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Review article

The risk of osteonecrosis of the jaw and adverse outcomes in patients using antiresorptive drugs undergoing orthodontic treatment: A systematic review

Julian Woolley [a], Oladapo Akintola [a], Julian Yates [b], Monica Diuana Calasans-Maia [c], Jose de Albuquerque Calasans-Maia [d], Iryna Kocherhina [e], Roberto Sacco [a,b,*]

[a] King's College Dental Hospital, Oral Surgery Department, London, UK
[b] The University of Manchester, Division of Dentistry, School of Medical Sciences, Oral Surgery Department, Manchester, UK
[c] Universidade Federal Fluminense, Dental School, Oral Surgery Department, Rio de Janeiro, Brazil
[d] Universidade Federal Fluminense, Dental School, Orthodontics Department, Rio de Janeiro, Brazil
[e] Orthodontics Postgraduate Center, Guy's Dental Hospital, London, UK

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ABSTRACT

Objectives: Medication-related osteonecrosis of the jaw (MRONJ) is rare. It is a serious adverse effect of certain drugs, of which bisphosphonates (BPs) are the most widely known. The aim of this systematic review was to analyze all published evidence for the reported adverse outcomes as a result of orthodontic treatment in patients undergoing antiresorptive therapy.

Data: All types of studies involving patients undergoing orthodontic treatment and treated with antiresorptive drugs were considered. A meta-analysis was not conducted due to the high amount of variability and heterogeneity in the reporting and presentation of data among the studies meeting the inclusion criteria.

Sources: A systematic search was performed using 4 databases (PubMed, MEDLINE, EMBASE and CINAHL).

Study selection: Seven studies matched the inclusion criteria for this review, reporting a total of 29 patients. MRONJ was only reported in 1 patient. The adverse outcomes following orthodontic treatment included difficulty achieving root parallelism ($n = 4$), difficulty achieving complete space closure ($n = 3$), exaggerated tooth mobility post-debond ($n = 2$), increased duration of orthodontic treatment beyond expected completion ($n = 1$), sclerotic alveolar bone changes seen on post-op radiographic images ($n = 2$), and an increased amount of root resorption ($n = 1$).

Conclusions: The high amount of heterogeneity and limited evidence precluded a valid interpretation and analysis of the results through pooling of data. Additional data with sufficient quality, a reduction of bias, and a greater prospective cohort of patients is crucial to assess adverse effects, mechanisms of action, and associated risk factors in at-risk patients.

Clinical significance: Based on the limited evidence available in the literature, it is unclear whether orthodontic treatment alone can precipitate MRONJ. However, antiresorptive drug therapy may be associated with a sub-optimal treatment outcome.

1. Introduction

Bisphosphonates (BPs) are antiresorptive drugs used to manage numerous conditions such as osteoporosis, fibrous dysplasia and metastatic bone diseases. Bisphosphonate therapy is generally well tolerated by patients [1, 2]. The purpose of antiresorptive drug therapies is to restore the bone density by decreasing remodelling of bone. BPs have direct effects on osteoclasts by significantly attenuating bone remodelling and decreasing skeletal-related complications in patients with malignant diseases or osteoporosis [1]. The first reported cases of patients developing a non-healing necrosis in the maxillofacial region was reported in 2003 by Marx et al. The disease was associated with patients taking bisphosphonates and therefore aptly named bisphosphonate-related osteonecrosis of the jaw (BRONJ) [3].

The work should be attributed to University of Manchester Division of Dentistry, School of Medical Sciences, Oral Surgery Department, Manchester, UK - Coupland 3 Building, Oxford Rd, Manchester, M13 9PL, UK.

* Corresponding author.
E-mail address: roberto.sacco@manchester.ac.uk (R. Sacco).

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More recently, researchers have uncovered other medications causative of osteonecrosis of the jaw (ONJ), such as monoclonal antibodies and bone-targeted agents (denosumab) [4, 5, 6]. As a result of these developments, the nomenclature of bisphosphonate-related ONJ was changed to medication-related ONJ (MRONJ) by the American Association of Oral and Maxillofacial Surgeons (AAOMS) specialist committee in a positional paper released in 2014 [7].

Several hypotheses on the pathophysiology of MRONJ have been proposed, including bone remodelling suppression, anti-angiogenesis, infection, genetic susceptibility, and others. Despite these findings, the exact mechanism of the development of MRONJ is not fully understood [8, 9, 10, 11].

The overall risk of developing MRONJ is affected by several factors. The medication, route of administration, cumulative dose of exposure and medical comorbidities are examples of the prior. For instance, the frequency of developing MRONJ in patients administered with bisphosphonates intravenously is far higher compared to bisphosphonates administered orally. The rates for intravenous administration ranges from 1.6% to 14.8% compared to 0.5% for the latter [7].

The most common aetiological trigger for MRONJ is related to invasive oral surgery procedures, reported in up to 52%–80% of all cases of MRONJ [12, 13]. Although the scientific studies relating aspects of antiresorptive use to ONJ are fairly well established, research and reports relating bone targeting drugs use to orthodontic-specific complications has been largely anecdotal, relying heavily on biologic plausibility [14, 15, 16].

The objective of this review is to appraise the evidence for the risks associated with orthodontic treatment in patients undergoing antiresorptive treatment. A previous systematic review was published in 2010 with interesting results. However, this considered predominantly experimental animal studies. Furthermore, the review was not performed according to PRISMA guidelines or PICOS framework, and contained several omissions leading to a lack of quality assurance [17, 18, 19]. This review seeks to improve the quality of previous research by evaluating all published evidence on the reported adverse outcomes, including ONJ, as a result of orthodontic treatment in patients undergoing antiresorptive therapy.

2. Materials and methods

2.1. Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed to conduct this systematic review [18]. The protocol for this review was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) under number INPLASY202070124.

2.2. Review question and PICO strategy

Is there any evidence that orthodontic treatment induces ONJ or other adverse outcomes in patients treated with antiresorptive drug therapy?

- **Population (P)**: patients previously or under antiresorptive drugs and orthodontic treatment
- **Interventions (I)**: any orthodontic treatment
- **Comparison (C)**: patients undergoing orthodontic therapy not subjected to bisphosphonate therapy (risk assumed as negligible)
- **Outcome (O)**: state of knowledge regarding the risk of medication-related ONJ as it refers to type of antiresorptive drug, dose, duration of treatment and rate of development in patients receiving orthodontic treatment

2.3. Information sources and search strategy

The following four databases were systematically searched; PubMed, EMBASE, Medline, and CINAHL (Figure 1). A comprehensive search strategy for all four databases was developed focussing on antiresorptive treatment in conjunction with orthodontic treatment. A search strategy for all databases was developed as follows:

1. Bisphosphonate OR diphosphonate OR antiresorptive OR denosumab OR alendronic acid OR zoledronic acid OR pamidronate OR etidronate OR clodronate OR ibandronate OR risedronate OR tiludronate OR romosuzumab
2. Osteonecrosis OR Avascular osteonecrosis OR Osteonecrosis of the jaw OR MRONJ OR ONJ OR BONJ OR ARONJ OR BRONJ
3. Orthodontic OR orthodontic appliance OR lingual orthodontics OR dental braces OR orthodontia OR teeth straightening OR removable orthodontia appliance OR fixed orthodontic appliance OR malocclusion OR teeth malposition treatment OR orthodontia treatment
4. 1 AND 2 AND 3

The search strategy included MeSH terms to represent particular concepts where applicable. In addition; if necessary, changes were made in the keywords to follow the syntax rules of each database.

2.4. Data items and collection

A comprehensive screening method was carried out to ensure precision within the search. One author *(hidden)* identified and removed duplicates. Using the inclusion and exclusion criteria, sixty-five abstracts were screened independently by two authors (*hidden* and *hidden*) to discard irrelevant or unrelated material. Disagreements were resolved by discussion until an agreement was achieved. If conflicts were not resolved, the studies were sent forward to a third reviewer for resolution (). Finally, two authors (*hidden* and *hidden*) independently conducted full-text screening and completed data extraction using a predefined and standardized Microsoft Excel form to verify the study eligibility and extract relevant data from the studies fitting the inclusion criteria. Intra-examiner conflicts were resolved by discussion until the disagreement was resolved. If the studies had missing or insufficient information, the authors were contacted directly using their corresponding email. Where the pooling of analogous data was inappropriate, the trials' results were reported as narrative descriptions. For studies presenting more than one patient, individual patient data were extracted onto the data collection form for a full comparison. No meta-analysis was performed due to the clinical heterogeneity and differences in the reporting of data among the included studies.

2.5. Selection criteria

Inclusion criteria were:

- Studies published after 2003
- Systemic treatment with antiresorptive medication
- Orthodontic treatment to correct malocclusion
- Human study participants
- No language or age restrictions were imposed on the search.

Articles were excluded if they were animal studies, review articles, opinion articles, letters, or were not appropriate to the objective of this review.

2.6. Outcomes measured

The primary outcome was to evaluate the current state of knowledge regarding the risk of ONJ as a result of antiresorptive drug therapy in patients undergoing orthodontic treatment for malocclusions.

The secondary outcomes were to determine whether the specific antiresorptive medication, duration of therapy, and indication for antiresorptive treatment contributed to adverse outcomes not limited to but including ONJ.

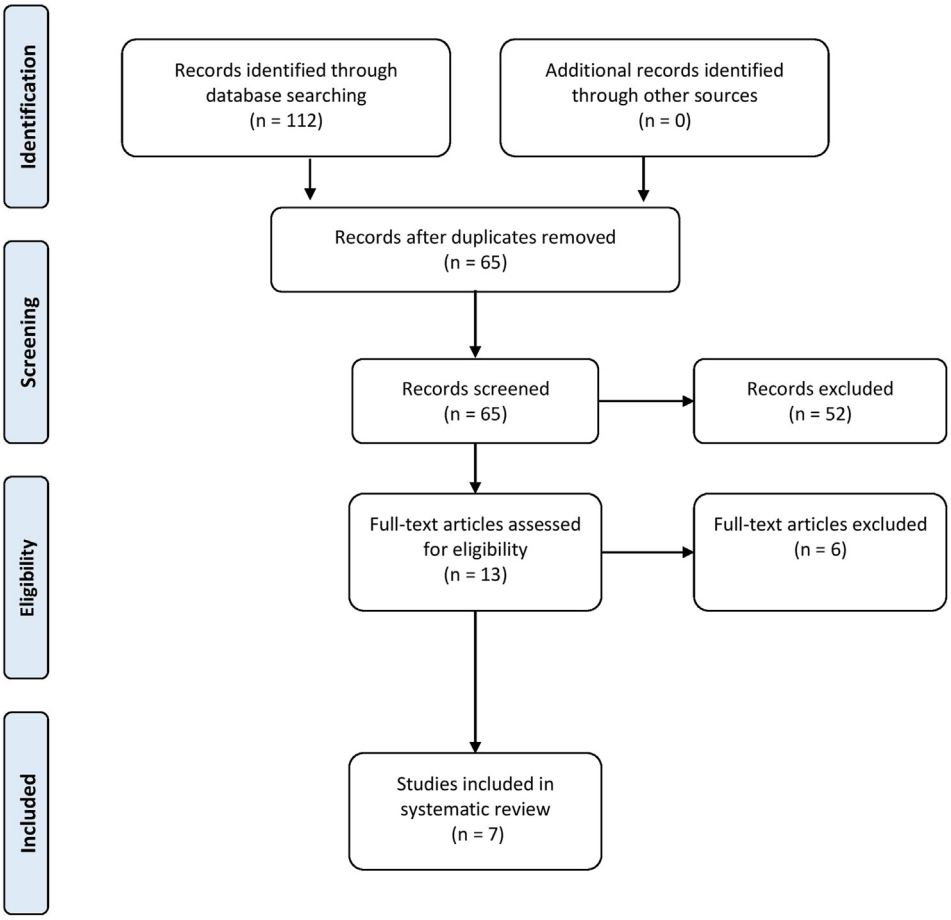

Figure 1. PRISMA flow diagram.

2.7. Data extracted

All included articles were assessed to identify the author(s), year article published, study type, sample, antiresorptive therapy details, and orthodontic treatment provided. All adverse outcomes were collected from all included articles.

2.8. Risk of bias and review of quality assessment

The risk of bias was assessed by 2 authors *(hidden)* independently. The authors used the consensus-based clinical case reporting guidelines development (CARE) checklist for case reports and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for case series and longitudinal studies [20, 21]. Any disagreements with the risk of bias assessments were referred to a third author *(hidden)* and subsequently resolved any conflict by discussion. The evidence level of each article was assessed according to the American Society of Plastic Surgeons (ASPS) criteria for assessing the level of evidence of therapeutic studies [22].

3. Results

3.1. Search results

The search generated 112 titles and abstracts (PubMed $n = 59$, EMBASE $n = 21$, Medline $n = 18$, CINAHL $n = 14$). After removing duplicates, 65 articles remained. Fifty-two were removed for not meeting the inclusion criteria. The remaining 13 papers were read in full and a further 6 were excluded for not providing orthodontic treatment to correct a malocclusion ($n = 3$) [23, 24, 25], an unsuitable paper ($n = 2$) [26,27] and no reported antiresorptive therapy ($n = 1$) [28] (Table 1). A total of 7 articles satisfied the criteria for inclusion [29, 30, 31, 32, 33, 34, 35]. There were no randomized controlled clinical trials or case-controlled studies identified. Articles included in this research were case reports ($n = 5$), case series ($n = 1$), and a retrospective cohort study ($n = 1$) (Table 1 and Table 2). Data unattained through the data collection stage was defined as Not Reported (NR).

3.2. Study and participant characteristics

The 7 articles included a total of 29 participants with an age range of 15–70 years (mean = 49.4). Twenty-seven patients were female and 2 were male. All patients were subjected to treatment with antiresorptive medications. These included: alendronate ($n = 23$), zoledronate ($n = 3$), ibandronate ($n = 4$), and pamidronate ($n = 2$). The duration of antiresorptive therapy before orthodontic treatment ranged from 7 to 60 months (mean = 30.7 months). The indications for antiresorptive therapy included treatment for osteoporosis ($n = 24$), type I osteogenesis imperfecta ($n = 1$), fibrous dysplasia ($n = 1$), sacral plasmacytoma ($n = 1$), unreported cancer ($n = 1$) and in the management of treatment with bone enhancing drugs for Addison's disease ($n = 1$) (Table 3).

All patients underwent orthodontic treatment to correct a malocclusion (Table 4). When reported, 7 out of 8 patients underwent orthodontic treatment while continuing antiresorptive therapy. The specific orthodontic malocclusion was reported in 6 patients and included class II div 1 malocclusion ($n = 3$), class III malocclusion ($n = 2$), and a class I malocclusion ($n = 1$). Treatment modalities varied and included fixed appliance treatment, removable appliance treatment, orthognathic treatment, insertion of a fixation plate to provide anchorage for tooth distalization, and

Table 1. Full text articles excluded and reason for exclusion.

Author(s)	Year	Reason for Exclusion
Hartsfield et al.	2009	No antiresorptive therapy
Krieger et al.	2013	Review paper
Morita et al.	2016	Incorrect orthodontic intervention
Ramalingam and Zacharin	2009	Abstract
Hoefert et al.	2014	Incorrect orthodontic intervention
Smidt et al.	2019	Incorrect orthodontic intervention

Table 2. Quality assessment for the included studies using the Levels of Evidence for Therapeutic Studies adapted from the American Society of Plastic Surgeons [22].

Author(s)	Study Type	Level of Evidence
Friedrich et al. (2019)	CR	Level 5
Lotwala et al. (2013)	RCS	Level 3
Kodama et al., 2012	CR	Level 5
Krieger et al. (2013)	CR	Level 5
Rinchuse et al. (2007)	CR	Level 5
Vitral et al. (2009)	CR	Level 5
Zahrowski (2009)	CS	Level 4

some treatment plans involved extractions for orthodontic purposes. The duration of treatment ranged from 12 to 78 months (mean 34.4 months).

3.3. Analysis of reported adverse outcomes

Outcomes were reported for all articles. 2 case reports reported no adverse outcomes following completion of orthodontic treatment [29, 34]. For the remaining 5 articles, the reported adverse outcomes included: difficulty achieving root parallelism ($n \approx 4$), difficulty achieving complete space closure ($n \approx 3$), exaggerated mobility post-debond ($n = 2$), increased duration of orthodontic treatment beyond expected completion ($n \approx 1$), sclerotic alveolar bone changes seen on post-op radiographic images ($n = 2$), an increased amount of root resorption ($n = 1$) and ONJ ($n = 1$).

The single case of development of ONJ was reported in a male patient undergoing fixed orthodontic treatment for a class II div 1 malocclusion. Antiresorptive treatment involved IV zoledronate for a duration of 11 months for management of a sacral plasmacytoma prior to orthodontic treatment. The patient was also undergoing radiotherapy and chemotherapy. ONJ developed in the right posterior sextant of the mandible and orthodontic treatment was ceased after 13 months [31].

3.4. Analysis of risk and quality assessment

In the five case report studies, considering the thirteen domains of the CARE checklist, all studies had a lack of clarity and missing data was identified (Table 5). The lack of clarity was predominantly due to a lack of reporting the duration of drug therapy and the type of diagnostic procedures carried out. Therefore, there was a high level of bias for all case reports. Regarding the retrospective and case series studies, it was determined to be lacking in many of the domains on the STROBE checklist (Table 5). These were predominantly regarding the study design and the method to measure outcomes. Therefore, there is a high level of bias for all retrospective reports and case series.

4. Discussion

This systematic review used a well-defined search strategy and validated protocols to investigate the reports of orthodontic treatment triggering the development of osteonecrosis in patients treated with antiresorptive medication. This review was also able to determine other associated adverse outcomes reported in the literature.

Bisphosphonates are the commonest antiresorptive medication used to treat a variety of medical conditions [6]. Following the administration of systemic bisphosphonates, they quickly bind to excess hydroxyapatite in the osseous matrix of bone. Once bound, they remain inactive until freed during remodelling. Once released, they can be shuffled into osteoclasts, inhibiting cell function and shortening the half-life. As a result, bone formation outmatches bone resorption due to unbalanced osteoblasts/osteoclasts on the bone surface [36, 37]. One widely known consequence of the use of antiresorptive drugs is ONJ. Several mechanisms have been reported, although the exact mechanism of this disorder is unknown. While the incidence of this is rare, the development can be devastating, and the management extremely difficult [6].

As orthodontics primarily involves bodily movement of teeth via alveolar bone resorption and remodelling, it is plausible that antiresorptive medications could interfere with this process. Therefore, understanding the pharmacodynamics of these medications is imperative to reducing any unfortunate and undesirable effects, and understand how the advantageous effects of bisphosphonates can be used to an orthodontist's advantage.

Bisphosphonate therapy aims to increase bone density and inhibit resorption. A previous systematic review alluded to the possible benefit of both local and systemic administration of bisphosphonates' to help improve anchorage and prevent post-orthodontic relapse. Although promising, the review gathered evidence from experimental animal studies. Furthermore, there was little research reporting the long-term follow-up after cessation of bisphosphonate therapy. As the systemic administration of antiresorptive

Table 3. Study characteristics from studies included in systematic review.

Author(s)	Subjects (n)	Mean age	Gender	AR medication	Method of administration	Indication for AR treatment	Total duration of AR treatment	Combined AR treatment + orthodontic treatment
Friedrich et al. (2019)	1	24 years	Male	PAM (12 months) ALD (24 months)	IV (12 months) Oral (24 months)	OI type I	36 months	NR
Lotwala et al. (2013)	20	20.5 years	Female (19)	ALD ($n = 17$) ZOL ($n = 1$) IBAN ($n = 2$)	IV ($n = 1$) Oral ($n = 19$)	OP ($n = 19$) Cancer ($n = 1$)	NR	NR
Kodama et al. (2012)	1	26.3 years	Female	PAM	IV	FD	20 months	Yes
Krieger et al. (2013)	1	66 years	Female	ALD	Oral	OP	7 months	Yes
Rinchuse et al. (2007)	2	52.5 years	Female (1) Male (1)	ALD (Female) ZOL (Male)	Oral (F) IV (M)	Addison's disease (F) Sacral plasmacytoma (M)	46 months (F) 13 months (M)	Yes ($n = 2$)
Vitral et al. (2009)	1	68 years	Female	IBAN	Oral	OP	NR	Yes
Zahrowski (2009)	3	61.3 years	Female	ALD	Oral	OP	60 months	Yes ($n = 2$) No ($n = 1$)

Table 4. Study characteristics from studies included in systematic review.

Author(s)	Pre-operative malocclusion	Orthodontic treatment	Mean duration of treatment (months)	Adverse outcomes reported (*n*)							
				Exaggerated mobility	Poor root parallelism	Poor space closure	↑duration of treatment	Sclerotic alveolar bone changes	↑ root resorption	ONJ	No adverse outcomes
Friedrich et al. (2019)	Class III	Fixed + orthognathic + extractions	36							Yes ($n = 1$)	
Lotwala et al. (2013)	NR	Fixed + removable + extractions	27.9		Yes (n = NR)	Yes (n = NR)	Yes (n = NR)				
Kodama et al. (2012)	Class III	Fixed + removable	72								Yes ($n = 1$)
Krieger et al. (2013)	NR	Fixed + extractions + anchorage using implants	11	Yes ($n = 1$)	Yes ($n = 1$)			Yes ($n = 1$)	Yes ($n = 1$)		
Rinchuse et al. (2007)	Class II div 1 ($n = 2$)	Fixed only (Male) Fixed + removable + extractions (Female)	13 (Male) 30 (Female)		Yes ($n = 2$)	Yes ($n = 2$)	Yes ($n = 1$)			Yes ($n = 1$) (Male)	
Vitral et al. (2009)	NR	Fixed + anchorage with mini-screws	6.5								Yes ($n = 1$)
Zahrowski (2009)	Class I ($n = 1$) Class II div 1 ($n = 1$) NR ($n = 1$)	Fixed + extractions	78	Yes ($n = 1$)	Yes ($n = 1$)	Yes ($n = 1$)		Yes ($n = 1$)			

medication is a known lifelong and long-term risk factor for development of MRONJ, this information is of vital importance [17].

This current review gathered several adverse outcomes from various studies following orthodontic treatment in patients taking bisphosphonates. These including exaggerated mobility post-debond, difficulty achieving root parallelism, difficulty achieving complete space closure, increased duration of orthodontic treatment, sclerotic alveolar bone changes seen on post-op radiographic images, and an increased amount of root resorption.

It is currently hypothesised that orthodontic tooth movement is slower or reduced following treatment with bisphosphonates [17]. In this review, one study retrospectively categorized patients taking bisphosphonates to those never having been treated with bisphosphonates. The results demonstrated that the bisphosphate group experienced a longer treatment duration and a higher rate of failure to close spaces than the control group [30]. This adverse outcome was also demonstrated in another study within this review [31].

Concerning root resorption, previous literature is contradictory and inconsistent. Previous studies have considered both local and systemic administration of bisphosphonates to prevent apical root resorption. Many experimental animal studies have found a reduction in root resorption using locally administered bisphosphonates, using clodronate and risedronate [38, 39, 40]. Contradictory evidence suggests that the administration of systemic bisphosphonates increases root resorption. The mechanism observed works via alteration of acellular cementum, transforming it into hyperplastic cementum which results in greater resorption when forces are applied to encourage bodily movement [41]. Again this research was conducted in animals and so careful interpretation is required. This current review, consisting of only human studies, supports the latter theory, albeit with a weak level of evidence.

Interestingly, the single case of ONJ found in this review was reported in a high-risk patient undergoing antiresorptive therapy for cancer [31]. Indeed, he was not a typical orthodontic patient. The patient had known comorbidities predisposing him to MRONJ, such as metastatic cancer with previous chemotherapy. He also had a history of concomitant corticosteroid use and was being treated with intravenous nitrogen-containing bisphosphonates [42]. Limited fixed orthodontic treatment (mandibular canine-to-canine) was carried out to close a space due to a missing mandibular lateral incisor. ONJ developed in the right posterior sextant of the mandible between the lower right first molar and an implant in the lower second premolar region. Therefore, it is unclear whether the orthodontic treatment precipitated the MRONJ development, or the bone exposure was spontaneous and unrelated, an uncommon but known aetiological finding [42]. Due to the heightened risk of developing MRONJ or other adverse outcomes, it is pragmatic to suggest that he was not an ideal candidate for orthodontic treatment.

Orthodontics is now far more accessible and common. It is not limited to pediatric patients, with one in four orthodontic patients an adult [43]. This leads to new challenges for orthodontists including altered physiological conditions, complex medical conditions and polypharmacy interactions that impact the orthodontic treatment. As orthodontic treatment can significantly improve a patients' quality of life, it is unfair to deny this treatment to at-risk patients. Instead, as professionals, we have a duty of care to investigate the risk factors further and provide up to date evidence s that patients can make an informed decision [44].

Orthodontists should be aware of the possible adverse outcomes of concurrent treatment with antiresorptive medication and liaise with other health professionals to determine the best course of action. This review found that in two cases, the treating orthodontist was unaware of the patient undergoing bisphosphonate therapy prior to starting treatment [33, 35]. This will likely be more profound in practice than the evidence suggests, and orthodontists should be wary of patients with medical issues that are likely to be medicated with antiresorptive medications, such as osteoporosis. Besides, an awareness of the current

Table 5. Summary of the quality assessment methodology and findings. National institute of health – quality assessment tool for studies (NIH); Clinical case reporting guidelines development (CARE checklist); Case series (CS), Retrospective Cohort Study (RCS), Case report (CR).

Study	Study Type/Design	Evaluating method	Risk of bias	Reason for risk category	Overall quality
Friedrich et al. (2019)	CR	CARE checklist	High	Reporting bias: diagnostic procedure during follow-up; duration of drug therapy	Low
Lotwala et al. (2013)	RCS	STROBE checklist	High	Reporting bias; study design; the outcome measurement methods.	Low
Kodama et al. (2012)	CR	CARE checklist	High	Reporting bias: diagnostic procedure during follow-up; duration of drug therapy	Low
Krieger et al. (2013)	CR	CARE checklist	High	Reporting bias: diagnostic procedure during follow-up; duration of drug therapy	Low
Rinchuse et al. (2007)	CR	CARE checklist	High	Reporting bias: diagnostic procedure during follow-up; duration of drug therapy	Low
Vitral et al. (2009)	CR	CARE checklist	High	Reporting bias: diagnostic procedure during follow-up; duration of drug therapy	Low
Zahrowski (2009)	CS	STROBE checklist	High	Reporting bias; study design; the outcome measurement methods.	Low

knowledge is paramount in discussing the risks to patients and obtaining consent.

The significant heterogeneity in data prevented quantitative analysis. While trends were evident in the collected data, these must be carefully interpreted within the context of varied reporting and important voids in the available information about specificities of patients, treatment strategies and long-term complications and follow-up. The results must also be taken with care as no clinical trial research was found in our search strategy. Direct extrapolation will require comprehensive observational studies with a large prospective cohort of subjects and a suitable control category of patients.

The authors encourage that specific protocols should be followed for future observational studies:

- If adverse outcomes are reported, these need to be described using standardized and reproducible scales. Calibration is necessary if multiple clinicians are participating in the research.
- To assure adequate and transparent reporting of randomized controlled trials, they should be conducted according to recommended guidelines such as CONSORT.
- An extended review period is essential to identify a predictable treatment outcome.
- A predictable radiological investigation, such as CT, CBCT or MRI scan should be encouraged for the length of the follow-up to determine stage 0 or local recurrence during or at the end of the treatment.

5. Conclusion

Based on the limited evidence available in the literature, it is unclear whether orthodontic treatment can precipitate MRONJ. Moreover, antiresorptive drug therapy has been associated with a sub-optimal treatment outcome.

In order to obtain a better quality of scientific evidence, more prospective studies or randomized clinical trials are needed to assess outcomes in patients undergoing orthodontic therapy previously or currently treated with antiresorptive medications.

Orthodontists should be aware of the possible adverse outcomes that may result and have a frank discussion with these patients prior to undertaking any orthodontic treatment.

Declarations

Author contribution statement

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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