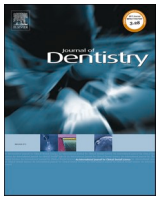
Journal of Dentistry 150 (2024) 105333

Contents lists available at ScienceDirect

Journal of Dentistry

journal homepage: www.elsevier.com/locate/jdent



Review article

Efficacy of topical application of corticosteroids in the remineralization of dental pulp tissue. A systematic review of the literature

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ARTICLE INFO

Keywords:
Corticosteroids
Mesenchymal stem cells
Mineralization
Odontogenic differentiation
Dental pulp

ABSTRACT

Objectives: The aim of this systematic review was to demonstrate the efficacy of topical application of corticosteroids in remineralization of dental pulp tissues to preserve their vitality and function.
Data, sources and study selection: An electronic search was performed using MEDLINE by PubMed, EMBASE, Web of Science (WOS), and Scopus databases. The inclusion criteria were in vitro studies that employed dental pulp tissue obtained from extracted healthy permanent human teeth and were subjected to topical administration of corticosteroids and evaluated tissue remineralization by performing any mineralization assay. A total of 11 studies were selected for inclusion. PRISMA guidelines were followed, and the methodological quality and risk of bias of the included studies were evaluated using the RoBDEMAT guidelines. Also, tables were designed for data extraction, including tissue mineralization and osteogenic differentiation as primary and secondary outcomes, respectively.
Conclusions: Alizarin Red S (ARS) has been able to demonstrate a possible mineralizing power of corticosteroids, applied at an adequate dose. The up-regulation of Alkaline phosphatase (ALP), osteocalcin (OCN), osteopontin (OSP), sialophosphoprotein (DSPP), runt-related transcription factor 2 (RUNX2), collagen type 1 alpha 1 (COL1α1) and dentin matrix protein 1 (DMP-1) induced the osteogenic/odontogenic differentiation of dental pulp stem cells (DPSCs).
Clinical significance: Deep carious lesions treatment is still challenging in restorative dentistry. Some treatments have been focused on dental pulp tissue remineralization to maintain the function and vitality. After corticosteroids topical application, mineral deposition and osteogenic differentiation have been detected.

1. Introduction

Dental caries is considered to be the most common disease in dentistry. Synthetic materials, such as composite resin, zirconia ceramic or new dental restorative materials are being used in regenerative dentistry to replace enamel and dentin affected by carious lesions and to stimulate tertiary dentin formation, a new reparative dentin layer [1–4]. The newly formed dentin acts as a barrier to protect dental pulp from external risk, maintaining the long-term vitality [5]. Treating deep carious lesions is still challenging in dentistry due to the possibility of pulp exposure, during decay removal, and loss of pulp vitality [5–7]. Vital pulp therapy has become an important approach to preserve pulp vitality and avoid root canal therapy, a key factor for long-term teeth preservation [8,9]. Capping agents, such as mineral trioxide aggregate

Abbreviations: ALP, alkaline phosphatase; ARS, alizarin red S; BETA, betamethasone; BG, betamethasone/gentamicin; BGN, bioactive glass nanoparticle; BSP, bone sialoprotein; COL1α1, collagen type 1, alpha 1; CSnp, chitosan nanoparticle; DEX, dexamethasone; DHHAM, dexamethasone hollow hydroxyapatite microespheres; DPH, diphenylhydantoin; DMP-1, dentin matrix protein 1; DPSC, dental pulp stem cells; DSPP, sialophosphoprotein; ECM, extracellular matrix; FBS, fetal bovine serum; HHAM, hollow hydroxyapatite microespheres; LPS, lipopolysaccharide; MEM, modified eagle medium; MEPE, matrix extracellular phosphoglycoprotein; MSCs, mesenchymal stem cells; MTA, mineral trioxide aggregate; OBM, osteogenic basal medium; OCN, osteocalcin; ODM, osteogenic dexamethasone medium; OSP, osteopontin; PDLSC, periodontal ligament stem cell; RUNX2, runt-related transcription factor 2; SCAP, apical papilla stem cell; SHED, human exfoliated deciduous teeth stem cells.

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https://doi.org/10.1016/j.jdent.2024.105333
Received 24 July 2024; Received in revised form 28 August 2024; Accepted 29 August 2024
Available online 30 August 2024

(MTA) and calcium hydroxide, have been widely employed in the treatment of the exposed pulp for the formation of secondary dentine [9,10]. When inflammation decreased, secondary dentine progressively forms to help the pulp heal [9]. However, the anti-inflammatory effect of these biomaterials is not sufficient to achieve the recovery of pulp tissues [10]. Tissue-specific stem cells have demonstrated a strong regeneration power, leading to a promising and more effective therapy for the treatment of damaged tissue [11]. Nevertheless, to date, the perfect pulp capping material for healing of inflamed pulp has not yet been described.

Recently, dental tissue engineering has been focused on the study of mesenchymal stem cells (MSCs), which has previously shown the capability of self-renewal and differentiation, as promising progenitor cell sources [12]. To stimulate odontogenesis and replace damaged pulp tissues [1], stem cells have been isolated from dental pulp (DPSCs), human exfoliated deciduous teeth (SHED), periodontal ligament (PDLSC) and the apical papilla (SCAP) [12–16]. Nonetheless, their clinical application is considerably restricted by the insufficient MSCs at vital pulp and the progressive decrease of their differentiation ability [17,18]. Besides an adequate cell source, to stimulate the formation of new tissues, a biodegradable scaffold, which imitates the extracellular matrix (ECM), and bioactive molecules are needed [1,19–21]. Preceding studies demonstrated that glucocorticoids could lead to the proliferation of MSCs [22] and the expression of odontogenic markers to produce in vitro remineralization [23,24]. Dexamethasone (DEX) is a synthetic glucocorticoid with a potent anti-inflammatory effect due its immunosuppressive activity [25]. Not only has the osteoinductive effect of DEX been stated, but also its pivotal role in dentin remineralization influencing odontoblasts odontogenic differentiation [22,26].

Nowadays, clinical use of corticosteroids in the field of restorative dentistry is still in doubt. Some previous studies have questioned the influence of dexamethasone in osteogenic differentiation, attributable to the use of large doses of this drug [8]. High concentrations of DEX can lead to a toxic side effect resulting in the necrosis of the tissue and increasing lipid formation [27]. Hence, one of the main objectives of researchers in dental materials field is to design an appropriate mechanism of localized and sustained release [4]. The progressive delivery of glucocorticoids to the target side could minimize inflammation, improve the angiogenesis and therefore stimulate the MSC differentiation, leading to the mineralization and new tissue formation [28–31].

Currently, DEX and other corticosteroids such as betamethasone and fluocinolone acetonide are being incorporated into synthetic scaffold biomaterials. Based on recent investigations, the long-term delivery of DEX, added to composite nanofibers, favored the proliferation and odontogenic differentiation of dental stem cell [22,32]. Because of these findings, many different types of scaffold materials dopped with glucocorticoids are being developed in this field, including hydrogels, bioactive glass nanoparticles, chitosan nanoparticles and hydroxyapatite microspheres [1,5,22,33].

With this background, the objective of this systematic review was to investigate the efficacy of topical administration of corticosteroids on the mineralization of dental pulp tissues to preserve their vitality and function. Also, the most recent evidence has been analyzed regarding the main vehicles and dosage of the employed corticosteroids and their ability to increase the expression of osteogenic biomarkers.

To the best of our knowledge, this is the first systematic review of in vitro studies that analyzed the available literature on the efficacy of topical administration of glucocorticoids in the remineralization of the dental pulp complex, as well as the most employed corticosteroids that were used, their doses and vehicles.

2. Material and methods

2.1. Study registration and protocol

In order to increase the transparency in the review process, a proposal of the developed protocol based on the efficacy of topical application of corticosteroids in remineralization of dental pulp tissue was registered in PROSPERO (International Prospective Register of Systematic Reviews) before conducting the review.

The structure of this systematic review was designed according to the PRISMA-P [34,35]. In addition, to increase the quality of this study, the PRISMA 2020 checklist [35] and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions were followed.

2.2. Focused question and PICOS elements

The following PICOS question was formulated intending to respond our focused query: In dental pulp tissue obtained from extracted healthy permanent teeth, what is the efficacy of topical application of corticosteroids compared to non-application, in terms of tissue remineralization?

The PICOS' question elements were as follows:

- *Population (P):* dental pulp tissue obtained from extracted healthy permanent teeth.
- *Intervention (I):* topical application of corticosteroids.
- *Comparison (C):* no application of corticosteroids.
- *Outcome (O):* outcomes measuring dental pulp tissue remineralization using ARS staining and dentinal bridge thickness.
- *Study design (S):* in vitro studies

2.3. Search strategy

An electronic search was conducted at the following online databases: The National Library of Medicine (MEDLINE by PubMed), EMBASE, Web of Science (WOS), and Scopus databases. Additionally, manual literature searches were performed consulting the lists of references of included articles and previous reviews. Authors searched for studies published in English up to May 2024 without any time filter using the following search strategy:

("corticoid" OR "dexamethasone" OR "betamethasone" OR "glucocorticoid" OR "corticosteroid" OR "steroid" OR "glucosteroid" OR "glucocorticosteroid" OR "prednisone" OR "prednisolone" OR "methylprednisolone" OR "fluocinolone acetonide") AND ("pulp" OR "dental pulp" OR "dentine" OR "pulp capping" OR "mesenchymal stem cell" OR "MSCs" OR "dental pulp stem cell" OR "DPSCs" OR "dentin pulp complex") AND ("mineralization" OR "remineralization")

2.4. Eligibility criteria

The following criteria was stablished for the study inclusion in our systematic review: (1) in vitro studies; (2) dental pulp tissue obtained from extracted healthy permanent teeth (third molar extraction or extracted for orthodontic reasons); (3) topical administration of corticosteroids; (4) human teeth; and (5) reporting information about tissue remineralization performing any mineralization assay. On the other hand, the exclusion criteria were: (1) in vivo studies; (2) dental pulp obtained from deciduous teeth; (3) systemic administration of corticosteroids; (4) studies performed in animals; (5) no results about remineralization; and (6) full-text not available in English language.

2.5. Study selection, data extraction and data synthesis

Title and abstracts from the online search were screened by three independent authors (M.P.-S., R.T. and A.A.-Z.) searching for eligibility. Disagreements were solved by the judgement of a fourth author (M.V.-R.). The level of agreement between researchers was calculated using the Fleiss' Kappa-coefficient. The final inclusion of the studies was performed after full-text reading and applying the aforementioned eligibility criteria.

Authors obtained the following data from the included studies: (1)

author and date; (2) study design; (3) sample size; (4) test group; (5) control group; (6) follow-up; (7) corticoid used and dosage; (8) corticoid vehicle; (9) medium; (10) number of passages; (11) primary outcome (remineralization); (12) secondary outcomes (ALP, OSP, DSPP, OCN, RUNX2, COL1α1 and DMP-1).

After extraction, data synthesis was performed introducing the obtained information into a predesigned template. It included: 1) the primary outcome (dental pulp tissue remineralization), measured using ARS staining or dentinal bridge thickness, and 2) the secondary outcome (osteogenic differentiation) analyzed by ALP, OSP, DSPP, OCN, RUNX2, COL1α1 and DMP-1 gene expression. Due to the detected heterogeneity between the different studies and because the outcomes were not reported quantitatively, it was not possible to perform a meta-analysis.

2.6. Assessment of risk of bias

The design and quality of the included studied was evaluated using the RoBDEMAT guide [36], a new risk of bias tool for systematic reviews designed to evaluate in vitro dental materials studies. RoBDEMAT tool is divided into four domains that assess different types of bias: study design and allocation (D1); preparation of the samples and their standardization (D2); the way in which the tests were carried out (D3); and statistical data treatment (D4). Each study was assessed by three independent authors (M.P.-S., R.T. and A.A.-Z.) who answered to nine questions, included in these four different domains. Disagreements were solved by the judgement of a fourth author (M.V.-R.). Each question was considered as "sufficiently reported/adequate", "insufficiently reported" or "not reported/not adequate". After the evaluation, included studies were categorized in "Low risk of bias", "Moderate risk of bias" and "High risk of bias".

2.7. Evaluation of certainty of evidence

The quality of evidence of the included studies was assessed using The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [37]. This tool evaluates a series of considerations such as study design, risk of bias, inconsistency, indirectness, imprecision, publication bias and other concerns. After being assessed using the online GRADEPro GDT (GRADEpro Guideline Development Tool) *(McMaster University and Evidence Prime, 2024. Available from gradepro.org),* studies were rated as "High certainty of evidence", "Moderate certainty of evidence", "Low certainty of

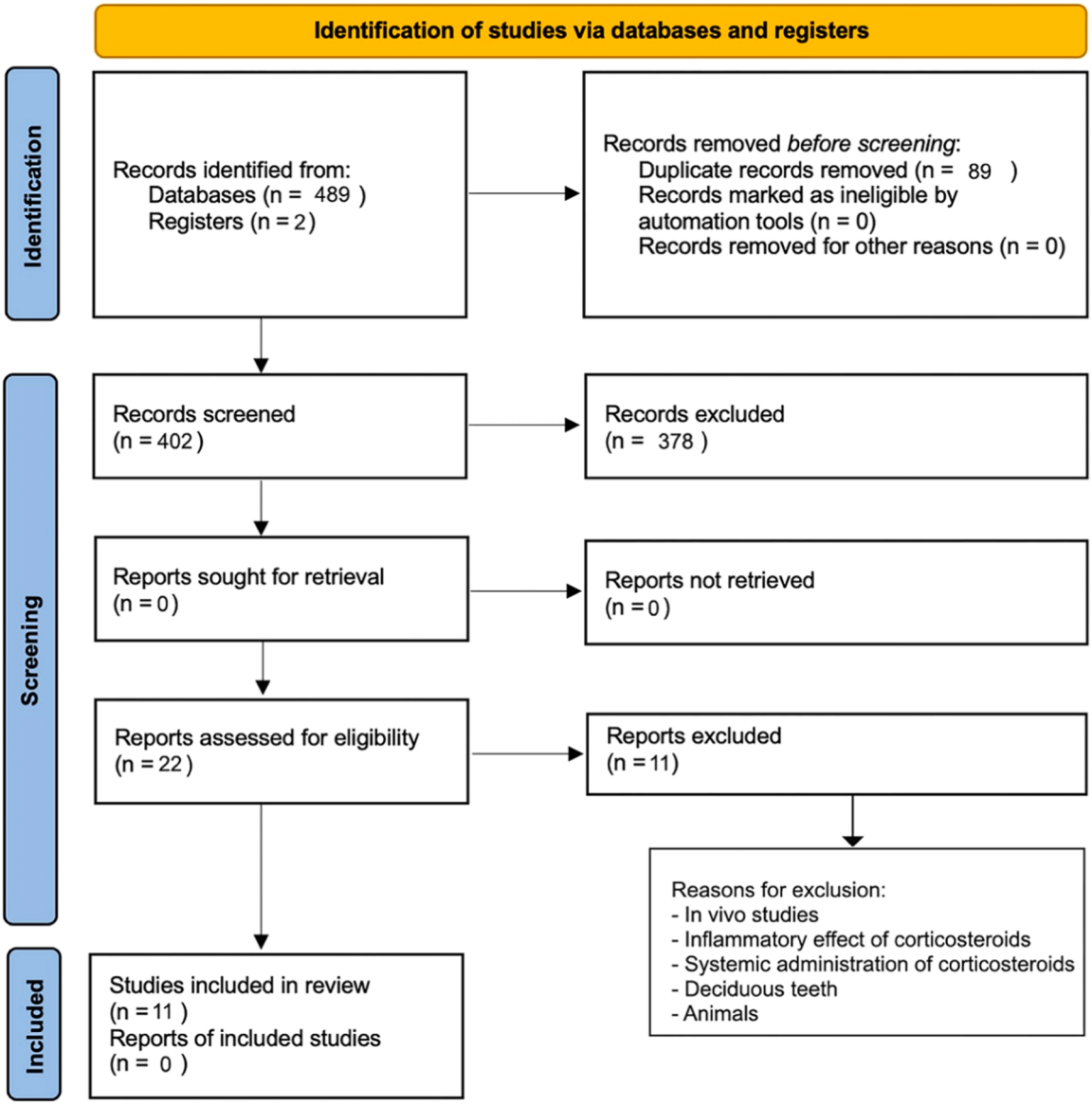

Fig. 1. Flow diagram about the screening process of this systematic review following the PRISMA guidelines.

evidence" or "Very low certainty of evidence".

3. Results

3.1. Search results

The information about search results and inclusion process, following the PRISMA guidelines, is represented in Fig. 1. A total of 491 articles were considered for inclusion. Introducing the search strategy for electronic search resulted in 489 articles, and the succeeding manual search identified 2 more publications. Then, 89 duplicated manuscripts were removed, resulting in 402 articles considered for reading their titles and/or abstracts. Only 22 articles were selected for full-text reading and screening. Finally, 11 manuscripts meeting the inclusion criteria were included in our systematic review. The Fleiss' Kappa-coefficient for title and/or abstract, and full-text assessment resulted in 0.76 and 0.93, respectively, showing a good agreement between researchers.

3.2. Study characteristics and data extraction

A total of 11 in vitro studies were included in our systematic review. The study characteristics and data extracted from the articles are shown in detail in Table 1.

Each study compared a test group, which administered topically a corticosteroid, with a control group in a modified media without the corticosteroid application. The most represented corticosteroid in this systematic review was dexamethasone, employed in eight included studies [1,5,8,11,12,22,33,38], followed by betamethasone, used in two

Table 1
Main extracted information about the included studies.

Author/Date	Study Design	Sample Size (DPSCs origin)	Test Groups (n)	Control Groups (n)	Follow-up	Corticosteroid (Dosage)	Vehicle	Medium
Alshwaimi et al. 2016 [39]	*In vitro*	36 first premolars	1) BG1= 9 2) BG2=10	1) MTA1= 8 2)MTA2= 9	2–8 weeks	Betamethasone (NR)	Cream	NR
Asgharian-Rezaee et al. 2020 [38]	*In vitro*	12 well plates (third molars)	1) ODM: (OBM+ Dex) = 3	1) Basal Cell culture media= 3 2) OBM= 3	10 days	Dexamethasone (0.1 μM)	NR	OBM: (α-MEM+10 %FBS+1 %Pen-Strep+50 μg/ml L-ascorbic acid+10 mM β-glycerophosphate)
Bakopoulou et al. 2011a [12]	*In vitro*	6 well plates (third molars)	MEM + Dex + +1.8 mM monopotassium phosphate+ +5 mM β -glycerophosphate (NR)	MEM (NR)	3 weeks	Dexamethasone (0 0.01 mM)	NR	Modified MEM
Bhatnagar et al. 2015 [1]	*In vitro*	6 well plates (third molars)	Induced media=3	Non-induced media= 3	35 days	Dexamethasone (0.00000001 M)	Hydrogels	α-MEM +10 % FBS+1 % Pen-Strep+10 mM β-glycerol phosphate+200 mM L-ascorbic acid 2-phosphate+2 mM L-glutamine
Lim et al. 2016 [22]	*In vitro*	NR	1) BGN + Dex (NR) 2) Dex-containing media (NR)	1) BGN (NR) 2) Dex-free (NR)	14 days	Dexamethasone (0.1 μM)	Bioactive glass nanoparticles	α-MEM +10 % FBS+50 μg/ml L-ascorbic acid+10 mM glycerophosphate
Liu et al. 2013a [10]	*In vitro*	12 well plates (first premolars)	1) 1-μmol/L = 4 2) 10-μmol/L = 4	1) 0-μmol/L = 4	21 days	Fluocinolone acetonide 1) (1-μmol/L) 2) (10-μmol/L)	NR	MEM +10 % FBS
Min et al. 2011 [11]	*In vitro*	NR (third molars)	Cell cultured + Additives (5 mM β -glycerophosphate + Dex + + 100 μM ascorbic acid) (NR)	Cell cultured (NR)	16–20 days	Dexamethasone (100 nM)	NR	MEM+20 %FBS+antibiotics
Shrestha et al. 2015 [33]	*In vitro*	24 well plates (NR)	1) Dex-chitosan nanoparticles (encapsulation method) = 6 2) Dex-chitosan nanoparticles (adsorption method) = 6	1) Control= 6 2) Chitosan nanoparticles without Dex= 6	3 weeks	Dexamethasone 1) 1.5 mg/mL 2) 100 mg	Chitosan nanoparticles	α-MEM +10 % FBS+2 mmol/ L-glutamine+100 U/mL antibiotic
Tang et al. 2023 [8]	*In vitro*	96 well plates (third molars)	1) Dex 1 = 24 2)Dex 10=24 3)Dex 100= 24	1) Dex 0 = 24	20 days	Dexamethasone 1) 1 nM 2) 10 nM 3) 100 nM	NR	α -MEM +10 % FBS+1 % antibiotics
Wang et al. 2019 [9]	*In vitro*	6 well plates (third molars)	1) OBM + BETA 2) OBM + LPS (1 μg/ml *Escherchia coli*) + BETA (NR)	1) OBM 2) OBM+LPS (1 μg/ml *Escherchia coli*) (NR)	7 days	Betamethasone (1 μmol/L)	NR	MEM+50 μg/ml ascorbate+10 mM β -glycerophosphate
Zhang et al. 2020 [5]	*In vitro*	12 well plates (premolars)	1) HHAM = 3 2) Dex= 3 3) DHHAM=3	1) Control= 3	28 days	Dexamethasone (10 mg/ml)	Hollow hydroxyapatite microspheres	MEM+20 %FBS+1 % antibiotics (penicillin)

BETA: betamethasone; BG: betamethasone/gentamicin; BGN: bioactive glass nanoparticle; Dex: dexamethasone; DPSCs: dental pulp stem cells; FBS: fetal bovine serum; HHAM: hollow hydroxyapatite microespheres; DHHAM: dexamethasone hollow hydroxyapatite microespheres; LPS: lipopolysaccharide; MEM: modified eagle medium; MTA: mineral trioxide aggregate; NR: not reported; OBM: osteogenic basal medium; ODM: osteogenic dexamethasone medium.

other articles [9,39], and acetonide fluocinolone presented in one study only [10]. The corticosteroid dosage changed between studies and some of them employed a vehicle for progressive delivery and reduce the toxic effect in the target side. The vehicles reported were cream [39], hydrogels [1], bioactive glass nanoparticles [22], chitosan nanoparticles [33], and hydroxyapatite microspheres [5].

The DPSCs isolation were also reported. Six studies obtained them from third molars after extraction [1,8,11,12,17,38], three from premolars extracted due to orthodontic reasons [5,10,39], and two did not report this information [22,33].

3.3. Quality assessment and risk of bias

For the quality assessment and risk of bias of the included studies, the RoBDEMAT tool [36] was employed. According to the RoBDEMAT tool, 7 articles [1,5,8,10,33,38,39] were classified as low, and just 4 studies [9,11,12,22] were classified as moderate. It should be resembled that none of the included articles showed high risk of bias, improving the reliability of the results obtained in the present systematic review. Results are represented in Fig. 2.

3.4. Primary and secondary outcomes

Included studies outcomes measurements for cell mineralization and osteogenic differentiation, as primary and secondary outcomes, respectively, are summarized in Table 2. As primary outcome, two different types of mineralization measurements were described in the included studies: 10 articles [1,5,8–12,22,33,38] employed the Alizarin Red S (ARS) to evaluate the calcium deposits in cells, and only 1 article [39] determined tissue mineralization measuring the percentage of hard tissue thickness (dentin bridge). In this study by Alshwaimi et al. 2016 [39], hard tissue thickness measurements resulted in a higher tissue mineralization in control groups; containing only MTA and obtaining the highest tissue formation in control group at 8 weeks of follow-up [39]. The other 10 studies [1,5,8–12,22,33,38], which employed the ARS staining to measure cell mineralization, showed different results. Most of them (8 studies) [5,8,9,11,12,22,33,38] showed higher remineralization in the test groups containing two different corticosteroids: DEX [5,8,11,12,22,33,38] and betamethasone [9]. Only 2 articles [1,10] found no difference between control and test groups, one of them using fluocinolone acetonide at different concentrations.

Another relevant information reported in these studies were the dosage and the vehicle used. When there was more than one test group comparing the corticosteroid dosage [8], the group containing the lowest dosage (1 nM) resulted in significantly higher mineralization than other corticosteroid concentrations (10 nM and 100 nM) [8]. The use of glucocorticoids vehicles for progressive delivery was studied in five of the included studies [1,5,22,33,39], and two of them [5,33] reported the highest mineralization in the test group containing the vehicles: chitosan nanoparticles [33] and hollow hydroxyapatite microspheres [5].

Osteogenic differentiation, as our secondary outcome, was evaluated mainly using alkaline phosphatase (ALP) [1,5,9–12,22,33,38]. Also, osteopontin (OSP) [38], dentine sialophosphoprotein (DSPP) [1,5,9–12,22,33], osteocalcine [1,5,9–12](OCN), bone sialoprotein (BSP) [10], runt-related transcription factor 2 (RUNX2) [5,9,22,38], collagen type 1 alpha 1(COL1α1) [8] and dentin matrix protein 1 (DMP-1) [11,22,33] were measurements employed in the included studied. The information obtained and important results for osteogenic differentiation are detailed in Table 2.

3.5. Evaluation of certainty of evidence

To evaluate the certainty of evidence of the included studies, GRADE approach was used [37]. After some considerations due to heterogeneity, in vitro studies were rated as “Moderate certainty of evidence”. Summary of findings for GRADE assessment is shown in Table 3.

4. Discussion

Direct capping of exposed, vital, painless pulps aims to maintain pulpal health, thereby allowing patients to retain their teeth longer and at lower costs compared to alternative, more invasive interventions like root canal treatment [40]. An important factor influencing the potential prognosis of directly capped pulps is the capping material. Corticosteroids have been used and are especially advocated for inflamed pulps [41]. In addition to their common clinical use, corticosteroids play an active role in promoting remineralization, since they can affect the migration, proliferation and odontogenic differentiation of odontoblasts [5,42]. The present systematic review investigated the effectiveness of topical corticosteroids in promoting remineralization in human dental pulp cell cultures, as well as their ability to increase the expression of osteogenic biomarkers such as ALP, OCN, RUNX2 or DSPP. In order to decrease the methodological differences between the articles, only studies that obtained DPSCs from extracted teeth were selected. The review considered 11 in vitro studies (as shown in Tables 1 and 2) that evaluated hard tissue formation through ARS. The corticosteroids studied were dexamethasone, addressed in 8 studies [1,5,8,11,12,22,33,38]; betamethasone approached in 2 studies [9,39]; and fluocinolone acetonide, applied in only 1 study [10].

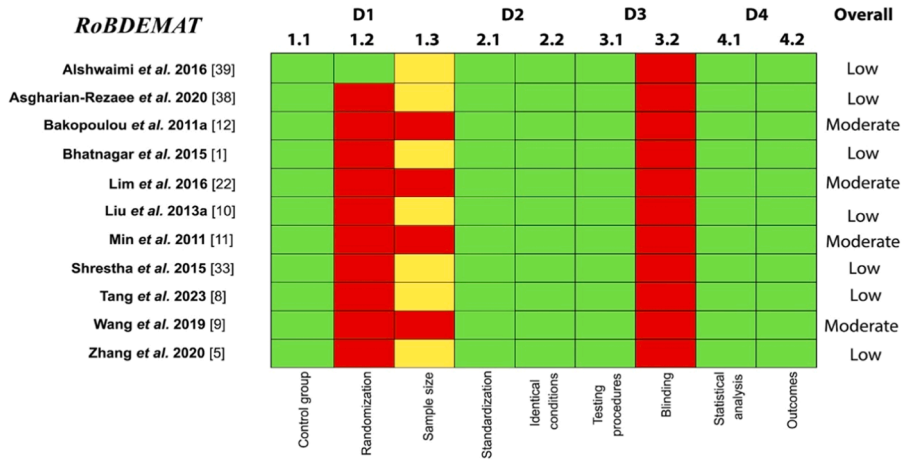

Fig. 2. Risk of bias assessment using RoBDEMAT tool. Each question was considered as “sufficiently reported” (green), “insufficiently reported” (yellow) or “not reported” (red).

Table 2
Primary and secondary outcomes related to cell mineralization and osteogenic differentiation.

Author/Date	Passages (n)	Mineralization	ALP Activity	Secondary Outcomes
Alshwaimi et al. 2016 [39]	NR	Thickness of dentinal bridge: 1) BG1= 7.19 μm (2 weeks) 2) BG2= 22 μm (8 weeks) 3) MTA1= 31.04 μm (2 weeks) 4) MTA2= 78.5 μm (8 weeks)	NR	NR
Asgharian-Rezaee et al. 2020 [38]	4	ARS: ODM group showed higher remineralization than control group and almost the same as other test group (OBM + diphenylhydantoin)	ODM group obtained higher ALP activity than control group but lower than the other test group (DPH)	OSP and RUNX2: No significant difference between test groups
Bakopoulou et al. 2011a [12]	2–6	ARS: 1) After 3 weeks, DPSCs and SCAP induced close to 100 % mineralization of the adherent monolayer 2) The mineralization potential was significantly higher in SCAP	90 % to 100 % of the cell population from SCAP and DPSCs-induced cultures obtained a strong ALP activity	DSPP and OCN: SCAP showed a significantly higher proliferation rate
Bhatnagar et al. 2015 [1]	NR	ARS: 1) The surfaces of all samples were covered by a solid sheet of mineralized deposit 2) The mineralized layer thickness seems to be the same for all samples and is not a consequence of the hydrogel modulus or the presence of dexamethasone.	ALP activity does not depend on dexamethasone. The non-induced hard gel obtained the highest ALP expression	DSPP and OCN: ALP = DSPP = OCN
Lim et al. 2016 [22]	NR	ARS: 1) Dex- containing media obtained the highest mineralization 2) BGN + Dex > BGN 3) Dex-containing media > BGN-Dex	1) Dex- containing media obtained the highest ALP activity 2) BGN + Dex > BGN 3) Dex-containing media > BGN-Dex	DSPP, RUNX2 and DMP-1: At day 14, BGN + Dex showed the highest expression
Liu et al. 2013a [10]	4–6	ARS: Fluocinolone acetonide groups do not formed any mineralized nodes	ALP activity was significantly higher when a concentration of 10 μmol/L was used compared to the concentration of 0-μmol/L	OCN: 1 μmol/L and 10 μmol/*L* > 0 μmol/L BSP and DSPP: 10 μmol/*L* > 1 μmol/*L* > 0 μmol/L (SS)
Min et al. 2011 [11]	13	ARS: After 2 weeks, cell cultured + additives group formed a wide sheath of mineral deposits, and the entire adherent layer was covered	ALP activity was significantly increased in cell cultured + additives group	OCN and DSPP: Cell cultured + additives group obtained higher expression levels than control group DMP-1: DMP-1 expression was slightly higher in cell cultured + additives group
Shrestha et al. 2015 [33]	3–5	ARS: At 3 weeks, Dex-CSnp II > Dex- CSnp *I* > > Csnp	1) At 2 weeks, Dex-CSnp II > Dex- CSnp I > Csnp 2) At 3 weeks ALP actvity decrease significantly	DSPP: At 3 weeks, Dex-CSnp II > Dex-CSnp *I* > > Csnp DMP-1: At 2 and 3 weeks, Dex-CSnp II > Dex- CSnp I > Csnp
Tang et al. 2023 [8]	3–4	ARS: Passage 3 and 4: Dex1 was significantly higher than Dex0, Dex10 and Dex 100	NR	COL1α1: COL1α1 expression significantly decreases in Dex groups
Wang et al. 2019 [9]	3–4	ARS: 1) Significantly more mineralized nodes formed in the betamethasone treated groups than in the other groups 2) OBM + LPS + BETA showed the highest results	Groups containing betamethasone resulted in a significantly higher ALP activity	OCN, RUNX2 and DSPP: Significantly higher in groups containing betamethasone
Zhang et al. 2020 [5]	2	ARS: 1) DHHAM > Dex > HHAM > Control 2) DHHAM was significantly higher than Dex	DHHAM group obtained more ALP activity than Dex group	OCN, RUNX2, DSPP and DMP-1: DHHAM > Dex > HHAM > Control

ALP: alkaline phosphatase; ARS: alizarin red S; BETA: betamethasone; BG: betamethasone/gentamicin; BGN: bioactive glass nanoparticle; BSP: bone sialoprotein; COL1α1: collagen type 1, alpha1; CSnp: chitosan nanoparticle; Dex: dexamethasone; DHHAM: dexamethasone hollow hydroxyapatite microspheres; DMP-1: dentin matrix protein 1; DPH: diphenylhydantoin group; DPSCs: dental pulp stem cells; DSPP: dentine sialophosphoprotein; HHAM: hollow hydroxyapatite microspheres; LPS: lipopolysaccharide; MTA: mineral trioxide aggregate; NR: not reported; OBM: osteogenic basal medium; OCN: osteocalcin; ODM: osteogenic dexamethasone medium; OSP: osteopontin; RUNX2: runt-related transcription factor 2; SCAP: stem cell from apical papilla; SS: statistical significance.

Regarding dexamethasone, several groups have used this corticosteroid to induce mineralization of dental-derived stem cells, including dental pulp stem cells, SCAP in vitro stem cells or dentin surface [12,23,42]. Nevertheless, the concentration of DEX used in these studies varies and no consensus has been achieved [8]. Variability in concentration could explain why preceding studies have led to contradictory findings regarding the effects on osteogenic differentiation. Some authors claimed that DEX suppresses osteoblast differentiation [43], whereas others reported the opposite [44]. A typical concentration of DEX used for inducing osteogenic differentiation ranges from 10 to 100 nmol/L [45]. In this systematic review, DEX achieved significantly positive results in terms of remineralization in all the studies [5,8,11,12,22,33,38], despite the fact that not all of them used the same concentrations or vehicles. Only the study by Bhatnagar et al. 2015 [1] did not find differences between groups.

The following four studies applied tissue engineering materials to deliver DEX [1,5,22,33]. Bhatnagar et al. 2015 [1] achieved similar results in terms of calcium deposits after 35 days in ARS using hydrogels

Table 3
Evaluation of Certainty of Evidence using GRADE. Summary of Findings (SoF) table.

Certainty Assessment							Nº of Patients		Effect		Certainty	Importance
N° of Studies	*Study Design*	*Risk of Bias*	*Inconsistency*	*Indirecness*	*Imprecision*	*Other Considerations*	*Topical application of corticosteroids (Test)*	*Non-application (Control)*	*Relative (95 % CI)*	*Absolute (95 % CI)*		
1. Primary Outcome: Dental Pulp Tissue Remineralization												
11	*in vitro*	Not serious	Serious[a]	Not serious	Not Serious	None	126	69	*	*	⨁⨁⨁◯ Moderate	Important
2. Secondary Outcome: ALP activity												
9	*in vitro*	Not serious	Serious[a]	Not serious	Not Serious	None	35	28	*	*	⨁⨁⨁◯ Moderate	Important

CI: confidence interval.
Explanations:.
[a] heterogeneity between studies.
* effects cannot be presented. Meta-analysis was not possible to perform due to the nature of the results.

in an induced medium with dexamethasone at a low concentration (0.00000001 M) compared to the hydrogel application in a non-induced medium (without dexamethasone). The authors suggested that the results obtained are attributable to the gelatin crosslinked hydrogel's inherent capability to induce remineralization [45]. On the other hand, Lim et al. 2016 [22] proposed the of use bioactive glass nanoparticles to carry DEX at a concentration of 0.1 μM, comparing it with DEX alone or the bioactive nanoparticles alone in a DPSCs cultured medium containing glycerophosphate (inducer). A similar study was conducted by Shreshta et al. 2015 [33] who utilized two different technologies to develop chitosan nanoparticles doped with DEX: an adsorption method and an encapsulation method, each contributing to different release kinetics. The most significant positive results were achieved with the adsorption design due to the faster release of DEX at 3 weeks. In contrast, Zhang et al. 2020 [5] employed hollow hydroxyapatite microspheres to carry DEX at a concentration of 10 mg/mL, observing significant positive results after 28 days compared to the control groups. Other studies using DEX either did not use carriers or did not report them; however, all obtained positive results [8,11,12,38]. Bakopoulou et al. 2011 [12] found that SCAPs were capable of producing significantly higher amounts of mineralization deposits compared to DPSCs, showing a more favorable differentiation and proliferation rates in the presence of DEX at 0 0.01 mM in a disodium phosphate medium (inducer).

In this systematic review, only the studies by Alshwaimi et al. 2016 [39] and Wang *et al.* 2019 [9] explored the possibility of betamethasone as a corticosteroid to induce remineralization. In the study by Alshwaimi et al. 2016 [39], betamethasone groups showed lower dentin bridge formation and a higher percentage of postoperative complication, such as abscesses and acute inflammation, compared to MTA groups when applied in vivo to premolars that were subsequently extracted. On the other hand Wang et al. 2019 [9] obtained positive results applying betamethasone in an osteogenic medium containing glycerophosphate, especially in the presence of LPS. Differences in the design of both studies do not allow for definitive conclusion to be drawn.

Regarding the application of FA, Liu et al. 2013 did not find influence after 21 days when comparing different concentrations (0 μmol/L, 1 μmol/L, and 10 μmol/L), in terms of remineralization. However, it has shown to increase ALP, OCN and DSPP expression. The authors attributed the results obtained to the absence of phosphate resources in the medium, suggesting that compounds like glycerophosphate may be necessary when using FA to promote new calcium deposits by DPSCs [10].

ALP and DMP-1 are recognized as early markers of osteo/odontogenic differentiation. OCN is indicative of the advanced stages of osteoblast differentiation. The OCN presence marks the onset of matrix deposition. BSP, a key sialoprotein in the bone extracellular matrix, is expressed simultaneously with matrix deposition and is intimately linked to the process of mineralization [22,46]. Another important biomarker is DSPP, which is initially synthesized as a precursor protein and subsequently cleaves into dentine phosphoprotein and dentine sialoprotein. These glycoproteins are commonly found in both bone and dental tissues [47]. Various transcription factors, including RUNX2, may also be analyzed in order to provide some insights about the differentiation rate of MSCs into osteoblasts and odontoblasts. These are crucial factors for ensuring mineralization during bone formation and remodeling [46]. OSP is involved in tissue mineralization. OSP production is considered a significant marker for the differentiation of dental pulp cells [48].

With reference to DPSCs activity-related marker expression, corticosteroids have shown an up-regulation of a series of odontogenic/osteogenic genes; ALP [1,5,8,11,12,22,33,38], DSPP [1,5,11,12,22,33], RUNX2 [5,9,22,38], OCN [1,5,9–12], OSP [38], DMP-1 [5,11,22,33] when compared to a control group. The up-regulation of these markers denotes their capability to induce odontogenic/osteogenic differentiation of DPSCs. Nevertheless, SCAPs seem to have a higher differentiation and proliferation rate [12]. Furthermore, a higher concentration does

not necessarily seem to be related to higher activity of biomarkers or related genes [8,10]. Tissue engineering materials could also influence the level of expression of odontogenic biomarkers, as shown by different authors [5,22,33]. Despite the variety of markers evaluated in this systematic review, the influence of corticosteroids on many of them, such as COL1α1 [8] and OSP [38], continue to be scarcely explored. Other cell activity-related biomarkers, such as matrix extracellular phosphoglycoprotein (MEPE) [49], have not yet been investigated. In addition, studies are needed to evaluate the expression of markers related to dental pulp cell migration in the presence of corticosteroids.

The nature of the control groups used for comparison was specified by all the included studies, distinguishing between negative and positive control groups. Results from the different ARS and odontogenic activity assays were analyzed using a negative control group as a reference, represented by the medium lacking the corticosteroid or the tissue engineering material, except in Bakopulou et al. 2011 [12], where the authors focused on comparing the capability of remineralization of different progenitor cells (SCAPs and DPSCs) in a DEX containing medium. Alpha minimum essential medium (α-MEM) with supplements was used by most of the investigations [1,8–10,12,22,33,38]. Other media used was Dulbecco's modified Eagle medium [10]. Supplements used included fetal bovine serum at different concentrations, and antibiotics. Some studies also included phosphate resources in the medium [1,9,10,22,38] which could positively influence the results obtained, even in control groups where corticosteroids are not present [10]. Regarding passages, most authors used a similar number of passages to reach the desired confluence, typically between 2 and 6, except for Min et al. 2011 [11] who performed 13 passages. Differences in culture media characteristics hinder the interpretation and comparison of results, highlighting the need for standardized procedures in future studies.

The application of tissue-engineered materials to carry dexamethasone or other corticosteroids seems beneficial, as they can provide a more sustainable release, reduce toxicity and allow for longer therapeutic effects [5,33,42]. This could explain why optimal results have not yet been achieved in vivo [39]. Despite noticeable methodological differences among the selected studies, the majority of corticoids at different concentrations showed a significant capability of promoting remineralization mediated by DPSCs. Additionally, an increased expression of various osteogenic biomarkers was observed. To the authors' knowledge, this is the first systematic review assessing the influence of different corticosteroids on human stem cells from extracted teeth. Considering the scarcity and in vitro characteristics of the available evidence on this matter, extrapolating the results obtained to a clinical level is premature. This represents the main limitation of this review. In addition, a quantitative analysis or meta-analysis could not be performed because of the methodological heterogeneity in both the assays conducted and the outcomes measured, along with the small number of studies included in this review. Due to this mentioned methodological heterogeneity, it would be impossible to perform a global meta-analysis. It should be necessary to perform sub-group analysis with a very limited number of included articles per group. Therefore, future standardized studies are needed to confirm the remineralizing capability of corticosteroids on DPSCs, as well as to determine their optimal concentrations and carriers. It would be advisable to advance into in vivo trials and expand the range of assays performed under different conditions, while maintaining uniformity in the used methodology.

5. Conclusion

Considering the scarcity of the available evidence, more studies are needed to affirm the effectiveness of topical corticosteroids as remineralizing agents. Overall, mineral deposition was observed in alizarin red staining when corticosteroids, especially dexamethasone, were employed. Additionally, the use of corticosteroids led to an up-regulation of different osteogenic/odontogenic biomarkers, enhancing the differentiation and proliferation of human dental pulp cells. Further high-quality clinical trials are required to confirm these findings.

Registration and protocol

PROSPERO identification number was CRD42023422073 after an exhaustive assessment.

CRediT authorship contribution statement

Marta Vallecillo-Rivas: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Enrique Fernández-Romero:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization. **Michelle Pérez-Segura:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Raquel Toledano:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Anisa Amar-Zetouni:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Manuel Toledano:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Cristina Vallecillo:** Writing – review & editing, Supervision, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The present study was supported by Grant PID2020–114694RB-I00 funded by MCIN/AEI 10.13039/501100011033.

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