1. General aspects of vitamin A

Vitamin A is a globally essential nutrient belonging to the group of fat-soluble vitamins that was first described in 1913 in a study of animals fed with ethereal egg or butter extract [1]. In the same year, Osborne and Mendel [2] made the first association of this vitamin with growth. Later, observations made by Steenbock [3] concluded their association with foods of yellow pigmentation (now known as β-carotene). The importance of vitamin A in vision health has been considered since ancient Egypt (1500 BC), where people suffering from night blindness were treated with a topical extract of hepatic liver extract (recognized today as a rich source of vitamin A) [3–6].

Its deficiency has typically been associated with continued malnutrition and childhood blindness; it is estimated that 254 million people suffer from vitamin A lack or related ocular disease [7]. It is now known that its benefits go beyond its role in vision yet include numerous essential metabolic and systemic functions [8].

To supply their metabolic functions and to avoid deficiency or overdosage, daily intake requirements were established according to their activity. This activity can be expressed as international units (IU) or retinol equivalents (RE): 1 IU is equivalent to 0.3 μg of total trans retinol or 0.6 μg of total all-trans-β-carotene, whereas 1 RE is equivalent to 1 μg of all-trans-retinol, 6 μg of all-trans-β-carotene, or 12 μg of another provitamin A carotenoids [9].

The recommended daily requirement for adult men and women is 900 and 700 μg RE/day, respectively, while 300 and 250 μg RE/day are the minimum intake limits. During pregnancy and lactation, recommendations are 700 and 950 μg RE/day, respectively [8, 9]. In the case of children in populations considered vitamin A deficient, doses of 60,000 μg RE/day are distributed twice a year [10]. According to Stephensen et al. [11], acute toxic reactions are uncommon at the dosages below 30,000 μg RE/day.

2. Basic chemistry and potential sources

Vitamin A is a lipophilic molecule; its structure was first elucidated by Paul Karrer in 1931 from fish liver oils, for which he won the Nobel [12]. It is now known that the term “vitamin A” is a generic term for retinol and its active metabolites, such as the retinal and retinoic acid [13]. Retinyl esters and carotenoids are also considered vitamin A forms; however, they are oxidized to active forms as soon as they enter the digestive tract of mammals [14].

In general, a retinoid is C₂₀ compound formally constituted of a β-ionone nucleus attached to four isoprenoid units and a functional group at the end of the acyclic chain [7]. As can be seen in Figure 1, retinol (all-trans-retinol) has an
alcoholic end group, where oxidation of this group gives rise to an aldehyde group which characterizes the retinal (all-trans-retinal) structure, which may be further converted to all-trans-retinoic acid [15, 16].

These structures are essential for life in mammals; however, they cannot be de novo synthesized, and their supply depends on dietary intake. They are supplied to the human body in different forms, such as carotenoids provitamin A (mainly β-carotene) or preformed vitamin A (retinyl esters) [13, 17–19].

Carotenoids of provitamin A are present in both plant (via de novo synthesis) and animal products (via dietary intake) [7]. Those having provitamin A activity have at least one β-ring unsubstituted with an 11-carbon polyene chain, which undergoes enzymatic cleavage (in humans and animals) to produce at least one molecule of retinol [20–22]. It is estimated that 1178 natural carotenoids were characterized correctly and reported in the literature [23, 24]. Of these, about 60 have provitamin A activity [20]. However, only some of these carotenoids are commonly found in foods, such as β-carotene, α-carotene, β-cryptoxanthin, and α-cryptoxanthin, with β-carotene being the only one with 100% activity [25].

On the other hand, preformed vitamin A, predominantly retinyl palmitate, is obtained only from sources of animal origin, the main related foods are milk, meat, and eggs [7]. Also, for infants, breast milk is the primary source of vitamin A, aimed at meeting the daily needs and the formation of hepatic reserve of this vitamin [26].

3. Metabolism and biological functions

Regardless of the source of origin, retinol can be stored in various tissues (predominantly in the liver) to maintain adequate serum levels for extended periods [8]. Among the three states of oxidation (retinol, retinal, and retinoic acid), retinol is the most active form, whereas retinoic acid is the only one that is not stored [27].
Figure 2 summarizes the metabolic fate of vitamin A. The different forms of diet enter the digestive tract and are predominantly absorbed in the proximal part of the small intestine [8].

Pro-vitamin A carotenoids are cleaved (via \(\beta\)-carotene dioxygenase) to retinal [28]. This retinal can be reversibly converted to retinol (via retinal reductase) or irreversibly to retinoic acid (via retinol dehydrogenase); such interconversion occurs in the gut of all mammals [29]. On the other hand, retinyl esters of animal origin are converted to retinol via ester hydrolases of retinyl (REHs) [30].

The retinol formed is esterified to long-chain saturated fatty acids (mainly palmitic acid), packaged in chylomicrons, secreted into the lymphatic system, and stored in the liver (80% of the body supply) [31]. Minor amounts are distributed and stored in extrahepatic tissues and organs (eye, lung, adipose tissue, kidneys, small intestine, adrenal gland, testis, uterus, bone marrow, thymus, skin, and spleen) [32, 33].

When the retinoids reach the hepatic system, they are hydrolyzed and complexed with the retinol-binding protein to be transported the target cells as required. In contrast, retinoic acid is carried in plasma bound to albumin [34].

The most common benefit of this vitamin relates to vision, due to the high demand for this supply by the retina and maintenance of the cornea [8]. However, they are still associated with several functions such as the maintenance of healthy epithelium, cell differentiation, reproduction, immunity, and growth [16].

According to Engelking [29], retinol, retinal, and retinoic acid bind to nuclear proteins, where they are most likely involved in the control of gene expression. Recent research has shown that vitamin A supplementation can positively regulate the expression levels of proteins that improve the intestinal barrier [35]. Mucosal healing was significantly higher in the vitamin A-supplemented group in cases of ulcerative colitis [36].
4. Deficiency of vitamin A and strategies of fortification

Some physiological implications about the intake of high doses of vitamin A have been reported; however, it is their deficiency that causes catastrophic damage. Depletion of this nutrient has become a global problem affecting millions of people worldwide, especially those in developing countries [37]. It harms the health of approximately 190 million children and 19 million pregnant women worldwide [37].

In developing countries, it is the leading cause of childhood blindness and further contributes significantly to the morbidity and mortality of common childhood infections such as continuous malnutrition [38]. Additionally, it causes potential changes in the epithelial barrier of vital organs and tissues [39]. It further reduces the synthesis of specific glycoproteins in the intestinal mucosa and liver, as well as the gene expression of glycosyltransferases, fibronectin, and transglutaminases, disrupting macrophage function, blood clotting, and adhesion. Also, it disrupts normal bone growth as it is essential for the activity of cells in the epiphyseal cartilage [29]. Studies with animals also indicate that in the deficiency of this nutrient, the spermatogenesis is blocked causing infertility [29]. Problems in the regulation of vitamin D receptors may also be affected by the lack of vitamin A [40].

Because of all these controversial effects, highlighting the high morbidity and mortality, government agencies have recognized the problem as a public calamity situation and since then have been developing and supporting strategies to combat vitamin A deficiency [41].

Typically, these approaches are based on the fortification of basic foods, food ready for use, condiments, and mostly milk [42]. Among them are microencapsulation techniques and genetic crosses (biofortification) [18, 43, 44].

Microencapsulation has emerged as an alternative to increasing the stability and bioavailability of labile compounds such as vitamin A, and for this reason, it is believed that this process may be a strategy in food fortification to treat vitamin A deficiency [16, 45]. It is based on the encapsulation of the nutrient into microparticles of polymeric material with the variable diameter [46].

In contrast, the biofortification is an integrated approach of agriculture and nutrition, which uses traditional breeding or genetic engineering techniques [47]. In this case, species of foods containing high β-carotene content are used to obtain hybrid species adapted to places where vitamin deficiency remains a severe problem [48]. For example, genetic crosses made from yellow maize rich in β-carotene gave rise to other tropically adapted maize species [43, 44]. Besides, hybridization of sweet potatoes has also been extensively explored, especially in sub-Saharan Africa [44]. “Golden rice” is another successful example in several vitamin A-deficient countries [49]. According to Tanumihardjo [50], cassava is also included in the basic crops targeted for biofortification.

The chapters presented in this book are intended to help provide a deeper understanding and insight processes of perception and challenges for vitamin A, contributing substantially to the role of future vitamin A effects on human health.
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References

[1] Mccollum EV, Davis M. The necessity of certain lipins in the diet during growth. Journal of Biological Chemistry. 1913;15:167-175

[2] Osborne TB, Mendel LB. The relation of growth to the chemical constituents of the diet. Journal of Biological Chemistry. 1913;15:311-326

[3] Steenbock H. White corns vs. yellow corn and a probable relation between the fat-soluble vitamin and yellow plants pigments. Science. 1919;50:352-353

[4] Ebell B. The Papyrus Ebers. The Greatest Egyptian Medical Document. Copenhagen: Munksgaard and Oxford University Press; 1937. 135 p. OCLC: 559248566

[5] Wolf G. A historical note on the mode of administration of vitamin A for the cure of night blindness. The American Journal of Clinical Nutrition. 1978;31(2):290-292

[6] Wolf G. A history of vitamin A and retinoids. FASEB Journal. 1996;10(9):1102-1107. DOI: 10.1096/fasebj.10.9.8801174

[7] Combs GF Jr, McClung JP. The Vitamins: Fundamental Aspects in Nutrition and Health. 5th ed. London: Academic Press; 2017. 628 p. ISBN: 9780128029657

[8] Saeed A, Hoekstra M, Hoeke MO, Heegsma J, Faber KN. The interrelationship between bile acid and vitamin A homeostasis. Biochimica et Biophysica Acta—Cell Biology of Lipids. 2017;1862(5):496-512. DOI: 10.1016/j.bbalip.2017.01.007

[9] Aronson JK. Vitamin A: Carotenoids. In: Aronson JK, editor. Meyler's Side Effects of Drugs. 6th ed.

Amsterdam: Elsevier Science; 2016. pp. 439-451. DOI: 10.1016/B978-0-444-53717-1.01636-X

[10] Committee On Medical Aspects of Food Policy. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values. Report on Health and Social Subjects. 41 ed. Department of Health. London: Her Majesty's Stationery Office; 1991

[11] Stephensen CB, Franchi LM, Hernandez H, Campos M, Gilman RH, Alvarez JO. Adverse effects of high-dose vitamin supplements in children hospitalized with pneumonia. Pediatrics. 1998;101(5):1-8. DOI: 10.1542/peds.101.5.e3

[12] Karrer P, Morf R, Schoepp K. Zur Kenntnis des Vitamins-A aus Fischtranen. Helvetica Chimica Acta. 1931;14:1431e-14436e. DOI: 10.1002/hlca.19310140511

[13] Blomhoff R, Blomhoff HK. Overview of retinoid metabolism and function. Journal of Neurobiology. 2006;66:606-630. DOI: 10.1002/neu.20242

[14] Chapman MS. Vitamin A: History, current uses, and controversies. Seminars in Cutaneous Medicine and Surgery. 2012;31(1):11-16. DOI: 10.1016/j.sder.2011.11.009

[15] Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: An overview of clinical efficacy and safety. Clinical Interventions in Aging. 2006;1(4):327-348. DOI: 10.2147/ciia.2006.1.4.327

[16] Gonçalves AB, Berta N, Rocha EF. Microencapsulation of vitamin A: A review. Trends in Food Science and Technology. 2016;51:76-87. DOI: 10.1016/j.tifs.2016.03.001
[17] Weber D, Grune T. The contribution of β-carotene to vitamin A supply of humans. Molecular Nutrition and Food Research. 2012;56:251-258. DOI: 10.1002/mnfr201100230

[18] Sauvant P, Cansell M, Sassi AH, Atgié C. Vitamin A enrichment: Caution with encapsulation strategies used for food applications. Food Research International. 2012;46:469-479. DOI: 10.1016/j.foodres.2011.09.025

[19] Rodriguez-Amaya DB. Carotenoids and food preparation: The retention of provitamin A carotenoids in prepared, processed and stored foods. John Snow, Inc/OMNI Project; 1997. 88 p

[20] Rodriguez-Amaya DB. A Guide to Carotenoid Analysis in Foods. Washington DC: ILSI Press; 2001. 71 p

[21] Lakshman MR. Alpha and omega of carotenoid cleavage. Journal of Nutrition. 2004;134(1):241S-245S. DOI: 10.1093/jn/134.1.241S

[22] Wyss A. Carotene oxygenases: A new family of double bond cleavage enzymes. Journal of Nutrition. 2004;134(1):246S-250S. DOI: 10.1093/jn/134.1.246S

[23] Yabuzaki J. Carotenoids Database. 2018. Available from: http://carotenoiddb.jp/ [Accessed: November 19, 2018]

[24] Fernandes AS, Nascimento TC, Jacob-Lopes E, De Rosso VV, Zepka LQ. Carotenoids: A brief overview on its structure, biosynthesis, synthesis, and applications. In: Zepka LQ, Jacob-Lopes E, De Rosso VV. Progress in Carotenoid Research. 1st ed. Rijeka, Croatia: London: IntechOpen; 2018. pp. 1-15. DOI: 10.5772/intechopen.79542

[25] Meléndez-Martínez AJ, Vicario IM, Heredia FJ. Provitamin A carotenoids and ascorbic acid contents of the different types of orange juices marketed in Spain. Food Chemistry. 2007;101:177-184. DOI: 10.1016/j.foodchem.2006.01.023

[26] Souza G, Dolinsky M, Matos A. Vitamin A concentration in human milk and its relationship with liver reserve formation and compliance with the recommended daily intake of vitamin A in pre-term and term infants in exclusive breastfeeding. Archives Gynecology Obstetrics. 2015;291(2):319-325. DOI: 10.1007/s00404-014-3404-4

[27] Shiota G. Retinoids in liver function. Liver Pathophysiology. 2017;1:705-713. DOI: 10.1016/b978-0-12-804274-8.00050-3

[28] Lintig JV, Wyss A. Molecular analysis of vitamin A formation: Cloning and characterization of beta-carotene 15, 15′-dioxygenases. Archives of Biochemistry and Biophysics. 2001;385:47-52. DOI: 10.1006/abbi.2000.2096. [Accessed: November 19, 2018]

[29] Engelking LR. Vitamin A. In: Engelking LR, editor. Textbook of Veterinary Physiological Chemistry. 3rd ed. London: Academic press; 2015. pp. 282-287. DOI: 10.1016/B978-0-12-391909-0.50044-X

[30] Moore T. The absence of the liver oil vitamin A from carotene; VI. The conversion of carotene to vitamin A in vivo. Biochemical Journal. 1930;24:692-702

[31] O’Byrne SM, Blaner WS. Retinol and retinyl esters: Biochemistry and physiology. The Journal of Lipid Research. 2013;54(7):1731-1743. DOI: 10.1194/jlr.R037648

[32] Nagy NE, Holven KB, Roos N, Senoo H, Kojima N, Norum KR, et al. Storage of vitamin A in extrahepatic
Vitamin A stellate cells in normal rat. Journal of Lipid Research. 1997;38:645-658. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9144080. [Accessed: November 15, 2018]

[33] Marill J, Idres N, Capron CC, Nguyen GGE. Chabot, retinoic acid metabolism and mechanism of action: A review. Current Drug Metabolism. 2003;4:1-10

[34] Blaner WS, Olson JA. Retinol and retinoic acid metabolism. In: Sporn MB, Roberts AB, Goodman DS, editors. The Retinoids: Biology, Chemistry, and Medicine. 2nd ed. New York: Raven Press; 1994. pp. 229-256

[35] Xiao L, Cui T, Liu S, Chen B, Wang Y, Yang T, et al. Vitamin A supplementation improves the intestinal mucosal barrier and facilitates the expression of tight junction proteins in rats with diarrhea. Nutrition. 2019;57:97-108. DOI: 10.1016/j.nut.2018.06.007

[36] Shirazi KM, Nikniaz Z, Shirazi AM, Rohani M. Vitamin A supplementation decreases disease activity index in patients with ulcerative colitis: A randomized controlled clinical trial. Complementary Therapies in Medicine. 2018;41:215-219. DOI: 10.1016/j.ctim.2018.09.026

[37] WHO. World Health Organization. Vitamin and Mineral Nutrition Information System, WHO Global Database on Vitamin A Deficiency. Geneva: World Health Organization; 2014

[38] Khandekar R, Kishore H, Mansu RM, Awan H. The status of childhood blindness and functional low vision in the Eastern Mediterranean region in 2012. Middle East African Journal of Ophthalmology. 2014;21(4):336-343. DOI: 10.4103/0974-9233.142273

[39] McCullough FW, Northrop-Clewes CA, Thurnham DI. The effect of vitamin A on epithelial integrity. Proceedings of the Nutrition Society. 1999;58:289-293. DOI: 10.1017/S0029665199000403

[40] Marchwicka A, Marcinkowska E. Regulation of expression of CEBP genes by variably expressed vitamin D receptor and retinoic acid receptor α in human acute myeloid leukemia. Cell Lines. 2018;19(7):2-14. DOI: 10.3390/ijms19071918

[41] WHO. World Health Organization. Guideline: Vitamin A Supplementation in Infants and Children 6-59 Months of Age. Geneva: World Health Organization; 2011

[42] Dary O, Mora JO. Food fortification to reduce vitamin A deficiency: International vitamin A consultative group recommendations. Journal of Nutrition. 2002;132:S2927-S2933. DOI: 10.1093/jn/132.9.2927S

[43] Halilu AD, Ado SG, Aba DA, Usman IS. Genetics of carotenoids for provitamin A biofortification in tropical-adapted maize. The Crop Journal. 2016;4(4):313-322. DOI: 10.1016/j.cj.2016.05.002

[44] Low JW, Mwanga ROM, Andrade M, Carey E, Ball AM. Tackling vitamin A deficiency with biofortified sweetpotato in sub-Saharan Africa. Global Food Security. 2017;14:23-30. DOI: 10.1016/j.gfs.2017.01.004

[45] Loveday SM, Singh H. Recent advances in technologies for vitamin A protection in foods. Trends in Food Science and Technology. 2008;19(12):657-668. DOI: 10.1016/j.tifs.2008.08.002

[46] Silva PT, Fries LLM, Menezes CR, Holkem AT, Schwan CL, Wigmann EF, et al. Microencapsulation: Concepts, mechanisms, methods and some applications in food technology. Ciencia Rural. 2014;44(7):1304-1311. DOI: 10.1590/0103-8478cr20130971
[47] Bouis HE, Saltzman A. Improving nutrition through biofortification: A review of evidence from HarvestPlus, 2003 through 2016. Global Food Security. 2017;12:49-58. DOI: 10.1016/j.gfs.2017.01.009

[48] Tanumihardjo SA. Food-based approaches for ensuring adequate vitamin A nutrition. Comprehensive Reviews in Food Science and Food Safety. 2008;7(4):373-381. Available from: http://agris.fao.org/agris-search/search.do?recordID=GB2012104692. [Accessed: November 15, 2018]

[49] Britton G, Liaaen-Jensen S, Pfander H. Carotenoids: A Colourful History. 1st ed. Münsingen: CaroteNature; 2017. 236 p

[50] Tanumihardjo SA. Nutrient-wise review of evidence and safety of fortification: Vitamin A. In: Mannar MGV, Hurrell RF, editors. Food Fortification in a Globalized World. 1st ed. London: Academic Press; 2018. pp. 247-253. DOI: 10.1016/B978-0-12-802861-2.00025-0