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Review

Therapeutic and maintenance regimens of vitamin D3 supplementation in healthy adults: A systematic review

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Abstract: Studies carried out assessing the effect of different doses of cholecalciferol (vitamin D3) on correcting serum 25-hydroxyvitamin D deficiency in healthy adults are limited and review studies are lacking. Moreover, the maintenance dose and its duration offered by these few studies are inconsistent. We performed a systematic review of randomized clinical controlled trials (RCTs) that assessed the effect of different doses of vitamin D3 on serum 25(OH)D in healthy adults. PubMed database was searched from 2010 to 2018 using the following search terms: "vitamin D deficiency", "Cholecalciferol", "vitamin D3 dose", "vitamin D supplement", "vitamin D therapy". RCTs and original articles that evaluated different doses of vitamin D3 were identified. A total of sixteen (out of 3016) acceptable studies fulfilling our inclusion criteria were included in the current systematic review. Our results revealed that supplementation with vitamin D3 had a significant positive effect in raising serum 25(OH) D concentrations. Our findings indicated that the best regimen of vitamin D3 supplement consisted of an initial large bolus dose either IM injection of 600.000 IU monthly or oral dose of 200.000 IU monthly or 50.000 IU weekly for 8 weeks, followed by a maintenance dose of 50.000 IU monthly or bimonthly. A large bolus therapeutic dose of vitamin D3, frequently or infrequently for 8 weeks, followed by long-term oral maintenance dose of 50.000 IU monthly or bimonthly optimiz and manitain vitamin D serum levels year round.

Key words: Vitamin D3 deficiency; Therapy; Maintenance dose.

Introduction

Since the discovery that cod liver oil cured rickets back in 1918, bone disease has been the hallmark of vitamin D-dependent deficiency (1). Today in 2018, we are decades later, but still we do not know the optimal vitamin D intake for our skeleton. Inadequate vitamin D status is associated not only with bone disease such as rickets, but also with skeletal and non-skeletal diseases. Indeed, it is linked to osteoporosis (2, 3), rheumatoid arthritis (4), systemic lupus erythematosus (5) and osteoarthritis (6). Furthermore, it is associated with several non-skeletal diseases including; multiple sclerosis (7), type1 diabetes mellitus (2), cardiovascular diseases (8), pancreatic cancer and breast cancer (9, 10). On the contrary, recent studies revealed that vitamin D supplementation did not prevent fractures or falls, or improved bone mineral density in adults (11).

The current guidelines on adequate intakes of vitamin D by healthy adults and children set by the Institute of Medicine's (IOM) Food and Nutrition Board (FNB) in 2011 are for medically unsupervised intake and do not apply to medically supervised treatment. The FNB says that the new upper limit is 4000 IU/day for adults and differs by age (12). The guideline of the Endocrine Society stated that the maintenance dose of vitamin D, which would need medical supervision, should be 10,000 IU/day to correct vitamin D deficiency for adults who are 19 years and older (13). Another guideline, that of Italian Society for Osteoporosis states that in subjects treated for vitamin D deficiency or insufficiency, a maintenance dose of 800-2000 IU/day (or weekly equivalent) is recommended; however, the highest tolerated daily dose has been identified as 4,000 IU/day (14).

Scientific evidence suggests that 25(OH)D serum levels should be over 30 ng/ml to achieve the beneficial biological effects of vitamin D in decreasing the risk of many chronic diseases (15).

The principal source of vitamin D comes from sun exposure in summer, which induces the synthesis of 20,000 IU of vitamin D after 30 minutes exposure (16) or as short as 9 minutes lunch time exposure in fair-skinned people (17). This amount of naturally-produced vitamin D is equivalent to taking 50 standard multivitamins tablets (400 IU/tablet). Such huge amount naturally-produced vitamin D in a few minutes, combined with vitamin D's basic genomic mechanism of action as steroid precursor indicates the importance and safety of large bolus therapeutic doses of vitamin in a short period in healthy people with vitamin D deficiency. Toxicity is rare and practical evidence of vitamin D toxicity in those chronically consuming 10,000 IU/day of vitamin D3 is absent in the literature (18).

Vitamin D3 is biologically inactive. It needs to be metabolized within the body to 25 (OH)D, also named Calcidiol. The latter is transformed by the enzyme 1, 25 hydroxylase into the biologically active form, 1, 25-(OH)2 D, also named Calcitriol. Measuring 25(OH)

D serum levels is the only way to diagnose vitamin D inadequacy. Vitamin D deficiency and insufficiency, for Caucasian population were defined in 2010 as follows; deficient < 25nmol/l (< 10 ng/ml), insufficient < 75nmol/l (< 30 ng/ml) and optimal ≥ 75nmol/l (≥ 30 ng/ml) (13, 19). The enzyme which induces the formation of 1, 25 (OH)2 D is present in a wide variety of human tissues other than kidney. Thus, locally produced 1, 25(OH) 2 D is under autonomous autocrine control. The autonomously made vitamin D3 directly affects numerous cells via its autocrine, and presumed paracrine functions (2, 20).

The aim of the current systematic review was to review all intervention studies, which investigated the effect of different therapeutic and maintenance doses of vitamin D3 on correcting and maintaining serum level of 25(OH) D in healthy adults.

Materials and Methods

Data search

We performed a systematic review study for published randomized controlled clinical trials (RCTs) on vitamin D3 (Cholecalciferol) supplementation in healthy adult subjects aged 18-59. Pub Med database was initially searched by two researchers for related published articles. The search was restricted to studies which feature the following: published in English language, human studies, clinical trials and original articles during the years 2010-2018. The search was performed by using various combinations of the following keywords: "vitamin D deficiency", "vitamin D3", "Cholecalciferol", "Vitamin D dose", "vitamin D supplement/s", "vitamin D therapy".

Study eligibility criteria

The RCTs that involved human, healthy adult subjects that directly compared the effects of different doses of vitamin D3 supplementation on serum 25(OH)D levels were initially included in this systematic review. However, reviews, systematic reviews, meta-analysis, letter to editor or case report articles were all excluded. Additionally, studies that had participants of unisex or lack of a control or placebo group were acceptable and were not causes for exclusion. No studies included that involved children, adolescence, pregnant or breastfeeding women or elderly (≥60 years). Studies that included mixed age i.e. adults with adolescences or elderly were also excluded. Exclusion criteria were also applied to articles if author or abstract or full-article was not found or if it was not about vitamin D deficiency, i.e. treating with vitamin D3 therapy without investigating vitamin D status (i.e., 25(OH) D levels). As a general overview, the recruitment criterion for each study was briefly described, all studies included in this review showed a clear methodology and subsequent reporting of results except few studies (studies are described in Table 1).

Data extraction

Four reviewers reviewed all trial characteristics (Table 1). They reviewed serum 25(OH) D concentrations at baseline, during or post treatment in association with the dose used, frequency, follow-upon duration, and use of either intramuscular (IM) or oral route, we also reviewed the range of age, gender and number of subjects involved in each study.

Results

Figure 1 shows the number of the studies included and excluded in the current systematic review. Twenty five RCTs (out of 3016) with sufficient data were available for the full article review and included in the primary analysis. The unavailable full articles were requested and provided by the Arabian Gulf University (AGU) library. A total of sixteen acceptable studies fulfilling our inclusion criteria were included for the final analysis. Our analysis showed that the total numbers of the participants included in this systematic review were 1747 subjects, aged 18-59 years, 69% (1214) of them were females.

The classification of the six regimens depicted in Table 2

We classified the different regimens used in this systematic review into six regimens as shown in Table 2. All studies tested supplement doses ranged from 200 to 600,000 IU and had a follow up period ranging from 4 to 52 weeks, however, 25% had follow up period up to 8 weeks only. Regarding vitamin D3 dosage, we classified the 16 studies into 3 groups; Oral vs IM, single vs multiple, large vs small.

Regimen1. Supplement with IM single large dose

Two studies evaluated a single large dose of 600.000 IU IM injection for 8-week duration (21, 36). They

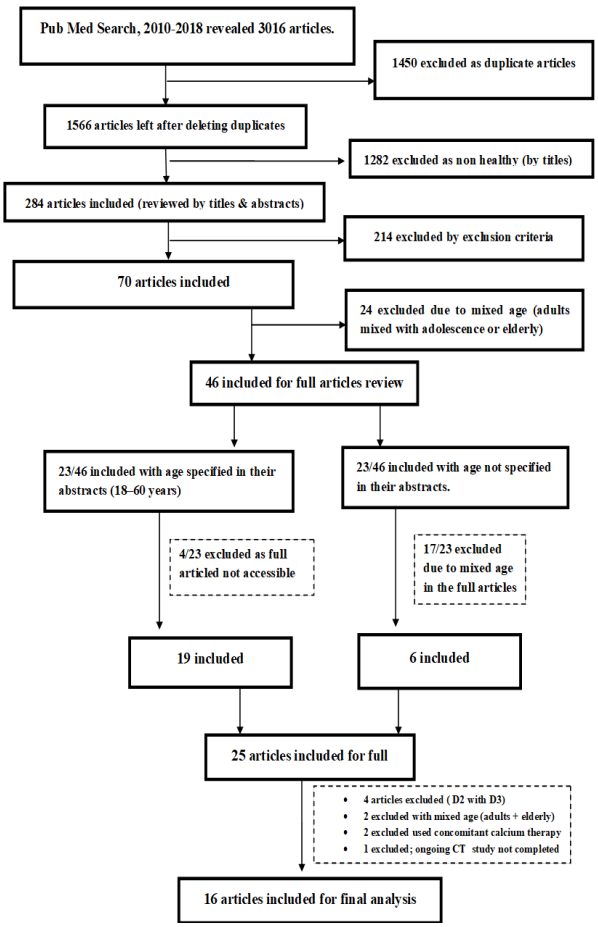

Figure 1. Flow diagram for the articles which were identified for the review.

Table1. Summary of the characteristics of the 16 studies that used different vitamin D3 regimes.

Author\year	F:M*/(T)* / Ageor(MA)*	(BL)*/PT*or (MC)*/ (PV)*	Vitamin D3 dose IU / duration in week (wk) or month (mth)	Outcomes Vitamin D3 (VD3)
1.Khan A 2012, (21) Pakistan	F:M 38:15 T(54) age : 30+-7	BL(17.4± 7.6)ng/ml / PT(26.5±7.7ng/ml)/ PV<0.0001	600.000 IU, IM/8 wks	A single VD3 injection of 600,000 IU significantly increase mean serum level of 25(OH)D
2.Khawaja N 2017, (22) Jordan	F:M :43:28/ T(71) MA:28.7 + 5.1	GA: BL(11.4 -+ 5.1)ng/ ml/PT(33.8 + 8.0)ng/ml GB: BL(11.7 + 6.4)ng/ ml/ PT(28.8 + 5.8)ng/ml PV: (.013)	(group A)(GA): 50.000 IU\wk*, 50. 000/ mth*, 50.000/2wks (group B(GB) 7000 IU D*/wk, 12.500 IU/wk 50.000 /mth	Timing and frequency of the dosing (daily vs weekly) have no effect on the rise in serum 25(OH)D levels and 50.000 IU bimonthly is required to maintain sufficient 25(OH)D levels
3.Priyambada 2014, (23) India	F:M(12:16) /T(30) Age (NS)	BL: 7.1±5.4(ng/mL) PT(1st 60000 IU): 11.1 ± 5.3 ng/ml PT (120000): 11.28 ± 4.7 ng/ml PT(2nd 60000) 18.4 ± 3.9 Final P value = 0.172.	60,000 U ,after 3mths, 120,000 IU or 180,000 U , after 3mths, 60,000 IU (maintenance dose)	An initial dose of 120,000-180,000 IU of VD3 is required to elevate 25(OH)D out of the deficiency range. Maintenance dose is needed at 8 weeks
4.Rana, 2014, (24) India	F:M(16:3) /T(19) /age 21.5	BL (3.4+\- 1.7)ng/ml/ PT: 26.9 ±9.75ng/ml/PV : 0.001	60 000 IU/wk for 12 wks	The serum level has been optimized after 12 weeks.
5.Schleck M 2015, (25) Belgium	F only/ (T)150 /age >18 years	BL in all Groups(>5ng/ mL and <20 ng/ml G1: MC (7.72 -+5.08) ng/ml G2 :MC 13.30 +\- 5.88ng/ml G3:MC 20.12 +\- 7.79ng/ml (PV < 0.0001)	3 Groups given (L* (G1), M*(G2) ,H* (G3) Dose)in (O, 4 ,8 WKS) 50,000, 100,000 or 200,000 IU (0wk) 25,000, 50,000 or 100,000IU (4wk) 25,000, 50,000 or 100,000IU (8 wk)	Loading dose of 200,000 IU VD3 followed by a monthly dose of 100,000 IU is the best dosing schedule to quickly and safely correct the VD status.
6. Yao 2016, (26) China	F:M(307:141) /T(448) /Age(20-42)	MC:12.2 ±6 (p: <.001)	, 2000 IU/d for 20 wk Control study	Conclusion, daily supplementation with a 2000 UL dose of VD3 in China significantly raised 25(OH) D in 75 % of the samples.
7.Cipriani C 2010, (27) Italy	F:M (35:13)/ T (48) MA :36.04 +\- 8.46	BL: 15.8±6.5ng/ml/ PT(3o day):62.4±26.1ng/ ml , PT (90 days):31.9± 12.6ng/ml/ P value :<.001	A single 600,000 IU for 3mths	A single oral dose of 600,000 IU of VD3 rapidly enhances 25(OH)D and reduces PTH in young people with vitamin D deficiency
8.Gallagher, 2014, (28) USA	F only/ T (198) Age (25-45)	BL (all 4 Groups):11.6 -14.6ng/ml PT: (G1) 13.1 ng/ml ,(G2) 13.8ng/ml , (G3) 13.3ng/m; ,(G4) : 14.1 ng/ml PV : (NS)	Four groups (G1: 400, G2 800, G3 1600, or G4 2400 IU/d). follow up after	The recommended dietary allowance (RDA) suggested by the Institute of Medicine for young people is 600 IU daily.
9.Gowda 2016, (29) Australia	F:M(137:68) /T(205)/ Age (18-55)	BL:(G1)(20-30) ng/ml L,(G2) 10-19.6ng/ml, and below 10ng/ml)G3) PT :(G1)33.3±9, (G2) 28.4 ±9.34 ng/ml (G3) and 28.3± P V : NS	50,000 IU follow up for 52 wks	High dose vitamin D3 50.000 IU is effective in achieving sufficient serum 25(OH)D among these populations who tend to have lower baseline serum 25(OH)D.
10. Green 2010, (30) Canada	Female only /T(73) Age (18-45)	BL: 30 ng/ml PT : decline to 20ng/ml PV of insufficiency (p < 0.001)	200 IU twice/day for 12 wks	This study suggests an AI of 5 µg (200 twice IU daily) may be inadequate for to allow for seasonal changes in sunlight exposure, and is unlikely sufficient for other populations with low sunlight exposure

11.A. Gupta, 2010, (31) india	F:M (12:17)/ (T):29/ MA, 28.4 ± 6.4	BL :18.9 ± 11.9ng/ml / PT 84.4 ± 34.9ng/ml /P: <0.0001	60 000 IU /wk for 8 wks	These findings support the need for improving the VD status of Asian Indians through dietary supplementation and exposure to sunshine
12.Harris 2011, (32) Georgia	AGE: 19-50	BL : 13.7 ng/ml / PT 40.4 ± 6.6 ng/ml /PV:.02	60,000 IU monthly for 16 wks	Supplementation of 60,000 IU monthly oral VD3 (~2000 IU per day) for 16 weeks is effective at improving vascular endothelial function in African American adults.
13.Habib A 2012, (21) Pakistan	F:M (14:6)(T(20) MA: 27 ± 3.5	BL: (14±6.4)\ PT(10.6±4)ng/ml/(p < 0.01)	IM 600,000 IU follow up after 8 wks	Single mega-dose of VD3 achieved optimal levels of 25OHD in 35% of subjects after eight weeks
14.Mazahery 2015, (33) Auckland	Female only /T(105) /age(20-50)	BL in all 17.5 ng/ml / PT (50000):94%reach 20ng/ml PT (100000_100% reach>30ng/ml PV: .0002	monthly either 50 000, 100 000 IU vitamin D3 or placebo for 26 wks	Monthly 100 000 IU VD3 for 26 weeks is more effective than 50 000 IU in achieving serum-25(OH)D⩾ 30 ng/ml; however, a third of women still did not achieve these levels.
15.Nowak 2016, (34) Switzerland	F:M(64:56\ T(120)/ MA 29±6 years,	ng/ml MC :14.±5.4 PV:<.001	single oral dose of 100,000 units	VD3 treatment significantly improved fatigue in otherwise healthy persons with vitamin D deficiency
16.Saleh 2017, (35) Switzerland	F:M (53:54)/T(107/ age (20–50)	BL (G1)(20-30) ng/ml &(g2)(>30 ng/ml) 15.7ng/ml (g1) ,23.9 ±7.6 ng/ml MC: (g2)/ PV:<.001	a single 100,000 IU)	Administration of a single high dose of VD3 leads to a significant increase in concentrations of 25(OH)D, 24,25(OH)2 D3

F: Female, M: male, T: total number NS: not specified, MA: mean age, L: low, M: moderate, H: high, BL: baseline, PT: post treatment, MC: mean change, PV: p value, , 1 ng /ml = 2.496 nmol/l.

Table2. Regime and dosage of oral vitamin D3 used in the 16 studies.

Oral Regime	No of study	Dosage (IU) used in the 16 intervention studies
Multiple large doses	6	25.000, 50.000, 60.000, 100.000, 200.000
Single large dose	3	50.000, 60.000, 100.000, 120.000, 180.000, 200.000 ; weekly or monthly
Multiple small doses	3	200, 600, 2000, 7000, 12.500
Single small dose	1	400, 800, 1600 or 2400, measurement at 0, 26, 52 weeks
Single large IM* dose	2	600.000 post measurement at 8 weeks
Combination of single and multiple large doses	1	50.000 once post measurement any time within 12 months, then 50.000/ week for 4 weeks, then 50.000 once / 4 weeks for 52 weeks

* IM = intramuscular injection.

proved that the difference in serum 25 (OH) D from the baseline was statistically significant and the increment was 22.6 and 31.5 nmol/l for the study cited as 21 and 36, respectively. But, the optimal levels were achieved in only 35% of the participants.

Regimen2. Supplement with oral single large dose

Three studies evaluated a single oral large dose, one study at 12 weeks (23) and other two at 4weeks (34, 35). A dose of 50.000, 60.000 and 100.000 IU increased serum level of 25(OH)D significantly with an increment ranging from 14.1 to 17ng/ml. However, this regimen was unable to raise or maintain adequate levels for 12 weeks. On the other hand, initial higher dose of 120.000, 180.000 and 200.000 IU were required to raise the 25(OH) D out of the deficiency range (>30 nmol/l), while 52% of the participants achieved levels >30 ng/ml, more than 75% achieved levels > 50nmol/l. Using these doses, an increment ranging from 11-28 ng/ml with higher raise in lower baseline levels. Even though these regimens were associated with 1.5 to 6.5 fold increase, it was recommended that maintenance dose (60.000IU) at 8 week was required and concluded that due to individual variations in response to therapy any given dose is unlikely to achieve optimal vitamin D status in all individuals.

Regimen3. Supplement with a single and multiple oral large dose

One study (29) evaluated an oral large dose of 50.000 IU as single and multiple doses at 26-52 weeks. It assessed its effects on the three levels of vitamin D status (<25 nmol/l, 25-49 nmol/l and 50-75nmol/l). The increments were>50nmol/l, <25 nmol/l and < 10 nmol/l for the above mentioned 3 levels, respectively. The authors concluded that the lower the baseline levels the

higher the increment.

Regimen4. Supplement with multiple oral large dose

Six studies evaluated administration of multiple large doses. Four studies evaluated a dose of 60.000 IU at duration of 8 weeks (31), 12 weeks (24), 16 weeks (32) and 26 weeks (33). The investigators showed that these regimens were effective in normalizing the serum levels with the increment of 26.24 ng/ml, 23.5 ng/ml, 26.68 ng/ml and 10.4 ng/ml, for the 8 weeks, 12 weeks, 17.3 weeks and 26 weeks follow-up periods, respectively. Interestingly, same dose was tested at different times with one month intervals, but unfortunately, no much data was concluded from those studies as they were intended to measure other parameters than vitamin D. One study evaluated the dose (25.000, 50.000, 100.000 and 200.000 IU) at zero week, 4 weeks and 8 weeks (25). It proved that loading dose of 200.000 IU followed by a dose of 100.000 monthly was the best dosing schedule to quickly and safely correct vitamin D status.

One very interesting study evaluated two regimens of vitamin D (22). One regimen tested a dose of 50.000 IU weekly for 8 weeks, then monthly for 2 months. Therapy was stopped for 2 months then resumed again every 2 weeks for total of 28 weeks. Second regime evaluated 7000 IU daily for 8 weeks, then 12,500 weekly for 8 weeks. Treatment was stopped for 8 weeks then resumed again 50.000 IU monthly for up to 28 weeks. No significant difference was found between the 2 regimens except for the last step after resuming the therapy, where the fist regime led to significantly higher serum levels of 25(OH)D. This study proved that timing and frequency of dosing (daily vs weekly) had no effect on the rise in serum 25(OH)D levels as long as the accumulative dose of Vitamin D3 is similar, thus, 50. 000 IU bimonthly is required to maintain sufficient 25(OH) D levels year round.

Regimen5. Supplement with multiple oral small dose

Three studies evaluated multiple small dose regimens. A dose of 2000 IU daily for 20 weeks unable to correct the deficiency of vitamin D in 25 % of the participants (37). Another study tested a dose of 200 IU twice daily for 12 weeks (30) and proved that the dose is inadequate to achieve optimal vitamin D levels. A third study assessed two doses of 800 and 1600 IU, given daily for 12 weeks. The increment in the mean serum levels was 7.2ng/ml and 11.61ng/ml, respectively. Although the serum level of 25(OH)D decreased during follow up, it remained above baseline (38).

Regimen6. Supplement with a single oral small dose daily

One study tested 4 different small daily doses (400, 800, 1600 or 2400 IU) for 52 weeks and proved that there was no difference in the increments between the 4 tested doses (28).

Discussion

Vitamin D deficiency or insufficiency could be a concern not only in healthy children (39) or healthy elderly (40), but also in healthy adult subjects. Studies investigating the prevalence of vitamin D deficiency and the best therapeutic regimen to correct it in this latter age group are limited. Natural vitamin D serum levels, in healthy subjects living in a sunny environment, are between 40-70 ng/mL, however, higher level of more than 75 ng/ml is recommended to reduce the risk for diseases associated with the deficiency of this vitamin (41). However, several questions remain unanswered regarding this issue: What is best regimen for vitamin D deficiency? What is the best dose, the frequency and the route of administration to correct deficiency and maintain normal levels?

We conducted this systematic review to evaluate the influence of variable doses of vitamin D supplementation on serum 25(OH) D levels in healthy adults. In general, we found that the included intervention studies were very heterogeneous in terms of their designs, a finding which made comparison between them difficult. Many factors contributed to this heterogeneity such as; the amount of the dose (small, intermediate or large), the frequency of dosing (daily, weekly, monthly or yearly), albeit not the route since all studies used oral route except two studies that used intramuscular route (21, 36). The sixteen RCTs included in our current review reported clinical trials of different regimens of vitamin D supplement.

In the current review, supplement with single large dose of 600.000 IU IM injection optimized vitamin D serum levels only in 35% of the participants. In comparison, the single large oral doses (23, 34, 35), showed that the initial dose of 200.000 IU was best to elevate the 25(OH) D out of the deficiency range in all participants, optimized the level (>20 ng/ml) in more than 75%, while 52% achieved levels >30 ng/ml. Although these regimes associated with 1.5 to 6.5 fold increase, a maintenance dose was required at 8 weeks since such levels do not continue to rise. Interestingly, toxicity was not recorded. Our results are augmented by another study (29) that tested the effect of single and multiple oral large doses on the known levels of vitamin D status and demonstrated that the lower the baseline levels the higher the increment. Our data are consistent with recent study, which showed that the target vitamin D serum level should be 20 - 24 ng/ml year round, with a conservative upper limit < 40 ng/ml (42).

In the present study six studies evaluated multiple administration of large dose of 60.000 IU up to 24 weeks. They proved that both dose and duration were effective in normalizing the serum levels. Scheck et al revealed that loading dose of 200.000 IU followed by a dose of 100.000 monthly was the best dosing schedule to quickly and safely correct vitamin D status (25). One interesting study (22) evaluated two regimens of vitamin D3 and proved that timing and frequency of the dosing (daily vs weekly) have no different effect on optimizing serum 25(OH)D levels as long as the accumulative dose of vitamin D3 was similar. Our results are consistent with another study showed that supplementation with vitamin D3 was very effective in raising serum 25(OH) D concentrations with larger and more infrequent bolus dosages, but the effect was lost with small daily doses (43). On the other hand, we are unable to verify the different effects between oral and IM administration of vitamin D3 by our current review since we

have only two articles using IM administration.

In the current review there is agreement between all studies evaluating oral multiple small doses regimens that the doses were inadequate to achieve optimal vitamin D. Our results with small dose regimen are consistent with two recent studies. One study determine the efficacy of small daily vitamin D supplementation suggested that the subsequent changes in 25(OH) D levels were dependent on its baseline and body mass (44). Another study revealed that both 1800 IU/day cholecalciferol can safely maintain vitamin D sufficiency in Chinese women, but higher doses are required with baseline concentration <75 nmol/L (45).

One of our intervention studies (22) showed that, in a fixed short period, no matter the dosage, the frequency or route of administration of vitamin D3 supplementation since the accumulative dose is the same and it produced significantly absolute increase of serum 25(OH) D from baseline and correct the hypovitaminosis. Thus, 50 000 IU vitamin D3 bimonthly is required to maintain sufficient 25(OH)D levels year-round. In such study, we noticed that the maintenance dose was both high and more frequent compared to others (22). This result is consistent with another study done in healthy adult and elderly subjects with hypovitaminosis that showed; the frequent oral dose of 50.000 IU is more effective in correcting hypovitaminosis (46). One more of our studies showed that monthly dose of 100.000 IU vitamin D for 6 months is more effective than 50.000 IU in achieving serum-25(OH) D⩾30 ng/ml; (33). This result is consistent with a recent RCT at 2017, which proved that vitamin D3 loading dose is superior, effective and safe in achieving higher vitamin D concentrations after weight loss surgery in vitamin D deficient morbidly obese patients (47).

Conversely, we did not assess the effects of these regimes across gender and ethnicity since the amount of vitamin D needed varies not only with age, but also with body weight, body fat, skin color, season, latitude, and sunning habits and almost all studies did not focus on those issues. However, there was a majority of females (69%, n=1214), which indicates that those reviewed studies could have high proportions of female participants.

Conclusion

In conclusion, in healthy adults and among all regimens used, the most efficient, cost-effective and safe dose of vitamin D3 in raising serum 25(OH)D concentrations was a large bolus dose regardless whether it is a singleor multiple, oral or IM, ranging from 50.000 to 600.000 IU, with the best dose being 200.000 IU orally or 600.000 IU parentally that followed by a maintenance dose of 50.000 IU with any dosing interval between 2 to 4 weeks to keep optimal levels year round. Change in serum 25(OH) D concentration at any given dose is highly variable among individuals and depends on the baseline i.e. the lower the baseline the higher the increment.

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