ORIGINAL RESEARCH

Nutrafoods (2018) 17:15-22
DOI 10.17470/NF-017-1009-1

Received: May 29, 2017
Accepted: February 04, 2018

Vitamin bioavailability, diet and prandial status: good tips for great results

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ABSTRACT

Vitamins are key to human health. Although vitamins are involved in several metabolic pathways, humans cannot biosynthesize them except for vitamin D and vitamin B3, so adequate intake in the diet is crucial. Vitamins are classified as fat-soluble or water-soluble. Fat-soluble vitamins include vitamins A, D, E and K, while water-soluble vitamins include vitamins B and C. Avitaminosis due to imbalanced nutrition, disease or genetic impairment leads to disease, but consumption of vitamin supplements or fortified foods can counteract vitamin deficiency. However, their absorption depends on the type of meal and food matrix composition. Vitamins A, D and E are mainly influenced by lipid content which promotes intestinal uptake. Surprisingly, the fat-soluble vitamin K seems to be unaffected by type of diet, although it has better bioavailability as a food supplement. Water-soluble vitamin absorption is not significantly affected by prandial status or dietary composition. No data are reported for vitamin C, while the vitamin B group needs evaluation by coenzyme.

Keywords
Vitamins
Bioavailability
Diet
Meal
Supplements

Introduction

Vitamins are organic compounds essential for life and involved in different physiological processes. They were first discovered by Casimir Funk in 1912, who called them 'vital amines' since they are 'vital' to the organism and were thought to all be amines. Except for vitamin D and vitamin B3 [1], vitamins are not synthesized by the human body so they must be obtained from the diet. Vitamins are required in small quantities, with deficiency leading to disorders and disease.

Vitamins are divided into fat-soluble and water-soluble vitamins. The fat-soluble vitamins include vitamins A, D, E and K, while vitamin C and the eight forms of vitamin B are water soluble (Fig. 1).

Fat-soluble vitamins are absorbed in the small intestine in the same process as lipids (triglycerides, phospholipids and cholesterol) (Fig. 2). After a meal, the pancreas and liver secrete pancreatic juices and bile, respectively. Bile salts trigger the formation of hydro-dispersed lipid-containing micelles, while enzymes in pancreatic juice promote the digestion of lipid macromolecules by breaking them down into easily absorbed smaller compounds. Emulsification allows better dispersion of fats into the intestinal lumen which promotes greater fat contact with microvilli on the unstirred water layer and subsequent uptake into the enterocytes. Conversely, water-soluble vitamins are absorbed via carrier-mediated processes or passive diffusion.

Since, most vitamins are not biosynthesized by the body, they are obtained through intestinal absorption. Several factors, including genetics, diet, gastrointestinal disorders and drug consumption, can influence vitamin uptake. The aim of this review is to describe how meal content can affect the absorption of vitamins and identify a better way to consume vitamin-based supplements according to diet.

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Vitamin A

The term vitamin A covers retinoids which include the three vitamers retinol, retinal and retinoic acid. Vitamin A is found in animal-derived food in its active form or as retinyl esters, and in vegetables and fruit as provitamin A carotenoids (mainly β-carotene, α-carotene, β-cryptoxanthin).

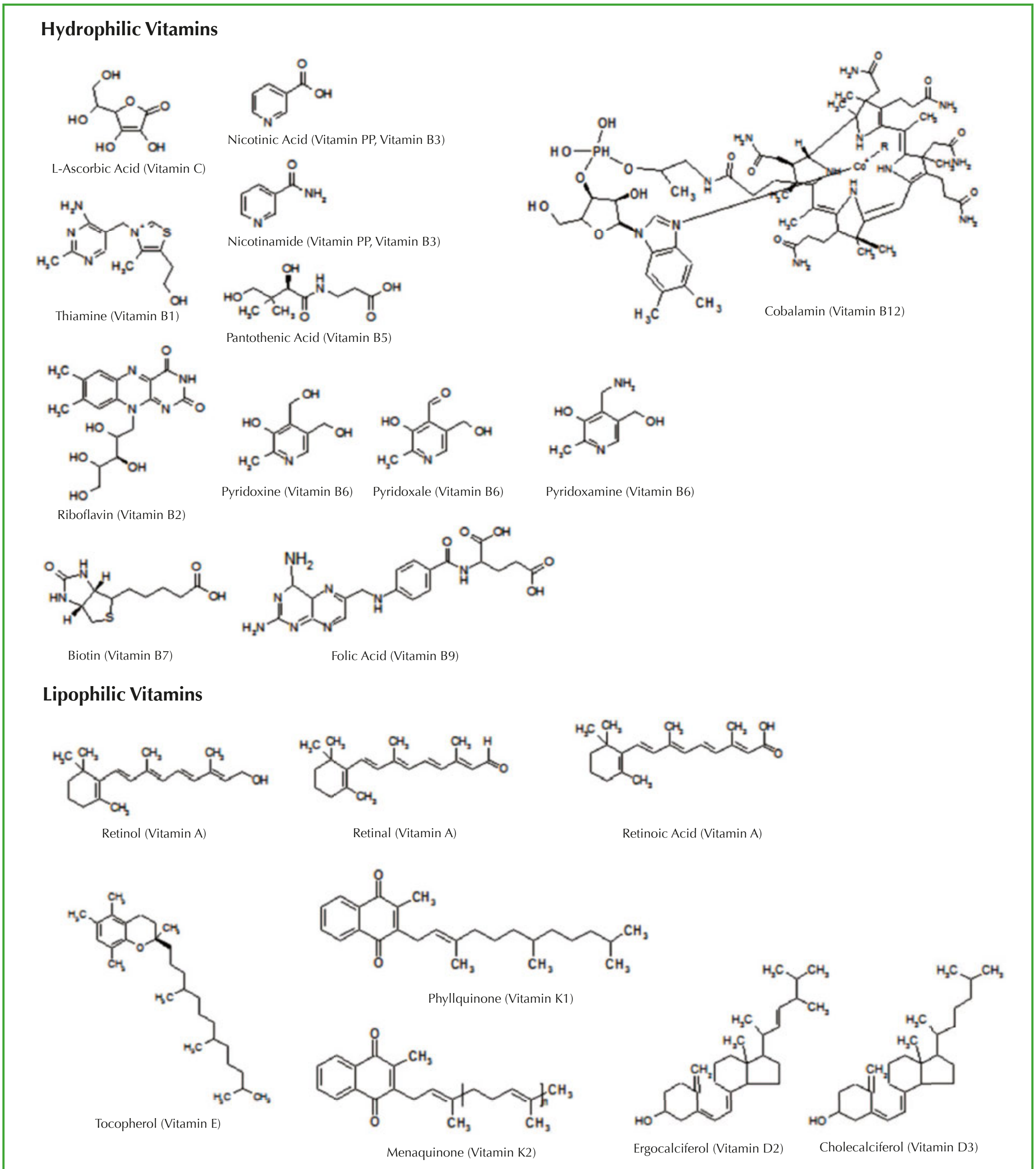

Figure 1 - Structure of hydrophilic and lipophilic vitamins

Vitamin A is important for vision, the immune system and skin differentiation. Vitamin A deficiency is a global health problem which mainly affects children and pregnant women. According to the World Health Organization (WHO), inadequate intake of vitamin A can lead to preventable blindness in children and night blindness (nyctalopia) in pregnant women [2]. Furthermore, vitamin A deficiency impairs the immune system [3], increasing the risk of severe disease.

Vitamin A is a fat-soluble vitamin and shares the same mechanism of absorption as lipids in the upper half of the small intestine. Although vitamin A is physiologically absorbed as a lipid, researchers debate the role of dietary fat on vitamin A bioavailability. Studies indicate that increased dietary fat improves vitamin A uptake [4, 5]. Conversely, other research has shown that 5–40 mg fat per meal does not affect vitamin A absorption [6, 7] or postprandial vitamin A homeostasis [6].

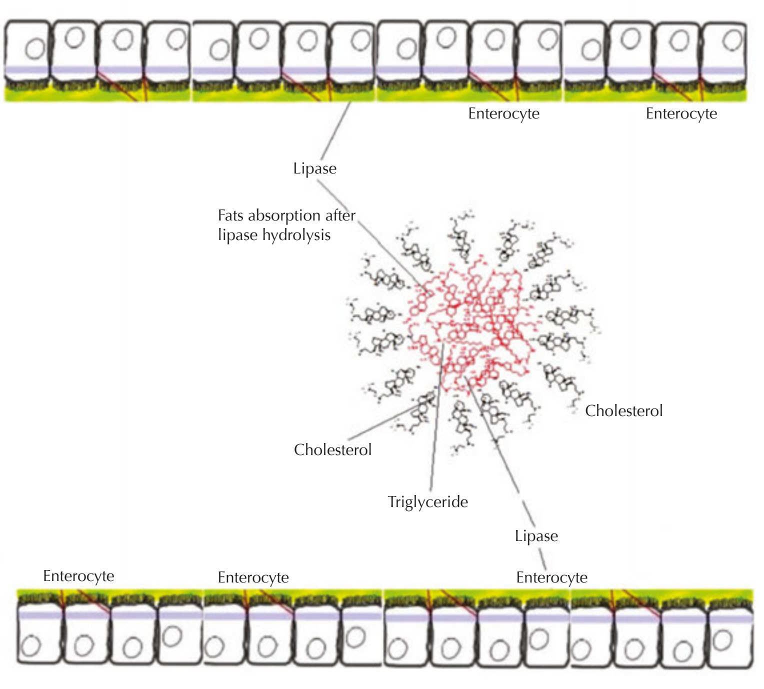

Figure 2 - Mechanism of intestinal lipid absorption

In contrast, it is agreed that β-carotene bioavailability is increased by dietary lipids [8–10]. In particular, Borel *et al* have shown that more β-carotene was present in chylomicrons after a meal containing long-chain triglycerides than a meal containing short-chain triglycerides [11]. It is generally thought that a minimum of 3–5 g of fats is required to improve carotenoid absorption [12], but further studies are needed.

Once absorbed, β-carotene is converted to retinol. It has been demonstrated that this process is influenced by the ingested dose of β-carotene. A randomized cross-over study showed that administration of a double dose of β-carotene (40 mg instead of 20 mg) resulted in an increase of only 36% of vitamin A. Despite the fact that the study was conducted with higher than normal β-carotene intake (20 mg of β-carotene, which is supplied by 230 g of carrots), Novotny *et al* also found that β-carotene conversion is limited by high administration [13].

These results suggest that vitamin A is adsorbed better if consumed with a meal, since its uptake requires bile salts and emulsifiers, while lipid content improves β-carotene bioavailability.

Vitamin D

Vitamin D is a fat-soluble vitamin which acts as a hormone and exists in two biologically inactive forms: vitamin D2 and D3. Vitamin D3 (cholecalciferol) is synthesized in human skin during exposure to UVB light; subsequent hydroxylation in the liver and kidney converts cholecalciferol to calcitriol, the biologically active form of vitamin D. Vitamin D2 (ergocalciferol) is produced by yeast as a result of UVB irradiation. Humans can convert vitamin D2 to vitamin D3. Humans are unable to synthesize vitamin D2 [14], but can obtain it through exposure to sunlight which leads to the production of vitamin D3 [14]. Both forms can also be obtained in the diet through the consumption of animal-based foods such as egg yolks and oily fish for vitamin D3, or dietary supplements or fortified foods for both forms of vitamin D [15]. The main function of vitamin D is the maintenance of calcium and phosphorus homeostasis, which is essential for bone mineralization and nervous system function. Vitamin D receptors (VDR) are also present in several tissues, demonstrating that vitamin D is also involved in modulation of the immune system, control of cell growth, and regulation of the renin-angiotensin system [16]. Vitamin D deficiency affects almost 50% of the global population [17], resulting principally in childhood rickets, adult osteomalacia, muscle pain and weakness.

Physiologically, vitamin D absorption occurs in the small intestine after emulsification in micelles formed by bile salts. Vitamin D bioavailability is closely related to the presence of dietary fat [18]. Lipid-rich food greatly enhances vitamin D uptake by enterocytes. Johnson *et al* demonstrated improved vitamin D absorption from fortified cheese [19], while Mulligan and Licata in a prospective cohort study examined the influence of the complete meal on vitamin D uptake. It has been shown that ingestion of a liquid or solid vitamin D supplement with the largest meal of the day increases calcitriol serum concentration by 50% [20].

Several studies have investigated the impact of vitamin D-enriched food on bioavailability. Fortification of whole milk, skim milk, corn oil and orange juice results in high vitamin D levels. Surprisingly, as it is free from lipids, orange juice fortified with vitamin D shows a 150% increase [21]. Vitamin D from fortified cheese and bread shows the same increases in bioavailability as cholecalciferol supplements [22, 23]. These results suggest that fats should be added to food supplements and the food matrix should be enriched with vitamin D for good bioavailability and easier consumption.

Vitamin E

Vitamin E includes eight isoforms of tocochromanols: α-, β-, γ- and δ-tocopherol and α-, β-, γ- and δ-tocotrienol. α-Tocopherol is the most active and has the highest serum concentrations. Vitamin E is a potent antioxidant, protecting unsaturated fatty acids, phospholipids, vitamin A, carotenoids and other lipids from peroxidation. Due to its lipophilic nature, vitamin E is mainly located in the cell and organelle membrane where it acts as a shield against free radical attack, ensuring cell integrity and combating damage associated with oxidative stress. Vitamin E regulates immune function, prevents the onset of skin disease, acts as an anti-inflammatory agent [24] and reduces cognitive impairment [25]. Vitamin E deficiency is rare and mainly associated with specific diseases rather than poor intake. Depletion of vitamin E leads to ataxia [26–28], peripheral neuropathy [26], myopathy [27, 28], retinopathy [27] and dementia [28].

Vitamin E is a lipid-soluble molecule which is absorbed with dietary fat after entering micelles formed in the small intestine. Uptake is higher when consumed with a meal. Vitamin E supplements taken for 15 days during meals induce an 84% increase in serum concentration compared with a 29% increase if administered 3 hours before a meal [29]. Vitamin E bioavailability is influenced by the amount of lipid ingested with the meal and food matrix composition [30, 31]. Dimitrov *et al* showed a significant increase in vitamin E bioavailability with a high-fat diet (115 g fat/day) compared with a low-fat diet (51 g fat/day) [30]. These results were confirmed by Jeanes *et al* who in a controlled study reported greater α-tocopherol concentrations after a high-fat meal (17.5 g fat) compared with a low-fat meal (2.7 g fat) or water (0 g fat) [31]. The nature of lipids can also affect bioavailability, since it has been reported that saturated fatty acids reduce vitamin E bioavailability [32].

Vitamin E uptake is further influenced by the food matrix. Leonard *et al* compared vitamin E concentrations after consumption of fortified breakfast cereal or incapsulated vitamin E, both with fat-free milk. The study showed bioavailability was greater after the fortified cereal, confirming that food is essential for optimal absorption [33]. Different uptakes were noted between meals with the same high lipid content. Consumption of toast and butter resulted in higher plasma-labelled α-tocopherol responses than consumption of high-fat cereal with full-fat milk [31]. In contrast to these findings, it was previously demonstrated that milk promotes vitamin E absorption, independently of fat concentration [34]. These results show that food properties can influence vitamin E absorption, which however is hard to predict. The main point is that vitamin E bioavailability depends on meal status, increases with a higher lipid content, and can be improved if administered in fortified food.

Vitamin K

Vitamin K exists as two natural vitamers, namely phylloquinone (vitamin K1) and menaquinone (vitamin K2), which in turn include several forms according to the number of isoprenoid residues. Vitamin K acts as a cofactor of the enzyme γ-glutamyl carboxylase and is very important for blood coagulation, bone metabolism and prevention of vascular mineralization [35]. Vitamin K is widely distributed in food and is mainly obtained from the diet as vitamin K2 can be synthesized by the human microbiota. Phylloquinone is the main source of vitamin K and is found in green leafy vegetables and some plant oils. Little vitamin K is stored in the body as, after being oxidised in the carboxylation reaction, the reduced form is regenerated by two-step reaction in a process known as the vitamin K-epoxide cycle. Vitamin K deficiency is quite uncommon because vitamin K is widely distributed in food and cellular recycling by means of the K-epoxide cycle allows vitamin regeneration. Any vitamin K deficiency is mainly related to diseases or drug therapy and leads to uncontrolled bleeding [36], osteoporosis [37] and vessel calcification [37]. Vitamin K is physiologically absorbed in the small intestine after emulsification by bile salts. Vitamin K2 synthetized by gut microflora is poorly adsorbed since micelles are formed in the small intestine. Studies have investigated the association between diet and vitamin K bioavailability, but results are unclear.

Gijsbers *et al* reported that less than 10% of vitamin K1 is absorbed from green vegetables and only a slight increase is reported after the addition of butter compared with 80% absorption after administration of the medicine Konakion® [38]. The same result was found by Garber *et al,* who reported greater availability after administration of phylloquinone tablets than raw spinach. In this case, the addition of fat did not improve bioavailability [39]. Findings are inconsistent as to whether vegetables and fortified oils affect vitamin K1 absorption [40–42]. However, data indicate that phylloquinone supplementation makes it more available than consumption from food sources. A study investigated the effect of the meal on vitamin K1 absorption, using a stable isotope-labelled phylloquinone. Three meals were examined: a 'convenience' meal rich in fast foods and poor in fruit and vegetables, a 'cosmopolitan' meal characterized by fruit, vegetables, fish and dairy products, and an 'animal-oriented' meal with abundant red meat and saturated fat. The three meals had similar total fat, protein and carbohydrate content. The 'cosmopolitan' and 'animal-oriented' meals resulted in similar and significantly higher phylloquinone plasma values than the 'convenience' meal. However, the authors emphasized that bioavailability depends on many variables, such as macronutrient content, gastric fullness and chyme viscosity, so it is hard to predict phylloquinone absorption from a complex matrix [43]. Little is known about vitamin K2 absorption. Gijsbers *et al* noted that in the presence of fat, menaquinone-4 absorption was more efficient than that of phylloquinone [38]. However, this result cannot be extrapolated to other menaquinone forms, so further investigation is required. In conclusion, vitamin K bioavailability is better if administered as a food supplement regardless of type of diet. Nutritional intake depends both on food source and vitamers, but the lack of reproducible data and inconsistent findings prevent specific recommendations for consumption.

Vitamin C

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin. Unlike other mammals, humans cannot synthesize vitamin C from glucose and so must obtain it from the diet. Vitamin C is a reducing agent functioning as an enzyme cofactor and a potent antioxidant. As a coenzyme, vitamin C is mainly involved in the hydroxylation of proline and lysine, an essential step for the proper formation of collagen fibre in connective tissue, bone, blood vessels and skin.

It also participates in the biosynthesis of carnitine, hormones, amino acids and neuropeptides. As an antioxidant, vitamin C blocks free radical cascade reactions, protecting essential molecules in the body and combating disease caused by oxidative stress. Vitamin C is absorbed in the small intestine through a saturable sodium-dependent active transporter or by passive diffusion. Dietary ascorbic acid is absorbed at a rate of 70–90% until intake reaches 1 g/day, after which absorption falls to about 50% [44]. Vitamin C deficiency is rare and its long half-life means symptoms appear very slowly [45]. Inadequate intake of vitamin C causes scurvy [46].

Vitamin C bioavailability seems to be independent of the food matrix and type of meal [46]. Mangels *et al* reported that uptake of vitamin C from different sources, in particular cooked broccoli and orange juice/fruit, is comparable to that from the synthetic form [47]. This was confirmed by Carr *et al* who demonstrated equal bioavailability between natural and synthetic forms of ascorbic acid [48].

These data show that the type of vitamin C does not affect bioavailability. However, little is known about the influence of meal type on vitamin C absorption.

Vitamin B

The term vitamin B covers includes eight water-soluble vitamins which act generally as coenzymes. Their active form is either an enzyme or an active cofactor. The vitamin B complex includes thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine, pyridoxal, pyridoxamine (B6), biotin (B7), folic acid (B9) and cobalamin (B12). Each molecule has to be considered individually. Activated cofactors and enzymes play a key role in several enzymatic processes and metabolic pathways. Activated forms and diseases related to vitamin B deficiency are summarized in Table 1. There are few data on the influence of the food matrix or fed or fasted state on the bioavailability of B vitamins. In humans there is evidence that thiamine ingestion after breakfast or on an empty stomach does not affect bioavailability [59]. Riboflavin absorption is enhanced when administered after a meal [60] and in the presence of bile salts [61]. Vitamin B6 absorption is 75% in a varied diet [62], while Reynolds demonstrated that animal-derived vitamin B6 shows higher absorption than plant-derived vitamin B6 [63]. Biotin in food

Vitamin B	Active coenzyme/ enzyme form	Main deficiency
Thiamine (B1)	Thiamine mono-, tri-, pyro-phosphate	Beriberi [49], Wernicke–Korsakoff syndrome [49]
Riboflavin (B2)	Flavin adenine dinucleotide (FAD) Flavin mononucleotide (FMN)	Pre-eclampsia [50]
Niacin (B3)	Nicotinamide adenine dinucleotide (NAD) Nicotinamide adenine dinucleotide phosphate (NADP)	Pellagra [51]
Pantothenic acid (B5)	Coenzyme A	Not linked to particular disease [52]
Pyridoxine, pyridoxal, pyridoxamine (B6)	Pyridoxal 5'-phosphate (PLP)	Cognitive impairment [53], dermatitis [54], seizures in infants [55]
Biotin (B7)	Biotin-dependent carboxylases	Neurological symptoms [56], alopecia [56]
Folic acid (B9)	Tetrahydrofolate (THF)	Megaloblastic anaemia [57]
Cobalamin (B12)	5'-Deoxyadenosylcobalamin Methylcobalamin	*Pernicious anaemia* [58], megaloblastic anaemia [57]

Table 1 - Vitamin B active forms and related deficiencies

sources is generally bound to proteins [64]. These covalent bonds are cleaved by biotinidase, although raw egg white contains a protein known as avidin which tightly binds biotin, hindering its uptake [65].

The uptake of vitamin B9, also known as folic acid and folate, is influenced by diet and food components. Folates are widely distributed in food and include a group of reduced polyglutamate forms with various substituted one-carbon forms, while folic acid is extremely rare in natural sources. Folates and folic acid have different absorption profiles. The bioavailability of folic acid supplements is 100% when consumed on an empty stomach [66], 85% when consumed as a supplement with a meal or in enriched food [67], and 50% if ingested as food folate [68]. The food matrix extraction and oxidation state affect the amount of vitamin absorbed. Therefore, in case of folate deficiency, consumption of a food supplement is preferred to consumption of folate-rich food, in agreement also with the findings of Cuskelly *et al* [69].

Vitamin B12 and cobalamin are general terms for cobalt-containing compounds, known as corrinoids. Uptake of vitamin B12, when consumed in food, is bound to protein. Physiological absorption of cobalamin occurs in the small intestine. After release from protein, cobalamin binds to the intrinsic factor forming a complex which interacts with ileal receptors and is taken up into the enterocytes. Absorption can become saturated, so increasing vitamin B12 dosage does not necessarily result in a linear increase in uptake. A maximum of about 1.5–2.0 μg per meal can be absorbed [70]. Lack of intrinsic factor is one of the causes of vitamin B12 malabsorption and deficiency. Vitamin B12 in food supplements is better adsorbed than dietary cobalamin, since it is not bound to food protein [71]. However, there is no evidence that other dietary factors influence vitamin B12 uptake.

It has not been elucidated how niacin and pantothenic acid bioavailability is influenced by the food matrix and by diet.

Conclusion

Many variables affect vitamin bioavailability so it is difficult to predict their impact on absorption. The food matrix is extremely complex and macronutrients are not the only factors influencing absorption. Viscosity, pH, particle size, gastric and intestinal transit all affect this process, making it difficult to determine how better bioavailability can be achieved. The literature provides some data, but further investigations are required. Diet and prandial status have more influence on fat-soluble vitamins than water-soluble vitamins. Although vitamins A, D, E and K share the same physiological mechanism of absorption, which includes emulsification of dietary lipids, the process of vitamin extraction from the food matrix and interaction with meal components has not yet been fully elucidated. Vitamers and provitamins also require further separate investigation. Since lipid-soluble vitamins and dietary fats are absorbed in the same way, it is generally assumed that consumption with a high-fat meal improves their absorption. This has been clearly shown for vitamins D, E and β-carotene, but not yet for vitamins A and K.

Regarding water-soluble vitamins, there are no data on the relationship between absorption of vitamins C, B3 and B5 and diet. The influence of meal type on B vitamin absorption varies. Vitamin B1 shows equal bioavailability if consumed after a meal or on an empty stomach, B2 has a better profile after a meal, while B9 and B12 show greater absorption if administered as a food supplement.

Food supplements and fortified food are good ways to combat vitamin deficiency [72]. It has already been demonstrated that vitamin A, D and E fortification increases bioavailability [19, 21, 29, 30, 73]. Food supplements also have high potential. In some cases, vitamins consumed as a supplement show greater bioavailability than vitamins obtained from food [38, 39]. Therefore, the development of new delivery technologies which enhance physiological mechanisms of absorption may help achieve greater bioavailability.

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