

The role of vitamin-D supplementation in pain relief for adult patient with chronic pain

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ABSTRACT

Background Vitamin D is a fat-soluble vitamin that occurs naturally in the body and has multiple roles from which the anti-inflammatory effect is included. This study investigated whether vitamin D relieves chronic pain and reduces analgesics use.

Methods This research is a randomized open label clinical trial. Oral vitamin-D was the intervention with a dose ranging from 2500-50000 IU; with or without analgesics in patients having chronic pain. Results were obtained based on the comparison between patients received vitamin D alone (VITD), analgesics alone (ANALG), and vitamin D with analgesics (VITDANA).

Results It has been observed that the average baseline of VASAL score in all arms was 5.65 with an average vitamin D level of 42.52 nmol/L. The average VASAL score of ANALG arm continued to be almost the same. While with other arms that reached normal serum vitamin D significantly ($p < 0.01$), VASAL score was significantly reduced in VITD and VITDANA arms ($p < 0.001$). The linear graph's AUC of VITD and VITDANA follow up were significantly ($p < 0.001$) higher than the linear graph of ANALG follow up.

Conclusions This study confirmed that vitamin D has a role in pain relief. VASAL score showed a reliable measure for pain severity in patients suffering from chronic pain. Although several studies showed debating conclusions on vitamin D capacity in reducing pain, yet this study confirmed in a significant manner that vitamin D reduces pain severity in several body sites.

Keywords: Vitamin D, analgesic, chronic pain

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INTRODUCTION

Pain is defined as an unpleasant sensation with actual or potential tissue damage that can range from mild and localized discomfort to severe pain.[1] It is transmitted to the brain as signals by sensory neurons and arises from various situations.[1] Injury or illnesses are examples of major causes of pain, which can arise from part of the tissue to the brain.[1] One of the substances that are released when tissue is injured or inflammation occurs is prostaglandin; which is oxygenated unsaturated cyclic fatty acid formed mainly through the action of cyclooxygenase (COX) enzyme from arachidonic acid, and by inhibiting COX-1 and or COX-2, analgesics suppress the pain.[2] Analgesia is used to describe pain absence in response to stimulations that is normally painful.[3,4] Therefore an analgesic is a medication relieves pain to achieve analgesia; it is known as painkiller such as paracetamol or acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids for severe pain.[3,4]

One of the most common reasons that patients seek medical attention is chronic pain which is defined as pain for 3 month or more, patients with pain experience limitations in mobility and daily activities, opioid dependence, depression and anxiety, poor health and humbled quality of life.[5,6] Centers of disease control and prevention published that in 2016 there were 20.4% of American adults with chronic pain and about 8% of American adults with high-impact chronic pain which is a pain that causes frequent limitations of life or work activities.[7] An epidemiological study of low back pain in Saudi Arabia found that seven cross-sectional studies showed pain prevalence ranging from 53.2% to

79.17%.[8] One of the cross-sectional studies in southwestern Saudi Arabia showed that the prevalence of low back pain requiring medications and or physiotherapy was 40.5%, while 20% of the prevalence with low back pain necessitating medical consultation.[9] Vitamin D is a fat-soluble vitamin that occurs naturally in the body and has multiple roles such as modulation of cell growth, neuromuscular and immune function.[10] Precisely, vitamin D has an anti-inflammatory effect by reducing the release of cytokines, suppressing T-cell responses in the body, inhibiting the synthesis of prostaglandin E2 (PGE2) and thus possibly relieving pain.[11,12] This concept has been supported by a systematic review and meta-analysis that took place in 2016.[13] Additionally, a randomized placebo-controlled trial was made about the efficacy of vitamin D replacement therapy on patients with chronic nonspecific widespread musculoskeletal pain with vitamin D deficiency.[14] Another study investigated the effects of vitamin D supplementation on nonspecific musculoskeletal pain, quality of life, self-related health and sexual satisfaction; exhibited a significant pain relief in vitamin D group after 8 weeks compared with the placebo group.[15]

Vitamin D supplementation in patients with vitamin D deficiency has enhanced the physical function, mental health and patient's quality of life.[16] Likewise, it has a role in cardiovascular protection and well-known osteoporosis prevention as well as reducing the fracture in elderly patients with osteoporosis.[17] Vitamin D supplementation has been always considered safe, however taking high doses for a long period of time without close monitoring of blood levels has a risk of

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experiencing vitamin D toxicity.[18] It is a rare but serious condition, accompanied with the risk of hypercalcemia, a formation of calcium stones and acute kidney injury.[19] On the other hand, Paracetamol or Acetaminophen which is a widely used analgesic and considered always effective, safe and well tolerated in the management of mild-moderate pain, yet it may cause hepatotoxicity as a result of overdosing.[12,20]

Non-steroidal anti-inflammatory drugs or NSAIDs have been used to relieve pain and inflammation by inhibiting cyclooxygenase enzyme and reducing the production of prostaglandin.[21] It is used in the management of mild-to-moderate pain especially in musculoskeletal conditions.[21] The risk of GI complications increases with high doses use of NSAIDs for an extended period of time, patients who used NSAIDs may develop gastric ulcers specifically those who are using multiple NSAIDs concomitantly.[21] Geriatric patients or patients with prior ulcer or bleeding complications are also at increased risk. NSAIDs also have a significant risk in developing acute kidney injury as well.[22]

Opioids or narcotics have been always avoided by clinicians and left to be the last choice for severe or uncontrolled pain because of their risk in dependence, addiction and overdose. [23] It also may cause gastrointestinal adverse effects, hormonal changes, cardiac adverse events and immunological alterations.[23]

Visual analogue scale for pain (VAS-pain) are psychometric measuring instruments made to document the characteristics of disease related pain severity and thereupon accomplish a rapid classification of pain severity and disease control.[24] However VAS pain scale is self-individual interpretation which might not be considered as a measurable scale unless if there is another confirmative pain scale, such as Allina health pain assessment scale which is a tool that is used to determine pain severity score in a detailed descriptive manner [25].

The purpose of this study is to spot the relationship between vitamin D levels and pain relief, and if there is any role for vitamin D as adjunct medication with analgesics.

Objectives and aim:

The primary outcome of this study is to investigate any evidence of vitamin D role in pain relief. While, the secondary outcome is to detect the possibility of decreasing dose and frequency of analgesics use.

METHODS

This is an open label randomized clinical trial conducted in six orthopedic and twelve family medicine clinics in Security Forces Hospital-Riyadh (SFH). Institutional Review Board approval from SFH with a log NO (H-01-R-069). Written bilingual consent was obtained from all participants after they were provided with detailed information about the research. Oral vitamin D was used in patients with chronic pain (more than 3 months). Patients with unstable co-morbidities, cartilage degeneration, dental pain, acute pain caused by trauma, those received vitamin D supplementation in the past 4 months, or who were treated with medications such as oral steroids and opioid were excluded. Stable patients aged 18 or older with chronic pain for three months who had vitamin-D levels below 75 nmol/L were enrolled and allocated to three arms in a simple randomization as vitamin D alone (VITD), analgesics alone (ANALG) or vitamin D with analgesics (VITDANA). Oral vitamin D

with a dose of 2500-50000 IU depending on patient's demands and vitamin D level was given with/without analgesics.

The number of patients screened for eligibility was 351, 190 were ruled out according to the exclusion criteria, the remaining three patients were excluded because of patient's literacy and other reasons (Figure 1). However only 158 patients were enrolled and allocated to the three arms. Of those, only 65 patients completed the study with the full protocol as, 25 patients received vitamin D alone, 8 received analgesics alone and 32 had analgesics and vitamin D.

All patients were assessed at baseline in the first visit; then assessed again every month for four months. Data were collected on an Excel sheet with the following variables: vitamin D levels and a combination of visual analogue scale for pain (VAS-pain) and then investigators verified it by Allina health pain assessment scale (VASAL) to give a solid number classified as; no pain (0), mild (1-3), moderate (4-6), severe (7-9) and worst pain (10). Patients were assessed either by physical attendance or telephone calls, as it is illustrated in **Table 1**.

Table 1: Action plan for patient visits

List of activities	Visit 1 Day 0	Visit 2 1 month	Visit 3 2 month	Visit 4 3 month	Visit 5 4 month
Vitamin D level	✓				✓
VAS-pain scale	✓	✓	✓	✓	✓
Allina Health Pain Scale	✓	✓	✓	✓	✓

Note: Investigators gave one solid number as a combination of VAS-pain and Allina health pain scales (VASAL), a scale was self-established classified from 0-10. The follow up was made on monthly basis giving a total of four follow ups for each patient to confirm VASAL score, analgesics use, compliance on vitamin D supplement and patient's comments. Patient's characteristics and vitamin D level baseline were addressed in the first visit as it is demonstrated in Table 2.

The primary outcome of this study was to prove the role of vitamin D in pain relief. While the secondary outcome is to find the possibility of decreasing the dose and frequency of analgesics use.

Statistical analysis:

This study operated in three arms, patients receiving vitamin D alone (VITD), patients receiving analgesics alone (ANALG), and patients receiving vitamin D with analgesics (VITDANA). Demographic data, vitamin D level and VASAL score data were collected in Excel sheet then transferred to SPSS-25 for analysis. For the primary outcome of this study, the means differences of vitamin D level were calculated at baseline and after four months for the three arms. Moreover, VASAL score along four months was determined in a linear relationship for pain severity, and then Area Under the Curve (AUC) was calculated for all patients, afterwards the mean differences were calculated using ANOVA.

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RESULTS

The outcome analysis was based on 65 patients whom were distributed randomly in three groups with similar baseline demographics and laboratory characteristics (Table 2). In general, 66% were females, the average BMI of all subjects was 30.57 (StDev ± 7.07). This study showed 48% patients had lower limb pain, 12% had upper limb pain, 15% had neck, back or hip pain and 25% had general pain. At baseline, VASAL score was addressed for all patients as 18.5% had pain score of 7, which was considered severe.

In this study, all three arms: VITD, ANALG, and VITDANA had an average baseline VASAL score of 5.6 (StDev ±0.5) as shown in Figure 2. While, the mean baseline serum vitamin D level of all arms was 42.53 nmol/L, as demonstrated in figure 3.

During follow up, a conspicuous reduction with VASAL score was demonstrated with the use of VITD and VITDANA arms, showing a markedly significant reduction ($p < 0.001$), with a difference of 3 scores for both arms. While, ANALG arm had no significant effect on VASAL score reduction. This arm sustained to be almost the same along with minor decline compared with the initial score during all four follow ups.

In comparison to the final vitamin D levels, both arms taking vitamin D were highly significant ($p < 0.001$) illustrating a remarkable increase in averages: 111.31 nmol/L of VITDANA arm and 98.72 nmol/L of VITD arm. What's more, serum vitamin D average of ANALG arm was still below normal ranges (< 75 nmol/L) perceived to be slightly higher with no significant change by the last follow up ending at 57.81 nmol/L.

In order to rely more on the same data, the area under the curve (AUC) of each patient in the three arms was calculated. It was found that the average AUC for VITD patients was 5.19 (StDev ± 2.8; SE= 0.56). While, the average of AUC for VITDANA patients was 6.43 (StDev ± 4.8; SE= 0.8).

These data of the two arms was found to be very significant ($p < 0.001$) compared with the third arm (ANALG) where the AUC was 0.95 (StDev ± 1.6; SE 0.53).

DISCUSSION

Vitamin D has eight mechanisms of action to describe the relationship between vitamin D deficiency, pain and inflammatory process, one of these mechanisms is inhibiting cyclo-oxygenase 2 expression in that which influences prostaglandin action [26]. This study was conducted on 65 patients of 66% were females, the average BMI of all subjects was 30.57 (StDev ± 7.07), 48% patients had lower limb pain, 25% had general pain, 15% had neck, back or hip pain, and 12% had upper limb pain. This is similar to previous founding that there was a strong association between vitamin D deficiency and lower back pain [27]. Therefore, it is expected that the severity of pain could have a correlation with patients having vitamin D deficiency.

In this study, Vitamin D levels baseline were almost similar in all three arms, which was below the standard level (75 nmol/L) in all patients included. Some patients were having vitamin D insufficiency (50 - 75 nmol/L) while the majority had vitamin D deficiency (< 50 nmol/L) accompanied by more severe symptoms like pain. At the end of the study, the two arms received vitamin D supplements with a dose of (2500 – 50000 IU) showed a significant increment in vitamin D level ($p < 0.001$), yet in ANALG arm (whom did not receive vitamin D

supplements) showed that vitamin D level was still below normal ranges (< 75 nmol/L) and observed to be slightly higher with no significant change.

There are several studies investigating the relationship between vitamin D and pain severity. A study showed that vitamin D level and pain severity were not correlated [28]. Contrarily, others showed a significant negative correlation between vitamin D levels and pain severity [29,30]; which is the same founding of this study. Vitamin D level at the baseline was low as it was associated with pain severity, but vitamin D level of the two arms taking vitamin D supplements became normal corresponding to the action of vitamin D supplements which resulted in reducing pain severity.

Vitamin D induces pain relief in patients with musculoskeletal pain who have low vitamin D levels [31]. In contrast, a study showed that low vitamin D levels are not associated with diffuse musculoskeletal pain even with vitamin D level repletion [32]. However, this study exhibited that vitamin D could have analgesic effect by itself or maybe used as adjunct therapy to relieve the pain. Patient were divided considering their site of pain to upper limb (shoulder, arm, elbow, wrist, hand), lower limb (thigh, knee, leg, ankle, foot), neck hip or back, and generalized pain. According to the site of pain, pain severity and vitamin D levels were compared, demonstrating that vitamin D supplements reduce pain severity in all pain sites as well as vitamin D level elevation.

A combination of visual analogue scale (VAS) and Allina health assessment scale (shortened as VASAL) was used to measure pain severity of all participants in this study. All three arms started with moderate pain scores (4-6). During follow up, patients expressed their satisfaction with the use of vitamin D supplements which was reflected in pain relief, also patients reported that the need of analgesics use was reduced and thus frequency was degraded.

Regarding ANALG arm follow up, the mean VASAL score showed pain consistency in relation to baseline, it has been also noticed that patients started having drug intolerance and subsequently they require higher doses or demand adding on new analgesics. On the other hand, both arms VITD and VITDANA mean VASAL score at baseline were moderate and accordingly their daily tasks were disturbed. Nevertheless along with vitamin D supplementation course, their pain decreased markedly to mild; described as the feeling of discomfort, which was rarely noticed, besides that accomplishing daily activity was easier.

The findings of this study, that pain had been reduced significantly after the utilization of vitamin D supplements, was supported with several studies not on site of pain only but it exceeded to the musculoskeletal pain, myalgia, arthritis and even pain in breast cancer patients [33–35]. It is suggested that measuring pain severity could be expressed by using pain scale such as VAS [36], where this study used VASAL for better expression to measure patients suffering from pain.

To confirm the results of this study, investigators calculated the area under the curve (AUC) along the four follow ups for all patients of the three arms. It was found that the AUC for all patients receiving Vitamin D with or without analgesics (VITD and VITDANA) were significantly higher than the AUC for patients receiving analgesics only (ANALG). To the extent of our knowledge, this is the first experience measuring AUC to prove that

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vitamin D has an effective analgesic action to reduce the pain severity of patients with chronic pain included in this study.

This study proved that vitamin D could have an analgesic action or perhaps the analgesic action followed vitamin D repletion in patients with vitamin D insufficiency or deficiency. Therefore, the anti-inflammatory mechanism of action for vitamin D is not clear. Thusly, it is recommended that all patients should have their vitamin D assessed and accordingly decide whether vitamin D supplements would be given.

CONCLUSION

This study confirmed that vitamin D has a role in pain relief; it had been shown that whenever patients with vitamin D deficiency or insufficiency, pain will be relieved after receiving vitamin D supplements. VASAL score showed a reliable measure for pain severity in patients suffering from chronic pain. Although several studies showed debating conclusions on vitamin D capacity in reducing pain, yet this study confirmed in a significant manner that vitamin D reduces pain severity in several body sites.

Limitations

This study went for more than 6 months to execute the methodology part, yet investigators appreciated interacting with all participants. However there are some limitations that could have played a role in enhancing patient's withdrawal from this project as following; patient's literacy as having some doubts about vitamin D supplements. Patient's culture represented a barrier during follow up, although most of the investigators were females, yet some female patients could not be reached. Patient's recruitment was the most difficult part in clinical research; this difficulty became more complicated with four months duration. Lastly, this project was carried on with no sponsorship to the extent that investigators found difficulty in vitamin D level follow up.

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Conflict of interest

Authors assure that there is no conflict of interest rising from carrying this project.

REFERENCE

1. Moayedi M and Davis K D 2013 Theories of pain: From specificity to gate control *J. Neurophysiol.* **109** 5-12
2. Hamberg M and Samuelsson B 1973 Detection and isolation of an endoperoxide intermediate in prostaglandin biosynthesis. *Proc. Natl. Acad. Sci. U. S. A.* **70** 899-903
3. Kumar K H and Elavarasi P 2016 Definition of pain and classification of pain disorders *J. Adv. Clin. Res. Insights* **3** 87-90
4. Kawabata A 2011 Prostaglandin E2 and pain - An update *Biol. Pharm. Bull.* **34** 1170-3
5. Gallacher H B B C V V R C D 2019 Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment *Rev. Med. Suisse* **15** 1488-95
6. Andersson H I, Ejlertsson G, Leden I and Scherstén B 1999 Musculoskeletal chronic pain in general practice: Studies of health care utilisation in comparison with pain prevalence *Scand. J. Prim. Health Care* **17** 87-92
7. Dahlhamer J M, Lucas J, Zelaya C, Nahin R, Mackey S, Debar L, Kerns R, Von Korff M, Porter L and Helmick C 2018 Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016 *Morb. Mortal. Wkly. Rep.* **67** 1001-6
8. Awaji M 2016 Epidemiology of Low Back Pain in Saudi Arabia *J. Adv. Med. Pharm. Sci.* **6** 1-9
9. Alnaami I, Awadalla N J, Alkhairy M, Alburidy S, Alqarni A, Algarni A, Alshehri R, Amrah B, Alasmari M and Mahfouz A A 2019 Prevalence and factors associated with low back pain among health care workers in southwestern Saudi Arabia *BMC Musculoskelet. Disord.* **20** 1-7
10. Franco A S, Freitas T Q, Bernardo W M and Pereira R M R 2017 Vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases *Med. (United States)* **96**
11. 1VA Medical Center, Department of Medicine and Dermatology, University of California S and Francisco, San Francisco, CA 94121 U 2012 Vitamin D Metabolism, Mechanism of Action, and Clinical Applications *Bone* **23** 1-7
12. Helde-Frankling M and Björkhem-Bergman L 2017 Vitamin D in pain management *Int. J. Mol. Sci.* **18** 1-9
13. Wu Z, Malihi Z, Stewart A W, Lawes C M M and Scragg R 2016 Effect of vitamin D supplementation on pain: A systematic review and meta-analysis *Pain Physician* **19** 415-27
14. Yilmaz R, Salli A, Cingoz H T, Kucuksen S and Ugurlu H 2016 Efficacy of vitamin D replacement therapy on patients with chronic nonspecific widespread musculoskeletal pain with vitamin D deficiency *Int. J. Rheum. Dis.* **19** 1255-62
15. Peyman Mottaghi, Maryam Miraghajani H H and R S A Effects of Vitamin D Supplementation on Nonspecific Musculoskeletal Pain, Quality of Life, Self-Related Health and Sexual Satisfaction: A Randomized Control Trial **17**
16. Manoy P, Yuktanandana P, Tanavalee A, Anomasiri W, Ngarmukos S, Tanpowpong T and Honsawek S 2017 Vitamin D supplementation improves quality of life and physical performance in osteoarthritis patients *Nutrients* **9** 1-13
17. Ramly M, Ming M F, Chinna K, Suboh S and Pendek R 2014 Effect of Vitamin D supplementation on cardiometabolic risks and health-related quality of life among urban premenopausal women in a tropical country - A randomized controlled trial *PLoS One* **9** 8-10
18. Marcinowska-Suchowierska E, Kupisz-Urbanska M, Lukaszkiwicz J, Pludowski P and Jones G 2018 Vitamin D Toxicity a clinical perspective *Front. Endocrinol. (Lausanne)*. **9** 1-7
19. Wani M, Wani I, Banday K A M The other side of vitamin D therapy: a case series of acute kidney injury due to malpractice-related vitamin D intoxication.
20. Palmer H, Graham G, Williams K and Day R 2010 A Risk-Benefit Assessment of Paracetamol (Acetaminophen) Combined with Caffeine *Pain Med.* **11** 951-65
21. Fendrick A M and Greenberg B P 2009 A review of the benefits and risks of nonsteroidal anti-inflammatory drugs in the management of mild-to-

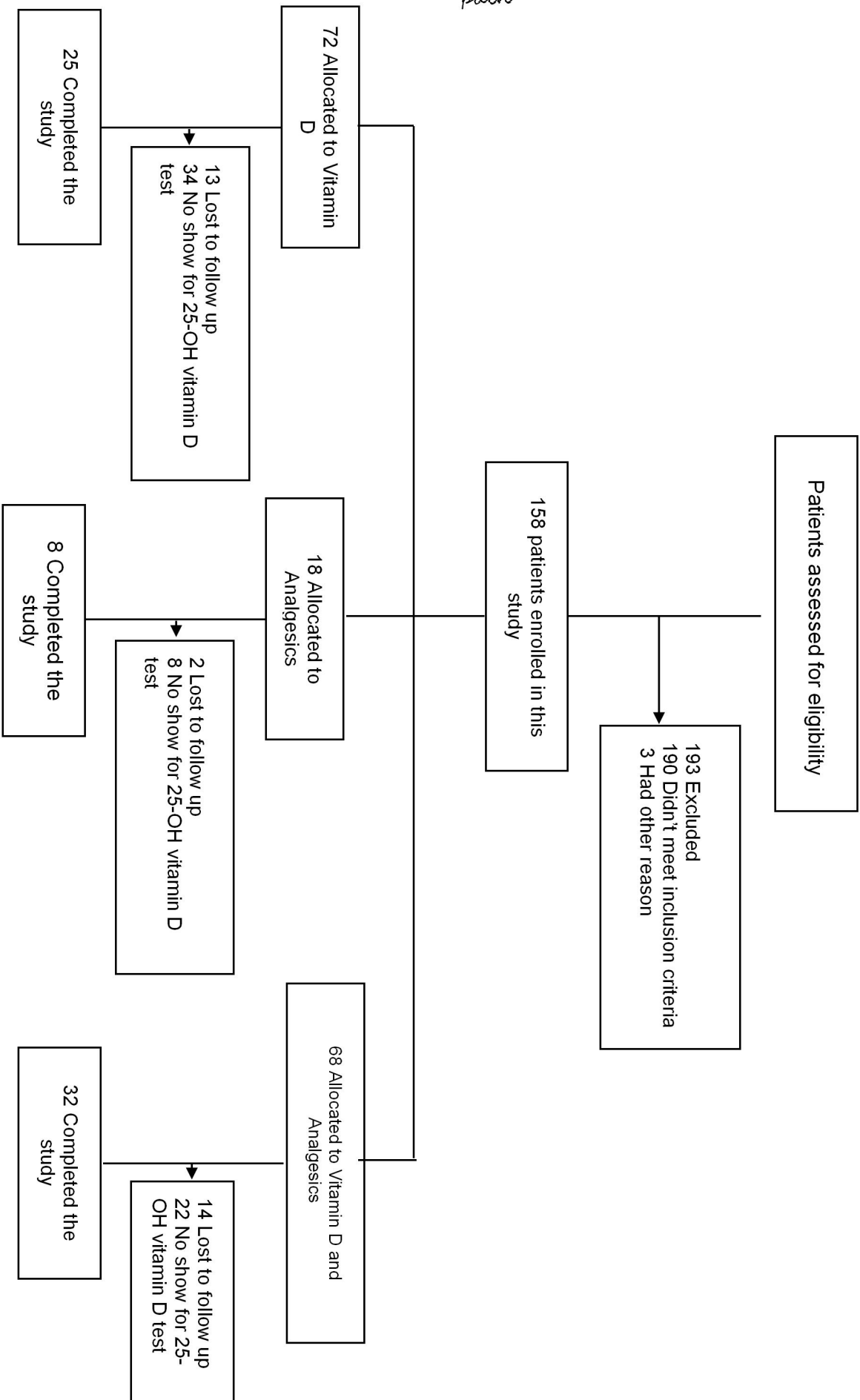
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moderate osteoarthritis *Osteopath. Med. Prim. Care* **3** 1-7

1457-9

22. Dixit M, Doan T, Kirschner R and Dixit N 2010 Significant acute kidney injury due to non-steroidal antiinflammatory drugs: Inpatient setting *Pharmaceuticals* **3** 1279-85
23. Khademi H, Kamangar F, Brennan P and Malekzadeh R 2016 Opioid therapy and its side effects: A review *Arch. Iran. Med.* **19** 870-6
24. Klimek L, Bergmann K C, Biedermann T, Bousquet J, Hellings P, Jung K, Merk H, Olze H, Schlechter W, Stock P, Ring J, Wagenmann M, Wehrmann W, Mösges R and Pfaar O 2017 Visual analogue scales (VAS) - Measuring instruments for the documentation of symptoms and therapy monitoring in case of allergic rhinitis in everyday health care *Allergo J.* **26** 36-47
25. Allina Health's Patient Education Department experts No Title *01/15/2011*
26. Shipton E A and Shipton E E 2015 Vitamin D and pain: Vitamin D and its role in the aetiology and maintenance of chronic pain states and associated comorbidities *Pain Res. Treat.* **2015**
27. Zadro J, Shirley D, Ferreira M, Carvalho-Silva A P, Lamb S E, Cooper C and Ferreira P H 2017 Mapping the association between vitamin D and low back pain: A systematic review and Meta-Analysis of observational studies *Pain Physician* **20** 611-40
28. Ghai B, Bansal D, Kapil G, Kanukula R, Lavudiya S and Sachdeva N 2015 High prevalence of hypovitaminosis D in Indian chronic low back patients *Pain Physician* **18** E853-62
29. Lotfi A, Abdel-Nasser A M, Hamdy A, Omran A A and El-Rehany M A 2007 Hypovitaminosis D in female patients with chronic low back pain *Clin. Rheumatol.* **26** 1895-901
30. Johansen J V, Manniche C and Kjaer P 2013 Vitamin D levels appear to be normal in Danish patients attending secondary care for low back pain and a weak positive correlation between serum level Vitamin D and Modic changes was demonstrated: A cross-sectional cohort study of consecutive patients wit *BMC Musculoskelet. Disord.* **14**
31. Ellis S D, Kelly S T, Shurlock J H and Hepburn A L N 2018 The role of vitamin D testing and replacement in fibromyalgia: a systematic literature review *BMC Rheumatol.* **2** 1-8
32. Warner A E and Arnsperger S A 2008 Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D *J. Clin. Rheumatol.* **14** 12-6
33. Schreuder F, Bernsen R M D and van der Wouden J C 2012 Vitamin D supplementation for nonspecific musculoskeletal pain in non-western immigrants: A randomized controlled trial *Ann. Fam. Med.* **10** 547-55
34. Gendelman O, Itzhaki D, Makarov S, Bennun M and Amital H 2015 A randomized double-blind placebo-controlled study adding high dose Vitamin D to analgesic regimens in patients with musculoskeletal pain *Lupus* **24** 483-9
35. Ghai B, Bansal D, Kanukula R, Gudala K, Sachdeva N, Dhatt S S and Kumar V 2017 Vitamin D supplementation in patients with chronic low back pain: An open label, single arm clinical trial *Pain Physician* **20** E99-105
36. Holick M F 2003 Mayo Clinic Proceedings. Vitamin D Deficiency: What a Pain It Is *Mayo Clin. Proc.* **78**

Figure 1. Patient's enrollment and disposition.



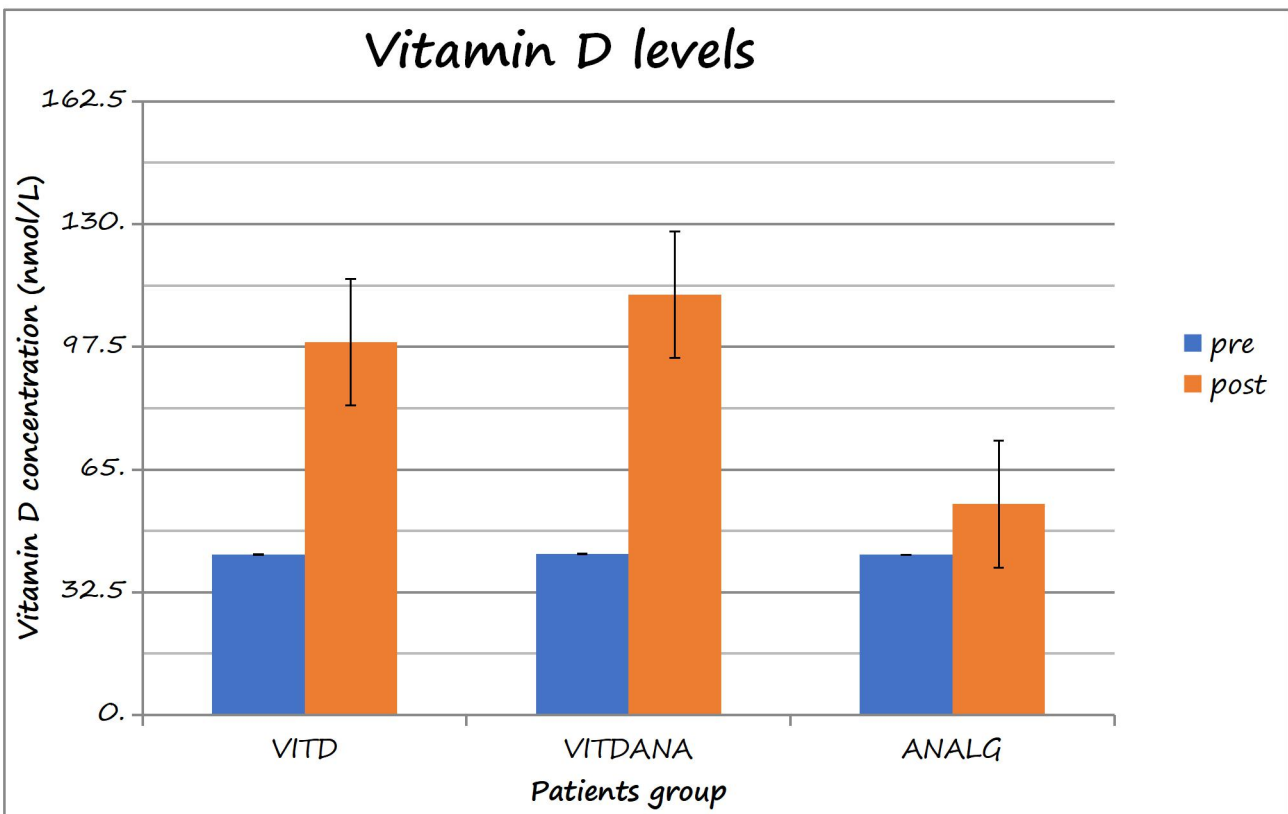
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Table 2. Patients demographics data and vitamin D level baseline n=65

		VITD*	ANALG**	VITDANA***
Average age		34.12	44.25	41.41
StDev		13.1	8.22	12.37
Average BMI		30.28	30.04	31.41
StDev		6.78	4.02	7.96
Vit.D Level Pre		42.49	42.42	42.68
StDev		39.76	9.50	48.53
Gender	Male	8	4	10
	Female	17	4	22
Number of subject		25	8	32

Note: *VITD: vitamin D alone arm, **ANALG: analgesics alone arm, ***VITDANA: vitamin D and analgesics arm.

Figure 2. Vitamin D level (nmol/L, ± Std Err) for all subjects in the three arms at the baseline (first visit) and at the end of



the study (after 4 months).

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Figure 3. The action of vitamin D on pain severity using VASAL score (± StDev) for 4 months follow up, through VITD and VITDANA compared with ANALG. The figure showed also the linearity of each arm along with their linear equation.

