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Vitamin D in Food Supplements: Labeling Survey

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ABSTRACT

An adequate vitamin D (vitD) intake (Recommended Daily Allowance, RDA= 5µg) is crucial for health maintenance and its deficiency is associated with several health problems. The increase in hypovitaminosis D cases and the proliferation of food supplements (FS) that are easily accessible by the population, have led to an unrestrained chronic consumption of FS. VitD may accumulate in the body and originate toxicity (Tolerable Upper Limit, UL=100 µg). The aim of this study was to evaluate if daily vitD doses mentioned in FS labels are in conformity with RDA. 210 solid and liquid FS (for pediatrics and adults) sold in Portuguese pharmacies, supermarkets, health shops and on the internet were examined for indicated daily intake of vitD and compared to RDA and UL values. 51.43% of FS have values higher than RDA, 8.57% higher than UL. The average vitD daily dose in FS is 24.48 µg, with a high variability between samples (0.25 - 250 µg). Majority of FS labels recommend vitD daily doses above RDA and some even above UL, regardless of being for adults or children. Therefore, it is crucial that vitD dose in FS is reviewed to ensure the safety of these products.

1. Introduction

Vitamin D (vitD) is a hormone crucial for the regulation of physiological processes, namely related to bone metabolism, immune system, cardiovascular and insulin synthesis, and has been associated with several pathologies^[1-3]. It is a fat-soluble vitamin and is obtained endogenously, mainly from sun exposure where ultraviolet rays hit the skin and initiate vit D synthesis. It is also present in very few foods (yeast, fungi, cod liver oil and oily fish) and available in many food supplements (FS) as well as in fortified foods, such as dairy products.

VitD has two isomers (vitD2 or ergocalciferol and

vitD3 or cholecalciferol). VitD itself is biologically inert and must undergo two hydroxylations for activation: in the liver (producing calcidiol or 25-hydroxyvitamin D [25(OH)D = 25(OH)D2 and 25(OH)D3]) and in the kidney (forming calcitriol or 1α, 25-dihydroxyvitamin D [1α, 25(OH)2D2 and 1α, 25(OH)2D3]^[4].

Homeostasis requires a daily plasma concentration of vitD. Human body levels are estimated mainly by the measurement of its major circulating form: 25(OH)D, which is considered an adequate indicator of the level of vitD in individuals^[1]. Optimal vitD status is an important health issue and it is generally agreed that plasma or

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serum levels of 25(OH)D should be used to assess vitD status, as they reflect both dietary intake and dermal production^[5-7]. According to the U.S Institute of Medicine (IOM) and the UK National Osteoporosis Society (NOS)^[4], 25(OH)D concentrations ≤ 30 nmol/L are considered deficient and concentrations between 30-50 nmol/L are insufficient. The scientific community consensually assumes that serum 25(OH)D concentrations below 25-30 nmol/L should be prevented and treated. Additionally, values higher or equal to 50 nmol/L are included in several guidelines as an optimal concentration^[7,8]. Regarding the consumption of vitamins and other nutrients, there are a number of terms that are used as such: the *Recommended Dietary Allowance (RDA)* which is the average daily intake, sufficient to meet the nutritional needs of the majority of the healthy population; *Adequate Intake (AI)*, parameter that indicates the value corresponding to adequate nutritional intake, and is only used when there is insufficient scientific evidence to determine RDA, particularly in newborns and infants; and *Tolerable Upper Intake Level (UL)* that refers to the maximum recommended daily intake that does not cause adverse health effects and can be safely ingested without generating toxicity in the majority of the population^[9,10]. In 2010, daily doses of 200 IU were considered by the Institute of Medicine, insufficient to maintain a desirable 25(OH)D level. Hence, doses of 400 IU/ day (10 μ g) for infants, 600 IU/ day (15 μ g) for children, teenagers and adults, and 800 IU/ day (20 μ g) for the elderly (over 70 years) were suggested^[19]. Although there are different recommendations for some subgroups of population, in most European countries, including Portugal, the RDA is set at 5 μ g for all^[11,12].

The dietary reference values (DRV) for vitD have been revised by the European Food Safety Authority (EFSA), based on an assessment carried out between 2013 and 2016. The panel derived as Adequate Intakes (AI) for the EU population, assuming minimal sunshine exposure: infants aged 7-11 months: 10 μ g/day and 15 μ g/day for all groups aged one year and more (including pregnant/lactating women). In the presence of cutaneous vitD synthesis, the values of intake should be lower or even zero^[13].

EFSA also revised the UL for vitD, setting it at 100 μ g/day for adults, pregnant women and children over 11 years old. UL values of 50 μ g/day and 25 μ g/day were proposed, respectively for 1-10 years old group and infants^[14].

Considering the threshold values of 25(OH)D concentrations described above, there is a high worldwide prevalence of vitD deficiency, whose negative impact

on public health requires public health measures such as fortification of foods with vitD^[7].

VitD deficiency is common in Middle East countries, reaching up to 80% of the population. In European countries the values are lower with a prevalence of approximately 20% in Northern Europe and 30-60% in Western, Southern and Eastern Europe, but, more than 10% of Europeans reveal a severe deficiency (serum 25(OH)D < 30 nmol/L)^[7].

Several serious pathologies seem to be associated with VitD deficiency, such as multiple sclerosis, diabetes, heart disease, cancer, rickets^[15-17].

Due to the growing awareness of vitD deficiency and associated health problems, it became a popular food supplement with a significant increase in the consumption of vitD-fortified food products, drugs and nutraceuticals. Given the high popularity of FS and the easy access to them by the general population without medical supervision, together with the growing number of prescriptions of vitD, including very high doses, there might be a greater risk of vitD intoxication, with or without hypervitaminosis^[2,16].

Usually, overproduction of vitD following sun exposure, and ultimate toxicity is not likely to happen because it is a process regulated by a feedback loop, leading to photodegradation of the excess vitD produced^[18,19]. On the other hand, exogenous forms of vitD may contribute to intoxication, when excessive amounts are consumed for a long time. The concern is greater for vitD3 than for vitD2 due to the higher bioavailability of the former^[20,21]. Moreover, different formulations of vitD FS, originate significantly different plasma levels of 25(OH)D^[22].

Although vitD toxicity is considered to be rare, the consequences on health can be serious. The initial symptoms include confusion, weakness, fatigue, headache, appetite loss, nausea, vomiting, abdominal pain, polyuria, polydipsia, cardiovascular symptoms, among others^[2,23]. Its clinical manifestations include severe hypercalcemia, hypercalciuria and hyperphosphatemia^[2,19,24,25].

Although the toxicity of vitD is rarely appreciated, the medical community and health regulators are aware of the fact that it is one of the most toxic fat-soluble vitamins, hence the growing concern about increasing its consumption^[7].

The policies and practices regarding voluntary fortification and legislation vary among European countries. The list of vitamin and minerals and their forms that can be added to FS is defined by The Commission Regulation (EC) No 1170/2009 of 30 November 2009^[25]. Commission Directive 2008/100/EC defines the labeling

of foodstuffs with respect to the recommended daily allowance (RDA) ^[11]. This recommendation assumes that 200 IU (5 g) vitD/day is sufficient to prevent rickets ^[26]. However, it ignores the physiological benefits of vitD. Currently, in Europe, most multivitamin preparations are labeled as “100% RDA” corresponding to 200 IU of cholecalciferol,

FS are not meant for therapeutic purposes and should be used as a complement of a regular dietary intake of vitD and sunlight exposure, in order to achieve the RDA values. Hence, the goal of our work was to evaluate the information present on the label of vitD FS available on the Portuguese market, in terms of dosage and recommended daily allowance of vitD.

2. Materials and Methods

The daily intake of vitD described on 210 FS labels was analyzed and compared with the RDA. FS were available in Portuguese pharmacies, health shops, supermarkets and internet. Liquid and solid pharmaceutical forms whose label indicates the presence of vitD in their composition (in addition to other ingredients) were considered in the study, regardless of the use of the FS.

For confidentiality issues, the commercial name of the products under study has been omitted and the designation FS has been adopted. Solid FS (SFS) included adult formulations, while liquid FS (LFS) included both pediatric and adult formulations.

A statistical analysis was carried out using Excel and SPSS Statistics (Statistical Package for Social Sciences) version 25.0 software for Windows.

3. Results

The 210 analyzed FS labels presented a vitD mean daily dose of 24.48 µg, with a high variability between samples (coefficient of variation =178.19%), with a minimum value of 0.25 and a maximum of 250 µg/day (Table 1).

Table 1. VitD label daily dose values

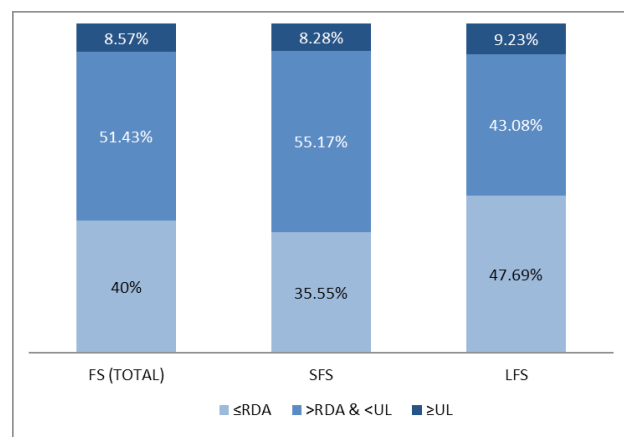
Formulation	N	VitD Label dose ^a (µg/day)	Mean ± SD ^b (µg/day)
Total FS	210	10.00 (0.25; 250.00)	24.48 ± 43.62
SFS	145	10.00 (1.20; 250.00)	24.56 ± 46.41
LFS	65	10.00 (0.25; 175.00)	24.31 ± 36.97

^a VitD label dose, expressed as medians, with minimum and maximum values given in brackets; ^b SD-Standard Deviation

Analyzing the solid and liquid formulations separately, both presented similar values. To perform the comparison of vitD daily dose between the SFS and LFS, the non-

parametric test of Mann Whitney was applied, since vitD data have a non-normal distribution ($p < 0.05$) in these groups. Following the application of the Mann Whitney test, no significant difference ($p > 0.05$) was found between vitD daily dose in SFS and LFS.

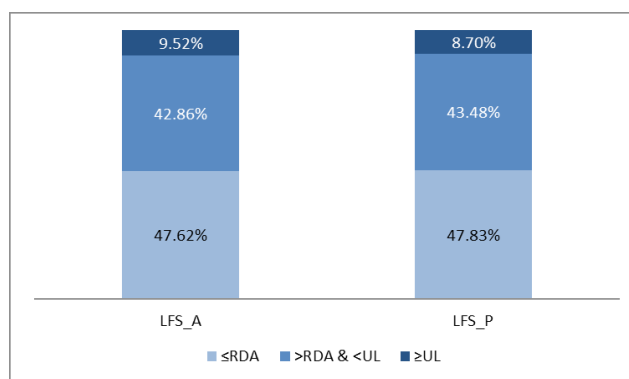
Comparing recommended vitD daily doses indicated on the labels with the RDA established for vitD in Europe (5 µg/day), it was found that the majority of FS, solids and liquids, have values far above RDA, including 12 SFS and 6 LFS samples equal or higher than UL (Graph 1).



Graph 1. VitD label daily doses in solid and liquid FS

SFS with the highest vitD label value are those containing this vitamin as the sole ingredient. In multivitamin preparations, the daily dose of vitD reaches a maximum of 30 µg/day (FS_051). On the other hand, in LFS the highest levels were observed in multivitamins, with values that reach 175 µg/day (LFS_037). In LFS containing only vitD, the maximum value mentioned in the label is 125 µg/day (LFS_040).

Since LFS included pediatric (LFS_P; N=23) and adult (LFS_A; N=42) formulations, a comparison was also made between both sample groups using the Mann Whitney test. LFS_P presented a mean value of 25.05 ± 30.67 µg/day (minimum= 0.25 µg/day, maximum=100 µg/day); LFS_A presented a mean value of 23.90 ± 40.35 µg/day (minimum= 0.5 µg/day, maximum=175 µg/day). The test result did not show any significant difference between these groups ($p > 0.05$). The majority of LFS_P and LFS_A labels mentioned values far above RDA, with two pediatric and four adult formulations equal or higher than UL, considering UL=100 µg/day in both groups (Graph 2). The number of LFS_P samples that exceeds UL rises to seven if the EFSA proposed UL value for children is taken into account.



Graph 2. VitD label doses in adult and pediatric LFS formulations

4. Discussion

In Europe, the established daily dose for vitD is 5 µg (RDA = 100%), which includes all sources of vitD (from diet to sun exposure and supplementation). However, there are FS that indicate values 50 times higher, which corresponds to 5000% of RDA and 250% of UL.

Since vitD is fat-soluble, it tends to be distributed in the fat compartment such as adipose tissue resulting in a reduced clearance and accumulation in the body. Thus, regular intake of high doses should be monitored to prevent adverse effects such as kidney and heart disease and musculoskeletal pain. In addition, ingestion of excessive amounts of this vitamin can lead to elevated plasma and urine calcium levels, probably related to the excessive amount of 25(OH)D, not followed by its conversion to 1,25(OH)₂D. In fact, plasma concentrations of 25(OH)D above 220 nmol/L can cause hypercalcemia leading to soft tissue calcification and ultimately damaging the heart and kidneys^[27]. Babies are particularly sensitive to vitD overdoses due to high bone turnover. A study case was reported of a 4-month-old girl who received daily 50,000 IU of vitD3 in liquid oral supplements, for two months, and suffered severe hypercalcemia, hypercalciuria and nephrocalcinosis^[28]. Recently, a cross-sectional study on vitD toxicity was conducted in a pediatric toxicological referral center from Iran, on children younger than 12 with a daily ingestion over 1500 IU of vitD^[29]. The acute vitD toxicity in the pediatric population in Iran was found to be benign and probably related to the high prevalence of vitD deficiency in that country. A literature review on the risk of vitD toxicity in pediatrics concluded that although rare, cases of vitD intoxication causing dramatic life-threatening symptoms still occur in children^[30].

Nevertheless, in our study, pediatric formulations had daily dose recommendations as high as those for adults, and in both cases, sometimes higher or equal than the UL

of 100 µg/day.

5. Conclusions

FS are readily available and are poorly regulated. These conditions contribute to their overuse which, in the case of vitD, can trigger hypercalcemia. It is not understandable that FS labels suggest daily vitD doses higher than the RDA, especially considering that FS are not meant to treat hypovitaminosis and should serve only as a complement of a normal dietary regimen. To safeguard consumer safety, it is essential to have adequate and strict FS labelling legislation, in particular by ensuring compliance with the RDA values.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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