Pulp Regeneration—Translational Opportunities

Depth and Activity of Carious Lesions as Indicators for the Regenerative Potential of Dental Pulp after Intervention

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Abstract

Studies on dental regeneration involving interventions for pulp therapy such as regeneration and revascularization procedures are promising for the injured tooth; however, a complete replication of the original pulp tissue does not seem to take place. In cases in which we wish to preserve or maintain parts of the pulp during treatment, it is apparent that the effectiveness of healing or biological regeneration is dependent on the degree of inflammation of the pulp tissue. Thus, the control or prevention of a pulp infection is still a major issue for the clinicians. Data indicate that the typical reason for performing endodontic treatment is deep caries. The biological concept of vital pulp therapy associated with deep caries takes the treatment and evaluation of the unexposed as well as the exposed pulp into account. Interestingly, the clinical diagnosis is typically the same. Deep caries with reversible pulpsitis may receive differing treatments such as excavation procedures aiming to avoid pulp exposure or more pulp invasive treatments such as pulp capping or pulpotomy. This should not be the case. Consequently, huge treatment variation is noted among clinicians based on the same caries diagnosis. Which treatment should be selected? High-quality trials are needed, and it is important to obtain information on the actual lesion depth and an estimate of the lesion activity before treatment. These may be basic indicators for the regenerative potential of dental pulp. Recent clinical trials dealing with the treatment of deep caries lesion are discussed, including pulp invasive and noninvasive concepts, to attempt to solve the task of getting the best clinical outcome for adult patients. (J Endod 2014;40:576–S81)

Key Words

Caries, direct pulp capping, endodontics, indirect pulp therapy, pulpotomy, stepwise excavation

Although oral health care in many parts of the Western world has been improving, with a marked decline in caries activity among children and adolescents (1), data indicate that caries is still the most frequent reason for performing endodontic treatment. In a questionnaire survey, 55% of previously performed root canal treatments were performed because of caries in a vital tooth by general practitioners (GDPs) (2). It is apparent that the effectiveness of healing or biological regeneration is dependent on the degree of inflammation in the pulp tissue (3) when preserving or maintaining parts of the pulp during caries treatment. This produces a dilemma not only in the clinic but also between the clinic and the laboratory because GDPs still lack a device for noninvasive measurements of pulp inflammation. How can pulp therapies be improved if the actual clinical condition of the pulp remains a diagnostic problem? A recent review dealing with the diagnosis of dental pulp has shown that the available diagnostic tools were insufficient to assess the proper status of the pulp (4). Is it possible to obtain information regarding the condition of the pulp if the diagnostic process was more focused on the characteristics of a specific carious lesion? Can patient age be related to the depth of the lesion? Similarly, when GDPs assess lesion activity by including established clinical variables on caries activity, is it possible to use this information as indicators for the regenerative potential of dental pulp after intervention?

Treatment Variation

The biological concept of vital pulp therapy associated with deep caries involves the treatment and evaluation of unexposed and exposed pulp, but, interestingly, the clinical diagnosis is typically the same (5, 6). In a dental practitioner environment, deep caries with reversible pulpsitis may receive differing treatment modalities such as avoidance of pulp exposure, pulp capping, or pulpotomy. These treatment options have led to both pulp-invasive (7, 8) and non—pulp-invasive treatment strategies (9—13). From network-based studies, it has been documented that GDPs are prone to perform different treatment modalities for the same “deep caries lesion scenario” (14). The vast majority of GDPs suggest 1 complete excavation or a root canal treatment, and less than 20% prefer a less invasive excavation procedure aiming to avoid exposure of the pulp. In a large questionnaire survey, this trend was recently confirmed because 2 groups of GDPs were identified with opposite approaches to caries excavation (15). Apparently, it matters which GDP is treating the deep carious lesion. The patient may receive a root canal treatment, a pulp capping procedure, complete caries excavation, or a less invasive excavation procedure. From the viewpoint of the patient, this treatment variation is not an optimal scenario. Efforts have been made to solve this clinical dilemma, and the contemporary perspectives on vital pulp therapy have been discussed by both endodontists and pediatric dentists (16), but, of course, more profound educational initiatives are needed to reduce treatment variation. Consensus within the clinical
community is an important prerequisite for developing improved treatment strategies for future collaboration within the scientific community.

**Caries Progression and the Pulp-Dentin Organ**

The belief that there is no correlation between pulp inflammation and the presence or absence of a toothache including an abnormal response to thermal testing has led to the opinion among clinicians that it is justified to excavate deep caries to pulp exposure (7) because the pulp may be severely inflamed even though it remains "silent" in terms of subjective symptoms. If caries remains untreated, a frank exposure may occur, and classic articles have shown that the pulp reacts with an infiltration of acute inflammatory cells and perhaps also the development of a small abscess (17, 18). Therefore, it seems logical that the removal of infected pulp tissue in such cases is the treatment of choice. The pulp becomes increasingly inflamed as caries progresses (Fig. 1). But, when is the point of no return? What happens if the speed of caries progression is reduced?

Since the article by Bränsström and Lind (19), a missing link has been made between the early signs of caries and the inflammatory reactions of the pulp. Because of histologic difficulties, this link could not be shown directly but rather by comparing tooth halves in the laboratory. Changes along the odontoblastic and subodontoblastic layers were noted subjacent to enamel lesions. Later, the use of thin undemineralized tooth sections made it possible to simultaneously examine the enamel lesion and the pulp-dentin organ, confirming not only early odontoblast cell reactions (20) but also a difference in tertiary dentin formation as a response to slow and active lesion activity (21).

Extracted third molars show findings regarding the influence of caries lesion activity on dentin and pulp (Fig. 2). A partially erupted mandibular third molar (Fig. 2A) shows evidence of an undisturbed cariogenic plaque, and a typical light yellow or yellow demineralized dentin is noted, reflecting an actively progressing lesion (Fig. 2A, inset). In a fully erupted maxillary third molar without the presence of cariogenic surface plaque, the occlusal surface displays a chronic/inactive discolored surface lesion and the appearance of a dark brown/black discolored demineralized dentin (Fig. 2B, inset). Alterations in the odontoblast cell layer can be noted both in arrested and active lesion sites, whereas a different appearance of the subodontoblastic region is apparent in subjacent active sites (Fig. 2C) as compared with the unaffected control (Fig. 2D). This may indicate that the pulp is able to react dynamically to caries without necessarily reaching stages of irreversible pulpitis, necrosis, or infection. In short, using classic qualitative histologic parameters, a different pulp response can be noted toward rapidly and slowly progressing caries (20–22). It is also well-known that dentin is a bioactive extracellular matrix (23–26), and during demineralization there is a release of bioactive molecules (27–29). Our knowledge of the odontoblast is steadily increasing (30) as well as our knowledge regarding the role of inflammation (31). Taken together, it might be possible to further investigate the relative influence of carious activity with respect to the use of both indirect pulp therapy (IPT) and pulp therapy. In particular, more information is needed during the dynamic nature of human caries progression and the clinical importance of the reservoir of bioactive molecules in the dentin during various concepts of caries excavation.

Several studies on the proteomics of human dentin have been performed that have shed light on the protein composition of the dentinal matrix (32, 33). Interestingly, the dentinal matrix appears, among a myriad of other proteins, to contain sequestered growth factors, and it has been shown that the dentinal matrix plays an active role because the sequestered bioactive substances can be released because of acidic and enzymatic dissolution of the dentinal matrix within the caries lesion (27–29). To our knowledge, no studies have
performed a comprehensive proteomic analysis of the caries lesion per se. In order to elucidate the proteomic profile of the caries lesion, a proteomic analysis of the carious dentin is currently being performed in our laboratory using the stepwise excavation procedure as the experimental setup. During the first visit, excavation of clinical active caries dentin is excavated and assessed on parameters developed by Bjørndal et al. (34). After the initial excavation, a temporary glass ionomer filling is placed. During the second visit (4–6 months after the initial excavation), the temporary filling is removed, and the remaining caries dentin are excavated and evaluated as inactive based on the previously referenced criteria. Active and inactive carious dentin samples are analyzed regarding their proteome, and results are compared with the proteome of sound human dentin. To sum up, the aim of this study was to evaluate whether caries activity can be linked with a certain biochemical profile, which may stimulate the pulp. Our hypothesis is that this profile may be used to characterize the resulting inflammatory state of the pulp. Might there be a difference in the inflammatory changes noted during active and arrested caries progression? Can these changes be linked to the differences seen in tertiary dentinogenesis? In short, can the biochemical profile of the carious lesion help in predicting the inflammatory changes seen histologically and maybe lead to a more evidence-based diagnosis of the dental pulp in cases of deep caries lesions and associated vital but inflamed dental pulps? In this light, various lesion activities (Fig. 2A and B) may have the potential of releasing different profiles of bioactive molecules.

The Conversion of Lesion Activity in Caries

It has previously been described in detail how the cariogenic ecosystem may change during the natural development of a deep caries lesion (35). When the demineralized enamel breaks down and the microbial ecosystem is converted from a closed environment toward a more open environment, the activity of the lesion is declining. Of course, in a clinical setting, it is not possible to follow a deep lesion during total breakdown, but when IPT is performed, the same principle changes within the cariogenic ecosystem are happening. The aim of IPT is to change the cariogenic environment and to reduce the transmission of cariogenic stimuli into the pulp. Clinically, a conversion is taking place as the carious dentin changes color from light to dark brown and the surface moisture from wet to dry (34, 36). IPT can be performed in either 1 or 2 steps; the latter is also described as the stepwise excavation approach. The IPT approach has become an acceptable treatment modality for asymptomatic carious permanent teeth in young patients (12–14). Notably, this technique has also shown success in case reports of symptomatic permanent teeth in children (37), but mainly the success of this approach has been documented in adults (9, 38, 39).

How Can Lesion Activity and Depth Be Monitored in a Clinical Setup?

A principle classification can categorize estimates on lesion activity in clinical terms (Fig. 3A–C). An example of an active progressing caries lesion is displayed showing a premolar during caries removal. The demineralized discolored dentin has a light yellow/yellow appearance, the surface texture has a wet/moist appearance, and it is easy to disintegrate the soft organic matrix (Fig. 3A). The signs of slowly progressing caries are a browner and dry surface texture (Fig. 3B). In cases of arrested caries, this pattern can be more marked (Fig. 3C). The darkest area of the demineralized dentin reflects the oldest part of the caries lesion. Such classification plates have been used to classify changes in lesion activity previously (34, 40, 41).

![Figure 3](image-url)
The specific depth of the carious lesions is seldom mentioned in clinical studies. This may also be a problem in getting a more precise estimation of the degree of pulp inflammation. It is well-known that GDPs have different thresholds for expecting an exposure of the pulp during caries excavation, and it may vary from caries penetrating half way into the dentin to caries involving the entire dentinal thickness (9). It is obvious that the inflammation of the pulp would not be the same within these 2 borderline cases. It can be hypothesized that the enrollment of various carious lesion sizes in a clinical trial may affect the final evaluation of the outcomes.

In a recent randomized clinical trial (38), this aspect was approached using an inclusion plate based on radiographs showing examples of caries lesions that could be either included or excluded. In the actual study, the inclusion of the lesion was defined as caries penetrating three quarters or more into the dentin and with a well-defined radiodense line separating the pulp from the demineralized dentin (Fig. 4). Data on lesion depth and activity might be the missing link that could be used in both the clinic and the laboratory as indicators for the regenerative potential of the dental pulp after intervention.

Direct and Indirect Pulp Therapy and Level of Evidence

Caries is mentioned several times in the review of the diagnostic condition of the pulp (4), but, as discussed earlier, it is not defined more accurately in terms of activity and depth. Nadin et al (42) performed a systematic Cochrane Review about pulp therapy in so-called extensive caries in primary molars. All included participants had symptom-free, cariously exposed vital pulp as a baseline description. However, it was not possible from the review to gain information about the carious depth before pulp exposure. The authors indicate that they primarily focused on the exposed pulp, but they did not exclude that IPT could have been an alternative treatment modality. Although based on primary molars, this clearly reflects the controversial aspect of the deep caries topic.

Randomized controlled clinical trials and meta-analyses are needed in order to obtain the best platform for selecting the correct treatment (43). This may explain 1 of the major reasons why treatment variation exists. The lack of the highest level of evidence does not mean that GDPs should select what they believe to be the best treatment modality; instead, they should rely on the best available data, which are typically reflected in country or specialty guidelines. Systematic reviews have addressed the need of high evidence trials concerning vital pulp therapy in cariously exposed and unexposed pulps (42,44–46), and the reviews all emphasize the limitation of comparing studies that are different in study design and the need for further studies of high quality.

Based on weighted pooled success rates (over time), evidence tables have recently been aligned for direct pulp capping, partial pulpotomy, and full pulpotomy (47). A range of patient age was included, with the youngest patients undergoing direct pulp capping and the oldest full pulpotomy. The success rate was 72.9% for direct pulp capping with a recall period more than 3 years (6–10 years of age, n = 231), 99.4% for partial pulpotomy (6–27 years of age, n = 23), and 99.3% (6–70 years of age, n = 37) for full pulpotomy. Note the remarkably low number of recalls after more than 3 years for all the pulpotomy treatments. Again, the only information that can be extracted from these studies regarding the inclusion criteria was that all the teeth had cariously exposed pulps. No specific characteristics about the caries lesions were presented. This may be a problem when using pooled data.

A more recent retrospective observational study (48) observed a 2-year survival rate of 56.2% (mean age = 41 years, N = 51) of teeth.
after pulp capping. The relatively low survival rate confirms previous observational data suggesting that the prognosis of pulp capping may be related to age (49). Concomitantly, a randomized clinical multicenter trial examined pulp capping versus partial pulpotomy in cariously exposed pulps in adults after the excavation of well-defined deep caries lesions (38). The results showed an even worse outcome after both pulp therapies, with a pooled pulpal survival rate of only 33.2% after 1.5 years. As opposed to other studies, this trial documented a more specific description of deep lesions being enrolled (Fig. 4). The results showed that a caries lesion, located in the inner quarter of the dentin in adults, may represent the threshold for success for pulp capping, which may be expected with our present treatment modalities. In addition, the low level of success in this study may also be related to the use of a concealed allocation sequence in relation to the randomization procedure. This is often underestimated in randomized clinical trials because without concealment the results may lead to overestimation of the treatment effect (42—44).

It has been suggested that a full pulpotomy might be a better alternative treatment for adults after pulp exposure (50). Based on preliminary data in a small serial case report, an outcome rate of 82% was obtained (children and adults, mean age = 37 years, \( N = 17 \)). When addressing the inclusion criteria, cases of exposure after the excavation of caries were included as well as cases of exposure after preparation for prosthetics restorations. This might be an important prognostic difference that should be evaluated before the initiation of a larger-scale study.

When patients with pain and clinical signs of irreversible pulpitis are included in clinical trials, it would be interesting to know the actual depth of carious lesions (described as extensive) in order to specify cases in which less invasive pulp therapies have to be excluded. Recently, a large randomized clinical multicenter study showed that full pulpotomy in extensive carious lesions with “partial” irreversible signs of pulpitis disclosed remarkably successful outcomes among patients (mean age = 27 years) using biomaterials (51). Because the majority of the actual scored pain levels appeared to be mild to moderate (and not severe), it would again have been relevant to know whether the actual lesions size varied as well.

Of course, the present theme is complex. It is important to note that the topic of dressing materials and final restorations has not been covered. The tools used for caries excavation should not be forgotten. At a case report level and with the use of the operating microscope, the technical aspect of excavation might push the borders of what we would expect. Notably, in asymptomatic cases in young teeth, a direct cap can be successfully performed even when caries radiographically reaches the pulp (8).

Conclusions

It might be beneficial to incorporate more details in clinical studies regarding the characteristics of caries lesions as indicators for the regenerative potential of the dental pulp after intervention. Literature is sparse within this topic. The following are suggested:

1. Future protocols for the regenerative potential of dental pulp (in the clinic as well in the laboratory) should include more details about the caries lesion before intervention (if present and possible).
2. It is hypothesized that the inclusion of unspecific caries lesions makes it difficult to interpret the actual degree of pulp inflammation, hence the actual clinical outcome.
3. The protocol should not only state teeth with cariously exposed pulps but also the caries lesion depth behind.
4. Classifying lesion activity by established clinical variables should be attempted (Fig. 3).
5. Reporting the actual caries lesion depth (eg, determined by radiographs) (Fig. 4) should be included.
6. Carious lesion characteristics should be reported irrespective of the clinical suggested pulp diagnosis.

The knowledge of lesion activity and lesion depth before treatment may create an important baseline and detailed platform for explaining and predicting treatment outcome in cases of pulp exposure after treatment. There may be a difference in the regenerative potential of dental pulp related to active and slowly progressing caries because dentin color, consistency, and surface environment (ie, wet or dry) may in reality reflect various gradients of bioactive molecules within carious dentin and, therefore, be more indicative of pulp inflammation and regeneration.

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The authors deny any conflicts of interest related to this study.

References

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