Effectiveness of Biology-Based Methods for Inhibiting Orthodontic Tooth Movement. A Systematic Review

Cadenas de Llano-Pérula M* /Yañez-Vico RM**/Solano-Reina E***/ Palma-Fernandez JC****/ Iglesias-Linares A*****

Introduction: *Several experimental studies in the literature have tested different biology-based methods for inhibiting or decreasing orthodontic tooth movement (OTM) in humans. This systematic review investigated the effects of these interventions on the rate of tooth movement.* ***Study design****: Electronic [MedLine; SCOPUS; Cochrane Library; OpenGrey;Web of Science] and manual searches were conducted up to January 26th, 2016 in order to identify publications of clinical trials that compared the decreasing or inhibiting effects of different biology-based methods over OTM in humans. A primary outcome (rate of OTM deceleration/ inhibition) and a number of secondary outcomes were examined (clinical applicability, orthodontic force used, possible side effects). Two reviewers selected the studies complying with the eligibility criteria (PICO format) and assessed risk of bias [Cochrane Collaboration's tool]. Data collection and analysis were performed following the Cochrane recommendations.* ***Results:*** *From the initial electronic search, 3726 articles were retrieved and 5 studies were finally included. Two types of biology-based techniques used to reduce the rate of OTM in humans were described: pharmacological and low-level laser therapy. In the first group, human Relaxin was compared to a placebo and administered orally. It was described as having no effect on the inhibition of OTM in humans after 32 days, while the drug tenoxicam, injected locally, inhibited the rate of OTM by up to 10% in humans after 42 days. In the second group, no statistically significant differences were reported, compared to placebo, for the rate of inhibition of OTM in humans after 90 days of observation when a 860 nm continuous wave GaAlA slow-level laser was used.* ***Conclusions:*** *The currently available data do not allow us to draw definitive conclusions about the use of various pharmacological substances and biology-based therapies in humans able to inhibit or decrease the OTM rate. There is an urgent need for more sound well-designed randomized clinical trials in the field.*

Key words: *OTM, decrease, inhibition, biology-based techniques, systematic review, humans, low-level laser therapy, medication.*

INTRODUCTION

Several biology-based methods for modifying the rate of tooth movement can be found in the literature in recent years. Most of them focus on reducing the length of treatment, although a few others are able to decrease or inhibit orthodontic tooth movement (OTM). These are mostly chemical methods, such as hormones, bisphosphonates or NSAIDs. These drugs are widely used by patients undergoing orthodontic treatment[1] and the extent of their effect on tooth movement should therefore be clarified. Nevertheless, most studies that concern the administration of pharmacologic substances were tested on animal models with very different doses and protocols, which makes it difficult for the clinician to make useful comparisons between the studies and their relevance, if any, in the clinical field.[2–4] Very few of these biology-based methods have been tested on humans so far[5] and some of them have reported controversial results regarding their effects on tooth movement.[1] The purpose of this systematic review was to gather available data from experimental biology-based studies in humans that decrease orthodontic tooth movement.

*Cadenas de Llano-Pérula M,Lecturer Master´s Program of Orthodontics, Department of Oral Health Sciences, KU Leuven, Belgium.
**Yañez-Vico RM,Associate Professor of Orthodontics. Department of Stomatology. University of Seville. Seville. Spain.
***Solano-Reina E, Chairman of Orthodontics. Department of Stomatology. University of Seville. Seville. Spain.
****Palma-Fernandez JC, Full Professor. Department of Orthodontics. Complutense University of Madrid. Madrid. Spain.
*****Iglesias-Linares A, Associate Professor. Department of Orthodontics. Complutense University of Madrid. Madrid. Spain.

Send all correspondence to:
Alejandro Iglesias-Linares.
School of Dentistry. Plaza Ramón y Cajal sn
Complutense University of Madrid.
28040. Madrid. Spain
Phone: +34636705246
Email: aleigl01@ucm.es

More specifically, using the PICO format,[6] the present systematic review aimed to answer the following focused question: what is the effectiveness of biology-based methods *(I)* in inhibiting OTM *(O)* among orthodontic patients (*P),* compared to placebo interventions or conventional orthodontic treatment *(C),* based on information gathered from available randomized clinical trials *(S).*

MATERIALS AND METHOD

The protocol for this systematic review was developed and registered prior to the start on the International Prospective Register of Systematic Reviews (PROSPERO,http://www.crd.york.ac.uk/Prospero/), number CRD42014014369. The reporting of the systematic review follows the guidelines for reporting of systematic reviews in dental research[5] and the PRISMA guidelines.www.prisma-statement.org[6]

Information resources and search strategy

The databases explored were MedLine (Entrez PubMed,www.ncbi.nim.nih.gov), SCOPUS (www.scopus.com) Web of Science (www.isiknowledge.com) and The Cochrane Library (www.thecochranelibrary.com) in order to find possible papers matching our established selection criteria. We included all articles published up to 26th January 2016, with no language restrictions or any other limits. In addition, the OpenGrey database (www.opengrey.eu) in EAGLE (European Association for Grey Literature Exploitation) was searched for grey literature, also up to January 26th, 2016. The main JCR-indexed orthodontic journals were also hand-searched to identify possible studies not included under the above-mentioned criteria. References listed in the included articles, as well as several related systematic reviews, were hand searched in order to identify relevant papers that might match our selection criteria.

Table I describes the full search strategy used in every database. The syntax varied slightly depending on the entry terms of the database used.

Eligibility

The inclusion criteria were established according to the PICO format:

Population: Humans; any clinical investigation with at least one experimental group and a minimum of 4 individuals per group.

Intervention: Biology-based methods of decreasing or inhibiting tooth movement with force applied by an orthodontic or orthopaedic device.

Comparison: Control group without the use of a biology-based method

Outcome: (1) Primary outcome: rate of OTM deceleration or inhibition. *(2) Secondary outcomes*: Clinical applicability, orthodontic force used, possible side effects.

Studies: The types of studies that were eligible were: clinical trials. Other types of articles that did not match the targets of this review or which were focused on root resorption or relapse were not included in the final selection.

Inclusion of studies

Studies were independently selected by two observers (M.C.L.P and R.Y.V). The first selection was made on the basis of title and abstract; the full-text articles were then reviewed. In cases where there was doubt as to whether or not to include the article, a third experienced reviewer was consulted (A.I.L) in order to achieve consensus. After the inclusion and exclusion criteria were applied to every article, concordance between the observers was established using the kappa index.

Data collection and analysis of characteristics

Data were collected by one of the reviewers (M.C.L.P) using a piloted data extraction sheet. Whenever there was conflict during the data collection process, a second (R.Y.V) or third observer (A.I.L) was consulted.

Data collected were: first author; year; study design; sample size; age and gender of the sample; methods used; applied force; total treatment/experimentation time; the effect on decrease in OTM; clinical applicability.

Assessment of the risk of bias in the publications

The methodological quality of the selected papers was assessed using the Cochrane Collaboration's tool for assessing risk of bias[7]. The key domains analyzed were: adequate sequence generation; allocation concealment; blinding; whether complete outcome data were addressed; no selective reporting or other source of bias.

Under this analysis, every checkpoint was assessed as "yes" when mentioned and correct, "no" when the criteria were not met or not specifically mentioned in the text, and "unclear" when there was insufficient information to make an accurate evaluation. In case of unclear information, authors were contacted. Risk of bias for each paper was therefore scored as Low ("yes" for all key domains), Unclear ("unclear" for one or more key domains), or High ("no" given for one or more key domains).

RESULTS

3726 articles were retrieved after the initial database search (1796 from Pubmed; 1457 from Scopus; 145 from Web of Science, 313 from Cochrane and 15 from OpenGrey for grey literature. A PRISMA flow diagram of the literature search can be found in Figure 1). After removing duplicates, applying the selection criteria and reviewing the title and abstract, only 5 articles were finally included. After manually searching other databases (OpenGrey), 13 extra articles were reviewed, although none of them met the established criteria. Two biology-based techniques were identified as responsible for reducing or delaying the rate of orthodontic tooth movement: chemical methods and low-level laser therapy. The two independent observers who selected the studies showed good concordance by the kappa index (k=0.87).

Characteristics of the studies included

The five articles included were all clinical trials (Table II, data extraction sheet). Only in one study, the sample size was higher than 25 subjects per group.[8] In three of the five included studies[9–11], the sample was randomized, and single or double blinding measures were used for every paper. (Table III). The included studies were designed to test the effects of specific chemical compounds[9,10] or low-level laser therapy[8,11,12] as biology-based methods leading to a decrease in orthodontic tooth movement (two and three articles, respectively), compared with a placebo. The substances evaluated in the selected randomized clinical trials were human relaxin[9] and tenoxicam[10].

Figure 1. PRISMA Flow Diagram

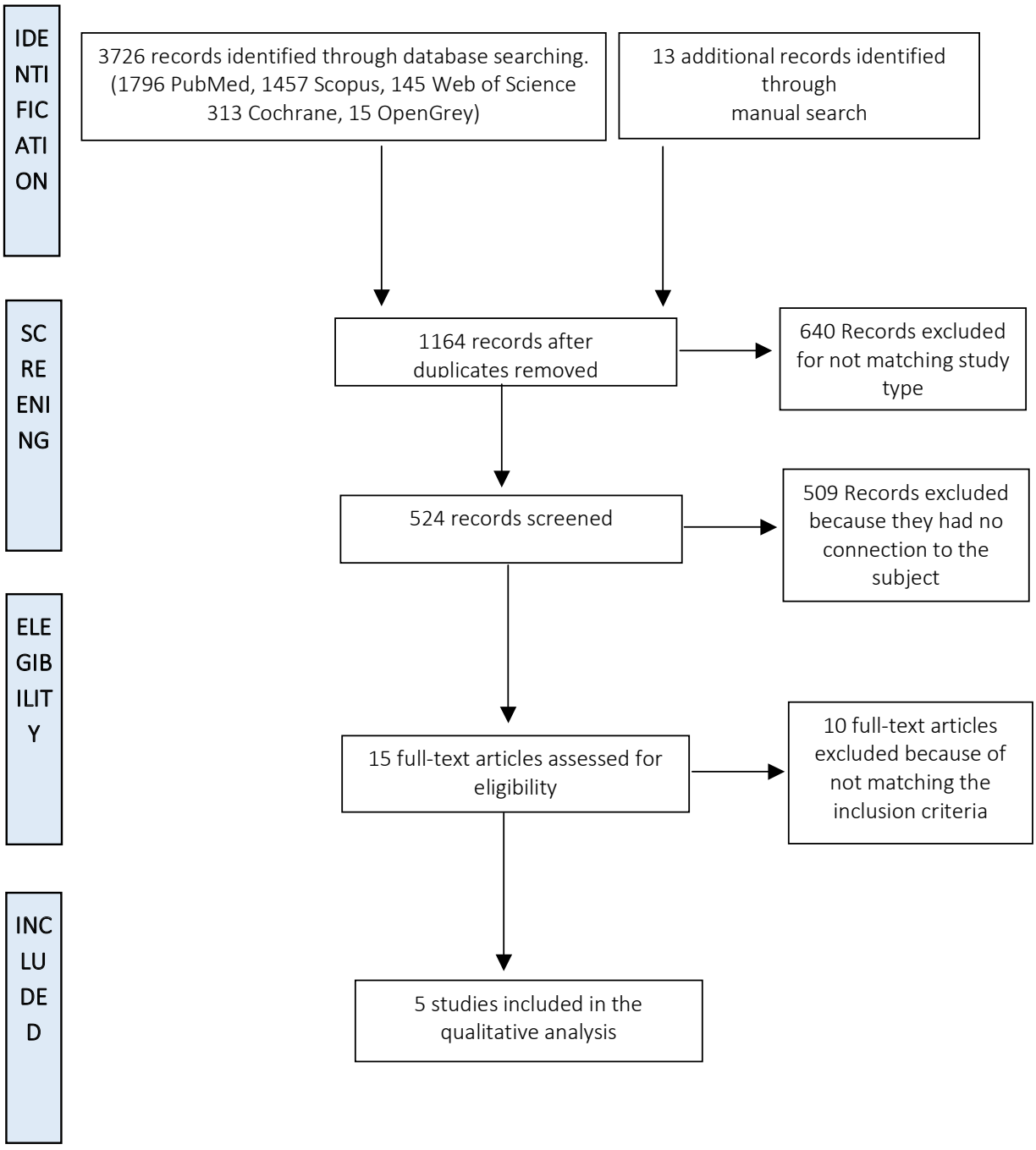

Table I. Search strategy in the different databases.

Database	Search string	Results after duplicates
Pubmed	(Tooth movement [Mesh:noexp] OR tooth movement[TiAb] AND (inhibition[TiAb] OR inhibit[TiAb] OR decrease[TiAb] OR inhibition OR inhibit OR decrease)) Orthodontics [Mesh] OR orthodontic* Tooth Movement [Mesh] OR mov* OR retract* decreas* OR inhibit* OR rate 2 AND 3 AND 4 1 AND 5 **ADDITIONAL SEARCHES:** (((orthodontic tooth movement[MeSH Terms])) AND (decreas* OR inhib* or reduc* OR supres* OR attenua*)) NOT (acceler* OR increas* OR enhanc* OR promot*) (orthodontic tooth movement[MeSH Terms]) AND (chemicals and drugs category[MeSH Terms])	260
Scopus	Tooth movement AND (inhibition OR inhibit OR decrease) AND (humans) NOT relapse OR increase OR promotion OR enhance* Orthodontics OR orthodontic* Tooth Movement OR mov* OR retract* decreas* OR inhibit* OR rate 2 AND 3 AND 4 1 AND 5 ADDITIONAL SEARCH: TITLE-ABS-KEY (“orthodontic tooth movement”) AND TITLE-ABS-KEY (human) AND TITLE-ABS-KEY (“clinical trial”) AND TITLE-ABS-KEY (decreas* OR inhib* OR reduc* OR supres* OR attenua*) AND NOT TITLE-ABS-KEY (acceler* OR increas* OR enhanc* OR promot*) AND SUBJAREA (mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal)	170
Cochrane	Tooth movement AND (inhibition OR inhibit OR decrease OR delay) AND (humans) Orthodontics OR orthodontic* Tooth Movement OR mov* OR retract* decreas* OR inhibit* OR rate 1 AND 2 AND 3 AND 4 ADDITIONAL SEARCH: Orthodontics or orthodontic* ‘Tooth Movement’ or mov* or retract* decreas* or inhib* or reduc* or supres* or attenua* acceler* OR increas* OR enhanc* OR promot* #1 and #2 and #3 and not #4	313
Web of Science	TOPIC: (“orthodontic tooth movement”) AND TOPIC: (decreas* OR inhib* or reduc* OR supres* OR attenua*) NOT TOPIC: (acceler* OR increas* OR enhanc* OR promot*)	145
OpenGrey	“tooth movement” OR (“orthodontic*” AND “time”) OR (“orthodontic*” AND (“decreas*” OR “inhibit*”)) OR (“orthodontic*” AND (“decreas*” OR “inhibit*”)) Orthodontics OR orthodontic* Tooth Movement OR mov* OR retract* decreas* OR inhibit* OR rate 2 AND 3 AND 4 1 AND 5	15

Table II. Summary of the articles included in the review.

Chemical Methods.

Author, Year	Study Design	Sample (n)	Groups Description	Age, Sex	Force (g)	Time (days)	Decrease Rate	Clinical Applicability
Mcgorray SP, 2012	CT	39	G1) OTM + placebo (CG) G2) OTM+ subgingival injections of human relaxin	26y, 11M/28F	NM	32	NSRD	NO
Arantes GM, 2009	CT	36	G1) 20 mg oral Tenoxicam for 45 minutes before orthodontic activation, placebo afterwards and 20 mg Tenoxicam 24 and 48 h later; G2) Placebo 45 minutes before orthodontic activation, 20 mg Tenoxicam after activation, 24 and 48 h later; G3) CG: placebo at every time point.	16-25y 18M/18F.	NM	42	Tenoxicam decreases OTM 5-10%, on the third monthly activation. NSRD for the rest of the groups	YES

Low-Level Laser Therapy

Author, Year	Study Design	Sample (n)	Groups Description	Age, Sex	Force (g)	Time (days)	Decrease Rate	Clinical Applicability
Limpanichkul W, 2006	CT	12	G1) One side (left/right) of the maxillary teeth randomly received OTM (canine retraction with a coil spring) + GaAlAs laser application ; G2) The other (left/right) received OTM+ Placebo.	20y, 4M/8F	150	90	NSRD	NO
Fujiyama K, 2008	CT	90	G1) OTM (Separation modules mesial and distal of the maxillary first molar) + CO2 laser application right after separation, G2) Control group: OTM only.	19,22y, 30M/60F	NM	7	NSRD	NO
Kansal A, 2013	CT	10	Split mouth: G1) In one quadrant, OTM (canine retraction with a coil spring) + GaAs laser application on days 1,3,7,14, 21, 28, 35, 42, 49 and 56) G2) In the opposite quadrant (control group) only OTM.	NM, NM	150	63	NSRD	NO

Abbreviations from the table:

CG: control group; **F:** female; **g:** grams; **G:** group; **h**: hours; **H:** human; **LLLT:** Low-Level Laser Therapy; **mg**: miligrams; **M:** male**; n:** number**; NM:** not mentioned; **NSRD:** no statistically relevant differences; **OTM:** orthodontic tooth movement**; CT:** clinical trial**; y:** years

Table III. Risk of bias of the articles included in the review assessed with the Cochrane Tool for Assessing Risk of Bias.

CHEMICAL METHODS

Author, Year	Adequate sequence generation?	Allocation concealment?	Blinding?	Complete outcome data addressed?	Free of selective reporting?	Free of other bias?	Total	Risk of bias
McGorray SP, 2012	YES	YES	YES	YES	YES	YES	3/0/0	LOW
Arantes GM, 2009	YES	YES	YES	YES	YES	YES	3/0/0	LOW

LOW-LEVEL LASER THERAPY

Author, Year	Adequate sequence generation?	Allocation concealment?	Blinding?	Complete outcome data addressed?	Free of selective reporting?	Free of other bias?	Total	Risk of bias
Limpanichkul, 2006	YES	YES	YES	YES	YES	YES	3/0/0	LOW
Fujiyama K, 2008	NO	NO	YES	NO	NO	NO	1/0/5	HIGH
Kansal A, 2013	NO	NO	YES	NO	NO	NO	1/0/5	HIGH

Quality of the studies and risk of bias

The included studies were so few and the study aims so different that the statistics were not meaningful, so we assessed risk of bias for quality, as shown in Table III. The articles were all clinical trials, with blinding measures and complete data reporting. In addition, three of them[9–11] were randomized and with proper sequence generation. These were categorized as papers of high quality methodology with low risk of bias (LB) and the other two[8,12] as high risk of bias (HB) when analysed with the Cochrane Tool[7]

Outcomes

Kansal[12] (HB) and Limpanichkul[11] (LB) studied the effect of low-level laser therapy with a Gallium-Aluminium-Arsenide laser (GaAlAs),along with tension coil springs and a fixed appliance, on 10 and 12 patients for three months in order to move canines distally. Both authors concluded that this type of biology-based therapy did not result in decreased OTM. No statistically relevant differences (NSRD) were found when compared to controls for the inhibition of orthodontic tooth movement in humans. CO2 laser was used by Fujiyama in 60 patients after placement of separating elastics in a total of 90 patients[9]. No significant differences were found regarding tooth movement between groups. More high quality studies are needed to confirm the inhibitory effect of laser therapy of this kind on orthodontic tooth movement or its benefits for anchorage reinforcement (Table II).

With respect to the administration of various pharmacological substances, the study by Arantes *et al*[10] tested tenoxicam, a non-steroidal anti-inflammatory drug (NSAID). They reported no statistically relevant differences between the groups, although there was 5% to 10% less orthodontic tooth movement shown on activation in the third month, compared to the control group. Another aim of this research group was to determine the best way of administering the drug for orthodontic purposes, whether 45 minutes before orthodontic treatment, immediately afterwards, or 24 h and 48 h after; no statistically significant differences between groups were found.

McGorray *et al,* [9] studied the effects of subgingival injections of human relaxin in a sample of 40 patients, compared to a control group under a placebo treatment. Although these authors stated that the doses could have been too low, the study found no significant differences in tooth movement between the groups after 8 weeks of orthodontic tooth movement and drug administration (Table II).

DISCUSSION

Most of the methods that have been reported in the orthodontic literature as decreasing or delaying OTM have been chemical substances, not just in animal models but also humans. [9–11] The randomized clinical trials included in this review were designed mainly to inform the clinician about possible interactions between the use of pharmacological substances and OTM. Other studies have also been carried out concerning avoiding pain secondary to orthodontic treatment, creating differential anchorage or avoiding relapse and root resorption. Surprisingly, a large majority of these studies were tested *in vitro* or in animal models only,[2–4] with just a few results observed in humans, which shows the poor bench-to-clinic transfer to date in this research field in orthodontics.

NSAIDS and other COX-2 selective inhibitors have long been studied and considered ideal for pain relief when it comes to orthodontic treatment. Several research studies as well as a few randomized clinical trials involving humans have been found that tested ibuprofen, [13,14] acetaminophen,[15] and valdecoxib,[16] although none of them considered their effect on OTM. In animals on the other hand, their properties for slowing down the rate of OTM have been studied to a much greater extent. These compounds are described as decreasing OTM by inhibiting cyclooxygenase, and therefore

influencing osteoclast recruitment by inhibiting prostaglandin (Pg) synthesis, at least in the rat model.[17] In this regard, the research conducted by Arantes *et al*,[10] a study with high methodological quality (Table III), concluded that tenoxicam, an NSAID from the oxicam family, is an effective way of controlling pain without affecting the rate of OTM in humans. Because of its long elimination half-life,[18] it was administered just once a day. However, the authors reported only three activations of cases of canine retraction, and in the third one, a 5-10% decrease in the rate of OTM was observed in the treated groups compared to controls. In this randomized clinical trial, tenoxicam was administered orally (oral administration of 20mg a day for three days before and after activation of the appliance). It is likely therefore that prolonged administration would result in decreased OTM (Table II), which would be consistent with findings reported in animals.[17]

In research involving animal models, acetaminophen, a member of the para-aminophenol family, has been reported as interfering with OTM,[2] while diclofenac on the other hand appears to inhibit it completely, and rofecoxib partially.[19] Among coxib therapies, rofecoxib has been described as being the most aggressive OTM inhibitor, and celecoxib the most suitable analgesic therapy during orthodontic treatment.[20] Nonetheless, there was considerable controversy about the use of celecoxib, which was later reported in the literature as reducing OTM by 30% and 48% when used in the short- and long-term, respectively,[21] and even by 50%, as shown in the rat model.[17]

This is not the case with other substances, such as bisphosphonates, which have been clearly proven to affect bone metabolism directly, by reducing both osteoclast numbers and activity. Bisphosphonates are drugs that are widely known for treating a wide range of pathologies, among them osteoporosis and other bone diseases.[22] The compounds act by selective adherence to bone mineral surfaces, inhibiting osteoclast activity and so preventing bone resorption.[23] They have been thoroughly studied in the field of orthodontic tooth movement research and their effects have been compiled in recent systematic reviews in orthodontics because of their frequent use.[24] Nevertheless, with respect to their effect on OTM in humans, not a single piece of research has so far been published on the topic, which highlights once more the need for new, high quality studies.

Hormones are other substances used for experimentally inhibiting OTM. These substances, as well as NSAIDS, have been associated with inhibiting or reducing OTM by directly affecting the bone turnover rate. Nevertheless, not all types of hormones have been studied for inhibition purposes. More specifically, the parathyroid hormone has more frequently been used to increase the rate of OTM,[25] although others, such as estradiol and norgestrel, which are commonly used contraceptives, have been reported as interfering with orthodontics, inhibiting OTM in rats by 39%.[26] Human relaxin has previously been proposed for enhancing OTM in animals and possibly also for controlling relapses;[27,28] in humans, however, the high quality randomized clinical trial conducted by McGorray[9] included in this review found no statistically significant differences in OTM. Furthermore, the results match those of other research papers carried out on rats,[29] in which the observed acceleratory effects were explained as possibly due to the effect of relaxin in reducing the level of PDL organization and mechanical strength and increasing tooth mobility at early time points.

In the last decade, several inflammatory mediators, or their receptors, with an impact on preventing bone resorption have been the subjects of numerous research papers in orthodontics. Some of these mediators interfere with osteoclastogenesis, and hence with OTM, via cytokines directly implicated in bone metabolism, such as IL-1, TNF, M-CSF or OPG.[30–32] Although studies in this field to date are only experimental, they have resolved what happens in the pathways involved in OTM and could be of considerable interest for application to humans in the near future when gene and cell therapies have overcome their current limitations.

Low-level laser therapy (LLLT), from the CO_2 laser[8] to the GaAlAs,[33,34] has been tested in humans mostly for alleviating pain during orthodontic treatment, with a positive effect on pain relief being observed. In addition, LLLT has been described as having the effect of enhancing tooth movement in animals,[35] and similar evidence has also recently been reported in humans.[36] Nonetheless, there is considerable controversy in the literature about its effect on the rate of OTM induced by LLLT, in other words, some studies have shown the opposite effect, reporting a decrease of 40 to 50% in the OTM rate in rats[37] and a 48.4% decrease in dogs when LLLT was combined with alveolar corticotomy surgery.[38] The only high quality study included in this review about the use of LLLT for inhibiting OTM, a randomized clinical trial by Limpanichkul *et al* , used a 860 nm continuous wave GaAlAs laser to irradiate a canine at three different points during retraction.[11] The authors found no statistically significant differences in the rate of OTM compared to controls and suggested that the low energy dose (25 J/cm^2) used in their study may have been the possible reason for this effect. Nonetheless, it contradicts evidence taken from other studies on humans in which even lower energy doses were used, and which observed an acceleratory effect.[36]

To sum up, when it comes to changes in orthodontic tooth movement rates, the substances tested in the articles included in this review were of very different kinds. Furthermore, even though they were tested on the same species, the doses and method of administration (tenoxicam was tested systemically while relaxin and LLLT were applied locally) were quite different, which makes comparisons between them difficult to establish. The sample sizes and distributions in these studies were similar, as were the observational periods. While no statistically significant differences were found in four of the five studies included in this review involving humans (studies of relaxin[9] and LLLT[8,11,12]), tenoxicam was described as producing a slight decrease in OTM after 3 months, compared to the controls.[10]

In the two studies about chemical substances tested on humans, the magnitude of force was not specified,[9,10] and in the studies of LLLT for the retraction of canines, a 150g force was used with a nickel-titanium closed coil spring in two articles[11,12] and not mentioned in the third[8]. McGorray *et al* [9] used removable aligners; Arantes *et al*[10] used nickel-titanium springs to induce OTM and a dynamometer to assess the level of force, but they did not mention the magnitude of the forces applied. The differences in the study characteristics, types of appliance and amount of force applied could account for some of the controversies observed in other papers in the literature.

When studying biological reactions to orthodontic tooth movement, the molecular or tissue responses experienced vary considerably depending on the method used to move the teeth. Whether the

force is constant or intermittent, the direction of the force and force decay of the different materials should be taken into account, since tissue reactions may vary at the molecular level. All the articles in this review involved humans, so that the variable of difference between species can be ruled out, which is why knowing what the magnitudes of the force exerted on the tissues were could enable us to draw safer conclusions.

The possible side effects of the individual therapies have not been clearly evaluated, and this should be a key feature in experimental research of this kind. In addition to their previously mentioned properties for pain relief, laser techniques are also described in the literature as having a beneficial effect on pulp healing[39] and soft tissue repair.[40] The side effect of pharmacological or chemical modification of OTM should be borne in mind, especially when using substances such as hormones. Decreased root resorption or relapse are generally reported in animal models,[4,41] as well as pain relief as the effect of administering tenoxicam.[10]

As described, various substances and techniques have been demonstrated as affecting the rate of tooth movement. In the literature, the most numerous are those aimed at reducing the length of treatment, although others, especially those involving the administration of different substances, have also been reported as inhibiting or decreasing tooth movement. Many of them have been tested on animal models and given us an approximate idea of their activity. Nonetheless, there is an obvious need for well-designed clinical trials in humans because few strictly evidence-based conclusions can be extracted from the very few high quality studies that are currently available in the literature. Furthermore, there is notable controversy about the scales used in systematic reviews for assessing methodological quality. Several scales have been used in recent years, showing clearly that there is as yet no ideal scale for properly evaluating the quality of studies. The present systematic review based its analysis on the well-known Cochrane Collaboration's tool for assessing risk of bias.[7] Even so, there remain limitations with this scale, with concerns that sample size limitations in randomized studies, previous calculation of statistical study power, the appropriateness of the experimental methodology quality itself, among others, are not considered by this scale, or others. This could contribute to significant sources of bias being concealed in some of the existing studies.[42]

CONCLUSION

The present systematic review regarding the biology-based inhibition of OTM in humans has analyzed the findings of the three high quality and two low quality clinical trials using the Cochrane Collaboration's tool for assessing risk of bias[7]. The very different substances and methods used in the studies, as well as the study methodologies, doses and ranges of orthodontic force do not allow us to extract absolute conclusions.

As orthodontic treatment is increasingly reaching the middle-aged group, we should be cautious about pharmacological interference and warn the patient, on the basis of the results of the studies, of the possibility of deceleration of OTM. This factor should be clarified properly with more appropriately designed randomized clinical trials on OTM inhibition. In the short term, the side effects of these therapies and more bench-to-clinic applications should be investigated in this field of orthodontic research.

REFERENCES

1. Angelopoulou, MV, Vlachou, V, Halazonetis, DJ. Pharmacological management of pain during orthodontic treatment: a meta-analysis. Orthod. Craniofac. Res; 15, 71–83, 2012.
2. Arias, OR, Marquez-Orozco, MC. Aspirin, acetaminophen, and ibuprofen: their effects on orthodontic tooth movement. Am. J. Orthod. Dentofacial Orthop; 130, 364–370, 2006.
3. Iglesias-Linares, A, Moreno-Fernandez, AM, Yañez-Vico, R, Mendoza-Mendoza, A, Gonzalez-Moles, M, Solano-Reina, E. The use of gene therapy vs. corticotomy surgery in accelerating orthodontic tooth movement. Orthod. Craniofac. Res;14, 138-48, 2011.
4. Choi, J, Baek, S-H, Lee, J-I, Chang, Y-I. Effects of clodronate on early alveolar bone remodeling and root resorption related to orthodontic forces: a histomorphometric analysis. Am. J. Orthod. Dentofacial Orthop; 138, 548. e1–8; discussion 548–9, 2010.
5. Maia, LC, Antonio, AG. Systematic reviews in dental research. A guideline. J. Clin. Pediatr. Dent; 37, 117–124, 2012.
6. Liberati, A, Altman, DG, Tetzlaff, J, Mulrow, C, Gøtzsche, PC, Ioannidis, JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J. Clin. Epidemiol; 62, e1–34, 2009.
7. Higgins, JPT, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ; 343, d5928, 2011.
8. Fujiyama, K. et al. Clinical effect of CO(2) laser in reducing pain in orthodontics. Angle Orthod; 78, 299–303, 2008.
9. McGorray, SP, Dolce, C, Kramer, S, Stewart, D, Wheeler, TT. A randomized, placebo-controlled clinical trial on the effects of recombinant human relaxin on tooth movement and short-term stability. Am. J. Orthod. Dentofacial Orthop; 141, 196–203, 2012.
10. Arantes, GM, Arantes, VMN, Ashmawi, HA, Posso, IP. Tenoxicam controls pain without altering orthodontic movement of maxillary canines. Orthod. Craniofac. Res; 12, 14–19, 2009.
11. Limpanichkul, W, Godfrey, K, Srisuk, N, Rattanayatikul, C. Effects of low-level laser therapy on the rate of orthodontic tooth movement. Orthod. Craniofac. Res; 9, 38–43, 2006.
12. Kansal, A, Kittur, N, Kumbhojkar, V, Keluskar, KM, Dahiya, P. Effects of low-intensity laser therapy on the rate of orthodontic tooth movement: A clinical trial. Dent. Res. J. (Isfahan);11, 481–488, 2014.
13. Steen Law, SL, Southard, KA, Law, AS, Logan, HL, Jakobsen, JR. An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. Am. J. Orthod. Dentofacial Orthop; 118, 629–635, 2000.
14. Bernhardt, MK, et al. The effect of preemptive and/or postoperative ibuprofen therapy for orthodontic pain. Am. J. Orthod. Dentofacial Orthop; 120, 20–27, 2001.
15. Bird, SE, Williams, K, Kula, K. Preoperative acetaminophen vs ibuprofen for control of pain after orthodontic separator placement. Am. J. Orthod. Dentofacial Orthop; 132, 504–510, 2007.
16. Young, AN, Taylor, RW, Taylor, SE, Linnebur, SA, Buschang, PH. Evaluation of preemptive valdecoxib therapy on initial archwire placement discomfort in adults. Angle Orthod; 76, 251–259, 2006.
17. Sodagar, A, et al. The effect of celecoxib on orthodontic tooth movement and root resorption in rat. J. Dent. (Tehran); 10, 303–311, 2013.
18. Nilsen, OG. Clinical pharmacokinetics of tenoxicam. Clin. Pharmacokinet; 26, 16–43,1994.
19. de Carlos, F, Cobo, J, Díaz-Esnal, B, Arguelles, J, Vijande, M, Costales, M. Orthodontic tooth movement after inhibition of cyclooxygenase-2. Am. J. Orthod. Dentofacial Orthop; 129, 402–406, 2006.
20. de Carlos, F, Cobo, J, Perillan, C, Garcia, MA, Arguelles, J, Vijande, M, et al. Orthodontic tooth movement after different coxib therapies. Eur. J. Orthod; 29, 596–599, 2007.
21. Hauber Gameiro, G, Nouer DF, Pereira Neto JS, Siqueira VC, Andrade ED, Duarte Novaes P, et al. Effects of short- and long-term celecoxib on orthodontic tooth movement. Angle Orthod; 78, 860–865, 2008.
22. Kaipatur, NR, Wu, Y, Adeeb, S, Stevenson, TR, Major, PW, Doschak, MR. Impact of bisphosphonate drug burden in alveolar bone during orthodontic tooth movement in a rat model: a pilot study. Am. J. Orthod. Dentofacial Orthop; 144, 557–567, 2013.
23. Russell, RGG. Bisphosphonates: mode of action and pharmacology. Pediatrics; 119 Suppl , S150–62, 2007.
24. Iglesias-Linares, A, Yanez-Vico, R-M, Solano-Reina, E, Torres-Lagares, D, Gonzalez Moles, MA. Influence of bisphosphonates in orthodontic therapy: Systematic review. J. Dent; 38, 603–611, 2010.
25. Soma, S, Matsumoto, S, Higuchi, Y, Takano-Yamamoto, T, Yamashita, K, Kurisu, K, et al. Local and chronic application of PTH accelerates tooth movement in rats. J. Dent. Res; 79, 1717–1724, 2000.
26. Olyaee, P, Mirzakouchaki, B, Ghajar, K, Seyyedi, SA, Shalchi, M, Garjani, A, et al. The effect of oral contraceptives on orthodontic tooth movement in rat. Med. Oral Patol. Oral Cir. Bucal; 18, e146–50, 2013.
27. Stewart, DR, Sherick, P, Kramer, S, Breining, P. Use of relaxin in orthodontics. Ann. N. Y. Acad. Sci; 1041, 379–387, 2005.
28. Liu, ZJ, King, GJ, Gu, GM., Shin, JY, Stewart, DR. Does human relaxin accelerate orthodontic tooth movement in rats? Ann. N. Y. Acad. Sci; 1041, 388–394, 2005.
29. Madan, MS, Liu, ZJ, Gu, GM, King, GJ. Effects of human relaxin on orthodontic tooth movement and periodontal ligaments in rats. Am. J. Orthod. Dentofacial Orthop; 131, 8.e1–10, 2007.
30. Jager, A, Zhang, D, Kawarizadeh, A, Tolba, R, Braumann, B, Lossdörfer, S, et al. Soluble cytokine receptor treatment in experimental orthodontic tooth movement in the rat. Eur. J. Orthod; 27, 1–11, 2005.
31. Yoshimatsu, M, Kitaura, H, Fujimura, Y, Kohara, H, Morita, Y, Eguchi, T, et al. Inhibitory effects of IL-12 on experimental tooth movement and root resorption in mice. Arch. Oral Biol. 57, 36–43, 2012.
32. Yabumoto, T, Miyazawa, K, Tabuchi, M, Shoji, S, Tanaka, M, Kadota, M, et al. Stabilization of tooth movement by administration of reveromycin A to osteoprotegerin-deficient knockout mice. Am. J. Orthod. Dentofacial Orthop; 144, 368–380, 2013.
33. Dominguez, A, Velasquez, SA. Effect of low-level laser therapy on pain following activation of orthodontic final archwires: a randomized controlled clinical trial. Photomed. Laser Surg; 31, 36–40, 2013.
34. Nobrega, C, da Silva, EMK, de Macedo, CR. Low-level laser therapy for treatment of pain associated with orthodontic elastomeric separator placement: a placebo-controlled randomized double-blind clinical trial. Photomed. Laser Surg; 31, 10–16, 2013.
35. Yamaguchi, M, Hayashi, M, Fujita, S, Yoshida, T, Utsunomiya, T, Yamamoto, H, et al. Low-energy laser irradiation facilitates the velocity of tooth movement and the expressions of matrix metalloproteinase-9, cathepsin K, and alpha(v) beta(3) integrin in rats. Eur. J. Orthod; 32, 131–139, 2010.
36. Sousa, MVS, Pinzan, A, Consolaro, A, Henriques, JFCde Freitas, MR. Systematic literature review: influence of low-level laser on orthodontic movement and pain control in humans. Photomed. Laser Surg; 32, 592–599, 2014.
37. Seifi, M, Shafeei, HA, Daneshdoost, S, Mir, M. Effects of two types of low-level laser wave lengths (850 and 630 nm) on the orthodontic tooth movements in rabbits. Lasers Med. Sci; 22, 261–264, 2007.
38. Kim, S-J, Moon, S-U, Kang, S-G, Park, Y-G. Effects of low-level laser therapy after Corticision on tooth movement and paradental remodeling. Lasers Surg. Med; 41, 524–533, 2009.
39. Shigetani, Y, Sasa, N, Suzuki, H, Okiji, T, Ohshima, H. GaAlAs laser irradiation induces active tertiary dentin formation after pulpal apoptosis and cell proliferation in rat molars. J. Endod; 37, 1086–1091, 2011.
40. Mozzati, M, Martinasso, G, Cocero, N, Pol, R, Maggiora, M, Muzio, G, et al. Influence of superpulsed laser therapy on healing processes following tooth extraction. Photomed. Laser Surg; 29, 565–571, 2011.
41. Iglesias-Linares A, Hartsfield JK Jr.Cellular and Molecular Pathways Leading to External Root Resorption. J Dent Res. 2017 Feb;96(2):145-152. doi: 10.1177/0022034516677539.
42. Gonzales, C, Hotokezaka, H, Karadeniz, EI, Miyazaki, T, Kobayashi, E, Darendeliler, MA, et al. Effects of fluoride intake on orthodontic tooth movement and orthodontically induced root resorption. Am. J. Orthod. Dentofacial Orthop; 139, 196–205, 2011.
43. Iglesias-Linares, A, Morford, LA, Hartsfield, JK Jr. Bone Density and Dental External Apical Root Resorption. Curr. Osteoporos. Rep;14, 292-309, 2016.
44. Cadenas-Perula, M, Yañez-Vico, RM, Solano-Reina, E, Iglesias-Linares, A. Effectiveness of biologic methods of inhibiting orthodontic tooth movement in animal studies. Am. J. Orthod. Dentofacial Orthop;150,33-48, 2016.
45. Papadopoulos, MA, Gkiaouris, I. A critical evaluation of meta-analyses in orthodontics. Am. J. Orthod. Dentofacial Orthop; 131, 589–599, 2007.