Dosing Strategy of Vitamin D therapy in Patients with Rheumatic Diseases in Bahrain

Short title: Hypovitaminosis D maintenance therapy

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Abstract

Purpose: The assessment of vitamin D status (25(OH)D) and dosing strategies for patients with rheumatic diseases (RDs) in Bahrain are lacking. The current study aimed to determine serum 25(OH)D levels at baseline and after Cholecalciferol (Vitamin D3) therapy and to assess the changes in serum levels in response to three different regimens in adult patients with RDs in Bahrain. Methods: Data was collected retrospectively from 158 patients with RDs, during a period 20132019- at King Abdullah Medical City. The mean age of the patients was 45 years (range 18 - 83 years). Two third (66.46%, 105) of them were females. The controls were adult sex- and age-matched healthy volunteers. All patients were investigated for vitamin D status during their first visits. Three regimens of Vitamin D3 therapy were assessed: Regimen1. A single parenteral dose of 600.000 IU. Regimen2. An oral dose of 50.000 IU weekly for 12 weeks, Regimen3. Maintenance oral dose whenever a patient achieved an optimal level. Results: The patients had lower serum levels of vitamin D3 compared to controls (P-Value=0.001; 95%C.I. (3.870, 15.599)). There was a statistically significant increase in mean serum levels of Vitamin D3 in Parenteral compared to Oral therapy (P-value<0.0005). In the patient group, vitamin D3 therapy leads to a statistically significant increase in its baseline level (P-value<0.0005), but the reduction in vitamin D3 from the therapeutic levels during maintenance was statistically not significant (P-value=0.177). Conclusion: The significant increase in serum 25(OH)D levels from baseline in response to Vitamin D3 regimens was best achieved with single parenteral therapy of 600.000 IU. Maintenance therapy to maintain optimal level year-round is a must, and the best dose was 50.000 IU orally every 24- weeks.

Keywords: Cholecalciferol, Maintenance, Parenteral, Vitamin D3 Dose, Rheumatic Diseases.

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Introduction

Vitamin D status if it is optimal or suboptimal, is indicated mainly by measuring serum levels of 25-hydroxyvitamin D3 (25(OH)D), which is the inactive form. The discovery

that most tissues and cells in the body have vitamin D receptors and possess the enzymatic machinery to convert the 25(OH)D to the active form named; 1,25-dihydroxy vitamin D3 (1, 25(OH)2 D3), has provided new insights into the function of this vitamin. Another study showed that optimal 25(OH)D level played an essential role in decreasing the risk of many chronic illnesses, including, cancers, infectious, cardiovascular, and autoimmune rheumatic diseases (ARDs) (Szabo, 2011). Furthermore, a recent study has shown that while 25(OH) D has potent actions on muscle gene expression and could influence muscle function, the serum 1, 25(OH)2 D3 is associated with increased muscle strength and lean mass (Hassan-Smith et al., 2017). Another study showed that serum 1, 25(OH)2 D3 improved muscle function and reduced recurrent falls in post-menopausal women (Iolascon, Moretti, de Sire, Calafiore, & Gimigliano, 2017). In osteoporosis, a disease of low BMD and increased risk of fracture, vitamin D supplementation showed to decrease the risk of osteoporotic fractures. Guideline of Italian Society for Osteoporosis recommended, a maintenance dose of 800-2000 IU/day (or weekly equivalent) for vitamin D deficiency (VDD) or insufficiency, however, the highest tolerated daily dose has been identified as 4,000 IU/day (Adami et al., 2011). Scientific evidence suggests that 25(OH)D serum levels should be higher than 30 ng/ml (or 50 nmol/l) to achieve the beneficial biological effects of vitamin D in decreasing the risk of chronic diseases (Battault et al., 2013). It has been recommended that to maintain serum 25(OH)D above 75 nmol/L to ensure optimal bone health. But, for beneficial extra-skeletal effects, including a decrease in the risk of inflammatory diseases, higher levels were required (Maurice & Karine, 2010).

In rheumatoid arthritis (RA) periarticular osteopenia is an early radiological sign; thus, osteoporosis is not uncommon, however, the bone loss in RA if it is due to an impaired vitamin D metabolism or not still needs to be clarified. In RA, it has been shown that 25(OH) D levels correlated with disease activity score (DAS-28) (Kiran & Debashish, 2011). In adult patients with systemic lupus erythematosus (SLE), VDD is very common (Farid, Jaradat, Al-Segai, & Hassan, 2017), many factors have been implicated in VDD in SLE patients such as; cumulative glucocorticoid dose and serum creatinine (Chaiamnuay et al., 2013; Toloza, Cole, Gladman, Ibanez, & Urowitz, 2010). Interestingly, in SLE VDD shown to be associated with higher disease activity and poor bone mineral density (BMD) response during treatment with bone-active agents (Yeap, Othman, Zain, & Chan, 2012), it is also associated with cognitive impairment (Tay, Ho, Ho, & Mak, 2015), SLE-related endothelial dysfunction (Diane & Jim, 2015), and to transition to SLE in genetically predisposed individuals (Young et al., 2017). In osteoarthritis (OA), it has been shown that high-loading dose treatment with cholecalciferol was needed to correct hypovitaminosis D of patients with ARDs in general and with OA in particular (Sainaghi et al., 2013). When darker skin type was a risk factor for VDD (Hata et al., 2014). In psoriasis, a short narrow-band ultraviolet B (NB-UVB) treatment significantly increases serum 25(OH)D in patients with psoriasis who are taking oral vitamin D supplementation, and the concentrations remain far from the toxicity level (Ala-Houhala et al., 2014). The exact mechanism of the reverse relationship between uric acid and vitamin D3 reported in some RDs such as SLE is still not clear (Hassan, Farid, Medani, Diab, & Al-Segai, 2019), and further studies in patients with different RDs are warranted.

The goal of this retrospective study was to investigate vitamin D status (25(OH)D) in adult patients with rheumatic illnesses living in Bahrain. We also wanted to see how 25(OH)D levels changed from baseline in response to three different cholecalciferol (vitamin D3) regimens, and to figure out which one was the most successful in correcting and maintaining adequate vitamin D3 levels year-round in our patient group.

Materials and Methods

Data were collected retrospectively from the patient's health records. Hundred and fifty-eight (158) patients with different rheumatic diseases have been investigated for their vitamin D status (serum 25(OH)D) as part of their health care service. The patients visited the rheumatology clinic running at King Abdullah Medical City (KAMC) / University Medical Centre (UMC), during the period from Jan 2013 to February 2019. Patients who had no vitamin D tests during their first visits were excluded. The controls were 70 adult sex-matched and age-matched (1-5 years) healthy volunteers who matched with the 70 patients who came back for the follow-up and continued the study to the end. More precisely, all prescriptions (100%) were for vitamin D_3 (cholecalciferol) not associated with calcium prescription.

Three regimens with vitamin D_3 therapy were prescribed. **Regimen1**; A single parenteral (intramuscular, IM) dose of 600.000 IU monthly up to 3 injections maximum. The first injection would be followed four weeks later by serum tests of 25 (OH)D and calcium and according to the lab result; if the optimal level were not achieved, that would be followed by; a second injection, then a third injection if needed. **Regimen2**; A high oral dose of 50.000 IU capsules /week for 12 weeks followed by tests of serum 25(OH)D and calcium at the end of the 12 weeks. **Regimen3**; A maintenance oral dose (10.000 IU weekly or 50.000 IU 2-4 weekly) was given for any patient whose first sample showed optimal level or after completion of the three months therapeutic period or at any time when a patient achieved the optimal serum level. Serum 25(OH)D and corrected serum calcium concentrations were evaluated at baseline and after completion of treatment of the different regimens applied in our clinic. After starting the maintenance therapy, the serum levels should be checked at three months, six months, or 12 months. In Bahrain, the levels of serum 25(OH)D were defined in 2013 by Golbahar et al., as follows; optimization was defined as values $\geq$ 50 nmol/l (range 50 - 150 nmol/l), insufficient as levels 30-49.9 nmol/l, and deficient as levels <30 nmol/l (Golbahar et al., 2013). Serum level of 25(OH)D was tested using electrochemiluminescence binding assay, where vitamin D binding protein labeled with a ruthenium complex and worked as a capture protein to bind 25(OH)D. Corrected serum calcium (mg/dL) was estimated, both calcium and albumin were tested using machine Roche Cobas 6000.

Statistical analysis was performed using the SPSS program**.** Paired samples t-test was used to test the mean difference in pre and post vitamin D therapy. A P-value of < 0.05 was considered statistically significant. Box plots were used to show the mean of vitamin D levels before the therapy, after the therapy, and during the maintenance.

Results

The mean age of the patients was 45 years (range 18 - 83 years). Two third (66.46%, 105) of them were females. The percentages of the patients with different diagnoses included in this study (Table 1) were as follows; 30 (18.98%) with only vitamin D Deficient/Insufficient (VDD/VDI) with no other comorbidities. Moreover, 20 (12.65%) OA, 7 (4.43%) Nodal OA, 18 (11.39%) OA with other co-morbidity and ANA positivity (1 with Paget's disease, 7 with low back pain, 4 with rotator cuff injury without trauma and 6 with Low BMD). RA were 26 (16.5%), 9 (5.69%) Ankylosing Spondylitis, 3 (1.89%) psoriatic arthritis, Low BMD was 13 (8.22%), GA was 9 (5.69%), SLE was 6 (3.78%), Sjogren's syndrome (SS) was 5 (3.16), Fibromyalgia was 3 (1.89%), Mixed Connective Tissue Disease (MCTD) was 2 (1.26%), Bechet's Disease (BD) was 3 (1.89%).

Table 1. Percentages of patients with rheumatic diseases with low vitamin D status.

Diagnosis	Patient No 158 (%)	Other co-morbidities
Vitamin D deficiency / insufficiency (VDD/VDI)	30 (18.98%)	No comorbidity
Osteoarthritis (OA)	45 (28.5%)	20 OA only, 7 NOA, 7 low back pain 1 Paget's disease, and 6 with low BMD and 4 RCI
Rheumatoid arthritis (RA)	26 (16.5%)	Low BMD, 2 RCI, 1 SLE (16 +veRA and 10 -ve RA)
Spondyloarthropathy (SpA)	12 (7.6%)	9 AS and 3 PsA
Low BMD	13 (8%)	6 Osteoporosis and 7 Osteopenia (all with other co-morbidities)
Gouty arthritis (GA)	9 (5.7%)	3 OA, 1 ReA, 1 CKD
Systemic Lupus Erythematosus (SLE)	6 (3.8%)	1 APL, 1 discoid Lupus, 1 RA
Sjogren's Syndrome (SS)	5 (3.2%)	No co-morbidity
Rotator cuff injury (RCI)	4 (2.5%)	All OA and 2 RA
Fibromyalgia	3 (1.9%)	No co-morbidity
Mixed Connective tissue Disease (MCTD)	2 (1.3%)	2 Osteoporosis
Bechet's Disease (BD)	3 (1.9%)	No co-morbidity

NOA = Nodal OA, AS = ankylosing spondylitis, PsA = psoriatic arthritis, APL= antiphospholipid, +ve RA = seropositive RA, -ve RA = seronegative RA, BMD = Bone mineral density, ReA= reactive arthritis.

Therapeutic regimens

Fortunately, all patients (158) who received vitamin D therapy came back to the clinic to check their results after the first four weeks and to continue their therapy. Therapeutic regimen (Table1) with a high dose of 50.000 IU oral capsule of vitamin D_3 (Regimen2) received by 95 patients (60.1%), while the single parenteral dose of 600.000 IU IM injections (Regimen1) was received by 63 patients (39.1%).

Regimen1 (High parenteral (IM) single dose of 600.000 IU)

Sixty-three patients were given a high single dose of 600.000 IU IM injection. This regimen was given for all patients who were severely deficient in vitamin D ($\leq$20 nmol/l), or rarely when was requested by the patient who had insufficient levels. The patient should come after four weeks to test his vitamin D serum levels to decide on the second dose. If the patient achieved his optimal level, which was the most frequent situation, then a maintenance dose will be prescribed. If they were still deficient or insufficient in vitamin D, which was a rare situation, then another IM injection will be given before the maintenance regimen.

Regimen2 (High oral dose of 50.000 IU capsule once per week for 12 weeks)

Ninety-five patients have received this regimen. This regimen was given for all patients

who were deficient in vitamin D (>20 ≤ 30 nmol/l) or insufficient (30-49.9 nmol/l), or rarely when the patient requested it. The patient should come for the follow-up to test his serum levels of vitamin D at four weeks then at 12 weeks which is the end of the therapeutic period when the patient achieved his optimal levels to start the maintenance regimen (Regimen3).

Maintenance therapy (Regimen3).

Only 70 patients (70/158) (Table 4) came back for follow up during the maintenance (VDM) to check their Vitamin D_3 levels, of whom 25 patients (25/63) from those who received the parenteral therapy (Regimen1) and 45 patients (45/95) from those who received the oral therapy (Regimen2).

The maintenance regimen (Regimen 3) of the high oral dose (50.000 IU oral therapy every 2-4 weeks) was received by all 70 patients, who came for the follow-up during the maintenance period, which was 3-12 months. The maintenance therapy is offered to any patient who achieved the optimal vitamin D level either after the single parenteral therapy (Regimen1) or completed the therapeutic period of 3 months of the oral therapy (Regimen2). The serum levels of 25(OH)D during the maintenance therapy were checked at three months, six months, or 12 months to ensure optimization of serum levels year-round. Therefore, the maintenance period ranged from 3-12 months, with a mean of 6 months (data not shown). Unfortunately, only 25 patients (35.72%) who received (Regimen1) came back for follow-up 3-12 months during the maintenance period. Regimen3 maintained the optimized levels in all 25 patients (100%). Regarding regimen2, the oral therapy, only 45 patients (45, 64.28%) who received (Regimen2) came back for follow up 3-12 months during the maintenance period, in this group, the regimen maintained the optimized levels in 91% of the patients (data not shown).

Table 2. Revealed that the mean serum levels for the 63 patients (79.06) who received Regimen1 after four weeks was higher compared to the mean serum levels for the 95 patients (30.87) who received Regimen 2 (the oral capsule dose of 50.000 IU weekly) for the first four weeks and the difference were statistically significant. The two-sample t-test indicates that there is a highly significant difference in the Regimen1 compared to Regimen2 (P-value < 0.0005; 95% C.I. (-53.47, -42.91).

Table 2. Comparison between Oral versus Parenteral Vitamin D3 Therapy after One Month in Patients with Rheumatic Diseases (n=158).

Oral* (n=95; 60.1%)	**Parenteral**** (n=63; 39.1%)	Mean Difference	P-Value	95% C.I	
Mean ± SD	Mean ± SD			Lower	Upper
30.87 ±10.23	79.06 ±22.83	- 48.19	<0.0005	-53.47	- 42.91

* Oral capsules of 50.000 IU weekly for 4 weeks,

** Intramuscular single injection of vitamin D3 at a dose of 600.000 IU after 4 weeks.

Table 3. Depicted the two-independent samples t-test, which indicates that there was a statistically significant difference in the means of vitamin D serum levels at baseline between the patient group and the control group. Thus, the patients had lower serum levels of vitamin D compared to the controls (P-Value = 0.001; 95% C.I (3.870, 15.599)). Also, there were highly statistically significant differences in the means of serum calcium

between the two groups. Thus, the patients had higher serum levels compared to the controls (P-value < 0.0005; 95% C.I (- 0.211, - 0.096)).

Table 3. Comparison of Vitamin D3 Baseline (VDB) serum levels between Patients and Controls.

Group	Control (n=70)	Patient (n=70)	Mean Difference	P-Value	95% C.I	
	Mean ± SD	Mean ± SD			Lower	Upper
VDB	45.04 ± 18.88	35.303±16.10	9.73	0.001	3.87	15.60
Ca mmol/l	2.16 ± 0.21	2.32 ± 0.11	- 0.15	<0.0005	- 0.21	- 0.10

Ca = Calcium; VD = Vitamin D3; VDB = Vitamin D Baseline before therapy

Table 4. The paired-samples t-test indicates that there was a large statistically significant difference between vitamin D levels at baseline and vitamin D after therapy in the patient group (P-value < 0.0005; 95% C.I (32.095, 49.656)) with an increment of 40.86 above the baseline. There was a reduction in the vitamin D serum levels during the maintenance therapy (Regimen3) below the therapeutic levels (Regimen 1 and 2), but the difference was statistically not significant (P-value = 0.177; 95% C.I (- 3.744, 19.940)).

Table 4. Pairwise Comparison between Vitamin D before Therapy (VDB) and after Therapy (VDT) and between the Therapy and Maintenance (VDM) in Patient Group.

Patient (n=70)	Mean ± SD	Mean Difference	P-Value	95% C.I	
				Lower	Upper
VDB – VDT	35.30±16.10 -76.18±35.82	40.86	< 0.0005	32.10	49.66
VDT – VDM	76.18±35.82 - 68.09±37.17	8.10	0.177	-3.744	19.94

VDT= vitamin D3 Therapy; VDB = vitamin D3 Baseline; VDM = vitamin D3 Maintenance

Table 5. The paired-samples t-test indicates that when the patient cohort was segregated into the oral and parenteral groups; there was a strong statistically significant difference between vitamin D levels after 3 months of oral therapy and the maintenance therapy (P-value < 0.0005; 95% C.I (15.46, 39.30)), with the reduction of 27.38 below the therapeutic level. On the other hand, no statistically significant difference was found between the means of vitamin D level after parenteral therapy (Regimen1) and the maintenance levels (Regimen3) (P-value = 0.316; 95% C.I (-10.58, 31.57)).

Table 5. Less reduction in Vitamin D3 Levels during Maintenance Therapy (VDM) in Parenteral (VDTP) Compared to Oral therapy (VDTO) in Patients with Rheumatic Diseases.

Patients (70)	Mean	Mean Difference	SD	P-Value	95% C.I	
VDTO–VDM (45)	73.86 – 46.48	27.38	39.68	< 0.0005	15.46	39.30
VDTP–VDM (25)	84.65 - 74.16	10.49	54.35	0.316	-10.58	31.57

Vitamin D = 25(OH) D3; VDM = Samples tested during maintenance; VDTO = Samples tested after 3 months oral Therapy (Regimen2); VDTP = Samples tested after Parenteral therapy (Regimen1), SD= standard deviation for the mean difference.

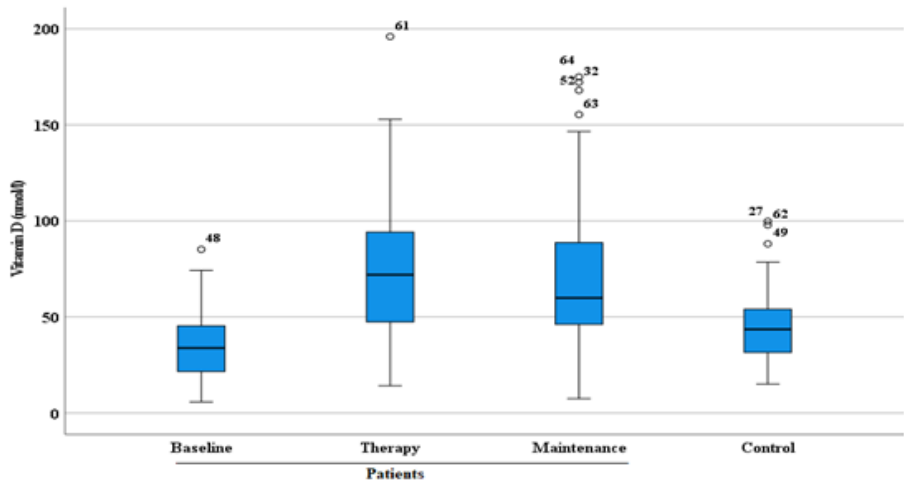
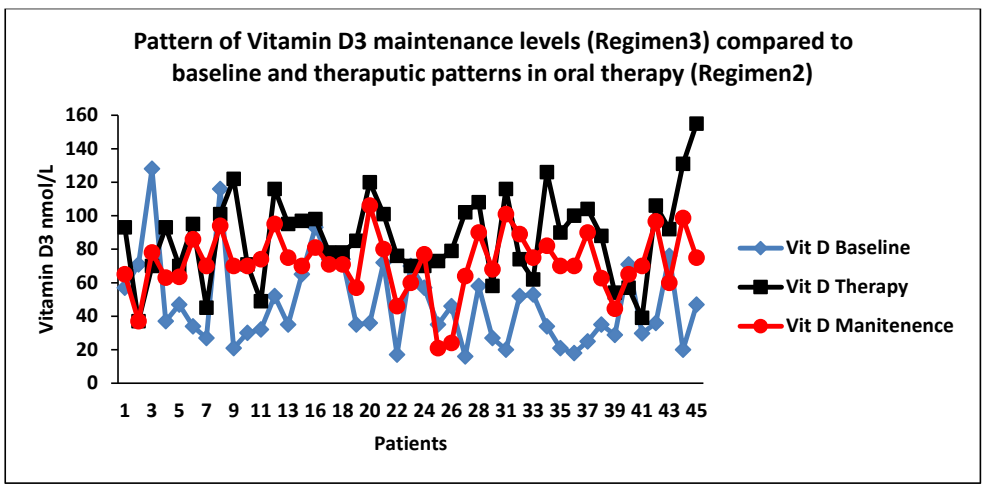
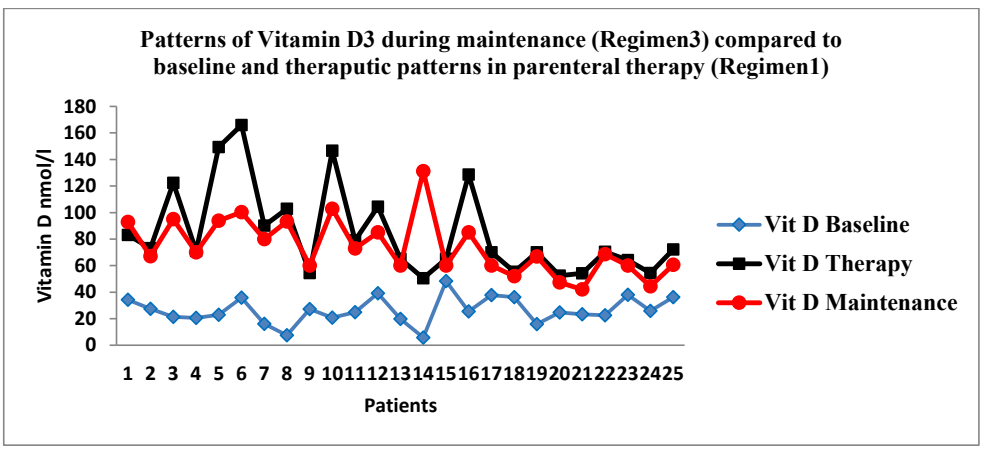


Figure 1. Box plot showed lower vitamin D3 serum concentration among patients (N=70) at baseline compared to controls (N=70). It also depicted vitamin D3 serum concentration before therapy (baseline), after therapy and during maintenance in patient's cohort.

Figure 2a and Figure 2b:



Vit D = Vitamin D3; Regimen2 = Oral capsules of vitamin D3 at a dose of 50.000 IU weekly. Regimen3 = Oral capsules of vitamin D3 at a dose of 50.000 IU 2-4 weekly.



Vit D = vitamin D3; Regimen1 = single Intramuscular injection of vitamin D3 at a dose of 600.000 IU. Regimen3 = Oral capsules of vitamin D3 at a dose of 50.000 IU 2-4 weekly.

Discussion

The deficiency of Vitamin D_3 (25(OH)D_3) is a potentially modifiable risk factor. Vitamin D_3 is an essential hormone-like vitamin that has well-known effects on immunity modulation and is necessary not only for bone but also for other organ systems (Wranicz & Szostak-Wegierek, 2014). There are insufficient data in the Middle East area on the prevalence of vitamin D deficiency among patients with rheumatic diseases (RDs). In Bahrain two studies were published by our group; one in the prevalence of Vitamin D deficiency in SLE and RA patients (Hassan, et al., 2019). However, neither the dose required for achieving optimal serum level nor the dose needed for maintaining it has been identified yet. The present study aimed to study vitamin D status and to evaluate the influence of high doses of vitamin D supplementation on serum 25(OH)D levels in adult patients with RDs and to report the effects of two therapeutic regimens and maintenance regimen of vitamin D_3 on maintaining optimal vitamin D serum levels year-round. we

Our present findings demonstrated that the patient group had lower vitamin D_3 levels than the controls, but higher mean blood calcium levels than the controls. The presence of secondary hyperparathyroidism as a compensatory mechanism for severe and long-term vitamin D insufficiency might explain the development of high mean blood calcium levels. In the current study, the need for vitamin D_3 therapy for any patient was decided based on his baseline of 25(OH)D serum concentrations. Both regimens effectively raised the serum levels in the patient cohort. The inclusion of only seventy patients (out of the total of 158 patients) for the final report because those were the patients who came back for the follow-up after they received the maintenance regimen, which was one of the most important aims of this article.

Among the two therapeutic regimens, Regimen1 was safely and quickly optimized vitamin D serum levels in all 63 patients (100%) who received it and came for follow-up after the first four weeks. Our results showed that Regimen1 led to higher mean serum levels compared to Regimen2. Furthermore, it was safely raised the serum levels to $\geq$75 nmol/l in almost all patients. Our results of the safety and efficacy of the parenteral loading regimen were consistent with a previous study (Schleck et al., 2015). In the current study, although the loading parenteral dose exhibited a long half-life, the steady-state plateau was hard to be attained after one single injection if discontinuation tried or maintenance dose was not given. Thus, when a patient achieved his optimal vitamin D level, only after the single parenteral dose, a maintenance regimen would be started immediately, after four weeks in this regimen. Our results were consistent with a previous study that showed difficulty to achieve a steady state of the corrective vitamin D levels after one year of therapy of 5000 IU a day if discontinuation occurred (Mocanu, & Vieth, 2013). Interestingly, in this group, our results clearly showed that the patients with the lowest vitamin D_3 levels at baseline had the highest increments after therapy. Generally, Regimen1 resulted in an increment of 2.2–10 folds in the baseline serum levels in different individual patients. The highest fold (10 folds) was achieved by a patient who had the lowest baseline level (5.8 nmol/l). On the other hand, the increment for the highest therapeutic levels achieved (166 nmol/l) by patient whose baseline was 35.9 nmol/l was only 4.2 folds. Interestingly, our results were supported by a recent study that tested the effect of single and multiple oral large doses on different levels of 25(OH)D and demonstrated that the lower the baseline levels, the higher the increment (Gowda, Ruwanpathirana, Fong, Kaur, & Renzaho, 2016). The maintenance regimen given to the patients in this group, maintained vitamin D levels close to the previous

optimized therapeutic levels, although mildly dropped in some patients, still, the levels were maintained above 70nmol/l in almost all patients and ≥ 90 in most of the patients. The current results should encourage the rheumatologist to use the parenteral regimen in patients with RDs since higher levels are needed by patients than by healthy subjects. It has been shown that normal vitamin D serum levels in healthy subjects, living in a sunny environment, were between 100-175 nmol/l. Moreover, there were many clinical trials, which showed that the risk for disease with serum 25(OH)D>75 nmol/l was lower than the risk for disease if the serum 25(OH)D was around 53 nmol/l (Vieth, 2011)

In this study, the oral therapeutic regimen with a large dose of 50.000 IU weekly for 12 weeks was effectively elevated 25(OH)D above the deficiency range in all participants. It optimized the levels (>50 nmol/l) in almost all patients (91%). Although this regimen was associated with a 1.5 to 5 folds increase from baseline, a maintenance dose was required at the end of the three months. Our results were consistent with other studies. Stoss therapy (a dose ranges from 100.000-200.000 IU) followed by maintenance oral vitamin D therapy, in children with Cystic Fibrosis who were vitamin D deficient (defined as baseline levels below 75 nmol/L) was effectively achieved and maintained levels of 25-hydroxyvitamin D greater than 75 nmol/L over 12 months (Shepherd et al., 2013). A regimen of high-dose oral cholecalciferol (oral tablet of cholecalciferol 50 000 IU daily for 10 days) was as effective at increasing serum 25(OH)D concentrations at 3 months compared to a longer, low-dose regimen (three tablets of cholecalciferol1000 IU daily). In both groups, ≥ 90% of patients achieved levels of 25(OH)D > 50 nmol/L, and about 60% achieved levels of ≥75 nmol/L, comparable with previous studies (Hackman et al., 2010). Our three months period for the oral therapeutic regimen was also supported by other studies, it was showed that the best increment was achieved by the 12 weeks therapy (Middleton, Stack, Riggs, & Bodenner, 2014).

Regarding the maintenance regimen in this group, the optimal levels were maintained in most of the patients but dropped significantly in a few patients whose levels before maintenance were just at the lower limit of optimal. Although the oral high therapeutic dose is less effective compared to the parenteral dose, still it is more effective than the weekly intermediate dose (10.000 IU) or the daily small therapeutic dose of 1000 IU per day as it has never been shown to be effective in raising serum 25(OH)D (Sainaghi et al., 2012). Furthermore, the massive monthly or bi-monthly oral dose was more convenient and was the best dose to maintain the levels relatively close to the previously optimized therapeutic levels in almost all patients year-round. Our results are consistent with a recent study that showed 50.000 IU vitamin D_3 bimonthly is required to maintain long-term sufficient 25(OH)D levels (Hassan, Hozayen, Alotaibi, & Tayem, 2018; Khawaja et al., 2017). Our results regarding the effectiveness of the larger bolus maintenance dose of 50.000 IU bimonthly in maintaining optimal serum 25(OH) D concentrations and even in some patients to ≥ 75 nmol/l, was inconsistent with other study that showed a higher monthly oral dose of 100.000 IU vitamin D for six months was more effective than a monthly dose of 50.000 IU in achieving serum-25(OH) D≥75 nmol/l (Mazahery, Stonehouse, & von Hurst, 2015). Our current results are also supported by another recent study, which proved that vitamin D_3 loading dose is superior and safe in achieving higher vitamin D concentrations after weight loss surgery in vitamin D deficient morbidly obese patients (Luger et al., 2017).

The present study illustrated those patients with rheumatic diseases are at high risk for vitamin D deficiency and highlighted the importance of the high dosage requirement in

those patient cohorts. Among all patients and with all regimens used in this study; neither hypercalcemia (serum calcium>2.5 mmol/l) nor hypervitaminosis D (serum 25(OH) D >225 nmol/l) were recorded in ~~our~~ patients' cohort, in this perspective our results were consistent with a previous study where no toxicity reported (Binkley, Ramamurthy, & Krueger, 2010). On the other hand, the weekly high dose of cholecalciferol compared to monthly therapy with the same dose was not only safe, effective, and faster in increasing 25(OH)D serum levels, but also associated with a greater improvement of muscular function (Corrado, Rotondo, Cici, Berardi, & Cantatore, 2021). Additionally, low vitamin D is associated with a low rate of one-year remission in patients with early rheumatoid arthritis whose diagnosis was established in winter (Herly et al., 2020). Also, it has been shown that in RA patients a better response to Tocilizumab (anti-IL-6 antibodies) when patients have sufficient serum vitamin D. Tocilizumab and 1,25(OH)2D synergistically suppress IL-17 production and osteoclast differentiation (Kim et al., 2020). Although the correction of hypovitaminosis D may have a beneficial effect on pain perception; moreover, the achievement of an adequate plasma vitamin D concentration obtained with high-dose regimens might evoke immunomodulatory activities of vitamin D and favourably impact disease control. Nevertheless, the current evidence is still not strong enough to support the use of cholecalciferol as a DMARD (disease-modifying antirheumatic drug) in RA, and further studies are required to clarify this issue (Bellan et al., 2020). In psoriasis Low concentrations of 25-hydroxyvitamin D_3 levels are associated with depression severity in men. Thus, further studies should examine whether effective anti-inflammatory treatments or vitamin D_3 supplementation can improve depression outcomes in these patients (Pietrzak et al., 2018). In Bahrain, there was one study that estimated the cumulative vitamin D doses from solar ultraviolet and dietary intakes and compared it to serum 25(OH)D in patients with depression and controls. The study showed that about 80% of the patients with depression and 70% of controls did not receive adequate daily doses of vitamin D (Jahrami et al., 2020).

The evidence for a protective role of vitamin D in COVID-19 is controversial. A final message based on all the practical issues discussed: keep the vitamin D serum concentrations during all the year between 40 and 60 ng/mL (100–150 nmol/L), it is one of the fundamental care to reduce, at least the risk of Respiratory Tract Infections included COVID-19 infection (Cutolo, Paolino, & Smith, 2020). Therefore, to keep such serum levels long-term maintenance therapy is crucial. Normalizing the hypovitaminosis without maintaining it with long-term maintenance therapy will be useless, this fact is supported by a recent study, which showed that among hospitalized patients with COVID-19, a single high dose of vitamin D_3, did not significantly reduce hospital length of stay. Thus, the study did not support the use of a high dose of vitamin D_3 for the treatment of moderate to severe COVID-19 (Murai et al., 2021). Based on the known protective effects of vitamin D in subjects at risk of chronic diseases, including rheumatic diseases high-dose vitamin D supplementation was recommended for such patients to keep the concentration above 50 ng/ml (125 nmol/l) which may substantially reduce the incidence severity of various viral infection including the coronavirus disease 19 (COVID-19) (Grant, Lahore, & Rockwell, 2020). Therefore, the rheumatologists' perspective in the era of coronavirus disease 19 (COVID-19), recommended the potential therapeutic targets for rheumatic patients to be vitamin D therapy in addition to hydroxychloroquine and corticosteroids (Misra, Agarwal, Gasparyan, & Zimba, 2020).

Given the strong links between vitamin D and immune function, muscular function, the severity of pain, disease activity, and depression, vitamin D treatment needs to be re-

evaluated, and further studies of vitamin D supplementation in subjects with RDs are warranted.

Limitation of the study

In general, there were some limitations. The main limitation was that many patients lost to follow-up. Patients did not return to be examined either after receiving treatment or after beginning maintenance. We had 234 patients at first, but only 70 remained, which is still a respectable amount.

Conclusions. A high loading dose of cholecalciferol was needed to correct hypovitaminosis D in patients with RDs. In the current study, among all regimens used, the most valuable, safe and cost-effective dose of vitamin D_3 in raising serum 25(OH)D concentrations was the large bolus dose of 600.000 IU parenterally, followed by a maintenance dose of 50.000 IU every 2-4 weeks. 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. Assessment of serum 25(OH)D level 3-12 months after starting the maintenance regimen was needed to judge the treatment response and to the subsequent vitamin D dosage to maintain 25(OH)D levels on steady-state year-round. Thus, if the maintenance dose stopped at any time, then the maintained optimal level will drop back to the deficient level again, and the patient should immediately be prescribed the therapeutic regimen once more before reassuming the maintenance regimen. The corrected levels before starting the maintenance regimen should be $\geq$70 nmol/l to be able to maintain the levels >75 nmol/l year-round.

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إستراتيجية جرعات العلاج بفيتامين د لمرضى امراض الروماتيزم في البحرين

عنوان قصير: الفعالية الفائقة للعلاج بحقن فيتامين د وأهمية جرعة المداومة

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المُستَخلَص

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الغرض: تقييم حالة فيتامين (د) واستراتيجيه الجرعات لمرضى الروماتيزم ، تهدف الدراسة الحالية إلى تحديد مستويات فيتامين (د) قبل وبعد الحقن بفيتامين د وتقييم التغيرات في مستويات الفيتامين بعد الاستجابة لثلاثة أنظمة مختلفة في المرضى البالغين المصابين بامراض الروماتيزم في البحرين.

الطريقة: تم جمع البيانات بأثر رجعي من 158 مريضاً مصاباً بأمراض الروماتيزم خلال الفترة 2013-2019 في مدينة الملك عبد الله الطبية. وكان متوسط عمر المرضى 45 سنة (من 18 إلى 83 سنة). وكان الثلثان منهم من الإناث 105 (66.5%). المشاركين في الدراسة كانو من المتطوعين البالغين الأصحاء المتطابقين في الجنس والمتوافقين في العمر تم فحص جميع المرضى لمعرفة حالة فيتامين (د) خلال زياراتهم الأولى. تم تقييم ثلاثة أنظمة من العلاج بفيتامين (د). النظام الأول: جرعة واحدة بالحقن 600.000 وحدة دولية. النظام الثاني: جرعة عن طريق الفم من 50.000 وحدة دولية أسبوعيا لمدة 12 أسبوعا ، النظام الثالث:. جرعة المداومة عن طريق الفم كلما حقق المريض المستوى الأمثل.

النتائج: كان لدى المرضى مستويات أقل من فيتامين (د) مقارنه مع الضوابط (قيمه الدلالة = 0.0001؛ وفترة 95% ثقة (3.870 ، 15.599) وكانت هناك زيادة ذات دلالة إحصائية في متوسط مستويات فيتامين (د) بالحقن مقارنة مع العلاج عن طريق الفم. (قيمه الدلالة اقل من 0.0005). هناك زيادة ذات دلالة إحصائية عن مستوى خط الأساس (قيمة الدلالة اقل من 0.0005) لمجموعة المرضى الذين حصلوا على جرعة من فيتامين د. لكن انخفضت مستويات فيتامين (د) عن خط الاساس أثناء الصيانة بقبمة ليست ذات دلالة إحصائية (قيمة الدلالة تساوي 0.0177)

الخلاصة: من خط الأساس استجابةً لأنظمة العلاج بفتامين د وكان بشكل افضل في تم تحقيق الزيادة الكبيرة في مستويات فيتامين د العلاج بالحقن الفردي بمقدار 600.000 وحدة دولية لا بد من مداومه العلاج للحفاظ على المستوى الأمثل على مدار العام ، و الجرعه الافضل للمداومه هي 50.000 وحدة دولية عن طريق الفم كل 2-4 أسابيع.

الكلمات الدالة: فيتامين د، أمراض روماتيزم.