Systematic Review

Effect of Fat-Soluble Vitamins on Osteogenic and Odontogenic Differentiation of Dental Mesenchymal Stem Cells: A Systematic Review

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ABSTRACT

Background: Tissue engineering–based regenerative approaches are rapidly expanding in dentistry, particularly within endodontics, where dental mesenchymal stem cells play a pivotal role. Fat-soluble vitamins have been proposed as potential modulators of osteogenic and odontogenic differentiation.

Purpose: This systematic review aimed to evaluate the effects of fat-soluble vitamins on the osteogenic and odontogenic differentiation of dental mesenchymal stem cells.

Materials and Method: A comprehensive search was conducted in Web of Science, PubMed, Scopus, and Embase, using predefined keywords, from database inception to the last search date. Two independent reviewers screened titles, abstracts, and full texts according to the PRISMA guidelines. Additional studies were identified through manual searches of reference lists, relevant conference proceedings, and academic theses. Studies investigating the impact of fat-soluble vitamins on osteogenic and/or odontogenic differentiation of DMSCs were included.

Results: The search yielded 1,124 records, of which 13 studies met the inclusion criteria. Among the included studies, nine investigated the effects of vitamin D, two evaluated vitamin A, two assessed vitamin K, and one examined vitamin E. Overall, the included evidence suggests that fat-soluble vitamins can enhance osteogenic and odontogenic differentiation markers in various types of dental mesenchymal stem cells, although the extent and mechanisms varied across studies.

Conclusion: Fat-soluble vitamins demonstrate promising adjunctive effects in promoting osteogenic and odontogenic differentiation of dental mesenchymal stem cells. However, heterogeneity in study methodologies and outcomes highlights the need for standardized experimental designs and further mechanistic research to clarify their potential clinical applicability.

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Introduction

Stem cells are recognized as the primary source for generating all cells in the body and possess the ability to self-renew and differentiate into various cell types, including neural, cardiac, blood, and cartilage cells [1-2]. Based on their origin, these cells are generally divided into two categories including embryonic stem cells, which are derived from embryos at early stages of de-

velopment, and adult stem cells, which are obtained after birth from tissues such as bone marrow [3]. A major advantage of adult stem cells is that they can be harvested from the patient themselves and, upon reinfusion, they encounter a reduced immune response; moreover, they largely avoid the ethical issues associated with the use of embryonic stem cells [4-5].

Despite these advantages, the isolation and clinical application of bone marrow-derived stem cells are accompanied by technical and biological challenges, including potential complications from the harvesting process and difficulties in broader clinical implementation [6].

In this context, there has been growing interest in the use of dental mesenchymal stem cells (DMSCs), as their isolation is relatively simpler and the healing process following their application has been reported to be shorter [7]. DMSCs derived from dental tissues exhibit high potential for applications in tissue engineering, particularly in the regeneration of hard tissues such as bone and teeth [8].

Recent studies have shown that DMSCs have a greater capacity for osteogenic differentiation and lower apoptosis compared to certain other stem cell sources; they also express markers such as alkaline phosphatase (ALP), type I collagen, osteocalcin (OCN), dentin matrix protein 1 (DMP1), and dentin sialophosphoprotein (DSPP), making them an excellent candidate for bone tissue engineering [9].

Multiple factors can influence the osteogenic and odontogenic differentiation of stem cells. Among these, fat-soluble vitamins, particularly vitamin D, have been highlighted for their critical role. Evidence suggests that these vitamins are keys in the differentiation and proliferation of dental pulp stem cells (DPSCs) and facilitate the mineralization process in dental tissues [10].

Several studies have investigated the effects of fat-soluble vitamins on the osteogenic and odontogenic differentiation of DMSCs; however, the findings have not been entirely consistent. For instance, one study reported that 1α,25-dihydroxyvitamin D_3 significantly enhanced alkaline phosphatase activity and calcium deposition in stem cells derived from primary teeth [11-12]. Another study demonstrated that vitamin D increased the expression of runt-related transcription factor 2 (RUNX2) and collagen I markers and promoted the formation of a mineralized matrix in DMSCs [13].

However, a study evaluating the combination of vitamin D_3 with another compound such as cannabidiol (CBD) revealed that cell responses varied depending on the source, and the effect of vitamin D was not uniform [14]. In other words, factors such as stem cell origin, vitamin dosage, treatment duration, and culture conditions may influence outcomes and contribute to inconsistencies across studies.

Therefore, this systematic review aimed to evaluate the effects of fat-soluble vitamins on the osteogenic and odontogenic differentiation of DMSCs and summarize potential underlying mechanisms.

Materials and Method

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the study protocol was registered in PROSPERO under the code CRD42024601255. A comprehensive search was performed in PubMed, Google Scholar, EMBASE, and Scopus, covering all records up to September 2024. The search strategy included combinations of terms related to dental pulp stem cells and fat-soluble vitamins, including “dental pulp stem cells,” “stem cells,” “dental pulp,” “isolation,” “human DPSCs,” as well as various forms and synonyms of vitamins A, D, E, and K, such as “Vitamin A,” “33-cis-Retinol,” “All-Trans-Retinol,” “Aquasol A,” “Retinol,” “Vitamin D,” “Cholecalciferol,” “Ergocalciferols,” “Vitamin E,” “Tocopherols,” “Tocotrienols,” “Vitamin K,” “Phytomenadione,” “Menaquinone,” and “Menadione,” together with the term “osteogenic differentiation.” The process of study selection and screening is illustrated in Figure 1.

Eligible studies were limited to full-text articles published in English up to September 2024. During the screening process, irrelevant studies, reviews, systematic reviews, meta-analyses, studies with insufficient information, quasi-experimental designs, and duplicate reports derived from the same dataset were excluded. Titles and abstracts retrieved from the initial search were imported into EndNote X5 to identify and remove duplicates, and two independent reviewers carried out the screening and full-text assessment. Data from the selected studies were extracted and summarized using a structured extraction form in Microsoft Excel 2010, as

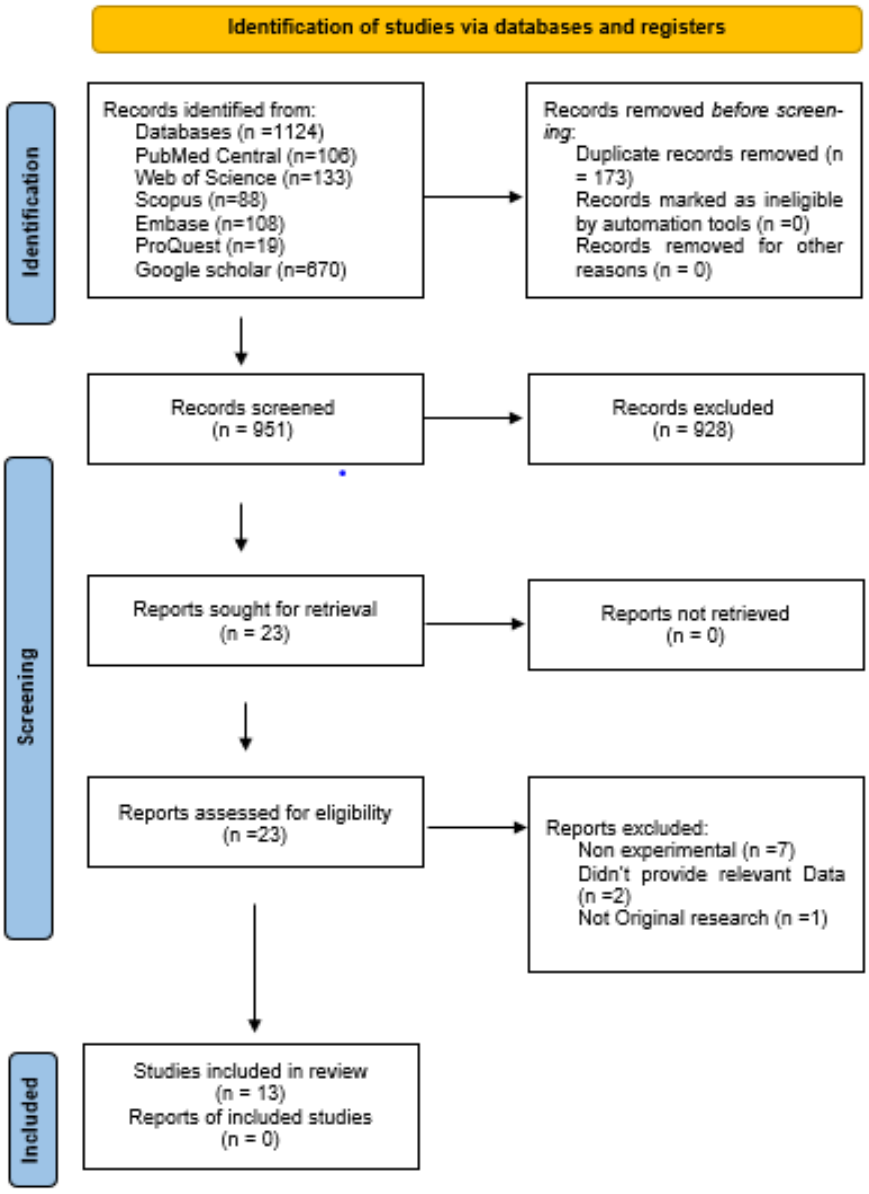

Figure 1: PRISMA flow diagram

presented in Table 1.

The risk of bias in the included studies was assessed using the Cochrane risk of bias tool, evaluating random sequence generation, allocation concealment, blinding of personnel and outcome assessors, completeness of outcome data, selective reporting, and other potential sources of bias. The primary outcomes of this review were osteogenic or odontogenic differentiation of DMSCs

Results

The initial keyword search identified 1,124 publications, from which 13 relevant studies were selected for final analysis according to the predefined criteria. Among these studies, nine investigated the effects of vitamin D, two focused on vitamin A, two on vitamin K, and one on vitamin E on the osteogenic differentiation of DPSCs. The studies were conducted between 2010 and 2022 in Egypt (n=1), Iran (n=3), Germany (n=2), China (n=4), Romania (n=1), Korea (n=1), and Turkey (n=1). Most studies examined individual vitamin supplementation, except for three studies in which vitamin A was studied along with ascorbic acid, or vitamin D was studied with curcumin or cannabidiol; in all cases, the effect of each vitamin on stem cells was analyzed separately. Study characteristics are summarized in Supplementary Table 1.

Fawzy El-Sayed *et al.* [15] investigated the influence

Table 1: Summary of risk of bias according to the Cochrane Collaboration

Other bias	Selective reporting	Incomplete outcome data	Blinding of outcome assessment	Blinding of participants and personnel	Allocation concealment	Random sequence generation	Study
+/-	?	-	+	?	+/-	+	Fawzy El-Sayed *et al.*, 2019 [15]
?	?	-	+	+	+/-	+	Fawzy El-Sayed *et al.*, 2021 [16]
?	-	-	+	+	+	+	Samiei *et al.*, 2021 [4]
?	-	-	?	?	+	-	Khanna-Jain *et al.*, 2010 [20]
?	-	-	+	+	?	+	Mojarad *et al.*, 2016 [11]
?	-	-	?	?	+	+	Uzunoglu-Ozyurek *et al.*, 2022 [22]
?	-	-	+	+	?	+	Ma *et al.*, 2021 [21]
?	-	-	?	?	+/-	+	Zhang *et al.*, 2020 [17]
?	?	-	?	?	+/-	+	Yawen ji *et al.*, 2018 [19]
?	-	-	?	?	+/-	+	Petrescu *et al.*, 2020 [14]
?	-	-	?	?	+/-	+	Woo *et al.*, 2015 [18]
?	-	-	?	?	?	+	Morsy *et al.*, 2018 [23]
?	-	-	?	?	+/-	+	Cui *et al.*, 2021 [24]
+/-	-	-	?	?	+/-	+	Rasouli-Ghahroud *et al.*, 2017 [25]

of retinol (vitamin A) and periodontal inflammatory cytokines (IL-1β, TNF-α, IFN-γ) on the proliferation and differentiation of gingival mesenchymal stem/ progenitor cells (G-MSCs). They found that short-term inflammatory stimuli combined with retinol modulate the Wnt/β-catenin signaling pathway, thereby affecting proliferation, differentiation, and maturation of gingival mesenchymal stem/progenitor cells. In a related study, Fawzy El-Sayed *et al.* [16] examined the combined effect of ascorbic acid and retinol on gene expression and regenerative potential of gingival mesenchymal stem/progenitor cells, showing that vitamin A mitigates inflammation and promotes proliferation and differentiation potential, likely via Wnt/β-catenin signaling important for stem cell self-renewal and lineage commitment.

The majority of studies (n=9) examined the effects of 1,25-dihydroxyvitamin D3 on osteogenic differentiation. Zhang *et al.* [17] stimulated human periodontal ligament stem cells (hPDLSCs) towards osteoblastic differentiation under inflammatory conditions and assessed the role of Periodontal Ligament-Associated Protein 1 (PLAP-1). They found that LPS inhibited osteogenic differentiation and increased PLAP-1 production, whereas treatment with 1,25(OH)2D3 reversed these effects, allowing differentiation with reduced PLAP-1 expression. A vitamin D response element (VDRE) in the PLAP-1 promoter region was identified as a negative regulator capable of binding to the vitamin D receptor (VDR). Moreover, Woo *et al.* [18] found that vitamin D3 treatment (10–100 nM) in human dental pulp cells (hDPCs) significantly increased DSPP and DMP1 gene expression, enhanced ALP activity, promoted mineralization, and activated Extracellular Signal-Regulated Kinases (ERKs). Notably, Inhibition of ERKs reduced the upregulation of DSPP and DMP1, highlighting the involvement of ERK signaling in vitamin D3-mediated differentiation. In addition, Ji *et al.* [19] reported that vitamin D3 increased osteogenic differentiation of hPDLSCs and identified TAZ, a key effector in the Hippo signaling pathway, as an important mediator of this pro-osteogenic effect. Petrescu *et al.* [14] developed a new protocol for differentiating mesenchymal stem cells isolated from dental follicles stem cells (DFSCs), DPSCs, and apical papilla (APSCs) of molar teeth. They demonstrated that treatment with CBD and vitamin D3 enhanced osteogenic differentiation in all three cell types. APSCs responded best to CBD, DPSCs responded best to vitamin D3, and low doses of both agents produced the highest bone differentiation responses.

Furthermore, Khanna-Jain *et al.* [20] showed that vitamin D metabolites α,25(OH)2D3 and 25-hydroxyvitamin D3 reduced proliferation in human dental pulp cells and human dental follicle cells (hDFCs). However, when combined with osteogenic supplements (L-ascorbic acid-2-phosphate and β-glycerophosphate), these metabolites significantly enhanced osteogenic markers, including ALP activity and mineral deposition, indicating their effectiveness as osteogenic inducers for

Suppl 1: Characteristics and extracted data of the included studies

Author & Year	Country	Subjects	Methods	Measurement	Outcome / Result
Fawzy El-Sayed *et al.*, 2019 [15]	Germany	G-MSCs from healthy gingival collars around partially impacted third molars	ELISA, PCR, Alizarin Red	PGK-1, RUNX2, ALP, PPARγ, LPL, ACAN, Nanog, Oct4, SOX2 genes	Controlled short-term inflammatory/retinol stimuli activate Wnt/β-catenin pathway, affecting G-MSCs pluripotency, proliferation, differentiation
Fawzy El-Sayed *et al.*, 2021 [16]	Germany	Gingival connective tissue cells from five healthy donors	ELISA, PCR, Alizarin Red	FOS, EGR1, SGK1, CXCL5, SIPA1L2, TFPI2, KRATP1-5, TMEM132A, PER1, CTSS, CD74, FKBP5, ZNF404	Vitamin A reduces inflammation, enhances MSC proliferation and differentiation
Samiei *et al.*, 2021 [4]	Iran	Human DPSCs from Shahid Beheshti University	Spectrophotometer, RT-qPCR, MTT assay	ALP Activity	Calcitriol promotes growth and osteogenic differentiation of DPSCs; effects dose- and origin-dependent
Mojarad *et al.*, 2016 [11]	Iran	15 sound exfoliated deciduous teeth from 10 children (6–11 years)	p-Nitrophenylphosphate, Alizarin Red	ALP activity	1α,25(OH)2D3 increases ALP activity of SHEDs
Uzunoglu-Ozyurek *et al.*, 2022 [22]	Turkey	DPSCs from control and T1DM donors	RT-qPCR, Western blot, ELISA	DSPP, DMP1, COL1A1, OCN, BSP II	Vitamin D3 enhances differentiation of DPSCs from T1DM patients
Ma *et al.*, 2021 [21]	China	Six premolars or third molars from orthodontic patients	Flow cytometry, RT-qPCR, Alizarin Red S	RUNX2, ALP, Col I, OCN	1,25-dihydroxyvitamin D3 promotes adhesion, proliferation, osteogenic differentiation of SCAPs
Zhang *et al.*, 2020 [17]	China	Premolars from 12–16-year-old patients	qRT-PCR, Western blot, IHC	RUNX2, ALP, COL1	1,25(OH)2D3 reverses LPS-induced suppression of hPDLSCs osteogenic differentiation
Yawen ji *et al.*, 2018 [19]	China	Two girls (13, 15) and two boys (12, 16)	Flow cytometry, Alizarin Red, RT-qPCR, Western blot	ALP, OCN, RUNX2, Col I, BSP, OPN	Calcitriol enhances osteogenic differentiation of PDLCs and periodontal tissue regeneration
Petrescu *et al.*, 2020 [14]	Romania	MSCs from pulp, apical papilla, and dental follicle of same donor	RT-qPCR, Alomar blue, Alizarin Red	ALP, OCN, RUNX2, Col I, BSP, OPN, CEMP-1, DLX5, CD271, CD146, STRO-1	Different dental MSC types respond variably to CBD and vitamin D3
Woo *et al.*, 2015 [18]	Korea	Maxillary supernumerary incisors and third molars from 3 healthy adults	MTT, RT-qPCR, Western blot, ELISA, Alizarin Red S	RUNX2, ALP, COL1A1, OC, DMP1, OSX, BSP, OPN, CD271, CD146, CD105	1α,25(OH)2D3 enhances early and late osteogenic differentiation of PDLSCs
Morsy *et al.*, 2018 [23]	Egypt	20 neonatal albino rats	Alizarin Red sulfate, qRT-PCR, MTT	ALP, CD34, CD29	Vitamin E alleviates nicotine-induced oxidative stress; promotes DFSC proliferation and osteogenic differentiation
Cui *et al.*, 2021 [24]	China	40 first premolars from 20 patients (14–18 years)	Flow cytometry, Alizarin Red S, Western blot, qRT-PCR	ALP, OCN, RUNX2	MK-4 promotes osteogenesis in PDLSCs via Wnt/β-catenin
Rasouli-Ghahroud *et al.*, 2017 [25]	Iran	Human DPSCs from third molars of healthy adults	RT-qPCR, ELISA, Alizarin Red, Flow cytometry	CD73, CD90, CD105, CD44, CD34, CD45, ALP activity	Vitamin K2 (10 µM) promotes DPSC differentiation into osteoblasts

Abbreviations: ALP: Alkaline Phosphatase; BSP: Bone Sialoprotein; CBD: Cannabidiol; CEMP-1: Cementum Protein 1; COL1A1: Collagen Type I; DMP1: Dentin Matrix Protein 1; DPSCs: Dental Pulp Stem Cells; DSPP: Dentin Sialophosphoprotein; ELISA: Enzyme-Linked Immunosorbent Assay; ERKs: Extracellular Signal-Regulated Kinases; hDPCs: Human Dental Pulp Cells; MSCs: Mesenchymal Stem Cells; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyl-2H-Tetrazolium Bromide; OC: Osteocalcin; OPN: Osteopontin; OSX: Osterix; PCR: Polymerase Chain Reaction; PLAP-1: Periodontal Ligament Associated Protein-1; Runx2: Runt-Related Transcription Factor 2; SHEDs: Stem Cells Derived from Human Exfoliated Deciduous Teeth; SACPs: Stem Cells from Apical Papilla; T1DM: Type 1 Diabetes Mellitus.

promoting differentiation in these cell types. Similarly, Samiei *et al.* [4] found that curcumin, alone or with calcitriol, significantly increased ALP activity and osteoblast-specific mRNA in DPSCs. Interestingly, calcitriol alone produced a greater increase in enzyme activity than the combination with curcumin. Moreover, No

toxic effects were observed except at 100 nM for 72 hours, and a combination of 0.5 μM curcumin and 10 nM calcitriol over 7 days supported cell growth.

In addition, Yonggang Ma *et al.* [21] investigated the effects of vitamin D3 on stem cells from the apical papilla (SCAPs). They found that vitamin D3 positively influenced adhesion, proliferation, and osteogenic differentiation by upregulating transcription of osteogenic markers. Importantly, stem cells from the apical papilla, characterized by their multiple differentiation potential and stem cell properties, were able to regenerate vascularized dental pulp-like tissue, indicating their potential as a source of odontoblast progenitor cells (OPCs) for root dentin formation.

Moreover, Mojarrad *et al.* [11] reported that treatment with 1α,25(OH)2D3 significantly increased ALP activity and the formation of mineralized nodules in stem cells derived from human exfoliated deciduous teeth (SHEDs). Alizarin red staining confirmed these results, indicating that 1α,25(OH)2D3 enhances osteoblast differentiation and improves the osteogenic potential of SHEDs.

Finally, Emel Uzunoglu-Ozyurek *et al.* [22] investigated DPSCs from patients with Type 1 Diabetes Mellitus (T1DM). They showed that vitamin D3, particularly when combined with mineral trioxide aggregate (MTA), significantly enhanced odonto/osteogenic differentiation compared to non-diabetic controls. DPSCs were cultured in various media: standard growth medium, differentiation medium (DM), DM with mineral trioxide aggregate, and DM with both mineral trioxide aggregate and vitamin D3. Differentiation was assessed via alizarin red staining and real-time PCR, demonstrating that cells treated with the combination showed improved mineralization and upregulation of osteogenic genes.

Morsy *et al.* [23] evaluated the effects of vitamin E on DFSCs in nicotine-exposed rats. They found that vitamin E reduced nicotine-induced oxidative stress, improved cell proliferation, and enhanced osteoblast differentiation, as indicated by increased ALP activity, assessed using MTT and Wright's staining methods.

Two studies examined the effects of vitamin K, including K1 and K2, on osteogenic differentiation of periodontal ligament stem cells. Cui *et al.* [24] showed that menaquinone-4 (MK-4), a member of the vitamin K2 family, promoted proliferation, osteoblast differentiation, and increased ALP activity, extracellular matrix mineralization, and gene/protein expression of ALP, Runx2, OCN, and Osterix, likely via the Wnt/β-catenin signaling pathway. Rasouli *et al.* [25] demonstrated that MK-4, at concentrations of 5–15 μM, improved osteogenic differentiation of DPSCs, with 10 μM significantly enhancing differentiation into osteoblasts at 14 days, as confirmed by ALP assay and alizarin red staining.

Discussion

This systematic review examines the impact of fat-soluble vitamins on the osteogenic differentiation of dental pulp stem cells. It emphasizes the positive effect of Vitamin D on the osteogenic differentiation of dental stem cells, a finding supported across all related studies [13-14, 20-21, 26-28]. The influence of vitamin D on tooth osteogenic differentiation can be understood from various perspectives. Calcitriol is the active form of vitamin D. It binds to VDR, responsible for vitamin D's functions. VDR plays a crucial role in maintaining calcium and phosphate levels in the body [29]. It also regulates cell differentiation, inflammation, and apoptosis in human diseases. *In vivo* studies have shown that calcitriol is important in mineralizing dental tissues [27]. VDR is present in human dental tissues such as ameloblasts and odontoblasts. Recent studies have demonstrated that adding 1a,25(OH)2D3 can upregulate VDR expression in human dental pulp cells and human dental follicle cells. VDR also regulates the expression of bone-modulating factors such as Runx2, ALP, OCN, and collagen I (COL1) [20, 30].

Mitogen-activated protein kinases (MAPKs) are a family of protein kinases that are highly conserved from yeast to humans. In mammals, there are three main groups of MAPKs: ERK, p38 MAPKs, and c-Jun NH_2-terminal kinases (JNK). Studies have demonstrated that MAPKs are involved in regulating the differentiation of osteoblasts and odontoblasts, and vitamin D3 and VDR can modulate the pathway of these kinases and may influence the process of dental osteogenic differentiation [31-32].

The following possible mechanism is that the PLAP-1 is a significant member of the leucine-rich repeat proteoglycan family, which plays a crucial role in maintaining the balance in periodontal tissues. It is predominantly located in the periodontal ligament and has

been shown to affect the mineralization of PDLSCs. Additionally, when overexpressed, it inhibits osteoblast differentiation of bone marrow stem cells (BMSCs). Given the high expression of PLAP-1 in bone diseases, it is possible that 1,25(OH)2D3 can suppress the expression of PLAP-1 during inflammatory conditions, which may lead to osteogenic differentiation and the last mechanism is that vitamin D can also improve osteogenic differentiation in the MSC in addition to normal conditions in oxidative stress. This vitamin can lead to a noteworthy decrease in H2O2 harm through the SIRT1/FOXO1 signaling pathway [26, 28].

In two studies on the role of MK-4 as an important member of the vitamin K2 family in dental stem c-ells, this vitamin positively affected the proliferation and osteogenic differentiation of PDLSCs and DPSC. The mechanism behind this effect is related to the Wnt/β-catenin signaling pathway. The Wnt/ β-catenin signaling pathway plays an important role in bone arrangement improvement in several cell types and induces osteogenic differentiation via changing microRNA (miRNA). When this pathway is activated, glycogen synthase kinase 3 loses its activity after phosphorylation, allowing beta-catenin to accumulate and enter the nucleus. There, it combines with transcription factors and regulates the expression of downstream target genes, initiating the replication process. Beta-catenin also regulates apoptosis, differentiation, and other metabolic activities of cells. The positive regulation of beta-catenin

can affect the activity of vitamin K and in turn, promote the osteogenic activity of this vitamin [24-25].

The role of vitamin A in osteogenic differentiation has also been expressed through the Wnt/β-catenin

signaling pathway. Wnt/β-catenin signaling is crucial for stem/progenitor cells' osteogenic differentiation by interacting with the retinoic acid receptor [15].

Vitamin E is regarded as an essential antioxidant that occurs naturally and primarily acts as a lipid-soluble free radical scavenger, which stops chain reactions occurring during lipid peroxidation. By protecting all the polyunsaturated fatty acids in cell membranes, vitamin E prevents oxidative damage and maintains cell health by decreasing the production of reactive oxygen species. Nicotine negatively affects the proliferation and osteogenic differentiation of DFSCs and therefore reduces regenerative capacity. Vitamin E significantly reduces nicotine-induced toxicity in DFSCs by increasing cell proliferation and osteogenic differentiation, likely due to its antioxidant ability to neutralize oxidative stress and help maintain a microenvironment within cells more conducive to differentiation. These results demonstrate the potential for vitamin E as a treatment for counteracting the harmful impact of nicotine on dental stem cell function and bone regeneration [23, 33]. In summary, this systematic review has revealed the substantial role of fat-soluble vitamins in osteogenic and odontogenic differentiation of DMSCs. Fat-soluble vitamins influence molecular pathways and gene expression that ultimately enhance differentiation, mineralization, and regeneration in multiple cell types. Although studies varied in their experimental conditions and types of cells evaluated, these findings suggest to support the potential intervention of fat-soluble vitamins to improve dental tissue engineering and regenerative dentistry. Further investigations are needed to evaluate appropriate dosing, combination effects, and long-term clinical implications that would help to develop and implement effective regenerative strategies that utilize dental stem cells for the regeneration of bone or teeth.

Conclusion

It is suggested that special studies be conducted in the future on the mechanisms of the effect of soluble vitamins in treating the osteogenic and odontogenic differentiation of DMSCs. By fully understanding the mechanism of the impact of these substances, it is possible to plan clinical studies and obtain from these substances the degree of improvement in the condition of the disease in all kinds of diseases related to gums and teeth.

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Ethics Approval

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Summary of work done by the contributors

All authors contributed substantially to the conception, design, data collection, analysis, interpretation, and manuscript drafting. All authors approved the final ver-

sion of the manuscript.

PROSPERO Registry Number

CRD42024601255

Reporting Guidelines

This study has been reported according to the PRISMA reporting guidelines (2009).

Patient Declaration of Consent

Not applicable.

Conflicting Interest

None

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