Complementary Food: International Comparison on Protein and Energy Requirement/Intakes

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Abstract

The possible role of early dietary habits as the origin of later consequences on health has raised questions on the optimal macronutrient intakes of the growing infant. Infants and toddlers in developed countries usually show a high dietary protein:energy ratio during the complementary feeding period, averaging 2.5–3, because of the protein density of solid weaning foods and the low percentage of mothers still breastfeeding beyond the first 6 months of life. In conditions of very high protein intakes, those in the higher classes of consumption seem to carry a higher risk of becoming obese later on. Over the limit of 14% energy from proteins in the 8- to 24-month period, some mechanisms may begin to operate leading young children towards an early adiposity rebound and overweight development. On the other hand, in many developing countries the only available weaning foods are cereals, with a low protein:energy ratio value. When the protein concentration of weaning foods falls below the limits of human milk (that is, from 1 g/100 kcal to lower levels), the infants’ dietary requirements cannot be met. In planning interventions, the coverage of infants’ dietary needs through all the various world regions should be considered together with the opportunity not to exceed higher limits.

While exclusive breastfeeding is strongly recommended for the first 6 months of life [1], solids should progressively be introduced afterwards in order to complement those nutrients becoming insufficient if supplied only by human milk (particularly energy, protein, iron, zinc and fat-soluble vitamins). The process is called ‘weaning’, and represents the progressive introduction of solid foods into children’s diet in order to fulfill their changing nutritional needs [2].

The recent interest in the role of dietary proteins at early ages and the possible origin of later consequences on health (first of all the connections with
overweight and obesity development) has raised questions regarding the optimal macronutrient intakes in terms of total proteins, energy and protein:energy ratio (PER; grams protein per 100 kcal energy) required by the growing infant.

Why the Protein:Energy Ratio?

As a general rule, higher energy intakes may allow more efficient utilization of nitrogenous sources derived from catabolic processes and intakes. Therefore, protein and energy are inversely associated for recommendations within definite ranges.

An example of the operational approach to calculate the changing protein requirements in relation to different energy intakes and applied to young, healthy male adults is given in figure 1 (here PER is given in grams per 1,000 kcal) [3]. To derive a reference PER in this way, one should divide the +2SD protein requirements (i.e., the safe level of protein intake) by the average

**Fig. 1.** An example of calculation of protein:energy ratios. Distributions of both protein requirements and energy requirements are portrayed on the axes. The published average energy need and recommended protein intake are marked by arrows. The values shown are based on 1983 Canadian requirement estimates for young male adults. Partially modified from Beaton [3].
energy need (mean requirement for energy) at all ages and then compute PER values, as portrayed schematically, by selecting various arbitrary points on the distributions. Since these factors are difficult to estimate, the results are based on assumptions. This approach, even if convenient, might not seem to be logical, since it does not convey the meaning of either the protein requirements (sufficient for almost all individuals) or the average energy needs (sufficient for half the individuals). The consequent ratio involves two factors, each with its own variance [4]. Finally, the example does not include the further variable of the additional protein/energy requirements of a growing individual, which would make the model even more complicated.

Pragmatic and physiological considerations justify expressing the protein requirements in relation to energy intake for situations as diverse as weaning diets, catch-up growth, and hypercatabolic states [4]. Infants and toddlers in developed countries usually show a high dietary PER during the complementary feeding period, averaging 2.5–3, because of the protein density of solid weaning foods and the low percentage of mothers still breastfeeding beyond the first 6 months of life [5]. In conditions of very high protein intakes, those in the higher classes of consumption seem to carry a major risk to become obese later on. On the other hand, in many developing countries the only available weaning foods are cereals, with a low PER value. When the protein concentration of weaning foods falls below the limits of human milk (with a PER of <1, i.e., <1 g protein/100 kcal to lower levels), the infants’ dietary requirements cannot usually be met [6].

Protein intakes and PER values show great variability in the 6- to 24-month period, starting from around 7% energy as protein (PER = 1.7) in 6-month-old infants at the end of the exclusive breastfeeding period. Given the variability of the average protein content of human milk, in those cases in which protein supply represents less than 6% energy (PER = 1.5), within a limited energy supply, even fully breast-fed infants are likely to enter a status of negative nutrient balance [7]. Indeed, Wharton [4] has already underlined that it is ‘probably unsafe to adopt the very low protein/energy ratio in breast milk as a minimum safe standard, since the nitrogen present is utilized with unusual efficiency’ and ‘there should be caution in accepting also very low ratios of 1.7’ for those who are not breast fed.

On the other hand, high protein intakes in the complementary feeding period (from the 8th up to 24th month) are even more frequently reported in both developed and developing countries considering children from both rich and poorer classes [8–10]. From the collected data, it seems that over the limit of 14% energy from proteins (PER = 3.5) in the 8- to 24-month period some mechanisms may begin to operate leading young children towards an early adiposity rebound and overweight development, beyond any genetic predisposition. Preliminary data seem to indicate a causal role for whole cow’s milk proteins.
In the following the limits mentioned here will be discussed as far as causes, potential consequences and measures to prevent low or high dietary PER values.

**Protein, Energy and PER in Developing Countries: Old Issues and New Questions**

In most developing countries the main (or even only) weaning foods are still represented by local staple cereal foods such as maize, rice or cassava. The daily servings supplied with these cereals should match an adequate amount of milk in order to keep both the PER value higher than 1.5 and enough energy to promote anabolic processes and prevent catabolic states, also considering the rates of infections in these child populations. Since different milk sources are theoretically available, schemes have been developed in order to check the adequacy of the source of complementary foods according to the type of milk supplied in the complementary feeding period. According to Wharton [4], possible options are human milk (advantageous for the high quality of the protein content, the anti-infective properties and the functional effects, including the close mother-infant relationship), a follow-on formula (balanced as far as nutrient composition but with more protein compared to human milk and lacking its anti-infective and functional properties), and whole cow’s milk (unbalanced as far as nutrient composition for a growing infant and with the highest PER ratio). For instance, in the case rice is the (almost) exclusive staple food, and considering the PER of the milk being supplied, the protein requirements may be met when human milk provides around 70% energy, follow-on formula 50%, and cow’s milk 30%. When oil is added to rice, the energy requirements may be met at lower intakes, but at the expense of the protein intake, since also the PER value of the complementary foods is proportionally reduced.

Recently, dietary enrichment with ‘ad-hoc’ designed complementary foods and/or drinks with enhanced protein and also enhanced (even if less marked) energy content has been considered to improve the PER value of diets and prevent malnutrition. Indeed, in communities where malnutrition is endemic the 6- to 24-month period is the most critical for nutritional interventions and the introduction of specifically designed supplementary feedings can prevent the onset of wasting in a large proportion of children [11].

In progressing (‘transition’) countries the PER values of diets are higher than 2 also in disadvantaged groups (for instance, those living in rural areas) [10, 12], but they generally result from an adequate protein intake and a lower than recommended energy supply with nutritionally poor food sources. Therefore, a ‘second level’ adjustment in terms of both total energy and micronutrient balance (vitamins, minerals, trace elements) is needed. Preliminary, ‘qualitative’ reports from China raises strong suspicious that large
groups of children (either deprived of complementary foods at appropriate ages or complemented by means of low PER foods, with proteins of low biologic value) are in a negative protein/energy balance [13, 14]. Since the simple addition of micronutrients does not reverse the effects of malnutrition on growth, energy intakes should be increased by supplying foods with a high energy density and/or more frequent meals. Care should be taken to prevent the energy addition through fat and/or sugars from further reducing the protein and micronutrient density below critical limits. Therefore, interventions to improve the quality of protein sources are still urgently required also in these environments in an advanced stage of socioeconomic transition, besides specific dietary enrichments (e.g., with iron, zinc and/or liposoluble vitamins).

Finally, child populations from Asian and African countries, still suffering from both protein and energy malnutrition, should progressively be involved in processes leading to an improvement in both the supply and adequacy of foods. Within these processes, the improvement in the infants’ general health conditions (including the prevention of vertical viral transmission from mothers) should be considered in order to improve their general nutrition status.

Economic conditions (e.g., the cost of complementary foods), environmental backgrounds (e.g., availability of additional foods, microbiological safety of waters and milk), family traditions and sociocultural convictions may all influence the final dietary schedules and intakes of children in developing countries during the complementary feeding period, the discussion of which goes well beyond the scope of this presentation.

**High Protein Intakes, High PER and Obesity**

Over the last 10 years, there has been a common consensus that the average PER in the diets of children from Western countries is around 2.5–3 [3, 7, 15], in some cases reaching values close to 5 [16] (table 1). Reports from low income urban families confirm that in Western countries the protein

### Table 1. Reports of nutrient intakes in European countries in the 8- to 24-month period

<table>
<thead>
<tr>
<th>Country</th>
<th>Age months</th>
<th>Protein g/kg</th>
<th>Protein %</th>
<th>Lipid %</th>
<th>Carbohydrate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>9</td>
<td>4.4</td>
<td>15.7</td>
<td>26.4</td>
<td>58</td>
</tr>
<tr>
<td>France</td>
<td>10</td>
<td>4.3</td>
<td>15.6</td>
<td>27.1</td>
<td>57</td>
</tr>
<tr>
<td>Italy</td>
<td>12</td>
<td>5.1</td>
<td>19.5</td>
<td>30.5</td>
<td>50</td>
</tr>
<tr>
<td>Denmark</td>
<td>12–36</td>
<td>3.3</td>
<td>15</td>
<td>28</td>
<td>57</td>
</tr>
</tbody>
</table>

Partially adapted from Agostoni et al. [7].
requirements are easily met and exceeded also under poor conditions [9], even if we lack data from communities of immigrants, whose nutritional conditions should be investigated in the near future.

In general high protein intakes are believed to have an impact on the glomerular filtration rate and to increase the renal solute load, while leading to elevations in certain plasma amino acid levels with possible effects on body metabolism and the production of neurotransmitters, which has not yet been sufficiently investigated [17].

Rolland-Cachera et al. [18] were the first to propose an early adiposity rebound as a first predictor of later obesity in infants. They speculated that the age at body mass index rebound may be influenced by the amount of protein supplied in the 10- to 24-month period [19]. They investigated 112 French children who were measured for weight and length and skin-fold thickness (two sites) at 10 months, 2, 4, 6 and 8 years of age. At 2 years of age, protein intake as percent of energy was \(<14.8\%\) (PER 3.7) in the lowest quartile, 14.8–18\% \((3.7–4.5\ PER)\) in the next two quartiles and more than 18\% \((4.5\ PER)\) in the highest quartile. Significant correlations were found between the percentage of protein and both body mass index and subscapular skin-fold thickness at 8 years after adjusting for energy intake at 2 years and parental body mass index. The percentage of protein at 2 years was also negatively associated with the age at adiposity rebound. Similar results were reported in 150 Italian children, followed from birth through 5 years [20]. At 5 years, children with a body mass index above the 90th percentile had a higher protein intake (as energy percentage) at 1 year than those who were not overweight \(<90\text{th percentile})\). The protein intakes at 12 months were very high, 22 and 20\% of energy (equivalent to 5.5 and 5 PER) in both the overweight and the non-overweight groups, respectively.

On the other hand, Dorosty et al. [21], who attempted to reproduce the results of the relatively small study of Rolland-Cachera et al. [19], followed a cohort of 889 British children born in 1991 and 1992 from birth through 5 years. Ten anthropometric measurements were performed in 5 years and two 3-day dietary records were taken at 8 and 18 months of age. Dietary proteins as percent of energy intake were on average 14 \(\pm\) 2\% \((3.5 \pm 0.5\ PER)\) at 18 months in each of the three categories in which the participants were subdivided on the basis of age at adiposity rebound (very early, early, later). Only parental body mass index or obesity were significantly correlated to an early adiposity rebound. In a Danish cohort, protein intakes averaging 13 (females) to 14\% \((\text{males})\) of energy intake (PER around 3.5) were not associated with the percentage of body fat at 10 years of age [22]. Similar findings have been reported in children treated for hyper-phenylalaninemic syndromes (classic and mild forms), who showed an association between overweight at age 8 years and early adiposity rebound, but no associations with early protein intakes [23]. Also in this case the average protein intake in the mild form (with the higher protein supply) averaged 14\% of the daily energy intake (3.5
PER) and overweight was more likely in children with, rather than without, parental overweight.

**Biologic Plausibility of the Protein Hypothesis: Role of Quantity and Quality**

Commenting on the results from the study by Dorosty et al. [21], Rolland-Cachera et al. [24] have underlined that, in spite of the contrasting results on proteins, a common finding is represented by the lack of any relationship between earlier energy and fat intakes and age at adiposity rebound. Indeed, human milk, the reference food, contains a low proportion of protein (around 7% energy) and a high proportion of fat (around 50% energy). Accordingly, a rapid metabolic adaptation to low fat intakes in the complementary feeding period would make the child unprepared to face a high-fat diet later on [24].

The first explanations on the high protein – early adiposity rebound association were almost speculative and hypothesized a possible stimulating effect of dietary proteins on insulin-like growth factor-1 (IGF-1) [25], inducing both adipocyte differentiation and adipogenesis [26]. Accepting this hypothesis, we could speculate that adipocytes, differentiated early and over-stimulated, would be more prone to be filled through the years by fats deriving (either directly or after endogenous synthesis) from the high energy, high saturated fat diets commonly reported in Western children. Then, according to our previous observations, the critical point would be represented by the dietary unbalance at 8–24 months of age, when dietary proteins approaching 4–5 g/kg weight/day (around 16–20% of total energy intake, PER = 4–5) are associated with later overweight [8], while with dietary proteins below 14% energy an association is not found.

A Danish group has recently published a series of reports partly expanding these hypotheses. At 2.5 years of age the serum IGF-1 concentration of 90 Danish children was positively associated with intakes of animal proteins and milk, but not with those of vegetable proteins or meat [27]. Height was also associated with serum IGF-1 and the intakes of animal proteins and milk. The 90th percentile of protein intake in this study was 4.0 g/kg/day (around 16% of energy, PER = 4), and presumably this level matched the maximum effect on IGF-1 secretion. Further randomized studies in 8-year-old children have shown that 7 days of increased protein intakes (13–20% of the daily energy, 3.2–5 PER) by additional milk supply (but not meat) increased serum IGF-1 by around 20% [28] and fasting serum insulin levels by 100% [29]. These observations, while raising debate on the possible long-term effects in older children, put more light on the mechanisms possibly linking early over-intake of proteins (particularly from milk and dairy products), synthesis of endocrine mediators, age at adiposity rebound and later overweight.
Solutions for the high PER levels are in line, but opposed to those for malnourished children: first of all, supporting breastfeeding at least up to 12 months in order to balance not just the excess protein but also balance the other macronutrients and micronutrients; then using less protein-dense weaning foods (with a PER ideally ranging 2–3), and finally introducing an appropriate formula with ‘adjusted’ PERs when human milk is insufficient. Within this context, producers and regulatory bodies should consider the opportunity to further modulate the PER level of follow-on formulae, to counteract the apparently unavoidable trend to a high protein, high PER diet. According to recent reports, follow-on formulae with 1.3 g/l protein and 67 kcal/100 ml (with a PER close to 2) are adequate for diets in Swedish infants [30, 31]. The protein content and PER levels of follow-on formulae could be tailored further according to dietary habits differing in usual weaning foods [32].

Conclusions

Protein intakes should be maintained in the safe range of 8–12% calories (equivalent to 2–3 PER) with a diet adequate in energy and balanced for both macronutrients and micronutrients. In planning interventions, the coverage of infants’ dietary needs through all the various world regions should be considered according to local traditions, food availability and the socioeconomic backgrounds. The maintenance of breastfeeding during the introduction of solids may help to modulate the trend towards excessive dietary proteins in developed countries and the declining protein quality in the case of poorer countries. In this case, a dietary PER ranging from 1.5 to 2 could be acceptable for providing adequate energy, for the high efficiency of human milk protein utilization. For developed countries, a reassessment of the composition of complementary foods, and also follow-on formulae in the case human milk is lacking, should be considered to prevent the overload of dietary proteins. Available data suggest that above the limit of 14% energy derived from dietary proteins (3.5 PER) in the 8- to 24-month period, some mechanisms may begin to operate, beyond, or unmasking, a genetic predisposition towards the phenomenon of early adiposity rebound and overweight development.

Finally, it is tempting to speculate that differences in early feeding habits (breastfeeding vs. formula feeding) could be associated with different schedules for the introduction of solids, and differences in suggested PER values of the complementary foods.

References

Complementary Food

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Discussion

Dr. Haschke: I was most interested in your studies. I think for the work from India that you cited at the beginning, and as far as I understood they were evaluating the effect of the so-called low and high energy density supplementary foods in relation to breast milk intake, the outcome was that there was no effect. But it is my understanding that an energy density of 35 kcal/100 g is not a high-density complementary food. So the question would be: if you were to take 100 kcal/100 g, which would be really energy dense, whether there would be an influence? So were the results influenced by the study design?

Dr. Agostoni: These two studies [1, 2] have been thoroughly discussed within the editorial committee of the Journal of Pediatric Gastroenterology and Nutrition, and we finally decided to publish them due to the clear differences in intakes on the short-term (24 h), even if data on the medium or long-term effects were lacking. Nevertheless, it could represent a good starting point to consider the effects of complementary feeding on breastfeeding for developing (or better, ‘transition’) countries. Perhaps Dr. Dewey could add some information from their previous studies in Central America.

Dr. Pencharz: What you have described is really important in infancy which is great, and we have actually done some work in children with cystic fibrosis (CF). But because they are compelled to thrive, the question is how to approach that. So we did one relatively long-term study [3] published a number of years ago where the children were under the classical fat-restricted diet. We followed them for a whole year because children grow at different rates at different times of the year, and then we gave them basically high caloric milk shakes made from grocery foods of 1 cal/ml or 100 cal/100 ml, and they grew faster. In that undernourished group who were taking a low fat feeding, we were able to get them to gain weight. Working later at the Hospital for Sick Children in Toronto we did a study which we called the boost study [4], that is a proprietary product which is 1 cal/ml which can be bought from the pharmacy in North America. Quite classically undernourished CF children in clinic would be given this boost, and all we found when we studied it was that it replaced food. In the clinic this pharmacological product boost, which was high in fat, in other words about 35% of calories as fat, and is complete nutrition, just displaced food. It was only when we went to tube feeding at night that we were able to increase the total calories in 24 h.

Dr. Agostoni: I am really now interested in CF because it is a very challenging model. I think that for CF infants we now are on the way to change some older beliefs, as you already underlined. First of all, there are very good examples of the functional benefits of human milk [5]. We have unpublished data showing that prolonged breastfeeding in CF patients, regardless of the genetic form of the disease, is associated with a 20% improvement in lung function years later. Once human milk was suggested not
to be good for CF, but today we know that it is also a good source of n-3 long-chain polyunsaturated fatty acids [6] that may be beneficial for CF patients [7]. Regarding weaning in breastfed CF patients, we also have some preliminary indications [unpublished] that those who got better are those who received complementary food earlier, before 6 months, perhaps preventing some marginal form of undernutrition, in association with their increased demand.

**Dr. Dewey:** I want to come back to the energy density issue. Our study that you were referring to was comparing intakes of infants whose mothers’ milk had different fat contents and therefore different energy density. The infants were quite able to compensate for that by changing the volume that was consumed, which is consistent with what Dr. Ziegler was describing for formula-fed infants in those early studies. But I think when it comes to complementary foods we still don’t completely understand the consequences of different energy density of complementary foods on intake. My colleague Ken Brown has done quite a few studies on this, most of them with non-breastfed children. In that case, increasing energy density of the foods does tend to increase the overall energy intake, even the volume consumed decreases a little bit. But in breastfed infants there is very little information. The study you showed from India was for only 24h. There is a small study in Bangladesh [8] which used a crossover design with higher and lower energy density complementary foods. The higher energy density did increase the total energy intake but when the children in that group crossed back over to the lower energy density diet, we expected that the breast milk intakes would respond by going back up, and that didn’t occur. I think we certainly need to keep in mind that although lactation is probably very flexible in early infancy we are not sure that it is quite as flexible later on. If you have a reduction in breast milk intake you may not be able to rebound quite as easily as when the baby is young. So adding fat or increasing the intake from other foods may permanently reduce breast milk intake, which may not be a desirable consequence.

**Dr. Agostoni:** Do you mean in the second part of the first year of life, for example?

**Dr. Dewey:** Yes, after 6 months, but I would like to ask a question about the studies that you mentioned on the relationship between breastfeeding and child obesity. You mentioned the most recent meta-analysis by Owen et al. [9] and I want to make two points about that. It is very different from the other meta-analyses because it is on the mean body mass index, not the percentage overweight, and that is important because breastfeeding may be affecting both ends of the distribution, both the percentage overweight and the percentage underweight. If that is true then the mean body mass index may not change at all even if you have a reduction in the percentage overweight. The other point is that they group all the ages together in terms of when body mass index was measured later on. From my reading of the literature the relationship between breastfeeding and later obesity is strongest when you look at overweight between, for example, 6 and 14 years of age. The relationship is not very clear in early childhood and it is not very clear after about 18 years. So by putting the age groups all together I think you dilute any relationship.

**Dr. Agostoni:** First of all, I would like to take the opportunity to give my opinion. Yesterday I mentioned that there are glutamine believers and glutamine non-believers. We can say the same about breastfeeding; we are humans and therefore have our opinions, and it is sometimes difficult to adjust for this. The second point, you mentioned correctly that the preventive effects of breastfeeding on obesity are more evident in the first 6–14 years. Some years ago in the New England Journal of Medicine, there was a paper showing that overweight in adolescence predicted a broad range of adverse health effects that were independent of adult weight after 55 years of follow-up [10]. Even if we still do not know when overweight has its major negative impact on the later outcome, a prevention of overweight in adolescence could also have relevant preventive effects.
**Dr. Barclay:** I have a question about the protein-energy ratio in complementary foods. For rural regions in developing countries, if I understood you correctly, you said that there is a risk of protein deficiency during weaning. You showed on one of your slides that the minimum protein-energy ratio required during weaning is about 6–7%. Now if you look at the protein-energy ratio of cereal-based diets, rice has a protein-energy ratio of about 7–8% and cereals such as wheat about up 12–15%. A large multicentric study in Mexico, Egypt and Kenya published by Beaton et al. [11] in the early 1990s showed that for young children consuming cereal-based diets, protein deficiency was unlikely as long as the energy requirements were covered, since the protein-energy ratio of the diet would be at least 8–12%. Although the protein requirements could be somewhat higher in these regions due to higher infection rates, can we conclude that there is a risk of protein deficiency?

**Dr. Agostoni:** This is a complex question. First of all I was referring to a mixed diet, including animal and vegetal proteins. Moreover, reaching the correct limits of energy requirements could also be positive with regard to the nitrogenous balance, since the re-utilization rate could be more efficient. Third, I would like to emphasize that when you add minimal amounts of animal protein, as a source of essential amino acids, you automatically improve the nutritional efficiency of vegetable proteins, because you also supply some essential amino acids otherwise limiting if you just supply vegetal proteins. The present indications for developing countries are to find local solutions combining some animal sources of ‘exceeding’ essential amino acids together with staple cereals. It is a matter of present research to optimize interventions in this way; it is not simply the question to increase the protein-energy ratio of foods.

**Dr. Axelsson:** You showed a slide about the recommendations for Italian infants on how to introduce different complementary feedings. We start with human milk and standard infant formula, and then when we have standard infant formula we try to make it similar to human milk. Then why do we adapt it to cows’ milk, and why do we need long-term formula?

**Dr. Agostoni:** There are some discrepancies between expert opinions and the political conclusions from regulatory bodies. My personal opinion would be to put much effort into the formula for the first weeks of life, to plan a sort of ‘functional formula’ very rich in bioactive compounds, followed by a different formula for the 4–6- to 52-week period, reduced in proteins compared to actual standards. Human milk composition in Italy seems always to be the same, starting from 10–15 days of lactation up to 12 months of age, as we have shown for fat content and composition [6].

**Dr. Axelsson:** Since evolution we have been adapting; we were hunters. But why can’t we make formulas for the later part of infancy on meat?

**Dr. Agostoni:** It is interesting because this is a typical question from Sweden or Norway, also considering the changing genetic pattern with regard to lactose tolerance from the north to the south. On the evolutionary standpoint there are some basic questions still unanswered: who is the best human to adapt himself; the most intelligent; the most beautiful for reproduction? Perhaps those who were stronger adapted themselves to meat; those who were more pacifist raised cows; so we would speculate that what people have done in the evolutionary process represents the basis of some different dietary habits.

**Dr. Roggero:** I was impressed by one of your slides showing that insulin-like growth factor-1 (IGF-1) doesn’t increase when you give meat to the children. It is known that IGF-1 increases when the protein intake increases and, from the lectures of this meeting, it appears that IGF-1 is related to the level of proteins. Can you comment on that?

**Dr. Agostoni:** I can just comment on the work from Hoppe et al. [12] who didn’t find any association between insulin secretion and blood levels of branched chain amino
acids. This is the key point as leucine (the main branched chain amino acid) is a strong promoter of insulin secretion and also IGF-1. Perhaps the tertiary structure of proteins plays some role, or something else that we still don't know. So we are still far from the explanation; we only have these preliminary, yet very interesting observations.

References
