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Hyalinization during orthodontic tooth movement: a systematic review on tissue reactions

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SUMMARY The purpose of this study was to perform a meta-analysis on the literature concerning hyalinization in relation to experimental tooth movement in animals and humans. A structured search of electronic databases as well as hand searching retrieved 70 publications concerning the subject. After application of inclusion and exclusion criteria, 39 studies remained, of which three were in humans. Articles on animal experiments were in the majority with most studies performed in rats. Among other data force magnitude, type of tooth movement, duration of the experimental period, and moment of first and last appearance of hyalinization were extracted from the included studies. The heterogeneity of the published studies and the limited data on appearance of hyalinization made it impossible to perform a meta-analysis. Therefore, the literature was systematically reviewed.

It appears that there are no major differences in tissue reaction between species during experimental tooth movement. Although hyalinization is considered to be an undesirable side-effect of orthodontic tooth movement, little attention has been paid to the phenomenon itself and its possible relationship with stress/strain levels in the periodontal ligament (PDL) and alveolar bone or the rate after the initial phase of tooth movement. There is a need for well-designed experimental studies to elucidate the role of hyalinization in orthodontic tooth movement.

Introduction

The purpose of orthodontic treatment is to move teeth as efficiently as possible with minimal adverse effects for the teeth and supporting tissue. Over the past 100 years, many studies on cellular, molecular, and tissue level reactions related to orthodontic tooth movement have been published, which were recently summarized in four reviews (Krishnan and Davidovitch, 2006; Masella and Meister, 2006; Meikle, 2006; Wise and King, 2008). It is assumed that an optimal force system is important for an adequate biological response in the periodontal ligament (PDL; Burstone, 1984). Factors such as the type and magnitude of force (Storey and Smith, 1952; Reitan, 1985; Maltha *et al.*, 2004) or treatment duration (Pilon *et al.*, 1996) are found to be coherent with undesirable tissue reactions such as sterile necrosis or root resorption. The appearance of necrotic tissue (also called hyalinization) is an important component in the process of tooth movement.

Mainly based on histological research, a pressure and a tension side are distinguished during orthodontic tooth movement. Although more recent research has shown that the pressure/tension side theory is not that straightforward as was previously assumed (Melsen, 2001), this terminology is still used for descriptive purposes. On the pressure side, the biological events are as follows: disturbance of blood flow in the compressed PDL, cell death in the compressed area of the PDL (hyalinization), resorption of the hyalinized tissue by macrophages, and undermining bone resorption by osteoclasts beside the hyalinized tissue, which ultimately results in tooth movement. On the tension side, blood flow is activated where the PDL is stretched, which promotes osteoblastic activity and osteoid deposition, which later mineralizes. Studies over the past 100 years have reported that hyalinization appears in local pressure zones of the PDL during 'the initial phase' of orthodontic tooth movement. Experimental studies have demonstrated advanced vascular and cellular changes in the PDL after only a few hours of force application. Recently, von Böhl *et al.* (2004b) showed that not only in the initial phase of orthodontic tooth movement could hyalinization be observed but also in the later stages small hyalinized patches were found. These findings confirmed the outcome of a study on changes of the PDL during experimental tooth movement with a similar experimental set-up by Kohno *et al.* (2002). However, these findings are contrary to the commonly accepted theory of the relationship between tooth displacement and hyalinization. Hyalinization during the later stages of tooth movement could, partly, explain the differences observed clinically in the rate of tooth movement between different patients.

Therefore, the aim of the present study was to perform a systematic review of the literature on hyalinization in relation to experimental tooth movement in animals and humans.

Material and methods

Search strategy for identification of studies and data selection

Medline, PubMed, and Embase were searched until 16 May 2008 using the following search strategy:

Furthermore, an Entrez cross-database search was performed using the same search strategy. The Cochrane

Searching keywords	Number of publications
#1 Search ("Tooth Movement"[MeSH] OR "Orthodontics"[MeSH] OR "Orthodontics, Interceptive"[MeSH] OR "Orthodontics, Corrective"[MeSH]	33192
#2 Search "Hyalin"[MeSH] OR hyalin*	11987
#3 Search #1 AND #2	60

Library (Cochrane Reviews database, Central and Dare) was searched for clinical studies until issue 2, 2008. Publications before 1945 and the most recent ones were hand searched in the main dental and orthodontic journals. Most articles were found in the following journals: American Journal of Orthodontics and Dentofacial Orthopedics, Angle Orthodontist, Archives of Oral Biology, European Journal of Orthodontics, International Journal of Calcified Tissue, and the European Journal of Oral Sciences, formerly the Scandinavian Journal of Dental Research. The reference lists of selected articles were searched and references to related articles were followed-up. The sources retrieved by #3 and by hand searching were evaluated by two independent observers (MVB and AMK-J) using the following inclusion criteria:

- Written in English or Dutch
- Primary data source
- Human, monkey, dog, cat, rabbit, rat, or mouse were used as species
- Sample size should be given
- Force level should be quantified
- Tooth type
- Data concerning hyalinization

Data extraction

The same two observers extracted, independent of each other, the following data from each included study:

- Year of publication
- Species
- Sample size
- Initial force magnitude
- Type of tooth movement
- Teeth moved
- Duration of experimental period in days
- Root preparation and cutting plane for histological evaluation
- Moment of first appearance of hyalinization after force application

If there was disagreement between the observers, the data were confirmed by mutual agreement.

Results

In total, 70 publications were found related to the topic of this review, 60 articles by electronic, and 10 by hand searching. After application of the inclusion criteria, 39 of the 70 studies remained (Tables 1 and 2). Thirty-six studies were performed in animals with a wide range of species but most of them in rats (n = 27). Three papers dealt with experiments in humans (Table 2).

The general results can be summarized as follows:

In 27 of the 39 included articles, experiments were performed in the rat and/or mouse (Table 1). The number of animals involved in these experiments varied from 10 to 160 and the duration of the experimental period from 30 minutes to 42 days. The applied forces ranged from 1.2 to 50 cN. In one experiment, the incisors were involved, while in the other rat studies, the maxillary molars were moved by tipping forces. In most studies, histological sections were cut parallel to the long axis of the tooth (sagittal), and in only three of the 27 studies was the cutting plane in two directions. In 13 studies, the first appearance of hyalinization was reported within the first 24 hours. The other studies reported various moments of first hyalinization.

The studies dealing with rabbit (n = 1), cat (n = 1), dog (n = 5), monkey (n = 2), and humans (n = 3) are shown in Table 2. The duration of the experiments ranged from 3 hours to 112 days. Severe damage to the PDL (no hyalinization) was described after rabbit incisors were moved for just 3 hours (Kuitert *et al.*, 1988). In the five studies on dogs, a wide variety of force levels were used ranging from 25 to 450 cN and mostly the teeth were moved bodily. The duration of the experimental period varied from 1 to 90 days. In all but one, the histological sections were cut parallel to the long axis of the teeth. The first appearance of hyalinization was seen after 1 day, while the last appearance of hyalinized tissue was not always exactly reported. Two studies found necrotic tissue not only in the phase of rest (between 4 and 20 days after force application) but also during and after the acceleration phase, at 28 days (Iino *et al.*, 2007) and after 40 and 80 days of tooth movement (Von Böhl *et al.*, 2004a).

In three of the 39 articles, experiments were performed in humans. The number of subjects, in the experiment, varied between 12 and 56 and forces ranged from 50 to 70 cN. The duration of the experiments varied from 5 to 76 days and the first appearance of hyalinization was reported after 5 days, while in one study hyalinized tissue was still observed at 49 days.

Discussion

In contrast to the classic narrative review, a systematic review analyses the literature according to type predefined inclusion and exclusion criteria. A special type of systematic

Table 1 Rat and mouse studies included in the review (*n* = 27). The type of tooth movement in all investigations was tipping. Studies are listed chronologically starting from the most recent.

Authors	Year	Species	*n*	Force (centri Newton)	Teeth (maxillar)	Time of sacrifice	Cutting plane	First hyalinization	Last hyalinization
Tomizuka *et al.*	2007	Rat	43	2.3 → 13.5 5→ 13.5	M1	1, 3, 7, 10, 14 d	Horizontal	1 d	10 d
Hamaya *et al.*	2002	Rat	84	10	M1	3, 6, 12 h; 1, 2, 4, 7 d	Horizontal	After 6 h	
Kohno *et al.*	2002	Rat	40	1.2, 3.6 6.5, 10	M1	7, 14 d	Horizontal	7 d	14 d
Nakamura *et al.*	2001	Rat	90	15	M1	1, 3, 5, 7 d	Horizontal	1 d	7 d
Miyoshi *et al.*	2001	Rat	100	16.5	M1	3, 7, 14, 21 d	Horizontal	7 d	14 d
Tengku *et al.*	2000	Rat	32	30	M1	1, 3, 7, 14 d	Sagittal	1 d	14 d
Vandevska-Radunovic *et al.*	1997b	Rat	31	50	M1	3, 7, 14, 21 d	Sagittal/horizontal	7 d	
Vandevska-Radunovic *et al.*	1997a	Rat	35	50	M1	3, 7, 14, 21 d	Sagittal/horizontal	7 d	14 d
Hellsing and Hammarström	1996	Rat	42	25	M1	1, 3, 7, 14, 21, 28, 35, 42 d	Sagittal	1 d	35 d
Kagayama *et al.*	1996	Rat	10	10	M1	3, 7 d	Horizontal	3 d	7 d
Brudvik and Rygh	1995	Rat	24	50	M1	2, 3,7,10,14, 21 d	Sagittal	2 d	10 d
Brudvik and Rygh	1994a	Rat	12	50	M1	7,10 d	Sagittal	7 d	10 d
Brudvik and Rygh	1994b	Rat/mouse	25	50	M1	7,14 d	Sagittal	7 d	14 d
Brudvik and Rygh	1993a	Rat/mouse	49	50	M1	1, 2, 3, 4, 5, 6, 7, 8 d	Sagittal	1 d	8 d
Brudvik and Rygh	1993b	Rat	21	50	M1	6, 12, 24 h, 2, 3, 4 d	Sagittal	1 d	4 d
Brudvik and Rygh	1991	Rat	25	50	M1	3, 7, 10 d	Sagittal	3 d	10 d
Hellsing and Hammarström	1991	Rat	16	15	M1	21 d	Sagittal	21 d	21 d
Bridges *et al.*	1988	Rat	48	60	M1/2	1, 3, 5, 7,14 d	Sagittal/horizontal	3 d	7 d
Engström *et al.*	1988	Rat	160	50	I1	3, 7 d	Horizontal	3 d	7 d
Rygh *et al.*	1986	Rat	45	18–40	M1	2, 7, 14, 28 d	Sagittal	2 d	14 d
Lindskog and Lilja	1984	Rat	12	20, 40	M1	3 h, 1, 3, 9 d	Horizontal	1 d	9 d
Rygh	1977	Rat	67	5, 10, 25	M1	30 min, 2, 6, 12, 24 h2, 3, 5, 14, 28 d	Sagittal	6 h	14 d
Rygh	1974a	Rat	67	5, 10, 25	M1	30 min, 2, 6, 12 h 1, 2, 3, 5, 14, 28 d	Sagittal	2 d	After 5 d still present
Rygh	1974b	Rat	67	5, 10, 25	M1	30 min, 2, 6, 12, 24 h 2, 3, 5, 7, 14, 28 d	Sagittal	6 h	After 5–7 d still present
Rygh	1973	Rat	67	5, 10, 25	M1	30 min, 2, 6, 12, 24 h 2, 3, 5, 7, 14, 28 d	Sagittal	6 h	14 d
Rygh	1972	Rat	67	5, 10, 25	M1	30 min, 2, 6, 12, 24 h 2, 3, 5, 7, 14, 28 d	Sagittal	6 h	After 5–7 d still present
Kvam	1972a	Rat	38	20	M1	1, 12 h, 1, 2, 3 d 4, 5, 6, 7, 9, 11 d	Sagittal	1 d	9 d

I1, central incisor; M1/M2, first/second molar; d, days; →, increasing force level during experiment.

review is the meta-analysis, which statistically combines the results from separate but comparable studies to provide an overall quantitative summary (Petrie *et al.*, 2003). In the present research, the aim was to perform a systematic review of existing data in the literature concerning hyalinization and tooth movement. While this aim was achieved, it was not possible to perform a subsequent meta-analysis as the data could not be combined for statistical analysis. Three main problems encountered were inhomogeneity of the experimental set-up, variability in the sections, which were evaluated for the presence of hyalinization, and a large interindividual variation in the biological response to force.

In most studies, tipping tooth movements had been performed, which leads to uneven stress and strain distribution in the PDL. This experimental set-up makes it impossible to induce hyalinization in a reproducible way. Furthermore, in most studies, the experimental period was rather short, which makes it questionable whether the linear phase of tooth movement was ever reached. This is important as structural changes in the bony and periodontal tissues during the different phases of tooth movement alter the local biomechanical environment, which leads to modulation of the biological response. Besides, in most studies, the orientation of the histological sections may have masked

Table 2 Studies on other species included in the review (n = 12). Listed by the first author and according to species.

First authors	Year	Species	n	Force cN	Type of movement	Teeth	Time of sacrifice	Cutting plane	First hyalinization	Last hyalinization
Kuitert *et al.*	1988	Rabbit	35	50	Tipping	I1 max	3, 6, 24 h	Horizontal	3 h	1 d
Furstman *et al.*	1971	Cat	3	150	Tipping	C max/mand	1, 3, 5 d	Sagittal	24 h	5 d
Iino *et al.*	2007	Dog	12	50	Tipping	P3 mand	7, 14, 28, 56 d	Sagittal (mesial–distal)	7 d	28 d
Von Böhl *et al.*	2004b	Dog	15	25	Bodily	P2/M1 mand	1, 4, 20, 40, 80 d	Sagittal (mesial–distal)	1 d	80 d
Von Böhl *et al.*	2004a	Dog	15	25,300	Bodily	P2/M1 mand	1, 4, 20, 40, 80 d	Sagittal (mesial-distal)	1 d	80 d
Oates *et al.*	1978	Dog	1	60	Bodily	P2 max	12 d	Sagittal (mesial-distal)	?	?
Fortin	1971	Dog	6	145–450	Bodily	P1 mand	30, 90 d	?	7–14 d	?
Melsen	2001	Monkey	6	10	Intrusion	I1−I2 max	112d	Horizontal	?	?
Melsen	1999	Monkey	5	100, 200, 300	Bodily	P2/M3 mand	77d	Horizontal	?	?
Kurol and Owman-Moll	1998	Human	56	50	Tipping	P1/P2 max	7, 14, 21, 28 d 35, 42, 49 d	Sagittal (bucco-palatal)	7 d	49 d
Buck and Church	1972	Human	12	70	Tipping	P1 max	7, 14, 21, 28 d	Horizontal	7 d	14 d
Kvam	1972b	Human	40	50	Tipping	P1 max	5, 10, 15, 25, 30, 35, 45, 76 d	?	5 d	10 d

n, sample size; cN, centiNewton; I1/I2, central/lateral incisor; C, canine; P1/P2/P3, first/second/third premolar; M1/M2/M3, first/second/third molar; max, maxilla; mand, mandible; d, days; →, increasing force level during experiment; ?, no information available in the publication.

the presence of hyalinization. Mostly, the roots were cut parallel to the long axis in the midsagittal plane of the tooth. However, it has been shown previously that as a consequence of local stress and shear concentrations, most hyalinized areas are not found in the area of the central plane but lingually and buccally from it (Von Böhl *et al.*, 2004a,b). Evaluation of only a few vertical sections around the central plane as carried out in most of the studies ignores the presence of hyalinization, which leads to different outcomes.

Finally, the data showed large interindividual variations in the biological response to a force, which makes it difficult to compare results of different studies. In an earlier systematic review on force magnitude in relation to orthodontic tooth movement (Ren *et al.*, 2003), the same problems were encountered, which prevented statistical analysis of summary results across the included studies.

In this review, both animal and human studies were included. Systematic reviews of animal studies continue to be controversial. According to the Reviewing Animal Trials Systematically (RATS) group, a great deal of animal research is wasted because of poor evaluation through systematic reviews and it should be made obligatory to conduct a systematic review of animal studies before human studies begin (Pound *et al.*, 2004). However, animal and clinical studies have important differences. Animal studies try to control all possible variables besides the studied intervention. For ethical reasons, the number of animals has to be restricted and earlier research cannot simply be repeated. Moreover, each experiment necessarily differs in its design, method, and outcome variables from those that have been carried out earlier making it difficult to combine data from different studies. For this reason, Lemon and Dunnett (2005) argued for a critical rather than a systematic review. The opinion held by the authors of the present study is that concurrent systematic analysis of experimental and human studies, as performed in this review, ensures the best use of available data.

In the present systematic review on hyalinization during orthodontic tooth movement, two main groups of studies were distinguished: those describing changes of bone, root surface, and PDL at the histological level and papers related to differences in response to applied forces.

Histological studies

Sandstedt (1904) reported bone resorption on the pressure side and bone deposition on the tension side after force application to a tooth, resulting in discussions about ideal or optimal magnitude of orthodontic forces. Schwarz (1932) stated that physiological tooth movement without damage to the PDL or root should be possible if the pressure in the PDL does not exceed capillary blood pressure. Vandevska-Radunovic *et al.* (1997a,b) more than 60 years later came to similar conclusions. Ultrastructural changes of the PDL have been investigated extensively by Rygh (1972, 1973, 1974a,b, 1977), Rygh *et al.* (1986), and Brudvik and Rygh (1991, 1993a,b, 1994a,b, 1995). All these studies proceed from the assumption that the normal structure and organization at the pressure side of the PDL is lost first and accompanies arrest in tooth movement, and secondly, the resulting necrotic tissue must be broken down by phagocytosis. In this process of undermining resorption, an influx of phagocytotic cells such as macrophages, foreign body giant cells, fibroblasts, and (pre)osteoclasts invade from the adjacent undamaged areas and eliminate the hyalinized tissue, which makes orthodontic tooth movement possible. In recent publications, however, necrotic tissue was found not only in the phase of arrest but also during acceleration and the linear phase of experimental tooth movement (Kohno *et al.*, 2002; von Böhl *et al.*, 2004a,b; Iino *et al.*, 2007). Interestingly Iino *et al.* (2007) found hyalinization of the PDL after corticotomy at the same side only after 7 days but not at later stages, possibly due to initial acceleration of the bone turnover mechanism. Taking all findings together, it is suggested that development and removal of hyalinization is a process instead of a single event during tooth displacement. This would explain the appearance of necrotic tissue not only during the second phase of the time-displacement curve (the phase of rest) but also in the linear phase. Therefore, the time point during orthodontic tooth movement at which histological evaluation takes place seems to be decisive in identifying hyalinization. In this respect, histological analysis of human material is limited by the fact that orthodontically moved teeth have to be extracted, which disrupts the PDL, while the surrounding bone cannot be investigated.

In addition, this review showed that in rats and mice hyalinization occurred earlier in the experimental phase than in other species. Reitan and Kvam (1971) reported that the alveolar bone in rats showed a higher density than in humans. In addition, the osteoid layer along the bone surface seems to be less abundant in rats than in humans, which could explain the faster hyalinization. The narrower width of the rats' PDL induces higher forces and relatively more local strain on the alveolar bone, which leads to a diminished blood flow and formation of a necrotic area. Another explanation could be the higher rate of bone turnover during the remodelling process incident to orthodontic tooth movement in rats than in humans (Kvam, 1967; Rygh, 1974b).

Studies related to individual differences in response to applied forces

The findings of this review showed a wide variety of applied force levels. However, a clear relationship between force level, timing, and extent of hyalinization could not be found. Even with a force as low as 5 cN, hyalinization occurred and the timing of the event seemed to be independent of the force level. The assumption that higher forces lead to more hyalinization cannot be confirmed from the data of this review. An interesting finding from a recent study, however, was that an initially light and gradually increasing force resulted in less hyalinization than a heavier initial force that increased to the same end force level (Tomizuka *et al.*, 2007).

The systematic review of Ren *et al.* (2003) showed, in both animal and human experiments that large individual differences exist in the amount and rate of tooth movement. Even with standardized, constant, and equal forces, the rate of orthodontic tooth movement varied among and within dogs (Pilon *et al.*, 1996; von Böhl *et al.*, 2004b). On the other hand, with a substantially different force regimen and force magnitude, the rates of tooth movement were almost the same among or within individuals (Owman-Moll *et al.*, 1996a,b; Van Leeuwen *et al.*, 1999).

It has been suggested that individual differences in tooth movement characteristics could be related to an individual variation in anatomic structures, bone/mineral density, or cellular activity within the PDL and alveolar bone. Supra-alveolar fibres and the structure of the collagen fibres of the PDL might also be attributed to individual differences. Other factors could be significant variations in metabolic capacity, which determine the rate of bone turnover and the reaction of the connective tissue. Klein-Nulend *et al.* (2003) assumed that the process of remodelling is determined by strain-derived canalicular fluid flow that regulates osteoclasts activity, while microdamage might also play a role in osteoclast guidance (Martin, 2007). Other factors, which could cause individual differences in the process of bone remodelling are possibly related to variation in the level of cytokines and growth factors such as PGE_2, IL-1ß, and TGF-ß1. These signalling proteins are products of the nervous, immune, and endocrine systems, but many locally produced growth factors have also been found to modulate tissue remodelling (Krishnan and Davidovitch, 2006; Meikle, 2006; Wise and King, 2008). Presently, it is not known exactly which role those factors play in the inflammatory reaction evoked by cell necrosis.

The major obstacle in performing this systematic review of the existing literature on hyalinization in relation to experimental tooth movement was the very limited number of studies that dealt specifically with the topic of hyalinization (Kohno *et al.*, 2002; von Böhl *et al.*, 2004a,b; Iino *et al*, 2007; Tomizuka *et al*, 2007). In most investigations on orthodontic tooth movement, initial hyalinization is described, but progress and decay are only mentioned as an aside. Most of the literature pertained to hyalinization as an undesirable event related to experimental tooth movement especially during the phase of arrest in the initial phase of orthodontic treatment. It must be emphasized that there is an urgent need for well-designed experimental studies to elucidate the role of hyalinization in orthodontic tooth movement. Such research requires a large sample size as hyalinization must be analysed at different time points especially during the late phases of orthodontic treatment. The location and timing of hyalinization during orthodontic tooth movement might be derived from simulation of orthodontic tooth movement in a finite element model, in which the PDL is also modelled.

Conclusion

Meta-analysis of the available data in the literature on orthodontic tooth movement and hyalinization is not possible due to heterogeneity of the published studies. Although hyalinization is considered to be an undesirable side effect of orthodontic tooth movement, little attention has been paid to the phenomenon itself and its possible relationship with stress/strain levels in the PDL and alveolar bone or the rate of tooth movement after the initial phase.

There is an urgent need for well-designed experimental studies to elucidate the role of hyalinization in orthodontic tooth movement. The new knowledge could improve the efficiency of future clinical orthodontic treatment.

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