Thesis

TITLE
Effects of teriparatide on periodontal regeneration compared to alendronate
A systematic literature review

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Graz, am 31.07.2024 Imam Laknizi eh.

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It is with a feeling of immense accomplishment that I dedicate this thesis to my parents.

Zusammenfassung

Hintergrund: Das therapeutische Potenzial von Teriparatid bei der Behandlung von Parodontitis gewinnt aufgrund seiner Fähigkeit, den Alveolarknochen zu modulieren, zunehmend an Aufmerksamkeit. Im Vergleich zu Alendronat könnte Teriparatid eine überlegene Knochenregeneration bieten, insbesondere bei der Behandlung von intraossären Defekten im Alveolarknochen.

Zielsetzung: Diese systematische Literaturübersicht zielt darauf ab, bestehende Forschung zu den Wirkungen von Teriparatid und Alendronat umfassend darzulegen, zu definieren und zu analysieren, wobei der Schwerpunkt auf deren Wirksamkeit in der menschlichen Mundhöhle liegt. Ziel ist es, die Mechanismen zur Verbesserung der Knochenregeneration in speziell parodontalen Defekten bei PatientInnen mit Osteoporose in den Fokus zu setzen.

Methoden: Für diese Studie wurden Veröffentlichungen aus renommierten Datenbanken wie PubMed, Wiley Library, Elsevier, Science Direct und Cochrane Central Register of Controlled Trials herangezogen. Die Überprüfung konzentrierte sich auf englischsprachige Studien ab dem Jahr 2014. Eine sorgfältige Suchstrategie, basierend auf Schlüsselwörtern und deren Synonymen, wurde entwickelt und auf jede der Datenbanken angewendet. Das Evidenzniveau jeder Studie wurde anhand des Levels of Evidence Framework von Melnyk und Fineout-Overholt (2023) bewertet und eingestuft, um eine rigorose Analyse zu gewährleisten.

Ergebnisse: Neun Studien erfüllten die Einschlusskriterien und wurden in die systematische Überprüfung aufgenommen. Alendronat zeigte eine signifikante Regeneration bei Knochendefekten und verbesserte klinische Attachment-Levels nach SRP (Scaling und Root Planing), was zu einer Reduktion der parodontalen Sondierungstiefe und verbesserten Plaque-Index-Werten in der gesamten Mundhöhle führte. Radiografische Analysen einiger Studien zeigten eine Verringerung der intraossären Defekte und eine erhöhte vertikale Defektfüllung bei ProbandInnen mit Alendronat-Medikation. Teriparatid, in Kombination mit parodontaler Behandlung, bot schnellere und günstigere Ergebnisse bei Fällen von Bisphosphonat-assoziierter Osteonekrose des Kiefers, förderte die Angiogenese und erhöhte Knochenumsatzmarker ohne unerwünschte Wirkungen.

Limitationen: Die Analyse der aktuellen Literatur weist jedoch Einschränkungen auf, darunter die begrenzte Anzahl der zur Verfügung stehenden Studien, Unterschiede in den

untersuchten Studienkohorten und der verwendeten Methoden sowie der diagnostischen Kriterien der parodontalen Erkrankung.

Fazit: Während sowohl Teriparatid (TPTD) als auch Alendronat (ALN) vielversprechend für die Knochenregeneration in der Mundhöhle zu sein scheint, ist bei der Interpretation der Ergebnisse Vorsicht geboten. Zusätzliche Faktoren wie Geschlecht, Alter, Medikamentensubstanzen, Verabreichungsform (lokal vs. systemisch) und Lebensstil der PatientInnen sollten berücksichtigt werden, um stärkere Schlussfolgerungen hinsichtlich des Einflusses von Teriparatid und Alendronat in der Behandlung von Parodontitis zu ziehen.

Abstract

Background: The therapeutic potential of teriparatide in treating periodontitis is gaining attention due to its capacity to modulate alveolar bone. Compared to alendronate, teriparatide may offer superior bone regeneration within the oral cavity, particularly in addressing intrabony defects in alveolar bone.

Purpose: This systematic literature review aims to comprehensively explore, define, summarize, and analyze existing research on the effects of teriparatide and alendronate, with a focus on their efficacy in the human oral cavity. The goal is to assess the feasibility and mechanisms of enhancing bone regeneration within the oral cavity, specifically targeting periodontal defects in patients with osteoporosis.

Methods: For this study, publications from reputable databases such as PubMed, Wiley Library, Elsevier, Science Direct and the Cochrane Central Register of Controlled Trials were sourced. The review concentrated on English-language studies from 2014 onwards. A meticulous search strategy, based on keywords and their synonyms, was devised and applied to each of the databases. The level of evidence for each study was evaluated and graded using the Levels of Evidence framework by Melnyk and Fineout-Overholt (2023) to ensure a rigorous analysis.

Results: Nine studies met the inclusion criteria and were included in the systematic review. Alendronate exhibited significant bone defect filling and improved clinical attachment levels post-scaling, leading to reductions in periodontal probing depth and improved full mouth plaque index scores. Radiographic analysis indicated reductions in intrabony defects and increased vertical defect fill in the alendronate group. Teriparatide, combined with periodontal care, provided faster and more favorable outcomes in cases of bisphosphonate-related osteonecrosis of the jaw, promoting angiogenesis and increased bone turnover markers without adverse effects.

Limitation: However, the review has limitations, including the small number of included studies, variations in subjects and used methodologies as well as inconsistencies in diagnosis criteria and disease severity of periodontal disease.

Conclusion: While both teriparatide (TPTD) and alendronate (ALN) show promising results in oral bone formation, caution is warranted in interpreting the results. Additional factors such as gender, age, medication substances, and lifestyle should be considered to

draw stronger conclusions regarding the effectiveness of teriparatide and alendronate in the treatment of periodontitis.

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Glossary

18F-fluoride PET-CT	18F-sodium fluoride (18F-NaF) with Positron Emission Tomography-Computed Tomography (PET/CT)
A. actinomycetemcomitans	Aggregatibacter actinomycetemcomitans
ABL	Alveolar Bone Loss
ACH	Alveolar Crest Height
ALP	Alkaline Phosphatase
APR	Acute Phase Response
B-cell	Bone marrow lymphocyte
BF	Bone Formation
BMD	Bone Mineral Density
BMSC	Bone Marrow Stromal Cells
BRONJ	Bisphosphonate-Related Osteonecrosis of the Jaw
CTx	C-telopeptide cross-linked type I collagen
C5aR1	Complement C5a Receptor 1
CAL	Clinical Attachment Loss
cAMP	Cyclic Adenosine Monophosphate
CD	Cluster of Differentiation
c-Fms	Macrophage colony-stimulating Factor 1 Receptor
CKD	Chronic Kidney Disease
COL1A1	Collagen, type 1, alpha 1
COL1A2	Collagen, type 1, alpha 2
CXCL	Chemokine (C-X-C motif) Ligand
CXCL8	chemokine (C-X-C motif) Ligand 8 or Interleukin 8
DAAM2	Dishevelled Associated Activator of Morphogenesis 2
DAMPs	Danger-Associated Molecular Patterns

DEL-1	Developmental Endothelial Locus
DXA	Dual Energy X-ray Absorptiometry
E1	Estrone
E2	Estradiol or 17β-Estradiol
E3	Estriol
EPH	Ecological Plaque Hypothesis
EPM	Extracellular Polymeric Matrix
EREs	Estrogen Response Elements
ERs	Estrogen Receptors
F. necrophorum	Fusobacterium necrophorum
F. nucleatum	Fusobacterium nucleatum
GCF	Gingival Crevicular Fluid
GI	Gastrointestinal
HbA1c	Glycated Hemoglobin A1c
HRgpA	High molecular weight gingipain R
IBD	Intrabony Defects
ICAM-1	Intercellular Adhesion Molecule 1
Ig	Immunoglobulin
IL	Interleukin
IMPEDE	Inflammation-mediated Polymicrobial-Emergence and Disease Exacerbation
IOP	Idiopathic Osteoporosis
IRF1	Interferon Regulatory Factor 1
L. rhamnosus SP-1	Lactobacillus rhamnosus SP 1
LAD-1	Leukocyte Adhesion Deficiency
LBG	Linear Bone Growth
LFA-1	Leukocyte Function Antigen
LPS	Lipopolysaccharide
LRP5	Low-density Lipoprotein Receptor-Related Protein 5
M-CSF	Macrophage Colony-Stimulating Factor
MCW	Mandibular Cortical Width
MMP9	Matrix Metalloproteinase 9
MMPs	Matrix metalloproteinases

MRONJ	Medication-Related Osteonecrosis of the Jaw
MSCs	Mesenchymal Stem Cells
MYD88	Myeloid Differentiation Primary Response 88
NFATc1	Nuclear Factor of Activated T cells 1
NF-kB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
nM	Nanomolar
NTx	Cross-linked N-telopeptides of type I collagen
ODF	Osteoclast Differentiation Factor
OMVs	Outer Membrane Vesicles
ONJ	Osteonecrosis of the Jaw
OPG	Osteoprotegerin
OPGL	Osteoprotegerin Ligand
ORNJ	Osteoradionecrosis of the Jaw
P. intermedia	Prevotella intermedia
P. gingivalis	Porphyromonas gingivalis
PAMPs	Pathogen-Associated Molecular Patterns
PDLF	Primary Human Periodontal Ligament Fibroblasts
PDLSC	Human Periodontal Ligament Stem Cells
PGE2	Prostaglandin E2
PI3K	Phosphoinositide 3-Kinases
P1CP	Procollagen type 1 C-terminal Propeptide
P1NP	Procollagen type 1 N-terminal Propeptide
PMN	Polymorphonuclear neutrophils
PMNL	polymorphonuclear leukocytes
PMOP	Postmenopausal osteoporosis
PD	Periodontal disease
PPD	Probing Pocket Depth
PRR	Pattern Recognition Receptor
PTH	Parathyroid Hormone
PTH (1-34)	Parathyroid Hormone (1-34), a highly purified peptide chemically synthesized by GenScript
PTH1R	Parathyroid Hormone Receptor 1

RANK	Receptor Activator of Nuclear factor Kappa-B
RANKL	Receptor Activator of Nuclear factor Kappa-B Ligand
RBL	Radiographic Bone Loss
RCT	Randomized Controlled Trial
RgpB	Low molecular weight gingipain R
S. oralis	Streptococcus oralis
SCC	Squamous Cell Carcinoma
SDF-1α	Stromal cell-Derived Factor 1 alpha
SERMs	Selective Estrogen Receptor Modulators
SMV	Simvastatin
SOP	Senile Osteoporosis
SOST	Sclerostin
SPH	Specific Plaque Hypothesis
SRP	Scaling and Root Planing
STAT1	Signal Transducer and Activator of Transcription 1
T. denticola	Treponema denticola
T. forsythia	Tannerella forsythia
T-cell	Thymus lymphocyte
Th	T helper cells
TLR	Toll-Like Receptor
TNFα	Tumor Necrosis Factor Alpha
TPTD	Teriparatide
TRANCE	Tumor Necrosis factor-Related Activation-induced Cytokine
TRAP	Tartrate-Resistant Acid Phosphatase
WNT	Wingless and Int-1(gene)
αVβ3	Integrin Alpha V Beta 3
β-TCP	Beta-Tri-Calcium-Phosphat
γδ-T cells	Gamma-delta (γδ) T cells are a subset of T cells. Role: promoting the inflammatory responses of lymphoid and myeloid lineages in the inflammatory and immune responses.

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1 Introduction

1.1 The periodontium

Several tissues such as : gingiva, periodontal ligament, root cementum, bundle bone and alveolar process form the periodontium (1). The periodontium plays an essential primary role, which consist of the anchoring of the tooth to the jawbone and upholding the integrity of the surface of the oral mucosa involved in chewing. Referred to as the supporting tissues of the teeth, the periodontium forms a cohesive unit that evolves both developmentally and functionally. It undergoes specific modifications with age and experiences morphological adjustments due to changes in function and the oral cavity (1-3).

The formation of periodontal tissues is initiated at an early stage of embryonic development, concurrently with the eruption of the teeth. Initially, the cells that originate from the crest derived from the ectoderm migrate into Meckel's branchial arch from the neural tube of the embryo and create a layer of ectomesenchyme under the epithelium of the stomatodaeum. Subsequently, factors released by the stomatodaeum epithelium trigger epithelial-ectomesenchymal interactions after the multipotent stem cells derived from the ectoderm have settled in the alveolar process. Once these interactions occur, the ectomesenchyme assumes a dominant role in further development. This process progresses through the odontogenesis (2, 3).

The odontoblasts condense alongside the dental epithelium, forming two distinct structures: the dental papilla, responsible for generating other tissues (dentin, pulp and the dental sac). The significance of ectomesenchyme in this process is underscored by its pivotal role in determining the shape and form of the tooth, as evidenced by the influence of dental papilla tissue (2, 3).

The crown and root of the tooth take shape, accompanied by the development of root cementum, desmodont and the portion of bone that lines the alveolus. The enamel organ serves as the formative center for enamel, while the dental papilla contributes to the formation of the dentin-pulp complex. The dental follicle acts as a shaping center for the attachment apparatus, which consists of cementum, desmodont and alveolar bone proper (2).

1.1.1 Gingiva

The gingiva refers to the portion of the oral mucosa responsible for covering the alveolar ridge and encircling the cervical margin, that includes an epithelial layer and the lamina propria. The coral pink gingiva culminates in the free gingival margin between the sulcular epithelium and the epithelium of the oral cavity (2, 4). Extending apically, the gingiva seamlessly transitions into the alveolar mucosa, with the border between them typically marked by a distinct line: the mucogingival junction.

The marginal gingiva and attached gingiva form the gingiva. The marginal gingiva is coral pink in color, has a matte surface texture and resilient consistency and encompasses the vestibular and lingual or palatal gingival tissues located 1.5 mm on the neck of the tooth, as well as the interdental tissues. Extending from the gingival margin towards the apical direction on both the vestibular and lingual sides of the teeth, the free gingiva reaches the free gingival groove, which aligns with the anatomic limit between the enamel and the cementum. The mucogingival junction borders apically the attached gingiva (2-4).

The free gingival margin typically exhibits a rounded contour, creating a sulcus between soft tissues and hard tissues of the tooth. By using a periodontal probe and directing it apically toward the cementoenamel junction, the soft tissues separate from the hard tissues of tooth and open a gingival sulcus. Under clinically healthy conditions, we can notice no gingival pocket, because the gingiva is in close contact with the enamel surface. After the odontogenesis and the eruption, the free gingival margin is typically 1.5 to 2 mm coronal to the cementoenamel junction (2, 5).

The attached gingiva extends and reaches apically the mucogingival junction, where it seamlessly transitions into the alveolar mucous membrane (2).

The attached gingiva exhibits a coral pink hue, a firm texture and often displays small stippling its surface like an orange peel. It is relatively immobile compared to the underlying tissue and anchored to the underlying root cementum and the alveolar bone through gingival fibers.

The epithelium covering the free gingiva can be categorized in oral epithelium, oral sulcular epithelium and junctional epithelium (2, 5).

1.1.2 Periodontal ligament

The periodontal ligament is a highly vascularized and cellular connective soft tissue enveloping the radix dentis, linking the socket wall with root cementum. In the coronal direction, it seamlessly transitions into the lamina propria of the gingiva and is distinguished from the gingiva by collagen alveolar crest fibers connecting the alveolar bone crest with radix dentis (2).

Radiographically, two types of alveolar bone are distinguishable:

- The alveolar bone proper that envelopes the alveolus, referred to as the lamina dura.
- The spongy bone that in radiographic images, exhibits a mesh-like appearance.

The alveolar bone encircles the tooth, extending approximately 1 mm apical to the cementoenamel junction. Its uppermost edge is referred to as the alveolar crest (2, 3, 5).

The desmodont width is typically around 0.25 mm (± 0,2 to 0,4mm). The distribution and absorption of forces generated during mastication and contacts between antagonist and proximal teeth is allowed by the desmodont.

The grade of the tooth mobility is largely influenced by the structure and quality of the periodontal ligament.

The connection between the tooth and the bone is facilitated by bundles of connective tissue fibers. These collagen fibers can be categorized into the four following principal groups: alveolar crest fibers, horizontal fibers, Oblique fibers, apical fibers (2, 5).

1.1.3 Root cementum

Cementum is a specialized mineralized tissue that coats radix dentis and on occasion, some areas of the tooth crown. Unlike bone, root cementum lacks blood or lymphatic vessels, nerve supply and does not undergo a remodeling but exhibits continuous apposition. Similar to the biological tissues, incorporating minerals into soft matrices, root cementum contains collagen fibers embedded in an organic matrix. Cementum is composed, mainly of hydroxyapatite, representing approximately 65% of its weight, a little more than that of bone (approximately 60%) (2, 5).

Cementum plays a vital role in the attachment between the fibers of the desmodont and radix dentis and has a significant role to the repair process following damage to radix dentis surface.

Different types of root cementum have been categorized as follows (2):
- Acellular, extrinsic fiber cementum: Predominantly located in the coronal and middle root segments, this type of cementum primarily comprises bundles of Sharpey's fibers.
- Mixed stratified cellular cementum: It contains both extrinsic and intrinsic fibers, as well as cementocytes. It is found in the apical third of the roots and in the furcations.
- Cellular, intrinsic fiber cementum: Mainly found within resorption lacunae and it consists of intrinsic fibers and cementocytes (2, 5).

1.1.4 Alveolar bone

The alveolar process refers to the portions of the maxilla and mandible responsible for creating and supporting the tooth sockets. Its development is closely linked to the growth and eruption of teeth. Comprised of bone, the alveolar process is formed both by cells originating from the dental follicle and cells independent of the odontogenesis. Working in conjunction with the root cementum and the desmodont, the alveolar bone forms the dentogingival complex and the periodontal ligament of the teeth, primarily tasked with distributing and absorbing forces generated during activities such as mastication and tooth contact (2).
The cortical bone envelops the alveolus walls. The spongiosa fills the space between sockets and the compact bone walls of the jaw and it dominates the interdental septa. Within the spongiosa lie bone trabeculae, whose form and dimensions are influenced by a combination of genetic factors and the forces encountered during tooth function (2).
The bone plate tends to be thicker on the palatal side and on the buccal side of the molars, but thinner in the anterior buccal region.
The alveolar bone proper often seamlessly connects with the compact or cortical bone at the lingual and buccal parts of the alveolar process. Furthermore, the thickness of the bone wall on the buccal and lingual aspects of the teeth can vary significantly, for instance, from the premolar to the molar region (2).
It's worth noting how the presence of the linea obliqua results in a bony projection on the buccal parts of the second and third molars. The compact bone, known as the alveolar bone proper, which lines the tooth socket and appears as lamina dura on radiographs, is perforated by numerous Volkmann's canals. The blood vessels, lymphatics and nerve fibers use Volkmann's canals as a passage from the alveolar bone to the desmodont.

Functionally and structurally, the bundle bone, where the principal Sharpey's fibers are embedded, shares many similarities with the cementum layer from the root surfaces (2).

1.1.5 Blood supply

The dental artery, a branch stemming from either the superior or inferior alveolar artery, gives rise to the intraseptal artery before entering the alveolus. It is through canals at different levels in the alveolus that the terminal branches of the intraseptal artery pass through the alveolar bone proper.

Within desmodont space, these branches anastomose, connecting with blood vessels originating from the apical portion of the desmodont, as well as with other the intraseptal artery terminal branches.

Before entering the root canal, the dental artery emits branches that provide blood supply apically to the periodontal ligament.

The blood supply of the gingiva is primarily derived from supraperiosteal blood vessels, which are terminal branches originating from arteries such as Arteria sublingualis, Arteria mentalis, Arteria buccalis, Arteria facialis, Arteria palatina descendens, Arteria infraorbitalis and Arteria alveolaris superior posterior (2-4, 6).

1.1.6 Lymphatic system

The lymphatic system comprises the smallest lymphatic vessels known as lymphatic capillaries, which create a widespread network within the connective tissue. These capillaries possess a wall, which contains single layer of endothelial cells, making them challenging to distinguish in standard histological sections. The absorption of the lymph from the tissue fluid is through the thin walls of these capillaries. Subsequently, the lymph moves into larger lymph vessels, often located near corresponding blood vessels.

Before lymph enters the bloodstream, it traverses through one or more lymph nodes, where it undergoes filtration and receives a supply of lymphocytes. Lymph vessels resemble veins and are equipped with valves to facilitate the one-way flow of lymph (2, 4).

1.1.7 Innervation

The periodontium harbors receptors responsible for detecting pain, touch, and pressure, including nociceptors and mechanoreceptors. The nerves responsible for sensing pain, touch and pressure have their trophic center located in the ganglion Gasseri and are distributed to the desmodont via branches of nervus trigeminus (2-4).

Hence, the periodontal mechanoreceptors, in conjunction with proprioceptors in muscles and tendons, play a vital role in regulating chewing movements and forces.

In terms of innervation, the gingiva on the labial aspect of maxillary incisors, canines, and premolars is supplied by superior labial branches originating from the infraorbital nerve (N. infraorbitalis) (2).

The buccal gingiva in the maxillary molar region receives innervation from branches of the posterior superior dental nerve. Meanwhile, the palatal gingiva is innervated by the palatal nerve (N. palatinus major), except for the incisor area, which is innervated by the sphenopalatine nerve (N. pterygopalatini). In the mandible, the lingual gingiva is innervated by the sublingual nerve (N. sublingualis), an end branch of the lingual nerve.

The labial aspect of mandibular incisors and canines is innervated by the mental nerve (N. mentalis), while the buccal aspect of the molars is innervated by the buccal nerve (N. buccalis). These two nerves often have overlapping innervation areas in the premolar region (7, 8).

The teeth and their associated periodontal ligaments in the mandible are innervated by the inferior alveolar nerve (n. alveolaris inf.), while those in the maxilla are innervated by the superior alveolar plexus (N. alveolares sup.).

The small nerves within the periodontium closely follow the pathways of the blood vessels. Nerves supplying the gingiva travel in the tissue superficial to the periosteum, emitting multiple branches to the oral epithelium as they proceed towards the free gingiva. Upon reaching the periodontal ligament, the nerves penetrate through Volkmann's canals in the alveolus wall. Within the periodontal ligament, these nerves merge with larger bundles that run parallel to the long axis of the tooth.

Neuronal endings such as Ruffini corpuscles and free nerve endings are discovered in the periodontal ligament (2, 3).

1.2 Periodontal disease and conditions

Periodontitis is a comprehensive term that encompasses forms of diseases and conditions, gingivitis and periodontitis, affecting the periodontium and they are induced by the accumulation of dental plaque biofilm. The inflammatory lesion localized to the gingiva is called gingivitis and may progress to the periodontitis, which is more several and destructive (9).

Studies suggest that the pathogenesis of several systemic diseases, including endocrine diseases, pathological process in the coronary arteries, chronic diseases, autoimmune disorders are independently linked to periodontal pathogens and the subsequent immune-inflammatory responses to them (10-13).

Periodontal pathogens, such as P. gingivalis, A. actinomycetemcomitans, T. forsythia, E. corrodens and F. nucleatum use the ulcerated pocket epithelium as a direct portal of vascular access to enter the systemic circuit and this type dissemination may directly or indirectly impact other organs (14-16).

1.2.1 Etiology

The main etiological factor responsible for the periodontal conditions development and progression is the dental plaque, along with other factors such as lifestyle and individual's genetic risk factors (17). A particular bacterium within the dental plaque biofilm, primarily S. mutans, S. sobrinus and lactobacilli were found to be partially indigenous, existing in both healthy and diseased conditions alongside the existence of potential periodontal pathogens. The basis of the specific plaque hypothesis is formed on the existence these bacterial complexes. Subsequently, other researchers proposed the non-specific plaque hypothesis, suggesting that the development of periodontitis was caused by the quantity of bacterial complexes rather than specific microorganisms (18).

Maturation of dental plaque: coaggregation dispersion of bacteria

The recognition of glycans or protein binding sites on the cell surface of early colonizers such as gram-positive bacteria, including S. mitis, S .sanguis, S. oralis, S. mutans and other bacteria, by late colonizers, including P. gingivalis, T. forsythia, F. nucleatum, T. denticola, P. intermedia and A. actinomycetemcomitans as shown in figure 1, is the first step of the maturation of the dental biofilm (19, 20). Consequently, the relative prevalence of late colonizers tends to rise, frequently with the decrease of early colonizers like Streptococci and Neisseria in the dental biofilm (21, 22). In mature dental biofilms, coaggregations of bacteria display distinctive patterns (19, 20). Socransky et al.'s research contributed significantly to our comprehension of the biofilm associated periodontal bacterial complexes within the subgingival microbiota (23). The pathogenic groups were classified into five complexes, each designated by a color code (24). P. gingivalis, T. forsythia and T. denticola are part of the red group of periodontal pathogens and are predominantly found in samples from individuals with periodontitis. Furthermore, pathogens in the orange group, such as F. nucleatum, P. intermedia, C. rectus, C. gracilis and other species are frequently associated with periodontitis.

Conversely, periodontal health is strongly characterized by complexes like the yellow complex and the green complex (Figure 1). The yellow, green and purple complexes are considered as early colonizers. These last ones viewed as prerequisites for the appearance of late colonizers, particularly, the orange and red complexes (Figure 1). This coaggregation of complexes is prevalent, nevertheless this is not a requirement and certain complexes may occasionally be detected independently of others (24).

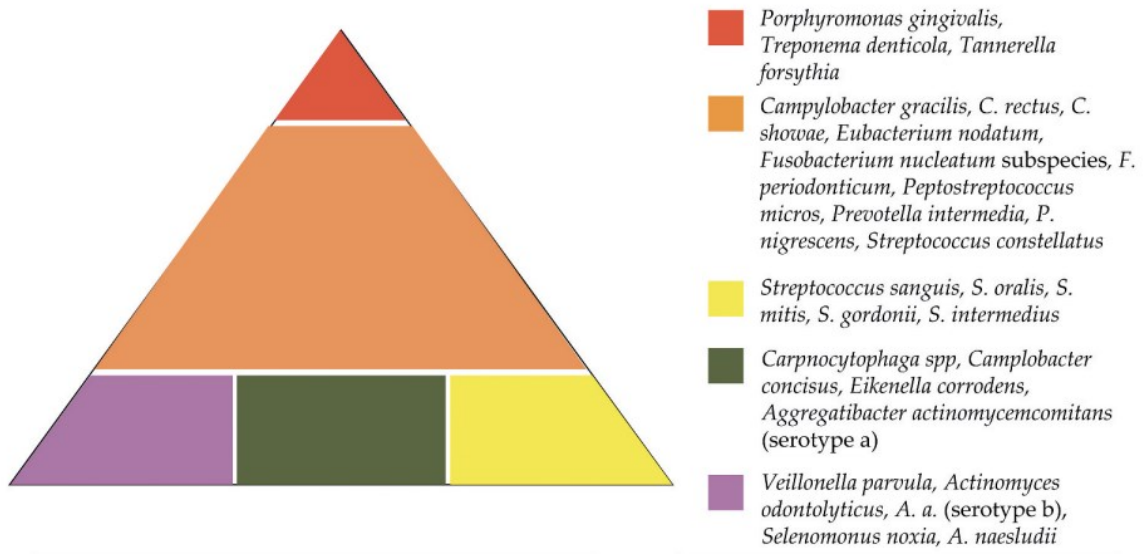

Figure 2: Bacterial complexes in periodontitis (Current concepts in the pathogenesis of periodontitis: from symbiosis to dysbiosis. Ali A. Abdulkareem et al. Adapted from Socransky et al.)

During the growth of mass and pathogens populations in the dental biofilm, individual pathogens or clusters of complexes detach and revert to a planktonic bacteria mode. While erosion and sloughing mechanisms of bacteria dispersion can occur through active or passive means, seeding is an active process confined to hollow cavities within the biofilm, where large numbers of solitary cells or bacterial masses are rapidly detached (25-29).

Structure of the dental biofilm

Biofilms consist of microbial cells encased within an extracellular polymeric matrix (EPM) derived from both the resident microbiota and the host (30, 31). The arrangement of the bacteria within dental biofilm is not randomly, but it's according to the function and space organized (32). The species of periodontal pathogens detected in the dental plaque and their abundance vary according to their niche (33, 34).

Adherence, iron uptake mechanisms and motility

The adhesion capability of fimbriae is crucial for dental plaque formation and development as they mediate the diverse periodontal pathogens coaggregation, facilitating the adhesion to host tissues (35). As an example, the fimbriae of P. gingivalis could aggregate with dentilisin, the T. denticola major surface protease (MSP) (36-38).

Moreover, P. gingivalis fimbriae enable interaction with essential human component of the glycolytic pathway, the glyceraldehyde-3-phosphate dehydrogenase, promoting the host cells invasion through the periodontal pathogen (35, 39).

The protective function of the extracellular polymer matrix of the dental biofilm promotes a close interaction between periodontal pathogens and host cells. And trough this supported interplay between host cells and pathogenic components, it can either contribute to health or precipitate an inflammatory disease (30). Furthermore, cell surface components such as adhesins and extracellular DNA are responsible for the initial adhesion to salivary pellicle and the periodontal pathogens coaggregation within the dental plaque (40, 41).

Mobility, alongside chemotaxis, constitutes an evolutionary mechanism enabling periodontal pathogens to track down nutrients and identify advantageous hideouts for colonization (42). Bacterial flagellar motility represents a prevalent molecular strong feature utilized by periodontal bacteria. Both bacterial flagellar motility and chemotaxis are recognized as virulence or pathogenicity factors in periodontal pathogens (43). The extent and type of motility varies between periodontal pathogens and spirochetal flagella exhibit diverse locations; for instance, in T. denticola, they are found in the periplasmic compartment, compared to other species, where flagella are exposed and not in the periplasmic compartment (44).

Activity and growth of bacteria

Increased growth serves as a strategy for periodontal bacteria to evade natural removal and mechanical debridement. The periodontal pocket provides a suitable environment for the proliferation of anaerobic, fastidious, low-adherent, and motile bacteria, particularly those belonging to the red and orange complexes (45, 46) (Figure 1). Moreover, the subgingival environment offers mechanical protection, anaerobic conditions, and a nutrient-rich milieu for periodontal bacteria. This includes specific growth factors like hemin, vitamins, hormones, and serum components derived from gingival crevicular fluid (47). Amino acids and proteins from the gingival crevicular fluid constitute an essential nutritive substance and the targets for the highly proteolytic periodontal pathogens from the red and orange complexes, which capable of hydrolyzing proteins. Hazardous metabolites, such as short chain carboxylic acids (SCCAs) (butanoic, propanoic, pentanoic, capronic acids and phenyl acetate) hydrogen nitride and hydrogen sulfide exhibits byproducts of this

heightened metabolic activity (46). The subsequent proliferation of periodontal bacteria triggers an escalation in metabolic activity and bacterial numbers. This expansion, coupled with the coaggregation of other periodontal pathogens, instigates an evolution, which is perpetual in the oral microbial ecology. This dynamic interplay endures until a state of equilibrium is achieved between the bacterial community and the host. This equilibrium may persist for extended periods, or even a lifetime, particularly in individuals with low susceptibility to periodontitis (46).

Evading host-defense mechanisms

Capsules, proteolytic enzymes and intracellular invasion

Many pathogenic microorganisms, particularly Gram-negative anaerobic rods like P. intermedia and P. gingivalis, produce capsules. These capsules serve as anti-phagocytosis mechanisms, thwarting the engulfment of bacteria by neutrophils and macrophages (48, 49). The precise significance of the capsule pathogenicity of bacteria encased by a polysaccharide capsule remains unclear, as most evidence originates from experiments and studies on animals (49).

Arg-gingipain and Lys-gingipain play a role in modulating response of neutrophils to chemical signals produced at sites of infection and activation by increasing the IL-8 chemotactic activity, which enhances the attraction of polymorphonuclear leukocytes to a site of inflammation, contributing to destruction of periodontal tissue (50). P. gingivalis releases the outer membrane vesicles (OMVs),which degrade IL-8, providing substantial resistance against host cells (51). Arg-gingipain and Lys-gingipain can cause the degradation of C3, providing the invading periodontal pathogens by facilitating their survival potential (52).

Dental biofilm: from health to disease

Initially, at early stages, a pathogenic biofilm accumulation below the gingival margin triggers the host's inflammatory-immune response. This leads to increased flow of GCF, which delivers nonspecific immune components like polymorphonuclear leukocytes, proteins of the complement cascade, chemotactic cytokines, interferons, interleukins and lymphokines, contributing to the defense against microbial invasion (53), in addition to the innate immune components, host molecules such as hemoglobin also contribute to the

defense mechanism. However, some proteolytic bacteria, like P. gingivalis, utilize hemoglobin as a substrate for their growth and virulence (54).

While the nonspecific immune response has an effect in case of sensitive periodontal pathogens, pathogenic strategies like overthrowing the function of polymorphonuclear leukocytes, influencing the degradation of the complement cascade and thus causing the inhibition of the phagocytosis can happen due to certain pathogens, exemplified by P. gingivalis (55). Species may enhance the resistance of organisms within the biofilm structure to the inflammatory response and thereby increasing their potential of surviving and it´s defined as the potential for cross protection. Inflammophilic periodontal pathogens can withstand the inflammatory conditions and leverage them for their growth and division (56), as well as changes in pH and strong alkali milieu subsequent to these local environmental shifts, changes occur in bacterial competitiveness and gene expression, particularly in periodontal pathogens like P. gingivalis (57). In the course of the inflammatory process the quantity and quality of GCF undergo alterations, serving as a crucial nutrient source that drives continuous changes in the pathogenic complex of the plaque (58). Such inter-bacterial interactions are exemplified by the development of T. denticola, as a reaction of a stimulus, which is the secreted isobutyric acid of P. gingivalis, while the development of P. gingivalis benefits from the succinic acid of T. denticola (59).

Host inflammatory response

The equilibrium between a healthy symbiotic biofilm and the local host response remains stable until environmental changes prompt shifts in microbial ecology towards a destructive and dysbiotic microbiota. Maintaining a healthy state depends crucially on the quantity, function and regulation of host inflammatory cells that surveil the local tissues, are recruited to target sites and participate in various innate and adaptive host responses. The primary host defense systems encountered by microbial dental plaque, supra- or subgingivally, include mucosal barriers, salivary defense mechanisms, PMN leukocytes, GCF and antimicrobial peptides (60). Furthermore, bioactive lipids such as resolvins, salivary mucins and agglutinins, as well as immunoglobulins IgA, IgG, and activated complement within GCF, may play pivotal roles as protective mediators in maintaining a healthy periodontium (61, 62). Epithelial integrity serves as a crucial physical barrier against microbial penetration during inflammation. Microbial-induced cytokines are released through direct interactions of gingival epithelium pattern recognition receptors

(PRRs), for instance Toll-like receptors (TLRs) together next to pathogen-associated molecular patterns (PAMPs) on pathogens surfaces, what triggers the secretion of anti-inflammatory and immune-regulatory cytokines, including interleukins (IL-6, IL-8 and IL-1α). This reaction stimulates the expression of proteases like cathelicidin, β-defensins and calprotectin. The invasion of bacteria finds a resistance from PMNs through their phagocytosis, nonspecific cell-derived mediators and degradative endopeptidase like matrix metalloproteinases (MMPs) (63, 64). The dominance PMNs as an inflammatory trigger is also evident in the burst model of periodontitis, characterized by progresses by short bursts of destruction followed by periods of no destruction: acute exacerbation following the remission period (65). Continuing inflammatory reaction to pathogens invasion within the inflammophilic dysbiotic dental biofilm, accentuates the proteolysis of polymorphonuclear leukocytes alongside their protective functions. This shift in balance may result in epithelial distortion, offering a gateway for microbial infiltration into the underlying connective tissues, thereby triggering tissue degradation and bone resorption (66). Neutrophils' destructive potential escalates when their activities deviate from the norm, be it through excessive or diminished recruitment, dysfunction or hyperactivity, ultimately resulting in exacerbated tissue degradation (67). For instance, single gene deficiencies may change the host-microbial homeostasis, such as those affecting LFA-1 integrin (leukocyte function associated antigen 1), which promotes the infiltration of neutrophils (68, 69). The release of receptor activator of nuclear factor kappa-B ligand (RANKL) on the osteoclast’s plasma membrane can be induced by neutrophils, thereby promoting the resorptive activity (70). Additionally, neutrophils promote the osteoclastogenic T-cell subset linked to bone loss, Th17 cells, and potentially contributing to the chronicity of inflammation by serving as a B-cell activator that enhances the production of immunoglobulins (71, 72). There is a shift in immune cell activity, while a gingivitis passes to advanced periodontitis. Antimicrobial peptides produced by neutrophils appear to be replaced by increased activity of Langerhans dendritic cells and γδ-T cells, which serve as a connection between innate and adaptive immune responses. These cells secrete various signaling inflammatory proteins, including interleukins (IL-1, IL-6, IL-17,IL-23) and TNF-α. Additionally, bacterial invasion-associated capillary activation induces endothelial expression of intercellular adhesion molecule ICAM-1 and selectin receptors, facilitating leukocyte transmigration and exudation (73).

In the early stages of acute inflammation or gingivitis, the complement cascade from the humoral, innate immunity release cytokines and initiate an amplifying cascade of further

cleavages. Gingival crevicular fluid serves as a conduit for complement proteins like complement component 3, which is released into the gingival sulcus after translocating through the nonkeratinized stratified squamous epithelium. This process triggers the following reactions: Amplification of the inflammatory response, bolstering of phagocytosis and enhancing the effectiveness of neutrophils in the destruction of pathogens. However, in advanced periodontitis, this system becomes dysregulated or subverted, leading to aberrant immune responses (62). As inflammation advances, the independent manipulation and exploitation of the bactericidal activity of the inflammatory reaction through the dysbiosis-associated microbiota initialize (74). The immunosuppression seems unsuitable for inflammophilic bacteria, because it would eliminate the inflammatory process necessary for providing nutritional basis for colonization and survival.

Following the keystone pathogen concept, P. gingivalis could undermine the host bactericidal activity, particularly neutrophils (75-77), by decoupling bactericidal activity from inflammation, certain key pathogens like P. gingivalis can provide a substantial advantage to the entire microbial community. This may involve manipulation of complement, TLR signaling and cytokine responses (78).

1.2.2 Pathophysiology of periodontal disease

Pathogenesis of alveolar bone loss

Subgingival plaque biofilms elicit a heightened proinflammatory immune response within the gingival fibers, prompting signaling, that is affected by secreted molecules that diffuse in extracellular space and whose range of action is limited by uptake into neighboring cells, degradation by extracellular enzymes and adsorption to components of the extracellular matrix and thus culminate in alveolar bone degradation. The range of effectiveness of subgingival plaque in inducing a resorption in alveolar bone spans approximately 2.5 mm (79). The distance from the apical extension of the subgingival plaque to the alveolar crest varies, ranging between 0.5 mm and 2.7 mm (80, 81).

The continuous stimulation from dental plaque biofilms triggers an overproduction of proinflammatory mediators. This excessive immune and inflammatory response induced by subgingival plaque disrupts the balanced tissue remodeling processes. Consequently, elevated levels of proteases, eicosanoids such as prostaglandins, matrix metallopeptidase, cytokines and various host enzymes are released from different host cells, including epithelial cells, fibroblasts, polymorphonuclear leukocytes, monocytes, macrophages, and osteoblasts (82-84). The persistent proinflammatory condition disrupts the normal remodeling process of the gingival fibers and the desmodont by fibroblasts and it results in dysregulation in quantity of collagen content and tissue integrity (82, 83). The apical extension of the junctional epithelium is the result of the detachment of periodontal ligament collagen fibers of the from the root surface. This extension facilitates the deeper penetration of subgingival plaque. With the increase of periodontal pocket depth, the anaerobic microenvironment becomes more favorable for gram-negative periodontal pathogenic bacteria, thereby increasing the risk of disease progression at the site (79, 85). The infiltration of inflammatory cells extends further into the connective tissue affected by periodontitis, initiating proinflammatory paracrine signaling cascades that disrupt the coordinated bone remodeling processes mediated by osteoclasts and osteoblasts. Within the periodontal ligament and environment, cells increase the RANKL production while reducing osteoprotegerin biomarker shifting the balance towards osteoclastic bone resorption (86, 87).

Various cells in the local microenvironment produce proinflammatory cytokines such as tumor necrosis factor, IL-1beta, IL-6, and IL-17. These cytokines not only increase RANKL production but also, further intensify the osteoclast-mediated bone resorption mechanism by the exhibition of synergistic effects on RANKL signaling (82-84).

Hence, the proinflammatory immune response triggered by subgingival plaque ultimately contributes to periodontal bone destruction by either enhancing osteoclast activity or suppressing osteoblastic function.

The advanced lesion manifests with an increased immune cell infiltration that permeates deep into the gingival connective tissue. This stage is characterized by progressive collagen loss beneath the pocket epithelium, causing migration of the epithelium either apically or laterally, and consequent destruction of the attachment of the periodontal ligament and the supporting alveolar bone. Typically, the crest of the interdental septum is the first affected location from the bone resorption, leading to thickening of the gingiva due to fibrosis. Exposed marrow spaces become hypercellular and undergo fibrotic changes. (88). Weinmann's alveolar bone fibrosis theory, as described during histological investigations of chronic periodontitis effects on human periodontal specimens obtained post-mortem, elucidated the process. In this theory, the resorption of the alveolar bone crest is due to the inflammatory infiltrate within the upper layer of the connective tissue. The transformation of fatty marrow into fibrous marrow is the result of the inflammatory reaction penetration through the blood vessels to the bone marrow spaces.

The red and white marrow become hypercellular, fibrotic and ultimately transform into scar-like connective tissue (89).

Aligned with the first principle, chronic periodontitis has been demonstrated to disrupt the equilibrium of osteoclast-osteoblast-mediated alveolar bone remodeling (90, 91), resulting in the transformation of alveolar bone marrow into fibrous scar-like tissue and its accumulation (88, 89, 92).

Aligned with the second principle, chronic periodontitis ultimately culminates in the deterioration of alveolar bone anatomy, what is associated with progressive decline in periodontal function. This decline leads to the loss of dentoalveolar support and to a high vertical and horizontal tooth mobility and therefore to tooth loss.

The fact that nonoral pathogens-host immune response effects contribute to fibrosis conditions further supports the idea that periodontitis-induced alveolar bone resorption is caused in part through fibrosis (93, 94).

1.2.3 Classification of periodontal disease and conditions

Periodontitis: Staging

Periodontitis classification relies on categorizing stages determined by severity, considering the reduction of interdental clinical attachment level, decrease of radiographic bone level and tooth loss, alongside factors such as complexity, extent, and distribution (95).

The initial stage ought to be assessed by clinical attachment loss (CAL), or if unavailable, radiographic bone loss (RBL) may be employed. Additionally, data on tooth loss predominantly due to periodontitis, if accessible, could influence the definition of the stage. Even in the absence of complexity factors, this remains true. Complexity factors can elevate the stage to a higher level. For example, furcation grades II or III would elevate to either stage III or IV regardless of clinical attachment loss. The differentiation between stage III and stage IV primarily relies on complexity factors. As an illustration, a significant degree of tooth mobility and/or posterior bite collapse would signify a diagnosis of stage IV. In any given case, only certain complexity factors may be present, not all. However, typically, it only requires one complexity factor to transition the diagnosis to a higher stage. It's important to highlight that these case definitions serve as guidelines and should be applied with careful clinical judgment to reach the most suitable clinical diagnosis. For patients' post-treatment, CAL and RBL continue to be the primary determinants of stage. If treatment successfully eliminates a stage-shifting complexity factors, the stage should not regress to a lower level. This is because the original stage complexity factor should always be taken into account in maintenance phase management (95) (Table 1).

Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	1 to 2 mm	3 to 4 mm	≥5 mm	≥5 mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to mid-third of root and beyond	Extending to mid-third of root and beyond
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤4 teeth	Tooth loss due to periodontitis of ≥5 teeth
Complexity	Local	Maximum probing depth ≤4 mm Mostly horizontal bone loss	Maximum probing depth ≤5 mm Mostly horizontal bone loss	In addition to stage II complexity: Probing depth ≥6 mm Vertical bone loss ≥3 mm Furcation involvement Class II or III Moderate ridge defect	In addition to stage III complexity: Need for complex rehabilitation due to: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree ≥2) Severe ridge defect Bite collapse, drifting, flaring Less than 20 remaining teeth (10 opposing pairs)
Extent and distribution	Add to stage as descriptor	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern			

Table 1: Periodontitis stage. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. 2017 World Workshop

Periodontitis: Grading

Periodontitis classification is structured around grades that mirror the biological characteristics of the disease. These grades encompass indicators of, or susceptibility to, rapid progression, expected treatment outcomes, and impacts on systemic health (95).

Grade serves as indicator for the rate of periodontitis advancement. The main criteria rely on either direct or indirect evidence of progression. Direct evidence is prioritized whenever accessible; if not, indirect estimation is employed, typically using bone loss relative to age at the most affected tooth or case presentation (expressed as RBL/age, radiographic bone loss as a percentage of root length divided by the age of the subject). Clinicians should initially presume grade B disease and actively search for specific evidence to potentially upgrade to grade A or downgrade to grade C if pertinent evidence is present. Once the grade is determined based on evidence of progression, it may be adjusted considering the presence of risk factors (95) (Table 2).

Periodontitis grade			Grade A: Slow rate of progression	Grade B: Moderate rate of progression	Grade C: Rapid rate of progression
Primary criteria	Direct evidence of progression	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss/age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normoglycemic/ no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes

Table 2: Periodontitis grade. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. 2017 World Workshop

1.3 Therapy of periodontitis

1.3.1 Initial cause-related therapy

Home care review

Reviewing home care is critical for the prevention of gingivitis and periodontitis, the ensuring of a successful periodontal treatment and the maintain of a periodontal health for a long term.

Clinicians must instruct patients about the significance of the thoroughly oral hygiene at home, particularly before undergoing active periodontal therapy. Emphasizing the importance of proper home care should be done regularly during both the initial and follow-up phases of periodontal treatment (96, 97).

Scaling and root planing

Once adequate home care or biofilm control is established, scaling and root planing should be performed at sites with periodontal probing depths of 5 mm or greater. The treatment phase should be accompanied by addressing local factors, extraction of non-salvageable teeth, management and conservative treatment of carious lesions. Prior to initiating non-

surgical periodontal therapy (scaling, root planing), the practitioner should give the patients sufficient local anesthesia to ensure comfort during the procedure.
The combination of piezoelectric or ultrasonic scalers with manual instruments at the treatment is advantageous (98, 99).
In areas where access is challenging, automated instruments may offer advantages over curettes for the removal of subgingival biofilm and calculus. Additionally, occlusal adjustment should be considered to alleviate issues such as fremitus, severe mobility or excessive central and lateral excursive contacts (100).

1.3.2 Periodontal re-evaluation

Four to six weeks after the completion of scaling and root planing, a re-evaluation should be conducted. This involves updating a comprehensive periodontal chart and comparing the findings to the initial assessment to gauge improvement. Additionally, patient compliance with the recommended home care routine and procedures must be thoroughly assessed.
For teeth with relatively probing depths between 1 mm and 5 mm, a non-surgical approach may be appropriate. This could include reevaluation and several sessions of root planing, if necessary, frequent periodontal maintenance therapy (recall) and consistent reinforcement of home care practices (101, 102).
However, for teeth with periodontal probing depths over 6 mm and deeper, the surgical periodontal therapy should be indicated.
It is crucial to note that excellent compliance with oral health care instruction is essential before proceeding with surgical intervention to ensure optimal outcomes. Therefore, if needed, periodontal surgery should be postponed until the patient demonstrates a cooperation and sufficient gingival and plaque index that allows to start the surgical therapy (103).

1.3.3 Periodontal surgical therapy

Resective periodontal surgery

During such surgery, intrabody osseous defects will be treated through osteotomy and osteoplasty to reduce or eliminate them.
Following this, the gingival tissue can be repositioned apically to the new height of the alveolar crest. This approach typically leads to the resolution or reduction of deep probing

depths. In cases, where areas with high probing depths persist without evident underlying alveolar bone defects, soft-tissue periodontal surgery may be an additional treatment option (104-107).
These may include decrease in attachment level in adjacent but less affected sites, hypersensitivity due to exposed root cementum, temporary high tooth mobility and loss of interdental papilla (108-111).

Regenerative periodontal surgery

Regenerative periodontal surgery aims to restore lost periodontal tissues caused by the disease process. Its primary objective is to rebuild the attachment level, normalize bone remodeling, stimulate the regeneration and minimize the tooth mobility. In cases vertical defects, periodontal regenerative therapy becomes an important consideration. Guided tissue regeneration is a technique employed in this context, involving the use of a barrier membrane along with various particulate bone graft materials (112-115).

Mucogingival surgery

After the completion of scaling and Root Planing mucogingival deformities should be thoroughly assessed and managed as needed. During the assessment, various clinical parameters are taken into consideration, including the classification of gingival recession, the clinical measurement of the keratinized gingiva width (WKG), mucogingival junction (MGJ), keratinized mucosa width (KMW), vestibular depth, presence of inflammation, hypersensitivity and the aesthetics. By carefully evaluating these parameters, clinicians can determine the appropriate treatment plan to address mucogingival deformities effectively (109).

1.3.4 Periodontal maintenance therapy

Patients who have previously experienced periodontal disease should receive regular and recurring periodontal maintenance, typically scheduled every 2 to 6 months. However, the specific interval should be established after active periodontal treatment is completed and it should be adjusted based on ongoing assessments of the modifiers for periodontitis. Parameters like medical history (including diabetes diagnosis), smoking status, existence of deep probing depth sites, presence of other modifiers mentioned and the home oral

hygiene quality should all be taken into account when determining the appropriate maintenance schedule. A consistent recall interval enables timely identification and management of disease recurrence or reactivation in patients previously treated for periodontitis. For instance, compliant patients who adhere to regular supportive periodontal therapy experience significantly fewer periodontitis associated tooth loss compared to those who are irregular or non-compliant. Throughout supportive therapy, updating periodontal charts and obtaining radiographs as necessary is essential. Additionally, thorough review of home oral health care practices is recommended. If sites with persistently or worsening probing depths are identified, consideration should be given to restarting active periodontal therapy (116-118).

1.4 Alveolar bone physiology and bone remodeling

The alveolar process depends on the development, eruption and maintenance of teeth. (119, 120). The alveolar bone serves two primary functions: the protection of roots and the support of the mastication. As a non-oral skeletal tissue, alveolar bone is considered as a reservoir of hematopoietic stem cells, mesenchymal stem cells, calcium, magnesium and phosphorus. and he responds to calciotropic hormones, such as PTH and thyreocalcitonin, that affect serum calcium homeostasis.

Alveolar bone proper, supporting trabecular bone and supporting cortical bone which includes the lingual and buccal cortical plates are the main parts of the alveolar bone. At the level of the alveolar bone crest, the lingual and buccal cortical plates are integrated with the alveolar bone proper (121-123). The interposition of trabecular bone between the alveolar bone proper and the lingual/buccal cortical plates is contingent upon the tooth morphology and the bucco-lingual morphology of the alveolar process (121-123). The number of trabeculae, thickness and distribution of the alveolar bone exhibit considerable variability and there is no evidence to suggest that these characteristics are influenced by age (124, 125).

The membranes that line the alveolar bone surfaces are well supplied with blood, are source of progenitor cells and include the periodontal ligament, periosteum and endosteum. Seminal reports have employed lineage tracing to track the Mesenchymal stem/progenitor cells (MSCs), which are responsible for the formation of bone-forming osteoblast cells.

Osteoblasts are derived from mesenchymal progenitors, which are origin from the bone marrow, endosteum and periosteum (126, 127).

The hematopoietic marrow, adipocytes and blood vessels are located inside alveolar bone medullary space. This latter is between the endocortical surfaces and surrounding the interposed trabecular bone (124, 125). Myelopoiesis and lymphopoiesis and erythropoiesis are sustained by the multipotent progenitor cells and the hematopoietic progenitor cells (HPCs) are self-renewing. Both these progenitor cells are contained in adult bone marrow (128, 129). It has been demonstrated that osteoblasts/stromal cells and osteoclasts secrete products that bring about the maintenance and modulation of hematopoietic progenitor cells function (129, 130).

Turnover is the process of continually renewing, in which the resorption followed by replacement by new bone with little change in shape, whereby the osteoclasts from the myeloid cell lineage, resorb old bone matrix and osteoblasts from the mesenchymal lineage subsequently form new bone matrix. For bone homeostasis to occur, it is necessary for the activity of these derived myeloid cell lineage and derived mesenchymal cell lineage to be balanced, with no excessive apposition or resorption of bone tissue (131-134). The bone Homeostasis bone is modulated by mechanical and biochemical stimuli, mediated juxtacrine and paracrine, immune cells and endocrine signaling reactions induced by hormones and immune factors (132). A fundamental multicellular unit comprises osteoclasts and osteoblasts, contributing bone remodeling in five sequential phases: activation Phase ,resorption phase, reversal Phase, formation phase, termination phase (135). Substantia spongiosa undergo remodeling approximately seven times faster than substantia corticalis (125, 136). This discrepancy underscores the potential vulnerability of trabecular bone to inflammatory bone loss. Moreover, it's worth noting that the average lifespan of human osteoclasts within the basic multicellular unit is around two weeks, while bone-forming osteoblasts have an estimated lifespan of approximately three months (125, 136).

Osteoblasts play a critical role in the regulation of periodontal bone loss (137).

This alveolar bone loss, that characterizes the periodontal disease is primarily attributed to markedly suppressed active bone remodeling and significantly heightened osteoclast genesis. The bone resorption observed in the sites with minimal plaque index was probably attributed to pathogens endotoxin (138).

1.4.1 Bone cells: Types and function

Osteoblasts, originating from the mesenchymal lineage, are responsible for bone formation. The osteoblast lineage encompasses various cell types, including osteoblast precursors, mature osteoblasts, bone lining cells and osteocytes. (139, 140). The regulation of osteoblast differentiation is influenced by the following factors: runt related transcription factors (RUNXs), transcription factor Sp7 and Activating transcription factors (ATFs) (139, 140). The RUNXs are essential for committing mesenchymal stem cells (MSCs) to the osteoblasts. Bone morphogenetic protein (BMP), peptide hormone insulin-like growth factor (IGF), Wnt signal transduction pathways and fibroblast growth factor (FGF) support the osteoblast differentiation and function, while NOTCH pathway serves as an inhibitory mechanism for osteoblast differentiation (139, 140). Osteoblasts predominantly secrete an extracellular matrix consisting of collagen type I (Col-I) and various non-collagenous proteins (NCPs) (140, 141). Osteoid, initially unmineralized bone matrix, is facilitated in its mineralization process by secreted non-collagenous proteins (140, 141). The mineralized inorganic component of the bone matrix is primarily composed of hydroxyapatite, Ca10(PO4)6(OH)2 (140, 141).

Osteocytes constitute an impressive majority, comprising over 90% of bone cells, derive from osteoblast (4%−6% of bone cells) and reside within lacunae of the mineralized bone matrix (140, 141). Osteocytes, nestled within a bony compartment known as the lacuna, extend dendrites, that traverse the bone matrix within tiny channels termed canaliculi (142, 143). Osteocytes secrete key biological factors, playing critical roles in regulating osteoblast activity, such as sclerostin and Dickkopf-1 (DKK1), which exhibits broad expression across various cells, while osteocytes predominantly synthesize sclerostin. The osteoblast induced bone formation is suppressed through the Sclerostin and DKK1 negative regulation of Wnt/β-catenin pathway (140, 144).

Osteoclasts are monocyte derived cell responsible for bone resorption, derived from monocyte-macrophage precursor cells. The macrophage colony-stimulating factor (M-CSF) and RANKL are critical signaling factors essential for osteoclast genesis (145-148). RANK is expressed on osteoclast precursors and mature osteoclasts. The promotion of osteoclast precursor cells proliferation and differentiation takes place as result of the expression of RANK induced by signaling through M-CSF receptor, c-Fms (149). Osteoclast differentiation start with the expression of nuclear factor of activated T-cells triggered by Binding of RANKL to RANK (150, 151). The binding of RANKL to its

receptor RANK on osteoclast cells facilitates the expression of effector genes responsible for driving osteoclast maturation, function, and survival. RANKL induce both DC-STAMP, the multi-pass transmembrane protein and OC-STAMP, the osteoclast stimulatory transmembrane protein, which play critical roles in osteoclast maturation. Nuclear Factor of Activated T Cells 1 mediated RANKL signaling is crucial for the osteoclastic proteolytic enzymes secretion including the osteoclast enzyme (TRAcP) 5b and lysosomal papain-like cysteine protease, Cathepsin K. The physiological osteoclastogenesis inhibitory factor, OPG regulate the process of RANKL-mediated osteoclastogenesis (150-154).

The downregulation of osteoclastogenesis is the result of the inhibition, at the RANK receptor, of the RANKL signaling through the binding of OPG to RANKL (140).

1.4.2 Receptor activator of nuclear factor-kappa B ligand-Osteoprotegerin axis

Osteoclasts serve as the specialized cells responsible for breaking down bone tissue. These large, multinucleated cells attach themselves to bone surfaces, forming a sealing zone and a ruffled membrane border. Within this border, proton pumps gather hydrogen ions from the environment, which then combine with chloride ions to produce hydrochloric acid. This acid is instrumental in breaking down the mineral content of the bone. Meanwhile, enzymes within acid-resistant endosomes and lysosomes target the collagen matrix, effectively dismantling collagen fibers and gradually removing small amounts of bone tissue (155). It has been widely acknowledged that osteoclast precursors are present in the circulating monocyte/macrophage population. These precursors undergo differentiation into preosteoclasts, which subsequently fuse together to generate large, bone-resorbing mature osteoclasts (156). Moreover, it has been acknowledged that inflammatory conditions such as rheumatoid arthritis and periodontal infection contribute to osteoclastic bone loss. This has led to speculation that inflammatory cytokines like Interleukin IL-1, tumor necrosis factor alpha (TNFα), and IL-6 might exert pivotal influences on osteoclast formation (157). These cytokines, when applied to purified monocytes, do not elicit significant osteoclast formation, suggesting an indirect mode of action. Given that bone formation and resorption are interdependent processes during bone modeling and remodeling, it was further conjectured that osteoblasts might regulate osteoclast activity. OPGL and ODF were found to be structurally and functionally identical, potently

promoting osteoclast formation in the absence of any other exogenous factors, except for the monocytic survival factor M-CSF. Interestingly, a factor structurally identical to OPGL and ODF had been previously reported by two independent groups of immunologists and had been named receptor activator of NF-κB ligand (RANKL) and tumor necrosis factor-related activation-induced cytokine (TRANCE) (158, 159). These research groups demonstrated that this factor, which is expressed by T cells, possesses immunomodulatory functions mediated through receptors (RANK/TRANCE-receptor) present on dendritic cells (158-160). While these terms were previously used interchangeably, in the context of bone biology, the preferred terminology has evolved. Presently, RANKL is the preferred term to describe the osteoclastogenic cytokine, OPG is used to denote its inhibitor, and RANK is designated as the receptor for RANKL. It is now evident that RANKL serves as the principal effector of osteoclastogenesis. In the presence of a permissive concentration of M-CSF, RANKL is capable of inducing osteoclast formation and enhancing osteoclast resorptive activity independently of other cytokines. OPG acts as a decoy receptor, obstructing the association of RANKL with the RANK receptor, thereby moderating osteoclastogenesis and bone resorption. (156, 160-162). These preosteoclasts can be identified in vitro or ex vivo by their expression of the enzyme tartrate-resistant acid phosphatase (TRAP). Subsequently, preosteoclasts fuse with polarized and multinucleated osteoclasts, capable of bone resorption. Mature osteoclasts express key osteoclast markers, including TRAP, calcitonin receptors, cathepsin K and MMP9 (163-166). The central role of RANKL in basal osteoclast formation and bone homeostasis has been established in animal models where genetic deletion of RANKL leads to an osteopetrotic phenotype characterized by a complete absence of osteoclasts and a failure of tooth eruption. The evidence supporting the RANK/RANKL/OPG system's pivotal role in osteoclast formation and bone resorption regulation is now overwhelmingly robust. Furthermore, it is now evident that inflammatory cytokines like IL-1, TNFα, and M-CSF, long implicated in osteoclastic bone loss, operate by promoting RANKL production by osteoblast precursors (bone marrow stromal cells (BMSC) and/or mature osteoblasts (167-170).

It was preclinically and clinically observed that dental plaque biofilms elevate RANKL expression, diminish OPG expression and result in an increased RANKL:OPG ratio (86, 171). Experimental administration of exogenous OPG in rodent with periodontitis attenuated osteoclastogenesis and decreased bone resorption, this illustrates the critical role of the RANKL: OPG axis in regulating periodontitis-driven alveolar bone loss. Recent advancements have shed light on the molecular mechanisms governing the cellular sources

of RANKL and OPG. Osteoblast-derived RANKL plays a pivotal role in regulating basal osteoclastogenesis (167, 172-175). RANKL derived from osteocytes, rather than osteoblasts, is crucial for supporting basal osteoclastogenesis and physiological bone remodeling (176, 177). Conditional knockout models targeting RANKL specifically in T and B cells did not show bone mass discrepancies, suggesting that RANKL does not play a significant role in regulating physiological bone remodeling. Under physiological conditions, the OPG expression is strongly influenced by T cells, that contribute to skeletal homeostasis by expressing cluster of differentiation (CD40) ligand, that influence the synthesis of OPG by an indirect regulation. Activation of the cluster of differentiation costimulatory receptor by CD40 ligand prompts B cell OPG production, this mechanism supports basal osteoclastogenesis and physiological bone remodeling (178-181).

RANKL originating from various cell types plays a critical role in regulating periodontitis-induced alveolar bone loss. The primary source of RANKL within the resorption lacunae are T cells and B Cells (182).

1.5 Osteoporosis

Osteoporosis is a multifaceted condition influenced by various factors including genetics, gender, age and environmental factors. It can be categorized into primary osteoporosis, typically associated with age-related changes and secondary osteoporosis, which arises from underlying medical conditions or medications affecting bone health.

Secondary osteoporosis, on the other hand, arises due to specific diseases or medications impacting bone metabolism. The condition results in increased bone fragility and susceptibility to fractures, leading to debilitating pain, impaired mobility and in severe cases, mortality.

As the global population ages, osteoporosis poses a growing challenge with significant implications for both individuals and society at large. Statistics show that approximately 30% of women and 20% of men worldwide either currently suffer from osteoporosis or are at risk of developing the condition in the future (183, 184).

The structural integrity of the bone tissue and his physiological function depends on the maintenance of his homeostasis, a dynamic equilibrium regulated by the activities of osteoblasts and osteoclasts. Following the attainment of peak bone mass around the age of 35 years, there is a gradual loss of matrix elements and minerals (185, 186). The dysregulation of bone remodeling processes progressively accumulates, leading to a decrease in bone mass and microarchitectural deterioration, culminating in osteoporosis. Menopause and aging exert distinct effects on the balance between osteoclast and osteoblast activity, thereby exhibiting different patterns of bone turnover rate.

Traditional therapies for osteoporosis encompass both antiresorptive and anabolic agents. Despite the development of numerous drugs aimed at fracture prevention, the compliance and the significant adverse effects prevent the administration sufficient treatment in many patients (187).

Postmenopausal osteoporosis is a systemic condition marked by diminished bone mass and deterioration of bone microarchitecture, resulting in heightened susceptibility to fractures (188). Reduced estrogen levels post-menopause disrupt the equilibrium between bone formation and resorption, tipping the balance in favor of bone resorption (188). Estrogen exerts direct effects on bone cells by enhancing osteogenic differentiation of mesenchymal stem cells (MSCs) and promoting osteoblast maturation, thereby facilitating bone

formation. Additionally, estrogen inhibits osteoclast formation and induces apoptosis in existing osteoclasts, which curtails bone resorption. Insufficient estrogen levels in females diminish these osteo-anabolic and anti-osteoclastic effects, resulting in continued bone degradation (189). Beyond its impact on bone cells and postmenopausal osteoporosis, estrogen influences various immune cells, contributing to a multifaceted disease affecting the entire body. Estrogen deficiency is associated with a chronic low-grade pro-inflammatory phenotype, highlighting its broader role in immune regulation (190-192).

1.5.1 Etiology

Genetic factors

Osteoporosis exhibits a robust genetic predisposition, as evidenced by family and twin studies. Research indicates that a considerable portion of the variability in peak bone mass is under genetic control, with estimates ranging from 25% to 45%. Furthermore, about 200 susceptibility loci associated with osteoporosis have been shown in studies, with genes such as Collagen Type I Alpha 1 Chain Collagen Type I Alpha 2 Chain, SOST-sclerostin and the Wnt co-receptor, LRP5. Despite these discoveries, the precise architecture, distribution and size of these loci remain largely elusive (193). Among these loci, DAAM2 was previously implicated in the β-Catenin-dependent signaling (194) .

Endocrine factors

Parathyroid hormone (PTH), testosterone, calcitonin, estrogen and other hormones plays essential roles in bone remodeling. For example, particularly during pregnancy or postmenopausal, estrogen level fluctuations cause bone loss and increase the risk of traumas (195, 196). Abnormalities in bone microstructure, reduced bone formation and high risk of vertebral fractures could occur due to chronic hypoparathyroidism (197, 198). Even in non-advanced cases, hyperparathyroidism led to increased bone resorption and reduced bone mineral density (BMD), what increase the susceptibility to fragility fractures (199). While calcitonin's physiological function is relatively weak, basal calcitonin levels or calcitonin reserve do not correlate with changes in BMD (200). Calcitonin, in conjunction with PTH, plays a role in maintaining normal mineral metabolism, what is crucial in preserving bone structure and composition (201, 202). Additionally, osteoporosis can be a result of hypermetabolism caused by hyperthyroidism (203).

Osteoporosis and senescence

Osteoporosis is prevalent among the elderly population, with declining hormone levels being a primary factor contributing to senile osteoporosis. Age-related reductions in hormone-binding globulin can result in the inactivation of testosterone and estrogen. Senescence also leads to diminished synthesis and secretion capacity of osteoblasts and osteoclasts, thereby decelerating the rate of bone remodeling (204).

Nutritional status and lifestyle

Sufficient intake of calcium, phosphorus, and magnesium is crucial for maintaining bone health, as these elements are essential components of bone tissue. Imbalances or deficiencies in these minerals can disrupt bone synthesis and increase the risk of bone loss. Ensuring adequate intake of calcium and dietary protein has been shown to reduce the risk of fractures (205). On the contrary, inadequate intake of dietary calcium and vitamin D can lead to conditions like osteoporosis, rickets and osteomalacia. These conditions are characterized by weakened bones and increased susceptibility to fractures (206). Supplementation with calcium to maintain proper calcium balance has become a standard approach for preventing and managing osteoporosis.

Tobacco consumption has been identified as a significant risk factor for osteoporosis, leading to decreased bone formation and acceleration of the bone resorption. However, it has been proven smoking cessation led to enhance bone mineral density and decrease the risk of fractures (207). The correlation between bone remodeling and alcohol depends on the amount consumed. Moderate alcohol intake, typically defined as less than 15 grams per day for light and less than 30 grams per day for moderate drinking, is generally associated with a reduced risk of fractures (208). Consuming higher amounts of alcohol can lead to a continuous increase in the risk of osteoporotic fractures (209). Moderate physical activity is considered as a protective factor for bone health, as it can provide bones mechanical stimulation and enhanced muscle activity and function and improve BMD (210). It has been revealed in a meta-analysis, that various types of muscle training have diverse impacts on BMD across various skeletal regions (211).

1.5.2 Pathogenesis of postmenopausal osteoporosis

Around half of women after reaching 50 years old expected to experience a fracture, primarily caused by decrease in estrogen levels (212). Certainly, women exhibit increased osteoporosis rate, compared to men, largely due to estrogen deficiency (213). Estrogen plays a crucial role in maintaining homeostasis in various systems, including the endocrine, cardiovascular, metabolic and skeletal systems. Deficiency in estrogen levels leads to disturbed bone remodeling in both substantia spongiosa and substantia compacta (214). Increased risk of osteoporosis in women is due to ovarian aging (215, 216). In men, estrogen continues to serve as a primary regulator of bone health (217). The basis for pathogenesis of postmenopausal osteoporosis requires the precise understanding of estrogen's role in bone remodeling. Estrogen operates in the following way: initially binding to receptors in the cytoplasm, followed by ER dimerization and translocation into nucleus. (218). The ligand-receptor complex then binds to specific sequences in the regulatory region of target genes, known as estrogen response elements (EREs) (219).

ERα and ERβ are two types of estrogen receptors with distinct affinities for estrogen and differing distributions throughout the body (220). ERs, part of the steroid/thyroid hormone superfamily of nuclear receptors, consist of three functional domains that interact with each other. Although ERα and ERβ share similarities, they differ in their DNA-binding domains and ligand-binding sites (221).

Postmenopause significantly impacts estrogen levels, leading to decreased concentrations of different estrogen forms. Postmenopausal changes entail a substantial reduction in E2 and E1 serum levels compared to mean premenopausal levels (E2: decrease of 85% to 90%. E1: decrease of 65% to 75%) (222). This postmenopausal decrease in E2 and E1 levels can have multifaceted effects on bone mass. Understanding these effects can provide valuable insights for making informed medical decisions (222).

The extensive array of potential targets for estrogen receptors includes cytokines like interleukin IL-1, (223, 224) IL-17, (225, 226) IL-6, (226, 227) IL-7, (228-230) and tumor necrosis factor-alpha (TNF-α) (224, 231). Estrogen impacts various cell types, including T and B lymphocytes, macrophages and dendritic cells (232).

1.5.3 Osteoporosis medication

The most therapeutic agents used are the bisphosphonate alendronate, peptides of the parathyroid hormone family, denosumab, raloxifene, selective estrogen receptor modulators, vitamin D derivatives, clodronate, ibandronate, risedronate and zoledronic acid (233).

1.6 Alendronate

Alendronate belongs to a class of bisphosphonate that are currently clinically administered and being investigated for various medical purposes (234, 235). Bisphosphonates are chemically stable analogues of inorganic pyrophosphate (PPi). In their chemical structure a carbon replaced the bridging oxygen, typically characterized by an aliphatic amino acid. The understanding that pyrophosphate can inhibit the formation and the calcium phosphate crystals dissolution, is the reason of the development of bisphosphonates (236). The characteristics of bisphosphonates hinted at their inhibition potential of bone resorption or inappropriate biomineralization occurring in soft tissues, the ectopic mineralization. The biochemical potentials of bisphosphonates, such as biochemical stability and pharmacological activity as bone resorption inhibitors, are proven, thus expanding their role in the clinical management of bone diseases. Investigational use of intravenous alendronate has been explored for managing hypercalcemia of malignancy (237, 238). Alendronate is approved for treating, preventing postmenopausal osteoporosis, Glucocorticoid (GC)-induced osteoporosis (GCOP) and Paget’s disease therapy , as an oral administration in over 80 countries globally. Notably, its side chain's amino group contributes to significantly higher potency and enhanced selectivity in inhibiting bone resorption compared to etidronate, an earlier clinically used bisphosphonate devoid of nitrogen (239-250).

1.6.1 Mechanism of action

While the exact pharmacological intricacies of bisphosphonates remain incompletely elucidated, available data allow for a broad understanding of alendronate's mechanism of action.

Alendronate undergoes rapid plasma clearance, with the compound being either excreted via the urine or sequestered within the skeletal system. The distribution of alendronate within bone is not uniform; rather, it is concentrated in areas where bone turnover is most active, reflecting its preferential uptake in regions of high physiological activity. More precisely, alendronate exhibits a preferential accumulation at sites where bone resorption is actively occurring (251-253).

After adhesion with bone hydroxyapatite , particularly in resorption lacunae, alendronate is released and this occurs, when osteoclasts create acidic conditions during bone resorption, leading to the solubilization of the bound alendronate (254). Alendronate is subsequently internalized by osteoclasts, where it exerts biochemical effects that render the osteoclast inactive, thereby inhibiting bone resorption (252).

Recent studies have identified two biochemical effects of alendronate, including inhibition of protein tyrosine phosphatase another biochemical effect of alendronate involves the inhibition of protein prenylation. The inhibition of protein prenylation in osteoclasts is attributed to the effect of nitrogen-containing bisphosphonates on enzymes involved in cholesterol biosynthesis (255-259). The reduction in osteoclast activity and number observed with long-term administration of alendronate raises questions about its mechanisms. It remains unclear whether this effect is primarily due to the decrease in bone resorption and alterations in bone turnover dynamics or if alendronate has additional impacts on osteoclast recruitment, differentiation, or apoptosis induction, the precise mechanisms underlying these effects remain uncertain. Some researchers have suggested that bisphosphonates like alendronate might need to interact with osteoblasts, the bone-forming cells, to exert their inhibitory effects on osteoclasts. However, further investigation is needed to fully elucidate the intricacies of bisphosphonate action in bone remodeling (260, 261).

In case of not absorption through the Osteoclasts of Alendronate from the areas of bone remodeling, becomes integrated within the bone matrix and enclosed by newly formed

bone. Researchers utilize the fluorescence of tetracyclines within bone as an indicator of bone formation. Similarly, alendronate incorporated into the mineralized bone matrix remains pharmacologically inactive until the removing of the overlying layers of bone through the subsequent resorption, exposing the alendronic acid and start an interaction with osteoclasts. These findings underscore that the main impact of alendronate on the skeletal system is the inhibition of bone resorption. The primary mechanism of action of alendronate is the cause of other observed long-term administration effects, including diminished bone remodeling (250, 252).

1.6.2 Pharmacology of alendronate

Bisphosphonates present challenges in pharmacokinetic characterization due to their low concentrations in biological fluids and complex disposition profiles, making plasma analysis difficult. Alendronic acid, primarily studied through allowing quantification via fluorescence detection, with limits of quantification at 5 μg/L in plasma and 1 μg/L in urine (262). Even after prolonged daily administration for up to 3 years at therapeutic doses (10 mg daily), plasma concentrations following oral administration of alendronate do not reach levels suitable for examining plasma kinetic (263). The pharmacokinetics of alendronate in humans were mostly examined from data on urinary excretion.

Understanding the pharmacokinetic-pharmacodynamic relationship for alendronate is complex due to its unique pharmacokinetics. At therapeutic doses, the plasma concentration profile of alendronate is not fully determinable and its relevance is limited. Estimating of the critical concentration of alendronate within bone and specifically in the resorption lacunae between active osteoclasts and bone, for determining the bone resorption inhibition, is feasible in controlled in vitro experiments, but it remains elusive in both humans and animals. Furthermore, the distinctive aspects of skeletal biology, especially the prolonged timeframe of normal bone remodeling, necessitate extended observation periods to comprehensively characterize the pharmacodynamic response to the drug. As a result, achieving a comprehensive understanding of the relationship between these three components: administered dose, plasma drug concentration and reaction, typical at the pharmacokinetic-pharmacodynamic assessments, remains unattainable.

About 25% of trabecular bone and 3% of cortical bone undergo turnover annually through this process. Thus, any intervention affecting one step of bone remodeling, such as inhibiting bone resorption, ultimately triggers an entire counteraction. Furthermore, the

bone mechanoreceptors responsive to skeletal loading, play a significant role in influencing the bone remodeling rate and the formation/resorption balance. Pathological conditions that disrupt this balance, leading to increased resorption relative to formation, ultimately result in a deficit of bone mass, as seen in postmenopausal bone loss (264, 265).

As previously mentioned, the role of alendronate is primarily to target the osteoclasts to achieve bone resorption suppression. The assessment of this process inhibition is checked in the clinical measurement of collagen degradation by tracking the biochemical markers, like Collagen Cross-Linked N-Telopeptide (NTx), urinary hydroxyproline and urinary deoxypyridinoline, as valuable tools for monitoring this activity (266-268).

Paget's disease serves as a valuable clinical model for illustrating the dynamic effects of bisphosphonates like alendronate. This condition is marked by localized regions of significantly increased bone turnover, which amplifies the biochemical impact of the medication (269).

The biochemical cascade of events, beginning with the inhibition of bone resorption followed by a reduction in bone formation, takes place in postmenopausal osteoporosis treated with alendronate. However, this process unfolds over an extended timeframe (240-242, 244, 247, 248).

In women with osteoporosis, several significant pharmacodynamic observations emerge:

- An early bone resorption inhibition as demonstrable effect, what characterizes the primary alendronic acid mechanism of action.
- The subsequent bone formation decrease occurs as a secondary response.
- Both resorption and formation processes are dose-dependently altered (241).

Due to the discrepancy favoring resorption and low bone remodeling rates, alendronate net effect, in osteoporosis, is to reduce turnover and create a resorption/formation balance or even surpass the resorption. Such dynamic changes in the skeleton lead to a gradual bone apposition (240-244). The exact duration required to reach a steady state for changes and a bone mineral density balance is challenging to predict, as it hinges on the rate of underlying remodeling and the rate and extent of alendronic acid impact. However, a change in rate of bone mineral density (BMD) is typically noticeable by the third year of alendronate treatment. This phenomenon is believed to arise from the destiny of alendronate, its integration into bone remodeling sites, in the bone matrix. Alendronic acid loses its pharmacological activity, until its exposition to a newly initiated resorption. Consequently, it is mainly the recently administered substance, directed at actively resorption focus, that elicits most of the biochemical response. The accumulation of the

drug in the skeleton over time does not lead to a continuous bone remodeling suppression beyond what is observed as the biochemical markers reach a state of little or no change after a period of activity. In fact, the plateau is reached after only small administrations of drug accumulating in the skeleton. It is estimated to be roughly 100 mg after ten years of alendronate therapy at a dose of 10 mg/day. While drug bioavailability in the plasma of alendronic acid cannot be directly monitored, it exists a predictable relationship between dose (indirect measure of drug accumulation in the skeleton) and the biochemical responses of the bone mass, of which timing is influenced by the specific skeletal disorder being treated, with its inherent pathophysiological dynamics, as well as the fundamental interaction of bone remodeling and alendronic acid. Clinically, the overall effect of alendronate manifests as increased bone mineral density, improved bone strength and a decreased risk of fractures (239-245).

1.6.3 Adverse effects

Gastrointestinal tract adverse events

Adverse effects in the upper gastrointestinal (GI) tract linked with the usage of bisphosphonates, such as nausea, vomiting, discomfort in the upper abdomen and indigestion, were documented shortly after the oral forms of these medications were introduced for treating osteoporosis. These undesirable effects stem from irritation of the mucous membrane in the upper GI tract related to bisphosphonates. Numerous esophagitis cases featuring erosions or ulcerations, connected to alendronate use, were identified in the initial stages of monitoring the drug after it entered the market (270). A surveillance, showed that patients experiencing more severe esophageal complications tended to ingest alendronate with minimal or no water, recline either during or shortly after taking the tablet, persist in using alendronate even after symptoms emerged or pre-existing esophageal conditions (270).

Suggestions for minimizing the likelihood of esophagitis involve consuming alendronate with 180 to 240 ml of water upon waking up in the morning, maintaining an upright posture for at least a half-hour after ingesting the tablet and until consuming the first meal and promptly ceasing the medication in case of any esophageal symptoms emerge (270). The dosing guidelines for oral bisphosphonates, which include instructions such as those mentioned, are typically provided on the drug labels. These guidelines likely contribute to

the subsequent occurrence reduction of upper GI tract side effects associated with drugs (270).

Nephrotoxicity

As of now, there is no evidence indicating that oral bisphosphonates, as prescribed for osteoporosis therapy, are linked to notable renal toxicity. However, cases of renal failure have been documented following the administration of intravenous bisphosphonates (271) and therefore it is advisable to exercise caution when utilizing intravenous bisphosphonates for osteoporosis treatment, especially in patients with impaired renal function (272).
The nephrotoxicity associated with intravenous bisphosphonates administered to patients with bone-related malignancies is likely exacerbated by various risk factors for kidney dysfunction commonly found in this patient population. These factors may include pre-existing chronic kidney disease (CKD), plasma cell myeloma, hypercalcemia, high blood pressure, chemotherapy, diabetes mellitus, senility, prior bisphosphonate therapy.
The calculated Cockcroft-Gault equation, creatinine clearance, is crucial for evaluating renal function in older Patients with osteoporosis, initially and also throughout the course of bisphosphonate treatment (273, 274).

Ophthalmic adverse events

The predominant bisphosphonates related ocular adverse effect is nonspecific conjunctivitis, that typically resolves without medical specific intervention, even with ongoing bisphosphonate treatment. In rare instances, treatment with a non-steroidal anti-inflammatory eye drop may be necessary (275). Several isolated cases have been observed as an alternative ophthalmic side effects, including eyelid inflammation, optic neuritis, ptosis, periorbital edema and cranial nerve palsy (275). The most several ophthalmic bisphosphonate-therapy related adverse effects, that necessitate the cessation of bisphosphonate treatment are uveitis and scleritis. Numerous documented instances of uveitis and scleritis arising during bisphosphonate therapy meet the criteria outlined in the causality assessment of adverse drug reactions. These cases exhibit a temporal association with bisphosphonate treatment, lack concurrent conditions predisposing to such adverse events, and demonstrate positive outcomes upon discontinuation and subsequent reintroduction of the medication (275, 276).

Acute phase reaction

Nitrogen-containing bisphosphonate (N-BP), which are administered intravenously, are recognized for inducing an adverse event akin to the systemic acute phase response (APR), and it is clinically marked by fever with rigors, influenza-like symptoms such as fatigue, malaise, myalgia, arthralgia and bone pain (277, 278). The acute phase response induced by bisphosphonates is dose-dependent and typically manifests after the initial N-BP infusion, particularly in individuals who have not previously received bisphosphonate treatment. Subsequent infusions of the drug rarely elicit this reaction (277, 278). The Acute Phase Response reaches its peak intensity approximately 28 to 36 hours following the intravenous administration of nitrogen-containing bisphosphonates. Despite continued treatment, symptoms typically diminish within 2 to 3 days thereafter (277). Approximately 30 to 35% of patients receiving their first dose of an N-BP have reported experiencing symptoms such as fever, myalgia and malaise (278).

Serum calcium and PTH-Level

Nitrogen-containing bisphosphonates exert potent inhibition on osteoclastic bone resorption. Consequently, six weeks post-initiation of alendronate therapy, there is a decrease in serum calcium and phosphorus levels, along with a significant increase in intact PTH levels, which correlates with the dose. Additionally, there is a reduction in calciuria and phosphaturia (279).

Musculoskeletal effects

In a large cohort study of osteoporosis patients receiving daily or once-weekly alendronate or risedronate, researchers scrutinized musculoskeletal events occurring within 48 hours of initiating bisphosphonate therapy, excluding those with other discernible causes. Notably, no significant musculoskeletal events were noted in patients receiving a daily dose of 10mg alendronate. Conversely, among those initially administered 70mg of alendronate per week, 20% reported events including arthralgia, back pain, myalgia, bone pain, chest pain and fever. Intriguingly, patients transitioning from daily to once-weekly bisphosphonate therapy later reported no musculoskeletal events (280).

Osteonecrosis of the jaw

The mechanism underlying bisphosphonate related osteonecrosis of the jaw (ONJ) remains unclear. However, individuals with bisphosphonate related ONJ have demonstrated consistently elevated levels of PTH compared to controls without osteonecrosis of the jaw. This suggests a potential involvement of high PTH levels in the pathogenesis of ONJ (281). Contrary evidence to this theory is observed in cases of patients with primary hyperparathyroidism and elevated PTH levels, in which oral cavity lesions typically manifest as reduced radicular lamina dura, diminished interproximal alveolar bone density and decreased substantia compacta at the gonial index (measurement of the mandibular cortical thickness). In contrast, bisphosphonate-associated ONJ presents with osseous sclerosis resembling osteopetrosis, characterized by thickening of the lamina dura, alveolar crest and sclerosis of the alveolar margin. This disparity suggests that the mechanism behind bisphosphonate related ONJ may differ from that associated with elevated PTH levels (282, 283).

Cardiac arrythmia

In an intervention trial which retrospectively examined data from a study, the occurrence of atrial fibrillation such as atrial fibrillation during the treatment of postmenopausal osteoporosis with oral bisphosphonate, was analyzed. The analysis revealed a tendency towards a higher frequency of severe atrial fibrillation in alendronate subjects compared to those given a placebo, although this difference did not reach statistical significance ($p=0.07$). However, the overall frequency of all cases of atrial fibrillation did not show a significant difference between patients treated with alendronate and those receiving a placebo (284, 285).

Atypical fractures

Nine patients undergoing long-term treatment with alendronate (ranging from 3 to 8 years) experienced uncommon, low-energy fractures not involving the spine. Among these cases, five patients sustained femoral shaft fractures, in with two individuals of them experiencing bilateral fractures. Bone marrow biopsies conducted on these patients

revealed pronounced suppression of bone remodeling, resembling characteristics of adynamic bone. This excessive suppression likely contributed to heightened bone fragility, leading to atypical fractures (286).

Oral manifestations

In several cases, habitual direct contact of oral alendronate with the oral mucosa, especially when the patients instead of swallowing tablets, they use to suck or chew them, led to contact stomatitis characterized by oral ulcerations (287-289).

1.6.4 Physiological disposition of Alendronate

Pharmacokinetic studies of intravenous alendronate have explored doses ranging from 20μg to 10mg (290, 291). Regardless of the dose, a significant portion of the administered drug was rapidly excreted in urine, accounting for approximately 45% of an intravenous dose within the first 8 hours, followed by a slower excretion rate (approximately 5% of the dose between 8 and 72 hours). By 72 hours after the drug administration, approximately 40% to 60% of the administered drug has been recovered as urinary excretion, with the remainder still retained in the body. The decrease of urinary excretion to very low concentrations by this time, was observed, indicating that the remaining alendronate had been tightly sequestered in a compartment with slow-release kinetics.

To investigate the impact of prior alendronate exposure on short-term (less than 72 hours) excretion of intravenous alendronate doses, a study was conducted involving 10 healthy postmenopausal patients (290). The group received a series of 7 intravenous doses of alendronate totaling 125μg over 18 days. Urinary excretion after the final dose was like that following the initial dose, indicating that prior administration of alendronate did not notably affect the elimination of subsequent doses.

The bioavailability of alendronate was assessed in three studies involving postmenopausal women and one study involving men. Across oral doses ranging from 5 to 80 mg and intravenous reference doses of 125 or 250 μg, there was no observed impact of dose on the extent of urinary excretion at individual collection intervals. The recovery of alendronate in urine exhibited linearity with dose, suggesting linear absorption and disposition over the studied dose range of 5 to 80 mg. The rate of the alendronate bioavailability in postmenopausal women averaged around 0.76% of the oral dose compared to the bioavailability in men, averaging approximately 0.6% (292).

1.7 Teriparatide

1.7.1 Pharmacodynamics and pharmacokinetics

Teriparatide is synthesized using Escherichia coli as a host organism. Its molecular effects are mediated through the G-protein-dependent membrane receptor known as parathyroid hormone receptor 1 (PTH1R), which is primarily found in osteoblasts and renal tubular cells. Studies on affinity suggest the presence of another receptor, parathyroid hormone receptor 2 (PTH2R), which has an affinity for the C-terminal part of the parathyroid hormone (1–84) molecule (293). When the ligand binds to PTH1R, it triggers the activation of adenylate cyclase and several phospholipases (A, C, and D), resulting in elevated levels of intracellular cyclic adenosine monophosphate (cAMP) and calcium. Interestingly, various forms of parathyroid hormone, including parathyroid hormone (1–31), (1–34), (1–38) and (1–84), appear to have similar anabolic effects on bone tissue indeed, shorter fragments and those truncated at the amino terminal end lack this bone-anabolic effect (294-300). Teriparatide exhibits comparable affinity to the parathyroid hormone-receptor-1 as the full-length molecule (1–84). Studies utilizing knock-out mice have elucidated the critical role of the parathyroid hormone-1 receptor in the normal development of bone and the regulation of calcium homeostasis (301).

Following subcutaneous administration, teriparatide demonstrates a high bioavailability of around 95%. Peak serum concentrations are typically reached within approximately 30 minutes (302). The half-life of teriparatide following subcutaneous administration is approximately 75 minutes. This is notably longer compared to the half-life of approximately 10 minutes observed after intravenous administration (302, 303). Teriparatide undergoes metabolism in the liver and kidneys, and no clinically significant drug interactions have been reported. Serum levels of teriparatide are 20–30% lower in men compared with women following subcutaneous administration.

Intermittent teriparatide administration increases the number of osteoblasts and promotes bone formation (304). The effects are primarily attributed to the preexisting osteoblasts activation, enhanced differentiation of lining cells into osteoblasts and decreased osteoblast apoptosis. In addition to its effects on preexisting osteoblasts and osteoblast precursor cells, treatment with teriparatide also promotes the differentiation of pre-osteoblasts. Continuous treatment with teriparatide contrasts with intermittent therapy, leading to hypercalcemia and abnormal bone histology. Osteoblasts have emerged as central

regulators of bone remodeling through the secretion of various cytokines. Among these, RANKL, a member of the tumor necrosis factor superfamily, plays a pivotal role by promoting osteoclastogenesis and bone resorption via its interaction with the RANK receptor on pre-osteoclasts. Osteoprotegerin (OPG), another product of osteoblasts, acts as a soluble decoy receptor for RANKL, thereby attenuating its effects (304-309).

In vitro studies have shown that parathyroid hormone can modulate the balance between RANKL and OPG production by osteoblasts. Specifically, under certain culture conditions, parathyroid hormone has been observed to increase the synthesis of RANKL while decreasing the levels of osteoprotegerin. This shift in the RANKL/OPG ratio favors osteoclast stimulation and bone resorption (310, 311). Additionally, studies in male rats have shown that intermittent administration of teriparatide predominantly enhances osteoblastic proliferation, whereas continuous stimulation with parathyroid hormone primarily activates osteoclasts to a greater extent than osteoblasts (304).

1.7.2 Comparison with other treatments

In a randomized clinical trial involving 146 postmenopausal women with osteoporosis, teriparatide (administered at a dosage of 40 µg/day, which is higher than the approved dosage) was compared head-to-head with alendronate (administered at a dosage of 10 µg/day). Following 14 months of treatment, a comparison between the teriparatide and the alendronate group was conducted. The results of 146 postmenopausal women with osteoporosis revealed a significantly greater increase in bone mineral density of the lumbar spine in the teriparatide group by 12.2% compared to the alendronate by 5.6%. As well, teriparatide led to a more pronounced increase in BMD of the femoral neck compared to alendronate. Interestingly, BMD in the distal radius decreased during the therapy with teriparatide, while no effect was observed in alendronate.

Moreover, the incidence of appendicular skeleton fractures in the teriparatide group was notably lower compared to the alendronate group; the absolute number of fractures was very small (3 versus 10) including non-osteoporotic fractures. Additionally, it's important to acknowledge that the correlation between the BMD increase during teriparatide treatment and its efficacy in preventing fractures is not fully understood (312).

1.7.3 Adverse effects

The most common adverse events associated with teriparatide include nausea, headache, vertigo and leg cramps. These side effects lead to treatment discontinuation in approximately 6% of patients receiving a dosage of 20 μg/day. Hypercalcemia occurred in at least 11% of patients at least once, though dose reduction or treatment discontinuation was necessary in only 3% and 0.2% of cases, respectively. Additionally, teriparatide can lead to urinary hypercalciuria, Hyperuricemia and increased magnesium Antibodies against teriparatide are observed in 3–8% of patients and they appear to lack any clinical significance. Orthostatic hypotension, typically of short duration spanning from minutes to a few hours, may occur following the initial administration of teriparatide, but it does not typically preclude the continuation of treatment.

Although there is a correlation of primary hyperparathyroidism with the increased prevalence of cardiovascular disease, high blood pressure, peptic ulcer disease and chronic kidney disease, none of these conditions have been associated with teriparatide. However, there is currently a paucity of data regarding patient compliance with teriparatide outside the confines of controlled clinical trials (313).

Teriparatide is contraindicated in patients with known hypersensitivity to teriparatide, pediatric patients, pregnant or lactating women. Additionally, it should not be administered to individuals with hypercalcemia, osteodystrophia deformans, malignant tumors of the skeleton or those who have undergone previous irradiation therapy to the skeleton (314).

1.7.4 Dosage and monitoring of treatment

The approved dosage for teriparatide is 20 μg/day for 18 months in Europe and 24 months in the US. Using a modified insulin pen makes subcutaneous administration easier. Although hypercalcemia occurrences during teriparatide treatment are rare, it's advisable to monitor serum calcium levels after, for example: 1, 4, and 12 weeks, followed by assessments every 3 months thereafter. The treatment's efficacy can be evaluated through dual-energy X-ray absorptiometry (DXA) scans after 18 months. Moreover, utilizing biochemical markers of bone metabolism such as procollagen type 1 N-terminal propeptide to monitor treatment effects in individual patients may be feasible (313, 314).

1.8 Periodontitis and Osteoporosis

Osteoporosis and periodontitis are both prevalent conditions, particularly among the elderly population. Osteoporosis affects approximately half of individuals aged over 65 and half of the adult population affected by periodontal conditions (184, 315). As the population ages, the prevalence of both osteoporosis and periodontitis is expected to rise. These conditions necessitate extensive and costly long-term medical and dental care. Osteoporosis, characterized by reduced bone density and strength, poses a heightened risk of bone fractures (316). Periodontitis is recognized as a localized infection that triggers an inflammatory response within the supportive tissues surrounding the teeth (317). Both osteoporosis and periodontitis are characterized by a predominance of bone resorption, with their progression or severity evaluated through systemic and/or local assessments. Given the interconnectedness of the skeletal system, the systemic skeletal changes inevitably influence the jaws and alveolar bone. The primary etiology of periodontitis was demonstrated as the relation to the bacterial plaque accumulation (88, 318). The multifactorial nature of the host responses to periodontal conditions, along with their reciprocal impact on the skeletal system, remains a topic of significant interest and debate within the field (319-321).

1.9 Correlation between osteoporosis and alveolar bone loss

The hypothesis suggests that osteoporosis, characterized by generalized thinning of trabecular and cortical bone, renders the alveolar bone surrounding the teeth more susceptible to bone loss associated with periodontitis. Clinical studies investigating the relationship between systemic BMD and alveolar bone loss (ABL) have consistently shown an inverse correlation. Studies utilized DXA of the lumbar vertebrae and/or femoral neck to determine osteoporosis. However, DXA is unable to measure alveolar BMD in edentulous subjects. Therefore, various alternative techniques were employed to assess ABL, including linear assessment of alveolar crest height (ACH) or ABL using intraoral imaging or panoramic radiographs, mandibular cortical width (MCW) using panoramic radiographs and digital densitometry analysis of alveolar BMD (322-332). Given that these parameters encapsulate both bone volume and density, including cortical and trabecular bone, the finding of an inverse correlation between ABL and systemic BMD is especially compelling. Additionally, it's worth noting that the ratio of compact cortical bone to

spongy trabecular bone varies significantly between the maxillae and mandible. While the spine and maxillae contain approximately 10% cortical bone, the mandible consists of up to 80% cortical bone and 20% trabecular bone (333). In the mandible, cortical bone is predominantly concentrated at the inferior cortex, gradually diminishing in width after the age of 50. Consequently, the mandibular cortical width serves as a reliable index for evaluating cortical bone using panoramic radiographs, which effectively capture the inferior cortex. Research has consistently demonstrated a significant correlation between decreased MCW and systemic BMD, suggesting its utility as a potential indicator for osteoporosis risk assessment (329, 334, 335). Studies have not found a significant association between MCW and systemic fracture risk. Unlike cortical bone, the trabecular bone pattern in the mandible has been found to be more closely associated with fracture risk and serves as a valuable predictor for osteoporosis in women (329, 335-339). It's noteworthy that while the mandibular trabecular pattern becomes more spaced and less connected with advanced age in most females, this pattern is preserved in most males (337, 340). Given the challenge of directly measuring trabecular pattern, many studies have utilized assessments of alveolar BMD through densitometry or measurements of alveolar crest height, as periodontal bone loss is typically concentrated in these areas. Consistently, both alveolar crest height and alveolar BMD are correlated with systemic BMD. This correlation is particularly evident in the predominantly trabecular maxillary bone, where alveolar BMD also correlates with lumbar and hip BMD. Generally, there is compelling evidence supporting the association between osteoporosis and increased susceptibility to alveolar bone loss in postmenopausal women (341).

1.10 The aim of the systematic literature review

This systematic literature review aims to thoroughly examine define, summarize and analyze the existing literature on the impacts of alendronate and teriparatide on the human oral cavity. Our goal is to assess the feasibility and mechanisms for enhancing bone regeneration within the oral cavity, specifically targeting periodontal defects in osteoporosis patients. We plan to achieve this by investigating the potential benefits of alternating between these two antiresorptive treatments -alendronate and teriparatide- administered through both local and systemic methods.

This research holds significance because, in addition to systemic periodontitis therapy, it's crucial to explore supplementary factors that could augment treatment effectiveness. Teriparatide emerges as a promising therapy for periodontitis due to its capacity to modulate alveolar bone. Evidence suggests that teriparatide might stimulate greater bone regeneration in the oral cavity compared to alendronate, thus offering potential for addressing intrabony defects in the alveolar bone.

Considering the patient-specific indications for antiresorptive therapy, whether teriparatide or alendronate, and their associated adverse effects, it is imperative to integrate and evaluate ongoing antiresorptive therapy as a modifying factor in the treatment of intrabony defects resulting from periodontitis. This consideration is particularly critical given that osteoporosis is acknowledged as a risk factor for periodontitis.

2 Material and methods

The introductory materials included books and e-books from the Medical University of Graz Library, as well as publications sourced from PubMed, Wiley Library, Elsevier, and Science Direct, Cochrane Central Register of Controlled Trials.

2.1 Search strategy and screening

Searches of this systematic literature review were conducted in Cochrane Central Register of Controlled Trials, PubMed, Science Direct and Wiley Library including results in English published from 2014 to present as shown in Figure 4.

The search strategy was based on keywords and their respective synonyms which were preliminarily defined and derived from the components of the research question. For the PubMed library, combinations of controlled terms (MeSH) and keywords were use whenever possible. PubMed was searched using the following search format with Boolean operators and an asterisk (*) as a truncation: (Alendronate [Mesh] OR Alendronate OR ALN) AND (Teriparatide [Mesh] OR TPTD OR Parathyroid hormone (1–34) OR PTH(1-34) [Mesh]) AND (Osteoporosis [Mesh] OR ONJ OR ORNJ OR MRONJ OR Medication related osteonecrosis of the jaws OR Osteonecrosis of jaw OR Osteoradionecrosis of the jaws [Mesh]) AND (“Periodontitis” [Mesh] OR “Periodontal Diseases” [Mesh] OR “Periodontal Pocket” [Mesh] OR “Periodontal Attachment Loss” [Mesh] OR periodontitis OR periodontal disease* OR periodontal osseous defects OR periodontal pocket* OR pocket depth OR attachment loss OR clinical attachment level OR alveolar bone loss OR bone defect fill OR bone defect depth OR periodontal non-surgical treatment OR periodontal non-surgical therapy OR periodontal treatment OR periodontal therapy [Mesh]).

The retrieval methods for the other databases were adjusted in accordance with the aforementioned terms.

2.2 Inclusion criteria and exclusion criteria

Incorporating a range of criteria, this systematic literature review included randomized controlled trials (RCT), in vitro or in vivo experiments involving human subjects or human-derived materials as shown in Figure 2. Specifically focusing on patients diagnosed

with periodontitis, osteoporosis, ONJ, ORN, BRONJ, MRONJ as shown in Figure 5, the study assessed the efficacy of alendronate and/or teriparatide treatments. Each study's level of evidence was assessed and graded on a scale of 1 to 3 in accordance with the Levels of Evidence framework proposed by Melnyk and Fineout-Overholt (2023) as shown in Table 3.

Studies involving animal experimentation were excluded from the analysis.

2.3 Data extraction

The following data were extracted from the included studies: Study design, Level of Evidence (Melnyk & Fineout-Overholt 2023, Table 3), gender and age of participants, subjects according to disease and substances (medication), adverse events and results.

Level of evidence	Description
Level 1	Evidence from a systematic review or meta-analysis of all relevant RCTs (randomized controlled trials)
Level 2	Evidence from at least one well-designed RCT (e.g. large multi-site RCT)
Level 3	Evidence from a single well-designed controlled trials without randomization (aka quasi-experimental studies) OR a systematic review of a complete BOE (integrative review of higher and lower evidence) OR mixed methods intervention studies
Level 4	Evidence from well-designed case-control or cohort studies
Level 5	Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis)
Level 6	Evidence from a single descriptive or qualitative study, EBP, EBQI and QI projects
Level 7	Evidence from the opinion of authorities and/or reports of expert committees, reports from committees of experts and narrative and literature reviews

Table 3: Level of evidence. Melnyk, & Fineout-Overholt, E. (2023). Evidence-based practice in nursing & healthcare: A guide to best practice (Fifth edition)

3 Results

3.1 Study selection

Initially, 1703 titles were identified in the electronic search. Following the removal of duplicates, 917 articles were selected for further consideration. A total of 396 abstracts were reviewed, and the full texts of the remaining 32 articles were obtained. Based on a careful reading of the full-text articles, 23 articles were excluded. Finally, the following 9 studies were identified as meeting the criteria for inclusion in this systematic review. A flowchart for the study selection process is given in Figure 3. The main characteristics of the 9 included studies are summarized in Table 4.

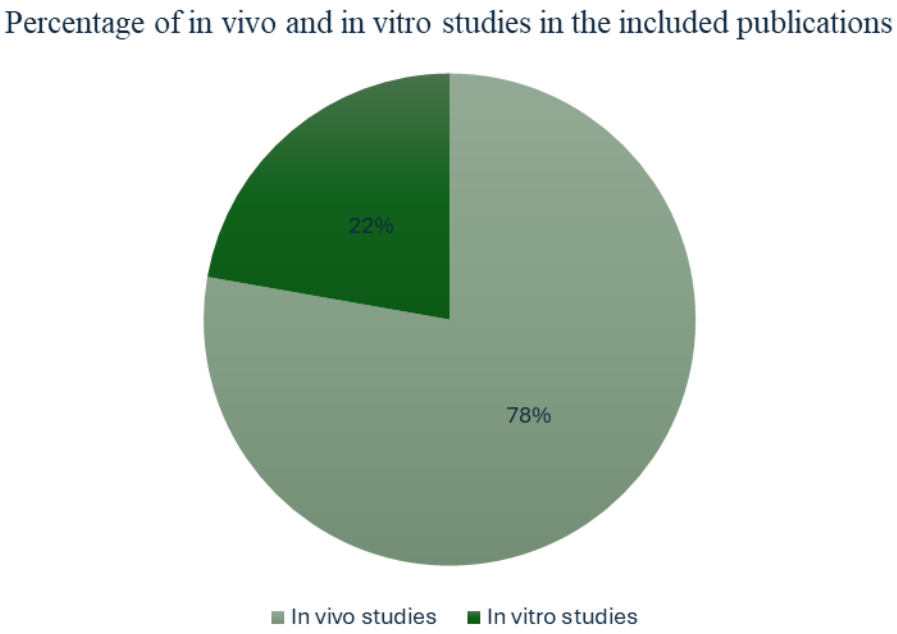

Figure 3: In vivo and in vitro studies in the included publications (own illustration)

Figure 4: Flow chart of the literature search and results selection (own illustration)

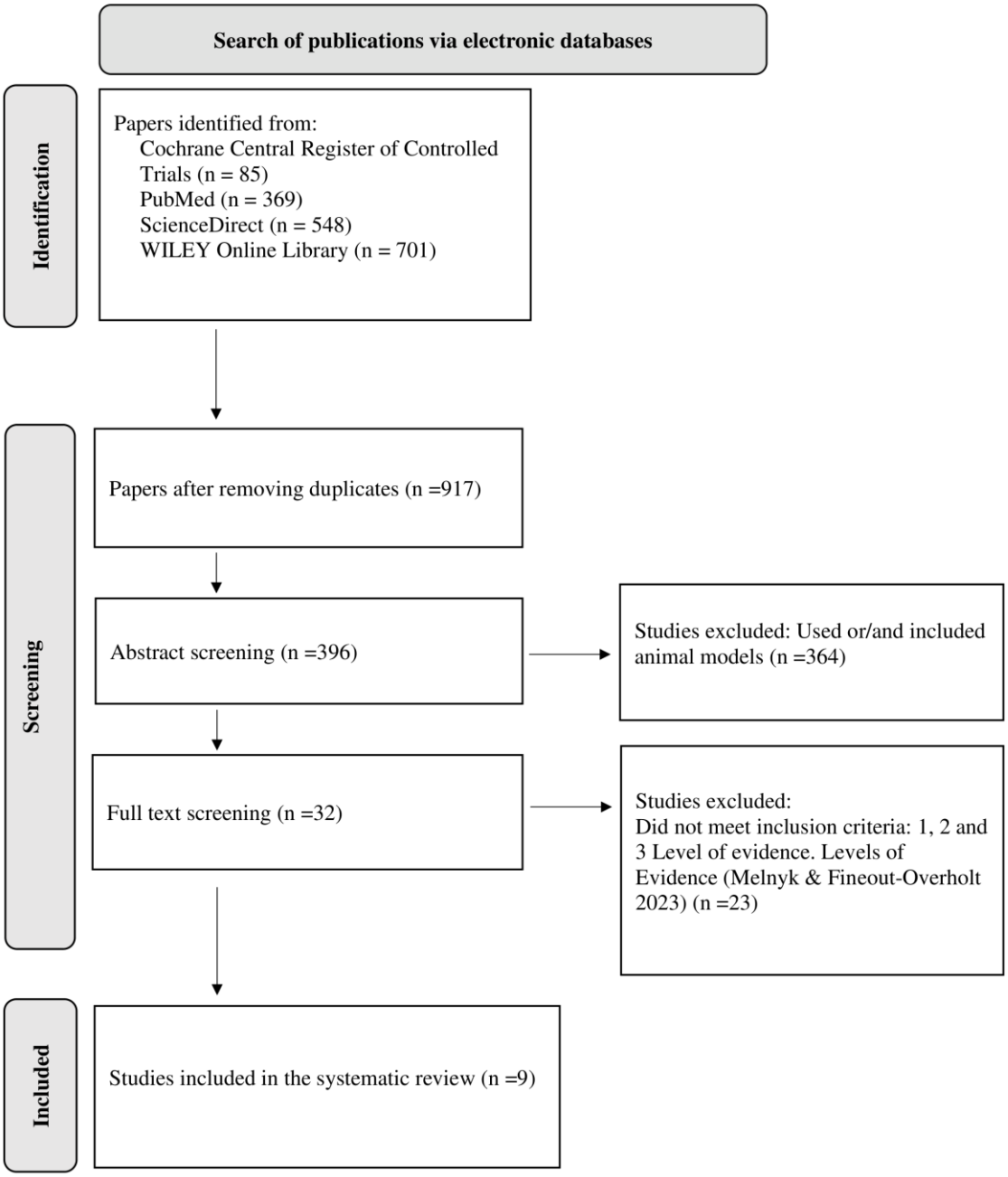

Figure 5: Number of the included publications in the respective year (own illustration)

Table 4: Characteristics of the included studies (n=9) (own illustration)

Reference Year of publication PMID	Study design	Levels of Evidence (Melnyk & Fineout-Overholt 2023)	Age(yr)/ Gender	Subjects/ Substances	Adverse events	Results
Dutra BC et al. 2016 PMID: 28678950	Randomized, split-mouth, placebo controlled clinical trial	Level 2	35-60 / F n=12 M n=8	Chronic periodontitis/ 1 % Alendronate	No adverse events	The alendronate group demonstrated a notable improvement in bone defect filling, as evidenced by a reduction in bone height and the reductions in PPD observed in both treatments at the six-month follow-up were comparable. Applying ALN after scaling led to a high increase in CAL at the three-month follow-up, and no periodontal abscesses were noted throughout the study period.

Sharma A et al. 2016 PMID: 28678942	6-month follow-up longitudinal interventional study	Level 3	30-50/ F n=0 M n=52	Chronic periodontitis/ Smokers/ 1% Alendronate	No adverse events	A greater improvement in full mouth plaque index score ($p<0.05$) was noticed in the alendronic acid group compared to the placebo group at the 6-month mark. A statistically significant mean radiographic parameter IBD reduction of 2.10±0.69 in the alendronate group was proven, compared to 0.12±0.04 mm by the placebo group. At 6 months, Alendronate sites exhibited a significantly greater vertical defect fill (41.05±11.40%) compared to placebo sites (2.5±0.93%).

Naineni R et al. 2016 PMID: 27656552	6-month, randomized, prospective, parallel, interventional, active-controlled study	Level 2	30-50/ F n=17 M n=15	Chronic periodontitis with least one interproximal periodontal defect/ ALN, β-TCP	No adverse events	The alendronate test group demonstrated significantly superior outcomes compared to the control group in terms of mean gain in CAL ($p<0.001$) and mean reduction in probing depth ($p=0.004$). Additionally, the test group exhibited a mean linear bone growth (LBG) of 2.88 ± 0.88 mm, which was statistically higher than the 1.70 ± 0.39 mm observed in the control group. Furthermore, the alendronate test group displayed crestal apposition, while the control group showed crestal resorption. Moreover, the %BF (bone formation) was notably higher in the test group compared to the control group, underscoring the efficacy of ALN in promoting bone formation.

Shetty B et al. 2022 PMID: 36582946	A split-mouth study. Randomized clinical trial	Level 2	25-65/ F n=11 M n=7	Chronic periodontitis/ Alendronate (ALN), Simvastatin (SMV)	No adverse events	In the current study, the ALN group exhibited a bone defect fill percentage of 21.48% at 6 months, whereas the SMV group showed 14.05% at the same time point. The significant decrease in intrabony defects observed in the ALN group at 6 months underscores its effective mechanism in bone formation. It may be caused by the heightened expression of bone morphogenetic protein 2 during bone regeneration, promotion of angiogenesis and anti-inflammatory effects during the healing process. The sustained and prolonged availability of this local drug concentration for up to 6 months may account for the additional improvements seen in pocket depth, clinical attachment level and bone fill.

Du L et al. 2016 PMID: 27523567	In Vitro controlled trials without randomization	Level 3	12-16/ F n=3 M n=3	Premolars extracted for orthodontic reasons from systemically healthy patients and used for tissue biopsy and PDL cell isolation/ PTH, SDF-1α	Not available	The PTH/SDF-1α combination improved the proliferation and migration of PDLSCs, significantly elevated ALP activity, promoted mineral deposition and enhanced the gene expression of osteogenic-specific markers.

Gilbert W et al. 2020 PMID: 32074331	In vitro controlled trials without randomization (experimental studies)	Level 3	Not available	Isolated human PDLFs from periodontally healthy and non-carious premolar teeth extracted for orthodontic reasons/ PTH	Not available	PTH may be essential for the metabolic regulation of PDLFs during the regenerative process. In the early stages of cell activity following wound creation, there is a dose- and time-dependent bi-phasic response. Both 10 and 20 nM (Nanomolar) concentrations of PTH enhanced proliferation and total wound repopulation by approximately 4.10% and 4.67%, respectively, on day 10, representing a roughly 10% increase compared to the control. This enhancement could potentially benefit regenerative therapy by facilitating the recruitment of cells to the area, a necessary step before tissue regeneration can commence. One possibility is that intermittent PTH treatment may negatively impact PDLFs proliferation by increasing apoptosis within the cell population. It is not unlikely that the reduction in proliferation may indicate a transition in the cell cycle phase, from proliferation to protein production, thereby signaling an accelerated shift towards tissue matrix production.

Kim KM et al. 2014 PMID: 24554340	Retrospective longitudinal study	Level 3	- TPTD group: Age 77.1±8.6 F n=14 M n=1 - Non-TPTD group: Age 73.8±6.57 F n=8 M n=1	Intractable BRONJ/ TPTD	Not available	The inclusion of supplementary TPTD alongside periodontal treatment resulted in expedited and more favorable clinical outcomes for previously resistant cases of (BRONJ) when compared to conventional dental treatment alone (consisting of surgery and antimicrobial therapy). Additionally, it was suggested that the levels of vitamin D may impact the effectiveness of TPTD treatment. Initial observations revealed a positive bone balance in the TPTD group during the early stages of therapy. Consequently, the administration of TPTD appears to create a window of bone anabolism, effectively counteracting the suppressed bone turnover seen in BRONJ cases and yielding advantageous therapeutic results. TPTD facilitates the development of small blood vessels in bone, thereby promoting skeletal repair.

Sim IW et al. 2020 PMID: 32614699	Double-blind, randomized, controlled trial	Level 2	≥ 18/ F n=16 M n=18	MRONJ/ TPTD	Nausea, anorexia, and musculoskeletal pain, most of mild severity	TPTD demonstrated the ability to trigger an osteoblastic response, which was evidenced both biochemically and radiologically and led to a clinically significant augmentation in P1NP levels in 85.7% of the participants. 18F-fluoride PET-CT scans revealed heightened tracer uptake within the jaw in association with TPTD administration. Furthermore, due to TPTD's osteoanabolic mechanism, there were concerns regarding its potential to stimulate cellular proliferation within bone, potentially exacerbating active malignant bone diseases or precipitating recurrence in patients who had previously undergone successful treatment and were in remission.

Cha YH et al. 2017 PMID: 29249017	Controlled trials without randomization (quasi-experimental studies)	Level 3	- Case 1: 83-year-old man - Case 2: 53-year-old woman F n=1 M n=1	ORNJ/ TPTD	No serious adverse events	Case 1: - Bone tissue enhancement in orthopantomograms, from 12.8% to 32.2% after 27 months of TPTD treatment. - Two distant metastatic lesions of SCC (Squamous Cell Carcinoma) were identified in the contralateral axillar and left upper paratracheal regions at 1- and 10-months post TPTD therapy, respectively and effectively managed through surgical excision and salvage radiotherapy. Case 2: - Serum levels of bone turnover markers, including CTx (C-telopeptide cross-linked type I collagen) and osteocalcin, exhibited increases during TPTD treatment. Moreover, the proportion of bone tissue within the defect area at the (ORN) site showed improvement, rising from 61.0% to 99.2% after 6 months of TPTD treatment. Additionally, elevated serum levels of CTx and osteocalcin were observed during TPTD treatment.

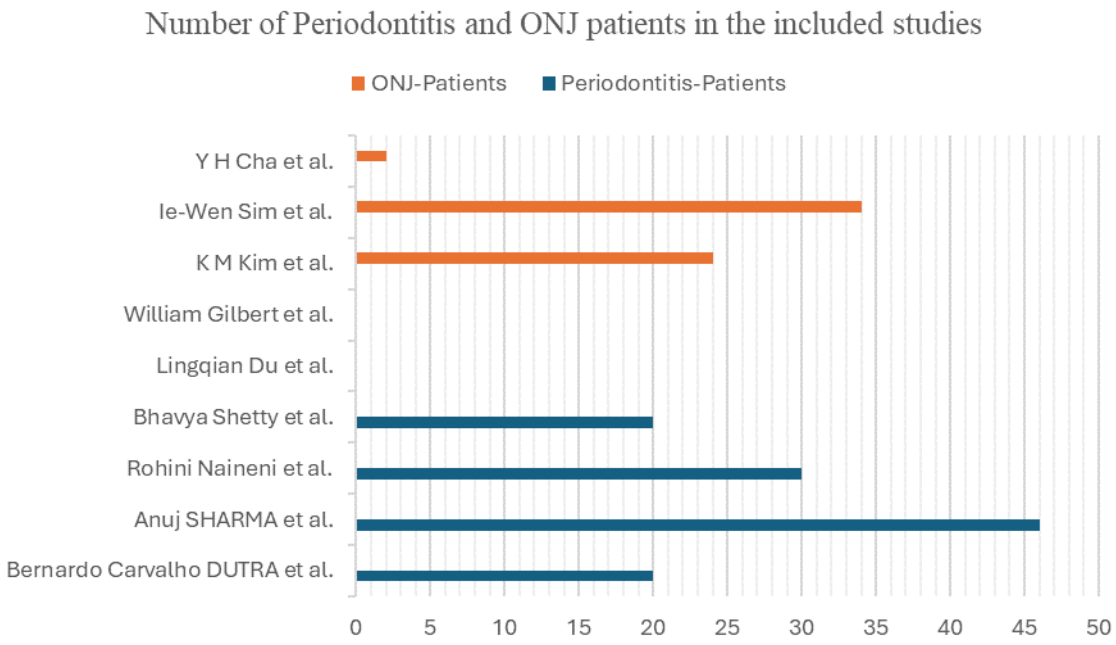

Figure 6: Periodontitis and ONJ patients in the included studies (own illustration)

3.2 Key findings

Alendronate group exhibited significant bone defect filling without local adverse effects as shown in Figure 6. Periodontal probing depth reductions with alendronate application post-scaling were leading to greater clinical attachment level gain. No periodontal abscesses occurred and all patients tolerated the medication well, with normal tissue healing and no notable visual differences (342).

Improvements in full mouth PI score were significantly higher in the alendronate group. Radiographic parameter IBD showed a statistically significant mean reduction in the alendronate group. Alendronate sites demonstrated significantly higher vertical defect fill (343).

Alendronate test group exhibited significantly improved results in mean gain in clinical attachment level and mean reduction in probing depth. Alendronate test group also showed crestal apposition, while the control group displayed crestal resorption. The %BF was significantly greater in the test group, indicating the effectiveness of in enhancing bone formation (344).

The percentage of bone defect fill in the Alendronate group at 6 months was higher compared to the SMV group. A significant reduction in intrabony defects in the Alendronate group suggests its role in bone formation, possibly attributed to enhanced expression of bone morphogenetic protein 2, angiogenesis, and anti-inflammatory effects (345).

The combination of PTH and SDF-1α enhanced proliferation, migration, ALP activity, mineral deposition, and gene expression of osteogenic markers in periodontal ligament stem cells (PDLSCs). PTH may also play a role in metabolic regulation of PDLFs during the regenerative process (346).

Dose- and time-dependent responses of PTH enhanced proliferation and wound repopulation, potentially beneficial in regenerative process. Intermittent treatment of PTH may negatively affect periodontal ligament fibroblasts (PLDFs) proliferation or signal a shift in the cell cycle towards tissue matrix production (347).

Supplementary TPTD in addition to periodontal treatment provided faster and more favorable clinical outcomes in refractory BRONJ cases compared to conventional dental

treatment. TPTD administration efficiently reversed suppressed bone turnover in BRONJ cases, promoting beneficial therapeutic outcomes (348).

Teriparatide promoted angiogenesis, elicited an osteoblastic response, and increased bone turnover markers. Participants tolerated teriparatide well without hypercalcemia or gastrointestinal symptoms, with no observed occurrence of osteosarcoma in the treated area (349) (Figure 6).

The proportion of bone tissue at the ORN site significantly improved after teriparatide treatment. Increased serum bone turnover markers during TPTD treatment were also observed. Teriparatide treatment was discontinued at 4 months with improved ORN without serious adverse events (350) (Figure 6).

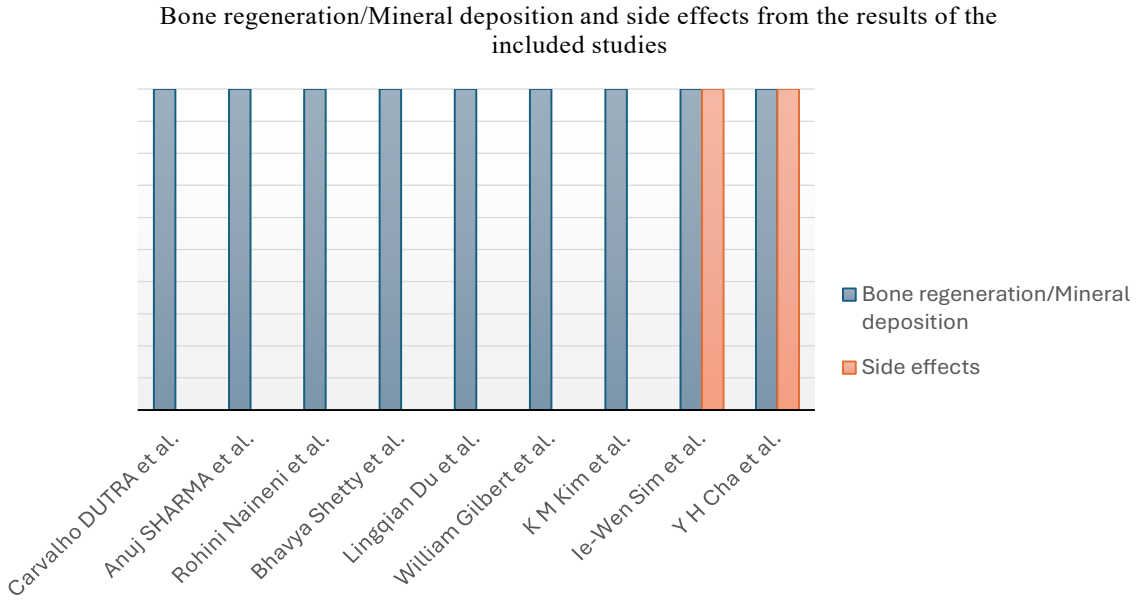

Figure 7: Depiction of the presence of bone regeneration/Mineral deposition and adverse effects from included trial results (own illustration)

4 Discussion

The objective of the present study was to assess and contrast the efficacy of teriparatide on periodontal regeneration and on bone formation in the oral cavity in general, in comparison to alendronate. Teriparatide is known as a catabolic hormone responsible, along with calcitonin, for calcium homeostasis (351). However, the bone stimulation of new bone formation with parathyroid extract, the field of PTH's anabolic action on enhancing bone remodeling, bone regeneration and mechanical bone strength has become a great scientific interest. Several different in vitro and in vivo studies have resulted from this area yielding useful information to the beneficial osteoporosis therapies from the approval of teriparatide to be used in the treatment of osteoporosis in both, Europe and US (313, 352, 353).

Teriparatide serves as a systemic osteoanabolic agent, undergoing investigation for its potential in oral bone regeneration. Teriparatide not only enhances BMD but also diminishes fracture risk by promoting new bone formation. Its primary mechanism of action involves stimulation of osteoblasts, alongside increased renal tubular re-absorption of calcium and phosphate excretion. Additionally, it indirectly boosts intestinal calcium absorption by influencing 1,25-dihydroxyvitamin D levels (354, 355).

Alendronate has shown efficacy as oral administration for treating and preventing postmenopausal osteoporosis, osteodystrophia deformans and Glucocorticoid-Induced Osteoporosis. The inhibition of the osteoclastic bone resorption is the main mechanism of action of alendronic acid (356).

Alendronic acid has been well received by periodontists as a promising adjunctive technique with SRP for the therapy of periodontitis due to its mechanism of action to modulate the host response and inhibit the resorptive action of osteoclasts. Previous studies have demonstrated that the topical administration of alendronic acid with SRP was more effective in the therapy of periodontitis than SRP therapy alone. Nevertheless, previous publications have presented conflicting evidence regarding the efficacy of systemic alendronic acid administration as an adjunctive therapy to non-surgical treatment. In other studies, it was demonstrated that systemic administration of alendronic acid as an adjunctive treatment improves clinical outcomes, whereas others have not (357-359).

Teriparatide is typically administered once daily via subcutaneous injection and is recommended for treating postmenopausal osteoporosis (360). A meta-analysis showed

that compared to alendronate, teriparatide led to a 3.46% increase in lumbar BMD. In contrast to the findings of the meta-analysis, Shen et al. (361) observed that PTH significantly elevated femoral head BMD in comparison to bisphosphonates. Moreover, they noted that this effect was contingent on both, the duration and dosage of the treatment. Additionally, Neer et al. (313) discovered that a 20mg dose of teriparatide resulted in a 9.7% increase in femoral neck BMD compared to a placebo. While 10mg of alendronic acid administration has demonstrated a post therapeutic effective increase in lumbar spine and hip BMD, in cases of postmenopausal osteoporosis compared to placebo, respectively 2 to 3 years and 3 to 4 years (362), the data suggests that teriparatide may be more effective than alendronic acid in increasing lumbar spine BMD in postmenopausal osteoporosis (363). The discrepancy in the percentage increase in lumbar spine BMD following teriparatide and alendronate treatments might be elucidated by their distinct mechanisms of action (364, 365). Teriparatide functions as a bone-forming agent, leading to elevated levels of biochemical markers associated with bone remodeling. Some previous studies indicate that teriparatide treatment accelerates and elevates markers of bone formation more prominently than markers of bone resorption, implying a skew towards bone formation in the turnover process (366, 367). Moreover, recombinant PTH may enhance trabecular connectivity. In contrast, most of the observed increases in BMD with alendronate treatment stem from enhanced mineralization of the pre-existing bone matrix (364).

The most frequently observed side effects induced by teriparatide include back pain worsening during the first phase (month) of therapy, cephalgia, vertigo and nausea. Conversely, the most common adverse drug reactions associated with the alendronic acid comprised arthralgia, dyspepsia and abdominal pain. The study found that the tolerability of alendronic acid was comparable to that of teriparatide (368).

This systematic literature review showed that the alendronate demonstrated significant bone defect filling without adverse local effects. Both alendronate and placebo groups showed similar reductions in probing pocket depth (PPD) at 6 months, but alendronate application post-scaling resulted in greater clinical attachment level gain at 3 months, no periodontal abscesses occurred, and all patients tolerated alendronate well with normal tissue healing (342). Improvements in full mouth plaque index (PI) scores were significantly high in the alendronate group at 6 months. Radiographic analysis revealed a notable reduction in intrabony defects (IBD) in the alendronate group compared to placebo, along with significantly higher vertical defect fill in alendronate sites (345). The

alendronate test group exhibited superior outcomes in CAL gain and PPD reduction compared to the control group, with evidence of crestal apposition. %BF was significantly greater in the alendronate group, indicating alendronate's effectiveness in enhancing bone formation (343, 344).

Teriparatide shows promise in the treatment of bisphosphonate-related osteonecrosis of the jaw cases, promoting bone turnover and tissue healing without significant adverse effects (348).

The combination of parathyroid hormone and stromal cell-derived factor 1 alpha (SDF-1α) enhanced various aspects of osteogenic activity in PDLSCs. Parathyroid hormone may also regulate PdLFs during the regenerative process (346) .

Dose and time-dependent responses of PTH enhanced wound healing, but intermittent treatment may affect PdLFs proliferation or signal a shift towards tissue matrix production (347).

In refractory bisphosphonate-related osteonecrosis of the jaw cases, teriparatide combined with periodontal treatment yielded faster and more favorable outcomes compared to conventional treatment. Teriparatide reversed suppressed bone remodeling in bisphosphonate-related osteonecrosis of the jaw, promoting therapeutic benefits without hypercalcemia or gastrointestinal symptoms (349).

Teriparatide promoted angiogenesis, osteoblastic responses, and increased bone turnover markers without observed osteosarcoma. Teriparatide treatment improved bone tissue proportion at the osteoradionecrosis site without serious adverse events, even after treatment discontinuation (350) (Figure 6).

5 Limitations of this systematic review

Some limitations of the present study should be recognized. First, only 9 studies were eligible for inclusion in the systematic review. As there were not enough in vivo studies, no meta-analysis could be performed. Additionally, the included studies encompassed both in vivo and in vitro research on alendronate and teriparatide in combination with other substances. Second, the subjects of the studies varied, including those with periodontitis, bisphosphonate-related osteonecrosis of the jaw, Osteoradionecrosis of the jaw, and medication-related osteonecrosis of the jaw as shown in figure 5. Factors such as lifestyle, gender, and hormonal influence were not consistently accounted for across all studies. Discrepancies in diagnosis criteria and severity of diseases among studies, may have influenced the results. Moreover, systemic and local drug delivery methods could also have affected the study outcomes. Taken together, these factors limit the generalizability of the results.

6 Conclusion

In conclusion, the results of this systematic review provide evidence that both teriparatide and Alendronate stimulate and regulate bone regeneration generally in the oral cavity and particularly in periodontal defects as systemic and local treatments.

Based upon the promising results of the current research finding, precautions must be exercised when interpreting the results. Additional factors such as gender, age, ethnicity of patients, concomitant diseases, substances used in medication, type of treatment (local or systemic), dose, duration of treatment, patient-related indications, side effects, lifestyle and other contributing factors need to be considered during the assessment of the effectiveness of parathyroid hormone and alendronate in periodontitis treatment to obtain stronger conclusions in this regard.

Further investigations/research in terms of in vivo clinical trials in periodontally compromised osteoporosis-patients are recommended to gain further knowledge by incorporating other methodological designs that allow us to offer a broader and increasingly reinforced vision of the interventions aimed at inducing the bone formation without or with less side effects, providing well founded conclusions.

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