Micronutrients and Vitamins

42

Olivier Claris and Guy Putet

Contents

Abstract

Vitamins and micronutrients are essential for many cellular processes, but excessive intake may also be toxic. Iron, zinc, and copper compete for intestinal absorption. The first sign of iron deficiency is anemia, while an excessive intake may cause oxidative stress and may also impact on cardiac and liver function. Zinc deficiency may cause growth arrest, irritability, anorexia, alopecia, esophagitis, and diarrhea. Copper deficiency is associated with hypochromic anemia, hypotonia, failure to grow, diarrhea, bone abnormalities, and neutropenia. Iodine deficiency may impair growth and intellectual performance. Thiamin deficiency is known as "beriberi," while Niacin deficiency is known as pellagra. This chapter summarizes the most recent recommendations for vitamin and micronutrient intake.

42.1 Salient Points

- Iron is mainly involved in erythropoiesis, but also in neurodevelopment, cardiac, and skeletal muscle function.
- Zinc participates in carbohydrate and protein metabolism.
- Copper is involved in oxidation and reduction.
- Iodine intervenes in thyroid function.
- Thiamine is essential for carbohydrate metabolism and lipid synthesis.
- Riboflavin is implicated in energy metabolism.
- Niacin is a cofactor for electron transport and energy metabolism.
- Pyridoxine has a role in the metabolism of aminoacids, prostaglandins, carbohydrate, in the development of the immune system and neurologic function.

O. Claris (✉)
Department of Neonatology, Hôpital Femme Mère Enfant, Bron, France

Hospices Civils de Lyon and Université Claude Bernard, Lyon, France

G. Putet
Department of Neonatology, Hopital de la Croix-Rousse, Hospices Civils de Lyon and Universite Claude Bernard, Lyon, France

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- Folate is active in the biosynthesis of purines, pyrimidine, and amino acid metabolism.
- Cobalamin is involved in DNA nucleotide synthesis.
- Pantothenic acid is a precursor of Coenzyme A (energy metabolism).
- Ascorbic acid has a role in hydroxylation and as an antioxidant.
- Vitamin A is implicated in protein synthesis and epithelial cell function, growth, and immune function; it is also a strong antioxidant.
- Vitamin E is an antioxidant that prevents lipid peroxidation.
- Vitamin K is essential for hepatic synthesis of coagulation factors.
- Vitamin D plays a physiologic role in neuromuscular function and cell growth and differentiation.

42.2 Micronutrients

Table 1 summarizes the most recent recommendations (Agostini et al. 2010; Tsang et al. 2005; Koletzko et al. 2005a, b).

Iron Iron (Fe) is an important micronutrient implicated in DNA replication, cellular metabolism and oxygen delivery. It is mainly involved in erythropoesis and is the first sign of deficiency in anemia, it is also implicated in neurodevelopment, and cardiac and skeletal muscle function. On the otherhand, it is a potentially toxic nutrient and, as a powerful prooxidant, it may play a major role in the oxidative stress. Furthermore, iron overload has a direct impact on cardiac and liver function. For all these reasons, the range between requirements and toxicity is narrow.

Iron is absorbed in the duodenum as ferrous. Absorption rates depend on the iron status, the form of iron given and the age of preterm (PT) infants. Iron absorption is particularly enhanced by human milk feeding and vitamin C status, and is decreased after erythrocyte transfusion and competes with zinc and copper absorption.

Iron supplementation may be started as soon as 2 weeks of age, at a dose of 2–3 mg/kg/day (Agostini et al. 2010). Infants receiving erythropoietin treatment require higher intake, but too high an intake may cause intestinal side effects and increase retinopathy of prematurity. It is

Table 1 Micronutrients: Human milk (HM) content and intake recommendations (Agostini et al. 2010; Tsang et al. 2005; Koletzko et al. 2005a, b)

	HM content FT	Requirements (Tsang et al. 2005)		Requirements (Agostini et al. 2010; Koletzko et al. 2005a, b)		
		Enteral PT	Parenteral PT	Enteral PT	Parenteral FT	Parenteral PT
Iron	0.5–1 mg/L	2–4 mg/kg	0.25–0.67 mg/kg[a]	2–3 mg/kg	0.5–1 mg/kg	0.2 mg/kg[b]
Zinc	0.5–2.5 mg/L[c]	1–2 mg/kg	0.4 mg/kg	1.1–2 mg/kg	0.25 mg/kg	0.45–0.5 mg/kg
Copper	600–800 µg/L	120–150 µg/kg	20 µg/kg	100–132 µg/kg	20 µg/kg	
Selenium	15–20 µg/L	1.3–4.5 µg/kg	1.5–4.5 µg/kg	5–10 µg/kg	2–3 µg/kg	
Iodine	70–90 µg/L	10–80 µg/kg	1 µg/kg	11–55 µg/kg	1 µg/day	
Chromium	0.3–0.5 µg/L	0.1–2.25 µg/kg	0.05–0.3 µg/kg	0.03–1.23 µg/kg	not necessary	
Manganese	5 µg/L	0.75–75 µg/kg	1 µg/kg	<27 µg/kg	1 µg/kg	<50 µg/day
Molybdenum	2 µg/L	0.3–4 µg/kg	0.25–1 µg/kg	0.3–5 µg/kg	0.25 µg/kg	1 µg/kg
					<5 µg/day	
Fluorine				1.5–60 µg/kg		

[a]After 2 weeks of life
[b]Unnecessary before 3 weeks
[c]Decrease with postnatal days

therefore why intakes above 5 mg/kg/d are not recommended (Franz et al. 2000).

Zinc Zinc (Zn) is an ubiquitous trace metal present in numerous enzymes and participates in carbohydrate (CHO) and protein metabolism. It is required for replication, transcription and repair of DNA, and plays an important role during embryogenesis and growth. Zn is absorbed in the distal duodenum and proximal jejunum, and this is impaired by high casein intake.

Zn deficiency is characterized by growth arrest, irritability, anorexia, alopecia, esophagitis, diarrhea and functional recommendations in immunity, skin lesions of the hands and feet and poor healing. True acrodermatitis enteropathica is rarely seen in PT infants but ELBW infants on TPN without Zn, SGA, and growing PT infants fed unfortified HM are at risk of Zn deficiency (Friel et al. 1988).

Copper (Cu) It is a component of numerous enzymes (superoxide dismutase) involved in oxidation and reduction. It helps to protect cell membranes from oxidative damage. Copper competes with Zn and iron for intestinal absorption. It is absorbed in the upper part of the intestine, and this decreases by high Zn and iron intakes. Deficiency is associated with hypochromic anemia not responding to iron supplementation, hypotonia, failure to grow, diarrhea, bone abnormalities, neutropenia. In the case of hepatic cholestasis, intake has to be reduced or stopped because of potential toxicity.

Selenium (Se) It is a glutathione peroxidase component, which protects cell membranes against peroxide induced drainage. Deficiency is only seen in infants on TPN without or with too little Se, or in Keshan disease (cardiomyopathy) areas where soil is Se deficient. Addition of Se to food or TPN must be cautious as most Se compounds are toxic if given in excess (Aggett et al. 1991).

Iodine (I) It intervenes in thyroid function (T3 and T4 synthesis), and iodine deficiency (before or after birth) may impair growth and intellectual performance. Excess iodine may also create hypothyroidism. PT infants often have transitory hypothyroidism as their mechanisms to control iodine levels are immature (Rogahn et al. 2000). Based on the mean content of iodine in HM some PT infants may be on negative iodine balance. Toxicity is more often due to percutaneous intake (antiseptic solution).

Chromium (Cr) It has a role in glucose homesostasis. Hyperglycemia and insulin resistance are part of Cr deficiency, never described in infants either breast or formula fed.

Manganese (Mn) It is a component of several enzymes acting in gluconeogenesis, mitochondrial membrane maintenance and in mucopolysaccharide synthesis. Mn deficiency has not been described in human conclusively, however Mn toxicity has been seen in adults with extrapyramidal symptoms. Advisable intakes are based on what is contained in human milk.

Molybdenum (Mo) It intervenes in the function of xanthine, aldehyde and sulfite involved in purine metabolism and sulfur excretion. Deficiency is only described in adults on very long term TPN. Advisable intakes are based on what is contained in HM.

Fluorine (F) It is found in bones and teeth mainly. There are no data to make any recommendation except that it is found in human milk and crosses the placenta.

42.3 Vitamins

Table 2 summarizes the most recent recommendations for vitamin intake (Tables 3, 4, and 5).

Vitamin B1 (**thiamine**) Vit B1 is a coenzyme essential for CHO metabolism and lipids synthesis once transformed by the liver into thiamine pyro phosphate. It is absorbed in the proximal small intestine. Deficiency is known as "beriberi". A thiamine deficient total parenteral nutrition (TPN) may induce severe lactic acidosis and death.

Vitamin B2 (**riboflavine**) Vit B2 is implicated in energy metabolism (it forms flavin, adenine, dinucleotides). It is absorbed in the small intestine. Deficiency leads to stomatitis, dermatitis and anemia. Requirements are based on HM content and are related to protein intake. If protein supply is given without Vit supplementation, a deficit can occur (Lucas and Bates 1984).

Table 2 Vitamins: human milk (HM) content and intake recommendations (Agostini et al. 2010; Tsang et al. 2005)

		Requirements (Tsang et al. 2005)		Requirements (Agostini et al. 2010)	
	HM content FT	Enteral PT	Parenteral PT	Enteral PT	Equivalents
Vit A	660–1000 IU/L	750–1500 IU/kg	750–1500 IU/kg	400–1000 μg RE/kg	1 RE = 1 μg all trans retinol
					1 RE = 3.33 IU Vit A
					1 RE = 6 μg β carotene
					1 RE = 12 μg other carotenoids
Vit D	20–30 IU/L	200–1000 IU/day	60–400 IU/day	800–1000 IU/day	1 μg cholecalciferol = 40 IU Vit D
Vit E	3–4 IU/L	6–12 IU/kg	2.8–3.5 IU/kg	2.2–11 mg/kg TE	1 IU = 1 TE
					1 IU = 0.67 mg α-tocopherol
					1 IU = 1 mg dl-α-TA
Vit K	5–10 μg/L	8–10 μg/kg	10 μg/kg	4.4–28 μg/kg	

IU international units, *RE* retinol equivalent, *TE* tocopherol equivalent, *TA* tocopherol acetate

Vitamin B3 (niacin) Vit B3 can be synthesized from tryptophane (Try) in the presence of B6, once this amino acid (AA) exceeds minimal intake (60 mg of Try →1 mg of niacin expressed as Niacin Equivalent). It is also a cofactor for electron transport and energy metabolism. Absorption is effective in the small intestine. Deficiency is known as pellagra (dermatitis, diarrhea and neurological symptoms). It usually results from multiple deficiency and poor protein intake not observed in newborn infants.

Vitamin B6 (pyridoxine) Vit B6 has a role in the metabolism of AA, prostaglandins, CHO, in the development of immune system and neurologic function. Its requirement is related to protein intake (15 μg of B6 should be available per g of protein). It is absorbed in the small intestine. Deficiency leads to vomiting, irritability, dermatitis, failure to thrive, hypochromic anemia and neurological symptoms as convulsions.

Vitamin B9 (folate) Vit B9 is active in the biosynthesis of purines, pyrimidine and AA metabolism. Its activity decreases by Zn deficiency. Deficiency is associated with megaloblastic anemia, leucopenia, thrombocytopenia, growth insufficiency, and lesions in small intestine, mostly in context of malabsorption syndromes.

Table 3 Vitamins: effect of temperature and light, and toxicity

	Temperature	Light	Toxicity
Vit A	↓	Photodegraded	Intra cranial hypertension if >5000 IU/day
Vit D	Stable	Stable	Hypercalcemia, hypercalciuria, anorexia, vomiting, failure to thrive, calcifications
Vit E	Stable	Slightly affected	Large doses associated with sepsis, NEC
Vit K	Stable	↓	Not reported

Vitamin B12 (cobalamin) Vit B12 is involved in DNA nucleotides synthesis. Absorption depends on gastric pH and occurs in the small intestine. Deficiency of cobalamin is known as leading to megaloblastic anemia, glossitis and neurologic signs, but although this is not seen in FT breast fed infants, it is well established in infants of vegetarian mothers.

Vitamin B5 (pantothenic acid) It is a precursor of Coenzyme A (energy metabolism). It is absorbed

Table 4 Vitamins: daily intake recommendations (Agostini et al. 2010; Tsang et al. 2005)

		Requirements (Tsang et al. 2005)			Requirements (Agostini et al. 2010)	
	Enteral FT	Enteral PT	Parenteral FT	Parenteral PT	Enteral PT	Parenteral FT
B1	30 μg/kg	300 μg/kg	1–2 mg/day	350 μg/kg	140–300 μg/kg	350–500 μg/kg
B2	40 μg/kg	450 μg/kg	150 μg/kg	150 μg/kg	200–400 μg/kg	150–200 μg/kg
B3	0.2 mg/kg	4.5–6 mg/kg	17 mg/day	5 mg/kg	0.3–5 mg/kg	4–6.8 mg/kg
B6	14 μg/kg	180–300 μg/kg	1000 μg/day	180 μg/kg	45–300 μg/kg	150–200 μg/kg
B9	9.4 μg/kg	45–50 μg/kg	140 μg/day	56 μg/kg	35–100 μg/kg	
B12	0.05 μg/kg	0.3 μg/kg	0.75 μg/day	0.3 μg/kg	0.1–0.77 μg/kg	0.3 μg/kg
B5	1.7 mg/day	2 mg/day	5 mg/day	2 mg/kg	0.33–2.1 mg/kg	1–2 mg/kg
B8	0.7 μg/kg	4–40 μg/kg	20 μg/day	6 μg/kg	1.7–1.65 μg/kg	5–8 μg/kg
Vit C	6 mg/kg	30–40 mg/kg	80 mg/day	25 mg/kg	11–46 mg/kg	15–25 mg/kg

Table 5 Vitamins: human milk (HM) content, effects of temperature and light, and toxicity

	HM	Temperature	Light	Toxicity
B1	165–220 μg/L	↓	Photo degraded	Only in adults
B2	350–575 μg/L		↓	Not clearly defined
B3	1.8–2.5 μg/L			No side effect with nicotinamide
B6	130–310 μg/L		Inactivated	Very rare only in adults
B9	80–135 μg/L	Destroyed	Inactivated	Very rare may mask Vit B12 deficit. May depress Zn absorption
B12	0.2–1 μg/L			Not reported
B5	2.2–5 mg/L			Not reported
B8	5–9 μg/L			Not reported
Vit C	35–85 mg/L	Inactivated		Rebound scurvy in newborn only after large doses during pregnancy

in the small intestine. Deficiency has not yet been reported as diet provides sufficient amounts.

Vitamin B8 (biotin) Except in some metabolic diseases, deficiency is not seen in enterally fed infants as it is synthesized in gut, but is seen in TPN (pallor, anemia, dermatitis, lethargy, EEG abnormalities). It is also absorbed in the small intestine.

Vitamin C (ascorbic acid) Vit C has a role as a cofactor in hydroxylation reactions (proline, lysine, norepinephrin synthesis and Try) and as an antioxidant. It also has a role in folic acid conversion to folinic acid (active form) and in the oxidation of tyrosine (Tyr), and in iron absorption. 1 IU of L Ascorbic Acid corresponds to 50 μg. It is absorbed in the small intestine. Deficiency is known as scurvy. A transient elevation of plasma Tyr and Phenylalanine has been reported in VLBW infants fed high protein casein formulae.

Vitamin A This term refers to compounds (retinoids) having similar activities and structure as retinol (natural molecule derived from beta-carotene). Vit A activity is expressed as RE (retinol equivalent), 1 RE = 1 μg retinol = 3.3 IU Vit A. Vit A is mainly stored in liver and circulates in blood linked to retinol binding protein (RBP), and is implicated in protein synthesis and epithelial cell functions, growth and immune functions. It has also strong antioxidant properties. It is absorbed in the upper part of the small intestine.

No clinical deficiency is described in FT breastfed infants and precise requirements for PT infants are still unknown with recommended intakes are based mainly on biological data. Vit A supplementation may play a role as an antioxidant factor, and as a protective factor for bronchopulmonary dysplasia (BPD) (Greer 2005).

Vitamin E The term of Vit E refers to eight compounds having similar activities. The most active compound is α-tocopherol, which shows a strong antioxidant capability by protecting from lipid peroxidation. Vit E is entirely expressed as α-tocopherol equivalent (αTE), 1 mg αTE = 1 mg d-α-tocopherol = 1.49 IU, and 1 IU = 1 mg dl-α-tocopherol acetate. Vit E requirements depend on polyunsaturated fatty acid intake. It is absorbed in the small intestine. Hemolytic anemia is the main consequence of Vit E deficiency. Some controversy still persists upon the role of Vit E in BPD and retinopathy of prematurity. Large intakes of Vit E (above 50 mg/kg) have been implicated in gastro intestinal adverse effects and sepsis (Raju et al. 1997).

Vitamin K There are to two forms: Vit K1 (phyloquinone: plant form) and Vit K2 (menaquinone: synthesized by bacteria). Vit K is necessary for hepatic synthesis of coagulation factors (II, VII, IX, X, protein C and protein S). It is absorbed in the small intestine. It is needed in a very small amount and, as it is synthesized partly in the gut, synthesis is less pronounced with HM, and deficiency is seldomly seen, except in neonates and in cases of malabsorption or hepatic disease (Greer 2005).

Vitamin D Along with calcium and phosphorus homeostasis (see also ▶ Chap. 41, "Calcium and Phosphorus Homeostasis: Pathophysiology"), Vit D plays a physiologic role in neuromuscular function and cell growth and differentiation. It is absorbed in the small intestine. As Vit D deficiency in pregnant women is still frequent, recommended supply for neonates needs to be given as soon as enteral feeding is established (Salle et al. 1982).

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