Because of the rapid rate of anabolic processes and brain growth, no patient faces a more critical need for optimal nutrition than the low birthweight (LBW) infant. Nutritional requirements of these infants, however, remain unclear. Much of the controversy centers on the question: How fast should they grow? The Committee on Nutrition of the American Academy of Pediatrics (1) has stated that: “The optimal diet for the low birthweight infant may be defined as one that supports a rate of growth approximating that of the third trimester of intra-uterine life without imposing stress on the developing metabolic and excretory systems.” Employing a factorial method, Ziegler et al. (2) summed the tissue accretion of nutrients with estimates of urinary and dermal losses and the extent of absorption to derive theoretical requirements of nutrients for infants of varying gestational ages. These calculations suggest that human milk and many formulas do not provide sufficient quantities of protein and certain minerals to support intrauterine rates of growth. In contrast, Räihä et al. (3,4) reported that preterm infants fed pooled human milk have less metabolic acidosis, low blood urea nitrogen and ammonia values, and fewer amino acid aberrations than infants fed high-protein formulas. These investigators contend that a growth rate and an accumulation of nutrients more important than those provided by human milk are not necessarily desirable. More recent studies conclude, however, that pooled breast milk is not ideal for LBW infants, since this feeding results in poorer fat absorption, a less desirable nutritional status, and slower weight gain when compared to fresh own-mother’s milk or formulas adapted for LBW infants (5-7). In this chapter, we suggest some guidelines concerning the nutritional requirements of LBW infants in the light of results of metabolic balance studies carried out by us in more than 100 preterm infants during the last 10 years.

PROTEIN

There are four major considerations affecting the quantity and quality of protein to be given to LBW infants: (a) requirements for maintenance, (b) requirements
for normal growth, (c) development of amino acid metabolism and renal function, and (d) energy intake or, more precisely, available energy for growth.

Protein intake must provide amino acids to replace the nitrogen loss resulting from protein turnover. According to studies by Pencharz et al. (8), about 12 g protein/kg are broken down and resynthesized each day in preterm infants. This protein turnover rate represents 10% of total body proteins and is three to four times greater than that observed in children or young adults. Skeletal muscle protein metabolism accounts for only 10 to 20% of whole body protein turnover in LBW infants, as opposed to 30% in adults. If we assume that the efficiency of the recycling of endogenous amino acids is 97%, this protein turnover rate leads to a nitrogen loss approximating 60 mg/kg body weight per day or 1 mg nitrogen/kcal expended. This calculation meshes with the lowest values of nitrogen urinary excretion measured in LBW infants receiving adequate energy and low protein intakes (9).

Protein requirement for new tissue synthesis can be estimated from chemical analyses of human fetal bodies of different gestational ages (10). Mean accumulation of nitrogen between 26 and 36 weeks of gestation is about 300 mg/kg/day or 2% of the weight gain, which corresponds to about 1.8 g protein/kg/day for a weight gain of 15 g/kg/day (11). The amount of protein to be given to LBW infants to achieve a nitrogen retention similar to that in utero depends on digestibility and utilization of the protein intake. In initial studies, we carried out metabolic balances in matched groups of LBW infants fed either banked human milk or various isocaloric formulas with different protein content (whey/casein ratio, 60:40). We observed that the fecal loss of nitrogen decreased with increasing postnatal age but was significantly higher in infants fed human milk than in those fed formulas (9,12). Coefficients of protein net absorption ranged from 81 to 87% with human milk as opposed to 86 to 94% with formulas.

The lower apparent digestibility of human milk proteins is probably due to the poorly degraded IgA immunoglobulins and the rapid transit time. Nevertheless, it may be concluded that even in the most premature infants, net absorption of protein is satisfactory. True digestibility of proteins from the diet is probably higher, since fecal nitrogen is partly of endogenous origin—desquamation of mucosal cells, digestive secretions, and bacterial debris. Urinary excretion of nitrogen was lowest in the LBW infants fed human milk (Table 1). It was related to nitrogen intake in those fed formulas and reached up to fourfold the value observed with human milk when protein intake was almost doubled. Nitrogen retention was about 250 mg/kg/day in the infants fed human milk or the low-protein formula, but reached only 320 mg/kg/day in those fed the high-protein formula. As a result, the coefficients of net protein utilization (nitrogen retention/nitrogen intake) were inversely related to protein intake. This means that, when protein intake increases excessively, a higher proportion is oxidized and used as a source of energy. These observations are similar to those made in studies performed in young animals. In isocaloric conditions, the response to protein supply is related to the logarithm of the intake;
TABLE 1. Nitrogen balances in LBW infants* fed human milk or isocaloric experimental formulas with various protein contents

<table>
<thead>
<tr>
<th>Nitrogen (mg/kg/day)</th>
<th>Human milk</th>
<th>Isocaloric formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>In intake</td>
<td>424 ± 32</td>
<td>415 ± 26</td>
</tr>
<tr>
<td>In feces</td>
<td>76 ± 9</td>
<td>55 ± 10</td>
</tr>
<tr>
<td>In urine</td>
<td>84 ± 12</td>
<td>115 ± 34</td>
</tr>
<tr>
<td>Retention</td>
<td>264 ± 33</td>
<td>245 ± 30</td>
</tr>
<tr>
<td>Absorption (%)</td>
<td>82 ± 4</td>
<td>87 ± 3</td>
</tr>
<tr>
<td>Retention (%)</td>
<td>62 ± 4</td>
<td>59 ± 7</td>
</tr>
</tbody>
</table>

*\( n = 20 \) in each group.

if nitrogen intake increases excessively, the increase in nitrogen retention tends to be small.

The key point in protein utilization is in fact the amount of energy available for growth (13). This amount depends on caloric intake, gut absorption, and energy expenditure. In LBW infants fed isocaloric diets, available energy varies mainly according to the importance of the steatorrhea. To investigate to what extent absorbed energy influenced nitrogen retention in our infants, we measured the net caloric supply by taking into account the fecal loss of fat. Figure 1 shows that there was a positive linear relationship between nitrogen retention and absorbed calories in all groups. However, the slope of the regression lines was sharper in the group of infants receiving a high protein intake. This means that a low calorie supply limits nitrogen retention, whereas at high caloric intakes, nitrogen retention is conditioned by protein intake.

In the light of these data, we carried out metabolic balance studies in preterm infants fed either human milk enriched in protein and energy with a semielemental diet (Alfaré, Nestlé), a human milk formula made of lyophilized bank human milk, or a LBW infant formula (Alprem, Nestlé). As shown in Table 2, nitrogen retentions similar to in utero accumulation rates were obtained with the three milks. Urinary excretions of nitrogen were only slightly higher than with human milk or the low-protein formula (see Table 1), and the coefficients of net protein utilization were satisfactory (14–16).

It is well demonstrated that too high an intake of protein may lead to a hazardous accumulation of amino acids, urea, and ammonia in LBW infants because of the immaturity of several enzymatic pathways and a low glomerular filtration rate. We previously reported the factors influencing the serum amino acid concentration in 163 LBW infants fed either parenterally or orally with human milk or adapted formulas (17–20). We observed that threonine, sulfur, and aromatic amino acid metabolism is impaired, whereas that of branched chain amino acids is enhanced in preterm infants. Low lysine concentration even with high protein intake suggests also that the lysine requirement is high or that the lysine content of formulas is not entirely available because of a Maillard reaction during heat processing.
FIG. 1. Relationship between nitrogen retention and amount of absorbed energy in LBW infants fed human milk (HM) or infant formulas (IF₁, IF₂) providing 2.5 ± 0.2, 3.0 ± 0.3, and 4.3 ± 0.3 g protein/kg/day, respectively. (From refs. 9, 12, and 14.)

From these studies on protein and amino acid metabolism, we suggest that, provided energy intake is adequate, optimal protein intake for orally fed LBW infants is about 3.2 g (500 mg nitrogen)/kg body weight/day. Essential amino acids (9,14–20) should constitute 53% of nitrogen intake.

CARBOHYDRATES

It is well known that brush border lactase activity develops later and is lower than maltase activity during fetal life (21); significant pancreatic alpha-amylase activity appears only several months after birth (22). The question arises: To what extent are LBW infants able to digest lactose and glucose polymers? Boellner et al. (23) observed a flat response curve with a delayed and lower peak of blood glucose in oral lactose tolerance tests in preterm infants during the first week of life. These results suggest that intestinal hydrolysis of lactose is relatively impaired in LBW infants during the early neonatal period. After 10 days of age, however,
TABLE 2. Nitrogen balances in LBW infants fed human milk (HM) supplemented with whey hydrolysate (WH), a human milk formula, or LBW infant formulas

<table>
<thead>
<tr>
<th>Nitrogen (mg/kg/day)</th>
<th>HM–WH* n = 20</th>
<th>HM formulab n = 13</th>
<th>LBW formulaa n = 14</th>
<th>LBW formulaa n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake</td>
<td>602 ± 40</td>
<td>553 ± 43</td>
<td>542 ± 33</td>
<td>594 ± 30</td>
</tr>
<tr>
<td>In feces</td>
<td>78 ± 15</td>
<td>105 ± 17</td>
<td>67 ± 20</td>
<td>45 ± 18</td>
</tr>
<tr>
<td>In urine</td>
<td>172 ± 23</td>
<td>132 ± 26</td>
<td>119 ± 30</td>
<td>161 ± 33</td>
</tr>
<tr>
<td>Retention</td>
<td>360 ± 52</td>
<td>317 ± 42</td>
<td>356 ± 30</td>
<td>388 ± 37</td>
</tr>
<tr>
<td>Absorption (%)</td>
<td>87 ± 5</td>
<td>81 ± 4</td>
<td>88 ± 4</td>
<td>92 ± 3</td>
</tr>
<tr>
<td>Retention (%)</td>
<td>60 ± 6</td>
<td>57 ± 5</td>
<td>66 ± 6</td>
<td>65 ± 5</td>
</tr>
</tbody>
</table>

*Pooled pasteurized human milk supplemented with 2 g/dl semielemental diet powder (Alfare, Nestlé, Switzerland).

bPooled pasteurized human milk supplemented with lyophilized skimmed milk, medium-chain triglyceride, and linoleate.

cLBW infant formulas: n = 14, Pregallia, Gallia, France; n = 20, Alprem, Nestlé, Switzerland.

oral lactose, maltose, and sucrose tolerance tests were shown to give similar rises in blood glucose in preterm infants with a mean birthweight of 1.5 kg (24).

Atkinson et al. (5) carried out metabolic balance studies in very LBW (VLBW) infants fed either own-mother’s milk or an infant formula and found net absorption of lactose ranging from 97 to 99% at the end of the first and second week of life. Metabolic balance studies, however, do not provide a true index of lactose absorption, since gut flora can metabolize lactose reaching the colon. MacLean and Fink (25) performed sequential studies of breath hydrogen excretion in response to lactose feeding in LBW infants of 29 to 38 weeks gestation. They reported that all infants were excreting large amounts of hydrogen during the first 7 weeks of life. Using the 5-hr mean hydrogen excretion, they estimated that 66% or more of ingested lactose was fermented in the colon.

Recent studies by Stevenson et al. (26), however, suggest that hydrogen production by LBW infants is not necessarily related to carbohydrate tolerance but reflects chiefly the composition of colonic flora. Cicco et al. (27) investigated the ability of LBW infants to digest glucose polymers and observed a similar glycemic response to maltodextrins or lactose oral tolerance tests in 2- to 3-week-old preterm infants; plasma insulin response, however, was significantly lower after glucose polymers feeding. These authors suggested that this could be due to a lower secretion of gastric inhibitory polypeptides.

Using a calorimetric bomb, Kien et al. (28) measured fecal energy derived from carbohydrates in two groups of VLBW infants fed a formula differing only in carbohydrate composition: 100% lactose or 50% lactose and 50% glucose polymers. The authors calculated that the coefficients of absorption of carbohydrates were similar and about 95% in both groups. Our metabolic balance studies carried out in LBW infants fed a formula providing 3.6 g/kg/day pregelatinized cornstarch
showed that starch absorption ranged between 80 and 97% (29). The good absorption of glucose polymers despite the lack of pancreatic alpha-amylase is probably due to the activity of salivary amylase and brush border glucoamylase, which have been shown to be well developed at birth (30).

In conclusion, the prematurely born infant has a reduced capacity to hydrolyze lactose only during the first days of life. The neonate is well equipped to deal with hydrolysis of sucrose, maltose, and glucose oligosaccharides. In contrast, starch digestion is limited. From a practical point of view, lactose, which has beneficial effects on absorption of minerals and composition of gut flora, must be the main source of carbohydrate in the diet of LBW infants. Maltodextrins, which have a low osmotic activity, are suitable for increasing carbohydrate intake when desired.

**FAT**

Fat malabsorption is common in LBW infants (31). The results of fat balance studies carried out in preterm infants fed various milks are shown in Fig. 2. In all groups, fat absorption improves with the increase of gestational age. Fat from pooled pasteurized human milk is no better absorbed than fat from most infant formulas. In contrast, fat from LBW infant formulas containing 40% medium chain triglycerides (Alprem, Nestlé) is well absorbed, whereas cow's milk fat is absorbed poorly.

Gas liquid chromatography of fatty acids in milk and stools showed that, whatever the milk, the longer the chain length of saturated fatty acids, the lower the coefficient of absorption; unsaturated fatty acids, such as oleic and linoleic acids, are better absorbed than their saturated homolog, stearic acid (Fig. 3). Watkins (32) has shown that the bile acid pool and the synthesis rate are much lower in preterm infants than in full-term babies or adults. As a result, bile salt concentration in duodenal fluid in LBW infants is often below the critical micellar concentration; this could explain the poor absorption of long chain saturated fatty acids.

Another factor of fat malabsorption in LBW infants is the low activity of pancreatic lipase resulting in impaired duodenal hydrolysis of triglycerides (33). Using thin layer chromatography, we observed that about 50% of fecal fat is neutral lipids. Fat absorption in LBW infants can be improved first by using raw instead of pasteurized human milk. Indeed, fresh human milk contains an active bile salt-stimulated lipase, which can contribute up to half the total lipase and esterase activity in the duodenum of preterm infants (34). Moreover, it has been shown that intraluminal concentration and pool size of bile salts are higher in preterm infants fed fresh human milk than in those fed formula (35). The practical advantage of feeding non-heat-treated human milk has been clearly demonstrated by Williamson et al. (36). These investigators showed that fat absorption is much better when preterm infants are fed raw human milk as compared to pasteurized or boiled human milk. The addition of raw breast milk to formula or pooled pasteurized human milk can also improve fat absorption (37). The particular structure of the triglycerides of breast milk (palmitic acid mainly esterified in the 2 position of the
FIG. 2. Percentage of fat absorption according to actual gestational age in LBW infants fed pasteurized pooled human milk (PAST-HM), infant formulas (IF), preterm formulas with 40% medium chain triglycerides (LBW-IF), or a cow's milk formula with 100% butter fat (CM). (From refs. 12,15,16, and 31.)
glycerol molecule) seems of less importance. Indeed, in contrast to pancreatic lipase, breast milk lipase hydrolyzes all three ester bonds in the triglycerides. In addition, it has been shown that 2-monopalmitate is not necessarily better absorbed than palmitic acid if duodenal concentration of bile salts is low (38).

In conclusion, fat malabsorption may lead to a significant fecal loss of energy in LBW infants. Steatorrhea can be minimized by the use of fresh breast milk or formulas containing medium chain triglycerides.

ENERGY

As previously reported, in order to appreciate the outcome of absorbed energy, metabolic balance studies and indirect calorimetry measurements were carried out.
in two groups of VLBW infants fed either banked human milk or a LBW infant formula (39). Energy intake varied from 100 to 130 kcal/kg/day. In all infants, about 50% of energy absorbed was stored for growth and 50% was utilized for energy expenditure and energy cost of growth. As shown in Fig. 4, in both groups, 80% of absorbed nitrogen was used for new tissue synthesis. About 75% of carbohydrate intake was oxidized and 25% stored, probably as fat. It was the inverse for fat: 35% was oxidized and 65% was stored. There was no difference in fat utilization despite the fact that 40% of fat in the formula were medium chain triglycerides. The LBW infants fed human milk had lower weight gain than those fed the formula. In both groups, however, energy stored was about 3 kcal/g weight gain, and energy cost of growth was estimated at 1 kcal/g weight gain. In both groups, protein deposition represented 10 to 12% of weight gain, as during fetal life. In contrast, fat deposition was about twice as much as in utero. Adipose tissue biopsies showed that this elevated fat deposition in preterm infants is associated with an increased cellularity and a lower lipid content of adipose cells when compared to full-term babies at birth (40). Insulin response to diet could play a role in this important accumulation of fat and multiplication of adipose cells during postnatal life.

**FIG. 4.** Proportion of energy (E.) oxidized and stored from absorbed carbohydrates (C.H.O.), fat, and proteins in VLBW infants fed pooled human milk (open columns) or a preterm formula (hatched columns). (From ref. 39.)
MINERALS

It has been known for many years that preterm infants fed human milk or formulas may develop signs of osteopenia or overt rickets. The pathogenesis of the skeletal lesions is often multifactorial. Inadequate calcium and/or phosphorus and poor vitamin D status have all been implicated (41).

From chemical analysis of human fetuses it can be calculated that the mean accumulations of calcium, phosphorus, and magnesium during the last trimester of gestation are about 130, 75, and 3.5 mg/kg/day, respectively (11). Human milk and most standard infant formulas do not contain enough calcium and phosphorus to allow preterm infants to accumulate these minerals at the intrauterine rate, even if all the calcium were absorbed and retained. In fact, calcium absorption is affected by a number of factors, such as lactose intake, quantity and quality of fat in the diet, amount of calcium and phosphorus in the milk, intestinal secretion of endogenous calcium, gestational and postnatal age, and vitamin D intake and metabolism (42).

Our metabolic balance studies carried out in LBW infants fed banked human milk show that net intestinal absorption of calcium is in the range of 50 to 70%, whereas that of phosphorus is about 90% (42). Because of the low calcium and phosphorus intake, however, preterm infants fed human milk retain only 20 to 25 mg calcium and phosphorus per kilogram body weight per day, which corresponds to 20% of the calcium and 30% of the phosphorus intrauterine accumulation rate (Table 3). In addition, they may present a phosphorus depletion syndrome characterized by hypophosphatemia, hypercalciuria, and no urinary excretion of phosphorus (43). The shortage of phosphorus is sometimes associated with signs of bone demineralization and high serum levels of alkaline phosphatase (44). In full-term babies, the low phosphorus intake from breast milk is sufficient to meet the requirements of growth, although even in those babies, the addition of phosphorus has been shown to improve calcium and phosphorus retention (45). In preterm infants, the low intake of phosphorus cannot meet the demand due to the rapid growth of skeletal and soft tissues and hypophosphatemia occurs more commonly

<table>
<thead>
<tr>
<th>Calcium (mg/kg/day)</th>
<th>Human milk&lt;sup&gt;a&lt;/sup&gt; (n = 8)</th>
<th>Infant formula&lt;sup&gt;b&lt;/sup&gt; (n = 19)</th>
<th>Preterm formula&lt;sup&gt;c&lt;/sup&gt; (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake</td>
<td>58 ± 11</td>
<td>81 ± 9</td>
<td>108 ± 12</td>
</tr>
<tr>
<td>In feces</td>
<td>25 ± 13</td>
<td>55 ± 12</td>
<td>45 ± 12</td>
</tr>
<tr>
<td>In urine</td>
<td>11 ± 6</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Retention</td>
<td>23 ± 10</td>
<td>24 ± 8</td>
<td>61 ± 15</td>
</tr>
<tr>
<td>Absorption (%)</td>
<td>58 ± 19</td>
<td>32 ± 13</td>
<td>59 ± 10</td>
</tr>
</tbody>
</table>

<sup>a</sup>Pooled pasteurized human milk.
<sup>b</sup>Alpren, Nestlé, Switzerland.
<sup>c</sup>Alprem, Nestlé, Switzerland.
as a result. Resolution of rickets and hypercalciuria with resultant increase in
calcium retention (43) and bone mineral content has been observed in preterm
infants fed human milk who were supplemented with phosphate alone (43,44) or
with both calcium and phosphorus (46).

The mineral content of most infant formulas is higher than that of human milk.
The percentage of absorption of calcium is generally lower, however, so that the
amount of calcium retained is not necessarily much higher than with human milk
(42,47). Unlike calcium, phosphorus is always well absorbed, net absorption rang-
ing from 80 to 94% (42) (Table 4). In formula-fed infants, in contrast to breastfed
infants, urinary excretion of calcium is usually low, whereas that of phosphorus is
high (42). Because of the poor calcium absorption, the good absorption of phos-
phorus, and the low glomerular filtration rate, hyperphosphatemia may develop,
causing hypocalcemia.

Supplementation of infant formulas with calcium salts and LBW infant formulas
with a high mineral content are generally associated with an improvement of
calcium retention (6,7,48). It has been claimed that oral calcium supplements, such
as calcium lactate, can result in a calcium retention similar to the intrauterine rate
(48); the interpretation of the balance data, however, is difficult, since phosphorus
retention was not affected by calcium supplementation, and the apparent calcium/
phosphorus retention ratio was at least 5:1. This strongly suggests that sedimenta-
tion of calcium salts had occurred in the bottle, so that infants received less calcium
than was thought. Increasing calcium and phosphorus intake probably results in an
improvement in retention of these elements, since sequential measurements of bone
mineral density have demonstrated better bone mineralization in preterm infants
fed formulas or human milk supplemented with calcium and phosphorus (46,49).
It is not clear whether it is necessary to accumulate minerals at the same rate as
in utero, however, since decreasing density and remodeling of bone occur in term
infants after birth and may be a physiological event. In fact, there is evidence that
in preterm infants, formulas containing 70 mg/dl calcium are sufficient to prevent
bone diseases (50).

### TABLE 4. Phosphorus balance in LBW infants fed
human milk, an infant formula, or a preterm formula

<table>
<thead>
<tr>
<th>Phosphorus (mg/kg/day)</th>
<th>Human milk</th>
<th>Infant formula</th>
<th>Preterm formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intake</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 ± 5</td>
<td>66 ± 8</td>
<td>68 ± 11</td>
<td></td>
</tr>
<tr>
<td><strong>In feces</strong></td>
<td>3 ± 1</td>
<td>4 ± 3</td>
<td>8 ± 2</td>
</tr>
<tr>
<td><strong>In urine</strong></td>
<td>1 ± 1</td>
<td>33 ± 10</td>
<td>16 ± 3</td>
</tr>
<tr>
<td><strong>Retention</strong></td>
<td>24 ± 5</td>
<td>29 ± 7</td>
<td>44 ± 7</td>
</tr>
<tr>
<td><strong>Absorption (%)</strong></td>
<td>89 ± 2</td>
<td>94 ± 5</td>
<td>89 ± 4</td>
</tr>
</tbody>
</table>

*Pooled, pasteurized human milk, n = 8.
*Nan, Nestlé, Switzerland.
*Alprem, Nestlé, Switzerland.
On the other hand, high intakes of minerals are not without risk in preterm infants. Too high an intake of phosphorus may lead to hyperphosphatemia, which blocks the production of 1,25-dihydroxy vitamin D \([1,25(OH)_{2}-D]\) and results in hypocalcemia. Too high an intake of calcium has been associated with fat bolus obstruction (51) and lactobezoar formation (52) in the gastrointestinal tract. In addition, high calcium intake may impede fat absorption (12,42,48,53), and high calcium retention may induce metabolic acidosis since calcification of the skeleton is a source of net acid (54).

While delayed bone mineralization in LBW infants is related to inadequate mineral intakes, the role of vitamin D metabolites on the regulation of calcium and phosphorus absorption and their direct and indirect effects on skeletal development cannot be ignored. Our studies clearly demonstrate that absorption and activation of vitamin D is operative in preterm infants after 30 weeks of gestation (42,55,56). There is a close relationship between the maternal and fetal pools of 25-hydroxy vitamin D (25-OHD). In some European countries, there is no systematic vitamin D supplementation, and most of those preterm infants born during winter or spring have low levels of 25-OHD at birth, which reflects a state of relative vitamin D deficiency of the mothers. Daily administration of 2,000 IU vitamin D\(_3\) increases the 25-OHD levels from birth; within 3 days, they are brought to levels observed in North America when seasonally adjusted norms are taken as reference (44,55,56,59). Administration of vitamin D\(_3\) also results in an increase of the circulating concentrations of 1,25(OH)\(_{2}\)D which, by 48 hr of age, are well above the range observed in adolescents (Fig. 5). This suggests that activation of vitamin D is mature in premature babies, but the substrate concentration is probably a limiting factor in the synthesis of 1,25(OH)\(_{2}\)D in LBW infants with a poor vitamin D status at birth. In those infants, the recommended daily allowance (400 IU) for term infants seems to be insufficient for adequate calcium homeostasis and bone mineralization.

**CONCLUSIONS**

Optimal nutrition for LBW infants remains a matter of considerable debate. Although it may not be necessary for the nutritional management of these infants, it has been recommended to provide them with energy, protein, and minerals in amounts that will allow accretion of nutrients at rates that would occur in utero during the third trimester of gestation.

In practice, when breast milk is available, LBW infants should be given preferably own-mother's milk. Raw instead of heat-treated human milk should be used, because it contains antiinfective factors and an active bile salt-stimulated lipase, which improves fat absorption. In growing VLBW infants, human milk should be supplemented with phosphorus, for instance, with 0.3 ml/dl of 1 M solution of disodium or dipotassium phosphate (9 mg P) in order to prevent or correct a phosphorus depletion syndrome. When LBW infants fed human milk are not growing satisfactorily, human milk can be supplemented with proteins (either
human milk protein or whey hydrolysate). Energy can be added as maltodextrins, and calcium salts can be increased after adaptation of phosphorus content. In LBW infants fed artificially, advisable intakes are 170 to 200 ml of fluid, 110 to 130 kcal, and 3.0 to 3.4 g protein per kg body weight per day. Lactose should account for at least 50% of carbohydrates. Medium chain triglycerides up to 40% of total lipids will ensure good fat absorption. About 120 mg calcium and 70 mg phosphorus appear sufficient for tissue growth and satisfactory bone mineralization, provided vitamin D status is adequate. Whatever the diet, however, it should be noted that postnatal growth seems to differ from fetal growth, especially with respect to fat deposition.

REFERENCES


DISCUSSION

**Dr. Barness:** What is the vitamin D requirement of prematurely born or LBW infants?

**Dr. Senterre:** The requirement may be different, for instance, in the United States and in Belgium. In the United States, the preterm baby has a good vitamin D status at birth, which is of course related to the vitamin D status of the mother. Under those conditions, it seems sufficient to give, from birth on, 10 µg/day vitamin D for maintaining adequate 25-OHD and 1,25(OH)₂D plasma levels. In Belgium, however, most preterm infants have a very low level of 25-OHD at birth, and it is necessary to give them at least from 30 to 60 µg/day vitamin D to achieve adequate plasma levels of vitamin D metabolites and good calcium absorption. In premature infants, it has been shown that the 1,25(OH)₂D plasma level is highly dependent on the 25-OHD level.

**Dr. Marini:** We are more interested now in studying growth in preterm babies during the first 2 weeks of life, because this is the most vulnerable time. Please comment.

**Dr. Senterre:** I do not completely agree. Of course, to stop growth in the first 2 weeks of life is probably not without any risk, but I think we must balance the risks. Indeed, it is practically impossible to have a VLBW infant growing after a few days, because that implies giving a high intake of fluid, protein, and calories. This will result in metabolic stresses, such as hyperglycemia, hyperaminoacidemia, and water retention, which are also deleterious. The problem is a bit different in small-for-date (SFD) infants, because those babies are more mature and they can generally tolerate earlier an energy intake that promotes rapid catch-up growth.

**Dr. Marini:** Did you find any difference between appropriate-for-gestational age (AGA) and SFD babies?

**Dr. Senterre:** Our balance studies were carried out in AGA preterm infants, but we have some data on SFD infants. In those infants, the intestinal absorption is impeded, like in preterm infants, probably because intrauterine malnutrition is associated with reduced intestinal function. However, by giving them a supplement of carbohydrates to compensate for fat malabsorption, it is relatively easy to bring them into positive nitrogen balance.

**Dr. Abdul Kader:** I have a question with respect to medium chain triglyceride (MCT) content. Why do you use 40% MCT instead of a higher or lower content? Have you looked at the rate of calcium absorption and nitrogen retention with increasing or decreasing concentrations of MCT in the diet?

**Dr. Senterre:** We have used commercially available formulas, which contain about 40% MCT. I think this is a good figure. It has been shown that 80% MCT instead of 40% improves slightly fat and calcium absorption and nitrogen retention in preterm infants. However, the difference is small, and we must take into account the fact that MCTs are artificial fats that are usually oxidized.

**Dr. Waterlow:** In your chapter, you showed that children were gaining at about 20 g/kg/day, and the energy available for growth after deducting heat production was about 60 kcal/kg. Therefore, you have an energy cost of growth of 3 kcal/kg, which is low by comparison with other figures, suggesting that the infants are storing relatively more lean tissue than fat. The first question is whether this is borne out by your actual figures. Second, if the preterm...
infant needs about 3.3 g protein/kg and 125 kcal, this is a mixture with a protein-energy ratio of roughly 0.1, which cannot be achieved by human milk.

**Dr. Senterre:** In our study, the premature infants fed human milk gained about 15 g/kg/day and stored about 45 kcal/kg/day; those fed the formula gained about 20 g/kg/day and stored about 60 kcal/kg/day. Thus in both groups, about 3 kcal were stored per gram of weight gain. The composition of weight gain was similar in both groups: about 11% of protein and 25% of fat. This means that, compared to fetuses of similar gestational age, protein deposition, in percentage, was a bit lower, whereas fat deposition was almost twice as high. Energy cost of protein and fat deposition was estimated by calculating the increase in energy expenditure according to the weight gain. It accounts for about 0.7 kcal/g weight gain with human milk and 1.4 kcal with the formula. Thus it seems that the utilization of energy available for growth is more efficient with human milk.

**Dr. Lechtig:** Another way of estimating nutrient intake efficiency is relating weight gain per month to total energy intake during the same period. This would allow us to make comparisons with other stages in the life cycle, for example, with the fetal period. Is this information available?

**Dr. Senterre:** In our studies, weight gain indeed was related to total energy intake or, more precisely, to the amount of energy absorbed. When energy absorbed varied from 85 to 100 and to 115 kcal/kg/day, weight gains were 13, 16, and 20 g/kg/day, respectively. In that range of energy absorbed, we observed that about half the calories were oxidized and half were stored. With higher energy intakes, it may be more difficult to maintain such a good utilization of energy supply.

**Dr. Zoppi:** In my opinion, during the first months of life, infants need at least 3 g/kg/day protein. If an infant is fed formula, whey protein should be added, which may be allergenic.

**Dr. Senterre:** It is a problem. Preterm infants are theoretically more at risk of protein intolerance because of the higher permeability of the gut. In my clinical experience, however, I have rarely seen an allergy to cow's milk protein in preterm infants. It is possible that the immunological functions are more immature. However, it has been shown that antigenic properties of cow's milk-based formulas may vary according to the technical processing. There is a place for more research in this field. When I supplement human milk with protein, I use preferably a milk powder made of whey protein hydrolysate without antigenic properties. For instance, I had good results by adding 2% of a semielemental diet (Alfaré, Nestlé) to pooled pasteurized human milk.

**Dr. Yips:** What is the optimal amount of glucose polymers that can be added to breast milk?

**Dr. Senterre:** First, I do not think there is a need to supplement human milk with energy alone because human milk has a low protein content and there is a risk of developing signs of protein deficiency. When there is a supplement of protein, glucose polymers, such as maltodextrins, can be added in order to increase the energy content. These are well absorbed, despite the lack of pancreatic amylase. This probably is due to the presence of amylase in the human milk and in the saliva, and most important to the activity of the brush border glucoamylase. We did not observe any trouble in preterm infants receiving up to 14 g maltodextrins/kg/day. In contrast, starch tolerance is much more limited: 2 to 3 g/kg/day.