Review Article

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

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Introduction: Orthodontic force application stimulates a biological response of the dental pulp. The pulpal response to orthodontic force involves cell damage, inflammation, and wound healing. The pulpal reparation rate, pulpal obliteration by secondary dentin formation, root resorption, and pulpal necrosis have all been associated with orthodontic treatment

Objective: The aim of this systematic review was to investigate the influence of orthodontic force on human pulpal reaction.

Methods: Electronic search was made until July 15, 2016. Additional studies were identified by hand search of reference list of relevant articles from the electronic search. Search terms were the following keywords: “orthodontic force”, “tooth movement”, orthodontic treatment”, “pulpal blood flow”, “vitality loss”, “necrosis”, “pulpal reaction”, “pulpal cellular response”, “pulpal alteration”, and “inflammatory response”. Two independent reviewers assessed the eligibility for inclusion, extracted the data, apply quality indicators, and grade level of evidence.

Results: Thirty-seven studies matched the inclusion criteria. The outcome concerned the effect of orthodontic force on pulpal blood flow (PBF) in 9 studies, the influence of orthodontic force on human pulpal cellular responses in 23 studies, and the pulpal reaction of orthodontic force on previously traumatized teeth in 5 studies.

Conclusion: There is a lack of high-quality scientific evidence to prove that orthodontic forces affect in alteration of human dental pulp. However, applying orthodontic force on traumatized teeth is considered a risk factor for vitality loss of dental pulp.

Keywords: dental pulp, human, orthodontic force, pulpal blood flow, pulpal reaction, tooth movement,

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Introduction

After orthodontic tooth movement, there is a series of changes in dental pulp. Because pulpal tissue is located in a rigid dentinal cover, its vitality depends on blood vessels passing through the apical foramen. Changes in pulpal blood flow or vascular tissue pressure can endanger the health of dental pulp.[1] The pulpal response to orthodontic force involves cell damage, inflammation, and wound healing. Force application from orthodontic tooth movement evokes an acute inflammatory response in the PDL, which is presented by vasodilatation and migration of leukocytes out of the capillaries. [2] These migratory cells produce various local biochemical signal molecules and cytokines, which interact with the population of native periodontal cells. A day or 2 later, the acute phase is replaced by a chronic process involving fibroblasts, endothelial cells, osteoblasts, and alveolar bone marrow cells. During this phase, leukocytes continue to migrate into strained periodontal tissues and modulate the remodeling process. [3,4]

Many researchers have examined the effect

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of orthodontic forces on the oral tissues. [5-9] The majority of these researchers were concern with the reactions of the alveolar bone and periodontal ligament, [7-9] while fewer have dealt with pulpal changes. [5,6]

There are various methods to evaluate the pulpal response after orthodontic force application. Human pulpal blood flow has been shown with the use of laser Doppler flowmetry (LDF), which is a noninvasive method that can repeatedly measure pulpal blood flow (PBF) without causing damage to the pulp. [10] Moreover, electrical pulp testing (EPT) and thermal pulp testing provide simple methods of acquiring information, which is helpful in evaluating the sensibility of a tooth. [11]

Furthermore, the histologic study have reported depression of pulp tissue respiration, vacuolization, circulatory disturbances, hemorrhage, fibro-hyalinosis and even necrosis as the major pulpal changes following orthodontic force application. [12-14] The prolonged and excessive orthodontic forces may result in loss of pulp vitality. [5]

Orthodontic treatment of traumatized teeth in several studies showed root resorption. [15-17] Only few studies have been made to analyze the effect of orthodontic tooth movement on the pulpal vitality of previously traumatized teeth. There was the incidence of pulp necrosis on previously traumatized teeth after orthodontic force application. [18,19]

Understanding the effects of orthodontic force on the pulp is importance, especially because altered pulpal reparation rate, pulpal obliteration by secondary dentin formation, internal root resorption, and pulpal necrosis have all been associated with orthodontic treatment. Therefore, the purpose of this systematic review was to investigate the relationship between orthodontic force and pulpal reaction in both traumatized and non-traumatized humans' teeth. The results of this systematic review could help orthodontists to understand whether the pathology of the pulp, which might occur in response to force-induced therapeutic tooth movement, is transient or permanent and could help them in determining long-term prognosis of the teeth.

Materials and methods

Focusing on this question, "Does orthodontic force affect to the reaction of human dental pulp?", this systematic review was undertaken by following the guidelines provided by the PRISMA statement. [20]

Data sources and searches

Electronic searches were conducted for published studies up to July 2016. The databases searched are shown in Table 1. The reference lists of the articles eligible for inclusion in this investigation were also manually reviewed. Citations of articles published in journals, dissertations, and conference proceedings were located by searching several electronic databases, using a search strategy appropriately adjusted for each individual database (Table 1).

No restrictions were applied concerning publication year, language, or status. Grey literature was not excluded from our search. If additional information was needed, the authors were contacted. Hand-searching of potentially relevant original and review articles was also performed. This was done to identify any studies that could have remains unidentified in the previous step and checked for disagreement via discussion among the authors.

Study selection

Two review authors (K.T. and K.N.) independently screened all titles and abstracts obtained from the database searches. Duplicate records, such as published articles also presented in conferences, studies with multiple publications, and dissertations also published as journal articles, were excluded. The same authors reviewed the

full texts of the potentially relevant titles and abstracts against the inclusion criteria. The eligibility of the trials was assessed independently. Any disagreement was resolved by consultation with the third and the fourth author (S.L. and N.T.) until a final consensus was achieved. Appropriate studies to be included in this systematic review fulfilled specific predefined inclusion criteria; only randomized controlled clinical trials (RCTs), prospective and retrospective controlled clinical trials (CCTs), and prospective cohort studies were included in current investigation (Table 2).

Data extraction

Two reviewers (K.T. and K.N.) independently extracted relevant data in a pre-designed collection form. Any disagreement was resolved by discussion with the third and the fourth author (S.L. and N.T.) until a final consensus was achieved.

Quality assessment

Two reviewers (K.T. and K.N.) evaluated independently the methodological quality of the included studies according to a grading system developed by the Swedish Council on Technology Assessment in Health Care, [21] which was based on the criteria for assessing study quality from the Centre for Reviews and Disseminations in York, United Kingdom. [22] The methodological quality criteria are listed as follows.

Grade A (High) – Randomized controlled trial or prospective study is composed of a well-defined control group; defined diagnosis and end points; diagnostic reliability tests and reproducibility tests described; and blinded outcome measurements (all criteria should be met).

Grade B (Moderate) – Cohort study or retrospective case series is composed of a defined control or reference group; defined diagnosis and end points; and diagnosis reliability tests and reproducibility tests described (all criteria should be met; if not, grade C).

Grade C (Low) – one or more of the following conditions are found: large attrition of the sample, unclear diagnosis and end points, and poorly defined patient material.

Table 1. The electronic databases searched, the search strategies used, and the corresponding results

Electronic database	Search strategy used	Extend of search	Hits
MEDLINE searched via PubMed on 15 July 2016 http://www.ncbi.nlm.nih.gov/pubmed/	(orthodontic force OR tooth movement OR orthodontic treatment) AND (pulpal blood flow OR vitality loss OR necrosis OR pulpal reaction OR pulpal cellular response OR pulpal alteration or inflammatory response)	All fields	428
Web of Science on 15 July 2016 https://webofknowledge.com/	(orthodontic force OR tooth movement OR orthodontic treatment) AND (pulpal blood flow OR vitality loss OR necrosis OR pulpal reaction OR pulpal cellular response OR pulpal alteration or inflammatory response)	Topic	334
Scopus on 15 July 2016 http://www.scopus.com/	(orthodontic force OR tooth movement OR orthodontic treatment) AND (pulpal blood flow OR vitality loss OR necrosis OR pulpal reaction OR pulpal cellular response OR pulpal alteration OR inflammatory response)	All fields	40

Table 2. Eligibility criteria used in this systematic review

Criteria category	Inclusion criteria	Exclusion criteria
Subjects	• Studies investigating in human teeth with and without history of trauma	• Unhealthy subjects including in study
Interventions	• Studies investigating any orthodontic treatments except orthognathic surgery and any orthodontic treatments with surgical intervention	• Distraction osteogenesis • Auto tooth transplant • Debonding orthodontic braces
Outcomes	• Studies investigating on the effect of orthodontic forces on pulpal blood flow or pulpal responses	
Study design	• Randomized controlled clinical trials • Quasirandomized controlled clinical trials • Prospective controlled clinical trials • Retrospective controlled clinical trials • Prospective cohort studies • Cross-sectional surveys • Case-control observational studies • Studies on molecular biology, histology or genetics • Full text only	• Prospective uncontrolled clinical trials • Retrospective uncontrolled clinical trials • Unsupported opinion of expert • Commentaries • Editor's choices • Books' abstracts • Narrative reviews • Systematic reviews • Meta-analyses • Animal studies • Replies to author/editor • Historic reviews • In vitro studies • Case series without a control • Case reports • Studies with missing English abstract or/and having no abstract at all • Abstract only (incompleteness of information) • Ongoing studies
Participants' characteristics		• Insufficient data • Inadequate sample size groups
Language	English language only	• Other languages (not English language)

Results

Effect of orthodontic forces on pulpal blood flow (PBF)

Nine studies reported the effect of orthodontic force on PBF (Table 3). Laser Doppler flowmetry was used in all of the studies to measure the PBF. Orthodontic force application had a significant effect on basal blood flow in every study. The number of study samples ranged between 8 and 30 patients. Types of orthodontic force were applied to achieve maxillary canine retraction in 1 study, intrusion of maxillary incisors in 5 studies, intrusion of maxillary first molars in 2 studies, and rapid maxillary expansion (RME) in 1

study. Eight studies [14,23-29] reported the orthodontic force applied to teeth ranged between 25 and 4,400 grams. Another study of RME did not report the amount of force. The duration for orthodontic force application ranged between 4 minutes and 6 months. Three studies [14,23,25] reported that intrusive force can reduce PBF temporarily, and the next three studies [24,26,27] found that decreasing of PBF after intrusive force application is a reversible effect. PBF decreased at day 3, continued to remain suppressed until 3 weeks, and it tended to return to baseline values in about 3 weeks. Moreover, Sabuncuoglu and Ersahan [28] found that after intrusion of incisors, PBF decreased significantly in 24 hours. Then, it continued to increase gradually in 3 days and 7 days, and finally returned to control level at 3 weeks. Sabuncuoglu and Ersahan [29] also reported that PBF underwent a significant decline at 24 hours after canine retraction, then returning to near-baseline levels within one month, and Babacan et al. [30] found that PBF increased in the first week, and decreased by the third week of RME because of separation of the median palatal suture. Then, PBF tended to return to baseline level after 3 months of retention.

Effect of orthodontic forces on the cellular responses of the dental pulp

There are 23 prospective studies reported the influence of orthodontic force on human pulpal cellular responses (Table 4). Patients' age ranges from 10 to 37 years. Types of orthodontic force included extrusion (8 studies), intrusion (7 studies), tipping (6 studies), and rapid palatal expansion (2 studies). All of them performed on premolar teeth. The magnitude of force ranged between 25 to 300 g for duration ranging between 21 minutes and 180 days. Almost all studies, including study of Veberiene et al., [31] reported even if orthodontic treatment can cause temporary metabolic changes in dental pulp, they are reversible. However, only one study [32] stated some of alterations, such as root anatomy and root resorption, were permanent in teeth which the root was not completed but pulp alteration, such as vacuolization, seemed to improve after removing intrusive force. Hamersky et al. [5] found that the orthodontic forces decrease pulpal respiration rate and increasing age causes a larger lowering rate. Han et al. [12] reported dental pulp still has vitality and no necrotic observed after intrusive treatment. Caviedes Bucheli et al. [33] reported CGRP expression increased in dental pulp of teeth submitted severe orthodontic forces. Four studies of Derringer [34-37] confirmed that extrusive forces stimulated angiogenic growth factor and subsequently increased numbers of microvessels in the pulp. However, Mostafa et al. [38] found circulatory disturbances, including vacuolization and edema of pulpal tissues.

Influence of orthodontic force on the pulpal responses in traumatized teeth

Five retrospective studies [18,19,39-41] on upper incisors investigated the pulpal reaction of orthodontic force on previously traumatized teeth (Table 5). Four studies [19,39-41] reported the type of tooth movement such as tipping, intrusion and extrusion. Three studies [19,39,40] reported the duration of orthodontic force application in previously traumatized teeth range from 3.2 to 7.2 months. All studies showed that there was a higher frequency of pulp necrosis of orthodontically treated previously traumatized teeth. [18,19,39-41] Incidence of pulp necrosis was especially found in teeth with fracture of enamel-dentine, teeth with subluxation, extrusion, lateral luxation and intrusion. [39] Moreover, traumatized teeth with total pulp obliteration had higher susceptibility to pulpal complication such as pulp necrosis during orthodontic intrusion than that without or with partial pulp obliteration. [19]

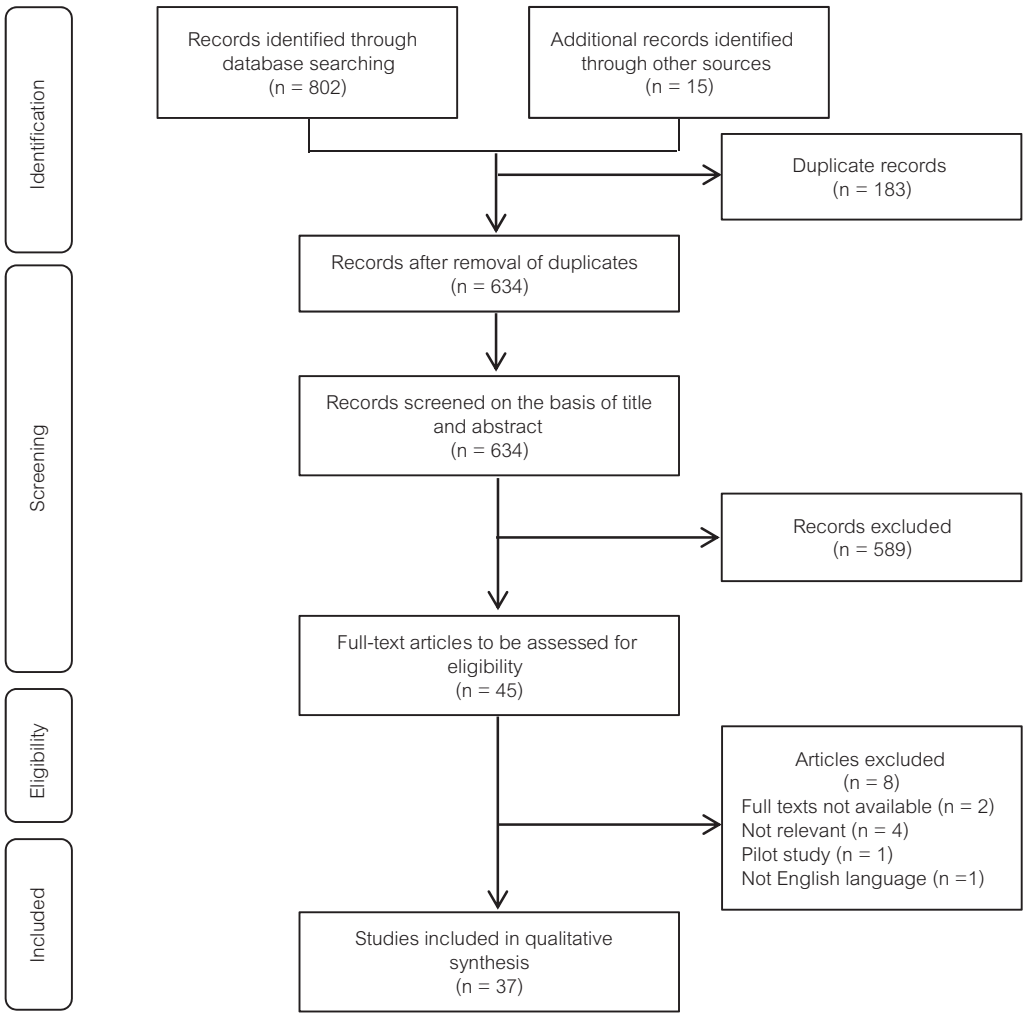

Figure 1. Flow diagram of the studies retrieved through the selection process

Discussion

Grading the evidence is complicate and numerous scales have been proposed to use. Using a scale to allocate points to individual quality items has proved to be inadequate. [53] From currently indexed literature, there is still no agreed goal standard quality assessment system. [54,55] Lack of high-quality scientific evidence such as randomized controlled trials studies and a disharmony in the study protocols are limitations of this systematic review. Most of the studies were graded moderate to low methodological quality (Table 3-5). Low grading was mainly based on no random assignment to experimental and control treatment groups and no description of reliability tests.

This systematic review was performed to evaluate the effect of orthodontic force on dental pulp tissues. It was hypothesized that long duration or high magnitude of orthodontic force is harmful for human pulp vitality. In the studies that assessed the influence of orthodontic force to PBF, there were various magnitude and duration of orthodontic force application (25 - 4,400 g and 4 minutes – 6 months, respectively). It is presumed that the application of light orthodontic force about 50 grams for a short duration might not cause any change or make just a minor change in PBF comparing with longer duration. However, there is no scientific evidence in the magnitude and duration of orthodontic force to PBF. Furthermore,

Table 3. Studies on the effect of orthodontic forces on pulpal blood flow.

Authors (Year)	Study subjects		No. of teeth		Type of force	Magnitude of force (g)	Duration of force (days)	Conclusion	Quality grade
	No.	Age range (Mean age) (years)	Experiment	Control					
Babacan et al. (2010)[30]	21	10-15 (13.1)	• 42 Upper central incisors • 28 Upper canines • 42 Upper first molars	Before expansion • 42 Upper central incisors • 28 Upper canines • 42 Upper first molars	RME (bonded type: upper first premolars to second molars) Measuring PBF on upper central incisors, canines and first molars	N/A (1 turn/day)	33.6 (4.8 ±0.7 weeks)	PBF increased in the first week, and decreased by the third week of RME. PBF tended to return to baseline level after 3 months of retention.	B
Barwick and Ramsay. (1996)[23]	8	25-49 (34.8)	8	8	Upper central incisor intrusion	• 76 ±8.5 • 123 ±3 • 499 ±41 • 4,400 ±257	0.0028 (4 minutes)	• Baseline PBF values did not differ among session. • Force level had no effect on PBF. • PBF drop after administration of the vasoconstrictor (L.A.).	A
Ikawa et al. (2001)[25]	17	24-29 (N/A)	17	17	Upper left central incisors intrusion	• 51 • 102 • 510	N/A	• Transient apical displacement (intrusive force) can reduce PBF temporarily. • Increase in intrusive force, PBF both with and without dam decreased significantly.	B
Ersahan et al. (2016)[24]	20	20-40 (27.6)	20	20	Upper first molars intrusion	• 125 • 250	180 (6 months)	• PBF decreased at 3 days and continued to remain suppressed until 3 weeks, after which a gradual trend of recovery was observed until 3 months, when the levels returned to near those measured before intrusion. • Despite slight regressive changes in pulpal tissue over the short term, PBF values tend to return to their initial levels within 3 months.	A

Table 3. con"t

Authors (Year)	Study subjects		No. of teeth		Type of force	Magnitude of force (g)	Duration of force (days)	Conclusion	Quality grade
	No.	Age range (Mean age) (years)	Experiment	Control					
Sabuncuoglu and Ersahan (2014)[26]	16	18-25 (21.7)	20	12	Upper first molar intrusion	100	180 (6 months)	Intrusive forces made short-term reduced PBF (3 days and 3 weeks) and it tended to return to baseline values, indicating that they are reversible effects.	B
Sabuncuoglu and Ersahan (2014)[27]	20	1-25 20.3)	E1:20 (light force) E2:20 (heavy force)	20	Upper central and lateral incisors intrusion	• 40 • 120	• 3 • 21 (3 weeks)	PBF values decreased in teeth subjected to 3 days of either light or heavy intrusive force, and tended to return to initial levels after 3 weeks.	B
Sabuncuoglu and Ersahan (2015)[28]	30	18-25 (21.7)	E1:40 (MIA) E2:40 (utility arches)	40	Upper central and lateral incisors intrusion	25	• 1 (24 hours) • 3 • 7 • 21 (3 weeks)	Mean PBF in experimental group decreased significantly in 24 hours, continued to increase gradually at 3 days and 7 days, and then returned to control level at 3 weeks.	B
Sabuncuoglu and Ersahan (2016)[29]	24	19-25 (21.91)	24	24	Maxillary canine retraction	100	• 1 (24 hours) • 3 • 7 • 30 (1 month) • 90 (3 months)	PBF underwent a significant decline at 24 hours after canine retraction, then returning to near-baseline levels within one month.	B
Sano et al. (2002)[14]	13	27-31 (N/A)	8	5	Upper left central incisors intrusion	• 50 • 99 • 101.97 • 203.94	6	PBF reduced during force application and followed by recovery to normal at the end.	B

No., Number; E, Experiment group; N/A, Non-available

Table 4. Studies on the influence of orthodontic force on the cellular responses of the dental pulp

Authors (Year)	Study subjects		No. of teeth		Type of force	Control group	Force applied (g)	Duration of force (days)	Pulpal response	Conclusion	Quality grade
	No.	Age range (Mean age) (years)	Experiment	Control							
Caviedes-Bucheli et al. (2011)[33]	N/A,	18-37 (N/A)	E1:10 (moderate force, 56 g) E2:10 (severe force, 224 g)	10	Premolars tipping and extrusion	No orthodontic force	56, 224	1	Increased CGRP expression in both severe- and moderate-force group (greater in severe-force) compared with control group	CGRP expression in human dental pulp increases when teeth are submitted to severe orthodontic forces.	C
Derringer et al. (1996)[35]	15	11-14 (N/A)	15	15	N/A, Fixed appliance at premolars	No orthodontic force	51-102	14	There were greater numbers of microvessels of culture in the pulp explants from orthodontically treated teeth compared with those from the pulps of control teeth.	There is an increase in angiogenic growth factors in the pulp of orthodontically moved teeth.	B
Derringer and Linden (2003)[36]	14	11-14 (N/A)	10	8	Upper second premolars extrusion	No orthodontic force	51-102	14	Angiogenic growth factors (VEGF, FGF2, PDGF, EGF and TGF β) are released in the pulp following orthodontic force. (NAs reduced microvessel numbers in the human dental pulp and rat-aorta co-culture assay)	Growth factors play a role in pulpal angiogenesis.	B
Derringer and Linden (2004)[37]	20	11-14 (N/A)	80	80	Upper and lower second premolars extrusion	No Ab (anti h VEGF, anti h FGF2, anti h-PDGF, anti TGF β) in co-cultures	51-102	14	VEGF, FGF2, PDGF and TGF β which are released after orthodontic force application causes the reduction of microvessel numbers.	Growth factors were released following orthodontic force application and play a role in the angiogenic response of the pulp. These factors may be more effective in combination.	B
Derringer and Linden (2007)[34]	10	11-14 (N/A)	10	10	Upper second premolars extrusion	Co-culture without anti-h EGF	51-102	14	Orthodontic forces stimulate the release of EGF in pulp tissues. (Co-culture with anti-h EGF resulted in a reduction in pulpal and rat aorta microvessels numbers)	Human epidermal growth factor (EGF) released following orthodontic force application plays a part in the angiogenic response of the pulp.	B

Table 4. con"t

Authors (Year)	Study subjects		No. of teeth		Type of force	Control group	Force applied (g)	Duration of force (days)	Pulpal response	Conclusion	Quality grade
	No.	Age range (Mean age) (years)	Experiment	Control							
Hamersky et al. (1980)[5]	17	11.7-25.7 (15)	34	34	Upper and lower first premolars extrusion	No orthodontic force	170	3	Orthodontic force decreases the pulpal respiration rate. Increasing age causes a larger depression in the pulpal respiration rate. The greater occurrence of root resorption and pulpal pathosis observed in adult orthodontic patient may be related to this greater depression in pulpal tissue respiration.	Orthodontic forces cause biochemical and biologic pulpal tissue alterations and orthodontic forces may be less biologically safe as the age of the patient increases.	C
Han et al. (2013)[12]	27	14-24 (17.9)	E1:24 (moderate force, 50 g) E2:24 (severe force, 300 g)	6	Upper first premolars intrusion	No orthodontic force	50, 300	7, 28, 56, 84	Odontoblast disruption, vacuolization, and moderate vascular congestion without necrosis (in both light- and heavy-force groups) Pulp stones in heavy-force group	Dental pulp still has vitality and no necrotic is observed after intrusive treatment.	C
Kayhan et al. (2000)[42]	N/A	15-17 (N/A)	E1:10 (1 month RME) E2:13 (3 month RME)	11	Upper premolars RME	No orthodontic force	N/A (1/2 turn/day)	21	Vessel area, minimum vessel diameters and maximum vessel diameters showed significant differences between control and 3-month groups. Maximum vessel diameters showed significant differences between 1-month and 3-month groups. Teeth in 3-month group found more fibrosis in pulp.	Force applied by RME caused an adaptive vascular tissue response and fibrotic changes.	B
Lazzaretti et al. (2014)[43]	17	12-19 (N/A)	17	17	Upper first premolar intrusion	No orthodontic force	60	21	Fibrous tissue and pulpal nodules were increased significantly in the experimental group.	Intrusive force caused vascular changes and increased the presence of fibrosis and the number of pulp calcifications without pulp necrosis.	B

Table 4. con"t

Authors (Year)	Study subjects		No. of teeth		Type of force	Control group	Force applied (g)	Duration of force (days)	Pulpal response	Conclusion	Quality grade
	No.	Age range (Mean age) (years)	Experiment	Control							
Mostafa et al. (1991)[38]	18	16-21 (18)	18	18	Upper first premolar extrusion	No orthodontic force	48-57	7, 14, 28	The pulpal reactions involve circulatory disturbances, odontoblastic degeneration, vacuolization and edema of the pulp tissues and fibronectic changes.	Many characteristic pulpal reactions arise from orthodontic extrusion.	B
Parris et al. (1989)[44]	20	11-29 (14.6)	44	36	Premolar tipping	No orthodontic force	120-245	0.015-0.054 (21-78 minutes)	Concentrations of ir-ME and ir-SP each correlated negatively with the magnitude of the orthodontic force.	Orthodontic forces and pulpal ir-ME and ir-SP concentrations are interlinked.	B
Perinetti et al. (2004)[45]	17	14-19 (N/A)	17	17	Upper first premolar tipping (alignment)	No orthodontic force	30-90	7	The AST activity in the test teeth is higher significantly than in the control teeth.	Application of mechanical load to teeth can cause metabolic changes in the pulp.	B
Perinetti et al. (2005)[46]	16	15-19 (17)	16	16	Upper first premolar tipping	No orthodontic force	30-90	7	ALP activity is significantly decreased in dental pulp tissue, explained by damage of the pulp cells responsive to the synthesis of this enzyme.	Orthodontic treatment can lead to significant early-phase reduction in ALP activity in pulp tissue.	B
Ramazanzadeh et al. (2009)[13]	26	14-24 (16.8)	E1:20 (intrusion) E2:20 (extrusion)	12	Upper premolar intrusion and extrusion	No orthodontic force	75; extrusion, 25; intrusion	21 (3 weeks; evaluated at 3 days and 3 weeks)	More fibrous tissue formation is seen from extrusion after 3 weeks	Histologic pulpal changes of intrusive force after 3 days and 3 weeks showed no significant difference.	C
Stenvik and Mjor (1970)[6]	N/A	10-13 (N/A)	35	35	Premolar intrusion	No orthodontic force	35-250	4-35	Vacuolization of the pulp tissue and circulatory disturbances occurred.	Intrusive forces cause histologic pulpal tissue alterations.	C
Stenvik (1971)[32]	N/A	12-13 (N/A)	26	35	Premolar extrusion and jiggling force	No orthodontic force	100-200	7-14	Minor reactions related to the circulatory system in the pulp were observed in experimental group.	The effect of extrusion on dentin and pulp seemed to be less than that of intrusive forces of the same magnitude.	C
Stenvik and Mjor (1971)[47]	N/A	10-13 (N/A)	60	35	Premolar intrusion	No orthodontic force	35-250	4-35	Alterations in apical anatomy were found only in teeth in which the root was not complete, while resorption defects were noted in most teeth in the experimental teeth.	Intrusive forces cause histologic pulpal tissue alterations. Some were of a permanent change, while others were partly resolvable.	C

Table 4. con"t

Authors (Year)	Study subjects		No. of teeth		Type of force	Control group	Force applied (g)	Duration of force (days)	Pulpal response	Conclusion	Quality grade
	No.	Age range (Mean age) (years)	Experiment	Control							
Subay et al. (2001)[48]	15	15-18 (N/A)	40	0	Premolar extrusion	None	75	10, 40	There was no evidence of inflammatory response and reparative dentin deposition.	Extrusive forces do not cause significant histopathological pulpal changes.	C
Taspinar et al. (2003)[49]	N/A	13-17 (N/A)	20	8	Upper first premolar RME	No orthodontic force	N/A (heavy force)	22	Vessel diameter, hemorrhage, congestion, inflammatory cell infiltration and fibrosis were changed at 3 months in experimental teeth, but gradually disappeared after 8 months.	Orthopedic forces exerted by RME caused reversible vascular changes in pulpal tissue of upper premolar teeth.	C
Veberiene et al. (2009)[50]	21	11-21 (15.5)	21	21	Premolar intrusion	No orthodontic force	61	7	Mean AST activity and EPT values were significantly higher in the test teeth compared to controls.	The short duration of the experiment does not allow firm conclusions to be drawn about existing pulp damage.	A
Veberiene et al. (2010)[51]	13	14-22 (16.5)	26	21	Premolar intrusion	No orthodontic force	85	7, 14	Mean AST values similar with and without mechanical load application but EPT values higher significantly.	Orthodontic forces do not influence pulpal AST activity but increase threshold to EPT.	A
Veberiene et al. (2015)[31]	16	N/A (25.7)	20	11	Upper premolar alignment	No orthodontic force	150-200 (per arch)	180 (6 months)	Mean AST levels in orthodontically treated teeth did not differ significantly from the untreated teeth, for 6 months of alignment.	Even if orthodontic treatment can cause temporary metabolic changes in dental pulp tissue during treatment, they are reversible.	B
Walker et al. (1987)[52]	17	N/A (N/A)	20	14	Upper premolar tipping	No orthodontic force	41-174	0.014-0.104 (20 minutes - 2.5 hours)	Orthodontic force caused a significant decrease in ME concentrations in the group of experimental teeth.	Orthodontic force mobilizes at least one neuropeptidergic pathway in the human tooth pulp.	C

No., Number; E, Experiment group; N/A, Non-available; CGRP, Calcitonin gene-related peptide; VEGF, Vascular endothelial cell growth factor; FGF2, Fibroblast growth factor 2; PDGF, Platelet derived growth factor; EGF, Epidermal growth factor; TGF β, Transforming growth factor β; NAs, Neutralising antibodies; Ab, Antibody; RME, Rapid maxillary expansion; ir-ME, Immunoreactive-methionine enkephalin; ir-SP, Immunoreactive-substance P; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; EPT, Electrical pulp testing; ME, Methionine encephalin

Table 5. Studies on the influence of orthodontic force on the pulpal responses in traumatized upper incisors teeth.

Authors (Year)	Study groups				Type and magnitude of force (g)	Duration of force (months)	Results	Quality grade
	Group 1	Group 2	Group 3	Control				
Brin et al. (1991)[41]	**Traumatized teeth without OT** • Subject=56 • No. of injured teeth=104 • YOA at trauma = 9.1±1.7 • YOA at present examination = 12±1.9	**Non-traumatized teeth with OT** • Subject=29 • YOA at start OT = 11.3±2.1 • YOA at present examination = 14.6±2	**Traumatized teeth with OT** • Subject=28 • No. of injured teeth=54 • YOA at trauma = 9.6±1.6 • YOA at start OT = 10.3±2.6 • YOA at present examination = 14.8±1.4	**Non-traumatized teeth without OT** • Subject=26 • YOA at present examination = 14.3±2.1	Tipping, removable appliance	N/A	The highest prevalence of loss of pulp vitality was found in group 3 while low sensibility (EPT 6.5-10) was prevalence in group 2.	C
Bauss et al. (2008)[19]	**Traumatized teeth with OT** • Subject =186 • n=269 • YOA at trauma = 9.5 (6.5-15.1) • YOA at the end of OT = 15 (13.7-17.1)	None	None	**Traumatized teeth without OT** • Subject=173 • n=173 • YOA at trauma = 9.3(6.6-16.4) • YOA at present examination = 14.7 (12.5-27.3)	Intrusion (15 g/tooth)	5.7 (4.6-7.2)	• Traumatized teeth with total pulp obliteration have higher susceptibility to pulpal complication such as pulp necrosis during orthodontic intrusion than that without or with partial pulp obliteration. • Pulp necrosis was detected in teeth in group 1 more than control.	C
Bauss et al. (2008)[39]	**Traumatized teeth with OT** • Subject =186 • n=269 (CI=194, LI=75) • YOA at trauma = 9.5 (6.5-15.1) • YOA at the end of OT = 15 (13.7-17.1)	**Non-traumatized teeth with OT** • Subject =200 • n=800 (CI=400, LI=400) • YOA at the end of OT = 14 (13.5-17.3)	None	**Traumatized teeth without OT** • Subject =173 • n=193 • YOA at trauma = 9.3 (6.6-16.4) • YOA at present examination = 14.7 (12.5-27.3)	Intrusion (15 g/tooth)	• Group 1: 5.7 (4.6-7.2) • Group 2: 6.2 (5.1-7.5)	• Pulp necrosis in group 1 had a significantly higher frequency than control and group 2. • Pulp necrosis in group 1 was diagnosed during orthodontic intrusion (64.3%), during active orthodontic tx after intrusion (28.6%), and at the end of retention (7.1%).	C

Table 5. con"t

Authors (Year)	Study groups				Type and magnitude of force (g)	Duration of force (months)	Results	Quality grade
	Group 1	Group 2	Group 3	Control				
Bauss et al. (2009)[18]	**Traumatized teeth during OT** • Subject =46 • n=59 (CI=43, LI=16) • YOA at the beginning of OT = 11.2 (9.5-16.7)	**Non-traumatized teeth during OT** • Subject =200 • n=800 (CI=400, LI=400) • YOA at the beginning of OT = 12.7 (9.7-17.5)	None	**Traumatized teeth without OT** • Subject 173 • n=193 (CI=146, LI=47) • YOA at trauma = 9.3 (6.6-16.4)	N/A	• Group 1: 5.7 (4.6-7.2) • Group 2: 6.2 (5.1-7.5)	• Higher frequency of pulp necrosis of group-1-teeth than group 2 or control. • Pulp necrosis in group 1 was observed in teeth with fracture of enamel-dentine, teeth with subluxation, extrusion, lateral luxation and intrusion.	C
Bauss et al. (2010)[40]	**Traumatized teeth with OT** • Subject =66 • n=77 (CI=50, LI=27) • YOA at trauma = 10 (7.3-16.7) • YOA at the end of OT = 15.5 (13.5-18.5)	**Non-traumatized teeth with OT** • Subject =100 • n=400 (CI=200, LI=200) • YOA at the end of OT = 15.9 (13.5-19.0)	None	**Traumatized teeth without OT** • Subject=173 • n=193; • YOA at trauma = 9.3 (6.6-16.4) • YOA at present examination = 14.7 (12.5-27.3)	Extrusion (20 g/tooth)	• Group 1: 4.8 (3.2-6.5) • Group 2: 5.2 (3.4-7)	• Pulp necrosis (group 1 > group 2) • Pulp necrosis (group 1 with periodontal injuries > group 2, control with periodontal injuries)	C

YOA, Year of age; OT, Orthodontic treatment; EPT, Electrical pulp testing; CI, Central incisors; LI, Lateral incisors

it is predisposed that application of high magnitude of orthodontic forces for a long duration can influences PBF significantly greater than short duration. Therefore, it is difficult to consider the association between PBF and magnitude of force.

Barwick and Ramsey [23] found that PBF in human maxillary central incisors was not altered significantly by the application of a transient intrusive force (4 minutes) at the maximum level of approximately 4,500 grams. This meant that there was no strangulation of PBF during a brief heavy intrusive force application. According to the study of Parfitt, [56] human central incisors could move 0.028 mm after applying 1,000 gram intrusive force for 15 seconds. Therefore, intrusive force of 4,500 grams would displace incisor for at least 0.028 mm. The average width of PDL space at the apex of teeth is 0.18 - 0.21 mm. [57] Then, there was a PDL space reduction after intrusive force application only about 16% which might be insufficient to compress the apical vasculature. In addition, Miura [58] indicated that blood circulation was not altered by the compression of PDL of 1/3 or less. Moreover, brief heavy forces might not easily cause excessive apical tooth movement because of the mechanical properties of the PDL are oriented to resist intrusive force and remain rigid when force application is transient. Furthermore, the finding of Goz and collegues [59] could confirm the adequate PDL circulation during brief orthodontic intrusive tooth movement. They found that there was no histologic evidence of circulatory disturbance in PDL after applying 2,000 grams intrusive force to the third premolars of Beagle dogs for a brief duration less than 3 hours.

It has been reported that the effect of orthodontic force on PBF is associated with various factors such as patients' age, size of apical foramen, and dentinogenic activity. [5,23] None of the studies in this systematic review assessed the influence of size of apical foramen and dentinogenic activity on PBF. However, it is pertinent to mention that in these studies [14,23-30] age of the study participants was also markedly unclear. The study by Sano et al., [14] individuals with age ranging between 27 and 31 years were included, whereas Sabuncuoglu and Ersahan. [27,28] assessed the effect of orthodontic forces on PBF among 18–25 year old patients with the same type of treatment, intrusion of the incisors. Further clinical studies with standardized parameters, particularly the magnitude and duration of force application, are needed to clarify the effect of orthodontic forces on PBF.

Being surrounded by the hard tissue, i.e., dentine, the pulp does not have collateral circulation and is therefore the most sensitive part of the human body, to various forms of stimuli. Many studies have reported that orthodontic force application may lead to significant pulpal reactions such as hyperemia, margination of white blood cells, stasis, vacuole formation in the odontoblastic layer, cyst formation, and hemorrhage. [60] These indicate inflammation and an adaptive process of pulpal tissue.

Cellular response will be discussed separated by type of orthodontic treatment. First of all, intrusive force, Proffit and Fields considered a range of 10-20 grams to be the optimum force magnitudes for intrusion, furthermore Woodside, Berger and Hanson considered 50-100 grams as light forces. [61,62] Most experiments used low to moderate intrusive force and found odontoblast disruption, vacuolization, presence of fibrosis, pulp calcification, and moderate vascular congestion. In studies of severe intrusive force (250-300 grams), they found stasis of pulp vessels, destruction of vessel walls, and pulp stones. Pulp necrosis was not found in any experiment. The results demonstrated that supplying vessels in the severe force group caused a reduced ability of the pulp to react to the impairment of pulpal blood, however, they maintain a sufficient blood supply compared with the low and moderate-force group. [12]

Reitan and Vanarsdall [63] recommended that the extrusive force for adults must be between 25 to 30 grams to prevent pulpal damage. However, Profitt and Fields [2] considered that a range of 50 to 75 grams force is the optimum force magnitude for extrusion. Force used in experiments was lower than 75 grams except the study of Stenvik [32] that applied 100 and 200 g only 10 days. Orthodontic extrusion causes odontoblastic degeneration, circulatory disturbances with congested blood vessels, vacuolization and edema of the pulp tissues, and appearance of fibrotic changes, with no necrosis. Moreover, the effect of extrusion on dentin and pulp seemed to be less than that of intrusive forces of the same magnitude.

Rapid maxillary expansion (RME) is used to correct maxillary constriction and posterior cross-bite by separate the mid-palatine suture. RME exerts a powerful force (7.54-15.8 kg) on the crown of the tooth that is transmitted, via the root, to the bone. [64] After expansion, a 3 to 6-month retention period is required. Taspinar and Kayhan found fibrosis and vessel diameter was significantly increased in 3 months, then disappeared in 18 months after RME. [42,49] This indicates that the vascular changes are reversible and orthodontic treatments using large forces in a short period are safe.

In clinical situations where fixed orthodontic treatment is performed, the teeth are affected by various types of force such as intrusion, extrusion, and tipping. It is almost impossible to define and reproduce the single tooth movements involved in specific clinical situations. The inability to completely control the magnitudes and directions of forces applied can be considered a limitation of these studies. Experimental and clinical techniques are usually limited with regard to applying known complex force systems. [31] Moreover, it can be hypothesized that application of heavy orthodontic force for long duration may cause a magnification of the pulp inflammatory process that could lead to irreversible pulpitis and necrosis. Therefore, it is important to point out the clinical relevance of using moderate and intermittent orthodontic forces, which are capable of generating an adequate tooth movement, limiting the damage, and allowing pulp to recover from the injury. [65] In addition, it is advisable to use controlled movements and long resting periods in order to achieve the esthetic and functional objectives of orthodontic treatment, without triggering severe inflammatory reaction capable of inducing irreversible damage to the dental pulp and periapical tissues. [33]

The quality grading of the studies on the influence of orthodontic force on the pulpal responses in traumatized upper incisors teeth is low. It is mainly because of the limited field of study and no description of reliability tests. However, it might state that severe periodontal injury, such as lateral luxation, extrusion and intrusion, revealed a significantly higher rate of pulp necrosis during orthodontic treatment, especially intrusive force, than teeth with only slight periodontal or hard tissue injury. All previously traumatized teeth showed a positive reaction to sensibility test prior to orthodontic treatment, implying an adequate vascular supply to the pulp. As mentioned above that orthodontic tooth movement can affect the blood supply to the dental pulp which decreases in PBF followed by a pulpal hyperemia that compensates for the lack of tissue perfusion. Therefore, it might be concluded that in teeth with severe periodontal injury, the capacity of the blood vessels supplying the pulp was insufficient for maintenance of an adequate pulpal blood flow during orthodontic treatment. Moreover, severe periodontal injury might cause permanent damage and reduction of the apical vessels. These previously traumatized teeth are more prone to pulp necrosis. In addition, previously traumatized teeth with total pulp obliteration have a higher risk for pulp necrosis than traumatized teeth without or only partial obliteration during

orthodontic force application. Pulp obliteration is caused by progressive hard tissue apposition along the pulp chamber that gradually decreases the pulpal lumen. [66] Therefore, it might imply that this hard tissue formation of total pulp obliteration leads to progressive compression and finally to constriction the existing pulpal vessels, resulting in an impaired blood supply. Progressive hard tissue apposition might lead to constriction of the apical foramen, and thus to compression of the neurovascular bundle. This may cause strangulation or even rupture of the apical vessels during orthodontic tooth movement. In contrast, a narrow apical foramen in teeth with partial obliteration might allow the pulpal circulatory system of these teeth to function adequately and to maintain sufficient pulpal perfusion during orthodontic treatment.

Conclusion

Temporary reduction of PBF after intrusive force application is a reversible effect, and it tends to return to baseline values in about 3 weeks. Although there is a lack of high-quality scientific evidence to prove that orthodontic forces affect in irreversible alterations of human dental pulp, short-term application of orthodontic forces can provoke a reversible biological response. However, previously traumatized teeth applying orthodontic force are considered a risk factor for vitality loss of dental pulp. The recommendation is to use appropriated optimum force, controlled tooth movement, and long resting period to accomplish goal of orthodontic treatment and avoid temporary side-effects.

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