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Etiopathogenesis of Root Resorption - A Brief Review

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A B S T R A C T

Under normal conditions permanent teeth do not resorb. Pathological stimulus like trauma and infections leads to immune-inflammatory process in roots of permanent teeth leading to resorption. These pathological stimuli damage the protective layers in the dentine and periodontal ligaments. Pathological process continues and leads to compromised blood supply causing cementoblast destruction and necrosis. There is activation of multinucleated odontoclasts which are similar to osteoclast leading to root resorption. Various molecular and cellular pathways initiate and progress the resorption. Several local and systemic factors are involved. Some of the factors which act as stimulators or inhibitors of root resorption are RANKL/RANK/ OPG, Interleukins, Bacterial lipopolysaccharides, Macrophages, parathormone, oestrogen etc. This article presents a review of physiologic protective and homeostatic mechanisms involved in protection of root resorption. This article also includes a brief overview of development of odontoclasts and RANK/RANLK/OPG system. This review briefly discusses about the pathogenesis of root resorption so as to provide direction in the future laboratory and clinical research to fill in the knowledge gaps.

Key words*: Root resorption, odontoclasts, RANK Ligand, dentoclasts, M-CSF*

INTRODUCTION

Bacterial insults or traumatic injuries to the oral cavity can harm the hard and soft tissues of teeth like enamel, dentin, cementum, alveolar bone, gingiva and pulp. These injuries can have both short-term and long-term effects.[1] Gingival and bone injuries may heal within days to weeks. Injuries to dental pulp and periodontal tissues do not readily heal causing long-lasting complications.[2] These injured structures affect the individual tooth prognosis. Soft tissue injuries are typically manifest as inflammation and gingival recession, whereas hard tissue damage manifest as dental attrition and abrasion, dental resorption, dental caries, and erosions.[3] Root resorption, as defined by Ne et al., is “a condition associated with either a physiological or a pathological process resulting in the loss of dentin, cementum, or bone.”[4] The first case of dental hard structure resorption which have been mentioned in literature dates back to the 16th century in "Artzney Biichlein".[5] Physiologic resorption is seen in

primary teeth that results in their exfoliation and allows eruption of their permanent successors.[6] Under normal circumstances, the hard tissues of permanent teeth—dentin, cementum, and enamel do not undergo resorption. Hard tissue resorption involves the removal of cementum and/or dentin through the activity of specialized tooth-resorbing cells, known as odontoclasts (dentoclasts).[7] Clinically, these resorptions go unnoticed unless severe degree of resorption has occurred leading to increased mobility.[6] This increase mobility may lead to loss of teeth.

Radiographically they can be diagnosed in Intra Oral Peri-Apical radiographs, Orthopantomographs, Lateral cephalograms, Cone Beamed Central Tomography.[8] They can be also diagnosed through biologic markers, microscopic and histologic evaluation.[9]

Traumatic and bacterial aetiologies have been reported which trigger root resorption.[10,11] These insults cause damage to cementoblast and odontoblast and predentine layers leading to development of odontoclasts which cause root resorption initiation. [12] There are series of molecular and cellular changes causing development of odontoclasts. Extensive research has been conducted about these cellular and molecular mechanisms that lead to pathologic root resorptions. Widespread research has been conducted about the development of odontoclasts/ dentoclasts, their structure, their interaction with interleukins (IL), Macrophage Colony-Stimulating Factor (M-CSF), receptor activator of nuclear factor kappa-B (RANK), receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG). Still the aetiology and pathogenesis of root resorption of is not clearly understood. The present article briefly reviews the protective mechanisms of root resorption, current etiopathogenesis of root resorption, so that the appropriate research at clinical and molecular level can be further conducted for proper treatment planning and improving the prognosis of teeth.

Etiology and Pathogenesis

Preventive (Protective) Mechanisms of Root Resorption in Permanent Teeth.

Resorption of roots of deciduous teeth is a physiologic process aiding in shedding of deciduous teeth and eruption of permanent teeth.[6] In bone, remodeling resorptive process is a physiologic process assisting for constant turn over and adaptive response to mechanical stress and for serum calcium balance.[13] Normally permanent teeth do not resorb because they are not subjected to physiologic remodeling. There are several protective mechanisms in permanent teeth which prevents dental hard tissues like cementum, dentine and enamel from being resorbed under normal, physiologic conditions. These protective mechanisms are as follows:[14]

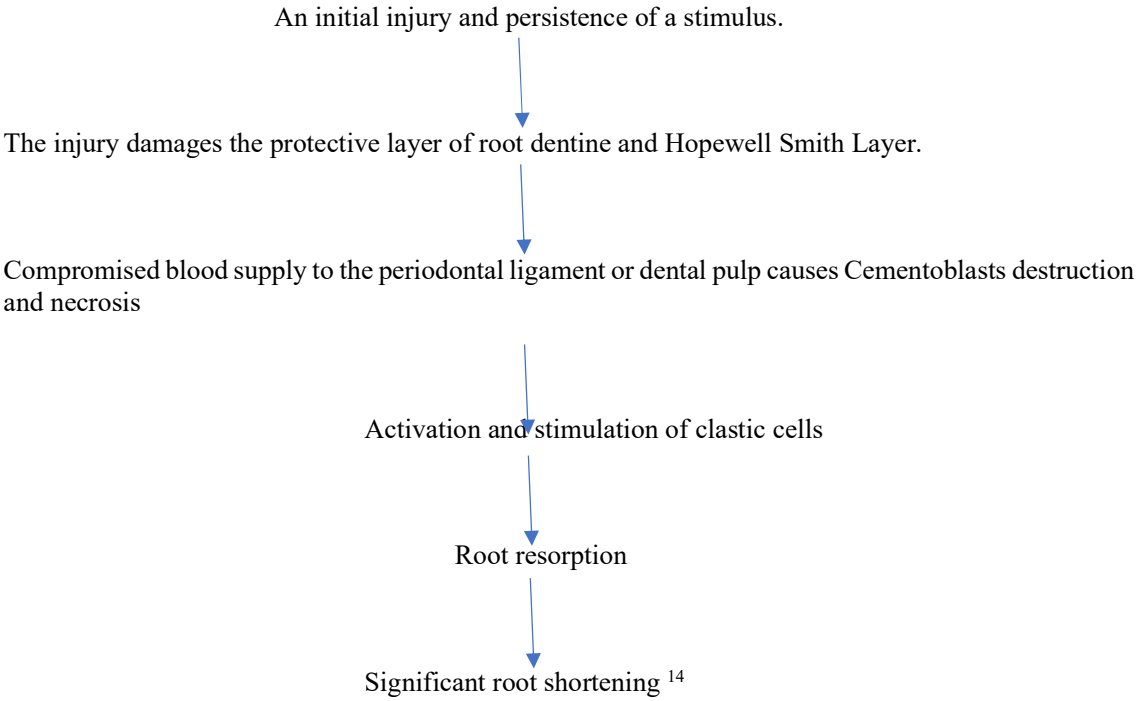
1. Remnants of Hertwig's epithelial root sheath (HERS) surrounding the tooth like net, prevents root resorption.[15]
2. Pathological destruction of cementum is also prevented by Amelogenin protein expression by remnants of HERS cells, due to their inhibitory effect.[16]
3. Unmineralized organic precementum lining the root surface protects the permanent teeth from resorption by forming barrier to the stimulus, injury and clastic cells.[17]
4. Layer of predentine and odontoblasts lines the endodontium internally thus preventing the exposure of hard tissue directly to clastic cells and injury.[18]
5. In the cervical third the acellular cementum covers the root. Apically cellular cementum, cementoblasts and cementocytes form a layer of non-mineralized cementoid.[15]
6. The collagen fibers of periodontal ligament (PDL) also forms a barrier. PDL cells synthesize protease inhibitors preventing recruitment of osteoclasts and invasion of osteoblasts in PDL.[19]
7. The hypermineralised Hyaline layer of Hopewell-Smith also acts as a protective layer preventing the penetration of bacterial products in PDL from Root canals and vice-versa.[14]
8. Cemental cells produced high quantities of OPG hence elevation of OPG to RANKL ratio occurs, thus inhibiting resorption of cementum [20]
9. The intrinsic factors of cementum and dentine also prohibit the development and activity of clastic cells.[14]

Destruction of any of the above stated protective layers can occur due to injury or any stimulus leading to exposure of the underlying dentine. This exposed dentine is now accessible to clastic cells.[21] These clastic cells have the ability to bind only to mineralized tissue to initiate the

resorption. Whenever there is damage to protective layer there is exposure of dentine. On this exposed dentine, osteoclasts via their integrin receptors, bind to cell-adhesive peptide sequences of matrix proteins. These cell-adhesive peptide sequences are RGD i.e. arginine-glycine-aspartic acid sequence.[14]

Etiological factors of root resorption

Roots resorption can be summarized as follows-



Causes of Root Injury

Injury can be induced by:

a) Trauma,
b) Surgical procedures,
c) Periodontitis,
d) Periodontal treatment,[22]
e) Impacted teeth, cysts or tumors which lead to root pressure [23]
f) Chemicals like hydrogen peroxide used for internal bleaching[24]
g) Orthodontic treatment[25,26]
h) Excessive occlusal load can promote resorption[27]
i) Root canal infections or periodontal ligament infections [28]
j) Hypo- and hyperparathyroidism, calcinosis, Gaucher's disease, Turner syndrome, Paget's disease and Herpes zoster are some of the systemic and endocrine diseases which are involved root resorption. [28]
k) Idiopathic.[29]

Mechanism of ERR

Cells Involved in Root Resorption

Well-orchestrated interaction between osteoclasts or odontoclast and immune system cells like monocytes, macrophages and dendritic cells is important for resorption.[30,31]

Osteoclasts/ Odontoclasts

These cells play an important role in both physiologic and pathologic root resorption. These are large, multi-nucleated cells of diameter approximately 30–100 μm with potential of bone resorption. [32] These cells originate from monocytic hematopoietic progenitors of bone marrow.[33] These mononuclear progenitor cells fuse to form multi-nucleated clastic cells under the influence of cytokines and growth factors, like M-CSF and RANKL.[34] Progenitor cells binds to M-CSF through its receptor present on them. M-CSF induces proliferation and expression of the RANK receptor on these progenitor cells, with simultaneous suppression of OPG.[35] M-CSF increases cell motility and prevents apoptosis in differentiated osteoclasts.[36] Osteoclasts differentiation also occurs when RANKL binds to RANK or M-CSF. RANKL and IL-1 activate the osteoclasts which after activation, become polarized and extend pseudopods and filopods, enabling ameboid movement. These clastic cells form the sealing zone confining the resorptive area. Disintegration of mineralizes tissue occurs along the "ruffled border" along indentations called Howship's lacunae. After the clearance of degradation products osteoclasts return to a non-resorbing state or they undergo apoptosis. [14,37]

Odontoclasts are cells that resorb dental hard tissues. A high degree of similarity is found between odontoclasts/ dentoclasts and osteoclasts. Odontoclasts like osteoclast originate from same progenitors They are multi-nucleated with equal ultrastructural and histochemical properties, polarised, use same enzymes, form Howship's Lacunae and ruffled border[38] and they also express RANK.[39] But odontoclasts are reported to be smaller, with fewer nuclei, form smaller sealing zones. The calcitonin receptor has not been reported in odontoclastic cells.[40] In addition, odontoclasts may form two ruffled borders and resorb dentine and bone simultaneously. Capability of dentine resorption has also been reported by osteoclasts. Other cells like Macrophages, monocytes and dendritic cells play important roles in the resorptive process under chemotactic signals. Cells which circulate in blood like Monocytes are leucocytes, can also migrate into adjacent tissues and transform into macrophages. These cells are also present in pulp and under the influence of chemical mediators they also act as progenitors for odontoclasts. [14,23]

Pathogenesis Of Root Resorption

There is incapability of osteoclasts to bind on non-mineralized surfaces.[41] There is local release of cytokines and chemokines after the traumatic and bacterial injury in root cementum and PDL which in turn attract T-cells. Macrophages and granulocytes are then further recruited and activated by T-cells. The initiation and continuation of pathological resorption is mediated by immunological mechanisms. The release of cytokines leads precursor cells to transform into osteoclast. Fusion of precursor cells leads to formation of multinucleated matured osteoclasts. These osteoclasts adhere to surface after polarization forming a ruffled border and sealing zone leading to demineralization of hydroxyapatite and disintegration the organic matrix in Howship's Lacunae.[14,42]

Disintegration of tissue barriers occurs when Junctional epithelium is ulcerated or dentine is exposed due to loss or alteration of cementum. The microorganisms and their products (toxins) get a portal of entry through these channels and bacterial toxins fortify this process. The initial immune response leads to differentiation of clastic cells as a part of repair process, later it becomes pathogenic on persistence of stimulus or injury. Tissue debris and microbes are ingested by macrophages. These macrophages not only produce proinflammatory cytokines such as IL-1β and TNFα, but also calcitriol, ProstaglandinsE2 (PGE2) and dexamethasone.[43,44] All these proteins and hormones stimulates the expression of RANKL in PDL fibroblasts and T-cells.[14] Once the cells adhesion takes place osteoclast mature, they bind to dentin sialoprotein and the RGD-motif via the integrin receptor.[45] This binding also leads to reorganization of the cytoskeleton and the stimulation of resorption. Cell mobility is further enabled by integrins and cadherins. They also aid in signal transduction, matrix recognition and induction of resorption. Hydroxyl- and chloride ions form Hydrochloric acid causing pH to fall up to 4.5 in the Howship's-lacuna. This fall in pH leads to disintegration of hydroxyapatite crystals i.e., resorption of mineralized structure.[46,47]Organic matrix is then degraded by enzymes such as tartrate-resistant acid phosphatase (TRAP) or cathepsin K, pro-collagenases and matrix metalloproteinases.[48,49] Calcium ions, phosphate ions and collagen fragments are sequestrated in the blood via transcytosis.[14]

There is substantial evidence that the cells and mediators of root resorption and bone resorption are identical. So, the resorption of dentine and cementum during root resorption is similar to bone resorption. RANKL/RANK/OPG system controls both the bone resorption as well as root resorption.[14]

RANKL/RANK/OPG system

Continuous remodelling in bone is crucial for growth and for adaptation to mechanical stresses, prevent fatigue, repair of microtrauma and calcium homeostasis.[50] An equilibrium exists between bone formation and resorption physiologically which occurs due to interdependence of osteoblasts and osteoclasts which is finely tuned and this interdependency is called as "coupling".[51] RANKL/RANK/OPG proteins of Tumor necrosis factor (TNF)- family play an important role in resorption of mineralised tissue, which can be any of the physiologic or pathologic resorption. RANKL/RANK/OPG system is a receptor-ligand system. RANKL protein which is either membrane-bound or soluble protein is expressed by osteoblasts.[52] Precursors of osteoclasts and osteoclasts both have RANK receptors.[53] Signal transduction via the transcription factor NF-Kb occurs with binding of RANKL to RANK. This induces the fusion as well as maturation of precursor osteoclasts. Soluble Decoy OPG competitively binds to RANKL and efficiently inhibits osteoclast formation and thus bone resorption.[54] The underlying cellular mechanisms also appear to be similar in both osteoclasts and odontoclasts.[55]Osteoblasts, odontoblasts, pulp- and PDL-fibroblasts, cementoblasts and activated T-cells all express RANKL, OPG is expressed by odontoblasts, ameloblasts, pulp- and PDL-fibroblasts.[14]

Stimulators and inhibitors of resorption

Systemic and local factors are involved in stimulating bone resorption

There are several systemic and local factors (Table 1) regulating bone remodelling in physiologic and pathologic conditions. Systemic factors involved are Parathormone (PTH), oestrogen and calcitonin etc. Local factors are immune cells, cytokines like IL-1, TNFα and IL-6 etc.[56]

RANKL expression in osteoblasts is stimulated by PTH. Osteoclast fusion is directly influenced by PTH. PTH also affects PDL cells. It is suggested that the stimulation by hormones or mechanical stress can change the OPG and RANKL ratio in these cells thus regulating the activity of periodontal tissues.[57,58] PTH also influences tooth eruption and orthodontic movement in a positive manner. It has been reported that there is an increase in the resorptive activity of mature osteoclasts by Calcitriol without increasing their number.[4,14]

Local factors also stimulate resorptive processes. Various cytokines are produced by macrophages and leucocytes during inflammation in response to bacteria, tissue debris and other cytokines, and most of these factors affect the RANKL/RANK/ OPG system. In resorption of periapical and periodontal tissues IL-1 is involved,[59] because it activates osteoclasts and stimulates the production of other inflammatory mediators such as PGE2. RANKL expression in stromal cells and osteoclast differentiation is enhanced by IL-6.[60] RANKL/OPG expression in cementoblasts is upregulated by PGE2 thus increasing the activity of cementoclasts. All the above stated factors demonstrate the close interconnection of resorptive process and inflammatory response.[14]

Bacteria and their products (acids and proteases) also stimulate the resorption process. Lipopolysaccharides (LPS) and Lipoteichoic acid (LTA) present in cells walls of gram negative and gram-positive bacteria respectively, either directly stimulates osteoclast activity or indirectly influence osteoblasts and macrophages to produce osteolytic factors like enzymes (collagenases), IL-1, IL-6, M-CSF and PGE2 thus increasing osteoclast activity. There is an increase in RANKL and PGE2 and decrease in OPG production.

Some periodontal pathogens like *Treponema denticola, Porphyromonas gingivalis* and *Treponema socranskii* induce osteoclast formation via increase in RANKL and PGE2 and decrease OPG.[61]

The clastic cells and thus resorption process can also be inhibited by various local and systemic factors. It has been reported that Calcitonin hormone reduces the mobility of clastic cells and withdraw them from the resorption front. Oestrogen, interferon and corticosteroids have also shown inhibitory effects. Locally, the factors which are responsible for inhibition are local cytokines like IL-4, IL-8, IL-10 and IL-18. FGF-2 has reported both stimulatory as well as inhibitory effects.[62,63] The stimulatory action is by effecting osteoclast differentiation and increases PGE2 production.[64] The inhibitory action may be due to directly inhibit osteoclast precursors or antagonistic effect on M-CSF.[28, 65]

Table 1: Local and systemic factors which stimulate and inhibit resorption[65]

	Stimulators	Inhibitors
Systemic	PTH	Calcitriol
	Diabetes	Oestrogen,
		Corticosteroids
Local	RANKL/RANK/ OPG system	OPG
	IL-1	IL-4,
	PGE2	IL-8,
	IL-6,	IL-10
	Macrophages	IL-18
	Leucocytes	Interferon
	M-CSF	FGF-2
	Bacterial LPS and LTA (*Treponema denticola, Porphyromonas gingivalis* and *Treponema socranskii* induce)	

CONCLUSION

Light has been thrown via the medium of the present article about the association between odontoclasts (osteoclasts / dentoclasts) and macrophages, interleukins, RANK/RANKL, various systemic and local factors which affect root resorption. Deep understanding about the mechanism of underlying root resorption has also been described. The underlying etiology has been discussed, but these factors are not universal as they trigger root resorption in some teeth whereas other teeth remain unaffected. These factors of etiopathogenesis are also not able to differentiate between self-limiting and progressive root resorptions. Root resorption in some cases may eventually lead to loss of teeth. So, proper diagnosis and treatment plan is necessary for these root resorbed teeth so that the prognosis of the individual teeth as well as the complete dentition can be improved. Clinical expertise along with deep knowledge of etiopathogenesis will aid in preventing misdiagnosis. The molecular cellular knowledge will also aid in development of diagnostic aids that may be laboratory or chair side so that proper therapy can be administered.

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