REVIEW ARTICLE

A Correlation between Clinical Classification of Dental Pulp and Periapical Diseases with its Patho Physiology and Pain Pathway

PV Samir[1], Niva Mahapatra[2], Brahmananda Dutta[3], Anandamoy Bagchi[4], Kanika S Dhull[5], Rajnish K Verma[6]

Abstract

Background: Dental pain due to pulpal involvement is difficult to diagnose due to the apparent inaccessibility of pulp to the clinical tests, indistinct symptoms, and referred toothache originating from the periodontal tissues. Though we have various clinical classification systems to categorize pulpal diseases, we are yet biased about the exact pathophysiology and pain pathway associated with it. Dental pulp has a complex physiology, and so is its pathophysiology.

Aims & objectives: To concisely reviews the basic understanding of the pathophysiology of pulp, pain pathway, and its correlation with the classification of various clinical conditions of pulpal inflammation and periapical diseases.

Methodology: Literature search on pulpal diseases and pathophysiology from the sources: MEDLINE, PubMed, Web of Science and Cochrane Databases dated from 1965 till December 2020 was carried on to collect 163 articles.

Results: Filtered search on the pathophysiology of pulp, pain pathway, and classification of various clinical conditions of pulpal inflammation resulted us to precise 36 articles required for our understanding and demystifying the correlation.

Conclusion: The emphasis should be laid on understanding the minute changes occurring inside the pulp in due course of inflammation to aid its diagnosis and a treatment plan accordingly.

Keywords: Inflammation, Pain, Pathway, Pathophysiology, Periapical, Pulp, Pulpitis, Stimulus.

International Journal of Clinical Pediatric Dentistry (2023): 10.5005/jp-journals-10005-2636

Introduction

The pulp is a unique soft connective tissue enclosed within the pulp chamber adjoining dentinal hard tissue. It also communicates with the periapical tissues *via* apical foramen and accessory canals. This rigid pulp chamber protects the dental pulp from microbial toxins, chemical irritants, mechanical, and thermal trauma.[1]

The pulp originates from the dental lamina due to the proliferation and condensation of neural crest cells. The undifferentiated mesenchymal cells of the dental papilla, under a specific stimulus, differentiate into stellate-shaped fibroblasts at the center and odontoblasts at the periphery of the pulp. The pulp organ undergoes organization and is innervated by axons from nerve fibers that accompany blood vessels forming the neurovascular bundle of the pulp core.[1,2]

Dental pain due to pulpal involvement is difficult to diagnose due to the apparent inaccessibility of pulp to the clinical tests, indistinct symptoms, and referred toothache originating from the periodontal tissues. The initial response of pulpal irritation is inflammation, eventually leading to pulp necrosis and periapical pathosis by spreading in the surrounding alveolar bone if unattended. Asepsis like purulent sinusitis, meningitis, brain abscess, orbital cellulitis, cavernous sinus thrombosis, Ludwig, angina, emphysema, mediastinitis, thrombophlebitis, etc., are also life-threatening serious consequences of an untreated pulpal pathosis.[3,4] Thus, in-depth insight into the histophysiology of mature pulp, along with brief pain history, thorough clinical examination, and diagnostic tests, are essential for an accurate diagnosis and efficacious treatment outcome.

[1,3–6]Department of Pedodontics and Preventive Dentistry, Kalinga Institute of Dental Sciences, KIIT (Deemed to be University), Bhubaneswar, Odisha, India

[2]Department of Oral and Maxillofacial Pathology, Kalinga Institute of Dental Sciences, KIIT (Deemed to be University), Bhubaneswar, Odisha, India

Corresponding Author: PV Samir, Department of Pedodontics and Preventive Dentistry, Kalinga Institute of Dental Sciences, KIIT (Deemed to be University), Bhubaneswar, Odisha, India, Phone: +91 9938938892, e-mail: v.samir@kids.ac.in; samirdiehard@gmail.com; pvsamirpedo@gmail.com

How to cite this article: Samir PV, Mahapatra N, Dutta B, *et al.* A Correlation between Clinical Classification of Dental Pulp and Periapical Diseases with its Patho Physiology and Pain Pathway. Int J Clin Pediatr Dent 2023;16(4):639–644.

Source of support: Nil

Conflict of interest: None

Background

Histophysiology of Dental Pulp

The pulp comprises cells (fibroblasts, odontoblasts, defense cells, undifferentiated mesenchymal cells) and collagen fibrils within a framework of the extracellular matrix that supports the cells and also serves as a channel for the transport of nutrients and metabolites from blood vessels to cells within the pulp.[5]

The fibroblasts are the most densely populated cells in pulp, maintaining the turnover rate of collagen fiber bundles of the pulp matrix. They also mediate the process of inflammation by secreting fibroblast growth factor-2, vascular endothelial growth factor, and cytokines that promote the healing of the pulp core.[1]

Odontoblasts are the second densely populated cells in the pulp that help in dentin formation. Undifferentiated mesenchymal cells, along with odontoblasts, retain the ability to form dentin throughout life by differentiating into dentin-forming cells under stimulus. Odontoblasts secrete the dentinal matrix and retreat towards the pulp center resulting in the production of wavier secondary dentin circumferentially with fewer tubules. Odontoblasts, along with fibroblasts, endothelial cells, and pericytes, differentiate by stimulation of tissue growth factor-β to produce reparative dentin at the pulp surface of primary dentine as a response to adverse stimuli.[6,7] The morphology of the odontoblast is such that it has a cell body present in pulp and a fine odontoblastic process that extends peripherally into the dentinal tubules. The dentinal tubules contain dentinal fluid and odontoblastic processes, which collectively behaves as a positively charged hydrogel capable of arresting bacteria entering the pulp.[8,9] Defense activity of pulp is further enhanced by the rate of the outward flow of dentinal fluid inhibiting the diffusion of toxic substances into the tubules from the oral cavity.[10,11] Possible buildup of immune complexes and precipitation of high molecular weight proteins like fibrinogen in the dentinal fluid reduces the dentin permeability by constricting the functional radius of dentinal tubules.[12]

The dental pulp also harbors a unique cell population called undifferentiated mesenchymal stem cells that are pluripotent in nature and are capable of differentiating into characteristic cell populations as required or in demand by stimulation in pulp diseases. The mature pulp core fosters defense cells (lymphocytes, eosinophils, plasma cells, and mast cells) and antigen-presenting dendritic cells that assist in regulating immunosurveillance against the spectrum of microbes.[13]

Microcirculation of Pulp

The dental pulp is a richly vascularized tissue on par with the most vascular parts of the brain and tongue.[14] Alveolar artery, a tributary of the maxillary artery, enters the tooth *via* arterioles resulting in an individual pulp microvasculature arranged in a hierarchical system. The arterioles are present at the center of the pulp, and they course peripherally to form a capillary network providing a nutritive supply to odontoblasts. Draining of blood occurs at the center of the pulp into the venules.[15–17]

The estimated blood flow in a mature pulp is around 40–50 mL/minute/100 gm of pulp tissue, relatively higher compared to other oral tissues and skeletal muscles.[18–20] Dental pulp is nonexpandable due to surrounding hard tissue and thereby cannot accommodate the increase in the volume of blood flow in the pulp. The onset of alterations in pulp microcirculation are the first changes to occur during pulpal inflammation.[21,22]

Odontoblasts regulate the blood flow in the pulp and the development of inflammation in the pulp. An enzyme nicotinamide adenine dinucleotide phosphate (NADPH)—diaphorase present in odontoblasts produces nitric oxide, a potential vasodilator that synthesizes the inflammatory mediator PGI causing excitation of surrounding nerves resulting in brief pain.

The intrapulpal pressure during inflammation is maintained by the following mechanisms[23,24]:

- Various shunts that is, arteriovenous anastomoses and venous anastomoses that open in response to increased pressure that maintains blood flow bypassing the capillary bed.
- The framework of ground substances, like proteoglycans and glycoproteins, also confine the inflammatory reaction.
- Positive net capillary filtration pressure causes movement of the fluid into the extraluminal fluid space balanced by lymphatic fluid return.
- The increased pressure causes fluid movement in dentinal tubules that eliminates the microbial by-products.

Failure to maintain homeostasis due to bacterial toxins and inflammatory mediators results in vasodilation. Consequentially raising the intrapulpal pressure, thereby collapsing the entire thin-walled blood vessels leading to focal ischemia and pulpal necrosis.[13]

Neurophysiology of Dental Pulp

The pulp is richly innervated by afferent nerve endings of trigeminal cranial nerves. These nerve fibers maintain close proximity with the blood vessels forming the neurovascular bundle. In the subodontoblastic zone, these fibers form a delicate network called as plexus of Raschkow. Large myelinated A-δ and A-β fibers of about 2.5 µm diameter and smaller unmyelinated C fibers of (0.3–1.2) µm are the major constituents of the plexus. These sensory nerve fibers are abundant in the cell-rich zone and odontoblastic regions. These nerve fibers lose their myelin sheath and form free nerve endings which penetrate up to 150–200 µm through the odontoblastic zone into the predentin zone next to odontoblastic processes.[25] A-δ fibers are peripherally located at the coronal portion of the pulp crowded at the pulp horn region, while C fibers are located at the pulp core extending into the cell-rich zone.

Pain Pathway and Pathophysiology of Pulp

Several hypothetical theories have been put forth to decode the transmission of pulpal pain, that is, hydrodynamic mechanism, odontoblastic transduction, and dentine innervation. Dentin innervation theory states direct mechanical stimulation of free nerve endings in the dentin enamel junction will initiate an action potential causing pain. Confinement of free nerve endings in the inner one-third of the dentin and failure of pain-producing substances like bradykinin to induce pain when applied to dentin resulted in disapproval of this hypothesis. The transduction theory states odontoblasts transduce a mechanical stimulus and transfer that signal to closely packed nerve terminals. Odontoblasts being matrix-forming cells, cannot be excitable, and the absence of their synapses with nerve terminals unable its chemical transmission questioned the transduction hypothesis.

The hydrodynamic theory is the most acceptable among the three. It states that the free nerve endings in the periphery of the pulp are extremely sensitive to fluid movement due to sudden pressure changes. The dentinal tubules in dentin consist of water-like dentinal fluid. The cold stimulus and compressed air extract the tubular fluid from the outer surface, causing its outward flow, while heat, chewing, and loose fillings drive the tubular fluid toward the pulp. This rapid fluid movement, both in and out, induce a direct mechanical deformity on low threshold A-δ fibers within the tubules and peripheral pulp. It will also induce concomitant movement of odontoblasts, causing deformity of the nerve fibers in contact with their process or cell body. The deformity of nerve fibers increases the sodium ion (Na^+) ions permeability. The rapid effusion of Na^+ depolarizes A-δ fibers initiating an action potential (pain impulse).

Adherence of odontoblasts and nerve fibers with gap junctions in between implies the communication of cells and a pathway of low electrical resistance between them. The hydrodynamic effects of fluid displacement within the dentinal tubules activate the mechanoreceptors of sensory nerve axons. Stretch-activated ion channels in the cell membrane of odontoblasts enable it for mechanotransduction.

Odontoblasts have a high oxidative metabolism and are most sensitive to ischemia. The average oxygen consumption rate of odontoblasts is 3.2 mL/O_2/minute/100 gm tissue, at par with that of the brain tissue. The earliest signs of pulpal irritation are aplasia and atrophy of odontoblasts. These changes occur in the odontoblast cell layer even before the appearance of inflammatory changes in the pulp. Hypoxia of odontoblasts due to microbial toxin infiltration through dentinal tubules can be the main contributing factor to the pulp inflammation.[26]

The pain process usually starts during the tissue damage, not after the tissue injury. A-δ fibers produce the initial response of rapid, sharp, and pricking pain to external stimuli without tissue injury. Excitation of A-δ fibers so early is attributed to its peripheral location, large diameter, the low threshold of 9.9 μA, myelin sheath, and fast conduction at the velocity of 12–30 m/second. C-fibers cause a slow, dull, burning, crushing, and crawling type of pain as a response to pulpal tissue damage and inflammatory process due to a high pain threshold of 37.4 μA, absence of myelin sheath, smaller diameter, slow conduction at a velocity of 0.5–2 m/second. A-δ fibers are responsive to electric pulp testing (EPT), while C-fibers need a much higher threshold than EPT for a response.[27] The excitation of the above fibers varies according to the stimulus and intrapulpal conditions, as illustrated in Table 1.

Discussion

Classification and Sequelae of Pulp Inflammation and Periapical Infection

The motto of any classification in diagnosis is to enable proper communication within the academics and clear application of a specific treatment plan. An accurate diagnosis by a clinician depends on precisely understanding the disease processes, diagnostic aids being used, and limitations. A clinically normal pulp is generally asymptomatic. A normal pulp under variable stimulus, exposure to dentin, and age may produce a mild to transient response.

The stimulus caused by irritants can be short-term, long-term, and trauma depending upon their constant irritation and interference with blood supply, as illustrated in Table 2. Short-term irritants like cavity preparation and nonluxative traumatic injuries to the tooth will generally cause acute inflammation followed by repair of the tissues as the irritant no longer persists after the moment. Long-term irritants like dental caries, loose fillings, cracks, erosion, and traumatic laxative injuries can result in chronic inflammation and, ultimately, pulp necrosis if untreated because of continuous stimulation due to the irritant and severing of blood supply to the tooth at the apex.

Table 1: Excitation of A-δ and C-fibers to stimulus and intrapulpal conditions

Stimulus and intrapulpal conditions	*A-δ fibers response*	*C-fibers response*
Cold	√	×
Heat	√	√
Ion effect	√	×
EPT	√	×
Hypoxia	×	√
↑Pulpal pressure	×	√
Hyperosmotic solutions	√	×
Inflammatory mediators	×	√

Dentine Hypersensitivity

A tooth with initially exposed dentin generally produces sensitivity. Patient complaints of sharp shooting type of pain associated with cold and osmotic stimuli, which subside immediately after its removal. This sharp shooting type of pain is not associated with inflammation of the pulp but increased osmotic pressure inside the dentinal tubules stimulating a few A-δ fibers present in the odontoblastic processes and upper periphery of pulp.

Reversible Pulpitis

The pain in reversible pulpitis is also sharp and shooting type. It can be differentiated from dentine sensitivity by the presence of any specific factors other than exposed dentine, like deep caries, tooth fractures, recent restorations, open restoration margins, etc. An initial stimulus to exposed pulp produces early morphological changes like odontoblast hypoplasia, hypotrophy, disruption of odontoblastic cell layers, chromatin clumping, and swollen mitochondria resulting in hypoxia in the circulation of pulp leading to inflammation.[28]

As mentioned above, in hydrodynamic theory, pain impulse is initiated due to the stimulation of free nerve endings at the periphery of the pulp due to increased osmosis and fluid movement inside the pulp. The increased osmosis is generally attributed to the extraction of tubular fluid outwards due to cold or compressed air or inward movement of tubular fluid to heat, biting pressure on loose filling.

Reversible pulpitis can be categorized into two types—acute and chronic reversible pulpitis. Chronic reversible pulpitis is generally a mild discomfort while chewing or cold items. An acute exacerbation of inflammation of the pulp due to trauma and initial exposure of dentinal tubules here is known as acute reversible pulpitis, which presents a sharp, shooting type of pain aggravated on cold and sweet food items relieved immediately after the removal of stimulus. In chronic reversible pulpitis, the pulp may be clinically normal with a degree of fibrosis as a result of previous stimuli.

Table 2: Different stimulus on pulp with its reaction and outcomes

Type of stimulus	*Examples*	*Reaction of pulp*	*Outcome if untreated*
Short term	Heat produced during cavity preparation, dentine cutting and drying in cavity preparation, trauma without luxation injuries	Acute inflammation	Healing and recovery
Long term	Dental caries, loose fillings, restoration breakdown, erosion, attrition, loss of tooth integrity due to chemical irritation	Chronic inflammation	Pulp necrosis, infective pulp space due to bacterial invasion, periapical diseases
Trauma	Luxation injuries, avulsion	Pulp necrosis	

No radiographic changes in and around the periodontal or periapical spaces are seen in reversible pulpitis except radiolucency due to loose fillings; therefore, it is considered only a provisional diagnosis. A treatment plan in accordance with reversible pulpitis should be done on a tooth, and a timely prognosis follow-up should be done to check for any progression in pulp pathology. The pulp sensibility tests should be carried out in the follow-up appointments to check the status of the pulp, and further indicative endodontic treatment should be performed in case of any inflammatory development or necrosis of the pulp.

Irreversible Pulpitis

The pain in irreversible pulpitis is more intensified as compared to reversible pulpitis. It can be classified into two types chronic irreversible pulpitis and acute irreversible pulpitis. The pain may arise from slight thermal changes like drinking tap water, breathing cold air, etc. The presence of a dull, throbbing, and lingering type of pain for a few minutes to a few hours are the classic symptoms of chronic irreversible pulpitis differentiating it from reversible. It may progress into a spontaneous, continuous, and highly intensified pain worsening during sleep or lying down with or without any thermal stimulus, known as acute irreversible pulpitis. The tooth, in acute cases, may be tender to bite and percussion both horizontal and vertical, indicative of the spread of inflammation to the periapical tissues. No definite radiographic changes are seen in any form of irreversible pulpitis.

The initial lingering type of pain in irreversible pulpitis is due to the stimulation of the majority of A-δ fibers in the plexus of Raschkow present in and around the superficially and sub-odontoblastic zone of the pulp. The increased pulp tissue pressure due to capillary vasodilation and transudation of fluids needs to be accommodated by an increase in the volume of the pulp tissue.[29] Capillary vasodilation is caused by nitric oxide, a potential vasodilator that is produced by an enzyme NADPH-diaphorase present in odontoblasts.[30,31] Dental pulp has resilient gelatin-like material ground substances, that is, proteoglycans, glycoproteins, and reinforced collagen fibers, which makes it firm and hard to expand. Inability to expand of pulp results in increased intrapulpal pressure at the site of irritation resulting in the collapse of venules at the region, causing vascular stasis and ischemia, and ultimately cell death in the region.[32] This increased intrapulpal pressure synthesis of inflammatory mediator prostaglandin (PGI) 2 causes mechanotransduction of nociceptors in nerve endings resulting in hyperalgesia. The increased intrapulpal pressure combines with inflammatory mediators in stimulating the low pain threshold C-fibers, causing intensified pain in acute irreversible pulpitis. The complex microvascular dynamics of the pulp are attributed to the change in irreversible pulpitis from a chronic asymptomatic form to an exaggerated acute pain within a few hours.

Like any other chronic infection, chronic pulpitis, too, has to pass through an acute phase. But the interesting part is that in the case of primary teeth, the acute phase is almost untraceable due to the aggressive pace of the spread of inflammation. This can be attributed to the comparatively thinner layers of enamel and dentin, the high vascularity of pulp, and the presence of multiple accessory canals facilitating the extravasation of inflammatory exudates.

Necrobiosis and Pulp Necrosis

The inflammatory process progresses from pulp space into the periapical area due to continuous increases in pulp tissue pressure resulting in loss of structural integrity of pulp and making it nonvital. The tooth in this phase can either be partially or completely necrotic depending upon the progression rate of infection due to bacterial colonization in the pulp space. Grossman termed a partially necrotic tooth with remaining inflamed pulp as necrobiosis. Necrobiosis can be seen as necrotic coronal and inflamed apical pulp in a tooth or as necrosis in one and inflammation in other canals of a tooth with multiple canals.[30] The presence of both inflammatory and necrotic pulp creates questions in pulp sensibility tests, thereby complexing the diagnosis of necrobiosis. The patient may elucidate mild intensity pain of intermittent episodes ranging from weeks to months. The inflammation may progress to the surrounding periapical area, causing apical periodontitis.[13]

The tooth will progress into complete pulp necrosis due to the complete loss of integrity of the pulp. Pulp necrosis is usually sequential progress from the inflammatory conditions of the pulp due to long-standing exposed dentin or may have a direct consequence on the tooth due to trauma. The tooth may be devoid of any vascular supply due to a fall in pulp microcirculation of terminal arteries and venules in the pulp causing collateral damage to the blood supply of the pulp during inflammation. This results in creating an ischaemic environment resulting in cell death in the pulp. Complete pulp necrosis is a long sequela due to its complex cell structure. Pulp necrosis of a tooth with a closed apex due to laxative injuries is comparatively faster as compared to a carious or an exposed tooth. It is attributed to the direct impact of the force of the sharp closed apex on the underlying arteriole bed resulting in a cut-off of the vascular supply to the tooth.[33] The response of a necrotic tooth to pulp sensibility tests is negative because of the absence of blood supply in the tooth. The tooth in complete pulp necrosis is generally asymptomatic. It is a hibernating phase of bacterial colonization inside the tooth, which aggravates the inflammation in the surrounding periapical area.[34]

Internal Resorption

The term internal resorption itself suggests the origin of resorptive cells internally from the tooth in the pulp space region. Internal resorption is generally categorized into internal surface resorption, internal inflammatory resorption, and internal replacement resorption. Surface resorption is hardly noticeable in the radiographs because of very minute resorptions in the canal walls. The resorption occurs during the transition phase of the tooth from pulpitis to necrosis, most commonly seen in necrobiosis.

In internal inflammatory resorption, the pulp undergoes metaplastic changes to transform into a vascularized inflammatory tissue which initiates the adjacent hard tissue resorption by activating dentinoclasts present in it. Dentinoclasts are derived from undifferentiated reserve connective tissue cells transported to the pulp through blood from general circulation. The patient is generally asymptomatic in inflammatory resorption. Mild pain may exist in association with apical periodontitis and exposure of metaplastic tissue to the environment due to coronal perforation (pink tooth).

Internal replacement resorption is a rare condition of dentine resorption, and its replacement is with a bony hard tissue associated with a pulp undergoing metaplastic changes. The patient is generally asymptomatic, and the radiograph illustrates an irregular enlargement of pulp space filled with bone-like hard tissue. The replacement phenomenon here is relatively unknown and scarce in the literature. The possible replacement concept may be related

to the possible mineralization around the nidi formed around the thrombosed pulp blood vessels and collagen sheaths.[34]

Apical Periodontitis and Periapical Diseases

The continuous increase in intrapulpal pressure during acute irreversible pulpitis finally pushes the inflammatory process circumferentially through the apical foramen into the periodontal ligament space (PDL) space and periapical area resulting in apical periodontitis. The patient elucidates throbbing pain, which aggravates chewing or biting. The presence of tenderness on vertical percussion is a classical feature differentiating apical periodontitis from any form of irreversible pulpitis. The pain mechanism in apical periodontitis is attributed to the release of various inflammatory mediators. Uniform loss of lamina dura due to the widening of PDL spaces due to inflammatory exudate from the pulp is a distinguishing radiological feature of apical periodontitis from pulpitis to periapical abscess. Apical periodontitis is not seen in the primary tooth because of the presence of a large number of lateral accessory canals present in the interradicular region and, secondly, open apices. The increased inflammatory pressure in pulp tissue escapes out through accessory canals in the interradicular space in the primary tooth.[35]

The pulp tissue becomes necrotic, and the canal becomes pulp-less and infected due to the continuous influx of bacteria through the pathway created by caries, loose fillings, etc. Bacterial aggregation in pulp is a mixture of both aerobic and preponderantly anaerobic flora. *Streptococcus mutans* is the first microbial entry into the pulp space aggravating inflammation by the release of bacterial toxins, enzymes, antigens, chemo toxins, and organic acids transported through the dentinal tubules into the pulp, causing its inflammation. The aggregation of microbial flora in the periapical area, along with the inflammatory exudate from the pulpal space, will result in the activation of various inflammatory cells like mast cells, neutrophils, and osteoclasts. The activated osteoclasts start resorbing the alveolus in the periapical area, causing further accumulation of degenerated debris, exudate and microflora, forming the pus in the periapical abscess.

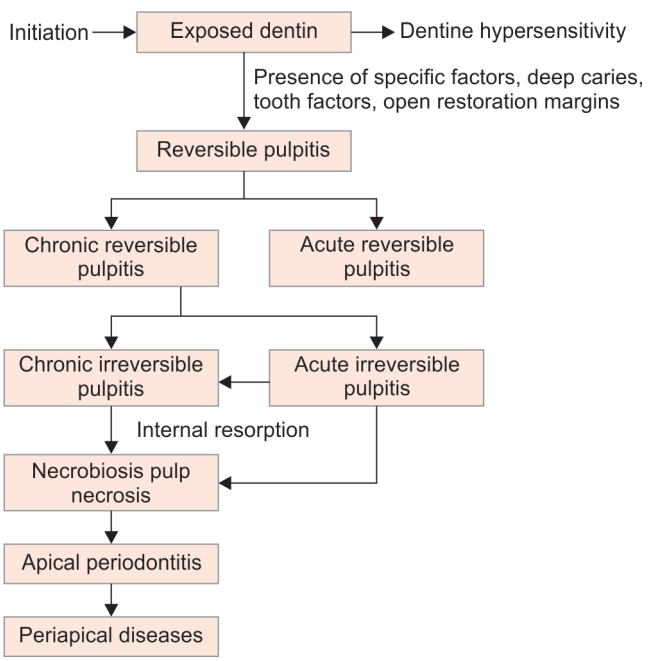

Fig. 1: Pathways of pulpal diseases

The golden rule to follow in the diagnosis of a periapical disease is examining the possibility of a preexisting pulpal inflammation and vice versa. A long-standing periapical abscess may either escape out through the periapical sinus or else can accumulate inside to intensify the resorptive activity by forming a periapical cyst or periapical granuloma.[35,36] The pathway of pulpal disease progression is illustrated in Figure 1.

Conclusion

Understanding how the pain is caused simplifies our treatment plan and betters the prognosis. An accurate diagnosis of pulp and periapical diseases, apart from proper history taking, clinical assessment, and radiographic investigations, also requires a comprehensive understanding of the pathophysiology and pain pathway of the pulp. These aid us in carrying out our treatment plan more precisely and confidently. Knowing how the pain has occurred after knowing when and why it has occurred is equivalently important.

Orcid

PV Samir https://orcid.org/0000-0002-7975-7019
Brahmananda Dutta https://orcid.org/0000-0001-5379-0702
Kanika S Dhull https://orcid.org/0000-0002-0002-8084

References

1. Berkovitz BK, Holland GH, Moxham BJ. Oral Anatomy, Histology and Embryology. 3rd ed. St. Louis, Mosby 2002: pp. 149–167.
2. Antonio Nanci. Tencate's oral histology development, structure & function. Elseiver 8th ed. 2013:185–187.
3. Walsh LJ. Serious complications of endodontic infections, some cautionary tales. Aust Dent J 1997;42(3):156–159. DOI: 10.1111/j.1834-7819.1997.tb00113.x
4. LeJeune HB, Amedee RG. A review of odontogenic infections. J La State Med Soc 1994;146(6):239–241.
5. Seltzer S, Bender IB. The Dental Pulp. 3rd ed. Philadelphia: JB Lippincott, 1984:281.
6. Yamamura T. Differentiation of pulpal cells and inductive influences of various matrices with reference to pulpal wound healing. J Dent Res 1985;64:530–540. DOI: 10.1177/002203458506400406
7. Nie X, Tian W, Zhang Y, et al. Induction of transforming growth factor-beta 1 on dentine pulp cells in different culture patterns. Cell Biol Int 2006;30(4):295–300. DOI: 10.1016/j.cellbi.2005.12.001
8. Lindén LA, Källskog O, Wolgast M. Human dentine as a hydrogel. Arch Oral Biol 1995;40(11):991–1004. DOI: 10.1016/0003-9969(95)00078-4
9. Vongsavan N, Matthews B. The permeability of cat dentine in vivo and in vitro. Arch Oral Biol 1991;36(9):641–646. DOI: 10.1016/0003-9969(91)90016-n
10. Matthews B, Vonsavan N. Interaction between neural and hydrodynamic mechanisms in dentine and pulp. Arch Oral Biol 1994;39 Suppl:887–895. DOI: 10.1016/0003-9969(94)90193-7
11. Vongsavan N, Matthews B. Fluid flow through cat dentine in vivo. Arch Oral Biol 1992;37(3):175–185. DOI: 10.1016/0003-9969(92)90087-o
12. Pashley DH, Galloway SE, Stewart F. Effects of fibrinogen in vivo on dentine permeability in the dog. Arch Oral Biol 1984;29(9):725–728. DOI: 10.1016/0003-9969(84)90179-1
13. Yu C, Abbot PV. An overview of dental pulp: it's functions and responses to injury. Aust Dent J 2007;52(1 Suppl):S4–S16. DOI: 10.1111/j.1834-7819.2007.tb00525.x
14. Vongsavan N, Matthews B. The vascularity of dental pulp in cats. J Dent Res 1992;71(12):1913–1915. DOI: 10.1177/00220345920710121101
15. Takahashi K, Kishi Y, Kim S. A scanning electron microscope study of the blood vessels of dog pulp using corrosion resin casts. J Endod 1982;8(3):131–135. DOI: 10.1016/S0099-2399(82)80249-5

16. Kishi Y, Kai K, Toris H, et al. Vascular architecture of the pulp in human teeth using resin cast examined under SEM. Shika Kiso Igakkai Zasshi 1989;31(1):112–114. DOI: 10.2330/joralbiosci1965.31.112
17. Kishi Y, Shimozato N, Takahashi K. Vascular architecture of cat pulp using corrosive resin cast under scanning electron microscopy. J Endod 1989;15(10):478–483. DOI: 10.1016/s0099-2399(89)80028-7
18. Meyer MW. Pulpal blood flow: use of radio-labelled microspheres. Int Endod J 1993;26(1):6–7. DOI: 10.1111/j.1365-2591.1993.tb00527.x
19. Path MG, Meyer MW. Quantification of pulpal blood flow in developing teeth of dogs. J Dent Res 1977;56(10):1245–1254. DOI: 10.1177/00220345770560102601
20. Kim S. Microcirculation of the dental pulp in health and disease. J Endod 1985;11(11):465–471. DOI: 10.1016/S0099-2399(85)80219-3
21. Trowbridge HO, Kim S. Pulp development, structure and function. In: Cohen S, Burns RC, eds. Pathways of the pulp. St. Louis: Mosby, 1998:386–424.
22. Kim S. Neurovascular interactions in the dental pulp in health and inflammation. J Endod 1990;16(2):48–53. DOI: 10.1016/S0099-2399(06)81563-3
23. Kim S, Schuessler G, Chien S. Measurement of blood flow in the dental pulp of dogs with the 133xenon washout method. Arch Oral Biol 1983;28(6):501–505. DOI: 10.1016/0003-9969(83)90181-4
24. Kim S, Lipowsky HH, Usami S, et al. Arteriovenous distribution of hemodynamic parameters in the rat dental pulp. Microvascular Res 1984;27(1):28–38. DOI: 10.1016/0026-2862(84)90039-6
25. Byers MR, Dong WK. Autoradiographic location of sensory nerve endings in dentin of monkey teeth. Anat Rec 1983;205(4):441–454. DOI: 10.1002/ar.1092050409
26. Chen NN. A transmission electron microscopy study of early changes in hypoxic pulps. California: Loma Linda University. Thesis.
27. Byers MR. Dental sensory receptors. Int Rev Neurobiol 1984;25:39–94. DOI: 10.1016/s0074-7742(08)60677-7
28. Smulson MH, Sieraski SM. Histophysiology and diseases of dental pulp. In: Weine FS, ed. Endodontic therapy. St. Louis; Mosby, 1996:84–165.
29. Heyeraas KJ, Kim S, Raab WH, et al. Effect of electrical tooth stimulation on blood flow, interstitial fluid pressure and substance P and CGRP-immunoreactive nerve fibres in the low compliant cat dental pulp. Microvascular Res 1994;47(3):329–343. DOI: 10.1006/mvre.1994.1026
30. Law AS, Baumgardner KR, Meller ST, et al. Localization and changes in NADPH- diaphorase reactivity and nitric oxide synthase immunoreactivity in rat pulp following tooth preparation. J Dent Res 1999;78(10):1585–1595. DOI: 10.1177/00220345990780100301
31. Kerezoudis NP, Olgart L, Fried K. Localization of NADPH-diaphorase activity in the dental pulp, periodontium and alveolar bone of the rat. Histochemistry 1993;100(4):319–322. DOI: 10.1007/BF00270053
32. Tønder KJ, Kvinnsland I. Micropuncture measurements of interstitial fluid pressure in normal and inflammed dental pulp in cats. J Endod 1983;9(3):105–109. DOI: 10.1016/S0099-2399(83)80106-X
33. Heyeraas KJ, Berggreen E. Interstitial fluid pressure in normal and inflammed pulp. Crit Rev Oral Biol Med 1999;10(3):328–336. DOI: 10.1177/10454411990100030501
34. Abbott P, Yu C. A clinical classification of the status of the pulp and the root canal system. Aust Dent J 2007;52(1 Suppl):S17–S31. DOI: 10.1111/j.1834-7819.2007.tb00522.x
35. Torabinejad M. Pulp and periradicular pathosis. In: Walton RE, Torabinejad M eds. Principles and practice of endodontics. 3rd ed. Philadelphia: WB Saunders Co., 2002:34–37.
36. Massler M. Pulpal reactions to dental caries. Int Dent J 1967;17(2):441–460.