ABSTRACT

BACKGROUND: 1,25 dihydroxycholecalciferol, the active form of vitamin D3 is known to play an important role in mineralization. Vitamin D3 is also known to have immune-supporting properties by regulating various cytokines and cell signalling pathways.

AIM: To review the role of 1,25-dihydroxycholecalciferol (Vitamin D3) on the rate of Orthodontic tooth movement.

METHODS: This study applied a systematic review to analyse the current literature to define and summarise the role of 1,25-dihydroxycholecalciferol on the rate of Orthodontic tooth movement. A comprehensive search was done using electronic databases such as PubMed Central, Cochrane Database of Systematic Reviews, Google Scholar, EMBASE and direct web search. The title scan was done to identify relevant articles which are further evaluated for inclusion by reading the abstract.

RESULTS: The electronic database search identified 28 articles. 3 articles were selected based on the selection criteria to meet the research question. There was about 60% faster rate of orthodontic tooth movement when a dosage of 40-50 pg/dl of 1,25 dihydroxycholecalciferol was supplemented. Administration of 1,25-dihydroxycholecalciferol showed no deleterious effects to the tooth roots or the surrounding tissues as evidenced from the periapical radiographs and CBCT.

CONCLUSION: Based on the collected data, the local administration of an active form of Vitamin D3, 1,25-dihydroxycholecalciferol can act as an effective supplement to accelerate Orthodontic Tooth Movement (OTM).

KEYWORDS: Orthodontic tooth movement, Vitamin D3, duration of treatment, local application.

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INTRODUCTION

Orthodontics in the treatment of malocclusion though developed greatly in terms of biomechanics, the treatment duration has always been a great concern to the clinician as well as the patient. \cite{1} Numerous trials have been done to decrease the treatment time by biological, biomechanical, physical, and surgical options.\cite{2-5} The principal trigger for orthodontic tooth movement is the strain of the periodontal ligament cells, bone-related cells, and the extracellular matrix. This strain eventually leads to changes in cell signaling pathways.\cite{6} Though various methods are available to achieve accelerated orthodontic tooth movement, there is a decrease in patient compliance with the surgical methods due to the invasive procedures involved. Numerous animal studies have evaluated the effect of biological substances on the rate of orthodontic tooth movement by targeting these cell signaling pathways. Various biological substances like prostaglandins, human relaxin hormone, Vitamin D, Vitamin C, and platelet-rich plasma were used and were shown to have positive results on accelerated orthodontic tooth movement. \cite{7-10} Vitamin D, though mainly known for its mineralization and maintenance of tissue integrity, is also known to have immune action by regulating various cytokines and cell signaling pathways. Previous literature reveals that Vitamin D administration during orthodontic tooth movement [OTM] stimulated the rate of osteoclast formation and active bone resorption, thereby increasing the rate of orthodontic tooth movement. The circulating metabolite 1,25-dihydroxycholecalciferol binds the vitamin D receptor and modulates inflammatory cytokine production.\cite{11,12}

Vitamin D3 has recently attracted the attention of various investigators as to whether it can bring about accelerated OTM and studies done so far have yielded promising results. Only a limited number of human trials have been reported in the literature about the role of Vitamin D on Orthodontic tooth movement. The present systematic review was carried out to evaluate the role of Vitamin D on the rate of Orthodontic tooth movement and to critically analyze the supplementation dosage and the effectiveness of Vitamin D on the rate of Orthodontic tooth movement.

MATERIALS AND METHODS

Protocol Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement.

SEARCH STRATEGY AND ELIGIBILITY CRITERIA:

Electronic databases including PUBMED, PubMed Central, Cochrane Database of Systematic Reviews, Google Scholar, EMBASE, and Direct web search up to June 2022 were performed. Key words were customized for each database and have been mentioned in Table 1.
Databases | Keywords
--- | ---
PUBMED | “Vitamin D” AND “Orthodontic Tooth Movement” AND “Humans”
Cochrane Database of Systematic Reviews | “Vitamin D” AND “Orthodontic Tooth Movement”
Google Scholar | “Vitamin D” AND “Orthodontic Tooth Movement”

**Table 1. Table showing the search strategy keywords customized for each database**

Initially, titles and abstracts of all studies identified through search strategies were screened by two independent authors (SS and SM) and irrelevant studies were excluded based on eligibility criteria. Full texts were then procured for the articles which fulfilled the inclusion criteria mentioned below. The reference lists of the identified articles were also hand searched for additional relevant studies. Bibliographies of the included full text articles were scanned for relevant studies. No restrictions were done on the language or date of publication when searching the electronic databases. PICO analysis for this review is mentioned in Table 2.

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients undergoing <strong>Fixed Orthodontic Treatment</strong></td>
<td>Animal Trials, Invitro studies, Patients undergoing treatment with removable appliances, Patients with systemic diseases,</td>
</tr>
<tr>
<td>Intervention</td>
<td>Patients undergoing Fixed Orthodontic Treatment <strong>with Vitamin D administration</strong></td>
<td>Use of other local factors</td>
</tr>
<tr>
<td>Comparison</td>
<td>Patients undergoing Fixed Orthodontic Treatment <strong>without Vitamin D administration</strong></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Rate of Orthodontic Tooth Movement Duration of Orthodontic Treatment</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Table showing the PICO analysis used for study selection**
ELIGIBILITY CRITERIA

Eligibility criteria for this review are mentioned in Table 2.

Study selection

Two authors (SS and SM) performed the search independently employing the search strategy mentioned (Table 1). Eligibility criteria mentioned (Table 2) was used to screen the studies and any disagreements regarding study selection were resolved by mutual discussion by the two authors.

Data collection process

All studies meeting the selection criteria were included in the review. The selection process of included studies is depicted in the PRISMA flow chart (Figure 1). Data required for analysis were extracted by both reviewers (SS and SM) independently. A table (Table 3) for describing the ‘Study characteristics’ of the included articles was made that included the following information: first author, year of publication, type and study design, sample size, age, gender, ethnicity, case selection criteria used, dosage, route of administration, outcome and limitations. Any (SS and SM) disagreements between the reviewers regarding data collection was handled by mutual discussion until a consensus was achieved. Any disagreements that remained were resolved by conversation with a third reviewer (PR).

<table>
<thead>
<tr>
<th>Sl.No.</th>
<th>Author/Year</th>
<th>Type of Study</th>
<th>Age/Gender</th>
<th>Sample/Ethnicity</th>
<th>Case Selection Criteria</th>
<th>Dosage/Route of Administration</th>
<th>Outcome</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Al-Hasani et al/2011</td>
<td>RCT (Split Mouth trial)</td>
<td>17-28 years/Not specified</td>
<td>4/Iran</td>
<td>Angle’s Class I, Class II malocclusion, 1st premolar extraction cases</td>
<td>3 Groups Group 1: 15pg/dl Group 2: 20pg/dl Group 3: 40pg/dl/ Local</td>
<td>Treatment duration decreased by 12 wks.</td>
<td>Small Sample Size</td>
</tr>
<tr>
<td>2</td>
<td>Ciur et al/2016</td>
<td>Prospective Clinical Trial (Split Mouth)</td>
<td>13-34 years/3 male, 3 female</td>
<td>6/France</td>
<td>Angle’s Class I, Class II malocclusion, 1st premolar extraction cases</td>
<td>42pg/ml per week for 3 weeks duration/ Intraligamentary</td>
<td>Treatment duration decreased by 3 months. No root resorption seen.</td>
<td>Small sample size, Age Criteria not selected properly</td>
</tr>
<tr>
<td>3</td>
<td>Varughese et al/2019</td>
<td>RCT</td>
<td>15-30 years/Not specified</td>
<td>15/India</td>
<td>Angle’s Class I, Class II malocclusion, 1st premolar extraction cases</td>
<td>50pg/0.2 ml per month for 3 months/ Intraligamentary</td>
<td>Treatment Duration decreased by 12 weeks.</td>
<td>Small Sample Size. Only Maxillary Arch was considered.</td>
</tr>
</tbody>
</table>

Table 3. Table showing the study characteristics of the included studies
Figure 1: Showing PRISMA flowchart for study selection

Review outcomes

The outcomes assessed in this review were rate of orthodontic tooth movement and the duration of orthodontic treatment with and without Vitamin D administration in patients undergoing orthodontic treatment. All the outcomes are mentioned in table 2.

Risk of Bias

The Cochrane risk of bias 2 (RoB2) tool was used for assessment of the risk of bias across the studies. The tool assesses risk of the included studies based on five domains: bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results. Two authors (SS and MY) performed the risk of bias independently and a third author (PR) was consulted for resolving any disagreements.
Quality Assessment and Level of Evidence

The quality assessment of the selected articles was checked using SPIRIT guidelines for Randomized Control Trials. Two studies are under Level 1 evidence whereas the other study came under Level 2 evidence. The quality of the evidence for the outcome was rated by two reviewers (SS and MY). Any disagreements between the reviewers (SS and MY) were resolved by the third author (PR). The results of the quality assessment are given in Table 4.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Title &amp; Abstract</th>
<th>Introduction</th>
<th>Methods</th>
<th>Participants</th>
<th>Intervention</th>
<th>Sample Size</th>
<th>Statistics</th>
<th>Randomization</th>
<th>Blinding</th>
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<th>Discussion</th>
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<td>Ciur et al 2016</td>
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<td>Varughese et al 2019</td>
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<td></td>
<td>Good</td>
</tr>
</tbody>
</table>

Table 4. The Quality Analysis of The Included Studies Using SPIRIT Guidelines

RESULTS

The electronic search identified a total of 28 studies. No studies were available from the database of EMBASE and manual search. After removal of duplicates and title screening there were a total of 14 articles, which were then subjected to further screening. After abstract scanning, a total of 11 were irrelevant and were excluded. Full text of 3 studies were retrieved and screened for eligibility criteria. The results of the search are illustrated in the PRISMA flow chart (Figure 1). A total of 25 participants were involved and all of them were treated with Vitamin D (Table 3).

RISK OF BIAS OF THE INCLUDED STUDIES

Results of risk of bias for included studies are presented in Figure 2 and Figure 3. When there was one confounding factor/ bias found, it was considered a low risk of bias whereas when there was more than one confounding factor/bias involved, it was considered as a high risk of bias. The overall assessment for the risk of bias for the selected articles was evaluated using RevMan5.4 and the risk of bias was low indicating a good experimental study design.
Role of 1,25 dihydroxycholecalciferol on the rate of orthodontic tooth movement

All the studies (100%) showed an increase in tooth movement with Vitamin D administration. The rate of tooth movement was found to be 60% higher when Vitamin D was administered (Fig 4).
Figure 4: Graph showing the rate of orthodontic tooth movement with and without Vitamin D administration.

Role of 1,25 dihydroxycholecalciferol on the duration of orthodontic treatment.

67% of the studies showed a decrease in treatment duration up to 12 weeks with Vitamin D administration. 33% of the studies showed a decrease in treatment duration up to 6 weeks with Vitamin D administration. 60% of the studies showed rapid tooth movement when Vitamin D was administered in the range of 40-50 pg/dl (Fig 5).

Figure 5: Graph showing the reduction in treatment duration with Vit.D administration.
DISCUSSION

Biological approaches to enhance Orthodontic Tooth Movement (OTM) include molecules of Prostaglandin (PG), Interleukin (IL), Receptor activator of nuclear factor kappa B ligand (RANK & RANKL), Osteoprotegerin (OPG), Vitamin D, Parathormone (PTH) and Relaxin. Numerous animal studies have been done with these molecules or their combination and have been successful. However, direct inference of information derived from animal experiments to human clinical settings may not be made. Hence, this systematic review evaluated whether locally administered biological substances such as Vitamin D had a role in OTM in humans.

The methods of achieving accelerated orthodontic tooth movement can be broadly divided into three based on the level of invasiveness- Conservative methods, Surgical methods, and Combined methods. The conservative methods include the use of pharmacological agents, physical stimuli and the use of clear stimuli, and self-ligating brackets. The surgical methods include corticotomy, periodontally accelerated osteogenic orthodontics, piezo incision, and micro-osteoperforations. Though many methods are available, patient compliance is achieved with conservative methods due to their non-invasive nature. The pharmacological methods to accelerate orthodontic tooth movement include the use of agents such as growth hormone, parathormone, vitamin D, thyroxine, and beta 2 adrenergic receptor agonists.

The action of Growth Hormone is based directly on increases in the proliferation and differentiation of osteoblasts, as well as on induction of protein synthesis and mineralization. However, studies have found that Growth Hormone reduces the synchronization between resorption and bone apposition and cannot be considered a method of high potential clinical relevancy.

Administration of parathormone results in the proliferation of osteoblasts and, with the participation of the RANK ligand, osteoclast activation. Depending on the frequency of administration, parathormone may stimulate bone formation (intermittent therapy) or its resorption (exposure longer than 1–2 years). However, Long-term research on the superiority of this method over the other methods is required.

Administration of thyroxine increases bone remodeling and stimulates resorption, which contributes to a decrease in bone density. This occurs due to the increased concentration of interleukin 1 (IL-1), which stimulates the formation of osteoclasts and the resorption process. Animal studies have confirmed accelerated tooth movement after administration of thyroxine.

Molecular and cellular events during OTM can be divided into two main phases, a catabolic phase and an anabolic phase. Osteoblasts are known to have a role in osteoclast formation through cell to cell contact, ephrin2/ephB4, MSF/MCP-1, OPG/RANKL/RANK, LGR4/RANKL/RANK, Sema3A/Nrp and Lysophosphatidic acid. Osteoclast apoptosis can be induced by osteoblasts. Also, osteoclasts are known to have a role in bone formation through Atp6v0d2, complement component 3a, Semaphorin 4D, Sclerostin and also through microRNAs and exosomes.
Other animal studies have assessed the role of various biological substances such as prostaglandins, human relaxin hormone, Vitamin C, Vitamin D and platelet-rich plasma on the rate of OTM and have shown good results. Prostaglandins (PG) were the most evaluated biological agents for accelerated OTM. Studies with human relaxin hormone (HRH) showed a decreased periodontal ligament organization in rats but yielded conflicting results in terms of its effects on OTM. Previous studies have also shown that Vitamin C and platelet-rich plasma (PRP) can increase the rate of OTM in animal models. Other pharmacological agents like denosumab and odanacatib are also known to have a role in osteoblast-osteoclast interaction but are not studied in relation to orthodontic tooth movement. However, most of these studies are done on animals and this cannot be applied directly to Human scenarios.

Vitamin D was found to be the most significant in OTM acceleration as they stimulate both osteoclasts and osteoblasts. All the included studies (100%) showed accelerated tooth movement with Vitamin D administration. This could be because when Vitamin D is at normal levels, it binds to the Vitamin D receptor (VDR) in mature osteoblasts and decreases the receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) ratio, thus leading to reduction of osteoclastic bone resorption. Also, Vitamin D acts in mature osteoblasts and increases the bone formation rate. However, when Vitamin D is administered, there will be an increase in Vitamin D levels, and this will act on less-mature osteoblasts elevating the RANKL/OPG ratio and increasing the rate of osteoclastic bone resorption. Hence administration of Vitamin D during Orthodontic treatment can accelerate tooth movement. The effects of Vitamin D on bone turnover also depend on the stage of osteoblast differentiation.

An average fixed Orthodontic appliance treatment takes about 18-24 months including 6 months of canine retraction phase or space closure phase. So accelerated orthodontics is gaining interest from various researchers to reduce the overall treatment duration. Studies showed that there is a significant rate of Canine distalization and cancellous bone density in patients administered with 1,25-dihydroxycholecalciferol. Based on the present analysis, administration of 1,25-dihydroxycholecalciferol can reduce the period of canine retraction by about 6 weeks which clinically means a reduction of 2 to 3 visits by the patient. The studies analyzed also showed that administration of Vitamin D had no damaging effects on the surrounding tissues as evidenced by periapical radiographs and CBCT. 60% of the studies showed accelerated tooth movement when Vitamin D was supplemented in the range of 40-50 pg/dl whereas the rest 40% of the studies showed accelerated OTM with 15-25pg/dl dosage. The conflicting results between the studies on the effect of Vitamin D on tooth movement might be attributed to the fact that these studies utilized different concentrations of Vitamin D. Thus, there may be a varied impact of Vitamin D depending on the dose at which it is supplemented. Hence further studies are required to come to an exact conclusion on the effective dosage of Vitamin D administration.

Based on the collected data, Vitamin D has a definitive role in both osteoblastic and osteoclastic activity during tooth movement. Also, the local administration of the active form of Vitamin D, 1,25-dihydroxycholecalciferol can be effectively used to accelerate OTM. Vitamin D administration can be effectively used to reduce the overall treatment time with no damaging effects on the surrounding tissues.
Limitations:
Very few human trials were available in published literature. There are no studies evaluating the salivary levels of Vitamin D during the different phases of tooth movement. The set of retrieved data is limited, and the level of confidence in the observed estimates was deemed to be variable due to the limited number of studies that have assessed each agent, small sample sizes, different age groups, different appliances for tooth movement, and methods of the magnitude of tooth movement assessment, the high risk of bias for some of the investigations, the different observational periods and frequencies of application for the biological agents.

CONCLUSION
The results of the present study show that local administration of an active form of Vitamin D, 1,25 DHC can be an effective agent to accelerate Orthodontic Tooth Movement (OTM). Also, local administration of 1,25DHC, in a dose-dependent pattern, is clinical and cost-effective in accelerating OTM in humans. Future studies can be done on a larger sample size evaluating the salivary levels of vitamin D during different phases of orthodontic tooth movement and correlating their role on the rate of Orthodontic tooth movement.

FUNDING
No sources of funding.

CONFLICT OF INTEREST
None declared.
REFERENCES


