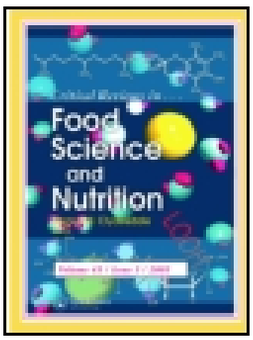

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REVIEW

Product indiscriminate use of vitamin risks: A review

Acsa Lima Marinho Fonseca de Mello, Karolynne Rodrigues de Melo, André Luiz Moreira Domingues de Sousa, Pedro José Rolim Neto, and Rosali Maria Ferreira da Silva

Departamento de Ciências Farmacêuticas, Centro de Ciências da Saúde, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil

ABSTRACT

Most of the population does not seek professional advice before taking vitamin products and their indiscriminate use can lead to serious health risks. This study aims to demonstrate, through bibliographic survey, the risks of indiscriminate use of vitamin products related to hypervitaminosis and major drug interactions which the multivitamins are involved. A bibliographic survey was conducted in the databases LILACS, SciELO, PubMed, Medline, Micromedex, Drugs.com and textbooks on the subject. Vitamins are commonly described as harmless products by the majority of the population, but these trace elements can interact with other substances, causing mild disconforts or treatment failure for the patient, severe consequences to the body and can lead to death. To avoid the indiscriminate use of vitamin products, it is necessary that health professionals know and use specific laboratory tests for the determination of vitamins in the body, preventing these products from being unnecesarily prescribed. Also, the knowledge about what the possible effects of the indiscriminate use of vitamin supplements can lead to the rational use of these products.

KEYWORDS

Dietary vitamins; drugs based on vitamins and minerals; micronutrients; vitamins

Introduction

Various vitamin supplements in the market are available as a single component product or as mixture of these substances. They are labeled as dietary supplements, according to the FDA, which defines dietary supplements as products taken by the mouth that contain a 'dietary ingredient'. Dietary ingredients include vitamins, minerals, amino acids and herbs or botanicals, as well as other substances that can be used to supplement the diet (FDA 2015). Some countries consider these products as drugs, other countries like Brazil classify them as food. However, it is important to know that vitamins are essential components for the body's well-being. Its deficiency can cause serious impairment to the body, but its excess can also bring health risks (Rangue and Dale 2004).

Products containing vitamins have a specific legislation. According to the Federal Food, Drug and Cosmetic Law, Section 201: 'Dietary supplements are products intended for ingestion, they are not represented for use as a conventional food or as a single item of a meal, and they are labeled as supplements dietary' (FDA 2005).

In Brazil, according to Resolution no. 54 of 2012, which revoked Portaria no. 27, of January 13, 1998, vitamin supplements are foods that serve to complement the daily diet, in cases when their intake from food is insufficient or when the diet requires supplementation. They must contain a minimum of 25% and a maximum of 100% of the Recommended Daily Intake (RDI) of vitamins, in the daily portion indicated by the manufacturer, not being able to substitute the foods, nor being considered as exclusive diet (BRASIL 2012).

Since 2013, the pharmacist can prescribe medications and other products for therapeutic purposes, when the dispesing does not require medical prescription (BRASIL 2013) which is the case of vitamin supplements. The act of prescribing needs to be done with caution and responsibility, always based on evidence and clinical examinations. The determination of the optimal dosage for each type of nutritional deficiency is made through the analysis of various factors such as gender, age, body composition, blood biochemistry, type of physical activity performed (or not) and, especially, clinical history of the patient. In addition, interactions between vitamins and other substances are fairly reported in scientific papers, but they are not well known among health professionals and the general population, resulting in the feeling that these products are harmless. So, it is necessary that these professionals have the knowledge about what risks the indiscriminate use of these products can result, such as hypervitaminosis and drug interactions, in order to prescribe it responsibly (Vannucchi et al. 1996).

Both isolated vitamins and multivitamins have recorded alarming sales growth in recente years in Brazil. Individual vitamins, for example, were up 71% from 2008 to 2013, moving R$1.1 billion in 2013, according to the Euromonitor Institute. Multivitamins generated R$923 million in 2013, an increase of 71.24% over the same period. According to IMS Health – MAT (Moving Annual Total), a company that audits the global pharmaceutical market, provided by

CONTACT Rosali Maria Ferreira da Silva rosaliltm@gmail.com Drug Technology Lab, Department of Pharmaceutical Sciences, Federal University of Pernambuco, Av. Sá Arthur, University City, Recife, PE, 50740-520, Brazil.

Abbott® Brazil, August 2014 data show that the Brazilian market for dietary supplements moves currently about 28 million units with growth of 25% in value and 9% in volume only in the last 12 months (Silva and Ferreira 2014).

These data reinforce the importance of researching what causes growth in the consumption profile and what the possible consequences that can be found if the use of these products is not done rationally. The importance of vitamins for the welfare of the organism is widespread but there are rare discussions on what the excess of these compounds can cause, as well as the risks associated with misuse. The objective of this article is to study the possible risks of the indiscriminate use of multivitamins, pointing out the risks related to hypervitaminosis and drug interactions caused by the misuse of vitamin supplements.

Search strategy

This is a bibliographic survey performed in the online research databases LILACS®, SciELO®, PubMed®, Medline®, Micromedex® and Drugs.com® and textbooks that cover the subject. Thus, a search was conducted on the symptoms related to hypervitaminosis and major drug interactions involving vitamin supplements, with the aim of identifying the possible risks related to the indiscriminate use of vitamin products through review of the literature on the subject.

In the initial search, the titles and summaries of the articles were considered for the wide selection of probable work of interest, and highlighted abstracts (articles that have no accessible text) and the complete text of articles, using as keywords the terms 'vitamins', 'vitamins in the diet', 'micronutrients', 'basic vitamins and minerals to drugs'.

The qualifiers used were: 'contraindication', 'adverse effects', 'poisoning', 'toxicity', 'interactions'. The keywords and descriptors are in accordance with the structured and trilingual vocabulary of the Virtual Health Library (VHL).

Inclusion criteria were articles published between 2000 and 2015, except for the classic quotes. The languages used in the search were Portuguese, English and Spanish. Studies were excluded in animals except for those vitamins that do not have studies in humans yet. Also, items that did not treat the harmful effects of vitamins were excluded.

To support this work, a review of articles that addressed the consumption of vitamin products to draw up a profile of users and laboratory tests that are commonly used to determine serum vitamin was performed.

Discussion

Current scenario

The market for vitamin-based products has grown worldwide. With growing concern for health and fitness, products that guarantee to prevent diseases and even improve physical ability are promising for the pharmaceutical market. Scientific research that proves its efficacy and its harmful effects do not seem to follow the emergence of new supplements in the market (COSTA 2013). According to data from IMS Health (2015), the market for vitamin supplements increased by R$1.042 billion in the period from March 2014 to February 2015, an increase of 80% when compared to the same period in 2011. As the volume growth in units sold was only 51% over the same period, data show that these products are also more expensive.

As shown in the Anuário 2014 of Institute of Science, Technology and Quality (ICTQ), according to research conducted in 2014 in partnership with the Datafolha, vitamin supplements occupy the 5th place among the most consumed therapeutic classes in Brazil, the 3rd group among the non-prescription medicines (NPMs).

Table 1 lists the most multivitamins sold in Brazil in value and volume.

The information on the consumption profile of these products in Brazil is still scarce and is mainly related to research commissioned by major pharmaceutical companies or pharmacy chains and to a few scientific articles in gym centers. Most studies show that among those who exercise, the percentage of people who consume dietary supplements (protein, energy products, vitamins and minerals) is approximately 40%, higher among men than women. pa Among these, 25% consume on their own initiative, 18.7% by instructor recommendation, and 20.5% by nutritionist recommendation (Rocha and Pereira 1998; Costa, Rocha, and Quintão 2013).

Women who practice physical activity seem to have less tendency to self-medication compared to men. In some gyms studied, the use of dietary supplements was 75% for the men surveyed (Souza and Ceni 2014; Correa and Navarro 2014).

These data vary in scientific data, but point in the same direction: the use of supplements often occurs without the guidance of a trained professional, without assessing the real need for supplementation.

The study of Alves and Lima (2009) on the consumption of multivitamins in adolescents corroborated with the studies mentioned above, stating that the use of these products is more common among young male adolescents who practice weightlifting and bodybuilding. This study also mentioned that the recommended doses are frequently exceeded.

A study conducted among college students has shown that consumption of vitamin products is higher among students who do regular exercise, and weight training and running the most involved in this consumption modes.

Table 1. Most sold multivitamins in Brazil in value and in volume, between March/2014 and February/2015.

Most sold Multivitamins (with or without minerals)		
	In value	In volume
1	Gerovital (SEM Pharma)	Gerovital (SEM Pharma)
2	Natus Gerin (Legrand)	Centrum Gender (Pfizer Consumer)
3	Centrum Gender (Pfizer Consumer)	Power Vita (Cimed)
4	Centrum Nf (Pfizer Consumer)	Protovit (Bayer Consumer Care)
5	Pharmaton (Boehringer Ingelheim)	Adefort (Gross)
6	Materna (Pfizer)	Centrum Nf (Pfizer Consumer)
7	Centrum Select (Pfizer Consumer)	Natus Gerin (Legrand)
8	Natele (Bayer Pharma)	Materna (Pfizer)
9	Lavitan (Cimed)	Natele (Bayer Pharma)
10	Power Vita (Cimed)	Pharmaton (Boehringer Ingelheim)

Source: *IMS Health* – Brasil PMB – Feb/2015.

Sedentary students showed vitamin C as the vitamin product of higher consumption among this group. In this study, it was found that 30% of college studies consume vitamin products, and the most used without indication of a professional, i.e. featuring self-medication. The indication of the clerks was singled out as one of the causes responsible for this practice (Santos and Barros Filho 2002a).

In Brazil, data on the consumption of micronutrients, such as vitamins, among pregnant women are scarce and controversial, since national surveys are carried out in public hospitals or clinics. Only one scientific article was carried out in the private health network, which is a case report. Therefore, these studies do not cover the population that makes use of the private health network, so there are no studies whose samples are really representative of all social classes.

Surveys conducted in the United States and Australia have shown that the less favored strata have a higher prevalence of nutritional need than the others. While much of the medical prescriptions for vitamin supplements are from the private network, since prenatal care is most effective for this portion of the population. Thus, pregnant women who make the most use of vitamin products are those that are part of the most economically favored classes and they are at greater risk of exceeding the limits allowed (Azevedo and Sampaio 2003).

One study evaluated the consumption of vitamins from the diet of pregnant women and found that generally the amounts of Recommended Daily Intake of vitamins C and A are reached by pregnant women, only with a balanced diet. Some pregnant women have exceeded the limits recommended for these vitamins when they did some type of supplementation. For folate alone, optimal levels were not achieved in most of the pregnant women and required supplementation (Nascimento and Souza 2002).

While Malta et al. (2008) reported that the prevalence of insufficient consumption for vitamins C and E were 60 and 91.5%, respectively, in pregnant women served in the basic health network of the city of Botucatu-SP. And the pregnant women that used vitamin supplementation obtained results superior to the recommended limits. Proving that vitamin supplementation can cause the intake of amounts higher than the recommended ones.

Another study conducted in a public hospital in São Paulo showed that 23% of pregnant women studied had insufficient intake for vitamin A, which can lead to birth defects. Although the study brings as high prevalence of insufficient consumption, these data reflect that in every 10 pregnant women, only two need supplementations for this vitamin (Ribeiro, Araújo, and Dimenstein 2009). Thus, it is necessary to carefully evaluate the vitamin intake by pregnant women from the diet, because each individual has a different diet that depends on social, economic and cultural factors that influence whether or not supplementation of each vitamin individually. The general consensus of the papers published in Brazil and in the world is that one should avoid exceeding the daily limit, because hyperdoses of vitamins can cause problems in fetal development and prematurity (Slater, Marchioni, and Fisberg 2004).

Although it is a rare situation, some studies on the consumption of drugs in the country report the widespread use of vitamin supplements in children. A study raised the profile of consumption of these products by children under six months of age in the state of Pernambuco-Brazil, and showed that the higher the household income, the higher the consumption of multivitamins by children, corroborating with other studies carried out in the country. This same study also found maternal age as being directly proportional to the consumption factor, as well as the first-born are the most exposed to the supplements (Melo, Santos, and Lira 2005).

A survey of 350 children under five years of age showed that multivitamins are among the most consumed drugs, second only to analgesics and antipyretics such as acetaminophen, ibuprofen, dipyrone, and amoxicillin. And the vitamins and nutrients supplementation is one of the main drug uses (De Bona Schraiber and Gallate 2013).

Global efforts to prevent nutritional deficiencies have focused particularly on the prevention and treatment of these lacks through diversification of diet, food fortification programs or nutrient supplementation. Most of the products are directed to children, including breakfast cereals, cookies, snacks and chocolates, which have added vitamins in their composition precisely to combat nutritional deficiencies. So, a child who does not have a diet rich in fruit and vegetables but eats these products containing added vitamins may not have vitamin deficiency and does not require supplementation. If parents do not pay attention to this fact, they can offer supplements on their own, and exceed the required values (Marques et al. 2013).

The same thought does not work only for children, but also for the whole population, since foods like pasta, oil, canned goods, flour, and other products also have vitamins in their composition that are added through industrial processes. Therefore, the intake of vitamin supplements is often unnecessary because most supplements already contain 100% of the recommended daily requirements, then the recommended daily dose would be exceeded.

Monte and Giugliani (2004) in their study on recommendations for complementary feeding of the child on breastfeeding pointed out that vitamin A supplementation is unnecessary if the mother has a diet with adequate intake and if she is provided with foods rich in this vitamin for the child. As for vitamin D, breast milk and complementary foods have a little contribution to daily needs, and exposure to the sunlight is essential to supply them. The article brings that in only 4 minutes a day of exposure to the sun, with the child wearing only diapers, provides the amount needed to avoid deficiency for several months. It is important to know that one should avoid sun exposure between 10 am and 16 hours. Children with dark skin pigmentation require longer exposure time to activate vitamin D compared with those with lighter skin pigmentation. Then the individual nutrient requirements vary according to age and supplementation should be done only when the lack of any vitamin.

The concern of the population is noticeable for living longer and better. Therefore, all offered service that aims to improve the quality of people's lives has a very promissing growth potential. The vitamin complex sector directed to the elderly is among the fastest growing sectors in the pharmaceutical industry and expanded more than 100% in recent years. This sector is responsible for a quarter of sales of vitamins in Brazil (Ventura 2010). Vitamin supplementation is necessary for most elderly people, but as for the rest of the population, it should not be made indiscriminately, because if for some vitamins need is increased with age to other necessity is decreased. The vitamin A requirements, for example, decrease with aging. This is due to the increase in gastrointestinal absorption and decreased catabolism rate of this vitamin, while the susceptibility to toxicity is increased when the amounts exceed the recommended daily dose. So, use of multivitamins may result in an higher risk of hypervitaminosis in older people than in the rest of the population (Moriguti 1998).

Vitamin C has been pointed out as the most commonly consumed vitamin by the elderly. For individuals who use products containing this vitamin, the intake is always higher than the necessary. The World Health Organization recommends that the daily dose should be 90 mg/day for elderly men and 75 for women, and most vitamin C products contain between 500 and 2000 mg per capsule or tablet, far exceeding the recommended daily dose (Moriguti 1998).

The deficiencies of B-complex vitamins among elderly population are quite rare, as well as vitamin E deficiency, because they are abundant in the diet. However, in alcoholics and smokers, deficiencies in pyridoxine (vitamin B6), thiamin (vitamin B1) and folate (vitamin B9) are well reported, making it necessary to evaluate the need for supplementation.

Similarly, for individuals over 50 years of age, vitamin D supplementation should be evaluated, as one study showed that a large proportion of this population does not reach 50% of the daily recommendation for vitamin D (Moriguti 1998).

In general, the prevalence of micronutrient deficiency with antioxidant function (Vitamin E, C and Betacarotenes) is related to the increased risk of developing chronic diseases, since free radicals are highly reactive and can cause serious damage to cellular structures. Thus, oxidative stress has been related to the emergence of pathologies such as cancer, neurodegenerative diseases and cardiovascular problems. Despite this, it has not been possible to confirm that the use of supplements of these vitamins provides some protection against these pathologies (Leite and Sarni 2003). On the other hand, some studies have suggested that vitamin supplementation may increase the risk of death (Huang et al. 2006). A study by the US National Institute of Health showed that men who used multivitamins seven days a week for five years were at increased risk for advanced or fatal prostate cancer. This risk was higher than the risk of men with a family history and men who took supplements containing individual vitamins (Lawson et al. 2007). A study investigating the effect of vitamin A and betacarotene supplementation on patients and workers exposed to asbestos had to be discontinued because supplementation in only three years of use showed a high incidence of death from any cause, including lung cancer (Silva and Naves 2001).

According to studies in other countries such as the United States and Spain, people who ingest vitamin supplements, because they are more concerned about health, have a greater tendency to have a balanced diet, rich in fruit, vegetables, dairy products and fish. If these individuals have a healthier diet then they are more likely to exceed the recommended dosages. In addition, individuals who take supplements are also pointed out as users of single vitamin supplements, such as vitamin C, for example. So, if the multivitamin supplement already has 100% of the recommended daily dose and the individual supplement of vitamin C has a minimum of more than 300%, the intake is extremely excessive and can cause long-term damage (Gómez-Salas 2009).

Most people believe that vitamin C works by preventing colds and flu, however, current scientific studies conclude that there is no such effect. Although the risks due to the consumption of high doses of these products are recognized by the population, as well as the need for professional follow-up, less than half the population believes in the possibility of vitamin C toxicity and less than 10% knows the risks associated with high doses of vitamin C. vitamin A (Santos and Barros Filho 2002b).

Therefore, the excellent reputation of the vitamins among the population can indicate a problem for the public health, since they are considered necessary, source of energy and harmless, which stimulates the indiscriminate consumption of multivitamins. It is necessary to disseminate information about the possible risks of using vitamin-containing products to promote rational use and to try to counter the idea that these micronutrients are harmless.

Drug interactions

Any chemical substances can interact with one another and trigger unwanted reactions or not. Since drugs are chemical substances, they may react with each other and cause different pharmacological responses than expected by single drug administration (Secoli 2001). These interactions are often difficult to predict, especially when the patients self-medicate and do not communicate with their physicians.

Often the population judges food supplements as harmless to health and they often make use of these products without the recommendation of a professional. However, although vitamin products in Brazil are classified as food rather than as medicines, these micronutrients can interact with drugs and cause serious harms to health (BRASIL 1998).

Drug interactions may appear in several levels, being classified as mild, moderate or severe. The mild and moderate are the most common, however, the serious ones are those of greater clinical importance, because they can lead to death.

Table 2. Severe vitamin related drug interaction.

Drugs that show interaction	Vitamin
Tetracycline	A (Retinol)
Hepatotoxic substances	B3 (Niacin)
Statins	B3 (Niacin)
Altretamine e Cisplatine	B6 (Pyridoxine)
Fluorouracil	B9 (Folic acid)
Capecitabine	B9 (Folic acid)
Deferoxamine	C (Ascorbic acid)
Amigdaline	C (Ascorbid acid)
Dicumarol	E (Tocopherol)

Source: The author.

Table 2 shows only the major interactions found in the databases searched on Micromedex® and Drugs.com® according to each vitamin.

The mild interactions do not cause great compromise for the patient and if concomitant use is essential, only the monitoration of the patient is necessary. Moderate interactions, however, need more attention and although they do not cause death, they can compromise therapy and cause uncomfortable and more serious symptoms. In that case concomitant use should be avoided. Attitudes such as changing dose intervals may prevent these interactions. While the serious interactions are those whose complications are severe and can lead to death. Therefore, these interactions are contraindicated, regardless of the interval between doses of each drug. Thus, the serious interactions will be approached in more detail in the present work.

A serious interaction involving vitamin A is the interaction with tetracyclines. Tetracyclines are antibiotics widely used in the treatment of infections. These drugs also have several non-antibiotic properties and can be used in other conditions such as acne and rosacea. Vitamin A and its relatives, such as isotretinoin, are also used in the treatment for acne. Thus, cases of interaction may occur. Studies have shown that tetracyclines alone increase intracranial pressure (brain pseudotumor), as well as the use of high doses of vitamin A also had the same effect (Feldman and Schlezinger 1970; Pasquariello, Schut, and Borns 1977). When used concomitantly, there was a significant increase in intracranial pressure, even at low doses of vitamin A. The risk is greater than when the drugs are given alone, so it is a synergistic effect. It is still uknown what the exact mechanism of interaction leading to increased cranial pressure is, but it is known that cranial hypertension can persist even after drug discontinuation. The tetracyclines that had the effect of cranial hypertension were: minocycline, doxycycline, oxytetracycline. These drugs were studied with products containing vitamin A and its correlates, such as tretinoin, isotretinoin, and acretionin. The symptoms involved with this interaction are: nausea, vomiting, visual disturbances, papilledema and visual loss may be irreversible (Piana and Do Canto 2011; Walters and Gubbay 1981).

Another study reports that ingestion of dietary supplements rich in calcium, iron, magnesium and other minerals should be done at different times of intake of drugs that are part of this class of antibiotics, as tetracyclines interact with metal ions, affecting the efficacy of antimicrobial action. This is a pharmacokinetic absorption reaction, because tetracycline forms chelates with the minerals, preventing its absorption. It is known that multivitamins are usually associated with minerals, so this is another reason to avoid concomitant use of tetracyclines with multivitamins (Pereira-Maia et al. 2010). Although it is not a serious interaction, the patient is at risk of death with such interaction depending on the stage of bacteremia.

All drug interactions proved by scientific studies should be included in the package leaflets to alert the consumer to the potential risks and should be read carefully by consumers. The package leaflets contain essential information for the correct use of these products, being a very important tool to reduce the indiscriminate use of medicines, since they avoid many problems related to medicines (Paula et al. 2009). Because they are free of registration, vitamin supplements do not require a label indicating the side effects and adverse effects, as well as the drug interactions of these products (BRASIL 2010). But, all registered medicines should indicate even the drug interactions with vitamins. In this way, it is possible to take as an example some package inserts indicating interactions with vitamins, so that the consumption of any product containing them should be avoided.

For vitamin B3 (niacin) an interaction is well reported in the package inserts of medications that cause liver damage, such as Leflunomide, teriflunomide, Mipomersen. Because it has hepatotoxic effects, niacin should not be used concomitantly with other drugs with the same effect. When used together with other substances that are also hepatotoxic the risk may be even greater. Concomitant use of these medications either before, during or after administration of niacin may lead to liver failure, so niacin-containing products should be avoided until the washout period, equivalent to four plasma half-lives (Mehal and Avlin 2009; Bhardwaj and Chalasani 2007).

Restrictions may also be found in the statin class of medication, which is a class of drugs widely used to control cholesterol (Guyton and Bays 2007; Sposito et al. 2007). Some studies have reported myopathy and rhabdomyolysis in a patient who used these substances at the same time as niacin. Statins studied were: Simvastatin (ZOCOR 2015), Cerivastatin (BAYCOL 2013), Lovastatin (MEVACOR 2012), Rosuvastatin (CRESTOR 2013), Pitavastatin (LIVALO 2014) and Atorvastatin (LIPITOR 2014).

A pharmacokinetic study demonstrated a 40% to 60% increase in simvastatin concentrations and their active metabolites when coadministered with niacin. Despite its severity, this interaction is considered rare. Patients with kidney problems should be monitored closely because they are at increased risk of developing rhabdomyolysis, as well as the risk is also increased in Chinese patients compared to other ethnicities (Alsheikh-Ali and Karas 2007, 2014; Cooke 1994).

In the package leaflet of medicines containing cisplatin, as Platistine® CS (2014), and In the package leaflet containing cisplatin, such as Platistine® CS (2014), and Altretamine have information on the interactions of these drugs with vitamin B6 (Pyridoxine). Wiernik et al (1992) reported in

her study that the response of these antineoplastics in the treatment of advanced ovarian cancer was decreased when used concomitantly with pyridoxine derivatives. So it may seem harmless to a cancer patient to make use of multivitamins, but this act can lead to ineffectiveness in fighting against the disease. On the other hand, more recent studies have demonstrated that Vitamin B6 confers increased immunogenicity of cisplatin (Aranda et al. 2014). It is important to remember that the 1992 study tested cisplatin along with altetramine and pyridoxine, all three being at the same time. In addition, high concentrations of pyridoxine seem to interfere with the metabolism of cisplatin, conferring accumulation of cisplatin in the body, which may lead to cisplatin toxicity, such as nephrotoxicity and myelotoxicity (Galluzzi et al. 2013).

An example of severe drug interaction involving vitamin supplements is the interaction between 5-fluorouracil (5-FU) and its prodrugs and products containing folic acid. 5-FU is a medicine used in the treatment of cancer and may have its toxic effects increased by the use of compounds containing Vitamin B9 (folic acid) in their composition. The mechanisms of this interaction are not yet known, but symptoms such as neutropenia, thrombocytopenia, stomatitis, gastrointestinal bleeding, severe diarrhea, vomiting, cutaneous reactions, and neuropathy may appear. Some studies have reported the death of some patients who have used 5-FU drugs and their derivatives, such as tegafur and capecitabine, along with folic acid supplementation (Clippe et al. 2003). Interactions involving thiamin and this drug have also been reported.

Another drug that has restrictions on the use of dietary supplementation is Desferal®, a medicine used as a chelator to remove excess iron or aluminum from the body. The active substance is desferrioxamine (Desferal, deferoxamine mesylate 2014). Patients who require repeated blood transfusions, such as thalassemia, may have iron accumulation in the body. This excess of iron can cause damage to important organs such as the liver and heart, and it is necessary to use chelants, such as desferroxamine to remove this excess (CEBION® 2015; Roeser 1983).

Vitamin C (ascorbic acid) is essential for the absorption of iron in the body. Thus, patients who have iron excess should avoid vitamin C supplementation. Desferal's package leaflet contains information from studies that have reported impaired cardiac function in patients with iron overload who received high doses of ascorbic acid (more than 500 mg per day in adults) with deferoxamine. To avoid this type of problem the patient should only make use of vitamin C supplementation after 1 month of regular treatments with deferoxamine and only if strictly necessary. This time is needed to lower serum iron levels before the vitamin is given. In addition, the ascorbic acid dose may not be higher than 200 mg per day in adults in fractionated doses and should not exceed 50 mg per day in children younger than 10 years (Desferal 2014).

A different drug interaction involving Vitamin C is the pharmacokinetic interaction of metabolism of Amygdalin, also known as vitamin B17. Some compounds are used as alternatives or supplements in the treatment of more serious diseases. Amygdalin and laetrile (a synthetic form of amygdalin) are an example of alternative cancer treatment. These compounds are cyanogenic glycosides present in several plants, such as pears, peaches and some almonds, which supposedly present antineoplastic activity (Milazzo, Lejeune, and Ernst 2007). Studies have shown that vitamin C increases the hydrolysis of amygdalin in cyanide and reduces the body's reserves of cysteine, which is used to detoxify cyanide. Therefore, patients who use medications or foods containing amygdalin should not receive vitamin C supplementation, as the consequences of cyanide poisoning are very serious, involving tonic-clonic complications, lactic acidosis, respiratory depression and may lead to death (Bromley et al. 2005).

Although there were no recent studies on the subject and the exact mechanism of interaction was not known, studies have shown that patients taking dicumarol and large amounts of vitamin E (more than 300 mg daily) had a high prothrombin time (Haeger 1968). What is known is that vitamin E can interact with coumarin anticoagulants, from the interference of vitamin E-dependent coagulation factors, increasing the risk of bleeding (Corrigan and Ulfers 1981).

For vitamin B2 (Riboflavin), B5 (pantothenic acid), H (Biotin), no drug interaction was reported. While vitamin B1 (Thiamin), D (Ergocalciferol and Cholecalciferol) and K (Fitonadione) had mild and moderate drug interactions, but no serious interactions were reported.

Hypervitaminosis and poisoning vitamins

The concepts of hypervitaminosis and vitamin intoxication are commonly confused. Some authors use as synonyms, other authors establish dose limits as being different. In general, hypervitaminosis is associated with the condition of a patient presenting symptoms related to a dose exceeding the recommended daily limits (overload) for a certain period of time, in this case, it is a condition promoted by the chronic use of products containing vitamins . On the other hand, intoxication is characterized by more severe symptoms, related to administration of very high doses in a short time ('overdose'), that is, it is an acute condition (Chiancone 1983; Majid 2014).

Vitamins are micronutrients not synthesized by the body or produced in insufficient quantities. For this reason, the ingestion of food containing them is imperative. They are essential to the body since they are important in the metabolism process of carbohydrates, lipids and proteins. In humans, the amount to be ingested may vary according to the age, gender, health status and physical activity of the individual (Golan et al. 2009).

These substances are classified according to their solubility and may be liposoluble or water soluble. Liposoluble vitamins A, D, K, stored in the liver, and vitamin E, which is distributed to adipose tissue. The liposoluble substances are not easily excreted by the body and tend to The water-soluble group is composed of vitamins C and B complex (1, 2, 3, 5, 6, 8 and 9), which remain in the body for a short

period of time before being excreted by the kidneys, so, for these reasons, they should be ingested daily and rarely cause hypervitaminosis. Vitamin B12 is also water soluble, but remains stored in the liver and its excess can also cause symptoms (Katzung 2010).

Studies on hypervitaminoses in Brazil are rather scarce; moreover, most studies on vitamins are quite outdated. In the databases searched, only five studies on hypervitaminosis A were found, being these in animals. Of these five, two were reported in the year 2007 and the others date from 1978, 1987 and 1993. For hypervitaminosis D, four articles were found, all of which were also performed on animals. These articles were published in the years 2008, 2010 and two articles in the year 2012, being more current than the previous ones. An article reports a case of vitamin D intoxication and was published in the year 2014. Nevertheless, no Brazilian scientific article was found that reported hypervitaminosis of the other vitamins, proving the scarcity of national scientific material to base the study of the risks of hypervitaminoses.

Hypervitaminosis A

Hypervitaminosis A is the best reported among all hypervitaminoses. Huk et al. (2013) determined the effects of excess vitamin A on the heart valve structure and its function and examined the changes induced by the signaling mechanisms of retinoic acids in the gene expression profile of the valves. This study demonstrated that ingestion of high doses of vitamin A for a period of one year caused in vivo aortic calcification and that hypervitaminosis A may be considered as a risk factor for calcified aortic valve disease in humans.

The exact mechanism of vitamin A toxicity has not been clarified yes, but there are some theories. The first theory involves the binding of vitamin A to the membrane of the lipid-stock cells. This binding promotes the production of factors such as laminin and type III collagen that induces fibrosis. The second theory involves the production of hepatotoxins produced when excess vitamin A is combined with ethanol. And the third hypothesis relates hypervitaminosis A to the activation of Kupffer cells that potentiate toxic effects even at low levels of hepatotoxins induced by substances such as ethanol, drugs and other agents.

Megadoses of vitamin A (25,000 to 50,000 IU per day) have been linked to joints and bone pain, hip fractures and decreased bone density. These conditions happen because retinoic acid, which is a derivative of vitamin A, stimulates the formation of osteoclasts leading to increased bone resorption, which causes hypercalcemia. The elderly are the most commonly affected by these problems and are the most exposed to hypervitaminosis A, as serum levels of retinoids increase with age, due to the low clearance rate of this vitamin in this age group (Lips 2003).

Symptoms of hypervitaminosis A include anorexia, anemia, alopecia, signs of chronic liver diseases such as cirrhosis and ascites, the latter especially when combined with ethanol. Some studies have also reported cases of intrahepatic cholestasis induced by excess vitamin A, especially in prolonged use of meal-replacing shakes (Ramanathan et al. 2010). Hypercalcemia, increased intracranial pressure, decreased cognition and mental confusion may also occur in the most severe cases, with ingestion of doses in excess of 25,000 IU/day. Because of this clinical condition, problems of diagnosis may occur, associating these simptoms with diseases such as alcoholism and dementia.

It is important to distinguish hypervitaminosis A from hypercarotenosis, because although beta-carotene is a precursor of vitamin A, its absorption and conversion rate is very low, so excess beta-carotene is not related to vitamin A toxicity. In addition, hypercarotenosis (ingestion$>$ 30 mg/day) causes different symptoms, such as the yellowish aspect of the palms of the hand and the soles of the feet, and does not cause jaundice, unlike hypervitaminosis A (Duerbeck and Dowling 2012).

The teratogenicity of vitamin A is well recognized and is recommended that pregnant women do not exceed the amount of 5000 IU per day, as several studies have determined that doses higher than 10,000 IU demonstrate high risk for fetal abnormalities, such as malformation of the heart, thymus, kidney, and central nervous system side (Penniston and Tanumihardjo 2006).

Hypervitaminosis D

Vitamin D increases the absorption of calcium through the gastrointestinal tract and increases bone resorption. This promotes an increase in serum calcium and calcium in the urine and also causes a decrease in parathyroid hormone (PTH). Hypercalcemia may exacerbate arrhythmic and convulsive effects and may potentiate the effect of digitalis, such as digoxin. If the effect is chronic there may be generalized vascular calcification, calcification in the cornea and other soft tissues, and also nephrocalcinosis. Serum levels of calcium and phosphorus should be monitored, especially in patients with chronic kidney disease (Jones 2008).

Symptoms indicative of vitamin D poisoning include weakness, fatigue, headache, drowsiness, dizziness, tinnitus, anorexia, nausea, vomiting, constipation, dry mouth, metallic taste, muscle pain, bone pain, ataxia, and hypotonia. Late symptoms may include polyuria, polydipsia, weight loss, nocturia, conjunctivitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, and cardiac arrhythmias. Megadoses of vitamin D over the long term have been associated with increased risk of falls and fractures (Ouweland et al. 2014). These complications can lead to death, so vitamin D intoxication is considered severe.

Generally, patients use several medicines and do not mind the fact that these medications may contain the same substance. Patients with hyperparathyroidism use medications containing paricalcitol, doxercalciferol, and calcitriol, which are derived from vitamin D. If in addition, patients use a multivitamin without medical advice, they are at risk of vitamin D intoxication (Anik et al. 2013). Because they have a narrow therapeutic index, vitamin D analogs should not be administered concomitantly, since they have an

additive effect, promoting toxic effects such as hypercalcemia, hyperphosphatemia and hypercalciuria.

Many cases of overdose have been reported in the literature. Most patients do not seek professional advice before taking vitamin products and end up exceeding the recommended daily intake because they do not know the recommended dose is or believe they are harmless. Dosage errors are very common in children, since parents promote the use of vitamins as a fortifier and do not supervise taking doses (Canal et al. 2011). In adults, dosing errors are less common, but cases of intoxication have been reported in vitamin supplements containing doses far higher than the label indicates. In this case, the error was not from the patient but from the pharmaceutical industry (Klontz and Acheson 2007).

It is important to note that vitamin supplements from compouding pharmacies constitute a significant part of the sale of multivitamins in the country. Many doctors prescribe supplements to be prepared in compouding pharmacies ir order to meet specific patient demand, which is often not available in the usual industrial dosages. Theoretically, the compouding products should be as safe as the industrialized ones, however, many cases of manipulation errors have been reported in the literature, including in Brazil. Marins et al. (2014) report a case of vitamin D intoxication in which a vitamin D supplement was prescribed at 2000 IU/day and the vitamin D content found was 2000 times higher than it should contain per capsule. Wrong manipulation of vitamin supplements has also been reported in children. In this case, the doses were 177 to 320 times higher than the recommended limits for children.

The upper limit of intake for vitamin D is not known, but doses up to 10,000 IU/day were considered safe for healthy individuals. And doses higher than 100,000 IU/day ingested over a period of one month are already considered to be toxic, as well as serum 25-hydroxyvitamin D levels higher than 750 nmol/L demonstrate symptoms of toxicity. 25-hydroxyvitamin D is the major metabolite of vitamin D. Its serum values should be maintained between 30 to 80 ng/mL, or 75 to 250 nmol/L. The maximum dose for vitamin D intake is 1000 IU/day for patients up to one year of age, 2000 IU/day for children up to nine years old (Kara et al. 2014) and 4000 IU/day for children above nine years, adults and pregnant women. The lethal dose (LD50) is 21 mg/kg (840,000 IU/kg) (Özkan, Hatun, and Bereket 2012).

The most exposed patients to hypervitaminosis D are children with loss of appetite, growth retardation, dentition, and mental and motor development. Doctors observe these signs and prescribe vitamins indiscriminately, believing that the diagnosis is rickets without any research for the specific diagnosis of vitamin deficiency (Özkan, Hatun, and Bereket 2012). Anik et al. (2013) reported hypervitaminosis in children who presented these symptoms and were recommended by their doctors for vitamin D supplementation, even without any other evidence of rickets and no laboratory data to confirm the deficiency. Corroborating this study, another study in India also recommends that vitamin D should not be used prophylactically and that parents should be cautious before giving a new dose of vitamin D to their children, since the symptoms of rickets take time to disappear without need additional doses (Bothra and Jain 2013)

Hypervitaminosis K

Excessive intake of vitamin K rarely occurs. The recommended adult dose is 65 µg. Excessive doses (>1000 times the RDI) may promote thrombogenesis and hemolysis. These doses may also increase the risk of jaundice (Markel and Kfir 2009). One study demonstrated that vitamin K can induce soft tissue calcifications in hemodialysis patients (Robert et al. 1985)

Hypervitaminosis E

Studies have shown that excess vitamin E (1000 mg/kg) did not show protective effects in the treatment of breast cancer (Ip 1982). Another study reported an increased risk of heart failure in cardiac patients who received supplementation of 400 IU/day of vitamin E for seven years (Walsh 2005). In the same year, a review showed that vitamin E supplementation is related to increased risk of death from any cause (Miller et al. 2005). Despite these results, there are few studies on excess vitamin E, even in animals. In fact, most studies attempt to show their beneficial properties and do not test the adverse effects of high doses of this micronutrient.

The recommended dose is 10 mg/day; however, side effects have only been found at doses higher than 1 g/kg. Excess vitamin E inhibits vitamin K which is important in clotting mechanisms. Therefore, increased bleeding, with increased prothrombin time have been reported. In addition, thromboxane production by platelets is also reduced, further decreasing coagulation. The treatment is the vitamin K itself that ends up displacing vitamin E, and stopping vitamin E supplementation (Traber 2007; Hanzawa et al. 2014).

Hypervitaminosis B

Thiamin (vitamin B1)

Megadoses of this vitamin produce paralysis effects such as those derived from curare, a poison of plant origin prepared by some American Indian tribes. Symptoms include: nerve transmission blockage, seizure, respiratory and cardiac failure, coma, and death. They may also interfere with lactation and fertility (Sure 1939; Perla 1937). Another study demonstrated that excess vitamin B1 causes magnesium depletion and increased serotonin in the bloodstream, causing peripheral vasodilation, but did not discuss the implications of these modifications (Itokawa, Tanaka, and Kimura 1972).

Riboflavin (vitamin B2)

Megadoses of vitamin B2 produce change in urine color that becomes orange, explained by crystallization of this vitamin in the kidney. Vomiting, fatigue, itching, numbness, burning

or tingling, sensitivity to light and hypotension may also occur (Vannucchi and Cunha 2009).

Niacin (vitamin B3)

For Niacin, therapeutic doses may already promote symptoms attributed to the release of prostaglandins, causing burning in the hands and facial flushing. To reduce these effects, the vitamin should be taken during meals and divided doses. The treatment of the vasodilator adverse effects of niacin can be minimized with the ingestion of acetylsalicylic acid or ibuprofen in low doses (De Maria and Moreira 2011).

Megadoses can cause urticaria, conjunctivitis, acanthosis nigrican, ichthyosis, vomiting, constipation, bloating, peptic ulcer, cardiac arrhythmias and hepatotoxicity. Niacin competes with uric acid, which can cause hyperuricemia in up to 40% of individuals who use excessive doses. Hepatic enzymes may also be increased, but cholestatic jaundice and hepatic necrosis rarely occur. It may generate insulin resistance and hyperglycemia, so its use should be cautious in diabetic patients (Guyton and Bays 2007).

Pantothenic acid (vitamin B5)

There are no hypervitaminosis reports for this vitamin.

Pyridoxine (B6)

Vitamin B6 hypervitaminosis was first described in 1983 (Schaumburg et al. 1983), but after this, many other studies have already proven detrimental effects. Symptoms that have been described include severe ataxia with sensory neuropathy. There is no consensus about to the toxic dose of vitamin B6, but it is known that doses higher than 200 mg/day already show the symptoms in a few weeks to months (Spencer, Schaumburg, and Ludolph 2002). Although the dose considered safe for adults with normal weight is 300 to 450 mg/day, some studies have reported toxic effects after dosages of 100 to 300 mg per day. In this way, the regulators of vitamin products established the dose of 100 mg per day as the limit of maximum daily intake tolerated. The recommended daily intake is only 2 mg/d and normal blood levels are 40 to 120 µg/L (Katan 2005).

The likely mechanism of pyridoxine toxicity is due to necrosis of the dorsal ganglia, accompanied by degeneration of the central and peripheral axons. These events occur not only because of excess pyridoxine but also because of the lack of pyridoxal phosphate. Pyridoxal phosphate is the coenzyme responsible for the phosphorylation of pyridoxine and is also involved in many other metabolic reactions of transamination and decarboxylation. Excess pyridoxine saturates the enzyme binding sites, promoting an apparent deficiency. If this coenzyme is deficient, then other reactions also stop working (Schaumburg et al. 1983; Parry and Bredesen 1985; Reis and Oliveira 1999).

Biotin (vitamin B8)

Biotin causes flaking of the skin due to hyperkeratosis of the follicular epithelium surface (Vannucchi and Cunha 2009).

Folic acid (vitamin B9)

Folic acid is involved in the production of red blood cells and DNA. However, megadosing may produce convulsions in epileptics and inhibit hepatic alcohol-deigrogenase. It can also promote stomach, skin and insomnia problems (Elango et al. 2015).

Cyanocobalamin (vitamin B12)

Vitamin B12 can also cause symptoms if ingested in excess, especially in patients who already have some pathology. Mangiarotti et al. (1986) evaluated the impact of megadoses of vitamin B12 on 106 hemodialysis patients. These patients had high serum levels of this vitamin, which only returned to normal within three years after stopping the vitamin. There may also be a decrease in reflexes of vascular size control, palpitation, tingling sensation and limb numbness (Chaves, Maia, and Almeida 2014).

Hypervitaminosis C

People commonly use Vitamin C for the prevention or treatment of colds and flu. However, studies have shown that excess vitamin C (doses higher than 1 g/day) does not reduce the duration or severity of these symptoms. In addition, the excess of this vitamin has also been related to the appearance of kidney stones, even in people who do not have a family history of renal lithiasis. This happens because at the dose of 1.000 mg per day of ascorbic acid, there is an increase of uric acid and oxalate in the urine (Akhilender 2009).

There is no benefit at doses higher than 1000 mg and this dosage can still lead to adverse effects. Serum levels close to saturation were found at a dosage of 400 mg per day. Especially for individuals with recurrent renal calculi, patients with renal or hemodialysis, and even for the healthy population, should avoid high doses of ascorbic acid (Sauberlich 1994).

There are reports that excessive doses of vitamin C in pregnant women can cause induction of metabolic enzymes in the fetus, causing scurvy rebound. Interference also occurs in the absorption of vitamin B12 and increased absorption of iron, being important in cases of thalassemia and hemochromatosis. Premature infants can be affected by hemolytic anemia due to the interference of vitamin C in the production of blood cells, causing fragility in their red blood cells (Naidu 2003).

Biochemical tests for determination of vitamins and RDI

Before start using vitamin supplementation, it is necessary to establish the diagnosis of changes in nutritional status

accurately. Many cases of nutritional imbalance are presented in the subclinical form, which requires the health professional to use all the available resources for the patient's examination. When the imbalances clinically appear, it is important that the doctor or nutritionist differentiates if it is the deficiency or the excess of nutrients that is causing the symptoms, since the symptomatology may be similar in some cases, including many other pathologies (Baynes and Dominiczak 2010).

It is also important to the professional involved in the anamnesis who knows the pathophysiological mechanisms involved in the etiology of vitamin changes, because whatever the alteration is, many biochemical modifications are involved. These biochemical changes should be used to direct the most accurate diagnosis prior to the prescription of any supplementation. In clinical practice, the most usual is the diagnosis of nutritional imbalances without these biochemical tests, based only on the symptomatology. Many patients complain of fatigue and lack of energy, and professionals already prescribe multivitamins. This practice is not correct, primarily because it is not based on biochemical evidence and then because there is no scientific evidence that vitamins are a source of energy. It should be avoided to overestimate an isolated data, be it clinical, anthropometric or laboratorial, since this conduct can promote mistaken conclusions and therapeutic decisions (Soares et al. 1994; Almeida et al. 2008).

Biochemical tests may be directly or indirectly used to prove a nutritional deficiency or excess. Some vitamins can be evaluated directly by serum or urine samples. Others are evaluated from their metabolites. And there are still some vitamins that are evaluated from other markers, since they cannot be measured directly in the biological samples. These tests can also evaluate the enzymatic activity that the vitamin presents as a cofactor. The most used methodologies are high performance liquid chromatography (HPLC) with spectrophotometric measurement, fluorescence detection or ultraviolet (UV) light, or by simple colorimetric methods (Vannucchi et al. 1996). Tables 3–5 show the recommended daily intake values for each vitamin according to each age group defined by the Health Surveillance Agency (ANVISA).

Table 6 shows the maximum recommended daily intake limits. These values should be observed, both by health professionals before prescribing vitamin products, and by patients to avoid excesses in the intake of vitamins. Health organizations do not recommend doses higher than these because studies have found symptoms associated with excessive intake.

Table 3. Recommended daily intake for adults.

Vitamin	Value
Vitamin A	600 µg/2000 UI
Vitamin D	5 µg/40 UI
Vitamin C	45 mg
Vitamin E	10 mg/14.9 UI
Vitamin B1	1.2 mg
Vitamin B2	1.3 mg
Vitamin B3	16 mg
Viamin B5 (Pantothenic acid)	5 mg
Vitamin B6	1.3 mg
Vitamin B9	240 µg
Vitamin B12	2.4 mg
Biotin (Vitamin H)	30 µg
Vitamin K	65 µg

Source: BRASIL. RDC 269/2005.

Determination of vitamin A

The ideal method for determining vitamin A-related pathologies would be the association of specific vitamin A deficiency conditions (e.g. night blindness) with direct measurement of vitamin A concentration in the liver (where it is stored) or in the bloodstream. Since this is not always possible, there are several more practical methods for estimating serum vitamin A levels, all of which have limitations. Each method has its utility for identifying deficiencies and excesses, but none of the proposed indicators is definitive or directly related to the occurrence of symptoms quantitatively speaking (Geraldo et al. 2003).

The World Health Organization (WHO) recommends that, whenever possible, a minimum of two indicators should be taken into consideration, one with clinical aspect and one with biochemical aspect, so they can be used to pointed to deficiency or hypervitaminosis. The biochemical indicator of preference is the distribution of serum levels of vitamin A (serum retinol). Only very low levels of reinol (<0.35 mmol/L) are related to corneal problems. Levels between 0.35 and 0.70 mmol/L may or may not result in clinical symptoms, but levels between 0.70 and 1.05 mmol/L generally cause no symptoms, whereas levels higher than 1.05 mmol/L rarely present them. For children of preschool age, levels below 0.70 mmol/L indicate vitamin A insufficiency, whereas adequate serum values are higher than 1.05 mmol/L. In some laboratories the values are measured in mg/L, so the reference is as follows: 0.2 to 0.4 mg/L (1 to 6 years old); 0.3 to 0.5 mg/L (7 to 12 years old); 0.3 to 0.7 mg/L (from 13 years old and adults). The most commonly used methodology is the HPLC (FAO/OMS 2005).

Determination of vitamin D

The best biochemical marker to define vitamin D status in the body is 25-hydroxy-vitamin D3 (25-OH-D3). This metabolite has a strong relationship with the bone state. To ensure normal bone health, 25-OH-D3 levels must be maintained above 27 nmol/L. However, levels of serum and urinary calcium, alkaline phosphatase and serum phosphorus can also be evaluated as indicators of blood vitamin D deficiency or excess. The reference values for children and young adults range from 15 to 40 µg/L and for the elderly the value is 10 to 20 µg/L. The method used is chemiluminescence (Caquet 2011).

Another metabolite that can be used as a biochemical indicator for this vitamin is 1,25-dihydroxy-vitamin D (1,25-(OH)2-D3). Vitamin D is synthesized in the skin under the influence of sunlight, then it is converted in the liver to 25-OH-D which goes into the kidneys and is then converted to 1,25-(OH)2-D3. Calcium uptake is controlled by this metabolite and not by 25-OH-D3. So, the best marker for vitamin

Table 4. Recommended daily intake for infants and children.

	Infant		Children		
Vitamin	0–6 months	7–11 months	1–3 years old	4–6 years old	7–10 years old
Vitamin A (μg)	375	400	400	450	500
Vitamin D (μg)	5	5	5	5	5
Vitamin C	25 mg	30	30	30	35
Vitamin E	2.7 mg	2.7	5	5	7
Vitamin B1	0.2 mg	0.3	0.5	0.6	0.9
Vitamin B2	0.3 mg	0.4	0.5	0.6	0.9
Vitamin B3	2 mg	4	6	8	12
Viamin B5 (pantothenic acid)	1.7 mg	1.8	2	3	4
Vitamin B6	0.1 mg	0.1	0.5	0.5	1
Vitamin B9 (μg)	48	48	95	118	177
Vitamin B12	0.4 mg	0.5	0.9	1.2	1.8
Biotin (μg)	5	6	8	12	20
Vitamin K (microgram)	5	10	15	20	25

Source: BRASIL. RDC 269/2005.

Table 5. Recommended daily intake for pregnant and lactating women.

Vitamin	Pregnant women	Lactating women
Vitamin A (μg)	800	850
Vitamin D (μg)	5	5
Vitamin C	55 mg	70 mg
Vitamin E	10 mg	10 mg
Vitamin B1	1.4 mg	1.4 mg
Vitamin B2	1.4 mg	1.6 mg
Vitamin B3	18 mg	17 mg
Viamin B5 (Pantothenic acid)	6 mg	7 mg
Vitamin B6	1.9 mg	2 mg
Vitamin B9 (μg)	355	295
Vitamin B12	2.6 mg	2.8 mg
Biotin (μg)	30	35
Vitamin K (μg)	55	55

Fonte: Adaptado de BRASIL. RDC 269/2005.

Table 6. Maximum recommended daily intake limits.

Vitamin	Children	Adults
Vitamin A	900 μg/3000 UI	3000 μg/10,000 UI
Vitamin D (μg)	75 μg/3000 UI	100 μg/4000 UI
Vitamin C	650 mg	2.0 g
Vitamin E	300	1000
Vitamin B1	NA	NA
Vitamin B2	NA	NA
Vitamin B3	15 mg	35 mg
Viamin B5 (Pantothenic acid)	NA	NA
Vitamin B6	40 mg	100 mg
Vitamin B9 (μg)	400	1000
Vitamin B12	NA	NA
Biotin (μg)	NA	NA
Vitamin K (μg)	NA	NA

NA, not available.
Source: Adapted from FAO/WHO (2004).

D-related calcium absorption measurement would be this renal metabolite. However the plasma level of 1,25-2(OH)2-D3 is regulated mainly by CYP1A gene expression and not by 25-OH-D3 plasma concentration. In addition, the increase of this metabolite is also related to pathologies such as tuberculosis, sarcoidoses and lymphomas, so it should not be used as the sole marker. The reference range for 1,25-2(OH)2-D3 is 20 to 50 μg/L. Thus, the ideal would be to evaluate the serum levels of the two markers (Caquet 2011).

Determination of vitamin K

For the determination of the vitamin K, conventional coagulation values may be used. Because vitamin K is intrinsically related to coagulation factors, then prothrombin time is a good indicator of vitamin K imbalance in the body. However, a more sensitive measure would be the detection of vitamin K-dependent subcarboxylated proteins (PIVKA). In deficiency of this vitamin, these sub-carboxylated species of vitamin K-dependent coagulation proteins are released from the liver into the blood. The greater the deficiency of vitamin K, the greater the release of these proteins. Since they are not able to bind calcium, they do not participate in the normal coagulation cascade (FAO/OMS 2005).

PIVKA-II is the prothrombin sub-carboxylate, and is the most useful and sensitive marker of subclinical vitamin K deficiency, since it is possible to determine it even before any change in coagulogram. Several methods of determination for PIVKA-II have been developed, which vary in their sensitivity. The most commonly used methodology is HPLC and the reference values range from 0.22 to 2.28 ng/mL (Caquet 2011).

There is another marker that is released by osteoblasts when vitamin K deficiency are species under-carboxylated osteocalcin (ucOC). This species is the product of carboxylation of Gla protein in bone tissue. It is also possible to perform the quantitation phylloquinone serum and urinary measurement of Gla, which have decreased in the case of vitamin K deficiency (FAO/OMS 2005).

Determination of vitamin E

Plasma concentrations higher than 25 to 30 mmol/L of alpha-tocopherol are considered optimal for the general population. The reference values in mg/L are: Premature: 2.5–3.7 mg/L; 1–12 years old: 3.0–9.0 mg/L; 13–19 years old: 6.0–10.0 mg/L; adults: 5.0–20.0 mg/L and the usual methodology is also by HPLC. However, caution should be exercised in the evaluation of these values, since the plasma concentrations of this vitamin do not necessarily reflect the intake, because the quantity in the circulation is extremely influenced by the lipid circulation. Then the tocopherol: lipid fraction ratio is the best indicator for Vitamin E levels. This ratio should be greater than 2.25, when calculated from mmol of tocopherol per mmol of cholesterol. Erythrocytes of individuals below this concentration may exhibit a tendency for hemolysis when exposed to oxidizing agents.

Therefore, the hemolysis test of red blood cells with hydrogen peroxide is also an important test for the evaluation of vitamin E imbalance (Vannucchi et al. 1994).

Determination of vitamin B

Thiamin (vitamin B1)

In vitamin B1 deficiency occurs the decrease of the enzyme pyruvate dehydrogenase, which causes in the increase of the plasma concentration of lactate and pyruvate. In clinical practice, it is possible to use oral glucose test and moderate exercise to determine metabolic acidosis. It is a nonspecific test, but it works as an indicative of thiamin deficiency, since total blood thiamin is not a sensitive indicator of the nutritional status of this vitamin, then vitamin B1 is used. The urinary thiamin test is performed with a fixed dose of 5 mg orally or 19 umol parenterally of this vitamin. After 4 hours of administration, the urine is evaluated and the normal value should be higher than 300 nmol of the vitamin. Values lower than this indicate vitamin deficiency (FAO/OMS 2005).

Another marker of nutritional status is the coefficient of erythrocyte transketolase activity. Like vitamin C, this marker is extremely sensitive and needs to be stored and handled correctly and as quickly as possible, because it is unstable to light and heat. Apotranscetolase is activated in the erythrocyte by thiamin diphosphate and this is the most accepted indicator currently. It is also possible to evaluate erythrocyte thiamin that directly measures the amount of thiamin pyrophosphate in the body by HPLC. The reference values are between 28.0 and 85.0 µg/L (Baynes and Dominiczak 2010).

Riboflavin (vitamin B2)

Urinary riboflavin (basal or after a test dose) is the main marker of nutritional status for this vitamin. Urinary excretion increases after tissues are saturated. However, it is important to note that individuals with intense protein catabolism may present increased urinary levels as a result of the breakdown of muscle tissue flavoproteins. Vitamin B2 erythrocyte better reflects tissue saturation than the serum vitamin. Another marker used is erythrocyte glutathione reductase, which reflects the depletion of riboflavin. This coefficient is calculated from the ratio between the activity of the enzyme stimulated by FAD and the basal activity of the enzyme. Values of 1.0 to 1.4 are considered adequate, while those greater than 1.7 indicate a state of vitamin deficiency. The reference values for this marker by HPLC were updated and the current reference values are: 137 to 370ug/L (Vannucchi et al. 1994).

Niacin (vitamin B3)

The available method is considered indirect because it evaluates the urinary excretion of N′-methyl-nicotinamide and its metabolite, methyl-pyridone-carboxamide. The ratio between the metabolite and urinary N′-methyl-nicotinamide should be between 1.3 and 4.0, even after overload of tryptophan and niacin. A ratio of less than 1.0 indicates depletion of body stores of niacin. It is also possible to measure serum pyridone, but it is not very common in clinical practice because it is less sensitive. The method is immunoenzymatic (De Maria and Moreira 2011).

Pantothenic acid (vitamin B5)

Urinary excretion of pantothenic acid reflects the pattern of its food intake, so this is the best biochemical marker for this vitamin. In normal conditions, the plasma concentration of pantothenic acid is around 1 µmol/L and does not correlate well with daily intake. Adults who consume between 5 and 7 mg/day of pantothenic acid present urinary excretion of 2 to 7 mg (9 to 32 µmol) and 1 to 2 mg (4.5 to 9 µmol) of fecal loss. Individuals maintained on experimental diets containing 10 mg/day of pantothenate had a urinary excretion ranging from 4 to 7 mg (18 to 32 µmol). Urinary excretion less than 1 mg (4.5 µmol) of pantothenic acid in 24 hours is considered to be abnormally low. Plasma vitamin B5 is measured by gas chromatography/mass spectrometry (GC/MS) and the reference values are 20.0 to 88.0 µg/L (Baynes and Dominiczak 2010)

Pyridoxine (vitamin B6)

The plasma concentration of this vitamin is an inaccurate parameter, so other laboratory techniques are used, such as the Tryptophan overload test, which evaluates the excretion of xanthurenic acid in the urine. Also, the excretion of pyridoxine, in particular its metabolite 4-pyridoxate, as well as plasma or erythrocyte pyridoxal 5′-phosphate dependent blood transaminases (AST and ALT), are techniques for assessing the nutritional status of pyridoxine. The usual methodology is also HPLC and plasma reference values are 8.7–27.2 µg/L (Almeida et al. 2008).

Biotin (vitamin H or vitamin B8)

Two major markers are used to assess the amounts of biotin: urinary excretion of biotin and excretion of 3-hydroxyisovalerate, a marker that conversely reflects the activity of B-methyl crotonyl-CoA carboxylase that is involved in the metabolism of leucine. The excretion rate is evaluated by HPLC-based radioimmunoassay with avidin. When biotin and its metabolite, bir-norbiotin, are decreased, the levels of hydroxyisovalerate increase and there is a decrease in B-methyl crotonyl-CoA carboxylase activity. It is currently possible to evaluate serum biotin by enzyme-linked immunosorbent assay. Values below 100 ng/L indicate deficiency, while the acceptable level is between 100 and 200 ng/L. Healthy subjects present values higher than 200 ng/L (FAO/OMS 2005).

Folic acid (vitamin B9)

Folate in red cells still continues to be used as an important parameter related to folate status in the body, as well as folate in plasma, but this one presents greater interferences. The methodology used is chemiluminescence and the values should be higher than 5.38 ng/mL. The hemogram is still essential as an indicator of vitamin B9 alteration. Red cell and erythrocyte changes demonstrate a deficiency of this vitamin. Homocysteine is a very sensitive biomarker and

should be used in conjunction with other markers (Almeida et al. 2008).

Cyanocobalamin (vitamin B12)

Serum levels of vitamin B12 are not good indicators of nutritional problems. Plasma homocysteine and methylmalonic acid (MMA) are more sensitive indicators. Although homocysteine may also rise with folate and vitamin B6 levels, and MMA, in addition to being related to the nutritional status of vitamin B12, is also related to renal failure, these two parameters together can be used to evaluate vitamin B12. Hemograms and myelograms are essential in determining deficiencies of this vitamin, because just like vitamin B9, cyanocobalamin is also involved with erythropoiesis and deficiency in these vitamins can lead to defects in blood cells (Paniz et al. 2005). The methodology used is chemiluminescence and the normal values are between 210.0 and 980.0 pg/mL (Almeida et al. 2008).

Determination of vitamin C

The concentration of saturation of ascorbate in the body of a male adult is about 20 mg/kg or 1500 mg. Clinical signs of vitamin C deficiency begin at concentrations below 300–400 mg. When concentrations are between 1000 and 1500 mg there are no symptoms. Evaluation of serum or urinary ascorbic acid is recommended. Because it is very sensitive to heat and alkaline pH, it is necessary to keep the sample at low temperatures, with no oxygen and cannot be exposed to light. Samples need to be processed as quickly as possible. The methodology usually used to determine this vitamin is by HPLC (FAO/OMS 2005).

Vitamin C intake higher than 30 mg/day already reaches 60 mmol/L of plasma, reaching a plateau of 80 mmol/L with doses of 200 mg day. Doses higher than this are not absorbed and are excreted. The reference values for women are slightly higher, since plasma concentration depletion is greater. In pregnant and lactating women the intake should be higher because of increased body fluid and segregation of ascorbate in breast milk (Ramalho, Flores, and Saunders 2002).

Final considerations

Nowadays, the population is increasingly concerned with quality of life and with ways to prevent diseases. This concern causes people to seek balanced diets and/or try to reach their needs with dietary supplements. This is the main reason for the significant increase in consumption of vitamin-containing products (Gómez-Salas 2009). Undoubtedly, vitamins are essential for the body's balance and their deficiency can cause great compromise to the body's normal metabolism. Despite this, they are not harmless, as much of the population believes. The health agencies recommend the values of daily intake, which should be used by health professionals to evaluate the need for supplementation, only in cases of vitamin deficiency.

One of the most recurring problems associated with the irrational use of vitamin products is the fact that individuals do not seek professional guidance before beginning use. Patients self-medicate or take advice from people who are not qualified. These attitudes characterize indiscriminate use. Such a practice can lead to over-dosing and drug interactions if the patient is taking other medications.

The drug interactions involving vitamins can also be harmful and pose a health risk, and can be classified according to seriousness, such as mild, moderate and severe. In all, more than 60 drug interactions were found in the databases researched, demonstrating that these products have a potential lethal, despite what is believed.

The excess of these micronutrients can also cause risk to the patient, especially for the fat-soluble vitamins that can accumulate in the body, such as vitamins A, D, K and E. However, according to the bibliographical review, excess water-soluble vitamins can also cause serious symptoms, such as vitamin C, which is related to the appearance of renal calculi, among other symptoms.

Only the clinical diagnosis cannot diagnose a deficiency, since the symptoms can be confused with those of other pathologies, therefore, one must use biochemical tests for a more accurate diagnosis. If there are so many laboratory tests to prove the deficiency, then the prescription of supplements not based on these tests is unfounded and even irresponsible. This practice also characterizes indiscriminate use, because without concrete evidence consumption can lead to compromise of the patient's health.

Therefore, indiscriminate use is avoided when the patient seeks guidance from a trained health care professional to prescribe such products, such as doctor, nutritionist and pharmacist, and also when this professional relies on laboratory tests to prescribe. In this way, it is possible to avoid cases of hypervitaminoses, drug interactions and reduce risks related to vitamin products.

ORCID

Rosali Maria Ferreira da Silva http://orcid.org/0000-0002-4139-6035

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