Abstract
Proteins are polymers composed of 30 or more amino acids; some of them are essential dietary components, since they are not synthetized by human metabolic processes. They are crucial for healthy growth and development and influence major functions of the body. The infant’s first year is a critical time of rapid growth and development, which must be supported by a high rate of protein synthesis. Breast milk, as a single specific food source in the first months of life, is providing the total protein and essential amino acids required. Infant formulas have been designed for infants who cannot be breastfed. They should be similar to breast milk in their composition and their functional outcomes, ensuring appropriate growth, optimal development, maturation of the immune system, easy digestion and healthy metabolic programming. By modifying their protein components, specific infant formulas have also been developed for specific needs. For example, partially hydrolyzed (prevention of atopic dermatitis) and extensively hydrolyzed or amino-acid-based infant formulas (reduction in allergy symptoms) have been designed for the management of cow’s milk protein allergy. In conclusion, proteins provided via breast milk or infant formula are essential components of the infant’s diet; therefore, the specific quality, quantity and conformation of proteins are of utmost importance for healthy growth and development.

Proteins, Peptides and Amino Acids: Definitions
Proteins, from the Greek proetios (meaning ‘first’), are a fundamental component for life. They are the second most abundant chemical compound in the body after water. Following digestion, dietary proteins are absorbed as amino acids, which then contribute to the total amino acid pool, from which the body’s
proteins are synthesized. Proteins are the main building blocks of the body and are involved in maintaining numerous body functions, in repairing or replacing cells or tissues, and in growth.

They are polymers, built from 20 different amino acids. The distinction between proteins and peptides is their size. Peptides are chains of 2–30 amino acids and proteins are peptides that consist of more than 30 amino acids. The various properties of peptides and proteins depend not only on their component amino acids and their sequence in peptide chains, but also on the way the peptide chains are stretched, coiled or folded in space in secondary structures. Proteins and large peptides adopt a geometric shape, which is referred to as tertiary structure, and finally many proteins are actually assemblies of several polypeptides, which are known as protein subunits.

Unlike other macronutrients such as fat or carbohydrates, the body does not have major protein stores. Therefore, proteins must be supplied from dietary sources. Some amino acids are essential dietary components, since they are not synthetized by human metabolic processes. All 20 amino acids are important for protein synthesis, but some can be synthetized from other metabolic precursors: they are called the nonessential amino acids. Others cannot be synthetized by the human body and then have to be supplied through nutrition: they are the essential amino acids. A third category consists of the conditionally essential amino acids; they can be synthetized by the human body except in certain conditions (e.g. trauma, stress, sepsis or surgery) when the physiological demands may result in the need for these nonessential amino acids to be greater than the body’s ability to produce them (table 1).

<table>
<thead>
<tr>
<th>Nonessential amino acids (can be synthetized by the human body)</th>
<th>Conditionally essential amino acids (can be synthetized by the human body except in certain conditions)</th>
<th>Essential amino acids (cannot be synthetized by the human body; must be supplied through nutrition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine Aspartate Glutamate</td>
<td>Arginine Asparagine Cysteine&lt;sup&gt;1&lt;/sup&gt; Glutamine Glycine Proline Serine Tyrosine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Histidine Isoleucine Leucine Lysine Methionine Phenylalanine Threonine Tryptophan Valine</td>
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<sup>1</sup> Requires essential amino acid precursors (methionine and phenylalanine).
Proteins, Peptides and Amino Acids

Proteins are nutrients essential to life. They are present in and vital to every living cell. They are essential for healthy growth and development, and also influence major functions of the body (fig. 1). In the form of skin, hair, callus, cartilage, muscles, tendons and ligaments, proteins hold together, protect and provide structure to the body. In the form of enzymes, hormones, antibodies and globulins, they catalyze, regulate and ensure proper functioning of the body. In the form of hemoglobin, myoglobin and various lipoproteins, they transport oxygen and other substances in the organism.

**Protein Needs in Infancy**

Current research is dedicated to understand the role and importance of nutrition in early postnatal life on health in later life. Optimal patterns of infant feeding are important first to support healthy growth and development in infancy but also as determinants of health in later life. It is known that inadequate nutrition and retardation of growth in infancy can result in permanent stunting as well as potentially long-lasting deficits in neurological function or metabolic health for example [1, 2].

The infant’s first year of life is a critical time of rapid growth and development. Growth and development between birth and weaning are crucial for long-term well-being. The rapid growth of the baby (the body weight of a baby dou-

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**Fig. 1.** Proteins influence all aspects of growth and development.
bles by 6 months) must be supported by a high rate of protein synthesis. The rate of protein synthesis and turnover are then exceptionally high in infants relative to their body weight. In the first month of life, they need around 3.5 times as much protein per kilogram of body weight as an adult. Although growth velocity, and thereby protein requirements, rapidly declines during the first 3 months of life, at the age of 4–6 months, infants still need more than 60%, and at 6–12 years around 40% more protein than adults per kilogram of body weight.

Requirements for proteins are expressed in terms of total proteins and individual amino acids, meaning that both the quantity and the quality of proteins supplied are important.

**Breast Milk**

The infant’s nutritional requirements in early life are primarily satisfied by a single and highly specific food source: breast milk. Human milk is recommended as the optimal nutrient source for infants and is associated with several short- and long-term benefits for child health. Health benefits of breast milk are multiple, but a reduced risk of infectious diarrhea and acute otitis media are the best documented \[3\], and evidence from developing countries demonstrates that under conditions of poor hygiene breastfeeding can be a matter of life or death \[4\]. It has also been suggested that breastfeeding is associated with a reduced risk of cardiovascular events, overweight, obesity, type 2 diabetes and disorders of the immune system, as well as with better cognitive development \[5, 6\].

There is no singular standard for breast milk composition: human milk composition is dynamic. Differences in the nutrient content of breast milk are observed within feeds, across the period of lactation (foremilk differs from hind milk, and colostrum is very different from transitional and mature milk) and between women \[7, 8\]. At least some of these changes in the composition of breast milk during lactation reflect changes in the requirements of infants, which are linked to changes in growth velocity and maturation of immunological and physiological functions. The complexity is also given by the diverse composition of breast milk. Nutrients (such as proteins, lipids, carbohydrates, minerals, vitamins and trace elements) are of high importance to meet the nutritional needs of young infants and ensure healthy normal growth and development, but human milk also contains numerous bioactive proteins and peptides including antimicrobial and immune-modulating factors, enzymes, hormones and growth factors \[9, 10\]. Several of these compounds affect the infant’s immune status, conferring a passive protection against infection, and facilitate immune development and maturation.

Although it is variable within mothers and across lactation, the macronutrient composition of human milk is conserved across populations. The mean
The macronutrient composition of mature, term milk is estimated to be approximately 0.9–1.2 g/dl for proteins, 3.2–3.6 g/dl for fat and 6.7–7.8 g/dl for lactose [11].

The proteins of human milk are divided into the whey and casein fractions comprising a large number of different proteins and peptides [12, 13]. The most abundant proteins are caseins, α-lactalbumin, lactoferrin, secretory IgA, lysozyme and serum albumin [9]. Nonprotein nitrogen-containing compounds, including urea, ureic acid, creatinine, creatine, amino acids and nucleotides, cover approximately 25% of human milk nitrogen.

Both total protein content and concentrations of individual proteins in human milk change throughout the first year of lactation to match the needs of the infant. Protein levels decrease in human milk over the first 4–6 weeks regardless of the timing of delivery (from 12–18 g/l in early milk to 8–9 g/l in mature milk) [14].

**Infant Formula**

Infant formulas have been designed for infants who cannot be breastfed. Until the 20th century, there was no safe and reliable alternative to breastfeeding. With the increasing knowledge on the composition of milk (linked to the development of techniques for chemical analyses of milk), better assessment of the energy requirements of infants and advances in dairy technology, substitutes for breast milk were developed from the milk of other mammals. Successive improvements enabled the launch of the first whey-dominant formula in 1961 and the first Codex Alimentarius standard for infant formulas was issued in 1972. Today, besides breast milk, infant formula is the only other milk product which the medical community considers nutritionally acceptable for infants under the age of 1 year (as opposed to unmodified cow’s or goat’s milk).

Protein sources and processes have been modified along the years to optimize both the quality and the quantity of proteins in infant formulas in order to be closer to the composition but also the functional outcomes of breast milk.

Modern infant formulas provide similar amino acid profiles and protein contents as those found in breast milk. The most commonly used infant formulas contain purified cow’s milk whey and casein as a protein source. The composition of milk varies according to the mammal from which it comes, providing the correct rate of growth and development for the young of that species; thus for the human infant, human milk is obviously more suitable than cow’s milk. While cow’s milk and human milk contain a similar percentage of water, the relative amount of carbohydrates, proteins, fats, vitamins and minerals varies, because they are fine tuned to meet the nutritional requirements of that particular animal (table 2). As an example, the protein content in cow’s milk (5 g/100 kcal) is more than 3 times higher than that of human milk (1.5 g/100 kcal). The ratio
between caseins and whey proteins is also very different between cow’s milk and human milk: human milk contains 30% caseins/70% whey proteins, while in cow’s milk the ratio is 80:20, respectively (table 2). Given that the amount of total protein in cow’s milk is more than double that of human milk, cow’s milk clearly contains considerably more caseins than human milk. Although cow’s milk is the basis of almost all infant formulas, plain cow’s milk is not suited for infants because of its high casein content and low whey content, which may stress infant’s immature kidneys. Therefore, unmodified cow’s milk is not recommended before the age of 12 months.

Looking at these figures (the quantity and the quality of proteins in human milk and cow’s milk), it is virtually impossible to obtain an amino acid profile similar to human milk using unmodified cow’s milk protein fractions, and, in order to do so, it would be necessary to provide more protein to ensure enough of the limiting amino acids.

To circumvent this issue, cow’s milk used for infant formula undergoes processing. This includes steps to make proteins more easily digestible and to alter the whey/casein protein balance in order to be closer to that of human milk. Improvements in the quality of the proteins (an amino acid composition similar to that of breast milk) allowed manufacturers to reduce the quantity of proteins in infant formula to better mimic the growth pattern of formula-fed infants to that of the breastfed infants. Different manufacturing processes have been developed by infant formula companies such as using sweet whey to demineralize and fractionate the proteins of sweet whey by the removal of CaseinGlycoMacroPeptides (Nestlé-patented process). Using this optimized process and protein fractions made thereof, the amino acid profile and the protein content of the infant formula (1.8 g/100 kcal) moved a further step closer to that of breast milk. The use of this type of infant formula has indeed been shown to support similar weight

| Table 2. Composition of mature breast milk and cow’s milk (in g/kg of milk) |
|---------------------|---------------------|
|                     | Breast milk         | Cow’s milk        |
| Lipids              |                     |                    |
| Proteins (% whey/% caseins) | 15 (70/30) | 35 (20/80) |
| Carbohydrates       | 70                  | 48                 |
| Minerals            |                     |                    |
| K                   | 0.51                | 1.4                |
| Na                  | 0.15                | 0.5                |
| Ca                  | 0.30                | 1.2                |
| Mg                  | 0.04                | 0.12               |
| P                   | 0.14                | 0.95               |
| Cl                  | 0.41                | 1.1                |
gain, body mass index and head circumference as observed in breastfed infants [15, 16].

Clinical data showing that lower protein content in infant formula (i.e. 1.8 g/100 kcal) has a long-term preventive impact on body mass index and obesity risk have been published very recently [17, 18]. Infant formulas with even lower protein content (1.61–1.65 g/100 kcal) have been developed and clinically proven to be adequate from 3 to 6 months of age [19, 20].

In addition to providing amino acids as building blocks for growth, milk is the source of numerous bioactive factors, proteins such as hormones, cytokines or growth factors, which are involved in multiple physiological processes. Continuous efforts are invested to better understand their biological functions in suckling infants. New technologies could be used to produce bioactive substances present in low concentrations in human milk, but absent from bovine milk, with proven effect on nutrient utilization or other health benefits. Rigorous safety and efficacy evaluations should, however, be put in place before their implementation [21].

**Specialized Infant Formula for Specific Needs**

In addition to guaranteeing healthy growth and development of bottle-fed infants, specific infant formulas have also been designed for specific needs, by modifying their protein component. As an example, three different types of infant formulas have been designed for the management of allergy to cow’s milk protein.

Allergy is an immune reaction mounted against normally harmless environmental proteins called allergens. It is a consequence of an unbalanced immune system that normally sustains active protection against harmful antigens (e.g. pathogens and toxic compounds) and does not react against ingested food, like proteins. In the gastrointestinal tract, lack of oral tolerance [22] can lead to immune-mediated gastrointestinal diseases such as food allergy, an increasingly prevalent disorder that causes significant medical and psychosocial stress for both patients and families. At present, allergy cannot be cured and the management of food allergy is based on avoidance of the offending food(s) and prompt recognition and treatment of allergic reactions resulting from an accidental exposure.

Food allergy is very common in infancy, and cow’s milk allergy is the most frequent food allergy at early age, affecting about 2.5% of infants during their first years of life [23] with skin, respiratory and/or gastrointestinal symptoms ranging from relatively mild to severe or, although rarely, life-threatening events [24]. Most children naturally outgrow their milk allergy by the age of 3 years, but in some of them milk allergy can persist until adulthood. Importantly, cow’s
Milk allergy has been associated with an increased risk of developing other forms of allergy, such as asthma, atopic dermatitis, rhinoconjunctivitis or egg allergy, later in life [25], hence the importance of preventing cow’s milk allergy.

The major milk allergens are caseins, α-lactalbumin and β-lactoglobulin, and, in most instances, patients develop an allergic response towards different cow’s milk proteins.

One way to decrease allergenicity of proteins is to disrupt the sequence or to modify the conformation of the allergenic epitopes by enzymatic hydrolysis. According to the process and degree of hydrolysis, different types of formulas can be obtained: partially (pHF) or extensively hydrolyzed formula (eHF) or amino-acid-based infant formulas (fig. 2). The differentiation between eHF and pHF is mostly established by the molecular weight profile and clinical demonstration of reduced allergenicity. Both eHF and pHF comprise a wide range of peptide sizes. In pHFs, the vast majority of the peptides are <5 kDa (with a size distribution of 3–10 kDa) while in eHFs almost all peptides have a molecular weight <3 kDa. Of note, commercially available pHFs may contain a significant percentage of peptides >6 kDa. Considering that peptides ≥3 kDa are able to elicit an allergic reaction [26], it is clear that pHFs are not intended for infants allergic to cow’s milk protein. Thus, present guidelines recommend the use of eHFs in case of cow’s milk protein allergy [27]. This most often allows infants to thrive while progressively outgrowing their cow’s milk protein allergy. However, in cases of very severe allergic reactions to cow’s milk proteins, only amino acid-based infant formulas are able to relieve symptoms since they are totally devoid of allergens.

As mentioned before, pHFs are not intended for cow’s milk protein-allergic infants. They have been developed for infants at high risk of allergy (based on a family history of atopy) to prevent onset of the disease. This is most probably
relying on the induction of oral tolerance to cow’s milk protein mediated through the interaction of specific peptides with the immune system [28, 29]. Specific pHFs have been clinically proven to prevent atopic dermatitis when used during the first 4 months in infants with a family history of allergy [30–32]. In the absence of breastfeeding, different pediatric international organizations recommend to use the clinically documented pHFs when breastfeeding is not possible. Moreover, the FDA has granted a health claim on the reduced risk of atopic dermatitis to be used for pHF.

Conclusion

Proteins provided via breast milk or infant formula are essential components of an infant’s diet not just because of their crucial importance for the first stages of growth and development in infancy but also for their effects on health in later life. Therefore, the quality, quantity and conformation of the proteins which are provided in early infancy are essential. Infant formulas should, therefore, mimic as much as possible the characteristics of breast milk proteins.

Disclosure Statement

S. Nutten is an employee of Nestec Ltd.

References