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Artículo de revisión

Critical review of clinical trials regarding Vitamin D supplementation

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RESUMEN

Revisión crítica de los ensayos clínicos publicados sobre la suplementación con vitamina D

La vitamina D se suplementa en individuos con o sin factores de riesgo de deficiencia, aun cuando sus efectos a dosis y frecuencia específicos son controvertidos. En consecuencia, nos planteamos el objetivo de revisar exhaustivamente los efectos de la suplementación con vitamina D en los ensayos clínicos aleatorizados en pacientes adultos, agrupados por sistema blanco y a los criterios de valoración establecida en los objetivos. En la búsqueda se incluyeron los ensayos clínicos publicados en los últimos 5 años en PubMed y EBSCO, con las palabras clave "vitamina D suplementación" y "efecto", en inglés o español, excluyendo a los participantes <19 años. Como resultado, la búsqueda inicial arrojó 91 resultados de dos bases de datos, de ellos 71 incluidos. Un total de 24 artículos publicaron un efecto significativo de la suplementación de vitamina D. Los efectos significativos se identifican en 3 de 4 estudios en pacientes posmenopáusicas sobre la densidad ósea y/o fortalecimiento del sistema musculoesquelético. Otros efectos significativos se observaron con la suplementación en pacientes con índice de masa corporal elevada, en el control de la glucosa y los niveles de hemoglobina glucosilada. En conclusión, los ensayos clínicos aleatorizados muestran efectos significativos en diferentes órganos y sistemas. El efecto sobre el control glucémico es prometedor aun cuando existen grupos humanos sobrerrepresentados.

ABSTRACT.

Vitamin D is supplemented in individuals with or without risk factors for deficiency, although its effects at specific doses and frequency are controversial. In consequence, we aimed to perform an exhaustive review on the effects of vitamin D supplementation in randomized clinical

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trials in adult patients, grouped by target system and the evaluation criteria established in the objectives, by searching clinical trials published in the last 5 years in PubMed and EBSCO are included, with the keywords "vitamin D supplementation" AND effect, in English or Spanish, excluding participants <19 years. Our initial search yielded 91 results from two databases, of which 71 were included. A total of 24 articles published a significant effect of vitamin D supplementation. Significant effects were identified in 3 of 4 studies in postmenopausal patients on bone density and/or strengthening of the musculoskeletal system. Other statistically significant effects were observed with supplementation in patients with high body mass index, in glucose control and glycosylated hemoglobin levels. We conclude that randomized clinical trials show significant effects in different organs and systems, the effect on glycemic control is promising, even when overrepresenting specific human groups.

INTRODUCTION

The variety and adaptability of our species has allowed humans to conquer, inhabit and reproduce successfully in all terrestrial ecosystems. Thus, phenotypic, genetic, and epigenetic differences between human groups influence the characteristic epidemiological panorama of populations in accordance with the region they inhabit.

It is impossible to consider differences in the prevalence of pathologies derived from vitamin D deficiency or its metabolism without considering that human populations living in regions with a short diurnal light period, since the effect of solar radiation on the skin is fundamental to the vitamin's synthesis. Moreover, there are individual health conditions that may promote vitamin D deficiency or its metabolism, and thus vitamin D supplementation is a logical measure for the well-being of people at increased risk or with diseases that, due to their pathogenic pathway, may manifest themselves with less severity if patients receive supplements. However, the healthy limits for supplementation, patient eligibility, and the exact processes that are specifically influenced by vitamin D supplementation are still a matter of debate.

Today we know that vitamin D serves as a hormone, with multiple functions in human body. Of all its purposes, the best studied and most important is related to bone health. Adequate deposits of the vitamin maintain calcium-phosphorus metabolism within the normal range. The main natural sources are cutaneous synthesis of the hormone, induced by solar radiation, and fish oil. In certain situations, cutaneous synthesis is not fully effective. This, together with the fact that natural foods contain low amounts of vitamin D, meaning that a large part of the population is at risk of deficiency/insufficiency of this micronutrient (1, 2).

Vitamin D is a necessary nutrient for health because it helps the body absorb calcium, one of the main substances needed for strong bones. Along with calcium, vitamin D helps prevent osteoporosis, a disease that makes bones thinner and weaker and more prone to fractures (1).

Human body also requires vitamin D for other functions. Muscles need it for movement and nerves need it to transmit messages between the brain and other parts of the body. Vitamin D is essential for the immune system to fight bacteria and viruses that attack it (2).

Vitamin D is an essential micronutrient involved in numerous biological processes and is produced endogenously as vitamin D3 (cholecalciferol) or obtained from the diet or supplements as vitamin D3 or vitamin D2 (ergocalciferol). While the importance of adequate vitamin D in preventing rickets and osteomalacia is well-established, there is growing epidemiological evidence to suggest that 25-hydroxyvitamin D (25-OHD) levels may also be relevant to the incidence and progression of cancer and cardiovascular disease as well (3).

While it is generally accepted that oral vitamin D supplementation is safe, supplementation should be between 800 and 1000 IU or 10 µg/day of calcifediol daily both for correction of vitamin D deficiency and for prevention of vitamin D deficiency or insufficiency. Although it has been reported, in the systematic review with meta-analysis by Zhang *et*

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al., that vitamin D supplementation could reduce the risk of death from cancer by 16%, it was also noted that vitamin D supplementation in adults by itself does not reduce all-cause mortality. While studies have shown that, on average, for each incremental increase of 100 IU of vitamin D3 supplement daily, the level of 25OHD will increase by 0.5 to 1 ng/ml, it is likely that much higher doses than required are administered to obese individuals with a greater volume of vitamin D distribution in fat, or those with intestinal malabsorption (including after bariatric surgery) (4, 5).

Vitamin D has many physiological functions, including positive regulation of intestinal calcium and phosphate absorption, mobilization of bone resorption, renal calcium reabsorption, as well as a role in a variety of pleiotropic functions. Many of the hormonal effects of vitamin D are thought to involve a transcriptional mechanism mediated by the 1,25-dihydroxyvitamin D3-vitamin D receptor that involves binding to cellular chromatin and regulation of hundreds of genes in many tissues (4). In humans, skin photosynthesis is the main endogenous source of vitamin D. When exposure is limited or in cases of vitamin D insufficiency, vitamin D supplementation is recommended, particularly in certain age groups (5-8).

However, there are several benefits that may be attributed to oral vitamin D supplementation (9). There is a growing interest in addressing the evaluation of vitamin D concentrations in specializations other than skeletal evaluation, such as, for example, in neurology, where benefits may be found for those with sclerosis or epilepsy, or in the improvement of sexual function in postmenopausal women (9-11). Given the wide range of beneficial effects that can be attributed to vitamin D supplementation (12-15), the present article has the objective to provide an exhaustive review of the various effects that have been identified through clinical trials regarding vitamin D supplementation, both in terms of the organs and systems involved and the effect studied.

Existing evidence on vitamin D supplementation effects

For the present review, a systematic search was performed in the PubMed and EBSCO databases for clinical trials published in the last 5 years that had been published in English or Spanish, with the keywords Vitamin D Supplementation in the title or abstract, AND effect OR results OR endocrinology OR metabolism OR immunity.

Articles in languages other than Spanish or English, and those involving populations under 19 years of age, were excluded. The remaining articles were included based on relevance until the present review was complete.

The search resulted in a total of 93 articles. The articles underwent an initial process in which each author downloaded them and checked from the abstract that they both met the inclusion criteria and had no exclusion criteria. Those that were duplicated were excluded. The initial search yielded 91 results from two databases, of which 70 were included for the purposes of the present article. This data included a total of 91774 participants, but it is important to mention that the same sample may be reported in more than one article. Single groups studies were tabulated, indicating the number of participants, the intervention, dosage, periodicity, duration, and outcomes, additionally, a column indicates whether the trial obtained significant results regarding vitamin D ($p<0.05$). The geographic distribution of the clinical trials is shown in **Figure 1**. In total, the clinical trials came from 20 countries, located in 4 different regions. The distribution by country is shown in **Table 1.**

Figure 1. Geographical distribution of vitamin D supplementation clinical trials.

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Table 1. Distribution of participants in clinical trials referring to Vitamin D supplementation by country (N:91,774)

Country	Participants	Country	Participants
Australia	21513	Lebanon	248
Austria	1859	Montenegro	130
Canada	311	Pakistan	140
Denmark	923	Russia	67
England	409	Scotland	305
Germany	288	Serbia	70
India	241	Spain	112
Iran	1227	Sweden	40
Israel	62	Turkey	180
Italy	187	United States	63462

A total of 24 articles published a significant effect of vitamin D supplementation at different doses and for different purposes. A single intervention in a same study group of individuals can reveal results on more than one outcome, while different outcomes and extensions of follow ups in a same intervention group can be published in separate articles; therefore the 24 articles reported 9 unique intervention groups, as showed in **Table 2**. The doses administered in the clinical trials varied and varied for the subgroups of some studies. The length of time of the trials varied from single-dose supplementations (16) with follow-up one week later, to six-year cohorts (17). Studies testing vitamin D supplementation as a preventive measure covered specific periods of supplementation such as pre-surgical (18, 19), post-surgical (20), post intensive care stay (21), during gestational period (22) and even those evaluating the safety of supplementation at doses 5-10 higher than recommended employed early proxy markers (23).

Vitamin D supplementation alters the metabolomic profile as evidenced by analysis of the serum and urinary metabolomic profile of subjects before and after 6 months of supplementation with varying doses of vitamin D3. Doses in clinical trials with weekly supplementation ranged from 16,000 to 60,000 IU (24-29); periodicity of supplementation also included single doses, every week, every second week, monthly, single dose, etcetera. Periodicity and doses are reported with a wide range of variation and results of the supplementations may be as heterogeneous as dose administration. Overall, the modal daily dose was 4,000 IU, with a range from 1,000 IU to evaluate for improvement in bone density at six months to 60,000 IU for seven days to accelerate negative seroconversion in patients who were asymptomatic or mild Sars-Cov2 positive (30).

Administration of vitamin D either as cholecalciferol or ergocalciferol was used concomitantly with calcium in 21 studies, but in others also with unspecified multivitamins, Omega 3, vitamin K (1, 30-32) and drugs prescribed for an underlying condition. The effects explored in the clinical trials included in this review were diverse and are summarized in **Figure 2**. In a study with doses of vitamin D increasing from 600 to 10,000 IU, it was observed that there are individual differences in vitamin D metabolism. No adverse effects were reported in any of the included articles. Among the various effects studied with vitamin D3 supplementation in older adults, a tendency towards a reduction in bone density loss was observed, but the effects on fragility and risk of falls did not show statistically significant differences, even at high doses (21, 24, 25, 33-35).

A series of metabolic parameters were measured, and it was concluded that there was no statistically significant difference between the two groups. Among the study's strengths is the use of state-of-the-art technological resources, as well as an integrative vision; among its limitations, as the authors acknowledge, is the drop-out rate of the patients, as well as the limited population studied and the large number of variables and parameters to be compared. In another study conducted in Austria, the effects of supplementation on surrogate markers of infertility in women with polycystic ovary syndrome were monitored, revealing significant effects on follicle-stimulating hormone levels and the luteinizing hormone/follicle-stimulating hormone ratio. However, vitamin D did not cause any change in amenorrhea or anovulation. In postmenopausal women, it is suggested that vaginal health status could be improved by vitamin D supplementation (36-38).

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Table 2. Effects of vitamin D supplementation in completed randomized controlled trials published in between 2017-2023

Reference number	Evaluated effect	Number participant	System /function	Frequency	Dose	Patients' age (years)	Pathologies & Additional conditions	Intervention duration	Significant at p<0.05	Results
1	Risk of autoimmune disease	25,871	Immune System	Daily	2000 IU	Male>50 Female>55	None	3 months	No	Did not reduce the risk of autoimmune disease
5	Changes in metabolomic profiles of obesity phenotypes with suboptimal vitamin D levels	215	Metabolism	Daily	4000 IU	18-50	Obesity	4 months	Yes	Influenced plasma metabolites only in unhealthy obese
6	Cancer and pre-cancer risk reduction	2385	Lipid and glucose metabolism	Daily	4000 Ul	≥30 years	Prediabetes and overweight/ obesity	2.9 years	No	No significant effect against the risk of cancer or pre-cancer
8	Bone density and strength and how they affect the development of tibial artery calcification	311	Bone	Everyday	10,000 IU	55-70	Bone mineral hypodensity	3 years	No	Vitamin D3 supplementation for 3 years was unrelated to progress in the development of tibial artery calcification
18	In vitro fertilization in women with polycystic ovary syndrome	212	Reproductive	Daily	4000 IU	20-42	Polycystic Ovary Syndrome	12 weeks	No	There was no significant difference in α microbiome diversity between the vitamin D and placebo groups
19	Vitamin D improves gut microbiota and gut inflammation	38	Digestive system	Daily	4000 IU	18-57	Overweight/ obesity, Vitamin D deficiency	16 weeks	No	There was no significant difference in α microbiome diversity between the vitamin D and placebo groups at baseline or follow-up.
21	Bone turnover in patients with heart failure	158	Cardiovascular	Daily	4000 IU	18-79	Vitamin D deficiency, Male	3 years	No	Did not influence bone turnover in patients with heart failure and low vitamin D levels. 24
22	Reduce Stroke Progression Rate	365	Central nervous system	Daily	25ug/ 75ug	65-74	Cerebral vascular accident	24 months	No	Does not influence the progression of stroke

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22	Effects on Central Nervous System Modulation Mediated Vitamin D Supplements	27	Central nervous system	Daily	30 μg D3	18-25	None	180 days	Yes	Vitamin D and calcium in young people with low S-25[OH]D can help modulate sympathetic nervous system
23	Treatment of premenstrual syndrome in vitamin D-deficient youth	130	Reproductive	Every second day	2000 IU	18-30	Premenstrual syndrome	12 weeks	No	Intake of 2,000 IU in youth with Premenstrual symptoms and vitamin D deficiency had no impact on symptoms
24	Effect of two doses on sarcopenic obesity	248	Metabolism and sarcopenia	Daily	600UI-3750 IU	>65	Obesity	12 months	No	Inconclusive regarding sarcopenic obesity
26	Endocrine and metabolic parameters in women w/WO polycystic ovary syndrome	330	Metabolism	Weekly	20000 IU	>18	Polycystic Ovary Syndrome	24 weeks	Yes	Significant effects on FSH levels and LH/FSH ratio were obtained in women with PCOS, but not amenorrhea
28	Body composition and cardiorespiratory fitness in obese and overweight men	40	Cardiac/ Respiratory	Daily	2000 IU	18-70	Overweight patients	6 months	No	Does not affect body composition or oxygen uptake in overweight or obese men
29	Vitamin D supplementation may affect glycemic and hormonal regulation.	150	Glucose and hormonal metabolism	Weekly	20000 UI	36 years	Pre-Menopausal	24 weeks	no/yes	It did not have a significant effect on glycosylated hemoglobin but on the homeostatic model of insulin resistance
29	Glycosylated hemoglobin	123	Metabolism	Everyday	2900 IU	M >18	Pre-Menopause and Polycystic Ovary Syndrome	24 weeks	No	There was no statistical difference
30	SARS-CoV-2 viral elimination.	40	Immune System	Daily	60,000 IU	36-51	Asymptomatic-mild CoV2, Vitamin D deficiency	7 days	Yes/No	Significantly decreased fibrinogen, but not viremia
34	Lipid profile and risk of cerebrovascular event	127	Metabolism and stroke	Daily	4000 IU	25-75	Type 2 Diabetes	48 weeks	No	Not affected lipid profile
36	D3 in FGF23 concentrations	181	Kidney function, hypertension	Daily	2800IU	18≥	Hypertension and with a serum vit D deficiency	8 weeks	No	Vitamin D3 supplementation had no significant effect on FGF23 in the entire study cohort

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43	Biomarkers of insulin resistance, inflammation, neurohormonal activation and lipids	289	Metabolism, biomarkers	Daily	4000 IU	18-50	Predictors of insulin resistance	6 months	No	Results not statistically significant, but suggest risk reduction
47	Impact on insulin sensitivity	18	Metabolism	Weekly	25000 IU	18-70	Vitamin D deficiency, BMI >25	3 months	Yes	Cholecalciferol in a weight loss program, significantly improves insulin sensitivity in healthy subjects with obesity
48	Cardiovascular diseases in the study of vitamin D and type 2 diabetes	2,423	Cardiovascular	Daily	4000 IU	60 years	Diabetes and prediabetes	3 years	no/yes	No significant difference between vitamin D and placebo in individual cardiovascular events, but there was in atherosclerosis
53	Effects initiated in the winter months on bone health.	81	Bone, muscle	Daily	2800 IU	60-79	Post-menopausal women	2 years	Yes/No	Improved bone strength and trabecular thickness in the tibia, bone mineral density in the trochanter and femoral neck, but not bone density
56	Insulin sensitivity and β cell function.	1774	Glucose and hormones	Daily	4000 IU	50-70	Prediabetes	24 months	Yes	One of the outcomes suggests a reduction in predictors of insulin resistance
61	Physical functions in older adults	688	Skeletal muscle	Daily	1000-4000 IU	≥70 years	High risk of falls	2 years	No	There is no consistent information that vitamin D helps improve physical function and predict the risk of falls in older adults.
66	Effect of vitamin D on markers of bone remodeling mineral density	200	Skeletal system	Weekly	20000 IU	≥18 and <70	Healthy middle-aged men	12 weeks	No	Did not influence bone density

67	Falls in older adults	405	Bone, muscle	Daily	4000 IU	>70	Frailty and falls	24 months	No	High dose did not prevent bone fragility
68	Reduces incidence of falls	25871	Locomotive	Daily	2000 IU	>50	Number of falls	5.3 years	No	Did not reduce falls
68	Risk and incidence of falls.	21315	Bone and muscle	Monthly	60,000 IU	60-84	Falls, frequency and severity	3-5 years	No	No, increase, opposite effect to the one explored
69	Bone mineral density (BMD) and biochemical parameters in women after sleeve gastrectomy	62	Calcium metabolism	Daily	4000 IU	>18	Pre-gastrectomy	2 months prior	No	Bone demineralization of the hip and femoral neck by gastrectomy was not modified by preoperative vitamin D
70	Reduce post-thyroidectomy hypocalcemia	160	Calcium metabolism	Single Dose	300,000 IU	>18	Pre-Thyroidectomy	7 days prior to surgery	No	Treatment prior to thyroidectomy with high-dose cholecalciferol did not reduce the overall rate of hypocalcemia after thyroidectomy.
75	Child-Pugh score of patients with liver cirrhosis in one year of vitamin D supplementation	70	Liver	Daily	1000 IU	57-63	Liver cirrhosis	12 months	Yes	In patients with all-cause liver cirrhosis went from a severe level of cirrhosis to a milder one.

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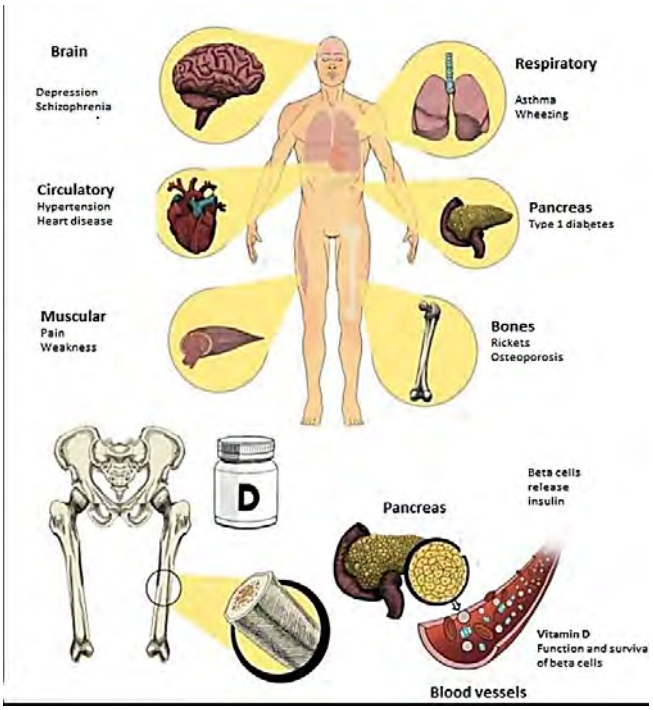

Figure 2. Illustration of organs and systems whose functioning has proven an effect from supplementation with vitamin D through clinical trials.

In patients with chronic conditions, vitamin D supplementation has shown diverse results: in asthma (39), vitamin D supplementation enhanced the effects of treatment and improved patients' quality of life. Significant effects on bone density and/or musculoskeletal system strengthening were identified in 3 out of 4 studies of postmenopausal patients, in patients with ostheoartritis and rheumatoid arthritis (40, 41).

As for its effect in patients with obesity and diabetes, oral supplementation could be a good option to control vitamin D deficiency in malabsorption and obesity (42, 43). In a study of infertile men at high risk of developing metabolic syndrome and type 2 diabetes, vitamin D supplementation prevented a decrease in insulin sensitivity and improved HDL cholesterol levels, but it is also suggested that vitamin supplementation had a potentially promising effect in patients with obesity and risk of Diabetes Mellitus. Recent studies reporting a significant effect on reducing the level of glycosylated hemoglobin show that, groups of patients with type 2 diabetes, peripheral insulin sensitivity and beta-cell function have also increased: daily oral doses of vitamin D at 2,000 IU reduced HbA1c levels over a period of 3 and 6 months In prediabetic women, there may be decreased serum glucose levels and truncal fat with overweight, obesity or vitamin D deficiency, so it may reduce the rate of progression towards diabetes. In patients with diabetes, it may help prevent progression of diabetic nephropathy by reducing proteinuria levels and inflammatory markers such as TNF-α and IL-6 (43-49).

During gestation, supplementation has been studied with the aim of preventing gestational 5, but there is not yet sufficient evidence to demonstrate its effect. Moreover, the potential of vitamin D supplementation for prevention of gestational diabetes in populations with sufficient vitamin D appears to be limited, although it may help to detect deficiency and thereby reduce the risk of adverse pregnancy outcomes (50).

Supplementation with vitamin D plus multivitamins has been assessed to improve epigenetic tracing in the gestational product, showing that methylation levels were significantly lower in the cholecalciferol-supplemented group than the placebo group; thus, maternal supplementation with cholecalciferol shows altered perinatal epigenetic tracing (51). On the other hand, after birth, oral vitamin D3 supplementation is more effective than sunlight in achieving vitamin D sufficiency in breastfed infants during the first 6 months (52).

In gynecological health, it has been observed that in women with premenstrual syndrome and vitamin D deficiency, supplementation of 2,000 IU in young women had no impact on premenstrual symptoms (23). In a study in Austria, 180 women with polycystic ovary syndrome who underwent supplementation with Vitamin D, after confirmation that they were below normal limits, were divided into two groups: intervention and placebo, at a 2:1 ratio (18). Effects on health related to ovarian cycle have been explored without finding significant differences on the intervention groups (53), including period related breast density (54). In menopause, vitamin D may alleviate Vulvovaginal Atrophy (55).

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The effects of vitamin D on lipid metabolism have been reported as potentially adverse, and although vitamin D supplementation has not had a significant effect on glucose, it is possible that, in a diet combined with a weight loss program, it may significantly improve insulin sensitivity in healthy subjects with obesity (56). On the other hand, the results on sarcopenia and adiposity in older adults have also not been significant (57, 58). Patients with Graves´ disease improve quality of life and muscle strength (59).

Although it is important that bone resistance and trabecular thickness in the tibia improve with supplementation in postmenopausal women from countries with short photoperiods, it must be noted that no differences have been shown in terms of bone density in general, only in one study in which bone density of the lumbar spine was evaluated in patients with low vitamin D, elevated PTH and osteoporosis (60-62). nevertheless, one study found that daily doses of supplementation with vitamin D in premenopausal women with deficiency/insufficiency are better for increasing muscular strength that single doses (23). In oligo-amenorrhoeic athletes, done mineral density may be improved (63).

For healthy men aged 18 to 70 years, vitamin D supplementation had no significant effect on markers of bone remodeling and bone mineral density (66). One study, the largest in number of participants, found an increased risk for falls among the intervention group when compared with placebo, suggesting a need to further explore the possible reasons (68). For specific purposes, such as supplementation prior to thyroidectomy or bowel segment resection, higher doses were used, up to 300,000 IU single dose (69, 70).

When it comes to oxygenation optimization, vitamin D has been proved to treat COVID-19 for short periods, in large doses (71). In individuals with malabsorption, Oral 25(OH)D3 ameliorates deficiency (72).

It has been reported that, in the cardiovascular system, vitamin D and calcium supplementation in normal young people with low concentrations can modulate the sympathetic nervous system, leading to alterations in heart rate and blood pressure. However, for ischemic disorders, it is important to note that vitamin D3 supplementation over three years showed no correlation with development of calcification, particularly in the tibial artery (22). On the hand, although no significant differences have been reported between vitamin D and placebo in individual cardiovascular events, vitamin D could perhaps have a positive impact on atherosclerosis (48).

Although with vitamin D supplementation there is no evidence of improved cardiac function in all patients with advanced heart failure, it does improve left ventricular function in patients with heart failure ≥50 years. In patients with heart failure, vitamin D supplementation does not prevent a decrease in testosterone levels (21).

In patients with various disorders leading to neuropathy and vitamin D deficiency, supplementation reduces the deficiency and, at the same time, the diabetic neuropathy (73), but notes are not provided regarding concomitant glycated haemoglobin control. For Khan et al, HbA1c improves in patients with oral vitamin D supplementation (74). Finally, high-dose vitamin D supplementation may be linked to a reduction in 28-day mortality in a mixed population of critically ill adults with vitamin D deficiency. However, this survival benefit remains independently when adjusted for other factors strongly associated with mortality (6).

Vitamin D supplementation in patients with cirrhosis of the liver may help them progress from a severe level of cirrhosis to a milder one (75). The evidence reviewed, derived exclusively from clinical trials, still shows discrepancies in terms of doses, periodicity of supplementation and short- and medium-term effects on different physiological, pathophysiological, and preventive processes.

Despite the widespread belief that “it is better to have too much than too little”, for several of the issues reviewed in the present study, it may still be considered as unnecessary to recommend

supplements for people not at risk of vitamin D deficiency.

Although in many parts of the world vitamin D deficiency is an endemic problem affecting the most vulnerable, fragile and elderly sectors of the community with particular severity (10), the evidence reviewed so far does not include the inhabitants of densely populated regions and, as with any drug, evidence from a diverse population is essential in order to avoid, first of all, harming those who might experience adverse responses due to idiosyncrasy or ethnicity (1, 2, 36, 38).

In the published evidence reviewed for the purposes of the present article, some population groups are over-represented, because of the locations in which the clinical trials were developed. Some geographic areas are over-represented, such as the United States, continental Europe including Sweden, Germany, Spain, Austria, and the United Kingdom. There is a large series from Australia and some countries in the Middle East, including Pakistan and Iran. But, in the tropics, in Central and South America, as well as Africa, but to our knowledge and resulting from the search we developed for the present article, there is no evidence of clinical trial research on vitamin D supplementation, although some authors living in these areas have participated in systematic reviews and meta-analysis.

Other significant effects were observed with supplementation in that there was a positive effect on insulin sensitization in patients with elevated body mass index. However, this data has been found in clinical trials that had different primary aims, for example, the search for a reduction in glycosylated hemoglobin in patients with diabetes or with a body mass index within normal limits (48) Other methodological deficiencies identified in studies on patients with diabetes and treatment with metformin include those in the study by Khan et al 2018, which omitted to give placebo to patients in the vitamin D group and thus did not rule out the possibility that there was a psychological effect that would have led patients in the treatment group to adhere more closely to the complementary measures of their treatment, such as diet and exercise (56).

CONCLUSIONS

Variability of dosages, periodicity of administration, application and of follow up after interventions were found even in studies aiming to prove similar outcomes, therefore, we suggest a cautious interpretation of data. By aiming to review the studied effects of vitamin D supplementation, we aimed at being able to compile the main results for health problems for which vitamin D supplementation is empirically recommended, thus, heterogeneity and size effects were not explored for the present study, given that the research unit was not comparable between studies, the reader may consider this limitation from this critical review.

Additionally, the doses used in clinical trials, even in the most recent ones, vary widely, and in some cases far exceed the recommendations for patients without Vitamin D deficiencies; and since there is only short-term evidence for the safety of supplementation at high doses, the potential effect that supplementation at higher than recommended doses may have in the medium and long term remains unknown.

Finally, our reader should be aware, that many the articles reviewed for the present article described clinical trials sponsored by the pharmaceutical industry that markets vitamin D supplements; fewer studies state that the authors or sponsors are not connected to industry-related organizations; and only 2 of the 70 studies reviewed claim to have been financed exclusively with federal funds. We hope that this caveat will help you to interpret the content we have presented with all due caution.

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