Chapter 2
Interaction Between Nutrition and Metabolism

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Abstract Diet plays a fundamental role in the nutritional status, in the homeostasis and in the capacity of an individual to adapt to the environment. A proper or an inadequate nutrition has an impact on the persistence, remission and incidence of various conditions, including the infectious diseases. Consequently, nutrition has a crucial importance on survival rates and health recovery of individuals or even populations around the globe. The synergistic relationship between nutritional needs and infectious processes has been demonstrated conclusively in diverse studies. This chapter will discuss the most important nutrients, their most common natural dietary sources, the different digestive processes for each one as well as the absorption, transport, storage, excretion and function of each of the nutrients within the organism. We also go through some concepts on the interaction between nutrition and the immune system, as well as examples on the influence of nutrition or specific nutrients on some infectious diseases, and their influence on the gene expression.

Keywords Metabolism · Infection · Disease · Nutrient · Immunonutrition · Nutrigenetic

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2.1 Introduction

The World Health Organization defines *nutrition* as the ingestion of food in relation to the dietary needs of the body (WHO 2017). *Metabolism* is a combination of physical processes and chemical reactions that take place in the body to obtain energy and use it to synthetize, process, transform and eliminate substances, starting from the ingestion of nutrients, in order to maintain life (Smith and Morowitz 2004; Gil Hernández and Sánchez de Medina Contreras 2010; Lee 2013). The current concept of *infectious disease* is not only restricted to microbe invasion and host reaction but rather an orchestration of factors that include elements such as pathogen virulence, infectious burden, route of inoculation and the host's susceptibility to infection and previous pharmacological treatment (Traore et al. 2016). Susceptibility to the installation and development of an infection is intrinsically related to the host's immunological capacity, whose dependence on a proper nutrition has been extensively demonstrated (Cunningham-Rundles et al. 2005; Krawinkel 2012).

During an infection, apart from keeping the host's body structure and function, nutrition assumes an additional function. It provides the immune system with elements for pathogen neutralization and elimination while repairing any resulting tissue damage. Nutrition and the consequent metabolic processes should accomplish specific goals. Nutrition must sustain an effective immune response. It must provide an environment for an adequate protective and efficient self-limiting and self-resolving inflammatory response, without additional cell and tissue damage. It also must offer elements to facilitate the body in the handling and removal of catabolites and/or by-products resulting from the immune response itself, tissue injury or malfunction as well as medications given during disease treatment. Moreover, proper nutrition will enable quick and precise tissue regeneration without feeding or protecting the pathogen within the host's body or without helping it escape the host immune system.

This chapter will explore some basic concepts and current knowledge of nutrition and metabolism in the context of diseases caused by several pathogen agents.

2.2 Aspects of Nutritional Biochemistry

Balanced nutrition plays a special role in maintaining the health of an individual. The body uses nutrients from food to produce energy, maintain or repair body structures and regulate or modulate metabolism. In turn, every disease has a metabolic component that can lead to a depletion of reserves and the aggravation of the clinical condition. It is fundamental to understand the processes of digestion, absorption, transport and metabolism of each of the nutrients from natural sources and their most important functions within the body.

2.2.1 Carbohydrates

Carbohydrates are sources of energy for the body. The main dietary carbohydrates are the polysaccharides, oligosaccharides, disaccharides and monosaccharides (FAO/WHO 1998; Ochoa et al. 2014). Natural dietary sources of polysaccharides are amides of vegetal origin (amylose and amylopectin) and glycogen of animal origin (McCance and Lawrence 1929; Lovegrove et al. 2017). Sucrose and maltose are disaccharides of vegetal origin, while lactose is a disaccharide of animal origin. Fructose is the only natural monosaccharide that comes from dietary sources. Most monosaccharides are not free molecules, but they exist as basic components of disaccharides and polysaccharides (Cummings and Stephen 2007). The hexoses are the most important monosaccharides and include glucose, galactose and fructose (Berg et al. 2002a; Lee 2013). Amide digestion starts in the mouth with salivary amylase and continues in the intestine by the action of the pancreatic α-amylase (Lee 2013). Within the body, the end products of the digestion of dietary carbohydrates are hexoses and pentoses, which are rapidly absorbed by the intestine (Norton et al. 2015). Glucose molecules require specific transport mechanisms to enter the intestinal cell. Glucose uptake can occur by *facilitated diffusion*, which is a passive process that involves glucose transporters GLUT-1 to GLUT-5, a family of proteins present in cell membranes that bind and carry glucose into the cell (Carruthers et al. 2009; Mueckler and Thorens 2013). A secondary active transport requires energy by hydrolysis of ATP and consists of a *sodium-coupled glucose transporter* (SGLT) against a concentration gradient, from a low concentration outside the cell to a high concentration inside (Wright et al. 2011).

Monosaccharides pass into the portal vein and go directly into the liver, where they are oxidized to produce energy and are stored as glycogen, or pass into the general circulation for use by other tissues. Once glucose enters the hepatic cell with the help of insulin, it is phosphorylated into glucose 6-phosphate, which may follow one of the pathways depending on metabolic needs, namely, glycogenesis, glycogenolysis, glycolysis and gluconeogenesis as described in Chap. 1.

2.2.2 Lipids

Animal and plant triglycerides, membrane phospholipids and sterols comprise the principal dietary lipids for humans and other animals. *Triglycerides* are composed of three molecules of fatty acids bound to one molecule of glycerol. *Phospholipids* are composed of phosphoric acid, fatty acids and a nitrogen base. *Sterols* include cholesterol and Vit D. Fatty acids are categorized according to the number of carbon atoms in short-chain (2–4 carbon atoms), medium-chain (8–14 carbon atoms) or long-chain (16–20 or more carbon atoms) fatty acids. Considering the presence of carbon-carbon double bonds, fatty acids that have no double bond are categorized as saturated, while unsaturated fatty acids are those that have one or more double

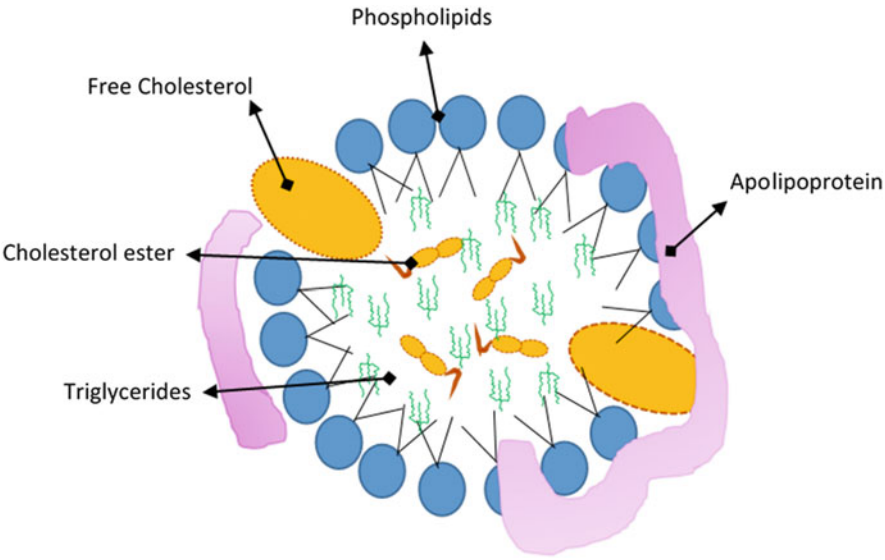

Fig. 2.1 Representation of the structure of a chylomicron, showing its nucleus of triglycerides and cholesterol esters, and the outer layer of apolipoproteins, cholesterol and phospholipids

bonds. The fatty acids obtained from land animals tend to be saturated, whereas the fatty acids of fish and plants are often polyunsaturated and therefore present as oils (Akoh and Min 2008; Berdanier and Zempleni 2009; Lee 2013).

Lipid digestion begins with lipase in gastric juice, but most fat digestion takes place in the duodenum, where fats are first emulsified by bile salts for optimal activity of lipases. Pancreatic lipase hydrolyses the triglyceride into mono- and diglycerides and free fatty acids, composing the digestion products, which together with liposoluble vitamins and cholesterol form micelles. Fatty acids containing less than 8–12 carbon atoms, thus being more soluble, pass through the intestinal mucosa and are transported linked by albumin directly into the portal vein, while the ones with more than 8–12 carbon atoms will form the micelles (Berdanier and Zempleni 2009; Lindquist and Hernell 2010; Lee 2013). Enterocytes take up the micellar compounds and resynthesize them into triglycerides that are packaged into chylomicrons, which are drained by lymphatic capillaries into the thoracic duct, and then discharged directly into the general circulation (Swift et al. 1990; Akoh and Min 2008). Chylomicrons are composed of a nucleus of triglycerides and cholesterol esters and an outer layer of lipoproteins, cholesterol and phospholipids (Fig. 2.1) (Akoh and Min 2008; Lindquist and Hernell 2010; Lee 2013). The chylomicrons circulate in blood vessels throughout the body to diverse tissues, such as the liver, adipose tissue and muscles. In the adipose tissue, the lipoprotein lipase (LPL) on the capillaries' endothelium partially digests the chylomicrons into free fatty acids, glycerol and chylomicron remnants (Lee 2013; Julve et al. 2016; Geldenhuys et al. 2017). Chylomicron remnants are lipoproteins rich in cholesterol and together with

chylomicrons compose the transporting system for exogenous dietary lipids (Julve et al. 2016). Adipocytes take up free fatty acids, but not glycerol and chylomicron remnants, which are removed from the circulation and metabolized by the liver. Inside adipocytes, fatty acids are resynthesized into triglycerides, in a process that uses glycerol derived from glucose in the glycolytic pathway, to be stored as a source for metabolic energy and released on demand by other tissues (Akoh and Min 2008). Lipoproteins, including very low-density (VLDL), low-density (LDL) and high-density (HDL) lipoproteins, are the transport system for endogenously synthesized lipids (Beisiegel 1998; Rosa et al. 2015).

Free fatty acids transported by albumin are the main energy source for various organs. They are extensively used by the heart, the brain and other tissues to oxidize fatty acids which in the presence of O_2 are then catabolized into CO_2 and H_2O, producing energy. Nearly 40% of this energy is stored as ATP, and the remaining is released as heat (Frayn et al. 2006; Lee 2013). In the liver, the glycerol that is released by lipase is phosphorylated by glycerol kinase, and the resulting glycerol 3-phosphate is oxidized to dihydroxyacetone phosphate (DHAP) which participates in glycolysis among other metabolic pathways (Hagopian et al. 2008). The glycolytic enzyme triose phosphate isomerase converts DHAP to glyceraldehyde 3-phosphate, which is oxidized via glycolysis or converted to glucose via gluconeogenesis (Nye et al. 2008). After releasing triglycerides into the adipose tissue, the chylomicron remnants carry the cholesterol to the liver, where it becomes part of biliary fluid or is incorporated into VLDL (Julve et al. 2016).

2.2.3 Proteins

Proteins are the most important source of structural elements in the body, and they are distributed mainly in the muscles (40%), followed by the blood and skin (30%), and in the liver and intestine (10%) (Webb 1990; Gil Hernández and Sánchez de Medina Contreras 2010). Good protein sources include foods from animal origin such as red meat, poultry, eggs, milk and milk products and fish and seafood. Vegetal sources include nuts, seeds and legumes (Berdanier and Zempleni 2009). Protein digestion begins in the stomach where pepsins hydrolyse peptide bonds at the junctions between the aromatic amino acids—phenylalanine (Phe), tyrosine (Tyr), diiodotyrosine (Dit) and thyroxine (Thy) (Dabrowski 1983; Lee 2013; Liu et al. 2015). Some amino acids are released into the intestinal lumen, but others are digested on the surface of the cells of the intestinal mucosa by the aminopeptidases and dipeptidases from the villi. Some dipeptides and tripeptides are actively transported into intestinal cells and hydrolysed by intracellular peptidases. Final amino acid digestion therefore occurs at three sites: the intestinal lumen, the villi and the cytoplasm of the mucosal cells (Matthews 1975). Nucleic acids are fragmented into nucleotides within the intestine by pancreatic nucleases, and these nucleotides are themselves fragmented into nucleosides and phosphoric acid. Absorption of the amino acids is rapid in the duodenum and jejunum, but slow in the ileum.

Approximately 50% of digested proteins come from ingested foods, 25% from proteins of digestive juices and 25% from desquamated mucous cells. Some of the ingested proteins enter the colon and are finally digested by the action of intestinal bacteria (Matthews 1975; Webb 1990; Lee 2013).

Amino acids are categorized as essential when they must be provided by the diet, as the body cannot synthesize them. Essential amino acids include L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan and L-valine. As infants are not fully capable of synthesizing L-arginine and L-histidine, these amino acids are also considered essential during early stages of body development (Fürst and Stehle 2004). On the other hand, L-alanine, L-aspartic acid, L-asparagine, L-glutamic acid, L-glycine, L-proline and L-serine, if not ingested in the diet in sufficient amounts, the body can synthesize them; they are therefore considered non-essential amino acids. They are also categorized as conditionally essential amino acids when their synthesis is reduced under certain pathophysiological conditions, such as prematurity in the infant or hypermetabolism or hypercatabolism. Conditionally essential amino acids are L-taurine, L-cystine, L-tyrosine, L-proline, L-serine and L-glycine (Reeds 2000; Obled et al. 2002; Lee 2013).

Amino acids are never stored in the body as proteins, and there is no reserve of free amino acids in the body; therefore they are synthesized de novo to satisfy demand (Lee 2013). The amino acid pool represents the amount of amino acids of dietary origin available for protein synthesis during a given time in the plasma and is adsorbed in cell surfaces after a meal (Picó et al. 1991; Proenza et al. 1994). During amino acid catabolism in the glycolytic pathways, the amino group is released in a process called deamination and is transformed mainly into ammonia in the liver. Most of the NH_3 formed is converted into urea and is secreted in the urine (Watford 2003).

Following the digestion of dietary nucleic acids, their purine and pyrimidine constituents are absorbed and metabolized, but most purines and pyrimidines in the body are synthesized from amino acids, especially in the liver (Liu et al. 2015). Purines or pyrimidines are combined with ribose to form nucleosides, which are components of a variety of coenzymes and related substances, such as uridine diphosphate glucose (UDPG), NAD, NADP and ATP. They also constitute ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). The pyrimidines are catabolized to CO_2 and NH_3, and the purines are converted into uric acid, which is filtered into the kidneys, 90% of which is reabsorbed and 10% excreted (Moffatt and Ashihara 2002; Lee 2013; Maiuolo et al. 2016).

2.2.4 Vitamins

Vitamins (Vit) are organic components that cannot be synthesized by the body, and therefore they must come from the diet. The only exception is Vit D, which is synthesized by the skin (Zempleni 2007). Vits are not a source of energy, but they

participate in the metabolism of macronutrients for energy production, usage and storage, as their most important function is to regulate and modulate metabolism. Vits are categorized according to the medium in which they are soluble. Vits A, D, E and K are liposoluble and stored in the liver with slow absorption and excretion processes. In excess, particularly Vit A and Vit D may become toxic. Hydrosoluble Vits include the ones in Group B and Vit C (Zempleni 2007), which are regularly required in the diet as they are not stored in large quantities, and generally any excess is non-toxic (Lee 2013).

2.2.4.1 Vitamin A: Retinol

Vit A is essential for all vertebrates and research on it spans about nine decades (Ross and Harrison 2007; Ross 2010). Vit A denomination includes a group of liposoluble compounds that exert retinol activity and exist as retinol, retinal and retinoic acid in dietary sources from animal origin, such as the liver, fish liver oils, milk and dairy, and eggs. Plant sources provide pro-Vit A carotenoids, found in green and yellow vegetables, such as carrots, sweet potatoes, pumpkin, kale, spinach, collards and squash (Tanumihardjo 2011; Lobo et al. 2012; Tanumihardjo et al. 2016). Animal products provide preformed Vit A in the form of an ester, called retinyl palmitate, while vegetables provide provitamin A mostly as β-carotene (Ross and Harrison 2007; Ross 2010). Hydrolysis of retinyl palmitate to become retinol requires at least two hydrolase enzymes, the pancreatic hydrolase retinyl ester in the proximal intestine and hydrolase on the surface of intestinal villi cells (Institute of Medicine 2001a; Ross and Harrison 2007). Free retinol then binds with the long-chain fatty acids, forming retinyl ester which is absorbed (Reboul 2013). Dietary β-carotene is absorbed by passive diffusion in the intestine and cleaved into two molecules of retinaldehyde within the cytoplasm of the cells of the mucosa (Hollander and Ruble 1978; Reboul 2013). Absorption of vegetable carotenoids in the small intestine is lower than that of animal previtamin A (Reboul 2013; Melse-Boonstra et al. 2017). In the digestive system, there is an efficient specific transporter system for retinol, whereas carotenoids are absorbed via non-specific transporters (Berdanier and Zempleni 2009). Retinaldehyde is esterified to form retinal and then becomes retinol, which couples with chylomicrons to be transported by the lymph into the blood and then to the liver (Nayak et al. 2001) where it is metabolized and stored as retinyl esters within stellate cells (Institute of Medicine 2001a; Ross and Harrison 2007). Lipoproteins carry carotenoids and retinyl esters to the fat portion of tissues that also store some Vit A. On the other hand, retinol, retinal and retinoic acid combine with specific retinoid-binding proteins within cells and in the plasma (Ross and Harrison 2007; Berdanier and Zempleni 2009). Studies have shown that more Vit A is synthesized from dietary β-carotene when subjects co-ingest β-carotene with Vit A, suggesting that retinoid status can influence carotenoid status (Ross 2006; Zempleni 2007). Either retinol or retinal can be converted to retinoic acid, but reverse reactions are not possible; moreover retinol and retinal are interconvertible only in the eye retina (Institute of Medicine 2001a). In the tissues, retinol is used either as retinol, retinal, or

converted to retinoic acid, which is used faster than retinol (Ross 2010). Studies have shown that retinoic acid metabolites are recovered from expired air, but the structures of all the metabolites excreted in the urine and faeces are not known (Institute of Medicine 2001a; Ross 2006; Berdanier and Zempleni 2009; Bayer 2013). Excess Vit A intake is associated with pathological accumulation in the liver, inducing oxidative stress in the mitochondria (Lobo et al. 2012; de Oliveira 2015), and many clinical signs (Smith and Goodman 1976; Ross 2010). Retinal is the Vit A derivative that is the most toxic, due to its chemical reactivity, randomly modifying proteins through Schiff base formation (Zhong et al. 2012). Hypervitaminosis A appears to be due to abnormal transport and distribution of Vit A and retinoids caused by overloading of the plasma transport mechanisms (Smith and Goodman 1976; Zhong et al. 2012). Long-term ingestion of $\geq$10 times the recommended dietary allowance of Vit A is associated with toxicity (Hathcock et al. 1990; Penniston and Tanumihardjo 2006). There is no treatment or antidote for hypervitaminosis A, and its management is based on intake interruption (Penniston and Tanumihardjo 2006).

Vit A participates in many metabolic processes which are fundamental in the synthesis of protein for body development, the formation of epithelial cells, vision and the functioning of the immune system (Gerster 1997; McLaren and Kraemer 2012). In the eye, retinal combines with opsin to form rhodopsin, the molecule responsible for photoreception (Lee 2013). Retinoic acid is required to maintain normal gene expression and tissue differentiation (Ross and Harrison 2007; Chen et al. 2008; Aoto et al. 2008). Retinoic acid is an irreversibly oxidized form of retinol, which is an important hormone-like growth factor for epithelial and immune cells (Ross and Ternus 1993; Reichrath et al. 2007). Retinoid-dependent processes are required for the expression of many proteins of the extracellular matrix, such as collagen, laminin and proteoglycans (Lobo et al. 2012). In the brain, the synthesis of the calcium-binding protein, calbindin, is regulated by retinoic acid and not by Vit D as it is in other tissues, such as the intestine and kidneys (Wang and Christakos 1995; Berdanier and Zempleni 2009). Vit A also interacts with the metabolism of zinc and iron and is required for the synthesis of haemoglobin and erythropoiesis (Roodenburg et al. 2000). Retinal and retinol participate in many enzymatic reactions related to lipid metabolism, carbohydrate metabolism, protein metabolism and hormonal function (Chen and Chen 2014). Carotenoids and Vit A act as antioxidants, protecting cells against the effects of oxidants generated in aerobic metabolism or oxidative stress (Sies 1993; Valko et al. 2007; Omur et al. 2016).

2.2.4.2 Vitamin B1: Thiamine

Thiamine acts as a coenzyme, which means that it is required so that enzymes can perform normal physiological actions. Dietary animal sources of thiamine (also called thiamin or aneurin) include the liver, lean pork and dairy products; vegetable sources include wholegrains, yeast and legumes. Thiamine is absorbed by active transport in the proximal duodenum when dietary amounts are scarce, while passive diffusion occurs when excessive amounts are available in the diet. Uptake of Vit B1

depends on phosphorylation in both the intestinal lumen by the intestinal phosphatases and within cells by the enzyme thiamine pyrophosphokinase, which acts as a carrier (Lonsdale 2006; Berdanier and Zempleni 2009; Manzetti et al. 2014). Thiamine is delivered to the liver through the portal circulation bound to proteins, mainly albumin (Lonsdale 2006; Berdanier and Zempleni 2009; Makarchikov 2009). In the liver, thiamine is phosphorylated to thiamine phosphate derivatives that perform functions such as coenzymes; phosphorylation also takes place in other tissues, but to a lesser extent (Makarchikov 2009). The known natural thiamine phosphate derivatives are thiamine monophosphate; thiamine diphosphate, also called thiamine pyrophosphate (TPP) or cocarboxylase; thiamine triphosphate; and the recently discovered adenosine thiamine triphosphate and adenosine thiamine diphosphate (Lee 2013). The best-characterized form is TPP, which acts as a coenzyme in the catabolism of sugars and amino acids (Bettendorff and Wins 2013). Thiamine phosphate derivatives participate in many cellular processes, and their degradation takes place within the various biochemical cycles in the cells; after which it is excreted in the urine.

In the mitochondria, TPP is a coenzyme for pyruvate dehydrogenase (PDH), one of the key factors in carbohydrate metabolism in biochemical pathways that result in the generation of adenosine triphosphate (ATP), which is a major form of energy for the cell (Thurnham 2005). Thiamine is essential for the metabolism of carbohydrates; in its absence, carbohydrate metabolism is the first to deteriorate (Thurnham 2005; Lonsdale 2006); and therefore animals and humans must obtain Vit B1 from the diet (Thurnham 2005; Lee 2013). In the nervous system, PDH is also involved in the production of acetylcholine, a neurotransmitter, and for myelin synthesis, and insufficient intake of thiamine is associated with diverse neural conditions, such as degenerative polyneuropathies, Wernicke-Korsakoff syndrome or convulsions due to increased intracranial pressure (Bitsch 2003).

2.2.4.3 Vitamin B2: Riboflavin

The best dietary sources of Vit B2 are animal-derived foods, such as milk, meat and eggs, while the richest vegetable sources include green vegetables, mushrooms, legumes or almonds (Halsted 2003; Rivlin 2007; Berdanier and Zempleni 2009; Lee 2013). Dietary riboflavin is naturally present in free forms or along with flavoproteins, which are proteins that contain a nucleic acid derivative of riboflavin: the flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN), which is a FAD precursor (McCormick 2003; Halsted 2003; Lee 2013). Riboflavin is actively absorbed in the proximal small intestine, after being dephosphorylated by the action of hydrolases from the villi membrane cells, by a pyrophosphatase that cleaves FMN and FAD and by an alkaline phosphatase that liberates the vitamin from its coenzyme form (Berdanier and Zempleni 2009). In humans, absorption is also regulated by availability and becomes active when dietary amounts are scarce (McCormick 2003). Following absorption, the free Vit B2 is carried to the liver in the bloodstream of the portal system bounded to albumin (Bayer 2013), but riboflavin has more

affinity with immunoglobulins (Gil Hernández and Sánchez de Medina Contreras 2010). In the cell, riboflavin enters as an important component of the intermediate metabolism in reactions that involve oxidation-reduction (McCormick 2003). Almost all tissues have the capacity to reconvert free riboflavin to FMN and FAD, which is particularly abundant in the liver, kidneys and myocardium, where flavoproteins are mainly located in the mitochondria because of their redox power (Lee 2013). Free riboflavin can be glycosylated, oxidized, demethylated and hydroxylated in the liver and excreted in the urine as a glycosylated metabolite or as free riboflavin. Vit B2 is not stored in the body for further uptake on demand, so it should come from the diet (Halsted 2003; Rivlin 2007; Berdanier and Zempleni 2009; Lee 2013).

Riboflavin has important functions as an antioxidant. Flavin adenine dinucleotide and flavin mononucleotide constitute the cofactors for flavoprotein enzymes, which catalyse oxidation-reduction reactions in cells and act as hydrogen transporters in the mitochondrial electron transport system (Walsh et al. 1978; McCormick 2003; Hühner et al. 2015). FAD has a more positive reduction potential than NAD+ and is a very strong oxidizing agent (Berg et al. 2002b; Mansoorabadi et al. 2007). FAD-linked proteins act in many metabolic pathways to execute functions such as DNA repair, nucleotide biosynthesis and synthesis of other cofactors such as coenzyme-A and coenzyme-Q (CoA, CoQ) and heme groups (Mansoorabadi et al. 2007). Other metabolic processes that require FAD include (1) the Krebs cycle (Berg et al. 2002b), (2) reduction of the oxidized form of glutathione (GSSG) to its reduced form (GSH) by glutathione reductase, (3) reduction of ubiquinone to ubiquinol (Xia et al. 2001; Berdanier and Zempleni 2009), (4) fatty acid oxidation by fatty acyl-CoA dehydrogenase (Powers 2003), (5) triglyceride synthesis by glycerol-3-phosphate dehydrogenase (Rivlin 2007) and (6) purine nucleotide catabolism by xanthine oxidase (McCormick 2003; Maiuolo et al. 2016). FAD also has important functions in the metabolism of other vitamins, such as the conversion of the amino acid tryptophan to niacin (Vit B3), production of 4-pyridoxic acid from pyridoxal (Vit B6), conversion of retinol (Vit A) to retinoic acid via cytosolic retinal dehydrogenase and synthesis of an active form of folic acid (McCormick 2003). Redox flavoproteins also act by non-covalent binding to FAD, for example, acetyl-CoA dehydrogenases, which function in the β-oxidation of fatty acids and in the catabolism of essential amino acids such as L-leucine, L-isoleucine, L-valine and L-lysine (Berdanier and Zempleni 2009).

2.2.4.4 Vitamin B3: Niacin

Niacin is the generic term for the two related and fast interconvertible chemical types, namely, nicotinamide (NAM) and nicotinic acid (NA). Niacin participates in metabolic cycles as a coenzyme to release energy from nutrients. Sources are wholegrain cereals and breads, milk, eggs, meats, liver, salmon, poultry, dry beans, dried fruit and green leafy vegetables (Institute of Medicine 1998a; Bender 2003a; Berdanier and Zempleni 2009; Lee 2013). In plants, niacin may be bound to

macronutrients, such as peptides, hexoses and pentose. In animal sources, it comes in the form of NA and NAM. Dietary niacin of plant origin, particularly from dry grains, comes covalently bounded to small peptides and carbohydrates which are not released during digestion by humans; therefore they need to be previously exposed to alkaline treatment or boiling (Bates 1998; Institute of Medicine 1998a; Lee 2013). Niacin is found in foods of animal origin in the form of coenzymes NADH (nicotinamide adenine dinucleotide) and NADPH (nicotinamide dinucleotide phosphate), which are digested to release NA and NAM. In the intestine, the resulting NA or its hydrolysis product NAM crosses the intestinal cells by simple diffusion when abundant, or by a transporting molecule when scarce (Bechgaard and Jespersen 1977; Henderson and Gross 1979; Bates 1998). In the plasma, both molecules circulate freely and enter the cell tissues by passive diffusion. Within cells, NA and NAM can be resynthesized for NADH and NADPH from quinolinic acid, a metabolite of the amino acid tryptophan synthesis pathway. Niacin diverse metabolites are excreted in the urine (Institute of Medicine 1998a; Bender 2003a).

Like the mechanisms of Vit B2, Vit B3 acts as a precursor, and the resulting NADH and NADPH coenzymes have essential functions in more than 200 enzymes involved in the metabolism of carbohydrates, fatty acids and amino acids (Berdanier and Zempleni 2009; Bayer 2013). NADH and NADPH act as electric transporters because they serve as hydrogen receptors and perform different functions in the metabolism of the cell. Vit B3 has critical roles in the maintenance of the redox state of the cell (Institute of Medicine 1998a; Kirkland 2007). NADH functions with mitochondrial enzymes of the respiratory chains, while NADPH acts with cytosolic enzymes in mechanisms in which NADPH generated in the oxidation of different substrates is used in different biosynthetic processes. Examples of NADH/NADPH functions include fatty acid, cholesterol or steroid hormone synthesis, β-oxidation of fatty acids, amino acid deamination, oxidative decarboxylation and biosynthesis of polyalcohols, ethanol metabolism and some participation in diverse metabolic pathways such as the glycolytic pathways, Krebs cycle, respiratory chain or pentose phosphate pathway (Bender 2003a; Depeint et al. 2006; Berdanier and Zempleni 2009). The adipose tissue, spleen, immune cells and keratinocytes express high levels of protein G-coupled niacin receptors, which act by inhibiting cyclic adenosine monophosphate (cAMP) production and thus fat breakdown in adipose tissue, resulting in a decrease in VLDL and LDL (Gille et al. 2008; Wanders and Judd 2011). On the other hand, niacin increases the apolipoprotein A1 (apoA-1) and inhibits HDL uptake in the liver by downregulating the cholesterol ester transfer protein, which results in increasing HDL levels (Kamanna and Kashyap 2008; Berdanier and Zempleni 2009).

2.2.4.5 Vitamin B5: Pantothenic Acid

Humans and animals need to obtain pantothenic acid from the diet to synthesize CoA and to synthesize and metabolize carbohydrates, proteins and lipids. Vit B5 is present in small amounts in most foods. The main sources are organ meats, eggs,

fish, mushrooms, avocados, broccoli and wholegrains. In foods, pantothenic acid is present mainly in the form of CoA and acyl carrier protein (ACP) that needs to be converted into free pantothenic acid to be absorbed by intestinal cells. The process requires hydrolysis of CoA and ACP into 4′-phosphopantetheine, which is dephosphorylated into pantetheine which undergoes hydrolysis by pantetheinase into free pantothenic acid (Bates 2005a; Trumbo 2006; Lee 2013). Free pantothenic acid is absorbed in the jejunum into intestinal cells by an active transport system that involves sodium and is saturable, which means that at high intake the absorption rate decreases (Institute of Medicine 1998b; Berdanier and Zempleni 2009). It is then transported in the form of free acid dissolved in the plasma and is captured by diffusion into the interior of the erythrocytes. Within the cell, Vit B5 becomes CoA, which is the predominant form in most tissues, particularly in the liver, adrenal glands, kidneys, brain, heart and testicles. Unlike the other B complex vitamers, pantothenic acid is not catabolized in the liver; it is excreted in its active form in the urine and faeces when in excess (Institute of Medicine 1998b; Bates 2005a; Berdanier and Zempleni 2009).

The main roles of Vit B5 are to act as a coenzyme in the metabolism of fatty acid and energy production. CoA binds to fatty acids in various reactions such as the synthesis of triglycerides, complex lipids, porphyrins and cholesterol or the catabolism of lipids and generation of ketone bodies. CoA also participates in other metabolic pathways in the synthesis and metabolism of carbohydrates and proteins in reactions such as acylation, fatty acid and pyruvate oxidation and the acetylation of choline. ACP groups act exclusively in the metabolism of fatty acid, where it is part of the synthetase multienzymatic complex (Institute of Medicine 1998b; Bates 2005a; Berdanier and Zempleni 2009; Lee 2013).

2.2.4.6 Vitamin B6: Pyridoxine

Vit B6 vitamers are also interconvertible chemical compounds in biological systems, similar to Vits B2 and B3. Vit B6 sources include meats, cereals, legumes, nuts, fruits and vegetables, as an aldehyde (pyridoxal), an alcohol (pyridoxine) or an amine (pyridoxamine). Most Vit B6 in foods of animal origin are in pyridoxal phosphate (PLP) or pyridoxamine phosphate forms, while plant foods contain mostly pyridoxine, which is more stable in cooking and other food processing (Merrill and Henderson 1990; Institute of Medicine 1998b; Berdanier and Zempleni 2009; Lee 2013). Depending on the ingested form, if free, glycosylated or bound with proteins, Vit B6 undergoes dephosphorylation by an alkaline phosphatase bound to intestinal cells (Merrill and Henderson 1990; Bender 2005). The vitamin is efficiently absorbed by passive diffusion in the jejunum and ileum after being converted into the active coenzyme form 5′-PLP by a pyridoxal kinase present in the cytoplasm of the cells (Merrill and Henderson 1990; Institute of Medicine 1998b; Berdanier and Zempleni 2009; Lee 2013). In the plasma, PLP circulates bound to albumin and haemoglobin to be distributed to the tissues, where it functions mainly in the metabolism of amino acids (Ink and Henderson 1984; Bender 2005; Lee 2013). In the liver, PLP is

dephosphorylated and oxidized by the FAD and NAD enzymes in reactions that result in 4-pyridoxic acid and other inactive metabolites, which are excreted in the urine. A small amount of pyridoxine is also excreted in the faeces (Ink and Henderson 1984; Berdanier and Zempleni 2009).

Vit B6's active form PLP acts as a coenzyme in about 100 enzyme reactions in amino acid, as well as in glucose and lipid metabolism (Dakshinamurti and Dakshinamurti 2007). The majority of reactions involving PLP are transaminations, which are fundamental in the metabolism of amino acids, cell growth and cell division (Lichtstein et al. 1945; Dakshinamurti and Dakshinamurti 2007). PLP is required as a coenzyme of glycogen phosphorylase, the enzyme that catalyses the release of hepatic and muscle glycogen as glucose 1-phosphate (Kohlmeier 2003; Bender 2005). It is fundamental for the metabolism of sphingolipids (Bourquin et al. 2011). Pyridoxine participates as a coenzyme in many reactions including racemization, elimination, replacement, decarboxylation and beta-group interconversion, which are required in pathways of macronutrient metabolism; as well, Vit B6 is required for gene expression and for the synthesis of haemoglobin, serotonin, histamine and niacin (Bender 2003b; Kohlmeier 2003; Dakshinamurti and Dakshinamurti 2007). PLP is also necessary for the absorption of other nutrients, such as Vit B12 and selenium (Institute of Medicine 1998b)

2.2.4.7 Vitamin B7: Biotin

Among all B complex vitamins that act as coenzymes, biotin is the only one that carries out its functions without the need for structural conversions (Gil Hernández and Sánchez de Medina Contreras 2010). Sources of biotin include brewer's yeast, organ meats, butter, some green legumes, eggs, royal jelly, soybeans, various ocean fish and wholegrains (Institute of Medicine 1998b; Lee 2013). Biotin is present in foods as a protein-bound coenzyme, linked to lysine residues (Mock 2007; Berdanier and Zempleni 2009). Gastrointestinal proteolytic digestion by proteases and peptidases releases biocytin (biotinyl-ε-lysine) and biotinylated peptides. The enzyme biotinidase, present in pancreatic and other intestinal secretions, intestinal flora and brush-border membranes, hydrolyses and releases biotin (Said 2008). In the colon, the intestinal microbiota synthesize biotin. In its free form, biotin is absorbed in the jejunum and proximal ileum by an active sodium-dependent multivitamin transporter (SMVT), which also has an affinity for pantothenic acid, and by a sodium-independent electrogenic system (Mock 2007; Berdanier and Zempleni 2009). Biotin circulates in the plasma in a free form and is bound to proteins, especially albumin (Berdanier and Zempleni 2009). Biotin uptake in the liver and peripheral tissues, as well as renal reabsorption, is mediated by the SMVT (Said 2008). Within cells, biotin is released from the proteins by the action of proteases and biotinidase, and this process is more intense in the liver, kidneys and adrenal gland and in the plasma (Mock 2007; Said 2008; Berdanier and Zempleni 2009). Biotin is catabolized by β-oxidation and sulphur oxidation and is mainly excreted

with the urine together with its catabolites; a minor amount is excreted in the faeces (Mock 2007; Said 2008; Berdanier and Zempleni 2009; Lee 2013).

Biotin functions as a necessary cofactor for carboxylases which catalyse a critical step in the intermediary metabolism of amino acids, fatty acids and cholesterol, and are required for lipogenesis, gluconeogenesis and other processes (Mock 2007; Lee 2013). It bonds covalently to enzymes that catalyse carboxyl group transfer, acting as a carboxyl transporter (Mock 2007). Biotin carries carboxyl groups for pyruvate carboxylase, which converts pyruvate to oxaloacetate during gluconeogenesis; for acetyl-CoA carboxylase, which synthesizes malonyl CoA in the synthesis of fatty acids; for propionyl CoA carboxylase, which converts propionate into succinate allowing odd-chain fatty acid use; and for 3-methylcrotonyl-CoA carboxylase in the catabolism of leucine (Waldrop 2015). This cofactor property of biotin links its functions with the metabolic functions of folic acid, pantothenic acid and cobalamin (Institute of Medicine 1998b). Furthermore, biotin covalently binds to lysine residues in histones (Kothapalli et al. 2005), a vitamin-dependent modification which is critical in the regulation of gene transcription, mitotic condensation of chromatin and DNA repair (Institute of Medicine 1998b; Mock 2007; Said 2008; Berdanier and Zempleni 2009; Lee 2013).

2.2.4.8 Vitamin B9: Folic Acid

Folic acids—or folates—are members of the family of pteroylglutamates or gamma-glutamyl derivatives. Folate and folic acid are the usual synonyms for pteroylglutamate and pteroylglutamic acid, respectively (Daly et al. 1997). They are essentially provided by the diet, from a variety of sources such as the liver, mushrooms, green leafy vegetables, poultry, meat, seafood, potatoes and fruit. Folates are widely present in 150 different forms, most of which are labile and easily oxidized (Institute of Medicine 1998b; Shane 2008; Mataix and Sánchez de Medina 2009; Lee 2013), so 50 to 95% of the vitamin is lost during food preparation and processing. Folates are generally in the form of polyglutamate (also folylpolyglutamates, containing 2–8 glutamate residues) linked to proteins and are released by the action of digestive proteases. Following the release of its glutamic residues by the action of hydrolases, the vitamin is absorbed at the intestinal level as monoglutamyl folate. These molecules enter the enterocytes by an active transport mechanism that involves a receptor and a transporter (Bailey 2007), which is intensified by the presence of glucose and galactose (Mataix and Sánchez de Medina 2009). Once within the hepatic cell, folate is metabolized upon dihydrofolate reductase action to 5-methyl tetrahydrofolate (THF) in a reaction that depends on Vit B3 (Benkovic and Hammes-Schiffer 2003). The vitamin is then largely bound to albumin to circulate in the plasma, but a small fraction of circulating 5-methyl THF is bound to a high-affinity transporter, which is a soluble form of the transmembrane transporter (Bailey 2007). The vitamin diffuses especially to the tissues that have a high level of cellular division, such as the bone marrow, gastrointestinal mucosa and immune system (Bates 2003). The excess folate that is not used by tissues is excreted

in the urine in different forms, and a very small amount is excreted in the faeces (Bates 2003; Lee 2013).

Folic acid is essential for the production and maintenance of cells in division, for DNA and RNA synthesis through methylation and for protecting DNA against modifications (Bates 2003; Bailey 2007). In the form of THF compounds, folates act as substrate in single-carbon transfers for methylation reactions (Shane 2008), which are required for the synthesis of purines and thymidylate and the remethylation of homocysteine to methionine (Fox and Stover 2008). Methyl group transfers also involve Vit B12 (Berdanier and Zempleni 2009). In the mitochondria, folates participate in the catabolism of choline, purines and histidine and in the interconversion of serine and glycine (Fox and Stover 2008). Because of its role in DNA and RNA synthesis, as well as in amino acid metabolism, folic acid is an essential nutrient in all processes that involve cell division, such as growth, gestation or immune responses (Bailey 2007; Lamers 2011).

2.2.4.9 Vitamin B12: Cobalamin

The structure of B12 vitamers has the element cobalt in the centre of a planar tetrapyrrole ring called a corrin ring, which makes it the most chemically complex of all the Vits (Institute of Medicine 1998b; FAO/WHO 2001). The natural form of Vit B12 is hydroxocobalamin, and conversion to the different forms of the vitamin occurs in the body after consumption (Institute of Medicine 1998b). The richest dietary sources of cobalamin include the liver and kidney, milk, eggs, fish, cheese and meats, but only bacteria and the microorganisms archaea are capable of synthetizing Vit B12 (Martens et al. 2002). Faeces are a rich source of Vit B12, and many animals, including rabbits, dogs and cats, eat faeces (Watanabe 2007). Ruminant animals absorb hydroxocobalamin of bacterial origin from the rumen, which precedes their small intestine, but they need to receive cobalt in their diet (McDowell 2000). Humans do not absorb bacteria-synthesized hydroxocobalamin, since absorption of Vit B12 occurs in the small intestine but bacterial synthesis occurs in the colon; thus humans must obtain Vit B12 from the diet. Dietary cobalamin comes bound to proteins and is released in the low pH of the stomach by the action of hydrochloric acid and pepsin. Still in the stomach, free forms of Vit B12 are rapidly bound to the salivary protein R, which is a haptocorrin (a family of B12 biding proteins). In the jejunum, the protein R is digested by pancreatic trypsin, and the free Vit B12 is bound to the gastric glycoprotein intrinsic factor (IF) to be absorbed (Green 2005; Zempleni 2007). The cobalamin-IF complex is absorbed via receptor binding in the presence of calcium on the cell membrane of the mucous cells of the terminal ileum (Seetharam 1999; Green 2005). Vit B12 is transported in the portal venous blood bound to one of the three transporter proteins called transcobalamins I, II and III. Transcobalamin II, a hepatic beta-globulin, is the main transporting form of Vit B12 to tissues such as the liver, bone marrow, reticulocytes, lymphoblasts, fibroblasts and kidneys. Transcobalamins I and III are granulocyte glycoproteins that have storage and lesser blood carriage functions

(Mataix and Sánchez de Medina 2009). In the tissues, transcobalamin II is degraded in the lysosomes, and the resulting mitochondrial and cytosolic free active forms, 5-deoxyadenosyl cobalamin and methylcobalamin, respectively, function as coenzymes for important cellular enzymes (FAO/WHO 2001; Green and Miller 2007). The main storage site for Vit B12 is the liver, and most is excreted via the bile. Most of the biliary B12 is recycled via enterohepatic circulation, and excess B12 beyond the blood's binding capacity is excreted in the urine.

Methylcobalamin interacts with folate in the metabolic pathways to form methionine, which is necessary for DNA synthesis in cells undergoing chromosomal replication and division, notably the bone marrow cells. It therefore plays a key role in the formation of erythrocytes and leukocytes (Martens et al. 2002). The folate-cobalamin interaction is critical for normal synthesis of purines and pyrimidines, as well as for amino acid metabolism in all tissues (Shane 2008). Furthermore Vit B12 has fundamental functions in the functioning of the brain and nervous system (Metz 1992). As a cofactor, cobalamins are essential for the mitochondrial methylmalonyl-CoA mutase conversion of methylmalonic acid to succinate, which is critical for fatty acid synthesis and myelin homeostasis, and thus brain and spinal cord functions (Mansoorabadi et al. 2005; Berdanier and Zempleni 2009). Methionine is also required in reactions for myelin sheath phospholipids and neurotransmitter metabolism, and methionine synthesis requires an adequate folate-cobalamin interaction, which means that Vit B12 plays an indirect role in the nervous system (Metz 1992; Mansoorabadi et al. 2005).

2.2.4.10 Vitamin C: Ascorbic Acid

Vit C is an essential nutrient, commonly ingested as ascorbic acid or its oxidized form, dehydroascorbic acid (Institute of Medicine 2000a; Kall 2003). Most animals and plants are able to synthesize Vit C by enzymatic reactions that convert monosaccharides to Vit C (Wheeler et al. 1998). Among the mammals that have lost the ability to synthesize Vit C are humans who need to obtain it from diet. Dietary sources of Vit C include raw vegetables and fruits such as papaya, rosehips, acerola, citrus fruit, guava, kiwi, broccoli, red peppers and other plants (Chatterjee et al. 1975; Ha et al. 2004; Lee 2013). Animal sources also contain Vit C, but it is broken down by cooking and other food processing (Bayer 2013). Ascorbic acid is easily absorbed into the small intestine by simple diffusion and by the active transport sodium vitamin co-transporters and glucose transporters (GLUTs) (Tsukaguchi et al. 1999; Daruwala et al. 1999; Li and Schellhorn 2007). The active form is rapidly oxidized to L-ascorbate acid and to stereoisomer L- and D-isoascorbate. In humans, the absorption rate varies between 70 and 95% with regular intake, but absorption decreases as intake increases. At high intake (1.25 g), human absorption of Vit C may be about 33%, while at low intake (<200 mg), the absorption rate can reach up to 98% (Levine et al. 1996; Wilson 2005). Ascorbic acid passes easily into the tissues and is found in high concentrations in the adrenals, kidneys, liver and spleen, due to the intense oxidative stress resulting from their metabolic processes (Mataix and Sánchez de

Medina 2009). Excess ascorbic acid is catabolized by oxidization by the action of L-ascorbate oxidase and excreted in the urine as Vit C metabolite oxalate, dehydroascorbic acid or ascorbate-2-sulphate; ascorbic acid is also excreted in the urine in its free form as a result of body saturation (Berdanier and Zempleni 2009).

Ascorbic acid is a powerful antioxidant and performs numerous physiological functions in the body. It deactivates free radicals that damage lipid membranes, proteins and DNA and protects other antioxidants such as Vit A and Vit E (Benzie 2003; Rahman 2007). It participates as a coenzyme in hydroxylation reactions in the synthesis of collagen (Carr and Frei 1999). Vit C also acts as a cofactor in the synthesis of carnitine, in the synthesis and catabolism of tyrosine and in the metabolism of microsome (Institute of Medicine 2000a). In reactions for biosynthesis, ascorbate donates electrons to keep iron and copper atoms in their reduced states, preventing oxidation (Jacob et al. 1987; Harris and Percival 1991; Hunt et al. 1994; Lee 2013). Throughout this reducing action to key enzymes, Vit C assures that the collagen molecule assumes its triple helix structure, essential to the development and maintenance of the scar tissue, blood vessels and cartilage (Institute of Medicine 2000a). The synthesis of carnitine, which is essential for the transport of fatty acids into the mitochondria for ATP generation, depends on the reducing action of Vit C (Dunn et al. 1984; Rebouche 1991). In the immune cells, Vit C is consumed in large quantities during infections, participating in the activities of phagocytes, the production of cytokines and lymphocytes (Shilotri and Bhat 1977; Delafuente et al. 1986; Ströhle and Hahn 2009).

2.2.4.11 Vitamin D: Cholecalciferol

Similarly to Vit A, Vit D is not a single compound, but a family of vitamers serving as provitamin D with a sterol structure that differ only in their side chains (Wolf 2004; Norman and Hentry 2007; Christakos et al. 2010; Lee 2013; Bikle 2014). Vit D2 comes from a common plant steroid, ergosterol (Bikle 2014). Most mammals can convert D2 to D3 and use it to make the active form (1,25-dihydroxycholecalciferol) which is responsible for its biological function (Berdanier and Zempleni 2009). Vit D3 is synthesized endogenously in the body, and its main dietary sources include fish, fish/cod liver oil, liver, buttermilk and egg yolks (Nair and Maseeh 2012; Lee 2013). Dietary Vit D is absorbed in the small intestine with long-chain fatty acids with the help of bile salts and becomes part of the chylomicrons in the lymphatic system (Norman and Hentry 2007; Nair and Maseeh 2012; Julve et al. 2016). Absorption takes place mainly in the jejunum and ileum. When there is more requirement, Vit D is reabsorbed in the duodenum from the bile, which is its principal excretory pathway (Berdanier and Zempleni 2009; Nair and Maseeh 2012). Absorbed Vit D is transported to the liver in its nonesterified form bound to the Vit D-binding protein, which is similar to the α-2 globulins and albumins (Berdanier and Zempleni 2009; Christakos et al. 2010; Bikle 2014). Dermal synthesis of Vit D also occurs when natural sunlight or ultraviolet irradiation acts on the 7-dehidrocholesterol to form cholecalciferol or D3, which is biologically inactive

(Webb et al. 1989; Holick 2005; Nair and Maseeh 2012). D3 undergoes two hydroxylation reactions; in the liver, cholecalciferol is converted to calcifediol (or 25-hydroxycholecalciferol or 25-hydroxyvitamin D), which is a biologically active metabolite. The other reaction occurs in the kidneys with the formation of calcitriol (1,25-dihydroxycholecalciferol or 1,25-dihydroxyvitamin D3), which is the hormonally active metabolite of Vit D. Calcitriol is capable of increasing calcium levels in the blood by inducing Ca uptake in the intestine, Ca reabsorption in the kidneys and Ca mobilization in the bone (Norman and Hentry 2007; Lee 2013; Hill and Aspray 2017). It is known that 25-hydroxycholecalciferol can accumulate in the heart, lungs, kidneys and liver (Christakos et al. 2010). Even though there are gaps in the knowledge of Vit D catabolism, the excretion of it and its metabolites occur primarily in the faeces with the aid of bile salts and small amounts in the urine (Norman and Hentry 2007; Lee 2013). Consumption of excess Vit D over extended periods of time causes toxic conditions resulting in excess calcification not only of bone but also of soft tissues, causing a variety of clinical alterations. The development of Vit D hypervitaminosis seems to depend on individual susceptibility (Morita et al. 1993; Holick 2005; Berdanier and Zempleni 2009).

The first understood Vit D function in the body was to regulate mineral homeostasis, mainly in calcium absorption and phosphate uptake (Holick 2005; Lee 2013; Bikle 2014). Calcitriol acts in conjunction with parathormone and calcitonin, to maintain serum calcium and phosphate levels by its actions on the intestine, kidneys, bone and parathyroid gland (Norman and Hentry 2007; Nair and Maseeh 2012). Calcitriol is also considered a hormone secosteroid (a subclass of steroids), which also promotes intestinal absorption of iron, magnesium, phosphate and zinc (Pérez-López 2007; Ghoneim et al. 2015). It also participates in neuromuscular and immune function (Lee 2013; Toussaint and Damasiewicz 2017). Muscle contraction is influenced by a direct effect on Ca^{2+} transport (Norman and Hentry 2007). Vit D influences insulin production by the endocrine pancreas (Nair and Maseeh 2012), skin and hair growth and regeneration (Bouillon et al. 2006). Concerning lipid metabolism, Vit D acts on the regulation of the glyoxylate cycle in the liver, stimulates cell proliferation in the adipose tissue via reactive oxygen species (ROS) (Sun and Zemel 2007) and modulates the adipocyte glucocorticoid function (Morris and Zemel 2005). Calcitriol regulates many genes (Omdahl et al. 2002) by binding to the Vit D-specific receptor in DNA sequences, following the typical mechanism of steroid hormone action (Pike and Meyer 2010). Thus, Vit D can be considered both a nutrient, particularly in conditions of little exposure to ultraviolet light, and a hormone because the body can completely synthesize the active form calcitriol from prohormone D2 or D3 (Norman 2008). Unlike herbivores and omnivores, dogs and cats are not able to synthesize Vit D3 adequately in the skin and are mainly dependent on dietary intake, which means that Vit D3 is an essential vitamin that should be present in dog and cat food (How et al. 1994).

2.2.4.12 Vitamin E: Tocopherol

Vit E includes two groups of compounds, tocopherols and tocotrienols, which come from animal sources such as fish oils and fats and vegetable sources such as wheat germ, rosehips, various nuts, corn, sunflower or soy oils. Four tocopherol and four tocotrienol molecules, identified by the prefixes alpha- (α), beta- (β), gamma- (γ) and delta- (δ), contribute to Vit E activity (Hacquebard and Carpentier 2005; Lee 2013). Alpha-tocopherol is the most biologically active form of the vitamin (Hacquebard and Carpentier 2005). During digestion, Vit E is included in micellar compounds together with lipids. Tocopherol favours the activity of Vit A to prevent its oxidation in the intestine. Additionally, other antioxidants affect Vit E absorption and organic levels; the intake of β-carotene, ascorbic acid and polyunsaturated fatty acid can markedly influence the rate of the use of α-tocopherol as an antioxidant (Omur et al. 2016). Low selenium intake increases the need for Vit E and vice versa, because selenium is a component of the glutathione peroxidase system, which suppresses free radical production (Berdanier and Zempleni 2009). Following absorption, Vit E is transported in the blood with the chylomicrons in the lymph to the liver. From the liver, tocopherol is transported with VLDL proteins in the blood to be stored in the adipose tissue (Drevon 1991; Lee 2013; Yang and McClements 2013; Goncalves et al. 2015). However, Vit E does not accumulate in the liver, suggesting that its catabolism and excretion are important (Brigelius-Flohé and Traber 1999; Herrera and Barbas 2001). Tocopherols are distributed to all cells in the body, and they are found in higher cell concentrations within adrenal, pituitary, testicular cells and platelets (Drevon 1991; Berdanier and Zempleni 2009). Tocopherol-specific binding proteins have been found within hepatic and heart cells, where α-tocopherol is transferred from liposomes to mitochondria (Stocker and Azzi 2000). The major excretion route is the intestine, via the elimination of hepatic Vit E into the bile, and a small part is excreted in the urine (Brigelius-Flohé and Traber 1999; Herrera and Barbas 2001).

Alpha-tocopherol is an important antioxidant that participates in the glutathione peroxidase pathway and protects cell membranes from oxidation by reacting with lipid free radicals produced by the peroxidation chain reaction, particularly on the phospholipids of the membranes (Omur et al. 2016). Besides removing the free radical intermediates as a peroxyl radical scavenger, α-tocopherol prevents oxidation from continuing in reactions that result in oxidized α-tocopheroxyl radicals (Hacquebard and Carpentier 2005). Other antioxidants, such as ascorbate, retinol or ubiquinol, act on the transformation of α-tocopheroxyl radicals into their active reduced form (Traber 2007; Omur et al. 2016). Thus, at the cellular level, α-tocopherol protects the membranes from oxidation resulting from the release of free radicals in many metabolic reactions, immune responses, inflammation or environmental toxins (Clarkson and Thompson 2000; Cases et al. 2005; Traber 2007; Choe and Min 2009). Glutathione peroxidase, a selenoenzyme, protects haemoglobin and the cell membranes by detoxifying lipid hydroperoxides to less toxic fatty acids and by preventing the formation of free radicals; Vit E potentiates its

action by serving as a free radical scavenger to prevent the formation of lipid hydroperoxide (Rowe and Wills 1976; Krajcovicová-Kudlácková et al. 2004; Berdanier and Zempleni 2009; Birben et al. 2012). In addition, α-tocopherol protects against iron toxicity related to free radical formation (Berdanier and Zempleni 2009). Other functions of Vit E include (1) protection against DNA oxidation thus benefiting erythropoiesis, (2) steroid hormone synthesis and spermatogenesis (McCall and Frei 1999; Rahman 2007), (3) interaction with zinc in the metabolism and protection of skin lipids (Park 2015), (4) participation in the neuromuscular functions (Muller 1986) and (5) inhibition on thromboxane, prostaglandin and enhancing prostacyclin, thus regulating inflammation and the aggregation of platelets (Rimbach et al. 2002; Norman and Hentry 2007).

2.2.4.13 Vitamin K: Phylloquinone (Vit K1) and Menaquinone (Vit K2)

The menaquinone (Vit K2) family of liposoluble vitamins occurs in animal and human tissues as isomers, which are abbreviated as MK-n (M = menaquinone; K = Vit K; n = number of isoprenoid side chain residues, up to 20) (Klack and de Carvalho 2006; Shearer and Newman 2008; Bayer 2013). Dietary sources of Vit K2 are mostly in the form of menaquinone-4 or MK-4 (also menatetrenone), a short-chain menaquinone present in egg yolk, meat, liver or dairy products. Phylloquinone (Vit K1) is found in vegetables where it plays roles in the photosynthesis. Green vegetables and cereals are important dietary sources of phylloquinone, which is considered a precursor of Vit K for animals (Shearer and Newman 2008). Menakinone-4 is the most common type of Vit K2 in animal products because MK-4 is synthesized from Vit K1 in animal tissues. Within human and animal digestive tracts, a species-dependent amount of Vit K1 is absorbed by the cells of intestine segments (Berdanier and Zempleni 2009); the other amount of phylloquinone is converted to menaquinone-7 by bacteria, which also produce other isomers of Vit K2 that play a role in the metabolism of intestinal microbiota (Bentley and Meganathan 1982; Walther et al. 2013). Absorption of Vit K is an active energy-dependent process that requires bile and pancreatic juice; subsequently either phylloquinone or menaquinone-4 is incorporated into chylomicrons and transported through lymphatic vessels to the bloodstream reaching the liver (Suttie 2007; Card et al. 2014). The liver has an exclusive role in Vit K1 catabolism and excretion in a very fast turnover, and this is the reason why the diet should provide regularly adequate amounts of K1 (Suttie 2007; Lee 2013; Gonçalves et al. 2015). Vit K is distributed throughout the body tissues by the blood and transported by lipoproteins (Shearer and Newman 2008). However, most of Vit K1 and MK-4 are transported by triacylglycerol-rich lipoproteins to be metabolized in the liver (Dôres et al. 2001) from which only a small fraction is released into the circulation where Vit K forms are transported by LDL and HDL. The liver acts as a site for storage and redistribution of long-chain menaquinones (such as MK-7, MK-8 or MK-9) coupled to LDL. Because LDL has a long half-life in the circulation, long-chain menaquinones become available for extra-hepatic tissues, where they accumulate

and perform Vit K functions not related to haemostasis, such as the suppression of inflammation, prevention of brain oxidative damage and a role in the synthesis of sphingolipids (Shearer and Newman 2008). On the other hand, tissues that accumulate high amounts of MK-4, such as the pancreas, arterial walls and testes, are the ones that have a significant capacity to convert the available Vit K1 into MK-4 (Thijssen and Drittij-Reijnders 1996; Suttie 2007). Conversion of phylloquinone or long-chain menaquinones to MK-4 is therefore a major metabolic pathway of Vit K use in tissues (Shearer et al. 2012; Lee 2013). Hepatic catabolism of Vit K involves oxidative degradation of the phytyl side chain, with the participation of enzymes also involved in fatty acids and steroids, and prostaglandin catabolism, and this results in the urinary excretion of catabolites (Bates 2005b; Shearer et al. 2012).

The functions of Vit K include those related to haemostasis and many others, more recently described (Shearer and Newman 2008), but in general terms, this vitamin serves as a co-substrate in the production of unique calcium-binding proteins in the blood, bone and kidneys (Berdanier and Zempleni 2009). In the liver, Vit K1 is reduced to hydronaphtoquinone (KH_2), which is the active cofactor for the enzyme carboxylase (Shearer and Newman 2008; Ferland 2012). Carboxylase acts on the carboxylation of glutamate residues in proteins to form gamma-carboxyglutamate (Gla), which has various functions. In the liver, Gla participates in the synthesis of coagulation factors prothrombin (factor II); factors VII, IX and X; and proteins C, S and Z (Suttie 2007). In bone metabolism, Gla forms osteocalcin, also called bone Gla protein which is secreted by osteoblasts and is essential for bone mineralization, periostin (Shanahan et al. 1998; Coutu et al. 2008) and the recently discovered Gla-rich protein (Viegas et al. 2008). Gla forms the matrix Gla protein, which is found in numerous body tissues and acts by inhibiting calcification, but its role is most pronounced in the cartilage, kidneys and arterial vessel walls (Cancela et al. 2012; Viegas et al. 2014). In the endothelial cells of arteries and leukocytes, Gla forms the growth arrest-specific protein-6 which acts for cell survival, proliferation, migration and adhesion (Hafizi and Dahlbäck 2006; Dihingia et al. 2017). Other non-cofactor functions of Vit K include modulation of inflammation, prevention of oxidative injury in the brain and a participation in the synthesis of sphingolipid (Shearer and Newman, 2008). Vit K2 acts in balance with Vit D3 to maintain calcium metabolism and homeostasis in the blood, bone and other tissues (Suttie 2007). A role for Vit K in the prevention of tumorigenesis has been described; synthetic menadione (K3) inhibits aryl hydrocarbon hydroxylase, thus reducing the levels of carcinogenic and mutagenic metabolites in the cell resulting in a reduction in tumour formation (Osada and Carr 2000; Osada et al. 2001).

2.2.5 Minerals

There are 103 known mineral elements. Living organisms are composed mainly of 11 of them, which are fundamental for maintaining key bodily functions. Minerals are categorized into macroelements, oligoelements and trace elements according to

the daily dietary requirements. Macroelements must be supplied in more than 100 mg/day (Ca, Mg, P, Na, K, Cl and S). Oligoelements must be supplied between 1 and 100 mg/day (Zn, Fe, Mn, Cu and F). Trace elements must be supplied in less than 1 mg/day (Se, Mo, I, Cr, B and Co) (Freeland-Graves and Trotter 2003; Mataix and Sánchez de Medina 2009; Lee 2013). In this section, the main functions of minerals in the metabolic processes of the cells are discussed, as well as dietary natural sources and overall absorption processes.

2.2.5.1 Calcium: Ca

Calcium is the most abundant mineral in the body and regulates many metabolic functions. It comprises 1.5% to 2% of body weight and 39% of total body minerals; 99% of the body's total amount of Ca is in the bones and teeth, and 1% is in blood, extracellular fluids and inside soft tissue cells. Dietary sources of Ca are milk and dairy products, eggs, green leafy vegetables, almonds, molasses, soybeans, fish and seafood (L'Abbé 2003; Peacock 2010; Institute of Medicine 2011). Calcium absorption from the diet is variable; about 23 to 8% is absorbed in the duodenum whose content is predominantly acidic, but absorption is greatly reduced in the lower part of the intestinal tract where the contents are more alkaline (McCormick 2002). In the duodenum and proximal jejunum, absorption occurs by active transport, controlled by the action of Vit D3, which increases the uptake of Ca at the brush border of the intestinal mucosal cell by stimulating the production of a calcium-binding protein (calbindin) (Ebeling et al. 1992; Kojetin et al. 2006; Berdanier and Zempleni 2009). The role of calbindins in intestinal absorption cells is to temporarily store Ca ions after a meal and to transport them to the basolateral membrane for the final passage of absorption. A second mechanism for Ca absorption does not depend on Vit D, rather it is passive and non-saturable and occurs throughout the intestine, mainly in the jejunum but also in the colon; this system prevails if the diet is very rich in Ca (Wasserman and Fullmer 1989; Xue and Fleet 2009; Institute of Medicine 2011). Factors that promote higher absorption of Ca include Vit D and the presence of other nutrients such as lactose and proteins in the digestive content. Decreased absorption of Ca occurs during Vit D deficiency and excess fibre, oxalate and phytate in the diet (Pereira et al. 2009). Ageing and poor absorption of fats impair Ca absorption due to the saponification of fatty acid with Ca in the digestive tract (Gacs and Barltrop 1977; Wang et al. 2013). Half of blood calcium is bound to proteins, mainly to albumin and globulin; the rest circulates the form of free ions and diffusible complexes (Peacock 2010). Approximately 5 to 20% of the ingested Ca is excreted in the urine; although its intake may vary greatly, calciuria is slightly modified. Tubular reabsorption of Ca in the kidneys occurs by transport mechanisms similar to those of the intestine. The urine contains little Ca compared to the amount filtered in the glomerulus, because the proximal tubule, the loop of Henle and the distal tubule reabsorb most of it (approximately 85%). An average loss of 10% of dietary intake of Ca occurs by skin exfoliation and sweating in humans (Goldschmied et al. 1975; Heaney and Rafferty 2001; Institute of Medicine 2011). The faeces contain Ca from

excess in diet, cell exfoliation of the whole digestive tract and Ca metabolites from bile (Abrams et al. 1991; Berdanier and Zempleni 2009).

Calcium functions as an integral part of all signalling systems (as a second messenger) between and within cells in the body, and metabolic regulation and interactions depend largely on cell communication (Berdanier and Zempleni 2009). The readily binding of Ca to proteins, changing the electrical charges on the protein chain, causes modification in the protein's tertiary structure, as occurs in the coagulation cascade that requires Ca as an activation factor. A large number of extracellular enzymes require Ca as a cofactor. Calcium participates in the contraction of the skeletal, smooth and heart muscles, neurotransmission, reactions during cellular division and various forms of endocrine and exocrine secretion (L'Abbé 2003; Peacock 2010; Institute of Medicine 2011). Calcium is involved in the transport of many nutrients in the cells of the digestive system and participates in many processes related to cell membrane homeostasis (Lee 2013).

2.2.5.2 Phosphorus: P

Phosphorus is one of the essential elements in nutrition, and it exists in the cells as phosphate (PO^{-}_{4}) compounds. In their free form, phosphates are called inorganic phosphate generally symbolized by Pi (Berdanier and Zempleni 2009). About 85% of phosphates in the body exist as calcium phosphate crystals in the bones and teeth, and the remaining is metabolically active and distributed in all cells of the body and in the extracellular fluid (Institute of Medicine 1997a; Anderson 2003; Lee 2013). Dietary sources of phosphates include meats, poultry, eggs, fish, dairy products, vegetables, cereals and legumes, where they are as organic and inorganic phosphates. Organic phosphates are bound to proteins, mostly at serine, threonine and tyrosine residues. Most inorganic phosphate is absorbed by the action of inorganic phosphatase. The presence of glucose in the diet enhances phosphate absorption. Absorbed phosphates are promptly distributed in the viscera, bones, skin and muscles (Wasserman 1981; Institute of Medicine 1997a; Anderson 2003; Lee 2013). The kidneys are the main site for phosphate regulation and excretion. Some phosphates are also excreted in the faeces and come from excess P in the diet and digestive tract secretions (Lee 2013).

Phosphorus plays an important role in organic and inorganic compounds and is involved in many aspects of metabolism and growth, including energy use, bone mineralization, blood buffering, cell membrane bipolarity and kinase-mediated signal transduction, and it has fundamental functions in immune responses (Kegley et al. 2001; Oster et al. 2016). Phosphorylation and dephosphorylation are important mechanisms for energy storage and are used in the regulation of metabolic processes involving ATP. Adenosine phosphates (AMP, ADP and ATP) release phosphates throughout hydrolysis by the action of phosphatases (Krebs and Beavo 1979; Kurosawa 1994; Berdanier and Zempleni 2009). Phosphorus is a component of adenine and guanine nucleotides and provides stability to DNA and RNA molecules, due to its capacity to retain a negative charge thus repelling other negatively charged

molecules such as peroxides (Lodish et al. 2000a; Berdanier and Zempleni 2009). Phosphates are present in phospholipids, which are necessary for the functional characteristics of the membranes of cells and organelles, and phosphoproteins (Berdanier and Zempleni 2009). Phosphorus works in conjunction with Vit D3 and calcium, either in metabolic processes related to the formation of hydroxyapatite in bone mineralization or in the regulation of the homeostasis of cells and system as a second messenger (Gil Hernández and Sánchez de Medina Contreras 2010). Phosphates participate in all anabolic and catabolic pathways (Institute of Medicine 1997a; Berg et al. 2002c; Anderson 2003; Berdanier and Zempleni 2009; Lee 2013).

2.2.5.3 Magnesium: Mg

Magnesium is an essential mineral nutrient that occurs as the Mg^{2+} ion (Griffin 2003). The main dietary sources are brewer's yeast, green leafy vegetables, nuts, seeds, soybeans, oats or milk. An average of 20 to 50% of dietary Mg is absorbed throughout the small intestine, but most of the absorption occurs in the jejunum by a transporter-dependent diffusion and simple diffusion. At low intraluminal concentrations, Mg is absorbed via saturable active diffusion, whereas a non-saturable passive diffusion acts at high concentrations (Fine et al. 1991; Griffin 2003; Vormann 2003; Lee 2013). Magnesium absorption depends on the quantity of protein in the diet because a protein intake which is too low or too high inhibits Mg absorption, as does the amount of phosphate, phytate and fat in the gut (Fine et al. 1991; Vormann 2003). In the plasma, Mg is transported as free ions (55%) or in complexes with proteins and phosphate (45%) (Griffin 2003). Because membranes are impermeable to Mg, as they are to other ions, intracellular and extracellular concentrations of free Mg are sustained by a balance between buffering by binding to proteins and other molecules and transferring Mg ions to storage or extracellular spaces (DiSilvestro 2005). Thus, serum Mg levels may be normal even when intracellular magnesium is deficient (Jahnen-Dechent and Ketteler 2012). In the body, 60% Mg is distributed in the bones, 26% in the muscles and the rest inside soft tissue cells; 1% of Mg is found in extracellular space and body fluids (Institute of Medicine 1997b; Jahnen-Dechent and Ketteler 2012). Intracellular Mg correlates with intracellular potassium, and increased Mg lowers Ca (Whang and Whang 1990; Institute of Medicine 1997b; Jahnen-Dechent and Ketteler 2012). Unabsorbed dietary Mg is excreted in the faeces, while absorbed Mg is excreted in the urine and sweat (Wester 1987; Vormann 2003).

Magnesium interacts closely with phosphate and plays an essential role in the metabolism of nucleic acid. About 300 enzymes involved in nucleic acid metabolism require Mg as a cofactor, and one of its most important functions is to stabilize the structure of ATP in ATP-dependent enzymatic reactions (Vormann 2003), as it helps to maintain the double helical structure of DNA (Hartwig 2001). Magnesium-bound ATP is the substrate for enzymes such as kinases. Magnesium-calcium interactions are fundamental for the function of excitable membranes and neuromuscular transmission (Griffin 2003), as they are for the humoral and cellular immunocompetence

by acting as an immunomodulatory agent and as an important element for thymic function (Keen et al. 2004).

2.2.5.4 Sodium Na, Chlorine Cl and Potassium K

Sodium, chlorine and potassium act together in the body being essential nutrients for metabolism. The body content of these three minerals is 2% sodium, 3% chlorine and 5% potassium. The main dietary source of Na and Cl is sodium chloride or common salt, while the main source of K are fruits and vegetables, fresh meat and milk (DiSilvestro 2005; Berdanier and Zempleni 2009; Lee 2013). All three elements are easily absorbed through the intestinal tract and distributed in all body fluids and tissues. The primary site of K absorption is the small intestine where most of the dietary K entry into the gastrointestinal tract occurs by passive diffusion (Stone et al. 2016). Sodium is the most prevalent metallic ion in extracellular fluid (Pohl et al. 2013), and ion transporters in the cell membrane maintain the balance between K and Na (Lodish et al. 2000b; Berdanier and Zempleni 2009; Lee 2013). A decrease in blood pressure and Na concentration triggers the kidneys' production of renin, which induces the liberation of aldosterone and angiotensin, which in turn promotes Na filtration from the urine. When the concentration of sodium increases, the receptors in the hypothalamus stimulate the sensation of thirst and the production of renin decreases, and excretion of Na in the urine by the kidneys returns to normal (Kurtzman et al. 1972; Greger 2000; Berdanier and Zempleni 2009). Ionized potassium is excreted in place of ionized sodium by the renal tubular exchange mechanism, which is also regulated by the renin-angiotensin system (Sealey et al. 1970; Laragh and Sealey 2011). Most Na excretion is via renal, but faeces and sweat excretion also occur. About 90% of dietary K is excreted in the urine and 10% in the faeces. Chlorine is excreted mostly as chloride acid in gastric secretion and the faeces (Klevay et al. 2007; Berdanier and Zempleni 2009).

Sodium regulates blood volume, blood pressure, osmotic equilibrium and pH throughout the renin-angiotensin system (Haddy 1991; Haddy et al. 2006; Lee 2013). Chlorine is needed for the production of hydrochloric acid in the stomach and in cellular pump functions and plays an important role in the acid-base balance (Linus Pauling Institute 2016). Potassium is the major cation inside cells, while Na is the major cation outside cells, and different concentrations of Na and K produce different intracellular and extracellular electric potential, which is called membrane potential. Electricity is fundamental for systems such as heart function, neurotransmission and muscle contraction (Alberts et al. 2002a; Berdanier and Zempleni 2009). This mechanism relies on Na^+/K^+-ATPase, an active transporter pumping ion against the gradient, and sodium/potassium channels (Lopina 2000). The transport of some amino acids requires the $Na^+/K^+/Ca$-ATPase pump system, which is also important in the regulation of the cell volume and the maintenance of membrane potential (Lopina 2000; Alberts et al. 2002b).

2.2.5.5 Sulphur: S

Sulphur is an essential element in nutrition. After calcium and phosphorus, it is the third most abundant element in the body and constitutes nucleic acids, amino acids, sulphate esters of polysaccharides, steroids, phenols and sulphur-containing coenzymes and cofactors (Nimni et al. 2007; Berdanier and Zempleni 2009; Lee 2013). Plant and animal dietary sources of sulphur are mostly proteins containing the amino acids cysteine and methionine, which are present in meats, fish, poultry, eggs, broccoli, cauliflower and beans. Methionine is an essential amino acid in diet, and apart from Vit B1 (thiamine), Vit B5 (pantothenic acid) and Vit B7 (biotin), cysteine and all sulphur-containing compounds in the body are synthesized from methionine (National Research Council 1989; Brosnan and Brosnan 2006; Berdanier and Zempleni 2009). Reduced sulphur is oxidized in the body by the enzyme sulphide oxidase, which is needed for the metabolism of methionine and cysteine (Florin et al. 1991; Sekowska et al. 2000; DiSilvestro 2005). As dietary sulphur comes with proteins, its digestion, absorption and transport are dependent on the processes that occur for protein metabolism in the body (see above). Cysteine and methionine are oxidized to sulphate by sulphide oxidase, eliminated in the urine or stored as glutathione, which can serve as a store for sulphur (Florin et al. 1991; Nimni et al. 2007). Moreover, the metabolism of other sulphur-containing amino acids such as homocysteine, a methionine catabolite, and taurine also generates inorganic acids, especially sulphate anions, in substantial amounts. Excess inorganic sulphur generated in the hepatic or renal metabolism is excreted in the urine, as sulphates (Florin et al. 1991).

Sulphur plays essential roles in amino acid and protein metabolism and functions. In cell metabolism, sulphur participates in reactions of oxidation-reduction as an antioxidant because the amino acids cysteine and methionine are used in the synthesis of glutathione. Reduced glutathione, a sulphur-containing tripeptide, is a reducing agent through its sulfhydryl (-SH) moiety derived from cysteine. Thioredoxins, a class of small proteins essential to all known life, use adjacent pairs of reduced cysteines to function as general protein reducing agents, with a redox similar function (Parcell 2002; Nimni et al. 2007; Berdanier and Zempleni 2009; Lee 2013; Mukwevho et al. 2014). In the metabolism of carbohydrates and fatty acids, important enzymes require sulphur-containing moieties in reactions involving acyl groups, such as CoA and alpha-lipoic acid (Oda 2006; Berdanier and Zempleni 2009). Sulphur is a component of heparin which acts as an anticoagulant and of chondroitin sulphate which constitutes cartilages and bones (Parcell 2002; Maeda et al. 2011; Sarrazin et al. 2011; Mikami and Kitagawa 2013).

2.2.5.6 Iron: Fe

Iron is distributed in the body as functional iron and as storage iron (DiSilvestro 2005; Lee 2013). Functional iron is included in haemoglobin, myoglobin, cytochromes and

various proteins that work in the transport, storage and use of oxygen. Storage iron compounds include ferritin and hemosiderin within the liver, bone marrow, spleen and muscle cells (Lynch 2003). Most body iron exists as heme within haemoglobin (about 70%) and myoglobin (about 2.5%); the remaining is distributed in tissue macrophages (about 5%) and liver hepatocytes (about 20%) (Papanikolaou and Pantopoulos 2017), while enzymes contain about 0.5% of it (Harris 2013). Depending on the dietary origin, iron is categorized as heminic or non-heminic. Heminic iron is found in haemoglobin and myoglobin present in the liver, kidney and heart and meat, fish and poultry; non-heminic iron comes from plants, mainly from green leafy vegetables and beans, and from animal proteins that do not contain heme iron, such as milk and eggs (Lee 2013; Wessling-Resnick 2014). Iron is more easily absorbed in the duodenum in the ferrous (Fe^{2+}) state as it occurs in rich heme-containing meat products, but most dietary iron is in the form of inorganic ferric iron (Fe^{3+}), which comes from non-heminic dietary sources (Lynch 2003). Apoferritin on the membrane of duodenum cells binds some Fe^{3+} to form cytosolic ferritin, which stores iron; this iron will be eliminated with dead cells shed into the faeces (Lynch 2003; Wessling-Resnick 2014). Gastric and intestinal secretions containing duodenal cytochrome-b or other ferrireductases reduce intraluminal Fe^{3+} to Fe^{2+} (Papanikolaou and Pantopoulos 2017), a process that is facilitated by ascorbic acid, sugar and sulphur-containing amino acids (Lee 2013). Inhibition of iron absorption occurs by excess phytates, phosphates, oxalates, tannins, calcium and fibre, as well as by heightened intestinal motility or poor digestion of fats (Gillooly et al. 1983; Hurrell and Egli 2010). Ferrous iron is transported across the membrane of enterocytes by the divalent metal transporter-1 (DMT1), to be then exported to the circulation via ferroportin. Ferroportin transporting is helped by re-oxidation of Fe^{2+} to Fe^{3+} by a membrane-bound hephaestin, a cupper-dependent ferroxidase, or by ceruloplasmin, a soluble ferroxidase (Papanikolaou and Pantopoulos 2017). Iron transporting by ferroportin is inhibited by hepcidin, a 25-amino acid peptide hormone produced in the liver that regulates iron efflux to the plasma (Ganz and Nemeth 2015). Absorption of dietary heme iron requires uptake by mucosal apoferritin (Jacobs 1971), catabolism of heme within enterocytes and release of Fe^{2+} that from this point undergoes the same process as inorganic dietary iron (Papanikolaou and Pantopoulos 2017). Transferrin, the plasma iron carrier, takes up Fe^{3+} and transports it to reticuloendothelial cells in the bone marrow, spleen and liver and muscle cells (Klawe 2003). These cells have transferrin receptors, which facilitate the uptake of iron by endocytosis. Within the acidic endosomal cells, transferrin releases iron, which is reduced by a ferrireductase and then transported into intracellular compartments via DMT1. Membrane apo-transferrin releases iron back into the bloodstream, and transferrin recaptures it to engage in further cycles of iron delivery to cells (Papanikolaou and Pantopoulos 2017). The contribution of dietary iron released by enterocytes to maintain the circulating transferrin iron pool is very low because iron is not excreted by any physiological regulatory mechanism (Abbaspour et al. 2014). There is a steady and slight iron loss via gastrointestinal blood loss, sweating and shedding cells of the skin and the mucosal lining of the gastrointestinal tract (Drakesmith and Prentice 2012; Wessling-Resnick 2014). In physiological conditions, apo-transferrin

is mostly reloaded with iron provided by tissue macrophages after erythrophagocytosis, the macrophage-mediated iron recycling system from senescent red blood cells into erythropoiesis (Knutson et al. 2005; Papanikolaou and Pantopoulos 2017). When plasma iron is limited, iron mobilization from ferritin contributes to erythropoiesis, via lysosomal ferritin degradation within the hepatocytes, bone marrow or spleen, and the liberated iron is exported to the bloodstream via ferroportin (Wang and Pantopoulos 2011; Ganz and Nemeth 2015). Hemosiderin is mostly found in macrophages, and it seems to result from the accumulation of ferritin or denatured ferritin following pathological conditions. The iron within the hemosiderin stores is much less bioavailable to supply iron on demand (Linder 2013; Abbaspour et al. 2014).

Several iron-containing proteins are involved in fundamental organic functions, such as cytochromes for energy production; ribonucleotide reductase, amino acid oxidases or fatty acid desaturases for intermediary metabolism and detoxification; tyrosine hydroxylase and thyroperoxidase for synthesis of hormones and neurotransmitters; and myeloperoxidase, nitric oxide synthases and lipoxygenases for host defence and inflammation (Ganz and Nemeth 2015). Iron acts as a cofactor for numerous metalloproteins, mainly as part of heme or iron-sulphur clusters, which are essential for oxygen transport and for electron transfer and catalytic reactions (Liu et al. 2014; Papanikolaou and Pantopoulos 2017). The chemical reactivity of iron makes it capable of interacting with proteins to function as an electron donor and acceptor in reduction and oxidation reactions (Berdanier and Zempleni 2009; Olson et al. 2013). However, this property makes iron extremely toxic in its free form because it acts as a catalyst of oxidative stress via the Fenton/Haber-Weiss reaction (Kanti Das et al. 2014; Papanikolaou and Pantopoulos 2017). The strict control of iron in the body assures its proper functioning while preventing its detrimental effects mainly by binding iron to proteins (DiSilvestro 2005; Gozzelino and Arosio 2016). The buffering capacity of apo-transferrin prevents the accumulation of free non-transferrin-bound iron, which is redox-active and toxic (Papanikolaou and Pantopoulos 2017). Controlling iron release in plasma is also an important mechanism of infection control by the body, because bacteria and other microorganisms have to obtain iron from the environment (DiSilvestro 2005; Drakesmith and Prentice 2012). The release of hepcidin as a response to signs of infection and inflammation causes intense hypoferremia due to iron retention in macrophages and inhibition of iron transport by ferroportin, resulting in the disruption of bacteria metabolic pathways and multiplication (Ganz and Nemeth 2015).

2.2.5.7 Zinc: Zn

Zinc acts as an intracellular ion and is an essential trace element for animals and humans. Zinc associates with more than 300 enzymes and is the only metal that appears in all enzyme classes (Sandstead 1994; Rink and Gabriel 2000; Institute of Medicine 2001b; Lee 2013). The body of an adult human contains about two grams of zinc, with higher concentrations in the brain, bones, liver, pancreas, kidneys,

bones and muscles, followed by the eye, prostate, spermatozoa, skin, hair and nails (Berdanier and Zempleni 2009; Kaur et al. 2014). Dietary sources of zinc include shellfish, meat, fish, poultry eggs, dairy, seeds, alfalfa, celery, legumes, nuts and wholegrains (Institute of Medicine 2001b; Solomons 2003; Kaur et al. 2014). Zinc absorption is relatively poor, an average 10 to 40% of all the ingested minerals with food, and it occurs in the small intestine by passive diffusion or throughout binding to metallothionein protein, which is favoured by Vit D3 (Berdanier and Zempleni 2009; Roohani et al. 2013). Dietary proteins, glucose and lactose favour zinc absorption, while phytates and excess fibre, phosphates and iron or calcium inhibit it and favour zinc excretion in the faeces (Lönnerdal 2000; Lee 2013). After entering enterocytes, Zn is bound to a cysteine-rich intestinal protein that in turn transfers it to either metallothionein or albumin, which carries it in the plasma (Berdanier and Zempleni 2009). In the plasma, albumin-, transferrin- or α-2 macroglobulin-bound Zn is chelated to free amino acids or small peptides (Foote and Delves 1984; Solomons 2003). This Zn^{+2} ultrafiltrate is excreted in the urine or faeces through biliary excretion (Baek et al. 2012). Most of the absorbed zinc is taken up by the liver, where it is stored bound to metallothionein, before it is distributed to other tissues (Osredkar 2011).

Zinc has structural, catalytic and regulatory functions in the cells (Maret 2013). As a cofactor for enzymes, zinc has roles in cell replication, tissue growth and repair, bone formation, skin integrity and immunity (Freeland-Graves and Bavik 2003). It is a catalytic agent in hydroxylation and other enzymatic reactions, participating in reactions that lead to the synthesis or degradation of nutrients such as carbohydrates, proteins, lipids, nucleic acids and vitamins (Ruz 2003; Berdanier and Zempleni 2009). In the brain, zinc modulates neuronal excitability and is stored in specific synaptic vesicles by glutamatergic neurons (Huang 1997). Zinc also participates in intracellular signalling pathways to regulate cell functions that include salivary glands, the prostate, the immune system and intestine cell proliferation and survival, ion transport and hormone secretion (Hershfinkel et al. 2007).

2.2.5.8 Copper: Cu

Copper is an essential dietary trace element with biological importance in reactions of electron transport and oxygen transport (Osredkar 2011). In the body, copper is found mainly in muscles, where about 40% of it is found, followed by the liver, brain, kidneys and heart (Berdanier and Zempleni 2009; Lee 2013). It exists in most foods in very small quantities, but the richest dietary sources include animal products such as shellfish, meat, kidney, liver and a few vegetable foods such as legumes, nuts and seeds (Johnson 2003; Lee 2013). A certain amount of copper is absorbed from the stomach, but the greatest amount is absorbed in the duodenum by passive diffusion or active transport regulated by metallothionein (Institute of Medicine 2001c). Following metallothionein binding and transport within enterocytes, copper binds mostly to albumin and in lesser proportions to transcuprein and small peptides to be transported to the liver in a similar fashion to zinc (Institute of Medicine 2001c;

Berdanier and Zempleni 2009). About 90% of plasma copper is incorporated into ceruloplasmin, a glycoprotein synthesized in the liver, to be carried to tissues where it is used for the synthesis of other copper-containing enzymes (DiSilvestro 2005; Lutsenko 2010; Ramos et al. 2016). This metal is secreted from the liver as a component of bile for excretion in the faeces. Small amounts of copper are excreted in the urine and sweat (National Research Council 2000).

Copper is a component of many metalloproteins and acts in several enzymes involved in the aerobic respiration, such as cytochrome *c* oxidase in mitochondria proteins, or carboxypeptidase and carbonic anhydrase (Institute of Medicine 2001c; Berdanier and Zempleni 2009). It also participates in the structure of some transcription-regulating proteins, playing a critical role in DNA and RNA metabolism (Berdanier and Zempleni 2009). Copper is required in the function of many superoxide dismutases, protecting against oxidant agents and oxidative stress (Johnson 2003; Birben et al. 2012), and favours the synthesis of melanin and catecholamines (Institute of Medicine 2001c). Bound to ceruloplasmin, copper serves in the oxidation of iron before being transported into the plasma (Ramos et al. 2016).

2.2.5.9 Cobalt: Co

Cobalt is an essential trace element in nutrition as it is necessary to form cobalamin (Vit B12). Much of the cobalt in the body appears as Vit B12 deposits in the liver (MacPherson and Dixon 2003; Berdanier and Zempleni 2009); in its mineral form, it is found in the liver, heart, bones, kidney, trachea and spleen, with the highest levels in the liver and kidneys (Wehner and Craig 1972; Brune et al. 1980; Berdanier and Zempleni 2009). It is fundamental in the diet of ruminants, owing to the role of ruminal bacteria that produce Vit B12, which are transferred to meat products for human nutrition (Smith 1987). The main dietary sources of cobalt include green leafy vegetables and meat products, in which cobalt derives from Vit B12 (Cobalt Development Institute 2006; Lee 2013). Enterocytes absorb both B12-linked cobalt bound to the gastric glycoprotein IF and Co in its free form (Taylor 1962; Berdanier and Zempleni 2009). The main route of cobalt excretion is urine, and it is also eliminated in small amounts in the faeces, sweat and hair (Gregus and Klaassen 1986; DiSilvestro 2005).

Cobalt functions and metabolism are known as those pertaining to cobalamin, which is essential for carbon transfer reactions involved in the synthesis of DNA and is necessary for the maturation of erythrocytes and the normal functioning of all cells (Institute of Medicine 1998b; Lee 2013). The enzyme methionine aminopeptidase 2 (MetAP2) is a cobalt protein, which binds cobalt directly, instead of using the corrin ring; MetAP2 catalyses the removal of N-terminal methionine residues (Freeland-Graves and Bavik 2003; Garrabrant et al. 2004) and is critical for tissue repair and protein degradation and participates in endothelial cell proliferation (Griffith et al. 1997).

2.2.5.10 Iodine: I

Iodine is an essential trace element in nutrition, and its main role in the body is to constitute the thyroid hormone (Pennington 2003; National Research Council 2005). The human body normally contains 20 to 30 mg of iodine, with more than 75% in the thyroid gland and the rest distributed throughout the body, particularly in the mammary glands, gastric mucosa and blood (Institute of Medicine 2001d; Ahad and Ganie 2010). As the main source of iodine on earth are the oceans, most dietary iodine comes from salt, seafood (seaweed and animals) and plant foods cultured in iodine-rich soil (Ahad and Ganie 2010), particularly those from the Cruciferae family such as cabbage (Berdanier and Zempleni 2009). The ingested iodine is converted to iodide, a negatively charged ion, and in this form, it is easily absorbed (Institute of Medicine 2001d; Zimmermann 2009), as occurs with dietary sodium iodide or protein-bound iodide. Iodide circulates in the blood both in free form and linked to proteins (Ahad and Ganie 2010), and most dietary iodide (about 80%) is retained in the thyroid gland, which uses it for the synthesis of thyroxine (Zimmermann 2009). However, like the thyroid, many tissues can uptake albumin-bound iodide, such as the mammary gland, directly by sodium-iodide symporter, a transmembrane glycoprotein (Rousset et al. 2000). Thyroxine is synthesized through the iodination of tyrosine. Upon the action of the thyroid-stimulating hormone (TSH), the thyroid gland secretes thyroglobulin whose tyrosine residues are iodinated by the iodide peroxidase, and following this monoiodothyronine is produced and then diiodothyronine, triiodothyronine and thyroxine (Pennington 2003). The thyroid secretes triiodothyronine (T3) and thyroxine (T4), which are carried to all cells in the body by the thyroid-binding protein (Institute of Medicine 2001d). T3 and T4 are metabolized in the liver and other tissues, and some thyroid hormone derivatives are secreted into the bile (Pennington 2003; Berdanier and Zempleni 2009). In the target cells, thyroxine is deiodinated to triiodothyronine by the action of 5′-deiodinase, a selenium-containing enzyme (Institute of Medicine 2001d; National Research Council 2005). The released iodide in the plasma is either used by the thyroid or excreted as organic iodide in the urine (Institute of Medicine 2001d).

The main role of iodine in the body is to coordinate and maintain the metabolism of all cells, pregnancy and body growth and development through the thyroid hormones (Pennington 2003). In the mammary glands, iodine is either transferred to the newborn or acts as a potent antioxidant owing to its electron donor ability (Ahad and Ganie 2010). The antioxidant function is also performed in the other tissues that uptake iodine (Smyth 2003; Berdanier and Zempleni 2009; Lee 2013). Other roles for iodine have been described such as stabilizing the function of adrenal glands during stress or participating in immune regulation (Institute of Medicine 2001d; Ahad and Ganie 2010). Even though the body is efficient at excreting iodide, it can be toxic when there is a deficiency of selenium or excess dietary or supplement intake. Iron deficiency impairs iodine function in the thyroid (Institute of Medicine 2001d; Zimmermann and Köhrle 2002).

2.2.5.11 Manganese: Mn

Bones contain the highest concentration of manganese in the body, followed by the pituitary gland, liver, pancreas and digestive tissue. Very little is known about manganese intake, needs, bioavailability from different foods and supplement sources or the influence of changes in nutritional status in the metabolism of the body (Institute of Medicine 2001e; Keen and Zidenberg-Cherr 2003; DiSilvestro 2005). Some dietary sources such as green leafy vegetables, beetroot, blueberries, wholegrains, fruits or some kinds of teas have been mentioned (Lee 2013). Manganese is absorbed in the small intestine in a regulated way against excessive uptake, and cobalt and iron compete with Mn for common bonding sites for absorption (Leach and Lilburn 1978; Institute of Medicine 2001e; DiSilvestro 2005). In the bloodstream, most dietary absorbed Mn binds to albumin and rapidly enters the liver, where some of it goes into liver enzymes and some is transported to other tissues or is excreted in the bile (Institute of Medicine 2001e; DiSilvestro 2005; Lee 2013). Manganese transport to the tissues occurs by transferrin and α-2-macroglobulin, and it seems that bone accumulation is passive (Institute of Medicine 2001e). Excretion occurs in the faeces following secretion into the intestine via bile, and it is regulated by the body's Mn content (Britton and Cotzias 1966; Lee 2013).

Manganese is a constituent of enzymatic systems in the body and is an essential cofactor in several metalloenzymes, such as superoxide dismutase, arginase and phosphoenolpyruvate carboxykinase, and therefore plays a crucial role in the control of oxidative stress and the metabolism of proteins and carbohydrates (Institute of Medicine 2001e; Keen and Zidenberg-Cherr 2003). As such, Mn abounds in mitochondria of hepatic cells. Manganese is also important in activating the glycosyltransferases, which are necessary for the formation of glycoproteins, which are involved in many processes including bone formation and maintenance (Institute of Medicine 2001e; Keen and Zidenberg-Cherr 2003; DiSilvestro 2005). Sequestration of Mn by neutrophil calprotectin has been considered an important mechanism of host defence against fungal and bacterial infection (Kehl-Fie et al. 2011; Brophy and Nolan 2015).

2.2.5.12 Molybdenum: Mb

Molybdenum is a cofactor for oxidation enzymes and is important for several biological systems (Mendel 2013a) and flavoproteins (Garattini et al. 2003). Dietary sources of Mo include vegetables, cereals, grains, dark green leafy vegetables and animal viscera (Institute of Medicine 2001f; Berdanier and Zempleni 2009). Most ingested Mo is absorbed by the epithelial cells of the gastrointestinal system and circulates in the blood in a protein-bound complex (Institute of Medicine 2001f; DiSilvestro 2005; Berdanier and Zempleni 2009). It is found mostly in the liver, kidneys, bones and skin (Institute of Medicine 2001f). The principal route for the

excretion of Mo is the urine, with small amounts excreted via the bile in the faeces (Berdanier and Zempleni 2009).

Molybdenum is considered an essential trace element that acts as a cofactor for molybdoenzymes (Schindelin et al. 1996; Romão et al. 1997; Mendel 2013b), in the mitochondrial amidoxime-reducing component, which performs important functions owing to its N-reductive activity (Ott et al. 2015). The enzymes xanthine oxidase, aldehyde oxidase and sulphate oxidase require a prosthetic group containing molybdenum (Rajagopalan 1988; Ott et al. 2015). Xanthine oxidase is necessary for the production of uric acid from purines; sulphite oxidase converts sulphite to sulphate; and aldehyde oxidase is involved in the hydroxylation of heterocyclic nitrogen compounds, such as nicotinic acid (Rajagopalan 1988; Garattini et al. 2003; Mendel 2013b). Thus, Mo is important for the metabolism of DNA and RNA, of iron and of energy (Maiuolo et al. 2016), as well as for sulphide detoxification (Wang 2012).

2.2.5.13 Selenium: Se

Selenium cooperates with Vit E as an antioxidant and has important functions in the immune system (Thomson 2003; Rayman 2012). In the body, selenium is distributed about 30% in the liver, 15% in the kidneys, 30% in muscles and 10% in plasma (Berdanier and Zempleni 2009; Lee 2013). Plant dietary Se sources reflect the quantity in the soil and include foods such as Brazil nuts, cereal grains, onions or soybeans, and animal sources are seafood and fish, meat, eggs and dairy (Institute of Medicine 2000b; Rayman 2012). Selenium is very well absorbed in the upper segment of the small intestine, with most ingested selenium absorbed readily from a variety of foods by mechanisms that include some overlap with amino acid absorption (Institute of Medicine 2000b; Berdanier and Zempleni 2009; Rayman 2012). Selenium absorption is not controlled by homeostatic mechanisms such as those for iron, so plasma selenium is proportional to selenium intake at both high and low levels (DiSilvestro 2005). Selenium is transported from the gut by LDL and VLDL to the tissues, and it is found in higher quantities in the liver, spleen, muscle, nails, hair and tooth enamel (Berdanier and Zempleni 2009). Most minerals that exist in metalloproteins are attached to selected amino acids, acting as a cofactor (Cook et al. 2008), or in the case of iron, by insertion into a heme or cytochrome structure, which can be inserted into a protein (Berdanier and Zempleni 2009; Jiang et al. 2009). Because selenium forms a selenium-sulphur bond using the SH group of a sulphur amino acid, methionine becomes a selenomethionine, or more typically cysteine becomes a selenocysteine amino acid (Thomson 2003; Schmidt and Simonović 2012). The particular synthesis mechanism for the incorporation of selenocysteine into protein requires Vit B6 as a coenzyme and results in selenoproteins (Soda et al. 1999; DiSilvestro 2005). Excess Se intake is toxic, but unlike iron and copper, whose excretion processes are not so efficient, it is actively excreted in the urine. The urinary system functions to maintain optimal selenium status, and under normal intake, equivalent amounts are excreted in both the urine and faeces (Institute of Medicine 2000b; Thomson 2003; Rayman 2012).

Selenium is important for almost all cell types in the body, owing to its critical role in glutathione peroxidase, which is the body's most powerful antioxidant and its isoenzymes (Thomson 2003; Rayman 2012). Glutathione peroxidase is fundamental for red blood cells because they lack mitochondria, an organelle that regulates the redox state. Erythrocytes contain haemoglobin; therefore they have to control the redox state so that haemoglobin can release oxygen in exchange for CO_2. Such a process favours the formation of hydrogen peroxide, which is inhibited by the action of glutathione peroxidase (DiSilvestro 2005; Berdanier and Zempleni 2009). Furthermore, glutathione peroxidase catalyses the reduction of various organic peroxides as well as hydrogen peroxides (Berdanier and Zempleni 2009). Membranes contain unsaturated fatty acids, which can be easily oxidized. The activity of glutathione peroxidase is critical to avoid stability impairment of these membranes through oxidation (Berdanier and Zempleni 2009; Lubos et al. 2011). Along with other enzymes of the antioxidant system, adequate provision of copper and vitamins A, E and C will assure that cell damage by free radicals is minimized, even if the diet is marginal in selenium (Clarkson and Thompson 2000; Choe and Min 2009; Omur et al. 2016). As an essential component of glutathione peroxidase, Vit E plays an important role in suppressing free radical production, but its site of action is distinct from that of Se (Berdanier and Zempleni 2009; Lubos et al. 2011). Different selenoproteins act as glutathione peroxidase isozymes, including a thioredoxin reductase (DiSilvestro 2005; Rayman 2012). Selenium is also an integral part of the enzyme iodothyronine deiodinase, which is necessary for thyroid hormone metabolism (DiSilvestro 2005; Schweizer et al. 2014). Adequate Se intake and metabolism have been associated with certain effects including (1) prevention of cancer (Naithani 2008; Brozmanová 2011; Chen et al. 2013), (2) infertility (Mistry et al. 2012; Pieczynska and Grajeta 2015), (3) cardiovascular diseases (Oster and Prellwitz 1990; Flores-Mateo et al. 2006) and (4) inflammatory conditions such as arthritis (Tarp et al. 1985; Huang et al. 2012; Mattmiller et al. 2013) or pancreatitis (Bowrey et al. 1999). The effects of selenium on the immune function have been extensively studied, and a variety of mechanisms have been identified, such as improving natural killer cell activity (Methenitou et al. 2001; Gershwin et al. 2004) or the production of lymphocytes and immunoglobulin (Keen et al. 2004; Rocha et al. 2016), as well as contributing to the maintenance of immune regulation (Kieliszek and Błażejak 2016).

2.2.5.14 Chromium: Cr

Chromium is associated with the metabolism of glucose (Mertz 1969, 1993, 1998). It has been found in bone and in breast milk of humans (DiSilvestro 2005; Berdanier and Zempleni 2009). Chromium dietary sources include corn oil, clams, grain cereals, yeast, meat and drinking water, and the amounts reflect its presence and quantity in soil (Anderson et al. 1992; Berdanier and Zempleni 2009). Organic chromium such as chromium picolinate is more efficiently absorbed than inorganic forms whose absorption is very low, under 2.5% in some studies (Ducros 1992;

Berdanier and Zempleni 2009). In blood, it can bind to a number of molecules, but it is mostly found in transferrin. Organic chromium is removed from the body in the urine (Mertz 1993; Institute of Medicine 2001g; Berdanier and Zempleni 2009).

Chromium enhances the action of insulin, which influences the metabolism of carbohydrates, lipids and proteins (Institute of Medicine 2001g; Berdanier and Zempleni 2009). It binds to DNA and has functions on the regulation of gene expression (Ye and Shi 2001; Hazane-Puch et al. 2010). Studies involving immune cells have demonstrated that Cr is required for lymphocyte proliferation (Keen et al. 2004). Some studies have also demonstrated that Cr may play a protective role against metabolic diseases such as obesity, hypertension and diabetes (Wiernsperger and Rapin 2010; Bai et al. 2015; Panchal et al. 2017).

2.3 Nutrition for Immune Response and Immunonutrition

Hypermetabolism and hypercatabolism characterize non-infectious conditions such as cancer (de Luis et al. 2014), burn injuries (Mendonça et al. 2011), post-surgery (Finnerty et al. 2013) and acute renal failure (Wooley et al. 2005) as well as infectious diseases such as sepsis (Longarela et al. 2000), tuberculosis (Gupta et al. 2009), malaria (Stettler et al. 1992) and HIV (Garcia-Lorda et al. 2000). These high stress conditions call for an increased need for nutrients, known as hypermetabolism—an abnormal increase in the basal metabolic rate—that will lead to a continual insufficiency of energy and/or protein to meet the metabolic demands of the body. This increased metabolic demand is for nutrients of all classes, such as carbohydrates, lipids and proteins, to provide energy and structure, as well as vitamins and minerals, which accomplish regulatory and modulatory functions in a number of metabolic processes, including hormonal homeostasis (Mehta and Duggan 2009).

Hypermetabolism is a process that if untreated evolves to hypercatabolism, which culminates in cachexia and fatal general organ failure. The concept of hypermetabolic response is well established (McClave and Snider 1994); however it is difficult to measure. In general, losses above 10% of total body weight in hospitalized patients are considered a threshold for diagnosing hypermetabolic response and equate to 15–20% losses of total body protein, a level beyond which significant deterioration in the clinical outcome is observed (Hansen et al. 2000; Gil Hernández and Sánchez de Medina Contreras 2010). The evaluation of the nutritional status is more appropriate to estimate the degree of hypercatabolism, which results from the consumption of structural proteins as cellular fuel for the maintenance of vital functions. Hypercatabolism is clinically assessed by using the Bistrian's index which determines the balance between ingested and excreted nitrogen (Bistrian 1979). A number of formulas have been designed to calculate needs for daily caloric requirements during illnesses associated with hypermetabolism, and Harries-Benedict's equation is the most used, so far (Harris and Benedict 1918; Japur et al. 2009). Based on an evaluation of the individual's

nutritional status, factors representing activity level, intensity of stress, changes in body weight and temperature are added to the Harries-Benedict's equation (Long et al. 1979) to calculate the proper nutrient combination for a given case.

Studies on HIV have greatly contributed to the knowledge of nutritional aspects associated with hypermetabolism and hypercatabolism (Stein et al. 1990; Garcia-Lorda et al. 2000; Cunningham-Rundles et al. 2005; Kosmiski 2011; Serrano-Villar et al. 2017). Because such studies have explored a variety of events and systems in depth, they can be applied to other debilitating infectious and inflammatory conditions. A number of studies have addressed how co-infections, such as those between HIV and various other pathogens, are frequent and represent a critical association with malnutrition, resulting in cachexia and poor clinical outcome by several mechanisms (Van Lettow et al. 2003; Janssen et al. 2005; Semba et al. 2010; Werneck et al. 2011; Katz 2012; Hicks et al. 2014; Church and Maitland 2014; Cohen et al. 2015; Mkhize et al. 2017). Intracellular parasites, such as *Leishmania* spp. or *Plasmodium* spp., not only exploit nutrients already available in the cell and the cell's energy-yielding system, but they further induce the cell to provide actively for their nutrition (Trager 1974; Haanstra et al. 2016; Srivastava et al. 2016). Leishmaniasis in its visceral or tegumentary form is among the most studied debilitating infectious diseases in people and animals. Malnutrition is a risk factor for the establishment, maintenance and progression of *Leishmania* infection in the host. Studies in rodents have described that lack of sufficient protein in the diet (Pérez et al. 1979) or general malnutrition (Reithinger et al. 2001) clearly favours susceptibility to *Leishmania* infection. On the other hand, human visceral leishmaniasis has been considered a natural model of infection-induced cachexia (Pearson et al. 1992). Several studies have shown that undernutrition has a direct influence on the outcome of any clinical form of leishmaniasis caused by different *Leishmania* species in diverse parts of the globe, resulting in more severe presentations (Badaró et al. 1986; Harrison et al. 1986; Cerf et al. 1987; Dye and Williams 1993; Weigel et al. 1994; Hida et al. 1999; Cunha et al. 2001; Machado-Coelho et al. 2005; Baba et al. 2006; Alvar et al. 2006; Rukunuzzaman and Rahman 2008; Malafaia 2009; Rijal et al. 2010; Harhay et al. 2011; Gatto et al. 2013). In fact, evidence of an interaction between malnutrition, leishmaniasis and immunosuppression has been demonstrated (Harrison et al. 1986; Anstead et al. 2001; Kumar et al. 2014). Poorer nutritional statuses have been associated with poor response to chemotherapy with sodium stibogluconate and lower serum levels of matrix metalloproteinase 9 (MMP9), a cytokine that inversely correlates with disease progression (de Oliveira et al. 2013; Gadisa et al. 2017). In malaria, a similar dynamic between infection and nutrition also occurs (Méndez and Dobaño 2004). A consequence of the immunosuppression caused by HIV, *Plasmodium* or *Leishmania* infection is the augmented susceptibility of the host to acquire other infections and to develop metabolic imbalances or degenerative conditions, generating co-morbidities and deepening nutritional deprivation in a vicious circle. Indeed, the literature contains several examples of poorer clinical evolution and response to pharmacological treatment of malaria, leishmaniasis, tuberculosis, AIDS and a number of helminthic diseases in populations where malnutrition is endemic (Cegielski and McMurray 2004; Cunningham-Rundles et al. 2005;

Krawinkel 2012; Bhargava et al. 2014; McCuskee et al. 2014; Starr et al. 2015; Zacarias et al. 2017).

Immune responses are greatly responsible for heightened caloric requirements in the course of infectious diseases (Schaible and Kaufmann 2007; França et al. 2009). The immune system is prepared to respond intensely to antigenic stimuli and inflammatory signals, which require the acceleration of cellular metabolism and thus increased energy demands (Palmer et al. 2016). Nevertheless, the immune system depends on the activity and balance of the other systems. Nutrient-sensitive hormones such as insulin, glucagon, corticosterone, growth hormone, thyroxin and catecholamine regulate the activity of leukocytes throughout hormone-receptor binding (Klasing 1994; Plummer and Deane 2016). Accordingly, an increase in neuroendocrine activity to ensure tissue repair and homeostasis characterizes hormonally induced increased glucose production, increased use of nitrogenous products and increased enzyme activity, whose consequences include the elevation of catabolism and reserve burning (Plank and Hill 2000; Simsek et al. 2014). Although such processes are not as well explored and described in infectious diseases that are not considered hypermetabolic, higher caloric expenditure should be expected as a result of an activated immune response to a given infection, in proportional levels.

Carbohydrates and lipids are the main sources of energy for the cells. Not only are their proportions in the diet important, but nowadays the quality of dietary carbohydrates and lipids with regard to metabolism and immune functions during disease is drawing attention (Vanderhoof 1998; Wolowczuk et al. 2008; Meckling 2009; Krawinkel 2012). Omega-3 fatty acids help reduce inflammation, while some omega-6 fatty acids tend to promote inflammation (Lachance et al. 2014). The caloric balance in the body as a whole has an impact on the progress and outcome of an infectious process (Schaible and Kaufmann 2007; França et al. 2009; Plummer and Deane 2016). Nutritional deficiency starting during intrauterine life interferes negatively with adult immunocompetence. Caloric overnutrition also negatively affects the immune response to infections (Krawinkel 2012). Extensive studies have demonstrated that glucose is not only the main energy source for the body, but its metabolic pathways participate in many processes related to immunity and its development (Vanderhoof 1998; Cunningham-Rundles et al. 2005; Norata et al. 2015), as well as in the pathophysiology of infectious diseases. Muscles are the primary source for glucose upon acute or immediate body demand, which explains why body losses occur at the expenses of muscles during intense disease processes and involves protein losses during hypercatabolism (Berg et al. 2013; Puthucheary et al. 2013; Preiser et al. 2015). Glucose from dietary sugars and body reserves associates with peptides to form glycoproteins, which are the molecular basis of a variety of functional elements of the immune response, such as antibodies, receptors, cytokines and chemokines, among others (Helderman 1981; Wolowczuk et al. 2008; Shi et al. 2011; Norata et al. 2015). Extrinsic signalling, such as MHC-TCR engagement, acts as a stimulation factor that regulates glucose uptake and metabolic activity in lymphocytes (Rathmell et al. 2000). Also, the glycolytic pathway plays a fundamental role in the differentiation of macrophages to the type 2 (M2) regulatory phenotype or to inflammatory type 1 (M1). Indeed, inhibition of glycolysis results in

loss of the regulatory phenotype, including Il-10 production (Suzuki et al. 2016). Host-pathogen interactions and infection outcomes involve crucial aspects of glucose pathways; as an example, viruses are able to interfere (Palmer et al. 2014) and even disrupt the glucose metabolic machinery of their host T cells and phagocytes (Palmer et al. 2016). Sugar metabolism imbalances are not only the consequences, but they also participate in the progress of tissue damage, catabolism and dysfunction under infection and inflammatory processes. During sepsis, hyperglycaemia, hypoglycaemia and glycaemic variability are associated with adverse outcomes and death, and they occur due to the massive activation of pro-inflammatory mediators and release of counter-regulatory hormones, leading to excessive hepatic gluconeogenesis and peripheral insulin resistance (Plummer and Deane 2016). As shown by Palmer and collaborators (Palmer et al. 2016), during HIV infection a continuous activation of T lymphocytes, characterized by increased surface expression of glucose transporter 1 (GLUT-1) and high glycolysis activity, results in metabolic exhaustion and cell death.

The roles of lipids as components of cell membranes, as constituents of hormones, as the means by which energy is stored in the body and as maintainers of body temperature are all crucial during an immune response (Hwang 1989; Alvarez-Curto and Milligan 2016). In the healthy individual, adipose tissue is formed from dietary carbohydrates and lipids, and it is stable as fat storage. In the course of infection and immune response, the heightened metabolic demand induces lipid mobilization, and lipids are transformed into readily usable glucose for energy (Weinstein et al. 1994; Sjögren et al. 2007; Palmer et al. 2016). Liposoluble vitamins are also mobilized from the host's adipose tissue under hypermetabolism and hypercatabolism due to infection, immune response and inflammation conditions. Protection against oxidative stress is a crucial function of Vits A, E, D and K for the cells during the course of mobilization of the immune system against pathogens (Chandra and Chandra 1986; Rahman 2007; Valko et al. 2007; Albahrani and Greaves 2016; Omur et al. 2016). Metabolic and catabolic consequences of attempted caloric balance critically involve gluconeogenesis in a host under hypermetabolic demand. During glucose synthesis from lipid reserves, a great amount of free radicals is produced, leading to oxidation of cell membranes and the formation of ketone, which increase organic acidification (Simsek et al. 2014). Moreover, if the proportion of adipose tissue is above optimum before infection and disease onset, the host is more susceptible to developing higher levels of inflammation, more oxidative stress and more acidification (Krawinkel 2012; Cousin et al. 2016). Cumulative results of research have found the evidence that rather than quantity, the quality of dietary lipids is important to provide essential fatty acids that participate in several metabolic functions (Broadhurst 1997; Chandrasekharan 1999; Diekman and Malcolm 2009; Jacobson et al. 2012; Abumrad and Davidson 2012). More than in health, diet-related metabolic functions are vital to the outcome of diseases, including infectious and inflammatory processes. Prostaglandins, leukotrienes and acute phase protein cascades are key defence components that are directly involved in handling infectious processes, through first-line inflammatory response, and the proportion of end products of these inflammatory cascades is

sharply influenced by the composition of available fatty acids from the diet (Calder 2013a; Alvarez-Curto and Milligan 2016; Marion-Letellier et al. 2016). On the other hand, it has been demonstrated in healthy individuals that there is an association between a lower grade of inflammation, as evaluated by inflammatory markers, such as IL-6, A1GP and haptoglobin, and the regulation of insulin sensitivity and lipid metabolism (Heliovaara et al. 2005). In a review of the role of infection in the development of atherosclerosis, Campbell and Rosenfeld (2015) discuss various studies that explore the interaction between hyperlipidemia, infection by several bacterial pathogens, and the development on inflammation.

The participation of proteins in the caloric balance also reflects the processes of hypermetabolism and hypercatabolism. This is because during gluconeogenesis, the muscular collagen, actin and myosin are mobilized and metabolized to produce glucose and thus energy (Gil Hernández and Sánchez de Medina Contreras 2010; Argilés et al. 2016). As muscle tissues function as storage of amino acids and glycogen for immediate release under elevated metabolic demand, during hypercatabolism the first losses occur in the musculature to preserve vital functions (Espinosa et al. 2016). When protein losses exceed 20% of total body protein, physiological systems begin to show functional deficiencies, especially in immunity, but also in cardiopulmonary and musculoskeletal systems. When protein losses surpass 30%, it means the glycogen and lipid reserves have been used, and then the body starts to catabolize its structure, and the survival rate reduces by 20% (Gil Hernández and Sánchez de Medina Contreras 2010). According to the Bistrian's index, the proportion of urea excreted in the urine helps to estimate the nitrogen balance in relation to the ingested amount of protein (Bistrian 1979). As proteins are made up of about 16% nitrogen, the excreted amount for a healthy individual should be proportional to that ingested. If the urinary losses of nitrogen are higher than the protein ingestion, this means that the protein reserves are being used or overcatabolized (Mahan et al. 2013; Ogunbileje et al. 2016). Thus, the protein balance should be re-established according to individual catabolic losses, which means that in diseases with greater structural losses, more proteins should be given to the patient. The nutrition of the individual under high demand will take into account not only maintenance of body mass but also the need to adapt to metabolic conditions associated with response to infections and recovery of the body (Mahan et al. 2013).

The concept of *immunonutrition* is somewhat different from the idea of general nutrition during a disease. The understanding of the role of malnutrition in the populations with a higher susceptibility to infectious agents, as well as in the development of more critical clinical pictures, together with the evolution of the knowledge in immunology, has led to the development of the concept of nutritional immunology or immunonutrition (Evoy et al. 1998; Grimble 2001; Mizock 2010; Chow and Barbul 2014; Mody et al. 2014; Murray et al. 2015; Vetvicka and Vetvickova 2016). Nutritional deficiencies underlie the impairment of immune functions in the course of diverse conditions, including infectious diseases (Keusch 2003; Zapatera et al. 2015). Immunonutrition is a growing area of interest. The initial publications pointing to the fact that interactions between infections and nutrition are synergistic date back to

little before the 1960s (Keusch 2003; Scrimshaw 2007). The advance in immunological tools has supported extensive investigations to elucidate the specific mechanisms involved in the complex interactions between nutrition, immunity and disease in its various presentations (Scrimshaw 2007; Afacan et al. 2012). Immunonutrition as a concept is the therapeutic application of the beneficial effect of some nutrients on the immune response, owing to specific nutrient actions that regulate various activities of the immune system (Grimble 2001). In this sense, specific food items or nutrients are administered in higher quantities than those present in the regular diet to satisfy the particular demands of the body undergoing disease. The most commonly used nutrients for immunonutrition include amino acids, nucleotides, polyunsaturated fatty acids (PUFAs), vitamins and minerals, in the form of supplements or of foodstuffs which are very rich in some specific nutrient (Mainous and Deitch 1994; Redmond et al. 1998; Efron and Barbul 2000; Grimble 2001, 2005; Singh et al. 2002; Chan 2008; Chow and Barbul 2014). Other dietary components with immunomodulatory potential include polyphenols and nutrients with the ability of modulating the gut microbiota such as fibre, prebiotics and probiotics (Romeo et al. 2010; Pérez-Cano et al. 2012). Immunonutrition remains a challenge to researchers, despite the proliferation of research in the area due to the vastitude of its scope and the unavoidable controversy it raises because much has yet to be understood. Naturally, a substantial number of studies have been published on the use of diverse nutrients as *immunonutrients* (Table 2.1).

The activity of the immune system impacts the requirements for micronutrients in such a way that the immune status can be regarded as a sensitive indicator of micronutrient supply (Ströhle et al. 2011). All groups of micronutrients have been studied as direct participants in immune functions. For example, macrophages and dendritic cells (DC) in the skin and mucosal epithelia produce retinoic acid from the dietary provision of Vit A; this retinoic acid plays important roles in cell growth and differentiation during immune responses, preventing autoimmunity and immunopathogenic consequences (Mucida et al. 2007; Manicassamy et al. 2009; Cassani et al. 2012; Zhou et al. 2012; Reza Dorosty-Motlagh et al. 2016). Immunopathogeny is a common pathophysiological aspect of some infectious diseases, such as cutaneous or visceral leishmaniasis (Goto and Prianti 2009; Soong et al. 2012) or viral hepatitis (Bayraktar et al. 1997; Cassani et al. 1997), for example. Dendritic cells (DC) depend on retinoic acid to perform their antigen-presenting functions and to induce differentiation of naïve T cells into T regulatory cells (Mucida et al. 2007; Cassani et al. 2012). In the course of infections, DC-produced Vit A participates in metabolic pathways that favour the development of effector $CD4^+$ T cells into T helper (Th) type 1 and the production of pro-inflammatory cytokines (Raverdeau and Mills 2014).

Vit D participates in the network between the immune-brain-gut systems. It has been shown that many factors associated with the brain function, innate immunity and the gut microbiome are related to immune regulation by Vit D (Pandolfi et al. 2017; Chirumbolo et al. 2017). Calcitriol has immunomodulatory effects on the different cell types of the immune system by biding to the Vit D receptor, including regulating T-lymphocyte proliferation, immunoglobulin production, natural killer

Table 2.1 Immunonutrition: some relevant types, common natural sources and effects of nutrients

Nutrient	Type	Natural sources	Effects
Complex or slowly absorbed carbohydrates	Oligosaccharides and polysaccharides	Vegetables, fruits	Reduce metabolizable energy relative to sucrose; reduce insulin secretion; as a substrate that favours a healthy colonic microbiota, positively alter the intestinal flora (Vanderhoof 1998)
Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), α-linolenic acid (ALA)	Omega-3 long-chain fatty acids	Deep sea fish, salmon, krill (EPA; DHA) Flaxseed or linseed oil (ALA)	Protect membranes against free radical damage; reduce pro-inflammatory cytokine production; increase the amounts of anti-inflammatory compounds such as resolvins and protectins in the site of inflammatory response; reduce systemic inflammation in diverse conditions, including sepsis (Alexander 1998; Grimble 2009; Pierre et al. 2013)
L-Glutamine	Non-essential amino acid	Meats, seafood, milk, nuts, eggs, cabbage, beans	Is a nutrient for immune cells and a substrate for glutathione formation; modulates the gut barrier function; precursor to the neurotransmitter γ-aminobutyric acid (GABA) (Grimble and Grimble 1998; Grimble 2009; Pierre et al. 2013)
L-Arginine	Dibasic conditionally essential amino acid	Meats, poultry, fish, seafood, eggs, milk, yogurt, cheese, nuts, seeds, oats, beans, wheat germ	Stimulates anabolic hormone release; improves nitrogen balance; augments lymphocyte mitogenesis in the thymus (Evoy et al. 1998; Grimble 2009; Pierre et al. 2013)
L-Leucine	Essential amino acid	Cheese, meats, fish, seafood, eggs, nuts, seeds, oats, beans, soybeans	Stimulates protein synthesis and is the only dietary amino acid that directly promotes cell growth in the body; slows down muscle

(continued)

Table 2.1 (continued)

Nutrient	Type	Natural sources	Effects
			proteolysis in the critically ill patient (Gershwin et al. 2004; Pierre et al. 2013)
L-Taurine	Conditionally essential, sulphonated β-amino acid	Shellfish, meat, beef, lamb, eggs	Stabilizes membranes and acts as an antioxidant for lymphocytes; stimulates glycolysis and glycogenesis; helps to preserve neutrophil phagocytic ability (Bachmann 2012)
L-Methionine and L-tryptophan	Essential sulphur amino acids	Fish, meat, eggs, milk, chicken, turkey, pork	Are substrates for glutathione synthesis; regulate T cell function, acute phase response, inflammatory response and cytokine production (Grimble and Grimble 1998)
Purines and pyrimidines	Nucleotides	Fish and seafood, organ meats, fresh vegetables	Participate in gut repair and mucosal defence, lipid metabolism and iron bioavailability (Gruenwedel 2003; Pierre et al. 2013)
Vit A	Liposoluble vitamin	Organ meats, fish liver, milk and dairy, eggs	Is necessary for epithelial metabolism and for vision and eye epithelia; stimulates collagen synthesis in wounds; promotes an efficient antiviral immune response; modulates innate tolerogenic dendritic cells and innate lymphoid cells in the gut; regulates the balance between Tregs and Th17 cells (Tanumihardjo et al. 2016; Elenius et al. 2017; Czarnewski et al. 2017; Erkelens and Mebius 2017)
Vit B6: pyridoxine	Hydrosoluble vitamin	Meats, cereals, legumes, nuts, fruits, vegetables	Is antioxidant, acting as a cofactor in the synthesis of L-cysteine which is a precursor for

(continued)

Table 2.1 (continued)

Nutrient	Type	Natural sources	Effects
			glutathione; required in the proliferation of lymphocytes and biosynthesis of antibodies (Grimble 1997)
Vit B9: folic acid	Hydrosoluble vitamin	Liver, mushrooms, green leafy vegetables, poultry, meat, seafood, potatoes, fruits	Has a protective function against cardiovascular disease, cancer and cognitive dysfunction; reduces hyperhomocysteinemia; regulates NK cell activities (Ebara 2017; Paniz et al. 2017)
Vit B12: cobalamin	Hydrosoluble vitamin	Liver and kidney, milk, eggs, fish, cheese, meats	Protects against haematological and neurological dysfunctions; has antioxidant functions and prevents hyperhomocysteinemia (Green et al. 2017)
Vit C	Hydrosoluble vitamin	Vegetables and fruits such as papaya, rosehips, acerola, citrus fruit, guava, kiwi, broccoli, red peppers and other plants	Is antioxidant, exerting free radical scavenging activity; enhances the neutrophil function; participates as a cofactor in the hydroxylation of L-proline and L-lysine residues in procollagen, favouring wound healing; protects against vascular leakage, epithelial barrier disruption and increased alveolar fluid levels during sepsis; reduce disease manifestations and prevent infections caused by bacteria, viruses and protozoa (Gershwin et al. 2004; Pierre et al. 2013; Hemilä 2017)
Vit D3	Liposoluble vitamin	Fish, fish/cod liver oil, liver, buttermilk, egg yolks	Regulates both adaptive and innate immunity and the inflammatory cascade; enhances lymphocyte responses by T cell activation, differentiation and migration;

(continued)

Table 2.1 (continued)

Nutrient	Type	Natural sources	Effects
			regulates gene expression involved in the interleukin signalling pathway, oxidative stress response, apoptosis signalling pathway and gonadotropin-releasing hormone receptor pathway (Jeffery et al. 2012; Szymczak and Pawliczak 2016; Pasing et al. 2017)
Vit E	Liposoluble vitamin	Wheat germ, rosehips, various nuts, corn, sunflower or soy oils	Is a potent antioxidant; protects the cell membranes against lipid peroxidation, particularly Vit E-rich immune cells; supports lymphocyte proliferation, IL-2 production and DTH response; restores an impaired response to infection by enhancing NK cell activity, IFN-γ production and neutrophil recruitment; has a role in the prevention against cardiovascular diseases, cancer, neurodegenerative conditions and pneumonia (Szymańska et al. 2017; Hemilä 2017; Pae and Wu 2017)
Vit K	Liposoluble vitamin	Egg yolk, meat, liver or dairy products	Inhibits calcification of soft tissues, participates in bone metabolism and protects against cardiovascular diseases, diabetes, arthritis and cancer; is necessary for brain metabolism, function and protection from oxidative stress (Ferland 2012; Schwalfenberg 2017; Suksomboon et al. 2017)

(continued)

Table 2.1 (continued)

Nutrient	Type	Natural sources	Effects
Magnesium	Macroelement	Brewer's yeast, green leafy vegetables, nuts, seeds, soybeans, oats or milk	Protects the DNA from oxidative damage; reduces insulin resistance when combined with chromium; has anti-inflammatory properties in chronicle inflammatory diseases (Petrović et al. 2016; Dou et al. 2016; Brenner et al. 2017)
Selenium	Essential trace element	Brazil nuts, cereal grains, onions or soybeans, and animal sources are seafood and fish, meat, eggs and dairy	Act as antioxidant; necessary for proliferation and differentiation of naïve CD4- T cells towards T-1 cells; directs macrophages towards the M2 phenotype (Pierre et al. 2013; Steinbrenner et al. 2015)
Zinc	Oligoelement	Shellfish, meat, fish, poultry eggs, dairy, seeds, alfalfa, celery, legumes, nuts and wholegrains	Regulates the innate and adaptive immune responses; enhances the defence against bacterial infection and sepsis; controls oxidative stress during inflammatory responses; necessary for pathogen elimination by neutrophil extracellular trap (NET) formation (Gammoh and Rink 2017)
β-Carotene (pro-Vit A)	Phytochemical	β-Carotene is found in green and yellow vegetables, such as carrots, sweet potatoes, pumpkin, kale, spinach, collards and squash	Enhances cell-mediated immune responses, expression of surface molecules on monocytes and secretion of the antitumoural cytokine and protects immune cells from oxidative damage by inhibiting lipid peroxidation on cell membranes (Hughes 2001)
Curcumin or diferuloylmethane	Phytochemical	It is a polyphenol found in the rhizome of *Curcuma longa*	Inhibit mediators of the inflammatory response; reduce the secretion of

(continued)

Table 2.1 (continued)

Nutrient	Type	Natural sources	Effects
		(turmeric) and in other *Curcuma* spp.	TNF-α and IL-1β and the production of COX-2-induced prostaglandin G2; potent antioxidant (Lestari and Indrayanto 2014; Ghosh et al. 2015; Pulido-Moran et al. 2016)
Flavonoids	Phytochemical Family of polyphenolic	*Flavonols* are found in onions, apples, berries, kale, leeks, broccoli, blueberries, red wine and tea; *flavones* are found in fruit skins, parsley and celery; *isoflavones* are present in leguminous plants, mainly soy and soy products; *flavanones* are exclusive of citrus fruits; *flavanols* are found in cocoa and tea; *anthocyanidins* are found in red wine and berry fruits	Act as anti-inflammatory and antioxidant; modulate gene expression and inflammatory response; activate the innate immune system and the immune system against tumours; regulate the activities of numerous cell types, as basophils, neutrophils, eosinophils, lymphocytes, macrophages, platelets, smooth muscle or hepatocytes (Middleton 1998; Pérez-Cano and Castell 2016)
Lycopene	Phytochemical	It is a red, lipophilic and naturally occurring carotenoid in many fruits and vegetables, such as tomatoes	Enhances the antioxidant response; inhibits tumour proliferation, induces apoptosis and decreases the metastatic capacity (Luo and Wu 2011; Holzapfel et al. 2013)
Resveratrol	Phytochemical Family of polyphenolic	Polyphenol is found in grapes and grape products such as red wine	Inhibits inflammation; modulates the development of cytokine-producing $CD4^+$ and $CD8^+$ T cells; regulates specific antigen-induced generation of cytotoxic T lymphocytes; modulates natural killer (NK) activity of PBMC (Falchetti et al. 2001; Kowalska et al. 2017)

(continued)

Table 2.1 (continued)

Nutrient	Type	Natural sources	Effects
Prebiotics, probiotics and synbiotics	Bacterial strains and metabolites	Selectively fermented foods, such as sauerkraut, kefir, natto, tempeh, kombucha, kimchi, pickles and yoghurt, containing vegetable fibres that cannot be digested by the host, but are metabolized by the colonic microbiome and live microorganisms. Synbiotics is the combination of probiotics and prebiotics	Modulate the metabolism of short-chain fatty acids, amino acids and plasma lipoproteins; regulate the balance between immune tolerance and inflammation, keeping a healthy intestinal microbiota and maintaining proper immune functions; prevent and treat immunological disorders (Romeo et al. 2010; Frei et al. 2015)

(NK) cell toxicity and cytokine production (White 2012; Pandolfi et al. 2017; Chirumbolo et al. 2017). As an example of the role of Vit D in host defence against infectious diseases, a recent study has demonstrated that Vit D3 supplementation protects against severe forms of tuberculosis in wild animals (Risco et al. 2016). Similar findings have been described in studies on domestic species and humans (Waters et al. 2001; Nursyam et al. 2006; Ströhle et al. 2011; Lalor et al. 2012). Furthermore, Vit D deficiency is consistently related to susceptibility to sepsis and mortality in people (de Haan et al. 2014).

Some of the roles for Vit E in the immune system include participation in the regulation of T cell functions, in the production of immunoglobulins, pro-inflammatory cytokines and chemokines, and in the control of oxidative stress (Grimble 1994; Field et al. 2002; Ramakrishnan et al. 2004; Molano and Meydani 2012; Azzi et al. 2016; Bou Ghanem et al. 2017; Pantelidou et al. 2017; Bouamama et al. 2017). Studies in animals have demonstrated that Vit E has effects such as (1) enhancing immunity against bacteria such as *Streptococcus pneumoniae* (Bou Ghanem et al. 2015, 2017) or *Listeria monocytogenes* (Wu et al. 2012), (2) reducing helminth *Haemonchus* parasite burden (De Wolf et al. 2014) and (3) modulating the immune response to herpes simplex virus (Sheridan and Beck 2008). In humans, Vit E supplementation has been considered helpful in the treatment of hepatitis B (Andreone et al. 2001; Dikici et al. 2007).

Vit K, like Vit D, also plays a role in preventing oxidative damage and inflammation-induced injury to the host (Shearer and Newman 2008). It has been demonstrated that the anti-inflammatory properties of Vit K include the downregulation of the pro-inflammatory cytokines TNF-α, IL-1β and NF-kB mediated by a Gla-rich protein (Viegas et al. 2017). Vit K derivatives produce an inhibition of the proliferative response and the induction of apoptosis in activated T cells (Hatanaka et al. 2014).

The criteria used to provide vitamins and other micronutrients to vulnerable patients and populations, however, raise concern (Ramakrishnan et al. 2004; Long et al. 2007; Mizock 2010; Chawla and Kvarnberg 2014; Mangin et al. 2014; Mundi et al. 2016; Smedberg and Wernerman 2016; Hemilä 2017; Balcells et al. 2017). Indeed, the indiscriminate use of vitamins has been criticized (Feleszko et al. 2014). The participation of hydrosoluble vitamins in reactions that influence the immune response and host protection against pathogens has been studied in animals and in the course of human conditions, and the subject has yielded a multitude of publications. Many studies have reported that supplementation with these micronutrients results in fewer infections (Selmi et al. 2004; Wintergerst et al. 2006; Elste et al. 2017). The beneficial effects of vitamins of the B complex have been reported for a number of conditions, but harmful consequences of overuse should also be considered (Chawla and Kvarnberg 2014). The Vitamin B family participates in the protection of mitochondria during processes that result in higher oxidative status, such as during inflammatory responses (Depeint et al. 2006; Zhang et al. 2016).

A recent review has discussed the outcome of Vit C studies in animals in infections by diverse types of pathogens, concluding that indeed Vit C does play a role in preventing, shortening and alleviating the manifestation of such diseases (Hemilä 2017). Vit C is considered a strong modulator of immunity, enhancing pathogen phagocytosis and antimicrobial activities by macrophages, and it contributes to the proper functioning of T and B cells (Hughes 1999; Ramakrishnan et al. 2004; Ströhle et al. 2011; Schwager et al. 2015; Ellulu 2017).

Among the minerals, calcium participates in events related to the recognition of pathogens by APCs, acting in intracellular signalling in immune cells such as macrophages, lymphocytes and polymorphonuclear and mast cells (Libako et al. 2015). Magnesium has a modulating function over immunoinflammatory responses and antagonizes the actions of Ca (Vormann 2003; Mazur et al. 2007; Libako et al. 2016). Because the intracellular Mg concentration is strictly regulated, Mg does not work as an intracellular second messenger, but acts on changing the direction of metabolism (Vormann 2003). This has been demonstrated by Libako et al. (2016) using Ca blockers which prevented lipopolysaccharide-induced transcription and release of IL-1β, IL-6 and TNF-α, while extracellular Mg showed a modulating action (Libako et al. 2016). Among the fundamental roles phosphorus plays in the immune responses, phosphorylation and dephosphorylation reactions take place during intracellular signalling which is essential for the accomplishment of all immune functions (Kegley et al. 2001; Oster et al. 2016). Several studies on different species suggest that dietary phosphorus is fundamental for an appropriate immune response during infections, particularly for the adaptive immune system, and to maintain a stable gut microbial ecosystem to act as a barrier against potential pathogens (Heyer et al. 2015). Sulphur is a component of sulphur amino acid glutathione (GSH), homocysteine (Hcy) and taurine (Tau), which play important roles in various mechanisms of the immune response (Grimble and Grimble 1998; Grimble 2006). Sulphate and taurine are the major end products of sulphur amino acid metabolism, and in animals, high taurine intakes are anti-inflammatory (Grimble 2006). Methionine and cysteine play a role in the immune surveillance

of the intestinal epithelial layer and regulation of the mucosal response to foreign antigens (Fang et al. 2010).

In the group of the trace elements, studies have found evidence of their importance in the immune response to infectious diseases (Weiss and Carver 2017). For example, an intrinsic relationship has been demonstrated between regulatory cytokines and blood levels of iron, copper, zinc and selenium in cutaneous leishmaniasis (Kocyigit et al. 2002). Selenium is essential for all mammalian species because it is required in various physiological functions, including important mechanisms of the reproductive system and notably in the immune system in resistance to infectious diseases (Kumar et al. 2008). Selenoproteins participate in macrophage activities (Zamamiri-Davis et al. 2002) as well as in the immune regulation (Kieliszek and Błażejak 2016). Selenium supplementation has been associated with enhancing immune competence, leukocyte function and specific immunity of humans and animals (Steinbrenner et al. 2015). Zinc contributes to form the structure of many enzymes and transcription factors and acts in the synthesis of acute phase proteins by the liver (Rink and Gabriel 2000; Osada 2013). Zinc deficiency has been shown to impact on B-cell lymphopoiesis and to induce potent atrophy of the thymus, subsequently leading to a decline in the number of peripheral T lymphocytes, both in a murine model of zinc deficiency (Keen and Gershwin 1990; King et al. 1995) and in zinc-deficient humans (Wolowczuk et al. 2008). In fact, for example, zinc deficiency has been associated with higher susceptibility to severe forms of diseases such as leishmaniasis (Mishra et al. 2010). Supplementation with zinc has resulted in protective effects in conditions related to diverse pathogens (Lazzerini and Wanzira 2016; Weiss and Carver 2017; Darling et al. 2017; Wang and Song 2017).

Some nutrients are categorized as conditionally essential nutrients because they are critical factors for a variety of functions in the course of diseases or determined metabolic conditions. In this miscellaneous group, nutrients such as carnitine, glutamine, arginine, choline and phosphatidylcholine, inositol, homocysteine, cysteine and taurine and a variety of phytochemicals that include flavonoids, carotenoids, lycopene, dietary fibres and phytosterols are included (Institute of Medicine 1998c; Craig and Beck 1999; Liu 2003; The editors 2004; Ploder et al. 2010; Hakim et al. 2012; Rasool et al. 2012; Marcinkiewicz and Kontny 2014; Elmahallawy et al. 2014; Leermakers et al. 2015). For example, glutamine is a much studied amino acid owing to its many properties as an immunonutrient and is considered an essential amino acid in patients undergoing hypercatabolism (McRae 2017). Glutamine is the preferred source of energy of enterocytes, and for this reason, it facilitates the digestion and absorption of other nutrients and keeps intestinal cells in the course of infectious diseases and their treatment (Kim and Kim 2017). This amino acid has been investigated as a useful nutrient for the therapeutic approach to various conditions including bacterial (Stehle et al. 2017; Liu et al. 2017), viral (Serrano-Villar et al. 2016; Wang et al. 2017) and protozoal infections (Kempaiah and Dokladny 2016), as well as to other conditions that favour infection, such as multiple trauma or extensive surgery (Lorenz et al. 2015).

2.4 Nutrient Absorption and Residue Excretion During Diseases

Disease interferes with nutrition in a variety of ways. Infection and body mechanisms to control infection can produce an infinity of manifestations and diverse effects on the body systems, at either local or systemic levels, including fever, anorexia and taste aversion (Nilsson et al. 2017). Fever slows down digestion. Inappetence and anorexia are evolutionarily conserved clinical consequences induced by infection and the immune response, involving cytokine-mediated signalling to the hypothalamus (van Niekerk et al. 2016; Rao et al. 2017) and on amygdala neurons (Francesconi et al. 2016). Furthermore, anorexia induced by acute or chronic inflammation is dependent on prostaglandins, which are synthesized by the cyclooxygenase-2 (COX-2) produced by different cell types involved in host defences (Nilsson et al. 2017). The nutritional approach to lack of appetite, anorexia or even medically induced fasting during disease can be controversial. For example, there is a debate as to whether a certain level of—and to what extent—fasting is beneficial in different disease conditions, including infections in their myriad of aspects (Wang et al. 2016). Moreover, a great issue is what would be the point at which nutraceutical intervention, perhaps before or after a specific fasting management, would be most beneficial in therapeutic terms.

A variety of infections can also cause local injury to any segment of the digestive tract, consequently leading to the development of pathological alterations such as dysphagia, pain, sensory disturbances, epithelial lesions and destruction, disturbances in the production and release of digestive juices, alterations in the pH and composition of digestive secretions, interference with exocrine gland secretion, alterations in gut motility and gut microbiota, organ metabolism malfunctions and altered catabolite handling and excretion (Ramig 2004; Andrade et al. 2011; Said 2011; Oliveira et al. 2013; Delgado et al. 2016). In general terms, the consequences of digestive disturbances are malabsorption and lack of nutrients on the one hand and toxaemia on the other (Sukhotnik et al. 2003; Shils and Shike 2006; Mahan et al. 2013).

Gastric juice acidity, bile and pancreatic enzymes exert bacteriostatic and bactericidal actions within the small intestine. The physiological propelling action of peristalsis drives the bacteria to the distal intestine, while the ileocecal valve prevents the migration of large numbers of colonic bacteria to the small intestine (Mahan et al. 2013). When intestinal homeostasis is compromised, either by invasion by pathogenic microbes, by toxicosis or by other factors related with microbiota overgrowth or imbalance, alterations in the digestive tube develop and result in clinical consequences, diarrhoea being the most common (Quera et al. 2005; Bondarenko et al. 2006). Examples of pathogenic bacteria that invade and colonize the intestine include *S. typhimurium*, *L. monocytogenes*, *Campylobacter* spp., *Shigella* spp. or enterotoxigenic *E. coli* (Khoshoo et al. 1990; Barbuddhe and Chakraborty 2009; Pawlowski et al. 2009; Taylor et al. 2017; Liu et al., 2017). Botulism caused by ingestion of food contaminated by *Clostridium* spp. is a common reported cause of

toxicosis and severe dysphagia (Burke et al. 2016). Overgrowth of the commensal bacteria of gut microbiota is associated with a number of predisposing causes, including diet, and results in clinical alterations associated with diarrhoea (Mahan et al. 2013; Davis et al. 2016). As well, enteral protozoan pathogens, helminths, viruses and fungus can cause several alterations in the digestive tract (Ali and Hill 2003; Donskey 2004; Hodges and Gill 2010). Systemic infectious diseases caused by viruses such as HIV (García et al. 2006; Dillingham et al. 2011); by protozoa such as *L. donovani*, *L. infantum* (Baba et al. 2006; Cota et al. 2012) or *P. falciparum*; or by bacteria such as *Leptospira* spp. or *Yersinia* spp. can also produce enteritis among several other pathophysiological alterations. Vomiting is another important cause of nutrient loss in the course of infections, and this frequently occurs together with diarrhoea (Karney and Tong 1972; Brasitus 1983; Uysal et al. 2016).

Nutrient malabsorption is an important pathophysiological element in the course of infections and their consequences on the body. Malnutrition is the direct sequela of malabsorption and comes together with the heightened requirements for the ongoing immune response, increased metabolic needs, increased losses of body reserves and reduced intake of food that all characterize illnesses. On the other hand, malfunction of organs responsible for metabolism of nutrients and excretion result in elevated catabolite and by-product accumulation, which intensify functional impairment, reducing the metabolic capacity of distinct systems leading to systemic failure. It is a vicious cycle. Thus, a normal diet is often not sufficient to meet the increased demands for micronutrients in infectious diseases (Steinbrenner et al. 2015).

A great number of studies have characterized malabsorption and nutrient deficiencies owing to infections. Rotaviruses are well-defined examples of infection-related malabsorption which may even culminate in growth impairment and death in children (Dennehy 2000; Estes et al. 2001; Ramig 2004; Shea-Donohue et al. 2017). Helminth infections are associated with multifactorial iron deficiency, from bleeding helminth adherence situ and from worm spoliation and inflammation of the intestine epithelia (Notari et al. 2014; Grencis et al. 2014; Shea-Donohue et al. 2017). Intestinal pathogens are common causes of decreased absorption of nutrients including amino acids, lipids, Vit A, Vit B12, thiamine, riboflavin and zinc (Shils and Shike 2006; Mahan et al. 2013; Shea-Donohue et al. 2017). Intolerance to carbohydrates is associated with sugar fermentation owing to overgrowth of intestinal bacteria, a common phenomenon during parasite infection (Ortiz et al. 2000; Born 2007). One of the consequences of inflammation of the hepatic parenchyma is the impairment of albumin synthesis, which in turn compromises the synthetic properties and functioning of the liver, including, for example, the absorption of calcium and many other minerals or fat-soluble vitamins (Zhou et al. 2015; Adinolfi et al. 2016; Afify et al. 2017; Wang and Feng 2017). Altered renal function has important effects on the metabolism of nutrients (Engel 2003; Boullata 2009). Renal inflammation and parenchyma losses are other common results of systemic infections (Chan 1983; Epstein et al. 1988; Mahan et al. 2013; Imig and Ryan 2013) and kidney dysfunction, whose direct consequences are the kidney-dependent absorption

and metabolism of Vit D, calcium, phosphorus, potassium, iron and some hydrosoluble vitamins (Engel 2003; Méndez and Dobaño 2004).

The involvement of the liver in various infectious conditions is an important cause of several metabolic dysfunctions that result in profound nutrient deficiencies on the one hand and in the accumulation of metabolites, catabolites and by-products, on the other hand, leading to toxic conditions. Hepatitises caused by bacterial infections, such as leptospirosis (Alvarado-Esquivel et al. 2016), bacterial pylephlebitis or hepatic abscesses, or yet involving viruses, protozoa and nematodes, are examples of direct causes of hepatic impairment (Tekwani et al. 1987; Davis et al. 1993; Shils and Shike 2006; Wahib et al. 2006; Fernando et al. 2016; Afify et al. 2017; Arain et al. 2017). Encephalopathy due to ammonia accumulation is an example of toxaemia caused by a dysfunctional liver (Souto et al. 2016). Bacteria in the gut produce ammonia as a catabolite from dietary protein metabolism, and ammonia is absorbed into the circulation. Because of hepatic malfunction, it cannot be converted to urea, which results in encephalopathy as ammonia crosses the brain-blood barrier and is neurotoxic (Holecek 2014; Souto et al. 2016). Kidney dysfunction during the course of diseases is also a significant cause of a toxaemic outcome. Diseases caused by infections commonly compromise the function of the kidneys, a crucial organ for excretion, and eventually reabsorption, of many catabolites, resulting in toxin accumulation and worsening of the metabolic conditions (Tanaka et al. 2017; Li et al. 2017; Leem et al. 2017; Roveran Genga et al. 2017). Uremia is an example of the accumulation of toxic nitrogen compounds from protein catabolism during renal failure (Boullata 2009; Rhee 2015; Chen and Koyner 2015). Even hydrosoluble vitamins and minerals that are considered non-toxic because in normal conditions any excess is easily excreted by a healthy liver and kidneys, during organ failure, these nutrients can accumulate and become toxic.

Altogether, the onset of diseases and their course have an influence on and are influenced by nutrient availability, absorption, distribution, synthesis, catabolism and excretion. The body's struggle during the health-disease process will result in variable levels of metabolism alterations and imbalances. The outcomes of these include malnutrition, even in the most advanced health-care centres of well-developed countries, as it commonly happens in the fields of the most deprived areas of the globe. Inadequate nutrition is the leading cause of morbidity and mortality for both humans and animals, as it impairs immunity, increases susceptibility to disease and severely alters the vital functions. Assuring proper nutrition must therefore also be an inseparable step of any therapeutic or preventive approach to diseases, including the infectious ones. As important as early detection of deficiencies or excess nutrients during an illness might make the difference between aggravation and recovery is the emerging knowledge of the power of certain nutrients as therapeutic agents themselves.

2.5 Nutrigenetics and Nutrigenomics in Health and Disease

Nutrigenomics is the study of how nutrients or diets affect gene expression, and nutrigenetics studies how genetic background affects the response to a nutrient or diet (Phillips 2013). The traditional "one-size-fits-all" approach is not optimal for genetic subgroups that may differ critically. The goal is to match the nutrient intake combination with the current genome status (inherited and acquired genome). In nutrigenetics and nutrigenomics, the study topics include (1) if nutrition can have an impact on health outcomes by affecting gene expression directly; (2) if the health effects of nutrients depend on inherited genetic variants that, for example, alter the metabolism of nutrients; and (3) if nutritional requirements should be customized for each individual so that better health outcomes can be achieved (Fenech et al. 2011).

Dietary macronutrients can alter the gene expression in the body. For example, overfeeding of carbohydrates increases the expression of sterol regulatory element-binding protein-1c (SREBP-1c), fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC), the key lipogenic enzymes in subcutaneous adipose tissue, resulting a 296% increase in de novo lipogenesis (Minehira et al. 2003). In addition, high-carbohydrate feeding induces the expression of interleukin-1β (IL-1 β), tumour-necrosis factor (TNF)-α and monocyte chemoattractant protein-1 (MCP1) in the liver, indicating inflammatory response (Li et al. 2015). On the other hand, a high-protein diet has been shown to increase the expression of glucose transporter 4 (GLUT-4) improving insulin sensitivity (Freudenberg et al. 2012). Biologically important long-chain omega-6 fatty acids, dihomo-gamma linolenic acid (DGLA) and arachidonic acid (AA) can be synthesized from linoleic acid (LA) via gamma-linolenic acid (GLA) by different enzymes, such as fatty acid desaturases 1 and 2 (FADS 1 and FADS 2) (Sergeant et al. 2016). The efficiency of this pathway is highly impacted by genetic variations within the FADS genes (Chilton et al. 2014), ultimately affecting the plasma GLA, DGLA and AA levels and ratios. DGLA-derived eicosanoids have long been recognized as anti-inflammatory; however, AA produces pro-inflammatory metabolites. While GLA supplementation has been reported to attenuate various inflammatory responses, for example, in atopic dermatitis and rheumatoid arthritis (Zurier et al. 1996; Andreassi et al. 1997), some reviews have questioned the results (van Gool et al. 2004; Macfarlane et al. 2012). The genetic variation in genes coding for enzymes used in the fatty acid pathway probably has significant importance in how different individuals respond to GLA supplementation. Fatty acids can also have nutrigenomic effects. For example, NF-κB is a pro-inflammatory transcription factor which is activated by inflammatory stimuli, such as bacterial lipopolysaccharides (LPS) (Calder 2013b), and eicosapentaenoic acid and fish oil have been shown to decrease the gene expression of the pro-inflammatory cytokine TNF by lowering NF-κB activity (Lo et al. 1999; Zhao et al. 2004). Th1-type cytokines seem to be more sensitive to the effects of fatty acids in the diet than Th2-type cytokines, and fish oil has been reported to induce a shift away from Th1-type response (Wallace et al. 2001), possibly explaining the low incidence of inflammatory and autoimmune disorders among Greenlandic Inuit

people (Kromann and Green 1980) and the benefits seen in patients with ulcerative colitis (Rodgers 1998), Crohn's disease (Belluzi and Miglio 1998) and psoriasis (Ziboh 1998) after the administration of fish oil.

Vit D receptor (VDR) is a protein that intermediates the effect of 1,25-dihydroxy-Vit D3 on a specific DNA segment. Through VDR, Vit D regulates the immune system, for example, downregulating inflammation-related genes such as IL-1, IL-6 and interferon-γ (IFN-γ) (Manolagas et al. 1994) and controlling macrophage and lymphocyte function (Wientroub et al. 1989). Vit D also activates many neurotrophic hormones, such as the glial cell-derived neurotrophic factor (Naveilhan et al. 1996), the leukaemia inhibitory factor (Furman et al. 1996), neurotrophin-3 (Neveu et al. 1994a) and the nerve growth factor (Neveu et al. 1994b), indicating a role of VDR in neural cell growth and differentiation.

Micronutrients such as zinc, copper and iron play an important role in maintaining and reinforcing the immune system and antioxidant performances. These micronutrients can affect many genes (nutrigenomic approach), and also genetic interindividual variability may affect the absorption and uptake of the micronutrients (nutrigenetic approach) (Mocchegiani et al. 2012). In addition to an adequate amount of zinc from the diet, the efficient functioning of the proteins which handle zinc ions is critical for maintaining good health (Maret and Sandstead 2006). Mutations in genes that code for zinc-related proteins are the basis for inborn errors of zinc metabolism, for example, mutation in zinc transporter Zip4 resulting in severe zinc deficiency (Küry et al. 2002), substitution in zinc transporter ZnT-8 resulting in the risk of type 2 diabetes (Sladek et al. 2007) and polymorphism in Zip2 associated with carotid artery disease (Giacconi et al. 2008). Age-related alterations in gene expression of zinc transporters Zip1, Zip2 and Zip3 are associated with reduced cellular zinc uptake (Giacconi et al. 2012). This is due to chronic inflammation and also DNA methylation, which can be linked to genomic instability in chronic inflammation, highlighting the pivotal role of zinc transporters in altering zinc homeostasis and metabolism (Cousins 2010; Mocchegiani et al. 2012). On the other hand, dietary zinc plays a key role in adaptive immunity, oxidative stress, DNA repair and protein degradation (Mocchegiani et al. 2012). For example, in zinc deficiency Th 1 cytokines (IFN-γ, IL-2) decrease and Th2 cytokines (IL-4, IL-10) increase leading to a shift towards Th2 production with chronic low-grade inflammation (Franceschi 2007). Furthermore, the expression of peroxisome proliferator-activated receptor-α (PPAR-α) is very sensitive to zinc signalling, and zinc deficiency leads to impaired reactive oxygen species (ROS) production (Meyer et al. 2002). Copper serves as an important cofactor for many proteins but is toxic in excessive amounts. Mutations in ATP7A/B genes are responsible for Wilson disease when copper accumulates in the liver (Mercer 2001), providing a nutrigenetic example of an individual's copper requirement. On the other hand, low copper intake has a nutrigenetic impact in adult humans, as it impairs IL-2 gene expression affecting innate immunity (Hopkins and Failla 1999). Iron affects many genes related to the inflammatory/immune response, cell functions and cell growth (Mocchegiani et al. 2012). Polymorphisms of the iron transporter Nramp1 influence the gene transcription causing vulnerability to infections and to altered

inflammatory/immune responses (Bellamy 1999; Zaahl et al. 2004), and a mutation of *Nramp2* gene leads to increased inflammation and iron overload (Iolascon et al. 2005). The altered gene expression of these transporters can lead to storage of iron in various tissues and organs together with inflammatory degenerative pathologies such as cancer and autoimmune diseases (Cellier et al. 2007).

Nutrigenetics highlights the importance of the genetic make-up of the individual for recommendations of different kinds of nutrients and diets and the benefits or disadvantages of supplements. Nutrigenomics shows the effect that nutrients can have on gene expression, changing it for the better or worse and affecting individuals' health. It also introduces the possibility of one's own health outcome being affected by lifestyle choices, despite the gene variants that are present in the individual's DNA.

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