Review

Influence of orthodontic forces on human dental pulp: A systematic review

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ARTICLE INFO

Article history:
Accepted 17 November 2014

Keywords:
Dental pulp
Growth factors
Orthodontic force
Pulpal blood flow

ABSTRACT

Aim: The aim of the present study was to systematically review the influence of orthodontic force on human dental pulp.

Methods and results: The addressed focused question was "Do orthodontic forces affect the human dental pulp?" which was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed according to the PICO (Participants, Interventions, Control, Outcomes) principle. Databases were explored from 1952 up to and including August 2014 using different combinations of the following keywords: "orthodontic force"; "dental pulp"; "reaction" and "tooth movement". Literature reviews, letters to the editor, commentaries and case-reports were excluded. Thirty studies were included. Six studies assessed the effect of orthodontic forces on pulpal blood flow and 20 studies investigated the pulpular cellular responses to orthodontic forces. In 4 studies, pulpular responses to orthodontic forces were compared between previously traumatized- and non-traumatized teeth.

Conclusions: There is insufficient scientific validation regarding the association between orthodontic forces and human dental pulp. However, a history of dental trauma maybe considered a risk factor for loss of pulp vitality during orthodontic treatment.

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1. Introduction

Application of orthodontic forces to teeth for specific time periods has been reported to induce molecular changes in the cells of the periodontal ligament, alveolar bone and the pulp-dentine complex. Histologic studies have reported depression of pulp tissue respiration, vacuolization, circulatory disturbances, haemorrhage, fibro-hyalinosis and even necrosis as the major pulpal changes that may be encountered following the application of orthodontic forces to teeth. Hamersky et al. suggested that excessive and prolonged orthodontic forces when applied to teeth may result in loss of pulp vitality.

Laser Doppler flowmetry (LDF) by McDonald and Pitt Ford have reported a temporary decrease in pulpal blood flow (PBF). The decrease in PBF has been associated with a drop in the oxygen tension thereby increasing the possibility of cellular injury and apoptosis as determined by alterations in the expression of pulpal markers such as Aspartate Aminotransferase (AST) and alkaline phosphatase (ALP). However, results by Barwick and Ramsay and Brodin et al. reported no significant effect of a orthodontic forces (intrusive and/or extrusive) on PBF. Studies have also reported that application of orthodontic forces on teeth for certain periods of time increase the expression of various growth factors (GFs), such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2) and transforming growth factor beta (TGF-β) in pulpal tissues, which in turn contribute to angiogenesis.

High levels of inflammatory mediators, such as interleukin (IL)-6, IL-1β tumour necrosis factor alpha and receptor activator of nuclear factor kappa B have been identified in pulpal tissues of teeth exposed to orthodontic forces. Levels of inflammatory mediators in the gingival crevicular fluid have also been reported to be significantly elevated during orthodontic therapy. Therefore, from a clinical perspective, it is hypothesized that long-term application of orthodontic forces jeopardizes pulp vitality. Furthermore, pulpal necrosis (PN) has also been reported after the induction of orthodontic forces such as intrusion, extrusion and retraction. It is tempting to speculate that the magnitude of pulpal inflammation or injury is directly proportional to the degree of orthodontic force applied on the teeth.

The aim of the present study was to systematically review the influence of orthodontic force on human dental pulp.

2. Materials and methods

2.1. Focused question

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed according to the PICO (Participants, Interventions, Control, Outcomes) principle. The addressed focused question was “Do orthodontic forces affect human dental pulp?”

(P) Participants: It was essential for participants to have undergone orthodontic treatment.

(I) Types of interventions: The interventions of interest were orthodontic forces (such as intrusion, extrusion, tipping, arch expansion and retraction).

(C) Control intervention: Teeth, which were either not subjected to orthodontic forces or pulp tissues which treated with antibodies other than those used in the test-groups, were considered as controls.

(O) Outcome measures: Human pulpal response to orthodontic forces.

2.2. Search protocol

In order to identify studies relevant to the PICO question, the MEDLINE (OVID) database, the EMBASE database, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Knowledge, The Cumulative Index to Nursing and Allied Health Literature and Google-Scholar databases were electronically searched for available data. Databases were searched from 1954 up to and including August 2014 using different combinations of the following key words: “orthodontic force”; “human dental pulp”; “reaction” and “tooth movement”. Titles and abstracts of studies identified using the above-described protocol were screened by two authors (FJ AAK and GER) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read by authors (FJ AAK and GER) and independently evaluated in accordance with the following eligibility criteria: clinical studies, application of orthodontic force on teeth and assessment of pulp tissues. Kappa scores (Cohen’s kappa coefficient) were employed to determine the level of agreement between the two reviewers. Letters to the Editor, historic reviews, commentaries, experimental (animal) studies and case-reports were excluded. Hand-searching of potentially relevant original and review articles was also performed. This was done to identify any studies that could
have remained unidentified in the previous step and checked for disagreement via discussion among the authors. Articles available online in electronic form ahead of print were considered eligible for inclusion. Fig. 1 summarizes the literature search strategy according to the PRISMA guidelines. The pattern of the present systematic review was customized to mainly summarize the relevant data.

2.3. Quality assessment

Three authors (FJ, AAK and GER) independently assessed the methodological quality of the included studies according to a grading system developed by the Swedish Council on Technology Assessment in Health Care.25 The following criteria were used for assessing the methodological quality of the studies included in the present review:

- Grade A (High)—A randomized controlled trial or prospective study, composed of a well-defined control group; defined diagnosis and end points; and diagnostic reliability tests and reproducibility tests described (all criteria should be met; otherwise, grade C).
- Grade C (Low)—One or more of the following settings are encountered: poorly defined patient material, unclear diagnosis and end points and large attrition of the samples.

2.4. Level of evidence

For each study included in the present review, level of evidence was judged in accordance with the following scale26:

- Strong Scientific Support (Evidence Grade 1)—Conclusion is based on at least 2 studies with level A-evidence. Studies with opposite conclusions may lower the evidence grade.
- Moderately Strong Support (Evidence Grade 2)—Conclusion is based on 1 study with strong evidence (A) and at least 2 with moderately strong evidence (B). Studies with opposite conclusions may lower the evidence grade.
- Limited Scientific Support (Evidence Grade 3)—Conclusion is based on at least 2 studies with moderately strong evidence (B). If studies contradicting the conclusion exist, the scientific basis is judged as contradictory or insufficient.
• Inconclusive Scientific Support (Evidence Grade 4)—If studies fulfilling the evidence criteria are lacking, the scientific basis for conclusion is considered insufficient.

3. Results

3.1. Effect of orthodontic forces on pulpal blood flow

Six studies\(^4\)\(^,\)\(^8\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^27\)\(^,\)\(^28\) addressed the effect of orthodontic forces on PBF (Table 1). The numbers of study participants ranged between 6 and 21 patients. In 5 studies,\(^4\)\(^,\)\(^8\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^27\)\(^,\)\(^28\) orthodontic forces were applied to achieve extrusion, intrusion and retraction of premolar teeth; whereas in the study by Babacan et al.,\(^27\) rapid maxillary expansion (RME) was performed. Five studies\(^4\)\(^,\)\(^8\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^28\) reported the orthodontic force applied to teeth which ranged between 0.5 Newton (N) and 44 N. In one study\(^27\) the amount of orthodontic force applied to perform RME was not reported. In these studies,\(^4\)\(^,\)\(^8\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^27\)\(^,\)\(^28\) the duration for which orthodontic forces were applied ranged between 20 s and 152 days. Three studies\(^4\)\(^,\)\(^13\)\(^,\)\(^28\) reported that intrusive orthodontic forces temporarily reduce PBF; and in the study by Barwick and Ramsay\(^2\) PBF remained unaltered during all orthodontic treatment sessions. In the study by Babacan et al.,\(^27\) PBF increased in the first week of RME and decreased significantly by the third week of RME.

3.2. Influence of orthodontic forces on the cellular responses of the human dental pulp

Twenty studies\(^1\)\(^,\)\(^5\)\(^,\)\(^7\)\(^,\)\(^9\)\(^,\)\(^11\)\(^,\)\(^14\)\(^,\)\(^16\)\(^,\)\(^21\)\(^,\)\(^29\)\(^-\)\(^37\) reported the influence of orthodontic forces on human pulp cellular responses (Table 2). In 18 studies,\(^1\)\(^,\)\(^3\)\(^,\)\(^5\)\(^,\)\(^7\)\(^,\)\(^9\)\(^,\)\(^11\)\(^,\)\(^14\)\(^,\)\(^16\)\(^,\)\(^21\)\(^,\)\(^29\)\(^-\)\(^32\)\(^,\)\(^34\)\(^,\)\(^36\)\(^,\)\(^37\) orthodontic forces were applied on premolars and in 2 studies\(^33,\)\(^35\) teeth exposed to orthodontic forces were not reported. The magnitude of orthodontic force ranged between 0.3 N and 6 N for durations ranging between 21 min and 84 days. Intrusion, extrusion and tipping movements were performed in 8,\(^3\)\(^,\)\(^11\)\(^,\)\(^30\)\(^,\)\(^31\)\(^,\)\(^34\)\(^,\)\(^37\)\(^-\)\(^32\)\(^,\)\(^36\) and 3\(^,\)\(^35,\)\(^36\) studies, respectively. In one study,\(^2\) both intrusion and extrusion forces were applied on premolars. Results by Lazzaretti et al.\(^37\) showed that intrusive orthodontic forces caused vascular changes in the pulp tissue and also increased the presence of fibrosis and the number of pulp calcifications. Four studies\(^1\)\(^,\)\(^1,\)\(^2,\)\(^21,\)\(^36\) reported orthodontic forces to cause vacuolization and disruption of osteoblasts in pulp tissues but without necrosis. Results by Caviedes-Bucheli et al.\(^3\) reported orthodontic forces of 0.56 N and 2.24 N to increase the pulp expression of calcitonin gene-related peptide (CGRP) as compared to the control group. Three studies\(^1\)\(^,\)\(^14,\)\(^16\) reported orthodontic forces to increase the expression of GFs in pulp tissues. Perinetti et al.\(^9\) and Veberiene et al.\(^11\) reported orthodontic forces to increase pulpal AST activity. In one study,\(^34\) pulpal AST levels were comparable with and without mechanical load application. Kucukkeles and Okar\(^11\) showed vascular degeneration in the pulps of orthodontically treated teeth; Derringer et al.\(^11\) reported angiogenesis to be significantly higher in orthodontically-treated teeth and control teeth. In 4 studies,\(^35,\)\(^33,\)\(^35,\)\(^36\) orthodontic forces were reported to cause minor disturbances in pulpal circulation. Concentration of substance P was negatively correlated with the magnitude of orthodontic force in the study by Parris et al.\(^35\) and Subay et al.\(^29\) reported no evidence of inflammatory reactions in the pulps of orthodontically moved teeth (Table 2).

3.3. Influence of orthodontic forces on the pulpal response in traumatized teeth

Four studies\(^38\)\(^-\)\(^41\) investigated the pulpal reaction of orthodontic forces on traumatized teeth. Two studies\(^38,\)\(^40\) reported the magnitude of orthodontic force applied on traumatized teeth, which were 0.2 N and 0.15 N. In these studies,\(^38\)\(^-\)\(^41\) duration of orthodontic treatment in previously traumatized teeth ranged between 22.4 and 54 months. All studies\(^38\)\(^-\)\(^41\) reported PN to be more frequent when orthodontic treatment was performed in previously traumatized teeth as compared to non-traumatized teeth (Table 3).

3.4. Quality assessment

Most of the studies were graded as “moderate to low” mainly because of their methodological quality (Tables 1–3). Low grading was mainly based on no randomized assignment to experimental and control treatment groups and no description of reliability tests.

4. Discussion

Since grading evidence is a complicated issue, we avoided using a scale that allocates points to individual quality items because this approach has proved to be inadequate.\(^42\) To our knowledge from indexed literature, a gold standard quality assessment tool is still missing.\(^33,\)\(^44\) Lack of randomized controlled trials and a disharmony in the study protocols are limitations of the studies included in this review. These factors may be held responsible for the moderate to low grading of most studies included in this review.

In a systematic review published in the year 2012, von Bohl et al.\(^45\) reported that there is no conclusive scientific evidence for a relation between force level and dental pulp tissue reaction in humans. Authors of this systematic review emphasized that there is a scarcity of long-term results regarding pulpal injury occurring as a result of orthodontic treatment.\(^45\) Since there is a debate among clinicians regarding the optimal orthodontic forces that teeth can endure without experiencing massive pulp inflammation and/or necrosis, we were tempted to re-search indexed literature to identify additional studies (published after the year 2012) that assessed the association between orthodontic force and its effects on human dental pulp tissues. Moreover, in the systematic review by von Bohl et al.\(^45\) the effect of orthodontic forces on human dental pulp were assessed in non-traumatized teeth only; however, in the present systematic review, we reviewed pertinent literature regarding the influence of orthodontic forces on human dental pulp tissues of non-traumatized and traumatized teeth.

In the present study, a systematic review of pertinent literature was performed in an attempt to assess the effect of orthodontic forces on dental pulp tissues. It was hypothesized that long-term application of orthodontic forces jeopardizes
Table 1 – Studies on the effect of orthodontic forces on pulpal blood flow.

<table>
<thead>
<tr>
<th>Authors et al.</th>
<th>Design</th>
<th>Study subjects</th>
<th>Type of treatment</th>
<th>Control group</th>
<th>Force applied (N)</th>
<th>Duration of force</th>
<th>Pulpal blood flow measured by</th>
<th>Results</th>
<th>Quality grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sano et al.4,7</td>
<td>Prospective</td>
<td>13</td>
<td>Intrusion</td>
<td>13 vital teeth without orthodontic force application</td>
<td>0.5, 1, 2</td>
<td>14 days</td>
<td>LDF</td>
<td>Intrusive forces temporarily reduced PBF. PBF changes returned to normal at the end of force application</td>
<td>B</td>
</tr>
<tr>
<td>McDonald and Pitt Ford8,*</td>
<td>Prospective</td>
<td>10</td>
<td>Canine retraction</td>
<td>10 vital teeth without orthodontic force application</td>
<td>0.5</td>
<td>Up to 4 days</td>
<td>LDF</td>
<td>PBF increased up to 48 h of load application but returned to preload values within 72 h</td>
<td>B</td>
</tr>
<tr>
<td>Barwick and Ramsay12,1</td>
<td>Prospective</td>
<td>8</td>
<td>Intrusion</td>
<td>None</td>
<td>0.75, 1.25, 5, 44</td>
<td>112 days</td>
<td>LDF</td>
<td>Baseline PBF remained unchanged during all treatment sessions</td>
<td>A</td>
</tr>
<tr>
<td>Brodin et al.13,1</td>
<td>Prospective</td>
<td>6</td>
<td>Intrusion and extrusion</td>
<td>None</td>
<td>0.5</td>
<td>152 days</td>
<td>LDF</td>
<td>Extrusion had no significant effect on PBF. Intrusion reduced the pulpal blood flow by 20% during the first minute only</td>
<td>C</td>
</tr>
<tr>
<td>Babacan et al.27,1</td>
<td>Prospective</td>
<td>21</td>
<td>RME</td>
<td>None</td>
<td>NR</td>
<td>Up to 84 days</td>
<td>LDF</td>
<td>PBF increased in the 1st week and decreased significantly by the 3rd week of RME</td>
<td>B</td>
</tr>
<tr>
<td>Ikawa et al.28,*</td>
<td>Prospective</td>
<td>17</td>
<td>Intrusion</td>
<td>None</td>
<td>0.5, 1, 5</td>
<td>20 s</td>
<td>LDF</td>
<td>Brief intrusive forces temporarily reduced PBF</td>
<td>B</td>
</tr>
</tbody>
</table>

LDF, laser Doppler flowmetry; NR, not reported; OT, orthodontic treatment; PBF, pulpal blood flow; RME, rapid maxillary expansion.

* High risk of bias.
† Low risk of bias.
<table>
<thead>
<tr>
<th>Authors et al.</th>
<th>Design</th>
<th>Subjects</th>
<th>Number of teeth</th>
<th>Type of movement</th>
<th>Force applied (N)</th>
<th>Control group</th>
<th>Duration of force</th>
<th>Pulpal response</th>
<th>Conclusion</th>
<th>Quality grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazzaretti et al.</td>
<td>Prospective</td>
<td>17</td>
<td>34</td>
<td>Intrusion</td>
<td>0.58</td>
<td>No orthodontic force applied</td>
<td>21 days</td>
<td>There was a significant increase in the number of pulpal nodules in the elements with no difference in the number of blood vessels between the groups</td>
<td>Intrusive orthodontic forces caused vascular changes in the pulpal tissue and also increased the presence of fibrosis and the number of pulp calcifications</td>
<td>B</td>
</tr>
<tr>
<td>Han et al.</td>
<td>Prospective</td>
<td>27</td>
<td>54</td>
<td>Intrusion</td>
<td>0.5, 3</td>
<td>No orthodontic force applied</td>
<td>Up to 84 days</td>
<td>In both force groups, odontoblasts disruption, vacuolization and moderate vascular congestion occurred but without PN</td>
<td>Intrusive orthodontic forces do not jeopardize pulp vitality</td>
<td>C</td>
</tr>
<tr>
<td>Ramazanza-deh et al.</td>
<td>Prospective</td>
<td>26</td>
<td>52</td>
<td>Intrusion and extrusion</td>
<td>0.25, 0.74</td>
<td>No orthodontic force applied</td>
<td>Up to 21 days</td>
<td>In both force groups, odontoblasts disruption, vacuolization and moderate vascular congestion occurred but without PN</td>
<td>Histologic pulpal changes between baseline and 21 days showed no statistically significant difference</td>
<td>C</td>
</tr>
<tr>
<td>Caviedes-Bucheli et al.</td>
<td>Prospective</td>
<td>NR</td>
<td>30</td>
<td>Extrusion</td>
<td>0.56, 2.24</td>
<td>No orthodontic force applied</td>
<td>1 day</td>
<td>In both force groups, pulpal CGRP expression was increased compared to the control group</td>
<td>Orthodontic forces increase CGRP expression in human dental pulp</td>
<td>C</td>
</tr>
<tr>
<td>Derringer and Linden</td>
<td>Prospective (In vitro)</td>
<td>20</td>
<td>80</td>
<td>Extrusion</td>
<td>0.5–1</td>
<td>Use of antibodies other than those for VEGF, FGF2 and TGFbeta</td>
<td>14 days</td>
<td>VEGF, FGF-2, PDGF and TGF-β are released following orthodontic force application</td>
<td>Growth factors are expressed in the pulp of teeth exposed to mechanical load</td>
<td>C</td>
</tr>
<tr>
<td>Hamersky et al.</td>
<td>Prospective</td>
<td>17</td>
<td>68</td>
<td>Extrusion</td>
<td>At least 0.6 N</td>
<td>No orthodontic force applied</td>
<td>3 days</td>
<td>Short-term orthodontic forces caused pulpal tissue hypoxia</td>
<td>Orthodontic forces cause biochemical and biologic pulpal tissue alterations</td>
<td>C</td>
</tr>
<tr>
<td>Perinetti et al.</td>
<td>Prospective</td>
<td>17</td>
<td>17</td>
<td>Tipping</td>
<td>0.3–0.9</td>
<td>No orthodontic force applied</td>
<td>7 days</td>
<td>Mean AST activity and EPT values were significantly higher in teeth exposed to mechanical load compared to controls</td>
<td>Application of mechanical load to teeth can cause metabolic changes in the pulp</td>
<td>B</td>
</tr>
<tr>
<td>Veberiene et al.</td>
<td>Prospective</td>
<td>21</td>
<td>42</td>
<td>Intrusion</td>
<td>0.61</td>
<td>No orthodontic force applied</td>
<td>7 days</td>
<td>Mean AST activity and EPT values were significantly higher in teeth exposed to mechanical load compared to controls</td>
<td>Application of mechanical load to teeth can cause metabolic changes in the pulp</td>
<td>A</td>
</tr>
<tr>
<td>Derringer and Linden</td>
<td>Prospective (In vitro)</td>
<td>10</td>
<td>10</td>
<td>Extrusion</td>
<td>0.5–1</td>
<td>Co-cultures without anti-h EGF</td>
<td>14 days</td>
<td>Orthodontic forces stimulate the release of EGF in pulp tissues</td>
<td>EGF released following orthodontic force application plays a role in pulp angiogenic response</td>
<td>B</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Group</td>
<td>Force Applied</td>
<td>Duration</td>
<td>Findings</td>
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<tr>
<td>Derringer et al.</td>
<td>Prospective</td>
<td>NR</td>
<td>30</td>
<td>Tipping</td>
<td>0.5–1</td>
<td>There were significantly greater numbers of microvessels in orthodontically treated teeth than control teeth.</td>
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<td></td>
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<td></td>
<td>No orthodontic force applied</td>
<td>5 days</td>
<td>VEGF, FGF-2, PDGF and TGF-β are released following orthodontic force application.</td>
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<td></td>
<td>Dilated and constricted blood vessels, odontoblastic degeneration, vacuolization and oedema of the pulp tissues, and fibrotic changes occurred in pulpal tissues.</td>
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</tr>
<tr>
<td>Derringer and Linden</td>
<td>Prospective</td>
<td>18</td>
<td>18</td>
<td>Extrusion</td>
<td>0.5–1</td>
<td>Growth factors are expressed in the pulp of teeth exposed to mechanical load.</td>
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<tr>
<td>Mostafa et al.</td>
<td>Prospective</td>
<td>18</td>
<td>36</td>
<td>Extrusion</td>
<td>~0.5</td>
<td>Growth factors play a role in pulpal angiogenesis.</td>
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<td></td>
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<td></td>
<td>No orthodontic force applied</td>
<td>Up to 28 days</td>
<td>Orthodontic forces can cause temporary inflammation and fibrosis in pulpal tissues.</td>
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<tr>
<td>Subay et al.</td>
<td>Prospective</td>
<td>15</td>
<td>40</td>
<td>Extrusion</td>
<td>0.75</td>
<td>There was no evidence of inflammatory reactions and/or reparative dentine formation in all teeth.</td>
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<td></td>
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<td></td>
<td>No control group (All teeth were extruded)</td>
<td>10 days, 40 days</td>
<td>Vascular degeneration occurred in the pulps of orthodontically-treated teeth.</td>
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<tr>
<td>Raiden et al.</td>
<td>Prospective</td>
<td>20</td>
<td>40</td>
<td>Intrusion</td>
<td>1.5</td>
<td>Histologic results showed alterations in predentine, calcium deposition, fibrohyalinosis, congestion, inflammation and haemorrhage</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>No orthodontic force applied</td>
<td>15–20 days</td>
<td>Extrusive forces do not cause significant pathological changes in pulp tissues.</td>
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<tr>
<td>Kucukkeles and Okar</td>
<td>Prospective</td>
<td>2</td>
<td>4</td>
<td>Intrusion</td>
<td>1.5</td>
<td>Intrusive forces jeopardize pulp vitality by causing vascular degeneration.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No orthodontic force applied</td>
<td>90 days</td>
<td>Orthodontic forces and pulpal ir-ME and ir-SP concentrations are interlinked.</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Parris et al.</td>
<td>Prospective</td>
<td>20</td>
<td>80</td>
<td>Tipping</td>
<td>1.2, 1.4, 1.5, 1.8, 2, 2.1, 2.15, 2.3, 2.45 and 6</td>
<td>Concentrations of ir-ME and ir-SP each correlated negatively with the magnitude of the orthodontic force</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No orthodontic force applied</td>
<td>21–78 min</td>
<td>Orthodontic forces cause biochemical and biologic pulpal tissue alterations.</td>
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<td>Orthodontic forces do not influence pulpal AST activity and EPT values.</td>
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<td>Stenvik et al.</td>
<td>Prospective</td>
<td>NR</td>
<td>NR</td>
<td>Extrusion</td>
<td>1–2</td>
<td>Minority reactions related to the pulpal circulatory system can occur.</td>
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<td></td>
<td>No orthodontic force applied</td>
<td>7–14 days</td>
<td>Mean pulpal AST levels and EPT values similar with and without mechanical load application.</td>
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<tr>
<td>Veberiene et al.</td>
<td>Prospective</td>
<td>13</td>
<td>26</td>
<td>Intrusion</td>
<td>0.65</td>
<td>Minor reactions related to the pulpal circulatory system can occur.</td>
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<td>No orthodontic force applied</td>
<td>14 days</td>
<td>Orthodontic forces cause biochemical and biologic pulpal tissue alterations.</td>
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<td>Stenvik and Mjor</td>
<td>Prospective</td>
<td>NR</td>
<td>25</td>
<td>Intrusion</td>
<td>0.5–2.5</td>
<td>Vascularization of the pulp tissue and circulatory disturbances occurred.</td>
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<td></td>
<td>No orthodontic force applied</td>
<td>5–28 days</td>
<td>Orthodontic forces cause biochemical and biologic pulpal tissue alterations.</td>
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<tr>
<td>Stenvik and Mjor</td>
<td>Prospective</td>
<td>NR</td>
<td>NR</td>
<td>Intrusion</td>
<td>0.35–2.5</td>
<td>Vacuolization of the pulp tissue and circulatory disturbances occurred.</td>
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ALP, alkaline phosphatase; AST, aspartate aminotransferase; Control, mechanical load not applied; CGRP, calcitonin gene-related peptide; EGF, epidermal growth factor; EPT, electric pulp testing; ir-ME, immunoreactive methionine enkephalin; ir-SP, immunoreactive substance P; NR, not reported; PM, premolars.

* High risk of bias.

† Low risk of bias.
pulp vitality; however, due to a variation in the magnitude and duration of orthodontic forces exerted on teeth in the studies included, it is exigent to scientifically validate the aforementioned hypothesis. Amongst the studies[^8,^12,^13,^27,^28] which assessed the influence of orthodontic forces on PBF, magnitude and duration of orthodontic force applied varied considerably (0.5 N–44 N and 20 s–152 days, respectively). It is allured that a low orthodontic force (for instance 0.5 N) exerted on teeth for a few minutes causes minor or no change in PBF than the same force being applied for longer durations. However, scientific evidence in this regard is still missing. Likewise, it may also be argued that long-term application of intense orthodontic forces to teeth influences PBF to a significantly greater extent than when the same forces are applied for a short duration. Therefore, it is difficult to contemplate a direct association between PBF and magnitude of orthodontic force. It has also been reported that the effects of orthodontic forces on PBF are associated with various factors including patients’ age, size of apical foramen, dentinogenic activity and not merely on the magnitude and duration of the force applied[^7,^12]. None of the studies[^8,^12,^13,^27,^28] that fulfilled the eligibility criteria assessed the influence of size of apical foramen on PBF in the study groups. It is however pertinent to mention that in these studies[^8,^12,^13,^27,^28], age of the study participants was also markedly incoherent. For example, in the study by Sano et al.,[^1] individuals with age ranging between 27 and 31 years were included; whereas Babacan et al.,[^27] assessed the effect of orthodontic forces on PBF among 10–15 year old patients. Further clinical trials with standardized parameters (particularly magnitude and duration of force application) are needed to clarify the effect of orthodontic forces on PBF.

CGRP is a potent vaso-dilatory peptide that is found in approximately 50% of the neurons of the trigeminal system.[^36,^47] Substance P (SP) is mediator of neurogenic inflammation and causes vasodilatation by direct action over endothelial cells and indirect mast cell stimulation for histamine release, a dual effect shared with CGRP.[^48] These molecules are capable of provoking a tolerable discomfort among patients following the activation of orthodontic intrusive forces.[^39] In the study by Caviedes-Bucheli et al.,[^3] orthodontic extrusion was associated with an increased expression of CGRP in the pulp. However, in this study,[^3] CGRP levels were measured after 24 h of force application. Likewise, Parris et al.,[^32] measured pulpal SP levels after 0.3–1.3 h after force application. To assess the significance of the results reported by Caviedes-Bucheli et al.,[^3] and Parris et al.,[^32] further studies with long-term application of orthodontic force are warranted.

Angiogenesis is defined as the process of development of new blood vessels from preexisting microvasculature. GFs may act either directly or indirectly to regulate the endothelial cell function and expression of other GFs by different cell types.[^50] Studies[^5,^14-^16] have used neutralizing antibodies (anti-VEGF, FGF2, PDGF, TGF-β and EGF) to investigate the presence of a combination of GFs in the human dental pulp during orthodontic force application. The neutralizing antibodies significantly reduced the number of microvessels in the evaluated in vitro cultures thereby confirming the presence of GFs in the pulp during orthodontic movement. This is an explanation for the study by Derringer et al.,[^15] in which the authors showed the presence of significantly greater numbers
of micro-vessels in orthodontically treated teeth than control teeth. Furthermore, in an experimental study on mice, Kaku et al. investigated the effect of recombinant human VEGF (rhVEGF) on the differentiation of osteoclasts during experimental tooth movement. The results suggested that local administration of rhVEGF enhances the number of osteoclasts and may increase the rate of orthodontic tooth movement.

It is known that pulpal fibroblasts and odontoblasts synthesize and release ALP. Therefore, it is hypothesized that application of orthodontic force on these cells reduces their ALP expression. AST is an essential mediator of inflammatory processes and is expressed in high concentrations in pulp inflammatory conditions.26,27,28 Therefore, there is no change in the symptoms of pulpitis when orthodontic treatment is performed. However, due to a limited number of studies that have assessed pulpal AST and ALP levels during orthodontic force application, the significance of these enzymes affecting pulpal tissues remains veiled.

A critical factor that could have biased the outcome of the studies included in the present review is their design and methodology. For example, in the studies2,4,8,12,13,27,28 that assessed the influence of orthodontic forces on human dental pulp, magnitude of force applied to teeth varied dramatically among as well as between the studies (0.5–44 N). Similarly, among studies that assessed the cellular response of dental pulp cells to orthodontic forces1,2,3,4,5,6,7,8,10,11,21,23,29–34, the amount of forces used in these studies also varied (0.3–6 N). It is therefore tempting to speculate that an intense orthodontic force (such as 44 N) when applied to teeth for prolonged durations cause pulpal damage to a greater extent as compared to when a low magnitude force is applied to teeth or the same time frame or even longer. Furthermore, regarding the 4 studies35–41 in which pulpal response to orthodontic treatment in previously traumatized teeth was assessed; the results showed loss of pulpal vitality following the application of orthodontic force. It is possible that the traumatic insult (such as periodontal trauma) itself may have damaged the dental pulp tissues even before the application of orthodontic force. Therefore, an in-depth assessment involving parameters such as expression of GFs, AST and ALP may yield pertinent information regarding the pulpal response to orthodontic forces in previously traumatized teeth. It is therefore exigent to depict a relationship between force level and the variables investigated in the studies included in the present systematic review.

5. Conclusion

There is insufficient scientific evidence to prove that orthodontic forces jeopardize the human dental pulp in terms of reducing PBF and irreversible alterations in pulpal cellular response. However, a history of dental trauma maybe considered a risk factor for loss of pulpal vitality during orthodontic treatment.

Funding

The authors declare that there was no external source of funding for the present study.

Competing interest

The authors declare that they have no conflict of interest.

Ethical approval

Not required.

Acknowledgement

The authors extend their appreciation to the Research Center, College of Applied Medical Sciences and Deanship of Scientific Research at King Saud University for funding this research. The authors also thank the Visiting Professor Program at King Saud University, Saudi Arabia for supporting this research project.

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