043 BMI per 1% increase in energy% protein) and weight (0.052 kg per 1% increase in energy% protein). There was no effect on height at 3 and 5 years of age. Thus, this study supports that also during the second year of life protein intake can have an effect on later weight gain. However, they did only find trends for an increased risk of obesity with increasing protein intake, but this might be because of the low number of obese children in the cohort (12% at 3 years and 6% at 5 years), and thus a power issue. They also found that substituting protein, using mathematical models, with either carbohydrate or fat was associated with lower BMI at 3 and 5 years. This suggests a true weight promoting effect of protein and not just a difference between overall macronutrient intakes. In line with these results, the Generation R study found that protein intake at 1 year of age was associated with higher BMI (0.05 SD increase per 10 g/day increase in protein) and fat mass index (0.06 SD increase per 10 g/day increase in protein), but not fat free mass index at age 6 years [13²³]. Body composition was measured by DXA. In line with Pimpin *et al.* [12²²], they too found no differences replacing protein with carbohydrate or fats whether it was saturated, monounsaturated, or polyunsaturated also suggesting that the association between BMI, fat mass, and protein intake, is not related to a different intake of other macronutrients [13²³]. They also found the associations between protein intake and fat mass to be stronger in girls than in boys, which suggest a sex-specific effect. This also fits well with an earlier publication from the CHOP study showing a stronger effect of high-protein intake on growth factor I [insulin-like growth factor I (IGF-I)] in girls than in boys [14]. In line with this they also found sex-specific effects of high-protein intake on insulin levels, which was significant in girls but not in boys. In boys, higher protein intake was linked to lower triglyceride levels [15]. Overall they also found lower diastolic blood pressure with higher protein intake, suggesting that the cardio-metabolic risk factors might not be as clearly adversely associated with high-protein intake as seen with adiposity measures.

PREDISPOSITION TO OBESITY AND PROTEIN INTAKE: DOES GROWTH PATTERNS AND GENOTYPE MODIFY THE EFFECTS?

Some subgroups might be particularly responsive to early protein intake, for example due to their genotype or growth pattern. An interesting finding in

the Generation R study was that the positive association of protein intake with later BMI and obesity at 6 years of age was mainly present in children that had catch-up growth [13²³], suggesting that these children are especially vulnerable to excess protein. On the contrary, infants without catch-up growth were not very sensitive to high-protein intake.

In our SKOT cohorts, we could show that early weight gain (from 0 to 5 months) was associated with BMI and fat mass index at 3 years [16⁹]. However, this effect was eliminated in infants being fully breastfed for 6 months, compared with full breastfeeding for less than 1 month, supporting that there are interactions between early growth, nutrition, and risk of later adiposity, which needs to be taken into consideration.

Along with early growth patterns and sex, interactions between protein intake and genotype have also been proposed. In a combinatory analysis of approximately 16 000 boys and girls the FTO genetic variant interacted with protein intake wherein the children having both the risk allele and high-protein intake had the highest BMI [17]. However, in the Generation R study they found no interaction between protein intake and having an obesogenic genotype [13²³]. Not many studies have examined the role of genotype as a potential modifying factor of early life protein intake and obesity, and more studies are needed to elucidate if this is important.

DOES THE SOURCES OF PROTEIN MATTER FOR LATER OBESITY?

Recent evidence suggests that not only the total amount of protein but also the type of protein should be considered when examining the effects on later obesity and health. Thorisdottir *et al.* [18²⁴] found that high-animal protein intake at 12 months of age was associated with higher BMI and weight, but not on length at 6 years of age. This was not the case for vegetable protein, which seemed to have an inverse relationship with weight and BMI. Animal protein intake, especially dairy protein at 12 months in girls but not in boys was also related to IGF-I concentrations at 6 years of age suggesting a programming effect on the growth hormone (GH)-IGF axis [18²⁴]. IGF-I has been suggested to have a role in modifying risk of obesity in early life and this might be one of the mechanisms that link early protein intake and later obesity [19²⁵,20].

In line with Thorisdottir *et al.*, the Generation R study also found that animal protein but not vegetable protein was associated with increased BMI and fat mass [13²³] but they found no differences between dairy protein and protein from meats [13²³]. A systematic review and meta-analysis have

looked closer into dairy consumption and risk of childhood obesity [21], however, very few studies in young children (<2 years) were included and these were not analyzed separately. It seems that dairy intake is inversely associated with obesity in older children from age 5 and onwards [21].

In an interesting trial, 5–6-month-old breastfed infants were randomized to complementary foods primarily with meat or cereal [22[■]]. There was a higher protein intake (≈ 17 vs. 9 energy% protein) in the meat group. This led to a higher length for age z-score (LAZ) and a higher WAZ in the meat group, but there was no difference in weight for length z-score between the groups [22[■]]. This study suggests that a relatively high-protein intake from meat in breastfed infants had no immediate effects on weight for length z-score.

NEW MECHANISTIC INSIGHT: THE EFFECT OF INDIVIDUAL AMINO ACIDS IN MODULATING GROWTH AND OBESITY RISK – INSULIN-LIKE GROWTH FACTOR I STIMULATION

The mechanisms explaining the programming effect of early protein intake on adiposity are not fully understood. One of the hypotheses is that high-protein intake will increase the concentrations of amino acids, and more specifically branched-chain amino acids (BCAAs), which then increase insulin and IGF-I secretion, which are known growth stimulators through rapamycin (mammalian target of rapamycin) signaling pathway [19[■],20]. One of the hypotheses is that certain amino acids might be particularly important for these signaling pathways. Especially the BCAA leucine is proposed to be particularly potent in increasing insulin and IGF-I secretion [19[■],20]. Thus, protein sources rich in leucine, such as cow's milk, may have a central role in the early programming effects of protein intake. This is in line with a recent study finding that the low-protein group had lower IGF-I concentrations compared with a higher protein formula group but found no difference in IGF-I concentration between the low-protein group and the breastfeeding group [11[■]]. However, Putet *et al.* [23[■]] suggested that other factors than IGF-I might play a role in the link between protein intake and later obesity, since they did not find altered IGF-I levels early in life with different levels of protein (1.8 vs. 2.7 g/100 kcal). This is in line with our own results showing no clear relationship between IGF-I and early development of overweight and obesity [24].

Kirchberg *et al.* [25[■]] have examined the mechanisms of high early protein intake in more detail and they showed that high-dietary protein intake

affected amino acid and acetylcarnitine metabolism. They show that there is a breaking point for BCAA degradation, especially leucine and isoleucine, wherein increasing levels of BCAA in blood does not increase degradation which will lead to increased BCAA plasma levels. The increased BCAA in plasma would then stimulate insulin secretion and thus stimulate growth, but in addition higher leucine could lower β -oxidation of fatty acids, which was shown by higher long-chain acylcarnitines in the low protein and breastfed group, indicating increased β -oxidation [25[■]]. Altogether they propose that this could be the underlying mechanism for how high-protein diets affect metabolic regulation. Another amino acid that is also getting more attention as having potential programming effects is methionine. A recent study found positive associations between methionine intake at 1 year of age and higher BMI and android:gynoid fat ratio even after adjusting for total protein intake [26]. Methionine is of interest as it is involved in epigenetic mechanisms namely methylation reactions such as DNA methylation [27]. DNA methylation and epigenetics is proposed to be part of the mechanisms, which can explain developmental plasticity [1]. This is in line with another study showing that pathways related to methionine methylation reactions are upregulated in formula fed compared with breastfed infants, and even more in high protein formula feeding [28].

In addition, methionine might affect obesity and growth by other mechanisms than through epigenetics; methionine restriction has been shown to produce a lean phenotype and protects various rat and mice obesity models against obesity [29]. Increased energy expenditure, a change in substrate oxidation, and an altered lipid metabolism has been suggested as possible mechanisms [29] and a recent human study suggested an increase in fat oxidation after methionine restriction [30].

In Fig. 1, we have summarized some of the current hypotheses on the mechanisms behind the association between early protein intake and later obesity.

FUTURE RESEARCH

Early life interventions seem to have a powerful effect of later risk of obesity and thus deserve more attention in counteracting the obesity epidemic. Lower protein intake in early life, with possible amino acid modifications in infant formula, has thus far shown promising results as a therapeutic intervention. However, the evidence for long-term effects on the risk of obesity is still sparse and more research is needed. One thing to consider is what to replace the lower

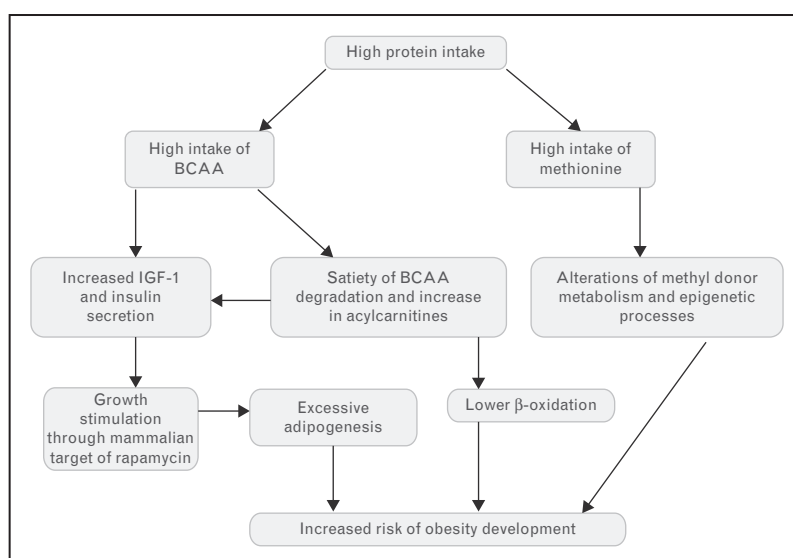


FIGURE 1. Current hypotheses on how high-protein intake in childhood might increase obesity risk. The figure was constructed based on current hypothesis [1,19^a,20,25^a,26,27].

protein content of the diet with. Should it be preferred to include more fat, especially long chain unsaturated fat or should the focus be on providing more complex carbohydrates? So far, the evidence points to that it does not matter which substitutions are made [12^{aa},13^{aa}] but this question deserves more attention. Several reviews based on ecological data and a small observational study suggest that a high fat intake protects against later obesity [31,32^a].

Care should be taken to target groups that are sensitive to high-protein intake in early life. These could include infants with a certain genotype, infants that had catch-up growth or perhaps especially girls. In addition, infants of overweight and obese mothers might also benefit more from a lower protein intake and thus slower growth. However, we have shown that maternal obesity is associated with higher protein content of the complementary diet and a general more unhealthy complementary diet suggesting that this might also be a group worth noticing [33]. These issues should be addressed in future studies. Future studies should preferably include measurements of body composition and analysis of separate effects on gender. A better understanding of these aspects is likely to improve our understanding of the mechanisms behind the association between early protein intake and later obesity.

CONCLUSION

Overall, high-dietary protein in early life has been associated with increase in later obesity. Results from RCTs seem to support this association. However, more knowledge is needed in order to understand the role of different dietary protein sources.

Furthermore, a better understanding of the mechanisms involved and which population groups are especially vulnerable to high-protein intake is needed. However, there is a need for effective preventive strategies for the obesity epidemic and it seems that avoiding high-protein intake in early life holds promise as a potential strategy.

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Conflicts of interest

There are no conflicts of interest.

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