

THE ROLE OF BONE ANABOLIC DRUGS IN THE MANAGEMENT OF PERIODONTITIS: A SCOPING REVIEW

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Abstract

The aim of this scoping review was to summarise current knowledge about the effects of bone anabolic drugs on periodontitis, in order to identify new therapeutic strategies for preventing disease progression and reducing tooth loss. A technical expert panel (TEP) was established of 11 medical specialists, including periodontists and bone specialists that followed the PRISMA-ScR model to perform the scoping review and considered for eligibility both pre-clinical and clinical studies published in the English language up to September 2020. 716 items were initially found. After duplicate removal and screening of articles for eligibility criteria, 25 articles published between 2001 and 2019 were selected. Only studies concerning teriparatide, strontium ranelate, sclerostin antibodies and DKK1 antibodies met the eligibility criteria. In particular, only for teriparatide were there both clinical studies and experimental studies available, while for other bone anabolic drugs only animal studies were found. Available evidence about the use of bone anabolic drugs in periodontology demonstrates beneficial effects of these agents on biological pathways and histological parameters involved in periodontal tissue regeneration that suggest relevant clinical implications for the management of periodontitis.

Keywords: Periodontitis, parathyroid hormone, teriparatide, strontium ranelate, romosozumab, calvarial bone defect, alveolar bone, DKK-1 antibodies, sclerostin antibodies.

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List of Abbreviations

ACS	absorbable collagen sponge	hnRNPL	heterogeneous nuclear ribonucleoprotein L
Akt	protein kinase B	HO-1	haem oxygenase-1
BMD	bone mineral density	ITR	Induced tissue regeneration
CAL	clinical attachment level	LRP 5/6	low-density lipoprotein receptor-related protein 5/6
C-AMP	cyclic adenosine monophosphate	MMP	matrix metalloproteinase
CaSR	calcium-sensing receptor	NCBI	National Center for Biotechnology Information
CBCT	cone beam computed tomography	NF-KB	nuclear factor kappa-light-chain-enhancer of activated B cells
CEJ	cemento-enamel junction	OCP	octacalcium phosphate
DBM	demineralised bone matrix	OFD	open flap debridement
DFDB	demineralised freeze-dried bone	OPG	osteoprotegerin
DKK1-AB	dikkopf-1 antibody	P	phosphate
DRESS	drug rash with eosinophilia and systemic symptoms	PCNA	proliferating nuclear antigen
EMA	European Medicines Agency	PD	probing depth
EMD	enamel matrix derivative	PDE4	phosphodiesterase type 4 inhibitor
GTR	Guided tissue regeneration	PDLC	periodontal ligament cell
HBO	hyperbaric oxygen therapy		

PMN	polymorphonuclear neutrophil leukocytes
PRISMA-ScR	Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PubMed	public MedLine, run by the National Center of Biotechnology Information, NCBI, of the National Library of Medicine of Bethesda, Bethesda, MD, USA
RANK	receptor activator of nuclear factor-kappa B
RANKL	receptor activator of nuclear factor-kappa B ligand
RCT	randomised clinical trial
rhBPM	recombinant human bone morphogenetic protein
rhPTH	recombinant human parathyroid hormone
Scl-Ab	antibodies neutralising sclerostin
SCL-AB	sclerostin antibody
SPG	self-assembling peptide gel
SOST	sclerostin
SR	strontium ranelate
SRP	scaling and root planing
TCP	tricalcium phosphate
TEP	technical expert panel
TGF	transforming growth factor
TPD	teriparatide
VEGF	vascular endothelial growth factor
Wnt	wingless and Int-1
β -cat	β -catenin

Introduction

Periodontitis is a chronic inflammatory, infectious disease of tooth-supporting tissues associated with dysbiotic dental plaque biofilms. The imbalance between local microbiota colonisation and reaction of host cells could amplify a pro-inflammatory cytokine cascade and specific immune cell recruitment, activation and differentiation (Bartold and Van Dyke, 2013) leading to the progressive loss of periodontal attachment, supporting bone, and, eventually, to tooth loss (Page *et al.*, 1997). In these complex pathophysiological mechanisms, bone homeostasis is altered by the inflammatory response due to periodontitis, with the activation of osteoclast cell populations and the impairment of osteoblast activity, thus leading to bone resorption and to the formation of periodontal bone defects (Hienz *et al.*, 2015; Schulze-Späte *et al.*, 2015). Periodontitis is the major cause of edentulism in adults of industrialised countries (Pihlstrom *et al.*, 2005). The primary aims of periodontal treatment are to resolve the inflammatory process, to arrest the progression of the disease and to prevent tooth loss. The mechanical debridement of dental and root surfaces by SRP is considered the gold standard for periodontal therapy (Van der Sluijs *et al.*, 2016). However, various surgical techniques can help in arresting the progression of the pathology and provide the patient with a stable and maintainable

condition. Regenerative surgery, one of the most fascinating approaches, leads to the true regeneration of periodontal deep tissues, including the alveolar bone, and restores the lost periodontal attachment (Cortellini and Tonetti, 2015a). Pharmacological treatment, administered either systemically or locally at the level of periodontal tissues, could improve the results of already recommended therapies.

Considering pathophysiological mechanism of periodontal disease, osteoanabolic agents have received an increasing interest as a potential adjunctive treatment. These drugs enhance bone remodelling, particularly bone formation, resulting in bone accrual, and are recommended for the treatment of severe osteoporosis (Khosla and Hofbauer, 2017). Several agents are included in this drug class. Teriparatide, a recombinant form of parathyroid hormone consisting of the first (N-terminus) 34 amino acids, which is the bioactive portion of the hormone, is the most commonly used bone anabolic drug for osteoporotic patients. This agent stimulates bone formation to a greater extent and earlier than bone resorption, creating a window during which its anabolic properties are maximised (anabolic window). Abaloparatide is a synthetic analogue of a PTHrP that interacts with the same receptor as teriparatide (PTHrP1), with stronger binding affinity to G protein-dependent RG conformations, resulting in higher activity of osteoblasts with enhanced anabolic effect (Hattersley *et al.*, 2016).

SR is an anti-osteoporotic drug consisting of 2 atoms of stable strontium and an organic moiety (ranelic acid). This agent seems to have a dual mode of action, by stimulating bone formation and reducing bone resorption, thus rebalancing bone turnover in favour of bone accrual (Iolascon *et al.*, 2014). At the cellular level, SR activates the CaSR in osteoblasts with consequent increase in intracellular calcium that seems to promote osteogenic gene expression in these cells.

Recently, new molecules that stimulate bone formation by targeting the Wnt/ β -cat pathway have appeared (Iolascon *et al.*, 2020). Scl-Ab and DKK1-Ab constitute a new drug class for osteoporosis treatment, acting through the Wnt pathway modulation that has a crucial role in osteoblast proliferation, differentiation, and function. Romosozumab is a humanised monoclonal sclerostin antibody that has completed phase III studies for the treatment of osteoporosis and has been marketed in USA, Canada, Japan, South Korea and Australia and it was authorised for use in the European Union in February 2020 by the EMA. Sclerostin, a protein produced by osteocytes, prevents binding of Wnt to its receptors (LRP 5/6 and Frizzled co-receptor) leading to the differentiation, proliferation and survival of osteoblasts, thus reducing bone formation. Romosozumab works by binding to sclerostin thus preventing inhibition of bone formation by modulating the Wnt pathway (Lim and Bolster, 2017). Considering the mechanism of action of these

Table 1. Search strategy.

(periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect) AND (teriparatide OR "parathyroid hormone (1-34)")
(periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect) AND strontium ranelate
(periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect) AND dkk1 antibody
(periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect) AND abaloparatide
(periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect) AND romosozumab
(periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect) AND Parathyroid hormone-related protein (1-84)
(periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect) AND (antisclerostin OR "sclerostin antibody")

Table 2. Eligibility criteria. The rat calvarial defect is considered to be a reliable model for pre-clinical evaluation of bone regeneration for human applications in the craniofacial complex (Gomes and Fernandes, 2011; Muschler *et al.*, 2010; Spicer *et al.*, 2012). It has been shown that its physiological behaviour is similar to that of human mandibular bone (An *et al.*, 2017); moreover, the compressive forces generated after bone regeneration in rat calvarial critical size defects are similar to those found in intraoral conditions (Choi *et al.*, 2010). Furthermore, such an experimental model may represent a useful screening platform for candidate osteoconductive and osteoinductive devices or substances (Pelaez *et al.*, 2014). For these reasons, rat calvarial critical size defect may represent a useful pre-clinical model in the field of periodontal regeneration.

Eligibility criteria
<p><i>Inclusion criteria:</i></p> <p>Preclinical studies:</p> <p>Animal studies about effects of osteoanabolic drugs, delivered locally or systemically, on:</p> <ul style="list-style-type: none"> • periodontal tissues • periodontitis • periodontal therapies, both surgical and non-surgical • regeneration of critical size rat calvarial defects (diameter > 5 mm)* <p>Clinical studies, both interventional and observational, about the efficacy and effectiveness of osteoanabolic drugs, delivered locally or systemically, on:</p> <ul style="list-style-type: none"> • periodontal tissues • periodontitis • periodontal therapies, both surgical and non-surgical
<p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"> • Review articles • Conference abstracts and editorials • Animal studies about the regeneration of defects different from rat calvarial critical size defects • Animal studies about the regeneration of rat calvarial non-critical size defects (diameter < 5 mm) • Studies about use of osteoanabolic drugs for the treatment of conditions other than periodontal disorders

bone anabolic drugs, their potential role for treating periodontal disease can also be speculated upon.

The aim of this scoping review was to summarise current knowledge concerning the role of osteoanabolic drugs on periodontal tissues, periodontitis and periodontal therapy, paying particular attention to periodontal regenerative treatment, in order to identify new therapeutic strategies useful for preventing disease progression and reduce tooth loss associated with periodontitis.

Materials and Methods

In performing this scoping review, the PRISMA-ScR model (Tricco *et al.*, 2018) was followed. As a first

step, a TEP consisting of 11 medical specialists was established. In particular, the TEP was composed of 4 periodontists (one expert in healing processes (G.C.), two in periodontal tissues regeneration (M.A. and L.N.) and one in dental implantology (L.G.)), one oral surgeon (L.L.), three bone specialists (G.I., F.G., and A.M.), one orthopedic surgeon (G.T.), and two experts in scoping review methodology (M.P. and S.L.). The TEP investigated the effects of the following osteoanabolic drugs used in the periodontal field: SR, PTH (1-84), teriparatide, abaloparatide, DKK1-AB, and SCL-AB.

Search strategy

The TEP planned a search on PubMed, with an *ad-hoc* search string of selected keywords for the periodontal

Table 3 – part 1. Characteristics and main findings of the included studies.

Author, year	Osteoanabolic drug	Study design	Administration route	Sample size: Total (group)	Main findings
Andreassen <i>et al.</i> , 2004	Teriparatide	Animal	Systemic	44 (22 × 2 groups)	Rats treated with PTH (1-34) (60 µg/kg daily) showed increased tissue dry weight, ash content and concentration of the new tissue, and mechanical strength compared with vehicle-injected animals inside 5 mm diameter rat calvarial defects covered with membranes.
Marques <i>et al.</i> , 2009	Teriparatide	Animal	Systemic	76 (38 × 2 groups)	Periodontal tissue samples from rats with experimental periodontitis treated with PTH (1-34) (40 µg/kg daily) showed a decreased MMP-9 activity, decreased level of interleukin-6 and of MMP-2, and a lower number of osteoclasts.
Yun <i>et al.</i> , 2010	Teriparatide	Animal	Systemic	100 (20 × 5 groups)	8 mm calvarial defects of rats treated with PTH (1-34) (15 µg/kg daily) without an adjunctive biomaterial showed significant bone formation, while in defects treated with β-TCP, with or without PTH (1-34), or DFDB or controls it was limited. Groups treated with β-TCP showed limited biomaterials resorption and bone formation.
Staocnven <i>et al.</i> , 2013	Teriparatide	Animal	Systemic	160 (20 × 8 groups)	PTH (1-34) (15 µg/kg daily) showed no meaningful additive effect on local bone formation in 8 mm diameter calvarial rat defects treated with DBM, ACS, rhBPM-2/ACS or left empty. The greatest bone formation was obtained with rhBPM-2/ACS.
Yakubovich <i>et al.</i> , 2017	Teriparatide	Animal	Systemic	36 (18 × 2 groups)	In mice with 5 mm diameter calvarial defects treated with decellularised allografts, leaving no direct contact with the host bone, teriparatide treatment (40 µg/kg daily) induces the formation of more developed capillary beds. Immunostaining showed lower levels of TGF-β in teriparatide-treated mice. Denser collagen fibres were found to bridge the gap between allograft and host in teriparatide-treated animals than in control animals, in which mesenchymal tissue was found within the gap. Bone volume was two times larger in animals treated with teriparatide. Altogether, these findings suggest that teriparatide redirects the fibrotic process taking place around the graft to regenerative bone formation.
Kajji <i>et al.</i> , 2018	Teriparatide	Animal	Local	18 (6 × 3 groups)	The addition of teriparatide solution (1.0 or 0.1 µg) on OCP/collagen disk implanted in 9 mm calvarial rat defects significantly improved bone regeneration, showing better results than OCP/collagen alone both at the µCT and at the histological analysis.
Iwai <i>et al.</i> , 2018	Teriparatide	Animal	Local	30 (5 × 6 groups)	The addition of teriparatide (1.0 or 0.1 µg) in disks composed by OCP or β-TCP and collagen significantly improved new bone formation in 9 mm diameter rat calvarial defects.
Park <i>et al.</i> , 2019	Teriparatide	Animal	Systemic	24 (8 × 3 groups)	rhPTH (1-34) (30 µg/kg daily) alone, or in combination with HBO significantly increased bone formation in 5 mm diameter calvarial defects in rats that previously received localised radiation in that region. The new bone surface and residual material surface density of the PTH/HBO group was significantly higher than that of the control and PTH groups.
Yoshida <i>et al.</i> , 2019	Teriparatide	Animal	Systemic	40 (10 × 4 groups)	Systemic PTH (1-34) (40 µg/kg every 2 days) treatment led to a significantly higher bone volume and significantly lower trabecular separation compared to placebo groups in surgically created periodontal defects in rats. The group treated with PTH (1-34) and SPC-178 showed the greatest bone formation.
Bashutski <i>et al.</i> , 2010	Teriparatide	RCT	Systemic	40 (20 × 2 groups)	At 12 months follow-up, patients treated with OFD and 20 µg of teriparatide from 3 d before surgery and for 6 weeks after showed a mean linear gain in bone of 1.86 mm, compared with 0.16 mm in patients not receiving teriparatide; the average reduction in PD was 2.42 mm in the teriparatide group, compared with 1.32 mm in the placebo group, and mean gains in CAL were 1.58 mm compared with 0.42 mm.
Bashutski <i>et al.</i> , 2012	Teriparatide	Case report	Systemic	N/A	A patient receiving OFD and daily assumption of 20 µg teriparatide from 3 days before surgery and for 6 weeks after showed a relevant reduction of PD and CAL values on palatal and buccal aspects of tooth #16 at both 1- and 4-years follow-up, indicating long-term stability. The patient had also a near-complete osseous fill of an intrabony defect on the mesial aspect of the same tooth evident with CBCT scans at 12 months and confirmed radiographically at 4 years.

Table 3 – part 2.

Buehler <i>et al.</i> , 2001	Strontium ranelate	Animal	Systemic	31 (8 × 3 groups, 7 × 1 group)	Monkeys treated for 6 months with of SR showed decreased histomorphometric indices of bone resorption, while no effect on bone formation parameters in alveolar bone was seen.
Nahass <i>et al.</i> , 2017	Strontium ranelate	Animal	Local	48 (8 × 6 groups)	The application of a single dose of SR (2.5 and 5 mg) dissolved in methylcellulose gel in 8 mm diameter calvarial defects led to more attempts at bone formation, with marked osteoblastic proliferation and less inflammatory reaction; while a 10 mg dose led to no osteoblastic proliferation at all; large areas of defect filled with fibroblasts, and collagen fibres with heavy inflammatory cell infiltrate.
Karakan <i>et al.</i> , 2017	Strontium ranelate	Animal	Systemic	40 (8 × 5 groups)	SR administration decreased osteoclast number and alveolar bone resorption in rats with ligature induced periodontitis. A high SR dose (900 mg/kg) led to a RANKL activity in ligature-induced periodontitis rats to levels comparable to control rats.
Masalskas <i>et al.</i> , 2018	Strontium ranelate	Animal	Local	21 (7 × 3 groups)	Local delivery of SR at 50 mmol/L results in higher bone volume, bone surface, trabecular thickness after 6 weeks in rats with critical calvaria bone defects of 5 mm, compared to defects treated with 5 mM of SR or without SR.
Souza <i>et al.</i> , 2018	Strontium ranelate	Animal	Systemic	48 (6 × 8 groups)	Strontium ranelate (100 mg/kg) reduces HO-1 mRNA expression on day 7 and reduced alveolar bone loss in rats with ligature induced periodontitis.
Denry <i>et al.</i> , 2018	Strontium ranelate	Animal	Local	40 (10 × 4 groups)	Strontium-free glass-ceramic scaffold use results in higher newly formed bone in rat calvarial defects of 8 mm than other scaffolds with strontium incorporation at 8-week follow-up.
Goker <i>et al.</i> , 2018	Strontium ranelate + PTH	Animal	Local	90 (10 × 9 groups)	The combination of PTH and SR-containing poloxamer implant tablets revealed statistically significant higher levels of new bone regeneration in rat calvarial critical size defects of 5 mm when compared to either treatment alone.
Jia <i>et al.</i> , 2019	Strontium ranelate	Animal	Local	15 (5 × 3 groups)	In osteoporotic rat with periodontal fenestration defect (2.8 × 1.4 × 0.5 mm), porous strontium-incorporated mesopore-bioglass scaffold down-regulates hnRNPL through the activation of AKT pathway stimulating osteogenic differentiation of PDLCs and promotes periodontal regeneration.
Marins <i>et al.</i> , 2020	Strontium ranelate	Animal	Systemic	96 (24 × 4 groups)	SR (625 mg/kg/d ²⁵) significantly increases trabecular bone area at 10 and 30 d in mandibular bone and prevents bone loss in rats with ligature induced periodontitis.
Taut <i>et al.</i> , 2013	Antisclerostin (ratified monoclonal Scl-Ab III)	Animal	Systemic and local	52 (15 systemic treatment vs. 17 control; 18 local treatment vs. 19 control)	In rats with localised alveolar bone defects created with ligatures, systemic administration of anti-sclerostin at a dose of 25 mg/kg, twice weekly reversed bone loss, with a significant improvement after 6-week treatment. In contrast, twice weekly local injection of anti-sclerostin after experimental periodontitis exhibited a limited regenerative effect on volumetric alveolar bone healing.
Chen <i>et al.</i> , 2015	Antisclerostin (ratified monoclonal Scl-AbVI)	Animal	Systemic	40 (10 × 4 groups)	6 weeks of antisclerostin treatment (25 mg/kg subcutaneously twice weekly) in rats with ligature induced periodontitis resulted in a significant decrease in the distance from CEJ to the alveolar bone crest, significantly higher bone mineral density, bone volume fraction, trabecular thickness and number compared to vehicle treated groups. Antisclerostin treated ovariectomised rats with periodontitis showed higher bone mineral apposition rate and lower alveolar bone resorption compared to rats receiving vehicle.
Han <i>et al.</i> , 2015	Antisclerostin (humanised monoclonal Scl-Ab III)	Animal	Local	12 (4 × 3 groups)	LiCl and sclerostin antibody stimulate new bone and cementum formation in periodontal defects of rats by enhancing canonical Wnt signalling in cementocytes, cementoblasts, osteoblasts and osteocytes.
Liu <i>et al.</i> , 2018	Antisclerostin (SAB-VI) and DKK1 antibody	Animal	Systemic	40 (10 × 4 groups)	Sclerostin antibody alone and in combination with DKK1 antibody administered subcutaneously twice-weekly for 5 weeks (both 18.1 mg/kg), increased the volume and height of alveolar ridges in ovariectomised rats. Height augmentation with sclerostin and DKK1 antibody combination significantly exceeded that of the sclerostin antibody alone.
Tamplen <i>et al.</i> , 2018	Antisclerostin (monoclonal Scl-Ab VI)	Animal	Systemic	19 (10 wild type and 9 Ts65)	Intravenous antisclerostin at 100 mg/kg, weekly for 3 weeks, significantly decreased the average CEJ-alveolar bone crest distance.

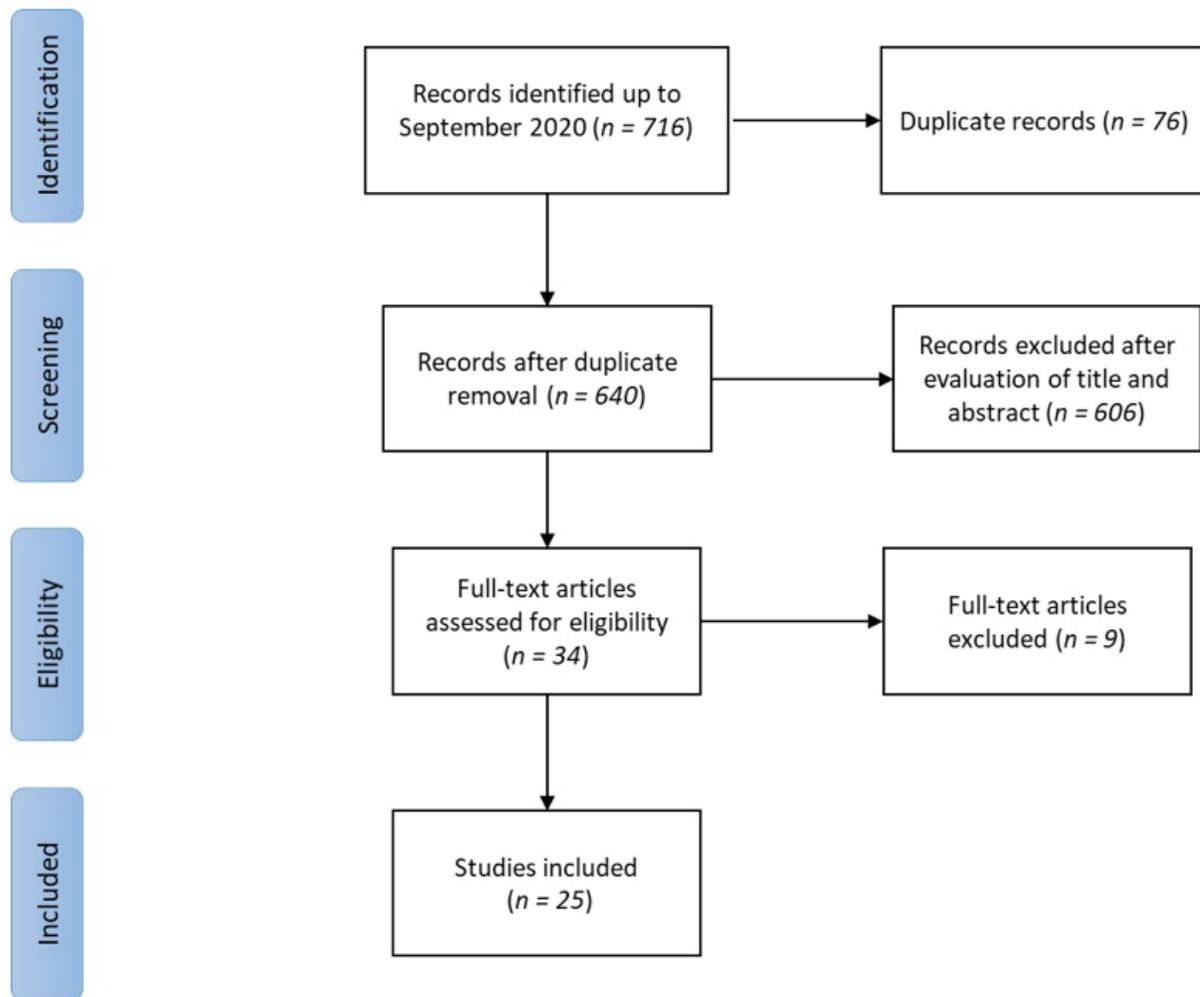


Fig. 1. Flow diagram of sources selection process.

field (periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect), combined with terms regarding osteoanabolic drugs [*e.g.* (periodontal OR periodontium OR periodontitis OR alveolar bone OR regeneration OR calvarial defect OR calvarial bone defect) AND (teriparatide OR “parathyroid hormone (1-34)”). More details about the search strategy are reported in Table 1.

Study selection

According to the study objective, the TEP defined the characteristics of the evidence sources, considering for eligibility any research published in the medical literature until September 1st 2020 and including only those in the English language. Eligibility criteria are reported in Table 2.

Data extraction and quality assessment

Animal studies meeting the eligibility criteria, clinical research including interventional (randomised or non-randomised controlled clinical trials) and observational studies, and case series or case reports were selected. Results and findings from each included study were analysed qualitatively.

Results

716 items were initially found. After duplicate removal, 640 records remained; they were screened on the basis of titles and abstracts for the inclusion/exclusion criteria and 606 studies were excluded. After full text reading of the remaining 34 papers, 9 of them were excluded because the characteristics of the tissue defect used in those studies did not fulfil the inclusion criteria. Finally, 25 articles published between 2001 and 2019 were selected for the present scoping review. Among osteoanabolic agents initially considered, only studies about teriparatide, SR, SCL-AB and DKK1-AB met the eligibility criteria. In particular, 11 papers were included regarding teriparatide, 2 clinical studies (1 randomised clinical trial, RCT, and 1 case report) and 9 animal studies, 9 animal studies about SR, 4 animal studies about SCL-AB and 1 study regarding sclerostin and DKK1 antibodies. No studies about abaloparatide, romosozumab and PTH 1-84 met the eligibility criteria. The selection process for papers is shown in Fig. 1. The characteristics and main findings of the included studies are shown in Table 3.

Among studies regarding teriparatide, 9 of them focused on its systemic administration, while 2 of

them on local administration. 4 studies investigated systemic administration effects of strontium ranelate and 5 investigated local administration effects. 1 study regarding sclerostin antibody evaluated the effects of both systemic and local administration, 2 regarded systemic administration only, 1 local administration. Only 1 study focused on combined systemic administration of sclerostin and DKK1 antibodies.

Teriparatide

Animal studies

7 studies focused on the effects of teriparatide, systemically or locally administered, on critical size defect regeneration in rat calvarial bone.

Andreassen and Cacciafesta (2004) showed that systemic administration of teriparatide (60 µg/kg daily) in rats increased tissue dry weight, ash content and concentration of the new tissue, and its mechanical strength in 5 mm calvarial defects treated with polytetrafluoroethylene membranes. Yun *et al.*, (2010) found that systemic teriparatide (15 µg/kg daily) stimulates higher levels of bone formation compared to local administration of biomaterials (β-tricalcium phosphate, TCP, or demineralised freeze-dried bone) for 8 mm critical calvarial defect treatment. Cohn Yakubovich *et al.* (2017) showed significantly more bone matrix in animals with 5 mm calvarial defects receiving teriparatide (40 µg/kg daily) compared to controls (treated with decellularised allografts). Furthermore, the authors highlighted that teriparatide improved capillary bed formation close to a graft with denser collagen fibres bridging the gap between defect margins and the graft, when compared to control group.

Park *et al.* (2019) demonstrated that systemic teriparatide (30 µg/kg daily) improved bone regeneration of calvarial defects in rats that had previously received localised radiation, both in combination or not with hyperbaric oxygen therapy. However, Staconven *et al.* (2013) showed that systemic teriparatide (15 µg/kg daily) caused no additional significant effect on local bone formation in 8 mm diameter calvarial rat defects treated with DBM, ACS, or ACS combined with rhBPM-2.

Considering local application of teriparatide (1.0 or 0.1 µg), Kajii *et al.* (2018) found that local drip of this drug into rat calvarial defects treated with OCP and collagen composite, led to a significantly higher percentage of newly formed bone, independently from teriparatide dosage. Similarly, Iwai *et al.* (2018) showed that adding teriparatide (1.0 or 0.1 µg) in disks composed by OCP or β-TCP with collagen, significantly enhanced bone healing of critical size defects in rat calvaria.

Marques *et al.* (2009) investigated the effects of systemic intermittent administration of teriparatide (40 µg/kg daily) on periodontal tissues in rats with ligature-induced experimental periodontitis. This intervention decreased the activity of MMP-9, the levels of interleukin-6, MMP-2 and osteoclasts

number in periodontal tissues. Yoshida *et al.* (2019) compared the effects of systemic teriparatide (40 µg/kg every 2 d) alone, a combination of teriparatide and SPG-178, and a combination of SPG-178 and saline injections on the tissue healing of surgically created periodontal defects in animal models. They found that teriparatide increased bone volume and reduced trabecular separation, whereas the teriparatide/SPG-178 resulted in the most bone formation, as observed histologically, probably by increasing osteoblast proliferation and differentiation as well as angiogenesis.

Clinical studies

In the present scoping review, 2 clinical studies regarding the effects of systemic teriparatide administration were included.

Bashutski *et al.* (2010), performed a RCT investigating the efficacy of teriparatide on periodontal osseous defect in 40 patients with periodontitis treated with OFD. Patients were randomly divided into 2 groups: 1 group received 20 µg of daily systemic subcutaneous teriparatide from 3 d before surgery to 6 weeks after, while the other group received a placebo. The treatment group, at 1-year follow-up, showed significantly more bone gain and CAL improvement with PD reduction compared to the placebo group (Table 3). These clinical and anatomical results were confirmed even at a 4-year follow-up in a case report published by same authors in 2012 (Bashutski *et al.*, 2012).

Strontium ranelate

Concerning the evidence about the effects of SR on the treatment of periodontal disorders, no clinical studies were found. 4 studies investigated the local effects of SR on bone healing of critical size defects of rat calvaria. Nahass *et al.* (2017) evaluated the effects of different doses of SR locally dissolved in a methylcellulose gel on the regeneration of 8 mm diameter calvarial defects in rats. They found that 2.5 mg and 5 mg doses helped bone regeneration by increasing osteoblastic proliferation and reducing inflammation. On the other hand, higher dosage (10 mg) of SR worsened the healing process, due to reduction of osteoblastic proliferation with large areas of the defects filled by fibroblasts and collagen fibres along with greater inflammatory cell infiltrate.

Masalskas *et al.* (2018) found that 50 mmol/L of SR, combined with collagen sponges, significantly enhanced bone regeneration of critical size rat calvarial defects – resulting in larger bone volume, bone surface and trabecular thickness compared to defects treated with 5 mmol/L of SR and collagen sponges or collagen sponges alone. Conversely, Denry *et al.* (2018) showed that adding strontium to akermanite glass-ceramic scaffolds did not result in increasing newly formed bone. Goker *et al.* (2018) reported that combined administration of PTH 1-34 and SR in poloxamer tablets resulted in statistically significant higher levels of new bone regeneration

compared to PTH or SR poloxamer tablets alone in critical size calvarial defects in ovariectomised rats.

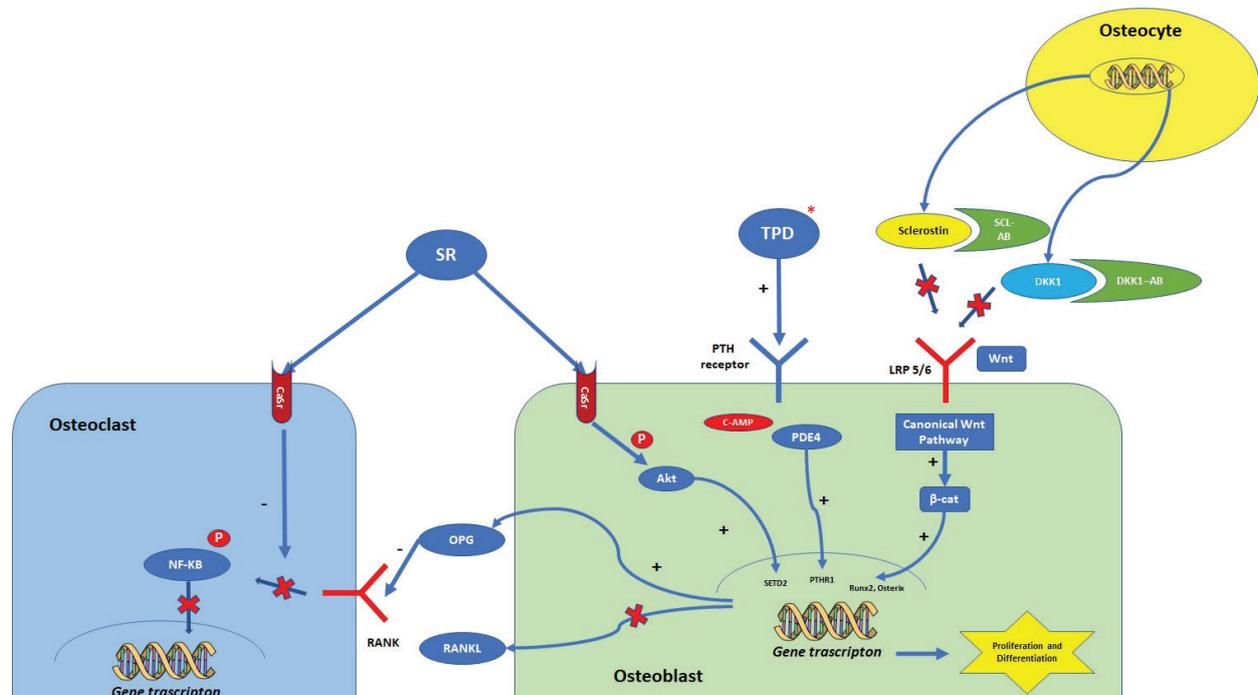
4 papers evaluated the effects of systemic SR in animal models of periodontitis. Karakan *et al.* (2017) showed that systemic administration of this drug decreased osteoclast number and alveolar bone resorption in rats with ligature-induced periodontitis. In particular, a high SR dose (900 mg/kg) decreased the RANKL activity up to levels comparable to control group without periodontitis. Also, Souza *et al.* (2018) found that systemic SR reduced alveolar bone loss in rats with periodontitis, with lower HO-1 mRNA expression involved in periodontitis. Marins *et al.* (2020) found a significant higher trabecular bone area at 10 and 30 d after systemic administration of SR in rats with ligature-induced periodontitis. Buehler *et al.* (2001) investigated the effects of systemic treatment with SR on the alveolar bone of monkeys. They found that a 6-month therapy decreased histomorphometric indices of bone resorption with no significant effects on bone formation parameters. Finally, Jia *et al.* (2019) found that the incorporation of strontium into porous mesopore-bioglass scaffolds exerted effects on heterogeneous nuclear ribonucleoprotein L, determining its down-regulation, through the activation of the Akt pathway. The same beneficial effects are shown on periodontal defects regeneration in osteoporotic rats, because of osteogenic differentiation stimulation of periodontal ligament cells.

Sclerostin and DKK-1 antibodies

No clinical studies investigating the effects of sclerostin and/or DKK-1 antibodies were found.

2 studies investigated the effects of systemic sclerostin antibody for treatment of periodontitis in animal models. Chen *et al.* (2015) analysed the effects of antisclerostin (25 mg/kg subcutaneously twice weekly) in rats with ligature induced periodontitis and found reduced alveolar bone loss, with a significantly decreased distance from the CEJ to the alveolar bone crest compared to animals with periodontitis receiving the vehicle (saline injection). Systemic antisclerostin led to higher bone mineral density, bone volume fraction, trabecular thickness and trabecular number. In rats with periodontitis and osteoporosis, antisclerostin improved mineral apposition rate and reduced alveolar bone resorption. Taut *et al.* (2013) found that 6 weeks of systemic antisclerostin administration restored levels of bone volume fraction and tissue mineral density in rats with unilaterally ligature-induced periodontitis. Conversely, a local injection of antisclerostin in gingival tissues showed a limited effect on bone healing.

Liu *et al.* (2018) and Tamplen *et al.* (2018) evaluated the effects of antisclerostin on the alveolar crest of rats. Both studies found that the systemic administration of the antibody increased the alveolar crest, identified as the reduction of the distance from the CEJ to the top of the alveolar bone crest. In addition, Liu *et al.* (2018) found that the combination of antisclerostin with DKK1-AB provided significantly better results compared to antisclerostin alone. Furthermore, Han *et al.* (2015) demonstrated that sclerostin antibodies had beneficial effects on periodontal regeneration, reporting that local injection of these molecules into periodontal defects promoted new



* Intermittent administration of teriparatide

Fig. 2. Biological pathways targeted by bone anabolic drugs studied for the treatment of periodontal disorders.

bone and cementum production by the activation of the canonical Wnt signalling in cementocytes, cementoblasts, osteoblasts and osteocytes (Fig. 2).

Discussion

As far as is known, this is the first PRISMA-driven scoping review aiming to investigate the putative role of osteoanabolic drugs on periodontal tissues, periodontitis and periodontal therapies.

Not many articles analysed osteoanabolic drugs in periodontology, including data about teriparatide, SR, sclerostin, and DKK1 antibodies. Most studies involve animal models whereas clinical research is rare. However, these data are in contrast with those of the epidemiological relevance of periodontal disorders. Indeed, recent World Health Organisation estimates suggest that 5-20 % of middle-aged (35-44 years) adults, and up to 40 % of older people (65-74 years) in Europe suffer from severe periodontitis (Web ref. 1). Periodontitis is a bacterial induced inflammatory disease characterised by progressive periodontal tissues loss (Page *et al.*, 1997), associated with individual genetic susceptibility (Loos *et al.*, 2005) and lifestyle, especially smoking and poor oral hygiene that allow bacteria to express their pathogenic potential (Heitz-Mayfield, 2005). Periodontitis may also be associated to systemic diseases with a common inflammatory substrate, since it is influenced by chronic, sub-clinical production of inflammatory factors, such as C-reactive protein, defined as “low-grade inflammation” (LGI) (Cecoro *et al.*, 2020).

Several inflammatory cells, including PMN, monocytes, macrophages, plasma cells (B lymphocytes), and T lymphocytes play a crucial role in periodontitis-related bone loss. These cells migrate to the alveolar bone and produce cytokines, such as interleukin-1, interleukin-6, tumour necrosis factor, and prostaglandin E2 (Galbraith *et al.*, 1997; Uden *et al.*, 1998), which induce a prolonged and persistent osteoclastic activation, responsible for bone loss (Kayal, 2013). Recently, some adipokines, such as leptin, adiponectin and visfatin, detected in the gingival crevicular fluid, have also been linked to periodontitis since they may have effects on periodontitis-related inflammatory status (Suresh and Mahendra, 2014). Considering the cascade of events involved in the pathophysiological mechanism of periodontitis, it may be speculated that the administration of osteoanabolic drugs may help in counteracting bone loss that occurs in this condition.

SRP plays a central role in non-surgical therapy of periodontitis, although SRP alone may be poorly effective, especially for the treatment of inaccessible areas, such as deep periodontal pockets, furcations, or interproximal areas of misaligned teeth. A conservative surgical approach allows a clinician to have an enhanced access to these areas. Furthermore, periodontal osseous defects may be treated by a

resective surgery or on the contrary, in selected cases, by procedures to achieve the regeneration of deep periodontal tissues (cementum, periodontal ligament and alveolar bone) (Cortellini and Tonetti, 2015a). This result can be achieved by 2 main techniques: 1. GTR, which enables the proliferation and regeneration of periodontal ligament, cementum, and alveolar bone by the utilisation of membranes, (Scantlebury, 1993); 2. ITR, based on the use of EMD, that influences the behaviour of several cell populations (Carinci *et al.*, 2006; Guida *et al.*, 2007b), favouring the regeneration of periodontal deep tissues. Nowadays, both GTR and ITR represent the most widely used techniques for the treatment of periodontal intrabony defects, with better long term results on PD reduction and CAL gain compared to other periodontal therapies (Sculean *et al.*, 2008a; Wu *et al.*, 2017). However, some issues in periodontal regenerative therapy should be considered. For example, regenerative techniques show better results in deep and narrow defects than in shallow and wide ones (Cortellini *et al.*, 1998; Cortellini and Tonetti, 2000). Nowadays, no evidence for the efficacy of GTR or ITR either for the treatment of suprabony (horizontal) defects or supracrestal components of intrabony ones is available (Cortellini *et al.*, 2015b). Furthermore, regenerative surgery may also have side effects, such as gingival recession, in particular GTR procedures in patients with a thin gingival phenotype (Anderegg *et al.*, 1995). Considering these criticisms, there is great interest in finding substances and techniques that may improve the efficacy and reduce the invasiveness of regenerative procedures, thus amplifying their indications. For example, the use of resorbable membranes and EMD, initially limited to self-supporting periodontal defects, has been validated in combination with biomaterials or autologous bone grafts (Guida *et al.*, 2007a; Needleman *et al.*, 2006; Sculean *et al.*, 2003; Sculean *et al.*, 2008b; Trombelli *et al.*, 2006; Zucchelli *et al.*, 2003) and these interventions are currently used in daily clinical practice. Moreover, the incision and suture techniques (*e.g.* supracrestal soft tissue preservation procedures) represent a key factor for the success of regenerative periodontal surgery (Annunziata *et al.*, 2019). Considering the well-recognised bone regenerative effects of osteoanabolic drugs in osteoporosis, they may play a role for the healing of bone defects in patients with periodontal disease.

The term “Critical Size Defect” has been defined as “the smallest size intra-osseous wound that will not heal spontaneously during the lifetime of the animal” (Schmitz and Hollinger, 1986). This condition is crucial, because it allows the researcher to discriminate the specific effects of techniques, biomaterials or drugs, since the defect could not heal without any intervention. A recent systematic review has established that a 5 mm diameter is the minimal dimension for a rat calvarial defect to be considered as critical size (Vajgel *et al.*, 2014). To assess the potential effects of osteoanabolic drugs on periodontal therapy

and, in particular, on the regeneration of periodontal bone defects, it was decided to also include studies investigating their effects on the regeneration of rat calvarial critical size defects with a minimum diameter of 5 mm, since these represent a good model to evaluate bone regeneration in periodontal field (An *et al.*, 2017; Pelaez *et al.*, 2014).

Teriparatide is the active fragment (recombinant human PTH 1–34) of the parathyroid hormone. PTH is secreted from parathyroid gland for modulating serum calcium levels by increasing bone and kidney calcium resorption. It also stimulates bone matrix resorption by osteoclasts, thus reducing bone strength. Conversely, intermittent exposure to PTH, as provided by teriparatide, will activate osteoblasts more than osteoclasts. Once-daily injections of teriparatide have a stimulating effect of new bone formation leading to increased bone-mineral density. Teriparatide improves bone strength by modulating different pathways. It reduces sclerostin secretion by osteocytes, thus inhibiting Wnt/ β -cat, and modulates the OPG/RANK/RANKL pathway by reducing RANKL and increasing OPG serum levels (Jilka, 2007). Teriparatide has already been used for about 15 years for the treatment of severe osteoporosis, by reducing vertebral fragility fractures of 65 % at the daily dosage of 20 μ g (Neer *et al.* 2001), and confirming its efficacy even in comparison with alendronate, one of the most used bisphosphonates, for osteoporosis (Wang *et al.*, 2017). Teriparatide shows a significant stimulating effect on bone formation particularly during the first 12 months of therapy (“anabolic window”). This drug could enhance the apposition of bone tissue thanks to proliferation and differentiation of osteoprogenitor cells promoting fracture healing in animal models (Alkhiary *et al.*, 2005; Komrakova *et al.* 2010). However, these results should be confirmed in humans (Shi *et al.*, 2016). In this scoping review studies were found investigating the use of this agent in both animal models and clinical settings.

As reported by Marques *et al.* (2009), teriparatide down-regulates the expression and activation of bone resorption biomarkers, such as interleukin-6, MMP-2, and MMP-9 that are responsible for bone resorption, reducing the number of mature osteoclasts. Subsequent animal studies included in this review confirmed the benefits of systematic administration of teriparatide in rat calvarial defects, showing significant increase of bone regeneration (Andreassen and Cacciafesta, 2004; Cohn Yakubovich *et al.*, 2017; Park *et al.*, 2019; Staconven *et al.*, 2013; Yoshida *et al.*, 2019; Yun *et al.*, 2010). Teriparatide may enhance periodontal healing as demonstrated by higher number of PCNA- and VEGF-positive cells, and increased osterix expression, thus promoting PDL cell proliferation, angiogenesis, and osteoblast differentiation (Yoshida *et al.*, 2019). Even local delivery thorough disks containing teriparatide solution seems to have similar effects, suggesting that this route of administration is effective while reducing the risk of potential systemic side effects

(Iwai *et al.*, 2018; Kajii *et al.*, 2018). However, it should be highlighted that dosing regimens of teriparatide used in animal studies are quite heterogeneous.

In clinical studies, including patients with periodontal osseous defects treated with OFD, systemic administration of teriparatide demonstrated a significant improvement compared to placebo on periodontal parameters at a 1 year follow-up (Bashutski *et al.*, 2010). These benefits were also maintained at a 4 years follow-up (Bashutski *et al.*, 2012).

SR is a strontium salt of ranelic acid used for the treatment of osteoporosis. Its mechanism of action is not completely known. This agent has a high affinity for bone and it is initially adsorbed onto the surface of the hydroxyapatite crystals, replacing calcium due to its similar chemical structure (Li *et al.*, 2010). SR seems to regulate bone metabolism in favour of the bone formation, activating CaSR that stimulates the Akt and ERK1/2 pathways, thus inhibiting osteoblast apoptosis and enhancing differentiation of preosteoblast to osteoblasts (Takaoka *et al.*, 2010). These positive effects on bone formation are confirmed by increased serum levels of early and late osteoblasts markers, such as type I collagen, alkaline phosphatase, bone sialoprotein, and osteocalcin following SR administration (Barbara *et al.*, 2004; Canalis *et al.*, 1996). Moreover, it has been suggested that an effect of SR on the OPG/RANK/RANKL system would explain its inhibitory action on osteoclastogenesis, mediated by its action on osteoblasts (Brennan *et al.*, 2009), although this mechanism has not yet been clearly described. From a clinical point of view, SR significantly increased bone mineral apposition (about 9 %) in women with osteoporosis (Arlot *et al.*, 2008). This drug is effective for reducing the risk of fragility fractures in women with postmenopausal osteoporosis (Iolascon *et al.*, 2014; Tarantino *et al.*, 2017). 2 trials reported a significant reduction of vertebral (Meunier *et al.*, 2009) and non-vertebral fractures (Reginster *et al.*, 2005) in osteoporotic women. However, its use has recently been limited because of potential safety issues, particularly cardiovascular events (Reginster, 2014). Finally, the effect of SR in promoting callus formation has been demonstrated in animal models, suggesting its adjuvant role in bone healing (Koukou *et al.*, 2020). However, this effect has yet to be confirmed in humans (Scaglione *et al.*, 2016).

In this review only animal studies were found concerning the use of SR in the periodontal field. Systemic administration of this drug showed positive effects on the course of periodontitis, since it increases trabecular bone area and reduces alveolar bone loss in experimental models of periodontitis (Karkan *et al.*, 2017; Marins *et al.*, 2020; Souza *et al.*, 2018). It has been hypothesised that these effects could be mediated by decreased RANKL activity (Karkan *et al.*, 2017) and HO-1 mRNA expression (Souza *et al.*, 2018), which are involved in alveolar bone loss and periodontitis. Buehler *et al.* (2001) showed that

SR improves bone histomorphometric indices by reducing osteoclast surface and number in monkeys, while no effect on bone formation was found. These findings also suggest potential benefits of systemic SR in humans that should be proven by clinical trials. Similarly, local delivery of low doses (2.5 and 5 mmol/L) and high dose (50 mmol/L) of SR results in greater bone volume, bone surface and trabecular thickness (Masalskas *et al.*, 2018; Nahass *et al.*, 2017). However, Denry *et al.* (2018) found controversial results using strontium-free glass-ceramic scaffolds, reporting more newly formed bone than in scaffolds with strontium incorporation. This is probably due to the presence of akermanite crystals on the surface of the strontium-free scaffold, which seems to result in increased bone formation (Denry *et al.*, 2018). Strontium also seems to improve periodontal regeneration through the activation of the Akt pathway (Jia *et al.*, 2019). Further studies are needed to clarify the potential role of strontium ranelate for treating periodontitis in clinical settings.

In this scoping review animal studies about sclerostin and DKK1 antibodies for periodontal applications were also included. Sclerostin is a glycoprotein secreted by osteocytes and encoded by the SOST gene. It prevents the activation of Wnt target genes and thus inhibits osteoblast differentiation, proliferation, and function. Recently, new monoclonal antibodies directed against this protein were developed for inhibiting the Wnt pathway as an innovative therapeutic strategy for osteoporosis. Among sclerostin monoclonal antibodies, romosozumab binds sclerostin LRP 5/6 receptors inhibiting signalling of the Wnt pathway, stimulating differentiation, proliferation, and survival of osteoblasts (Shah *et al.*, 2015). It has been recently marketed in 5 countries (USA, Canada, Japan, South Korea, and Australia), although data about its effectiveness in real world are not yet available. Significant increase in bone mass and trabecular thickness has been reported in osteoporotic women treated with romosozumab (Chavassieux *et al.*, 2019). This agent reduced vertebral fracture incidence in osteoporotic women (Cosman *et al.*, 2016), and increased spine and hip BMD in osteoporotic men at 12 months (Lewiecki *et al.*, 2018). Only 1 study evaluated the effect of romosozumab on tibial-fracture healing, not reporting any significant acceleration of callus formation, compared to placebo, in patients treated for 24 weeks (Bhandari *et al.*, 2020). In the context of periodontal disease, systemic administration of romosozumab in animals promotes bone and cemental regeneration with periodontal healing in large alveolar bone defects by blocking sclerostin release from osteocytes. On the other hand, local administration seemed not to have the same benefit, probably due to lower doses provided through this approach (Yao *et al.*, 2020).

Regarding periodontal tissues, available data suggest that the efficacy of local administration of sclerostin antibodies remains questionable due to

heterogeneous results (Han *et al.*, 2015; Taut *et al.*, 2013). Systemic administration of these agents has showed significant effects on the periodontium, increasing the height of alveolar crest and reducing the distance from CEJ to the alveolar bone crest (Liu *et al.*, 2018; Tamplen *et al.*, 2018). Furthermore, systemic administration of these antibodies also showed positive effects in animal models of periodontitis, with an increase in bone-mineral apposition rate, bone density, bone-volume fraction, trabecular number and thickness, with a reversion of bone loss due to periodontitis and a reduced CEJ-alveolar crest distance (Chen *et al.*, 2015; Taut *et al.*, 2013). This latter result could be further investigated for the treatment of suprabony (horizontal) defects, opening a new frontier for regenerative procedures to overcome their current limits in the treatment of horizontal defects.

The combined use of different osteoanabolic agents has been investigated in 2 studies. Goker *et al.* (2018) reported that local implantation of tablets containing 1-34 PTH and SR led to a greater bone stimulation in rat calvarial critical size defects of 5 mm than either treatment alone. Sclerostin antibodies, also in combination with DKK1-AB, significantly increased alveolar ridge height when compared to sclerostin antibodies alone (Liu *et al.*, 2018). These results suggest a new treatment strategy based on 2 or more anabolic drugs, with different mechanisms of action to improve regenerative therapy effects and maintain the periodontal health.

There needs to be some consideration of the safety profile of osteoanabolic drugs. According to the current review, only Bashutski *et al.* (2010) addressed this topic, reporting no significant between-group differences in the incidence of clinical symptoms (*e.g.* dizziness, nausea, dyspnoea) or in changes of serum calcium, compared to those receiving placebo, in patients receiving teriparatide.

Some adverse events have been reported with systemic use of SR, particularly serious cardiovascular events (*i.e.* myocardial infarction, ischaemic heart disease or embolic and thrombotic venous events) (Reginster *et al.*, 2015). Moreover, DRESS must be considered in patients receiving SR. This syndrome is characterised by fever, rash, eosinophilia ($\geq 1,500$ cells/ μ L) due to a hypersensitivity reaction, usually occurring within 3 to 6 weeks of starting therapy with SR (Cacoub *et al.*, 2013).

Romosozumab seems to be associated to an increased risk of cardiovascular events, in comparison with alendronate, probably due to a protective effect of bisphosphonates (Saag *et al.*, 2017). This putative adverse event has not been confirmed in studies comparing the safety profile of romosozumab and placebo (Cosman *et al.*, 2016; Lewiecki *et al.*, 2018).

Data concerning the risk of adverse events for systemic use of anabolic drugs, in humans with periodontal disease, are still lacking in this specific context. Such events might be avoided by local application of these drugs, although available

evidence about the efficacy of this administration route in the treatment of periodontal disease is conflicting. Benefits have been reported for teriparatide and strontium ranelate in improving bone regeneration, but evidence supporting local administration of romosozumab for periodontal disease are not yet available.

Conclusions

According to the pathogenesis of periodontal disease, there is a strong rationale for using pharmacological modulation as an ancillary intervention. This scoping review demonstrated increasing evidence about the effects of bone anabolic drugs in periodontology. Nevertheless, there was a significant shortage of clinical studies, since most of available evidence is drawn from animal models. Experimental studies are characterised by heterogeneity in methodological approaches and related results, making difficult their translational application to clinical settings. However, bone anabolic drugs are widely used in other conditions, such as osteoporosis, demonstrating significant reduction in the risk of fragility fractures.

Available evidence also suggests that some benefits, in both biochemical and histological parameters of periodontal tissue regeneration, support an ancillary role of these drugs for the management of periodontitis.

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Editor's note: There were no questions from reviewers for this paper, therefore there is no Discussion with Reviewers section. The Scientific Editor responsible for this paper was Thimios Mitsiadis