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REVIEW ARTICLE

Hypersensitivity to Vitamins with a Focus on Immediate-Type Reactions: Food or Drug Allergy?

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Abstract: Vitamins are essential substances for normal cell functions, growth, and development. However, they cannot be produced by the human organism, so intake must be through the diet. Vitamin deficiency causes the onset of different diseases, ranging from pellagra to pernicious anemia, which can be corrected by reintroducing the missing vitamin form. To supply the right amount of vitamins to the body, every vitamin naturally occurring in foodstuff has been identified, extracted and synthetically produced, thus allowing either food fortification with these compounds or their pharmaceutical production. Furthermore, the increased importance attributed nowadays to body wellness and the pursuit of a permanent status of health at all costs has greatly encouraged a high consumption of vitamin supplements in modern society, since vitamin megadoses may be responsible for adverse or toxic effects. However, excessive vitamins can induce hypervitaminosis. In the USA, a national survey confirmed that 52% of adult Americans take at least one or more supplement products, vitamins and minerals being the most popular supplements in that country. Although vitamins are widespread natural substances, they may induce immediate or delayed type hypersensitivity reactions. Such adverse events are still underestimated and poorly recognized because only single cases have been reported in the literature, and no general review has yet investigated the mechanisms underlying sensitization to each vitamin, the diagnosis, and the management strategies adopted for vitamin hypersensitivity. Although delayed-type reactions to different vitamins are described in the literature, in our review, attention has been focused mainly on immediate-type reactions. Due to the importance of vitamins, further information regarding the above aspects (pathomechanisms, diagnosis and management) would be highly desirable to focus the state of the art on this particular, underestimated form of allergy, thus increasing allergists' awareness on these elusive hypersensitivity reactions.

Keywords: Vitamins, anaphylaxis, immediate-type reaction, food allergy, drug allergy, multivitamins.

1. INTRODUCTION

Vitamins are essential organic compounds which function as co-enzymes and antioxidant agents in the human body. However, humans cannot produce vitamins de-novo, so they must absorb vitamins through the diet [1]. Vitamins are divided into two groups: 1) fat-soluble vitamins, including pro-vitamin A, vitamin A, vitamin D, vitamin E, and vitamin K, and 2) hydrosoluble vitamins including vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B6 (pyridoxine), vitamin B12 (cobalamin), vitamin B9 (folic acid or pteroylglutamic acid), vitamin B3 (nicotinic acid or nicotinamide or niacin), vitamin B5 (pantothenic acid), vitamin H (biotin), and vitamin C (ascorbic acid). Vitamin deficiency may be caused by the inadequate absorption of one or more of these compounds as a consequence of either insufficient dietary intake and/or malnutrition [1]. In Table **1**, all the main vitamins are shown, with the list of foods containing them, and the diseases related to deficiencies.

Vitamins act as cofactors in several cellular enzymatic pathways [1], and it has been suggested that due to their antioxidant properties, an increased daily consumption of vitamins, taken as megadoses, might protect against aging and degenerative diseases [1]. In 1988, both multivitamin and multimineral supplements were reported to improve the performance of 30 school children in Wrexham (UK), who

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Table 1. Main vitamins, sources and deficiency diseases.

Usual Name	Pharmaceutical Name	Necessary Daily Intake	Diseases Due to Deficiency	Sources
Vitamin A	Retinol	1 mg	Xerophthalmia	Apricots, melon, pumpkin, carrots spinach, broccoli, eggs, eel, peaches.
Vitamin B1	Thiamin	1 mg	Beri-beri, Wernicke Encephalopathy	Whole wheat, poultry, wheat germ yeast, pulses, nuts.
Vitamin B2	Riboflavin	1-5 mg	Angular stomatitis, Cheilitis, anemia	Liver, kidney, milk, yoghurt, eggs mushrooms, wheat germ.
Vitamin B3	Niacin	15-20 mg	Pellagra	Whole meal wheat, peanuts, meat, fish, coffee.
Vitamin B5	Panthenol	5 mg	Rare	Most of foodstuff
Vitamin B6	Pyroxidine	3 mg	Ataxia (rare)	Liver, meat, fish, peanuts, bananas, walnuts, avocados, potato, eggs, cereals.
Vitamin B9	Folates	200-400 mg	Megaloblastic anemia	Spinach, beans, peanuts, cabbage, lettuce, orange, avocados, lima beans.
Vitamin B12	Cobalamin	3-5 mg	Megaloblastic anemia neuropathy	Liver, kidney, sardines, oyster, rabbit, eggs, cheese, other meats.
Vitamin C	Ascorbic acid	30-60 mg	Scurvy	Oranges, lemons, sprouts, cabbage, potatoes, cauliflower, broccoli, guavas.
Vitamin D	Calcitriol/Calciferol	3 mcg	Rickets	Fish liver oils, fatty fish as sardines, tuna, herring, salmon, cod, eggs, milk, liver
Vitamin E	alpha-Tocopherol	10 mg	Haemolytic anaemia	Broccoli, wholemeal cereals, vegetable oils as olive oil
Vitamin K	Phitonadione (K1)	100 mcg	Haemostasis disorders	Cabbage, lettuce, liver, broccoli, turnip

were administered non-verbal intelligence tests as part of an 8-month double-blind clinical trial [2].

Although the British nutrition establishment found many weaknesses in the trial, and some attempts to confirm the results failed, the myth of unnecessary intake of vitamins at high doses had started.

On the other hand, clinical practitioners have emphasized the importance of vitamins in specific groups of people at risk for vitamin deficiency, such as newborns and infants who specifically need vitamin K, and pregnant women, who are recommended to take folic acid [3]. Moreover, vitamin D may be essential for children living in northern European countries during the winter; while alcohol-addicted patients are recommended to take supplemental thiamine.

Multi-vitamin supplements may also be useful in treating patients with a low-calorie intake caused by an inappropriate diet or decreased appetite, as well as emotionally disturbed patients, i.e. anorexics, as well as patients receiving total parenteral nutrition. In developing countries, there is increasing evidence that vitamin deficiencies are associated with an increased individual susceptibility to infections and with a higher incidence of mortality [4]. Food fortification is a useful strategy to prevent vitamin deficiency, and has been safely and effectively employed in developed countries for well over a century. For example, vitamin A-fortified margarine was introduced in Denmark in 1918; and in the 1930s, vitamin A-fortified milk and flour supplemented with iron and vitamin B complex were introduced in several developed countries [5].

A wide variety of foods are fortified with various nutritional ingredients, and vitamin enriched-foods may be grouped into three broad categories: staples such as wheat, rice, and oils, condiments including soy and sauces, and processed commercial foods such as noodles, cereals, infant complementary foods, and dairy products. Furthermore, there is a growing interest in the administration of vitamins as therapeutic agents to attenuate the toxic effects or to improve the clinical efficacy of certain chemotherapeutic alkylates used to treat cancer patients. Folinic acid or leucovorin is the reduced form of folic acid; it can be administered as an antidote to folic acid antagonists such as methotrexate, or given intravenously with 5-fluorouracyl (5-FU) to enhance the cytotoxic effects of chemotherapy in resected colon cancer patients [6]. Hereafter, it is necessary to distinguish between vitamins, which naturally occur in foodstuffs, and their semi-synthetic homologs, obtained by chemical procedures, as in the case of thiamine. Naturally occurring vitamin B1, or thiamine, is a water-soluble vitamin found in plants and usually bound to phosphate.

However, synthetic vitamin B1 (i.e., thiamine hydrochloride) is obtained from coal tar, ammonia, acetone, and hydrochloric acid [7]. For that reason, it is necessary to consider that the refined vitamin is usually a compound that is not completely identical to the naturally occurring form, because it is a salt unconjugated to the phosphate moiety [7]. Nevertheless, semi-synthetic vitamins may have some advantages, because they can be administered intravenously to rapidly achieve a therapeutic dose to treat a vitamin deficiency, or as an antidote, such as vitamin K given to contrast a coumarin overdose. Moreover, semi-synthetic vitamin formulations can be easily stored, and are not affected by food deterioration.

Unfortunately, some semi-synthetic vitamins may induce an immediate-type hypersensitivity reaction when consumed as components of multi-vitamin preparations [8], intravenous formulations for total parenteral nutrition [9], or energy drinks [10]. Additionally, semi-synthetic vitamins contained in enriched foods may induce or maintain a hidden sensitization [11] to the naturally occurring vitamin

[12]. Compared to fat-soluble vitamins, hydro-soluble vitamins are more likely to induce an allergic reaction, and among hydro-soluble vitamins, B complex is frequently responsible for an immediate-type adverse event.

However, it is often difficult to correctly identify the culprit vitamin in a multivitamin compound [9, 13, 14]. Lastly, preservatives or additives such as polysorbates 80 [15], benzyl alcohol [16], and ethoxyquin [17] may play a role as sensitizing agents, which is not an issue when using natural vitamins.

As far as delayed-type reactions to vitamins are concerned, they mainly consist of allergic contact dermatitis and it can be induced according to two pathways:

- From the topical use of vitamins as antioxidant or anti-aging agents in cosmetics;

- From an occupational exposure to vitamins in pharmaceutical industry workers or in health workers handling vitamin compounds.

2. HYDRO-SOLUBLE VITAMINS

2.1. Vitamin B1 (Thiamine)

Thiamine (vitamin B1) participates in the metabolism of carbohydrates, alcohols, and branched-chain amino acids. Thiamine deficiency is responsible for the onset of beri-beri disease and Wernicke Korsakoff syndrome [17]. The main molecular features of thiamine include its linked pyrimidine and thiazole rings, the presence of a hydroxyethyl side chain at position 5 of the thiazole ring, an amino group at position 4' of the pyrimidine ring, and an unsubstituted carbon at position 2 of the thiazole ring, which is capable of forming a carbanion. Hydrochloride and mononitrate salts are the most widely commercially produced synthetic esters of thiamine.

Thiamine hydrochloride is a colorless, crystalline, hygroscopic, and highly water-soluble substance. Thiamine mononitrate is an alternative, commercially available salt that is less hygroscopic than the chloride salt, and is often the preferred compound used in food fortification. Lastly, thiamine pyrophosphate, also known as cocarboxylase, is an old form of thiamine that was used as a drug during the 1960s [17]. The first immediate-type adverse reactions induced by thiamine were reported in 1940 following intravenous or intramuscular administration [18-20]. Wrenn and Slovis [21] studied the clinical effects of intravenous thiamine in 989 patients and found only "minor reactions" (usually a burning sensation at the injection site) in 11 patients, and only one case of generalized pruritus, suggesting that thiamine is safe when administered intravenously.

However, both the parenteral or intra-articular administration of thiamine chloride may induce a severe anaphylactic reaction [18-20, 22, 23]. Furthermore, occupational asthma, due to thiamine exposure, has been described in two workers employed in the breakfast cereal manufacturing industry. The cereals were enriched with vitamins, and the workers showed a positive reaction to a bronchial challenge test with thiamine [24]. Specific IgE antibody to thiamine was identified by enzyme-linked-immune-assay (ELISA) in two case reports [25, 26], suggesting a true allergy to thiamine. An allergic reaction to thiamine frequently manifests as a life-threatening event requiring intensive care [27], and it may have a fatal outcome [18, 28]. The mechanism for induction of an allergy by oral administration of thiamine has not been fully elucidated. A 47-year-old patient with thiamine-specific IgE, and an anaphylactic reaction following the intraarticular administration of thiamine chloride showed tolerance to oral intake of thiamine 400 mg [26].

Additionally, Leung *et al*. [29] investigated two patients who developed anaphylaxis to parenteral thiamine, and displayed positive skin tests. However, only one of these patients showed a positive reaction to an oral challenge, probably because thiamine chloride may generate 20 different metabolites in the human body [25]. Thiamine may act as a hapten. Its binding to an azoprotein has been proposed as the mechanism for conjugating thiamine to a carrier protein [25], thus various parts of the thiamine molecule have been suggested to be immunogenic. Leung [29], for instance, suggested that thiamine contains a quaternary amine group which binds IgE antibodies, although the thiazole ring could also be immunogenic. Finally, a case of parental desensitization to thiamine at doses up to 100 mg/day was reported in the early 1940s [30], but it could be difficult to use desensitization protocol in patients with Wernicke-Korsakoff syndrome (WKS). WKS is an acute encephalopathy occurring in alcohol-addicted patients with neuropsychiatric changes that render them non-compliant to a desensitization procedure. Because WKS is a life-threatening condition requiring intravenous administration of vitamin B1 at doses up to 250 mg, in rare cases of thiamine sensitization, management with intravenous thiamine treatment is suggested [31].

2.2. Vitamin B2 (Riboflavin)

Riboflavin is a yellow substance with a high degree of natural fluorescence when excited by UV light. The molecular structure of riboflavin comprises a planar isoalloxazine ring linked to a ribitol molecule [10]. The structure of the initial coenzyme formed sequentially from riboflavin (riboflavin-50-phosphate), also called flavin mono-nucleotide (FMN) was established by Theorell [32], while the structure of the second coenzyme formed, flavin adenine di-nucleotide (FAD), was established by Warburg and Christian [32]. Two different case reports indicated that riboflavin may induce anaphylactic reactions, when consumed orally by two young patients. The first patient consumed riboflavin in an energy drink [10], and the other one in multivitamin tablets [33]. Because riboflavin sodium phosphate was the ester responsible for the adverse reactions, that formulation was used for skin prick tests. One patient showed positive skin tests for both riboflavin sodium phosphate and riboflavin tetrabutyrate, but not for flavin adenine dinucleotide sodium [33], which is the form more similar to natural riboflavin [32].

2.3. Vitamin B5 (Pantothenic Acid)

The name pantothenic acid was coined from the Greek word meaning "from everywhere", to indicate the wide distribution of this vitamin in numerous foodstuffs.

Pantothenic acid, also known as vitamin B5, forms the core structure of coenzyme A (CoA), which is an essential cofactor in pathways involved in oxidative respiration and lipid metabolism [34]. Due to its wide distribution in natural foods, vitamin B5 deficiency is extremely rare [34]. Pure pantothenic acid is water-soluble, viscous, and yellow. It is stable at neutral pH, but it readily degrades in both acid and alkaline solutions, and it is unstable in heat. Calcium pantothenate, a white, odorless, crystalline substance, is the form of pantothenic acid most often used in commercially available vitamin supplements, because it is more stable than pure vitamin B5. Panthenol, also known as pro-vitamin B5, is the alcohol analog of pantothenic acid. Panthenol is quickly oxidized to pantothenate, which has two isomers. However, only D-panthenol (dexpanthenol) is biologically active [34].

Dexpanthenol usually causes various forms of allergic contact dermatitis [35-37], including contact urticaria [38]. A case of anaphylaxis due to dexpanthenol consumed in a multivitamin product has been described [8]. The patient, a 30-year-old woman, consumed a multivitamin compound daily, and skin tests showed a positive reaction to dexpanthenol 5% formulated in purified vaseline. Interestingly, the patient also mentioned that dexpanthenol-containing sunscreens had previously caused pruritus and local urticaria. The possibility of contact dermatitis resulting from panthenol in sunscreens had been previously reported [39]. Because vitamin B5 is readily metabolized [37], a cross-sensitization between natural pantothenic acid from foods and dexpanthenol has been described only in cell-mediated delayed--type hypersensitivity [40].

2.4. Vitamin B6 (Pyridoxine)

The term "vitamin B6" refers to a group of naturally occurring pyridine compounds including pyridoxine (pyridoxol), which is the alcohol form; pyridoxal, which is the aldehyde form; pyridoxamine, the amine form; and their phosphorylated derivatives [41]. Vitamin B6 is also referred to as pyridoxine, to indicate its structural homology to pyridine. In the body, vitamin B6 is readily taken up by cells, and then enzymatically phosphorylated to produce pyridoxine 5-phosphate (PNP), pyridoxal 5-phosphate (PLP), and pyridoxamine 5-phosphate (PMP), all of which can be interconverted [41]. Vitamin B6 has been synthesized in the form of a salt, (pyridoxine hydrochloride) to increase its hydrosolubility and permit its use as a dietary supplement [41]. Vitamin B6 is a weak sensitizer, anecdotal cases of contact dermatitis and photo-allergic dermatitis, related to the pyridoxine hydrochloride form of vitamin B6, have been reported in the literature [42]. Japanese researchers described the case of a 45-year-old female non-atopic patient who manifested two episodes of anaphylactic reactions with flushing, hypotension and blurred consciousness, following infusion of a multivitamin solution [43]. Because the multivitamin preparation included thiamine, riboflavin, pyridoxal-5-phosphate (PLP), ascorbic acid, and phytonadione, skin prick tests only evidenced cutaneous positivity to PLP. The researchers then investigated patient's tolerance to other forms of vitamin B6, by performing skin tests, lymphocyte stimulation tests, and a histamine release test.

The results showed a cross-reactivity among PLP, PMP, and PNP, but no reactions to pyridoxine hydrochloride, and adenosine 5-diphosphate. Based on those results, the authors speculated that, in that particular patient, the antigenic recognition involved the entire vitamin B6 molecule, and not just the pyridine ring, as in the case of pyridoxine hydrochloride, although no oral challenge test was performed to confirm their hypothesis [43].

2.5. Vitamin B9 (Folates)

Folic acid is a water-soluble vitamin that was first identified and synthesized in the 1940s, and was widely used for treating megaloblastic anemia. Folates include a group of compounds characterized by different oxidation states, by the length of the glutamate side chain, and by the specific carbon units attached to the molecule [44]. Folic acid has a molecular weight of 441.4 Daltons, and consists of a pteridine ring linked to para-aminobenzoic acid joined at the other end to a molecule of glutamic acid [44]. The folate or folic acid structure can be altered by either reduction of the pteridine moiety, to form dihydrofolic acid and tetrahydrofolic acid [THF], or by elongation of the glutamate chain, or by substitution of one-carbon units to the polyglutamated form of the THF molecule [44]. The optimal daily intake of folates is estimated to be 400 mcg [45], which can be difficult to achieve on an average diet. Therefore, consumption of a multivitamin or folate enriched-food can be necessary [11]. The first case report of folic acid hypersensitivity was published in 1949, It described a 35-year-old female patient who developed maculopapular dermatitis following oral intake of folic acid. The patient also experienced anaphylaxis due to the intravenous administration of 50 mg of folate [46].

Pteroylmonoglutamic acid, also known as folic acid [FA], is the synthetic form of folate containing only the monoglutamate conjugate used in multi-vitamin tablets, and often provided as a supplement vitamin in fortified foods [11]. FA has been responsible for several cases of severe anaphylactic reactions in female patients when consumed orally as multivitamin tablet or supplement [11, 46-55]. FA has also been reported to cause cases of angioedema accompanied by acute urticaria [11, 55, 56], fever [57], and chronic urticaria [12, 58]. An IgE-mediated pathomechanism has been demonstrated *in vitro* [51, 52, 54] and it explains the ability of folic acid solutions to elicit a positive immediate skin reaction [11, 12, 45-58]. The results suggested that folic acid must be able to rapidly combine with self-proteins or polypeptides in the skin to form a complete allergen, and it is quickly recognized as an allergen by mucosa, triggering an immediate-type reaction a few minutes after its ingestion. A similar mechanism for allergic reactions has also been observed in the case of thiamine, although FA is able to elicit an immediate-type reaction either orally or intravenously. Some authors have speculated that dietary folates are present in their polyglutamate form in foods, as opposed to the

monoglutamate form found in pharmaceutical preparations. This is because, at high concentrations, monoglutamates may exhaust the body's capacity to achieve their methylation and reduction to 5-ethyltetra-hydrofolate by dihydrofolate-reductase, leading to abnormally high concentrations of monoglutamates and non-metabolized folic acid in plasma. Such high concentrations may facilitate allergic sensitization and consequently the onset of an immediate-type hypersensitivity reaction [11, 59]. Most of the reactions have been reported after oral assumption of FA, and sometimes after its intravenous administration [46, 47, 49]. On the other hand, anaphylactic reactions following intravenous administration of Folinic acid (5-formyl-tetrahydrofolic acid), or leucovorin, a synthetic folate analogue, usually administered intravenously in colon cancer patients, have been described, although neither skin tests nor allergic examinations were performed in the patients [60-63]. A recent investigation in five patients with mild or severe hypersensitivity reactions to folinic acid was unable to elicit positive skin tests (prick and intradermal) responses to folinic acid and to levoleucovorin, its pharmacologically active levoisomer [64]. Three patients, who agreed to undergo an intravenous drug provocation test, displayed the same hypersensitivity symptoms with both the agents [64]. All the patients refused a drug provocation test with FA to investigate cross-reactivity. Although an IgE mediated mechanism was not evidenced by skin tests, the authors speculated about a potential sensitization due to folic acid ingestion from folate-enriched foods or multivitamin compounds, because two patients developed symptoms at their first infusion of leucovorin while the other three subjects displayed the onset of hypersensitivity at the 8th, 18th and 19th dose of leucovorin, respectively [63].

Allergic cross-reactivity between folic acid and folinic acid has been demonstrated in skin tests [54] and challenge test [59], although skin tests results were negative in other case reports [48, 52]. In the case of vitamin B9, it is necessary to consider the potential cross-reactivity between FA and methotrexate (4-amino-10-methylfolic acid), a folic acid antagonist drug, used to treat neoplasms and inflammatory diseases.

Such cross-reactivity was investigated again with skin tests [51, 52, 54], and the results were confirmed with basophil histamine release tests [51]. Interestingly, an IgE mediated pathomechanism has also been suggested in the case of methotrexate hypersensitivity [65], and oral desensitization schedules used for leucovorin [66] or methotrexate [67] could probably be adapted also for FA administration.

Although other anti-folate drugs, which are structural analogs of folates, i.e. edatrexate, pralatrexate, trimetrexate and pemetrexed are available for cancer chemotherapy, the cross-reactivity of FA has been evaluated with methotrexate only. However, Gaeta *et al*. suggested that patients with FA allergy should be considered at increased risk of sensitivity to methotrexate and related drugs and, conversely, patients with immediate-type reactions to methotrexate and folinic acid could be at increased risk of reactions against FA from supplements and fortified foods [54, 63] or surprisingly, even against natural folates [12]. Skin tests are useful tools for identifying folic acid as a culprit agent in multivitamin compounds, although they are little used to investigate allergic cross-reactivity between FA and other similar compounds such as folinic acid, tetrahydrofolic acid, methyl tetrahydrofolic acid, and aminopterin (4-amino-pteroylglutamic acid), while a cross-sensitivity between FA and methylfolate has been evidenced in skin tests [54]. However, the interaction between folic acid and the above compounds shows a great variability in cutaneous responses to skin tests [11, 12, 47, 51, 52], probably due to metabolic alterations of the folates [44], although according to Chanarin *et al*., such compounds may be contaminated with folic acid [47].

2.6. Vitamin B12 (Cobalamin)

Cobalamin was the last vitamin to be isolated, in 1948, by two different research groups who performed purification and crystallization of the reddish needle-like crystals of the new vitamin, designated as vitamin B12 [68]. The structure and chemical properties of B12 are highly complex. Vitamin B12 is an organometallic compound with a molecular weight of 1300–1400 Da, characterized by highly unusual properties including the structural presence of a carbon-metal bond [68].

The structure of vitamin B12 consists of a planar group and a nucleotide set located at right angles to each other. The core planar group is a corrin ring with a single cobalt atom coordinated in the center of the ring. The nucleotide consists of a base (5,6-dimethylbenzimidazole), and a phosphorylated sugar (ribose-3-phosphate) [68]. The biologically active forms of vitamin B12 found in nature are 5'deoxy-adenosylcobalamin and methylcobalamin. The latter is the predominant form in human plasma [68]. At the center of the tetrapyrrole ring, there is a chelated cobalt atom that can be attached to several groups, including the methyl, deoxyadenosyl, hydroxyl or cyano groups. Cyanocobalamin is both the synthetic and most stable pharmacological form of the vitamin B12 [68], used for pharmacological purposes, although hydroxocobalamin, methylcobalamin and adenosylcobalamin (cobamamide) are also included in formularies in some countries [68]. Hydroxycobalamin has a higher protein-binding capacity than that of cyanocobalamin, and it has advantages due to its slower metabolism in cells.

Furthermore, there are several other forms of cobalamin such as glutathionylcobalamin, sulfitocobalamin, and nitritocobalamin; however, their physiological roles are unclear and they are reputed to be artifacts of the extraction process [68]. Pernicious anemia usually displays a very early onset in infants compared to adults who have vitamin B12 stored in the liver [1]. Total vegetarians, i.e. vegans, are a specific group of patients at high risk for vitamin B12 deficiency, who can display neurological symptoms, too [1, 68]. One of the first case reports describing an anaphylactic reaction to vitamin B12 was published in 1968. A 67-year-old man with pernicious anemia was alternatively treated with intramuscular administration of cyanocobalamin or hydroxocobalamin.

Although the hydroxycobalamin preparation had induced the anaphylactic shock, the patient exhibited a positive skin test to both cyano and hydroxocobalamin [69].

Additionally, the skin tests were positive for specially prepared and highly purified hydroxocobalamin, cyanocobalamin, and methylcobalamin, suggesting that the patient was sensitized to the vitamin B12 molecule itself [69].

A second reported case of an anaphylactic reaction to vitamin B12 involved a patient who exhibited anaphylaxis to cyanocobalamin and chronic urticaria in response to hydroxycobalamin, without displaying positive skin tests [70]. Patients who show such double sensitization to hydroxocobalamin and cyanocobalamin, and also show positive skin tests to these compounds, have been described in the literature [71-73]. The mechanisms of immediate-type reactions induced by vitamin B12 are controversial. Some authors have defined these reactions as anaphylactoid [70], while other researchers have suggested that hypersensitivity reactions are genuinely IgE-mediated [74]. The latter point of view is supported by the in-vitro release of histamine by basophils isolated from a patient receiving intramuscular hydroxycobalamin. Interestingly, the adverse reaction was not elicited by the administration of cyanocobalamin [74]. One probable cause of vitamin B12 allergic reactions is the molecular complexity and high molecular weight of the vitamin, thus Olesen *et al*. suggested that treatment with exogenous B12 may cause the formation of an immunogenic complex [75]. Administration of extrinsic cobalamin may induce both IgG production [76], and probably even an IgE mediated response in the organism [74, 76], and this is especially true in patients treated with vitamin B12 for an extended time period [77]. Alternatively, Bedford had suggested that impurities formed during vitamin B12 biosynthesis could be responsible for sensitization, although purification methods are now more efficient than 50 years ago.

Interestingly, Moloney *et al*. described two different groups of time-pattern patients: a small group of "reactors", who display an adverse reaction immediately after the first administrations of vitamin B12 sensitizing doses, and a larger group of patients who can receive vitamin B12 supplementation for extended periods of months to years before a reaction [78]. Vitamin B12 replacement therapy has been traditionally performed using intramuscular injections. Other routes of administration are avoided because the absorption of B12 through the gastrointestinal tract may be deficient [68], although immediate-type hypersensitivity reactions have been reported in patients receiving the compound orally [69] or intravenously [13, 79]. Such reactions are probably caused by the ingestion of vitamin B12-fortified foodstuffs that may stimulate the onset or maintenance of sensitization [79]. A case report describing high tolerance to oral B12 was also published by Bilwani *et al*. [80].

They reported a 52-year-old female patient who had developed anaphylactic shock following the administration of intramuscular cyanocobalamin, but showed a high tolerance to oral cyanocobalamin. Their observation has been confirmed recently by a similar case report [81]. It has been seen that some patients sensitized to hydroxocobalamin may tolerate cyanocobalamin [74, 82-85], while patients who display an immediate-type reaction to cyanocobalamin may consume hydroxocobalamin without showing any adverse effects [78, 85]. However, previous reports suggest that cross-reactivity between cyano and hydroxocobalamin is unpredictable [70-73], and not closely related to the route of administration. Although skin tests may be a helpful tool for predicting an individual tolerance to another form of vitamin B12 molecule [78], a challenge test should be performed to confirm the tolerability. When treating vitamin B12 deficiency, and particularly pernicious anemia, the administration of vitamin B12 is usually unavoidable, and it should be continued lifelong. In such cases, some protocols for desensitization to vitamin B12 have been devised to allow the consumption of cyanocobalamin, which is the more stable form of cobalamin. A rapid desensitization procedure requiring about 6 hours to reach a standard dose of 500 mcgr was first described by Branco-Ferreira *et al*. [71]. Later, the same protocol was modified by Caballero *et al*. [72] and successfully performed in three cases [72, 73]. Cyanocobalamin was given intramuscularly [71] or subcutaneously [72].

After the first treatment cycle, the desensitization protocol needs to be repeated at intervals of 1, 2 and 4 weeks between sessions. The persistence of negative results in intradermal testing before each desensitization procedure was used to indicate the protocol effectiveness [72]. Recently, a very short desensitization protocol, lasting 2 hours and 30 minutes, has been proposed by Portuguese authors, and cyanocobalamin was administered subcutaneously to a 61-year-old male patient with malabsorption due to Barrett metaplasia. The patient also showed cross-reactivity with adenosylcobalamin in the skin tests [86].

A pharmacological premedication with intravenous hydrocortisone (200 mg), chlorpheniramine (10 mg), and ranitidine (150 mg), before administering a full therapeutic intramuscular dose of hydroxycobalamin 1000 mcg, to prevent the onset of adverse reactions has been reported anecdotally [87].

Then, because of the presence of a cobalt atom in its chemical formula, the patient may develop an urticaria-like contact dermatitis following cyanocobalamin administration, with skin prick tests and patch tests positive to cobalt [88] Lastly, even benzyl alcohol, which is frequently used as a preservative in vitamin B12 formulations, or other preservatives, may be the true culprit agent in adverse reactions thought to be induced by vitamin B12 [16, 89].

As far as the remaining hydro-soluble vitamins are concerned, there is no case report describing an immediate-type reaction to biotin (vitamin B7) in the English literature, while a short report described anaphylaxis due to niacin (also known as nicotinic acid or vitamin B3) in two patients [90], and a cardio-circulatory collapse induced by nicotinic acid injected intravenously in another one [91], both published at the end of the 1940s. Recently, a case of urticaria induced by vitamin C (ascorbic acid) has been described by American authors. Although the symptoms were not so se-

vere, the patient avoided any consumption of vitamin C from multivitamin compounds and from fresh vegetables or citrus fruit, until he developed scurvy. For that reason, a desensitization protocol for ascorbic acid was carried out, starting from 1/10,000 up to a final dose of 100 mg with an incremental step every 30 minutes, after which the patient needed to take 100 mg vitamin C three times daily [92]

3. LIPID-SOLUBLE VITAMINS

The human body is capable of efficiently storing vitamins A, D, E, and K for periods of at least 3 months; thus fat-soluble vitamins deficiency is less common [3], although, because of their presence in cosmetics and their topical use as anti-aging products, this group of vitamins may induce mainly delayed-type, cell-mediated hypersensitivity reactions such as contact dermatitis to vitamin K, A and E [93, 94]. Nevertheless, immediate-type reactions following the use of fat-soluble vitamin D and K have been reported in the literature.

3.1. Vitamin D (Cholecalciferol/Calcitriol)

The generic term vitamin D refers to a group of chemically related compounds characterized by antirachitic activity; adequate supplies of these compounds are very important for maintaining bone calcium homeostasis. Vitamin D can also be considered as a hormone, because members of the D vitamin family share the cyclopentanoperhydrophenanthrene ring system, derived from cholesterol, with other steroid hormones, so that groups of vitamers are also designated as secosteroids [95]. Furthermore, vitamin D is produced by the human organism in the skin following the sunlight exposure, converting its precursor, 7-dehydrocholesterol to calcidiol and then to cholecalciferol, so it cannot be considered properly a vitamin [95]. Various naturally occurring members of the vitamin D family are differentiated only by the structures of their side chains [95]. The active form of vitamin D is 1,25-dihydroxyvitamin D (1α,25 [OH]2D3), which is also known as calcitriol [95], but in the market, vitamin D can be found as cholecalciferol, i.e. the pro-drug. The first case of immediate-type hypersensitivity to calcitriol involving a 52-year-old female Caucasian patient with end-stage renal disease has been reported.

The patient had been on hemodialysis for 11 years, and her clinical history was characterized by atopic dermatitis, asthmatic bronchitis, and sinusitis [96]. Following a subtotal parathyroidectomy for secondary hyperparathyroidism, her doctor prescribed a regimen of oral calcitriol (0.25 mg) and intravenous calcitriol (1.0 mg) to be administered at each dialysis treatment [96]. Seven days later, the patient was treated with intravenous calcitriol, that after 4 hours, caused the appearance of a severe pruritic urticarial rash on both forearms. The parenteral calcitriol was substituted with oral diphenhydramine, and the patient's condition improved. After 10 days of daily oral calcitriol administration (0.25 mg), the patient developed generalized hives with difficulty in swallowing, and the oral calcitriol was discontinued. The results of skin tests were negative, and the patient was successfully desensitized using a protocol developed for desensitization to parenteral and oral beta-lactams [96]. A starting dose of parenteral calcitriol (0.00002 mg) was administered intravenously, and later replaced by oral calcitriol (0.0078 mg). After completing the protocol, the administration of both oral calcitriol (0.25 mg) and intravenous calcitriol (1.0 mg) on dialysis days was resumed [96].

Turkish authors reported a 52-year-old woman with vitamin D deficiency who experienced itching and hives on taking her first dose of cholecalciferol. They performed skin tests with dilutions of cholecalciferol 1 mg/mL and intradermal testing with cholecalciferol at a 1/100 concentration with negative results. However, an oral challenge test was positive up to the total dose of 50 000 IU, i.e. 15 mL, eliciting an anaphylactic reaction. Because no alternative treatment was available, a 5-hour desensitization protocol with oral drops of cholecalciferol was successfully carried out [97]. Calcitriol is the active metabolite of cholecalciferol, but probably because skin tests were negative, the authors did not investigate the potential cross-reactivity between the two substances. A delayed-type desensitization strategy to cholecalciferol has recently been described in a 76-year-old Caucasian female patient who had developed a morbilliform rash on the trunk following three weeks of cholecalciferol, 25 mg weekly. After having excluded the excipients, an 8--day desensitization to cholecalcifeol was successfully performed [98].

Although other forms of vitamin D such as ergocalciferol, i.e. (vitamin D2, D3) are available in some markets, the potential cross-sensitivity has never been evaluated. Other types of vitamin D such as calcipotriol and tacalcitol, are used as a topical treatment of psoriasis and have been responsible for allergic contact dermatitis in topical formulations [99, 100].

Foti *et al*. demonstrated, in three psoriasis patients who had developed an allergic contact dermatitis following calcipotriol use, no cross-reactivity between calcitriol and its analogues for skin applications, after conducting patch tests, so presumably no cutaneous rash could be elicited by systemic administration of calcitriol in these patients [101].

3.2. Vitamin K (Phytomenadione)

Vitamin K (from the German word "Koagulation") is an essential factor required for post-translational modification of coagulation factors II, VII, IX, and X. While seven different molecules are biochemically designated as vitamin K, vitamin K occurs naturally in only two forms (vitamin K1 and K2), as vitamins K3-K7 are synthetic compounds [102]. Vitamin K1 is found in plants and vitamin K2 is synthesized by Gram-positive bacteria found in normal intestinal flora [101]. The chemical structure of vitamin K1 consists of a basal 2,4-naphthoquinone molecule with two important functional groups: a methyl group, and an isoprenoid side chain containing 20-30 carbon atoms. The most widely used intravenous preparation of vitamin K is phytomenadione (phytonadione), a fat-soluble synthetic derivative identical to the naturally occurring vitamin K1.

Moreover, synthetically prepared vitamins K1, K3, K4, and K5 are currently used in clinical practice, and vitamins K3 and K4 are available as water-soluble salts, but vitamin K1 is the only form of vitamin K available for oral, intramuscular, subcutaneous, and intravenous administration [102].

Intramuscular and subcutaneous injections of vitamin K1 are known to induce three types of cutaneous reactions [103]:

- Eczematous reactions occurring 10-14 days after injection. This allergic mechanism has been confirmed in several patients by intradermal and/or epicutaneous testing. There were positive patch test reactions to vitamin K1, while vitamin K3 was negative [103].
- Scleroderma-like patches at the injection site, occurring several months or years after injection. Sensitization was evidenced in 4 patients by intradermal tests.
- Urticaria [103].

Furthermore, vitamin K1 may induce anaphylactic shock in patients when administered intravenously, intramuscularly, and subcutaneously [102, 104].

The incidence rate of immediate-type reactions to phytomenadione is 3 per 10,000 intravenous doses [104]. The response is usually considered a non-immunologic hypersensitivity, because the dispersants used in many vitamin K formulations (e.g., polyethoxylated castor oil or PECO, also known as Cremophor EL) are themselves capable of inducing immediate-type reactions, often classified as "anaphylactoid" [102]. The non-immunologic nature of these types of reactions was confirmed in a recent study performed in dogs [105]. It has been suggested that comorbidities, such as chronic hepatitis and autoimmune diseases like systemic lupus erythematosus, may have a predisposing effect on the development of delayed-type hypersensitivity reactions to vitamin K [102].

Nevertheless, the risk factors for immediate-type hypersensitivity are still unknown and such reactions may occur even during a very slow infusion of vitamin K1 [104].

Moreover, PECO, when combined with other drugs, such as paclitaxel and cyclosporin, is known to induce immediate-type reactions following intravenous administration [104]. On the other hand, IgE mediated reactions to PECO itself have also been reported [106, 107]. An allergic reaction occurred after an initial infusion of cyclosporin, suggesting the presence of unrecognized pathways for sensitization to PECO [107].

Additionally, the presence of IgE to PECO might explain the onset of anaphylaxis following the subcutaneous administration of vitamin K in a patient who had previously suffered from anaphylaxis after receiving intravenous cyclosporin [108], because the subcutaneous route is an unusual pathway to elicit an immediate-type adverse reaction. Although anaphylactic reactions to vitamin K are often attributed to the accompanying preservatives, it has been evidenced that a specific IgG is capable of interacting with the whole hydroxy-phytomenadione molecule, and the phytyl side chain might be the epitope of vitamin K [109]. Therefore, it is possible that coupling of vitamin K1 to a macromolecular carrier may elicit antibodies directed against vitamin K1 [108]. Neither laboratory assays nor skin tests have y*et al*lowed us to identify vitamin K as the culprit agent. Only a single case report of skin prick tests showing an immediate positive response to pure preservative-free phytomenadione 10% in petrolatum has been described [110]. Cases of occupational contact dermatitis involving the hands and face of individuals exposed to vitamin K1 have been reported [103].

CONCLUSION

It has been estimated that more than 90,000 dietary supplementation products, containing vitamins and minerals available in the USA market, foster an industry worth about 30 billion USD, although the real beneficial effects on patients' health status induced by vitamins megadoses are doubtful [111].

This review suggests the need for greater precautions in the management of vitamins and polyvitamins intake, because they are more similar to drugs than food components. It has become increasingly popular to consume vitamins either as multivitamin formulations or vitamin megadoses. For example, the "Myers cocktail," which is often intravenously injected to treat or prevent various chronic diseases, contains high doses of hydroxycobalamin, pyridoxine, dexpanthenol, ascorbic acid, magnesium, and calcium gluconate [112]. Unfortunately, such empirical "do-it-yourself" multivitamin treatments may cause serious adverse effects, including hypervitaminosis, rather than supposed benefits to the body [1]. The current incidence of immediate-type hypersensitivity to vitamins has not been established, although a recent retrospective study regarding the incidence of drug-induced anaphylaxis, conducted in Portugal over a 4 years period (from January 2007 to December 2010), analyzed 313 patients, and found that only 4 patients among them (0.26% per year) had experienced an anaphylactic reaction due to the consumption of vitamin B12 (3 cases) or vitamin D3 (1 case) [113]. However, minor reactions such as urticaria or angioedema were not included in that study. Then it is important to conduct a careful allergic work-up to identify possible culprit compounds in each multivitamin formulation; for that reason, a skin test is required for each component, vitamin and excipient [8-10, 12, 15, 16, 53, 89], because excipients may play a role in some hypersensitivity reactions, so they should not be undervalued. Additionally, some vitamin derivatives such as ascorbates or the vitamins themselves like riboflavins and beta-carotenoids, that is provitamin A, are used and approved by European and American regulations as preservatives or colorants to be included in fresh and industrial foodstuff or beverages, which increases the hidden sources of exposure [114].

Moreover, a challenge test would be required to confirm the results of negative skin tests, although in certain cohorts of patients, i.e. those receiving parenteral nutrition, allergic

Table 2. Mechanisms involved in immediate-type reactions to vitamins extrapolated from literature.

Usual Name	Pharmaceutical	Pathomechanism	Symptoms	Management
Vitamin B1	Thiamin	IgE mediated	Urticaria, Anaphylaxis	Oral assumption Desensitization?
Vitamin B2	Riboflavin	Probably IgE-mediated	Anaphylaxis	unproposed
Vitamin B3	Unknown (few cases) Nicotinamide/Nicotinic acid	Unknown (few cases)	Anaphylaxis Collapse	unproposed
Vitamin B5	Panthenol	Probably IgE mediated	Urticaria/Anaphylaxis	Increased assumption of naturally rich foods
Vitamin B6	Pyroxidine	IgE-mediated	Anaphylaxis	
Vitamin B9	Folates	IgE mediated	Urticaria/Anaphylaxis	Desensitization?
Vitamin B12	Cobalamin	IgE-mediated	Urticaria/Anaphylaxis	Oral administration as Alternative route Desensitization Alternative B12 mojety Premedication?
Vitamin C	Ascorbic acid	Unidentified	Urticaria	Desensitization
Vitamin D	Calcitriol/Calciferol	Unidenitfied	Anaphylaxis	Desensitization
Vitamin K	Phytomenadione	Non-immunologic Hypersensitivity	Anaphylaxis/urticaria	Alternative vitamer or alternative route

investigations with skin tests or challenge tests could be very difficult, because of their poor compliance and compromised clinical conditions [9, 115]. Lastly, it is difficult to establish whether vitamin-enriched foodstuffs may induce a hidden sensitization or maintain a long-lasting sensitization to synthetic vitamins. Today, relevant medical literature making it possible to predict the tolerability of oral vitamin formulations in sensitized patients is still lacking. Specific IgE have been surely isolated *in vitro* for thiamin [26] and folic acid [52, 54], while other vitamins which may recognize also an IgE mediated pathomechanism are the vitamin B2 [10], vitamin B6 [43] and vitamin B12 [74], identified by skin tests and histamine release tests. For all the other vitamins, only skin tests allow to suggest or exclude exclude a reaginic response or alternatively cause non-immunologic hypersensitivity, as illustrated in Table **2**.

Further studies and tests, including a careful allergic workup with skin tests and challenge tests or new laboratory tests like Basophil Activation Test (BAT), should be conducted to identify patients with vitamin induced immediate--type hypersensitivity.

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CONFLICT OF INTEREST

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