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REVIEW

Do orthodontic tooth movements induce pulp necrosis? A systematic review

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Abstract

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Background Orthodontic tooth movements are performed by applying forces on teeth, which may cause alterations within the dental pulp. Previously published systematic reviews on the subject only included a small number of studies that assessed pulp status through reliable diagnostic methods. Since then, new evidence has been published, and a further systematic review on the subject is necessary.

Objectives To evaluate whether there is scientific evidence to support the possibility that orthodontic tooth movements could induce pulp necrosis.

Methods A systematic search of articles published until June 2020 was performed using MeSH and free terms in the PubMed, Cochrane Library, LILACS, SciELO, Web of Science, EMBASE, Open Grey and Grey Literature databases. Randomized clinical trials (RCTs), nonrandomized clinical trials (nRCTs) and longitudinal (prospective or retrospective) studies that evaluated the pulp status of teeth subjected to orthodontic movements using laser Doppler flowmetry or pulse oximetry were included. The revised Cochrane risk of bias tools for randomized trials (RoB 2) and nonrandomized interventions (ROBINS-I) were used to assess the quality of the included studies. Relevant findings were summarized and evaluated. The overall quality of evidence was assessed through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.

Results Initial screening of databases resulted in 353 studies. In total, 285 studies were excluded because they were duplicates. Of 68 eligible papers, fourteen met the inclusion criteria and were selected for full-text reading. Two studies were excluded due to the methods used to evaluate pulp status. Twelve studies (five RCTs, one nRCT and six prospective) were included. Four RCTs were classified as having an unclear risk of bias and one as having a high risk of bias. The nRCT was classified as having a low risk of bias. Two prospective studies were classified as having a moderate risk of bias and four as having a serious risk of bias. The GRADE analysis demonstrated a low to very low quality of evidence.

Discussion Significant limitations regarding the randomization processes within the included RCTs and a lack of control of confounders on most nonrandomized and longitudinal studies were verified.

Conclusions This systematic review indicates that orthodontic movements do not induce loss of pulp vitality with low to very low certainty of evidence.

Keywords: dental pulp necrosis, orthodontic movement, systematic review.

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Introduction

Orthodontic treatments aim to correct malocclusions in the hope of improving the oral health-related quality of life of patients (Ferrando-Magraner *et al.* 2019). Forces are applied to teeth and surrounding structures in order to create tooth movement and, when considering the effects of these forces on the dental pulp, it has been reported that cellular and enzymatic alterations occur in the pulp tissue (Mostafa *et al.* 1991, Derringer & Linden 1998, Perinetti *et al.* 2004, 2005, Ramazanzadeh *et al.* 2009, Veberiene *et al.* 2009, 2010, Han *et al.* 2013), as well as circulatory disturbances (Derringer *et al.* 1996, Han *et al.* 2013, Lazzaretti *et al.* 2014), induction of tissue fibrosis (Mostafa *et al.* 1991, Ramazanzadeh *et al.* 2009, Lazzaretti *et al.* 2014), pulp calcification (Lazzaretti *et al.* 2014), oedema (Mostafa *et al.* 1991, Han *et al.* 2013), vacuolization (Stenvik & Mjör 1970, Mostafa *et al.* 1991, Ramazanzadeh *et al.* 2009) and a decrease in the pulpal respiration rate (Hamersky *et al.* 1980, Unsterseher *et al.* 1987). Furthermore, it has been reported that teeth undergoing orthodontic movement for an extended time and with excessive force are more susceptible to develop inflammatory root resorption (Weltman *et al.* 2010), pulp stones (Ertas *et al.* 2017) and invasive cervical resorption (Heithersay 1999). Such histological changes on the pulp may lead to the loss of vitality (Hamersky *et al.* 1980), leading to the need for a root canal treatment.

Several studies have been performed to verify the effects of orthodontic treatment on pulp vitality (Popp *et al.* 1992, Veberiene *et al.* 2009, 2010, Bauss *et al.* 2010, Han *et al.* 2013). However, these studies have substantial limitations, such as the methods used to evaluate pulp status: periapical and panoramic radiographs, electric and thermal sensibility tests. It is well established that periapical and panoramic radiographs provide limited information due to the two-dimensional images provided (Aminoshariae *et al.* 2018, Antony *et al.* 2020), which can lead to an erroneous diagnosis. Also, electrical and thermal sensitivity tests evaluate only the neural response of the tooth, regardless of the presence or absence of blood circulation, providing subjective and limited results (Hall & Freer 1998, Gopikrishna *et al.* 2007, Alomari *et al.* 2011, Mainkar & Kim 2018). Laser Doppler flowmetry (LDF) and pulse oximetry (PO) have been evaluated as diagnostic methods to verify pulp status by assessing the pulp blood flow, without relying on the patients' response, and, when compared to the other diagnostic methods, are considered to be the most accurate (Gopikrishna *et al.* 2007, Karayilmaz & Kirzioğlu 2011, Dastmalchi *et al.* 2012, Mainkar & Kim 2018).

Two systematic reviews (Von Böhl *et al.* 2012, Javed *et al.* 2015) have been conducted to determine the effects of orthodontic movements on the dental pulp. They concluded that there is no scientific evidence that orthodontic movements induce irreversible alterations in the dental pulp (Javed *et al.* 2015); and that, although a biological response within the pulp occurs, there is a lack of high-quality studies to establish a relation between orthodontic forces and pulp tissue reactions (Von Böhl *et al.* 2012). However, these systematic reviews only assessed a small number of studies that evaluated changes in pulpal blood flow from orthodontically moved teeth or included studies that evaluated such outcomes using less accurate diagnostic methods to determine the pulp status. Besides, since these systematic reviews were conducted, new evidence (Sabuncuoğlu & Ersahan 2016, Ersahan & Sabuncuoğlu 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020) on the subject has appeared, requiring a further systematic review that includes this new data.

Therefore, this systematic review aimed to answer the focused question 'Do orthodontic movements induce pulp necrosis?', limiting the search for studies that had used only LDF and/or PO for the evaluation of the pulp status of patients undergoing orthodontic movements, in order to obtain a more accurate answer on the influence of these movements on the status of the dental pulp.

Materials and methods

This systematic review followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations (http://www.prisma-statement.org) and was registered on the PROSPERO database under number CRD42020189710.

Search strategy

The search was performed independently by two examiners (T.W. and M.V.R.S.) in the following electronic databases: PubMed, Cochrane Library, LILACS, SciELO, Web of Science, EMBASE, Open Grey and Grey Literature Database. The search was conducted in June 2020, without a year restriction, and only included studies written in English. The electronic search strategy was developed using the most cited descriptors in previous publications on this theme combining Medical Subject Heading (MeSH) terms and text words (tw.). For each database, the following terms were combined: 'Orthodontic movements', 'Orthodontic forces', 'Pulp necrosis', 'Dental pulp', 'Laser Doppler', 'Pulse oximetry', 'Root resorption', 'Traumatized teeth'. The Boolean operators 'AND' and 'OR' were applied to combine the terms and create a search strategy. The search strategies for each database and the following findings are summarized in Supplementary File 1. An additional screening on the references of the selected studies was performed, and the related articles were searched in the PubMed database. All articles selected were imported into the Mendeley© (Mendeley Ltd, London, UK) reference manager to catalogue the references and facilitate the exclusion of duplicates.

Eligibility criteria

The eligibility criteria were based on the PICOS strategy (PRISMA-P 2015; Maia & Antonio 2012, Moher *et al.* 2015), as follows:

- Population (P): teeth with vital pulps.
- Intervention (I): orthodontic movements.
- Comparison (C): teeth which were not orthodontically moved.
- Outcome (O): pulpal status after orthodontic movements.
- Study design (S): randomized clinical trials (RCTs), nonrandomized clinical trials (nRCTs) and longitudinal studies.

Only studies that evaluated the pulp status of teeth subjected to orthodontic movements using LDF or PO were included.

Studies performed in animals, histological studies, cross-sectional studies, systematic reviews with and without meta-analysis, reviews, letters, opinion articles, conference abstracts, case reports, serial cases and *in vitro* studies were excluded.

Selection of studies

The first stage consisted of excluding duplicated studies, considering them only once and examining the retrieved titles and abstracts of the selected studies by two independent authors (T.W. and M.V.R.S.). When it was not possible to judge the studies by title and abstract, the full text was assessed and read for the final decision. The second stage consisted of reading the full texts of the potentially eligible studies based on the eligibility criteria through the PICOS strategy. Disagreements on study inclusion were solved by consensus with a third author (E.J.N.L.S.).

Data extraction

Two authors (T.W. and M.V.R.S.) independently collected the data from the included studies. Disagreements were solved by a third author (E.J.N.L.S.). The following data were extracted from the included studies: author(s), year of publication, research design, number of patients, type of orthodontic device, number and type of teeth, type of movement, force applied, comparison, times of pulp status assessment, duration of force and outcome variables. In cases of missing data, the authors were contacted three times by email.

Quality assessment and strength of evidence

The methodological risk assessment of bias for each study was performed by two independent authors (T.W. and M.V.R.S.), and, in case of disagreement, it was resolved by a third author (E.J.N.L.S.).

For randomized clinical trials, the qualitative analysis of the studies was performed from the risk of bias assessment using the Cochrane risk of bias tool for randomized clinical trials (RoB 2): 'Bias Risk Assessment of Randomised Controlled Studies' – Cochrane Handbook 6.0 (Sterne *et al.* 2019). The following domains were considered:

1. Randomization process.
2. Deviations from intended interventions.
3. Missing outcome data.
4. Measurement of the outcome.
5. Selection of the reported results.

The blinding of operators was not considered since it is impossible to perform in these types of interventions. Each included study was judged as 'high' risk of bias for negative domain response (red), 'low' risk of bias for positive domain response (green) and risk of 'unclear' bias (yellow) when the response was not clear. When the study was judged as 'unclear', the authors were contacted by email at least three times for more information that allowed them to be classified as 'low' (green) or 'high' (red) risk of bias. When this information was not acquired, the articles were classified as with some 'unclear' bias risks. Overall quality was based on the scores in individual domains. When a low risk of bias was verified for all domains, the overall quality was of low risk of bias. When at least one domain was of unclear risk, the overall quality was unclear risk of bias. Also, the assessment of at least one domain as high risk or three or more domains as unclear risk resulted in an overall quality of high risk of bias.

The Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I; Sterne *et al.* 2016) tool was used for the analysis of the nonrandomized clinical trials and the longitudinal studies (prospective and retrospective). The domains confounding factors, selection of participants into the study, classification of intervention, deviation from intended interventions, missing data, measurement of outcomes and selection of the reported results were assessed as follows:

1. Confounding factors: 'low' risk of bias was considered when all possible confounding factors were controlled in the design (e.g. by matching conditions and/or excluding diseases) or in the statistical analysis (e.g. by an adjustment based on an appropriate regression analysis); 'moderate' risk of bias when some possible confounding factors were controlled; 'serious' risk of bias when no possible confounding factors were controlled; and 'critical' risk of bias when possible confounding factors were not even discussed.
2. Selection of participants into the study: 'low' risk of bias was considered when all eligible participants were included in the study; 'moderate' risk of bias when the participant selection may have been related to intervention/outcome; 'serious' risk of bias when participant selection was related to intervention/outcome; and 'critical' risk of bias when the selection process was not described.
3. Classification of interventions: 'low' risk of bias was considered when the orthodontic intervention was well described; 'moderate' risk of bias when the orthodontic intervention presented some missing information but the missing data were not relevant to the purpose of the included study; 'serious' risk of bias when the orthodontic intervention was not well described; and 'critical' risk of bias when the orthodontic intervention was not described at all.
4. Deviations from intended interventions: 'low' risk of bias was considered when no differences occurred after the beginning of the study, or differences in one or both groups occurred after the beginning of the study, but the participant continued (for analysis purposes) to be part of the study; 'moderate' risk of bias when differences occurred after the beginning of the study but it not seem to affect its outcome (e.g. the nonadherence of participants to the intervention); 'serious' risk of bias when few differences occurred after the beginning of the study and changes in the sample or intervention were required, or when co-interventions between groups were not well balanced; and 'critical' risk of bias when several differences occurred after the beginning of the study.
5. Missing data: 'low' risk of bias was considered when the number of orthodontically treated and nontreated teeth and/or participants, teeth group, orthodontic movement and pulpal status was well reported; 'moderate' risk of bias when there were some missing data but the missing data were not relevant to the purpose of the included study; 'serious' risk of bias when there were some relevant missing data; and 'critical' risk of bias when there were several relevant missing data.
6. Measurement of outcomes: 'low' risk of bias was considered when a valid methodology was used to assess the pulp status; 'moderate' risk of bias when it was not used a valid methodology, but the methodology was well described; 'serious' risk of bias when the methodology was not well described; and 'critical' risk of bias when the methodology used was not described.
7. Selection of the reported results: 'low' risk of bias was considered when changes in PBF amongst groups were well reported; 'moderate' risk of bias when changes in PBF amongst groups were well reported but not described; 'serious' risk of bias when there was a substantial difference in the description of data amongst groups; and 'critical' risk of bias when there was missing information regarding PBF changes.

Each domain was recorded as low, moderate, serious, critical or no information available for risk of bias. The overall risk of bias judgement was determined by combining the levels of bias in each domain.

The strength of the evidence of the included studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime Inc.), available from gradepro.org: https://gdt.gradepro.org/app/handbook/handbook.html#h.rkkjpmwb6m6z (Guyatt *et al.* 2011a). The GRADE tool has five domains that can be downgraded and reduce the quality of the evidence (Grades of Recommendation Assessment Development & Evaluation (GRADE) Working Group 2004). For both randomized and nonrandomized studies, the following domains were considered to assess the strength of the evidence:

1. Risk of bias.
2. Inconsistency.
3. Indirectness.
4. Imprecision.
5. Other consideration.

Results

Study selection

Figure 1 presents the flow diagram of the search strategy. Initial screening of databases resulted in 353 studies, with 285 excluded as they were duplicates. From the analysis of the titles and abstracts of the 68 eligible papers, fourteen studies (McDonald & Pitt Ford 1994, Barwick & Ramsay 1996, Brodin *et al.* 1996, Sano *et al.* 2002, Bauss *et al.* 2008a,b, Babacan *et al.* 2010, Salles *et al.* 2013, Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2015, 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020) met the inclusion criteria and were selected for full-text reading.

Two studies (Bauss *et al.* 2008a,b) were excluded due to the methods used to evaluate pulp status (cold sensibility test, periapical radiographs and crown colour alteration). Therefore, twelve studies were included in the present review (McDonald & Pitt Ford 1994, Barwick & Ramsay 1996, Brodin *et al.* 1996, Sano *et al.* 2002, Babacan *et al.* 2010, Salles *et al.* 2013, Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2015, 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020).

Data extraction

Table 1 presents the characteristics and main findings of the included studies.

Authors of studies containing insufficient data were contacted three times by e-mail, but no additional information was obtained.

Regarding the diagnostic method, all the included studies used laser Doppler flowmetry (LDF) to evaluate the pulp status (McDonald & Pitt Ford 1994, Barwick & Ramsay 1996, Brodin *et al.* 1996, Sano *et al.* 2002, Babacan *et al.* 2010, Salles *et al.* 2013, Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2015, 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020).

Concerning the orthodontic device, four studies used pre-adjusted edgewise fixed appliances (Salles *et al.* 2013, Ersahan & Sabuncuoğlu 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020), one study used clear aligners in one of the groups (Abu Alhaija *et al.* 2019), three used mini-implants (Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2015), one used self-ligating brackets in one of the groups (Abu Alhaija & Taha 2020), two studies used an intrusive force apparatus (Barwick & Ramsay 1996, Sano *et al.* 2002), one study used a removable device (McDonald & Pitt Ford 1994), one study used a modified acrylic bonded device for rapid maxillary expansion (RME; Babacan *et al.* 2010), and two studies used fixed orthodontic devices (Brodin *et al.* 1996, Sano *et al.* 2002).

As for the type of tooth movement, one study reported tipping movement (Abu Alhaija *et al.* 2019), two referred to retraction movement (McDonald & Pitt Ford 1994, Sabuncuoğlu & Ersahan 2016), five studies reported intrusive movement (Barwick & Ramsay 1996, Brodin *et al.* 1996, Sano *et al.* 2002, Sabuncuoğlu & Ersahan 2014, Ersahan & Sabuncuoğlu 2015), one reported maxillary expansion (Babacan *et al.* 2010), one reported extrusive movement (Brodin *et al.* 1996), and three studies reported alignment and levelling (Salles *et al.* 2013, Ersahan & Sabuncuoğlu 2018, Abu Alhaija & Taha 2020). However, only one study (Salles *et al.* 2013) specified the movements applied to align and level the teeth. One study did not specify the movements applied in one of the groups (Abu Alhaija *et al.* 2019).

About the force applied, four studies reported the forces in grams (g), with forces varying from 5 to 500 g (McDonald & Pitt Ford 1994, Barwick & Ramsay 1996, Ersahan & Sabuncuoğlu 2015, Sabuncuoğlu & Ersahan 2016). Three studies reported the forces in Newtons (N), with forces varying from 0.5 to 2 N (Brodin *et al.* 1996, Sano *et al.* 2002, Salles *et al.* 2013). One study, due to the use of a device for rapid maxillary expansion, described the force application as one-quarter turn once a day (Babacan *et al.* 2010). Three studies did not reference the force applied (Ersahan & Sabuncuoğlu 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020).

When considering the duration of forces, a wide range of time was observed: from 4 min to 6 months

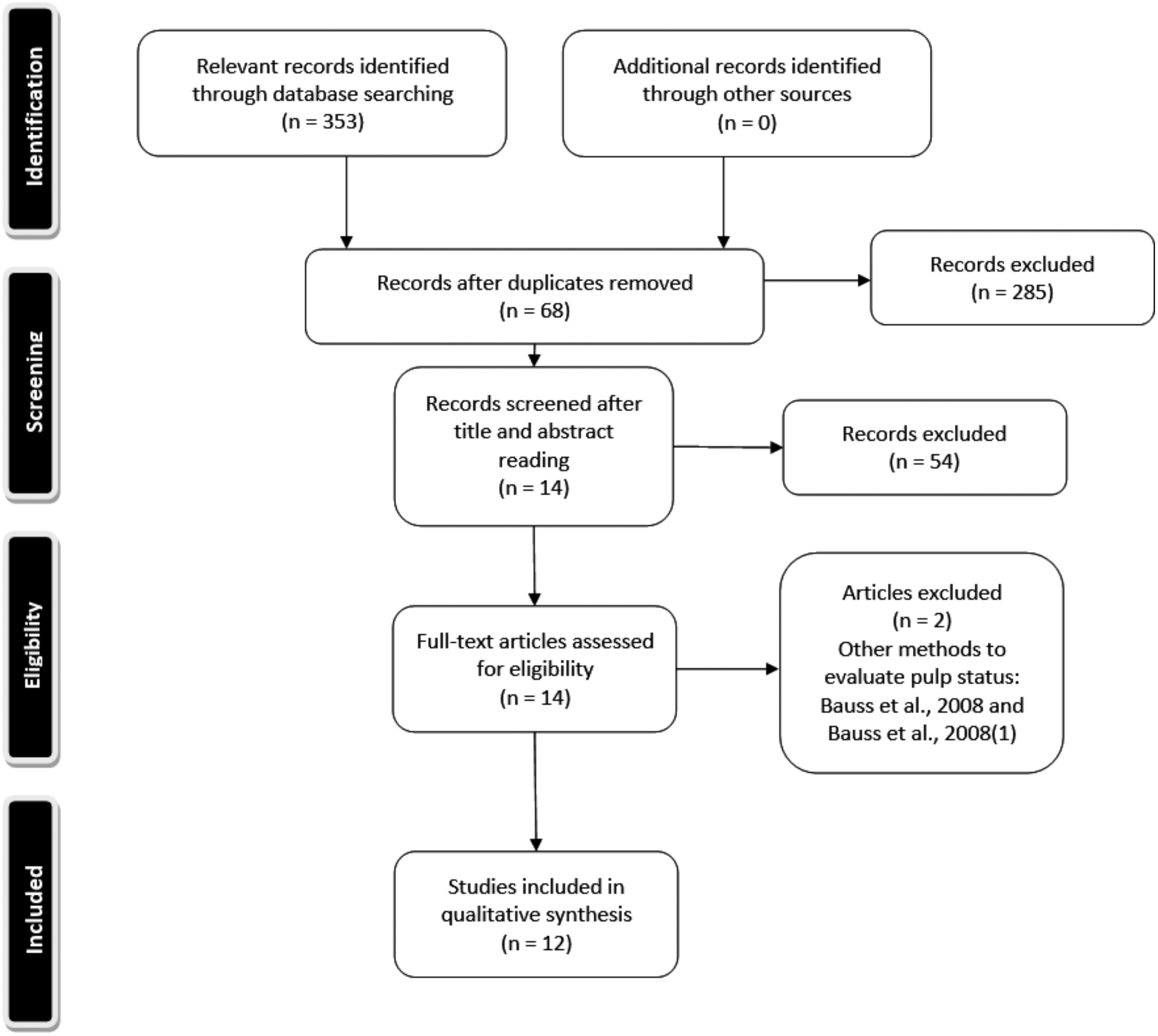

Figure 1 PRISMA flow diagram representing the systematic review process.

(McDonald & Pitt Ford 1994, Barwick & Ramsay 1996, Brodin *et al.* 1996, Sano *et al.* 2002, Babacan *et al.* 2010, Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2015) of duration. Four studies did not report this information (Salles *et al.* 2013, Ersahan & Sabuncuoğlu 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020). Regarding the type of teeth evaluated, four studies (Babacan *et al.* 2010, Ersahan & Sabuncuoğlu 2015, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020) evaluated the pulpal blood flow (PBF) of posterior teeth (molar and premolars). Ten studies (McDonald & Pitt Ford 1994, Barwick & Ramsay 1996, Brodin *et al.* 1996, Sano *et al.* 2002, Salles *et al.* 2013, Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2018) evaluated the PBF of anterior teeth (incisors and canines).

The majority of studies reported vascular alterations causing a reduction in pulpal blood flow, followed by an increase and return to average values (McDonald & Pitt Ford 1994, Brodin *et al.* 1996, Sano *et al.* 2002, Salles *et al.* 2013, Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2015, 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020). Also, one study referenced a more pronounced reduction in PBF when heavier forces (250 g) were applied (Ersahan & Sabuncuoğlu 2015), one described in older participants a more severe and longer reduction in PBF (Ersahan & Sabuncuoğlu 2018), one study reported no alterations on PBF with intrusive brief force application (Barwick & Ramsay 1996), one other reported no alterations on PBF with extrusive brief force and a temporary reduction in PBF with intrusive brief force (Brodin *et al.* 1996), and one study reported an increase in PBF, followed by a decrease returning to baseline values (Babacan *et al.* 2010).

Quality assessment

Figure 2 summarizes the risk of bias of the randomized clinical trials. Figure 3 summarizes the risk of bias of the nonrandomized studies.

For the quality assessment of the randomized clinical trials, the blinding of operators was not considered since it is impossible to perform in these types of interventions.

From the five randomized clinical trials included, four studies were classified as having unclear bias, with only one domain (randomization) presenting some concerns (Sabuncuoğlu & Ersahan 2014, Ersahan & Sabuncuoğlu 2015, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020), and one study was considered as having a high risk of bias, with one domain (randomization) classified as high risk of bias (Sabuncuoğlu & Ersahan 2016).

From the seven nonrandomized studies, one study was considered as having a low risk of bias (Ersahan & Sabuncuoğlu 2018), two studies were considered as having a moderate risk of bias, with one domain (confounding factors) classified as moderate risk of bias (Barwick & Ramsay 1996, Sano *et al.* 2002), and four studies were considered as having a serious risk of bias, with one domain (confounding factors) classified as a serious risk of bias in the four studies (McDonald & Pitt Ford 1994, Brodin *et al.* 1996, Babacan *et al.* 2010, Salles *et al.* 2013), and two domains (selection bias and deviations from interventions) classified as a serious and moderate risk of bias, respectively, in one study (Babacan *et al.* 2010).

Strength of evidence

GRADE results are presented in Table 2. The GRADE tool demonstrated a low to very low quality of evidence for the included studies. The nonrandomized studies received the 'very serious' classification for risk of bias, 'serious' classification for imprecision and 'not serious' classification for inconsistency, indirectness and none other considerations (McDonald & Pitt Ford 1994, Barwick & Ramsay 1996, Brodin *et al.* 1996, Sano *et al.* 2002, Babacan *et al.* 2010, Salles *et al.* 2013, Ersahan & Sabuncuoğlu 2018). The randomized clinical trials received the 'serious' classification for risk of bias and imprecision and 'not serious' classification for inconsistency, indirectness and none other considerations (Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2015, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020).

Discussion

Since the loss of pulp vitality is a significant concern when forces and movements are applied to teeth, this systematic review aimed to verify the impact orthodontic treatment has on dental pulp status. Although other systematic reviews on this subject (Böhl *et al.* 2012, Javed *et al.* 2015) already exist, both assessed a small number of studies that evaluated pulp status through more accurate methods (LDF and PO). Also, due to the emergence of more evidence on the subject (Sabuncuoğlu & Ersahan 2016, Ersahan & Sabuncuoğlu 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020) since the last systematic review (Javed *et al.* 2015) was performed, a new systematic review that considers such studies is necessary.

The current systematic review was conducted with a robust methodology, registered *a priori* in the PROSPERO database, used eight electronic databases, searched by two independent authors that were also involved on the study selection and data extraction. In order to provide a reliable source of knowledge on the question raised on this study, only randomized clinical trials, nonrandomized clinical trials and longitudinal (prospective or retrospective) studies that evaluated pulp status using laser Doppler flowmetry (LDF) or pulse oximetry (PO) were included. These selection criteria are based on studies that indicate that these tests present a more accurate response on the diagnosis of the dental pulp status (Gopikrishna *et al.* 2007, Karayilmaz & Kirzioğlu 2011, Dastmalchi *et al.* 2012, Mainkar & Kim 2018) since it can directly assess the presence or absence of blood flow. Through the data extracted from the included studies, it was possible to verify that all of them evaluated pulp status using LDF. This can be explained due to the lack of pulse oximetry probes manufactured especially for dental purposes, limiting its usage in the dental practice (Dastmalchi *et al.* 2012).

The risk of bias assessment of the RCTs presented major concerns regarding randomization bias. Two

Table 1 Characteristics of the included studies

Authors (year of publication) – study design	Number of participants	Participants' age (mean)	Type of orthodontic device	Type of teeth evaluated	Type of movement	Force applied	Comparison	Number of teeth per group	Times of pulp status assessment	Duration of forces	Outcome	Main finding
Abu Alhaija *et al.* (2019) – RCT	45 (Group 1: 25; Group 2: 20)	16-22 (Group 1: 18.77; Group 2: 19.04) years	Pre-adjusted edgewise fixed appliance (Group 1); Clear aligner (Group 2)	Maxillary central incisor to the maxillary first molar of the right quadrant; Mandibular central incisor to the mandibular first molar of the left quadrant	Tipping movement (pre-adjusted edgewise fixed appliance); Not reported (clear aligner)	NR	Same teeth before orthodontic movement	12 teeth per participant Group 1: $n = 300$; Group 2: $n = 240$	Before fixed appliance bond up and insertion of clear aligners; 20 min, 48, 72 h and 1 month after the fitting NiTi arch wire and after the insertion of second stage clear aligner	NR	In both groups, PBF decreased after the insertion of the orthodontic appliances and significant changes occurred up to 48 to 72 h, returning to normal values within 1 month. PBF values between the 2 groups did not reach any statistical significance difference	PBF changes occurred up to 72 h, returning to normal values within 1 month
Abu Alhaija & Taha (2020) – RCT/Split-mouth	22	19 ± 2.53 years	Pre-adjusted edgewise fixed appliance (one side of lower arch); Self-ligating brackets (other side of the lower arch)	Mandibular central incisor to the mandibular first molar of the left side; Mandibular central incisor to the mandibular first molar of the right side	Alignment and levelling (not specified)	NR	Same teeth before orthodontic movement	6 teeth per group / 12 teeth per participant Pre-adjusted edgewise fixed appliance: $n = 132$; Self-ligating brackets: $n = 132$	Before fixed appliance bond up; 20 min, 24, 72 h, 1 week and 1 month after fitting each arch wire	NR	Significant PBF decrease was observed after 20 min to 72 h in both groups; PBF returned to its normal values within 1 month of force application	Reduction in PBF occurred up to 72 h, returning to normal values within 1 month
Babacan *et al.* (2010) – Prospective	21	10-15 (13.1) years	Modified acrylic bonded RME (rapid maxillary expansion) device	Maxillary central incisors, canines and first molars	Maxillary expansion	One-quarter turn once a day	Same teeth before orthodontic movement	$n = 42$ central incisors; $n = 28$ canines; $n = 42$ first molars	Just before expansion; at the first week of expansion and at the end of expansion; and at the third, seventh, and 12th weeks of retention	4,7 weeks (mean)	Mean PBF baseline of all set of teeth were similar; Statistical differences were not found when compared each set of teeth at each time-point; Mean PBF values significantly increased at the end of the first week; decreased significantly at the end of the expansion; and return to baseline after twelve weeks for all teeth	RME induced a significant PBF increase, which returned to normal values during retention period for all teeth

Table 1 Continued

Authors (year of publication) – study design	Number of participants	Participants' age (mean)	Type of orthodontic device	Type of teeth evaluated	Type of movement	Force applied	Comparison	Number of teeth per group	Times of pulp status assessment	Duration of forces	Outcome	Main finding
Barwick & Ramsay (1996) – Prospective	8	25-49 (34.8) years	Intrusive force apparatus	Maxillary central incisors	Intrusive	Weights of 0, 5, 50 or 500 g (forces ranging between 76, 123, 499 and 4400 g, respectively)	Same teeth before orthodontic movement	1 tooth per participant *n* = 8	During 4 min with bioplast splint, during 4 min prior to intrusive force; 4 min of force appliance and 12 min after force removal. During a final session, after the administration of 1 mL of local anaesthetic with vasoconstrictor	4 min	Intrusive force apparatus baseline PBF did not differ amongst sessions and compared to bioplast splint measures; Force levels had no statistically significant effect on PBF; PBF drop significantly after administration of the vasoconstrictor	PBF is not altered during the application of a brief intrusive orthodontic force
Brodin *et al.* (1996) – Prospective	6	NR	Fixed orthodontic device (experimental group)	Lateral incisors	Intrusive and extrusive	2 N	Contralateral lateral incisors	2 teeth per participant Experimental group: *n* = 10; Control group: *n* = 10	After and before 5 min of intrusion or extrusion	10 min	2 teeth were excluded due to technical problems; No significant changes in PBF during and after 5 min extrusion was observed; Intrusion significantly reduced PBF after 5 min, gradually returning to its normal values	Intrusive forces produced a temporary reduction in PBF, whereas extrusion had no effects on PBF
Ersahan & Sabuncuoğlu (2015) – RCT	20 (Group 1: 10; Group 2: 10)	20-40 (27.6) years	Mini-implant	Maxillary first molars	Intrusive	125 g (Group 1 – Light Forces); 250 g (Group 2 – Heavy Forces)	Contralateral molars	2 teeth per participant (1 submitted to intrusive forces and 1 as contralateral control group) Group 1: *n* = 10; Control group 1: *n* = 10; Group 2: *n* = 10; Control group 2: *n* = 10	Before intrusion; 24 h, 3, 7 days, 3, 4 weeks, 3 and 6 months after intrusion.	6 months	No significant changes in PBF were observed in the control group at any point during the study; IN RELATION TO THE DURATION OF INTRUSION: PBF in study groups did not statistically change at 24 h; significantly decreased after 3 days and remained suppressed up to 3 weeks. PBF increased after 3 weeks, returning to normal values after 3 months and remaining normal after 6 months IN RELATION TO THE AMOUNT OF INTRUSIVE FORCE: No significant differences were found between the study groups at 24 h; Significant decrease in PBF was observed in the heavy force group at 3 and 7 days compared to the light forces group;	PBF reduction occurred up to 3 weeks, returning to normal values after 3 months; A more pronounced PBF reduction was observed at 3 to 7 days in the heavy forces group, without differences at other time-points.

Table 1 Continued

Authors (year of publication) – study design	Number of participants	Participants' age (mean)	Type of orthodontic device	Type of teeth evaluated	Type of movement	Force applied	Comparison	Number of teeth per group	Times of pulp status assessment	Duration of forces	Outcome	Main finding
											No significant differences between both study groups were observed at any other times	
Ersahan & Sabuncuoğlu (2018) – nRCT	28 (Young group: 14; Old group: 14)	Young group: 18-25 (20.3) years; Old group: 42-55 (47.6) years	Pre-adjusted edgewise fixed appliance	Maxillary left central and lateral incisors	Alignment and levelling (not specified)	NR	Contralateral central and lateral incisors	4 teeth per participant (2 submitted to fixed orthodontic treatment and 2 as contralateral control group) Young group: n = 28; Control young group: n = 28; Old group: n = 28; Control old group: n = 28	Prior to orthodontic bracket bonding; 24 h, 3, 7 days, 3 weeks and 1 month following the application of orthodontic force	NR	PBF did not change in the control teeth at any point; PBF at baseline significantly differ amongst groups; Young group presented higher PBF values compared to the old group at all time-points; YOUNG GROUP: PBF reduced significantly after 24 h, 3 and 7 days, returning to normal values after 3 weeks and remaining normal after 1 month; OLD GROUP: PBF reduced significantly after 24 h and 3 days. Increased significantly after 7 days and 3 weeks, but did not returned to baseline levels at the end of the study	Younger participants had significantly higher PBF values compared to older participants at all time-points; PBF decreased in the young and old participants; Returned to normal values within 1 month for the younger participants; PBF decrease in the older participants was more severe and of longer duration
McDonald & Pitt Ford (1994) – Prospective	10	11.2-13.4 (12.6) years	Removable device	Maxillary canines	Retraction	50 g	Contralateral canines	2 teeth per participant (1 submitted to retraction forces and 1 serving as control group) Removable appliance group: n = 10; Control group: n = 10	Prior to force appliance; 10, 30 and 60 min after force appliance; 1, 2 and 3 days after force appliance	4 days	Statistically significant PBF decrease, followed by a significant increase, was observed up to 32.3 (mean) minutes; PBF increase was observed at 24 and 48 h, returning to baseline values within 72 h	A decrease followed by an increase on PBF was observed, returning to normal values within 72 h
Sabuncuoğlu & Ersahan (2014) – RCT	20 (Group 1: 10; Group 2: 10)	18-25 (20.3) years	Mini-implant	Left central and lateral incisors	Intrusive	40 g (Group 1 – Light Forces); 120 g (Group 2 – Heavy Forces)	Contralateral incisors	4 teeth per participant (2 submitted to intrusive forces and 2 as	Prior to intrusion; 3 days and 3 weeks after intrusion	5–6 months	No significant changes in PBF were observed at baseline values amongst groups and in the control group at any point during the study;	Regardless of the force applied, PBF decrease was observed at 3 days of

Table 1 Continued

Authors (year of publication) – study design	Number of participants	Participants' age (mean)	Type of orthodontic device	Type of teeth evaluated	Type of movement	Force applied	Comparison	Number of teeth per group	Times of pulp status assessment	Duration of forces	Outcome	Main finding
								contralateral control group) Group 1: *n* = 20; Control group 1: *n* = 20; Group 2: *n* = 20; Control group 2: *n* = 20			In both experimental groups, significant PBF decrease was observed at 3 days of intrusion, returning to baseline values after 3 weeks; No significant differences were observed between mean PBF values of the two experimental groups at any of the observation times	intrusion, returning to normal values within 3 weeks
Sabuncuoğlu & Ersahan (2016) – RCT	24 (Experimental group: 12; Control group: 12)	19-25 (21.91) years	Mini-implant	Maxillary canines	Retraction	100 g (after 1 week of placement)	Same teeth before orthodontic movement	2 teeth per participant Experimental group: *n* = 24; Control group: *n* = 24	Prior to canine retraction, 24 h, 3 days, 7 days, 4 weeks after the retraction; at the end of the retraction	4 months	No significant changes in PBF were observed in the control group at any point during the study; PBF in the study group significantly increased at 24 hand decreased after 3 to 7 days; No statistical differences were observed before 4 weeks and at the end of retraction compared to baseline	PBF changes occurred up to 7 days, returning to normal values within 1 month
Salles *et al.* (2013) – Prospective	12	17.5 ± 3 years	Pre-adjusted edgewise fixed appliance	Maxillary left central incisors	Alignment and levelling – (tipping, intrusion or extrusion)	0.7 – 1 N	Same teeth before orthodontic movement	1 tooth per participant *n* = 12	Prior to the wire activation, after the placement of the wire, 20 min, 48, 72 h and one month after setting the wire	NR	Statistically significant decrease of PBF was observed at 20 min, 48, and 72 h; No differences were found comparing PBF on day 30 and the corresponding basal values	Decrease in PBF was verified during the initial phase of the treatment, followed by a recovery after 30 days
Sano *et al.* (2002) – Prospective	13 (Experimental group: 8; Control group: 5)	27-31 years	Fixed orthodontic device (continuous intrusive force); Intrusive force apparatus (gram gauge – brief intrusive force)	Maxillary left central incisors	Intrusive	Continuous force: 0.5 N; Brief force: 0.5, 1 and 2 N, during 20 sec each force and with an interval of 30 sec between force application, every session before temporarily removing the arch wire	Maxillary left central incisors	1 tooth per participant Experimental group: *n* = 8; Control group: *n* = 5	Continuous forces: Four times during the 2 weeks before wire engagement (intervals 1-5 days); during wire engagement (days 1, 2, 3, 4, 5 and 6); post-engagement (days 1, 3 and 5); Brief forces: after force application	14 days	PBF did not change in the control teeth at any point; PBF in continuous force group significantly reduced during force application, returning to normal values after wire removal; Brief intrusive force produced a significant reduction on PBF, without differences during the observation periods	PBF reduced in continuous force application, returning to normal values in post-engagement period; Brief forces reduced PBF regardless of the observation period

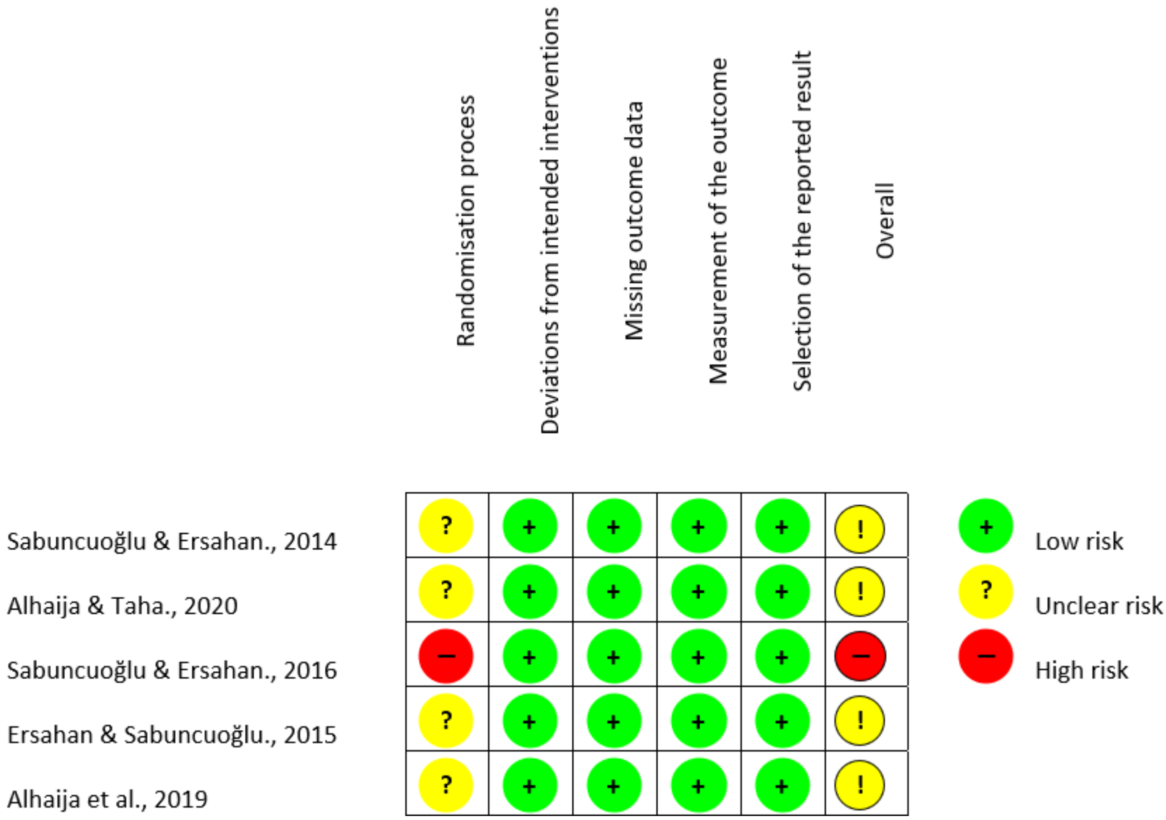

Figure 2 Quality assessment of the randomized clinical trials according to Cochrane Collaboration common scheme for bias and RoB 2 tool.

studies (Sabuncuoğlu & Ersahan 2014, Ersahan & Sabuncuoğlu 2015) stated that the random distribution of participants was performed but did not describe the randomization method, nor the method of allocation concealment. One study (Abu Alhaija *et al.* 2019) stated the method of randomization (coin toss) and did not apprise the method for allocation concealment. Another study (Abu Alhaija & Taha 2020) did not describe the randomization method but reported the allocation concealment (opaque envelopes). Whilst these four studies were considered to present unclear bias, one study (Sabuncuoğlu & Ersahan 2016) was classified as having a high risk of bias due to the lack of randomization and allocation concealment.

Regarding the risk of bias assessment of the non-randomized studies, although controlling for all possible confounding factors is difficult, four prospective studies (McDonald & Pitt Ford 1994, Brodin *et al.* 1996, Babacan *et al.* 2010, Salles *et al.* 2013) did not report on the control for any confounders, whilst two others (Barwick & Ramsay 1996, Sano *et al.* 2002) specified control for only a few confounders, resulting in a serious to moderate risk of bias, respectively. Only the nRCT study (Ersahan & Sabuncuoğlu 2018) was considered as having a low risk of bias.

Mainly due to these limitations of the included studies, the overall quality of evidence classified using the GRADE tool was low to very low. The GRADE tool has five domains that can be downgraded and reduce the quality of evidence (Grades of Recommendation Assessment Development & Evaluation (GRADE) Working Group 2004). The domain 'risk of bias' includes the assessment of several parameters such as eligibility criteria, measurement of exposure and outcome, and control of confounding factors (Guyatt *et al.* 2011b). In this domain, the randomized clinical trials received the 'serious' classification because four studies did not perform or report a random sequence allocation (Sabuncuoğlu & Ersahan 2014, 2016,

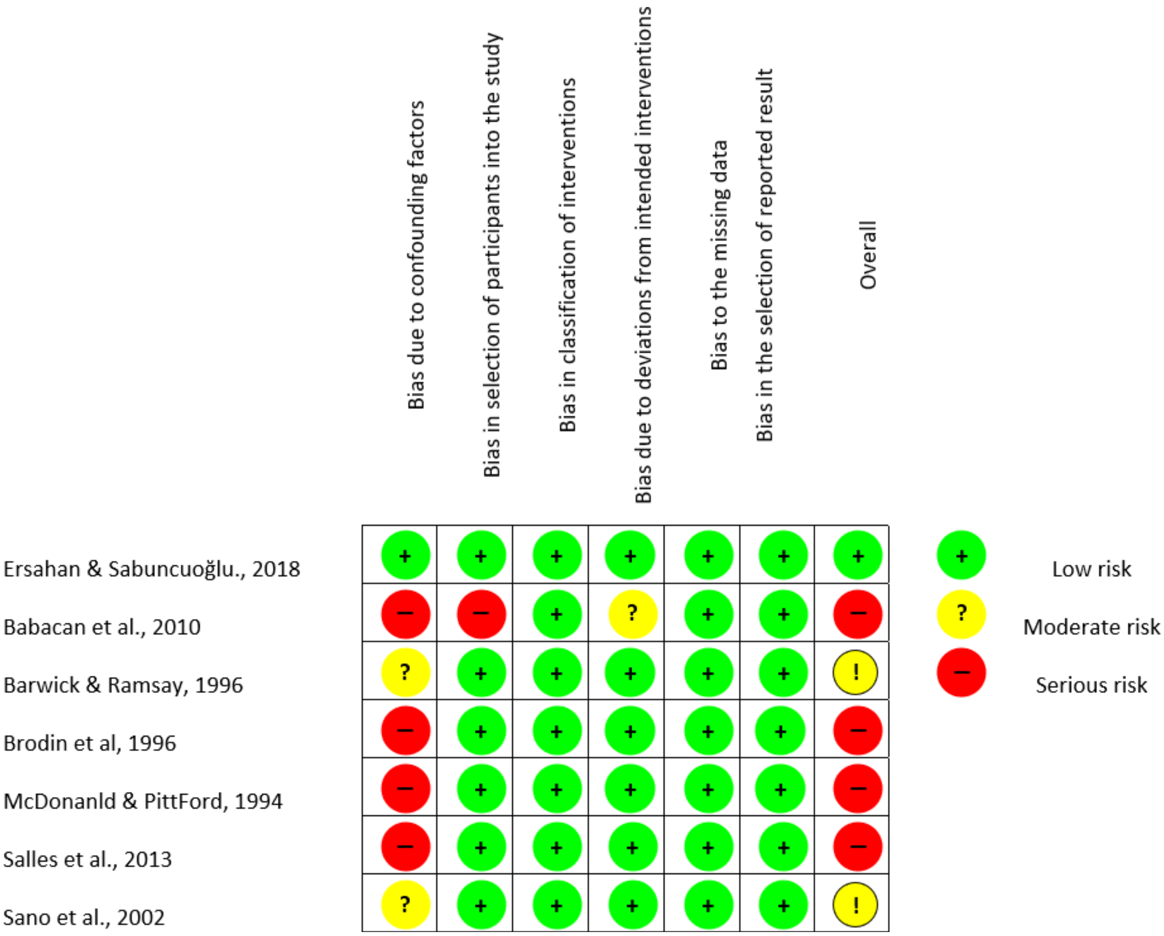

Figure 3 Quality assessment of the nonrandomized studies according to Cochrane Collaboration common scheme for bias and ROBINS-I tool.

Ersahan & Sabuncuoğlu 2015, Abu Alhaija & Taha 2020), three studies did not provide information on allocation concealment (Sabuncuoğlu & Ersahan 2014, Ersahan & Sabuncuoğlu 2015, Abu Alhaija *et al.* 2019), and one study did not perform an allocation concealment (Sabuncuoğlu & Ersahan 2016). The nonrandomized studies received the 'very serious' classification for risk of bias because three studies did not have any control and used only baseline values for comparison (Barwick & Ramsay 1996, Babacan *et al.* 2010, Salles *et al.* 2013), one study used a non-reliable method to measure for confounding factors (Salles *et al.* 2013), three studies did not report for control of confounding factors (McDonald & Pitt Ford 1994, Brodin *et al.* 1996, Babacan *et al.* 2010), and three studies did not control for all possible confounding factors (Barwick & Ramsay 1996, Sano *et al.* 2002, Salles *et al.* 2013). The domain 'inconsistency' refers to an unexplained heterogeneity of results (Guyatt *et al.* 2011c), and it was considered 'not serious' since all included studies did not present unexplained heterogeneity. The domain 'indirectness' is made up of differences in population, interventions, outcomes measures and indirect comparisons (Guyatt *et al.* 2011d), and it was considered 'not serious' since all included studies presented more than 3 'no' for the assessed parameters. The domain 'imprecision' was assessed following the recommendations of Murad *et al.* (2017), since the present systematic review did not include a meta-analysis and, for this reason, the single pooled estimate of the effect could not be assessed. The recommendations are to consider the total number of participants (i.e. the pooled sample size) of the included studies and the confidence

Table 2 Quality of evidence for changes in pulpal blood flow in orthodontically treated teeth

Certainty assessment							
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence
5	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW
7	Nonrandomized studies[c]	Very serious[d]	Not serious	Not serious	Serious[b]	None	⊕◯◯◯ VERY LOW

[a]4/5 studies did not perform or inform a random sequence allocation, 3/5 studies did not inform about allocation concealment, and 1/5 did not perform allocation concealment.
[b]Pool sample size lower than 400.
[c]1 nonrandomized clinical trial and six prospective studies.
[d]3/7 studies did not report any control group and used only baseline values for comparison, 1/7 study used a nonreliable method to measure confounding factors, 3/7 studies did not report for control of confounding factors, and 3/7 studies did not control for all possible confounding factors.

interval (CI) of the largest studies (Murad *et al.* 2017). A pooled sample size of less than 400 is concerning for imprecision, as well as results may be imprecise when the CIs of the largest studies include no effect and meaningful benefits or harms (Murad *et al.* 2017). Therefore, the domain 'imprecision' was considered 'serious' for both randomized and nonrandomized studies, since their pooled sample size was less than 400, and the 95% CI of the studies with the widest samples did not include meaningful benefit or harm. The domain 'other consideration' included the assessment of publication bias, large effect, plausible confounding and dose–response gradient (Guyatt *et al.* 2011e, Ryan & Hill 2016), and none of them were likely to interfere in the results or downgrade the certainty of evidence of the included studies.

When evaluating the main findings presented by the majority of the studies, the evidence confirmed that orthodontic movements were associated with a reduction in pulpal blood flow, followed by a return to average values (McDonald & Pitt Ford 1994, Brodin *et al.* 1996, Sano *et al.* 2002, Salles *et al.* 2013, Sabuncuoğlu & Ersahan 2014, 2016, Ersahan & Sabuncuoğlu 2015, 2018, Abu Alhaija *et al.* 2019, Abu Alhaija & Taha 2020), regardless of the type of orthodontic device, force duration, force applied or types of teeth treated orthodontically.

These findings suggest that orthodontic movements induce reversible metabolic changes of the pulp, as previously reported (Veberiene *et al.* 2010). The initial PBF reduction might be associated with the strangulation of the blood flow, causing a consequent oxygen reduction and metabolic and histological changes (Stenvik & Mjör 1970, Hamersky *et al.* 1980, Mostafa *et al.* 1991, Perinetti *et al.* 2005). Due to these alterations, cellular degeneration occurs (Mostafa *et al.* 1991, Han *et al.* 2013), causing an increase of aspartate aminotransferase (AST Perinetti *et al.* 2004, Veberiene *et al.* 2009, 2010). Besides being a biological marker of cell necrosis, AST is also an essential mediator of the inflammatory process (Spoto *et al.* 2001). This inflammatory process takes places, and the liberation of several growth factors occurs (Derringer *et al.* 1996, Derringer & Linden 1998), resulting in a histological rearrangement, mainly characterized by vascular changes along with the presence of fibrotic tissue (Mostafa *et al.* 1991, Ramazanzadeh *et al.* 2009, Lazzaretti *et al.* 2014) and possible pulp calcifications (Han *et al.* 2013, Lazzaretti *et al.* 2014).

Moreover, one study (Ersahan & Sabuncuoğlu 2015) reported a more pronounced PBF reduction when large forces (250 g) were applied. These results follow previous findings that demonstrated that large orthodontic forces could induce more significant alterations in the pulp tissues (Stenvik & Mjör 1970, Han *et al.* 2013). Although the loss of pulp vitality was not observed, it is essential to emphasize that there seems to be a correlation between the increase in orthodontic forces and the occurrence of root resorption (Stenvik & Mjör 1970, Weltman *et al.* 2010, Han *et al.* 2013). Another study (Ersahan & Sabuncuoğlu 2018) reported a more severe and longer duration PBF reduction in older patients. These results also follow previous findings that verified a positive correlation between age increase and respiratory depression increase, indicating a relationship between the biological effect of an orthodontic force and the maturity of the tooth (Hamersky *et al.* 1980, Unsterseher *et al.* 1987).

Only one study (Babacan *et al.* 2010) reported a PBF increase without a preceding PBF reduction, probably because the authors evaluated the orthodontic device and treatment. In this study, a device for rapid maxillary expansion was used, and LDF evaluated the PBF of maxillary central incisors, canines and first molars. Since the basis for this orthopaedic procedure is to create forces at the midpalatal suture to achieve suture separation, the anchor teeth may not directly receive the forces applied. Therefore, only a PBF increase is observed due to the inflammatory process established, decreasing and returning to average values after opening of the suture (Babacan *et al.* 2010).

Regarding the studies that evaluated the PBF of teeth after applying brief forces (Barwick & Ramsay 1996, Brodin *et al.* 1996), the divergent results reported when brief intrusive forces were evaluated might be explained due to methodological variations amongst these studies.

Due to the high heterogeneity of the methodological aspects of the studies, a meta-analysis was not conducted. This systematic review was also limited in verifying if the orthodontic movements could induce the loss of pulp vitality and did not evaluate other aspects such as correlations between orthodontic movements and root resorptions or pulp calcifications. Another limitation of this systematic review is that it was not possible to establish a possible relationship between the influence of orthodontic movements and the loss of pulp vitality in traumatized teeth since, no studies have evaluated such aspects through the use of the diagnostic methods (LDF and PO) included in this systematic review.

When comparing the results of this systematic review with those presented by previous ones (Böhl *et al.* 2012, Javed *et al.* 2015), it is possible to verify a similarity regarding the information provided. There is a lack of high-quality studies and a need for more research to confirm the findings. However, as previously stated, in this systematic review, only studies that used LDF or PO were included, unlike the previous studies that were not limited to these methods. Therefore, a stricter comparison of results was not possible.

As for the implications of this systematic review on future research, it has confirmed the need for well-conducted research on the subject, with a great need to adopt stricter criteria regarding randomization and allocation concealment processes as well as controlling for confounders. Regarding the future directions for clinical practice, the results of the present systematic review suggest that orthodontic movements do not induce pulp necrosis, without considering co-factors that were not evaluated such as history of traumatism, orthodontic and/or endodontic treatments and the presence of alterations such as pulp stones, calcifications, mobility, caries and/or restorations. However, this suggestion is based on a very low to low quality of evidence. Meanwhile, in the absence of better-quality information that can confirm the above suggestions, orthodontic treatments, respecting the use of low orthodontic forces, appear to be safe in terms of pulp vitality.

Conclusion

It is possible to conclude that, when evaluating the pulp status after orthodontic treatments, using LDF, there is evidence that these treatments do not induce pulp necrosis. However, this evidence has low to very low quality and more well-designed studies are necessary. Therefore, orthodontic treatments should still be performed with caution, respecting the use of low forces.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Search strategy in each database.

