Review

SEJODR

Response to orthodontic treatment with fixed appliances in adult patients compared to adolescents. A systematic review.

Marcial Andres Guiñez Coelho; Gabriela Paz Letelier Sepúlveda**

** Dentistry, Private practice in GamaSmile Clinic, Santiago, Chile.*

ABSTRACT

Objectives: This systematic review will seek to answer whether there are differences in the response to orthodontic treatment according to age, sex, and periodontal condition.

Data sources: A qualitative systematic review was carried out between 2016 and March 2021 in the electronic databases of PubMed, EBSCO Host, ClínicalKey, and BVS, selecting studies in English and Spanish with a maximum age of 5 years. The study was carried out according to the PRISMA statement.

Data selection: All the studies based on findings of orthodontic treatments in adult and adolescent human groups, healthy and/or with some conditions that may affect orthodontic treatment (periodontitis, postmenopausal) were included.

Data extraction: Study selection and data extraction were undertaken independently and in duplicate by two reviewers. There was a high degree of inter-examiner agreement for the eligibility assessment of the included articles ($\kappa = 0.8637$). Two reviewers assessed the quality of the included studies using AMSTAR-2, Cochrane's RoB 2.0, ROBINS-I, and Tools for cross-sectional, case-control and case reports studies from The National Institutes of Health (NIH).

Results: The search strategy used provided 1,350 papers of which 18 were selected for this study. Only 1 study showed a low risk of bias and 10 studies showed a high risk of bias. Adults show a late response after orthodontic activation. Periodontal conditions show improvement when periodontal and orthodontic treatment are combined. The response to orthodontic treatment does not show significant differences between adolescents and adults, or between premenopausal and postmenopausal women.

Conclusions: The studies indicate that there is no difference in the response to orthodontic treatment according to age, sex, and periodontal condition, although there is great heterogeneity between the included studies and the majority present a high risk of bias, therefore the results must be carefully analyzed.

Guiñez CMA, Letelier Sepúlveda GP. Response to orthodontic treatment with fixed appliances in adult patients compared to adolescents: A systematic review. South Eur J Orthod Dentofac Res. 2021;8(2):31-45.

INTRODUCTION

Context

An increasing number of adult patients, especially women, are seeking to undergo orthodontic treatments, mainly to improve aesthetics and function, with the intention of improving their quality of life and self-esteem. This is due to technological advances and the greater access to information that people have, added to the increase in the longevity of the population, which allows greater awareness and importance of oral health care.[1-9] Currently, oral health is not always considered with the importance that is required, omitting all the psychosocial consequences that its neglect can cause. Orthodontic treatment not only has an aesthetic effect but also improves function and enables comprehensive treatments. On the other hand, it has been seen that most patients undergoing orthodontic treatments have a greater commitment and care with their oral health [9], which is why orthodontic treatment can contribute to the population being more careful, reducing public health problems that derive from functional alterations and oral and/

Corresponding Author:
Marcial Andres Guinez Coelho.
Av. Salvador 95, Providencia, Santiago, Chile.
Email: marcial.guinezc@gmail.com

or systemic diseases that adults can suffer if they do not have an adequate state of health, which includes oral health.

The literature has described for years that facial attractiveness is an important element in self-esteem, social acceptance, and interaction with others; being the reason why people with attractive faces are kinder and more successful; which motivates the population, and especially adults, to seek orthodontic treatment to correct their dentofacial alterations.[5,9,10] However, we must consider that aesthetics is a subjective element dependent on socio-cultural, historical, emotional, personal, and sex factors. For this reason, beauty patterns are not stable over time, which can also influence the degree of satisfaction with orthodontic treatment.[6,10]

Orthodontic treatment in adult patients is a challenge given the unfavorable biomechanical conditions they present; such as possible periodontal sequelae, lack of growth, tooth loss, bone alterations in postmenopausal women, or alterations typical of aging, among others; even causing that not all orthodontists want to treat adults.[2,6,11] For this reason, it is essential to carry out an adequate diagnosis and treatment plan with a multidisciplinary team, added to with adequate psychological management because, many times, adult patients seek short-term treatments, with more aesthetic devices and with very high expectations which are necessary to bring to reality, a task in which the new technologies offered by digital orthodontics can contribute, together with adequate management of anxiety and expectations in each patient.[8-10,12,13] For this, effective communication and involving patients in their treatments are key elements to achieve satisfactory results.[14]

Three types of adult patients seeking orthodontic treatment have been described: (1) those who did not have the resources to undergo orthodontic treatment during their childhood/adolescence,(2) those who require orthodontic treatment as a complement to rehabilitation comprehensive, and (3) those who received orthodontic treatment during childhood/adolescence but had recurrence.9 However, many adult patients regret undergoing orthodontic treatment due to embarrassment when using fixed appliances, fear of pain or economic cost, factors in which the emotional support of their close environment and dental team is essential, as well as of the new technologies.[6,9]

Studies on orthodontic treatments in adults are not very widespread, and if the population with a systemic condition is considered, these studies are even more scarce, so this review will seek to reduce this limitation by including a wide variety of studies and inviting conducting more clinical studies in this population.

Advances in orthodontics have shown that orthodontic treatments in children and adolescents are predictable and successful, but is it just as successful in adult patients? This study will seek to collect updated scientific evidence on the response of orthodontic treatment in adult patients compared to adolescents patients, as well as to determine the response to treatment in healthy adult patients and with some systemic and/or periodontal condition to collect the evidence that gives us the necessary tools to face the new challenges that orthodontics will face due to the sustained aging of the population, together with the greater access, knowledge, and demand for orthodontic treatment.

Aims

The general objective of this review was to determine the response to orthodontic treatment among adults and adolescents patients. From this objective, two specific objectives emerged: (1) to determine the response, evolution, or prognosis of orthodontic treatment in patients with periodontal diseases, (2) to know the differences in the response, evolution, or prognosis of the orthodontic treatment between women and men.

To determine if age, sex, and/or periodontal condition influence the response to orthodontic treatment, we carried out a bibliographic search that included adolescents and adult patients, men and women, healthy patients with or without periodontal disease, who received orthodontic treatment with fixed appliances with the intention of comparing the baseline state with the post-treatment state between control and test groups to answer the research question regarding whether "age, sex, and/or periodontal conditions influence the response to orthodontic treatment?". For this, various studies such as systematic reviews, RCTs (Randomized controlled trials), NRS (Non-randomized controlled trials), Cross-sectional studies, case-control studies, and case report studies were reviewed to obtain a greater amount of information.

Finally, our null hypothesis is "There are no differences in the response to orthodontic treatment between adult/adolescents, male/female, or with/without periodontal disease".

MATERIALS AND METHODS

Study design

Protocol and registration: This literature review was performed according to the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions.15 The investigation was not registered because PROSPERO does not currently accept registrations for scoping reviews, literature reviews or mapping reviews.

Materials

Eligibility criteria

The Population Intervention Comparison Outcome (PICOS) framework was used to define the research question, objectives, inclusion and exclusion criteria and the search strategy:

- Population: Adolescents, adults, and the elderly have undergone orthodontic treatment. Studies with systemically healthy patients were evaluated.
- Intervention: Orthodontic tooth movement induced by fixed appliances.

- Comparison: Baseline characteristics versus posttreatment characteristics.
- Outcome:
  - Changes in the composition of the GCF,
  - Response to orthodontic treatment,
  - Periodontal response, and/or
  - External root resorption and/or bone resorption
- Study types: Meta-analysis, systematics reviews, randomized or nonrandomized clinical trials, case-control, and case reports.

Bibliographic database: A review from 2016 to March 2021 was carried out in the electronic databases of PubMed, EBSCO Host (Medline, CINAHL; Dentistry & Oral Science Sources), ClinicalKey and BVS.

Sampling technique: The limits established were studies with an antiquity of up to 5 years in English or Spanish. The keywords used were determined by DeCS/MeSH terms. The references of the selected articles were examined to identify new relevant publications considering the same limits expressed previously. The inclusion criteria were human studies that included a population aged 40 years or older and written in English or Spanish.

Search queries: The literature search strategy and the MeSH terms combinations is presented in Table I for PubMed. The strategy used was the same for all databases.

Table 1. *PubMed search strategy*

Database searched: PubMed **Data Coverage: 2016 – March 2021**	
1	Orthodontics [tiab]
2	(periodontal diseases [tiab] OR treatment [tiab] OR tooth movement techniques [tiab] OR prognosis [tiab]
3	(middle aged [tiab] OR adult [tiab]
4	#1 AND #2 (AND #3)
5	#1 AND #3
6	#2 AND #3

Exclusion criteria: The exclusion criteria were studies that investigated the effect of a drug on the response to orthodontic treatment, in vitro and older than 5 years.

Methods

Collected Data: Two authors (MG, GL) carried out an independent search in the databases with the previously defined search strategy. Duplicate studies were eliminated for subsequent review of titles and abstracts of the resulting studies and manual search. The selected articles were included in the Mendeley reference management software (Elsevier, version 1.19.8).

Reading the full text determined the eligibility of the included articles. In case of disagreement, a consensus was reached through discussion. All the studies included in this review were based on findings of orthodontic treatments in adult and adolescent human groups, healthy and with some conditions that may affect orthodontic treatment (periodontitis, postmenopausal). These authors extracted the results independently following a matrix constructed for this study. The variables searched were the following:

- *Patient characteristics*: Distribution by gender, age of the participants (age range, mean age ± standard deviation), the health status of the participants, periodontal screening, distribution of control and test group.
- *Study characteristic:* The methodology used, total duration of treatment application, treatment application times, site, and time of GCF collection, type of imaging tests used and control intervals.

In each study, information related to (1) characteristics of the participants such as age, sex, systemic condition, periodontal and radiographic examination methods, orthodontic diagnoses were extracted; (2) type of intervention such as type of orthodontic technique, characteristics of the orthodontic appliances used (fixed or removable), duration of orthodontic treatment, characteristics of periodontal treatment performed (surgical and/or non-surgical), presence of adjuvant therapies (use of mini implants, guided bone regeneration), (3) way of evaluating the result with respect to the basal state and the control group.

All variables were defined at the beginning of the study. The study interest group, which was considered as an adult, was over 40 years of age.

Analysis: This review had a qualitative analysis. The selected studies were examined for biases with the AMSTAR-2 tools for systematic reviews, Cochrane's RoB 2.0 and ROBINS-I for RCT and NRS respectively, and the tools for cross-sectional, case-control, and case reports studies from The National Institutes of Health (NIH).[16-19] The two authors (MG, GL) independently assessed the quality of the included studies. Differences were discussed until a consensus was reached.

RESULTS

Study selection: The search strategy applied in the databases provided 1,350 studies. After elimination of duplicates and manual searching (N=9), the titles and abstracts of 1,015 papers were reviewed. Forty-three papers were eligible for full reading, 18 of which were included in this review. Table II shows the exclusion reason for the 24 papers that were fully read. The flow diagram is presented in figure 1 shows the article selection process according to PRISMA.[15] The inter-examiner reliability of the two authors (MG and GL) was measured for the eligibility assessment of the included articles ($\kappa = 0.8637$) indicating a high degree of agreement.[20] For more information on the included papers, see Appendix 1 and 2.

Study characteristics: The included studies were identified as systematic reviews, randomized controlled trials (RCT), Non-Randomized controlled Study (NRS), cross-sectional studies, case-control studies, case series, and case reports whose data are available in Supplementary Tables I and II.

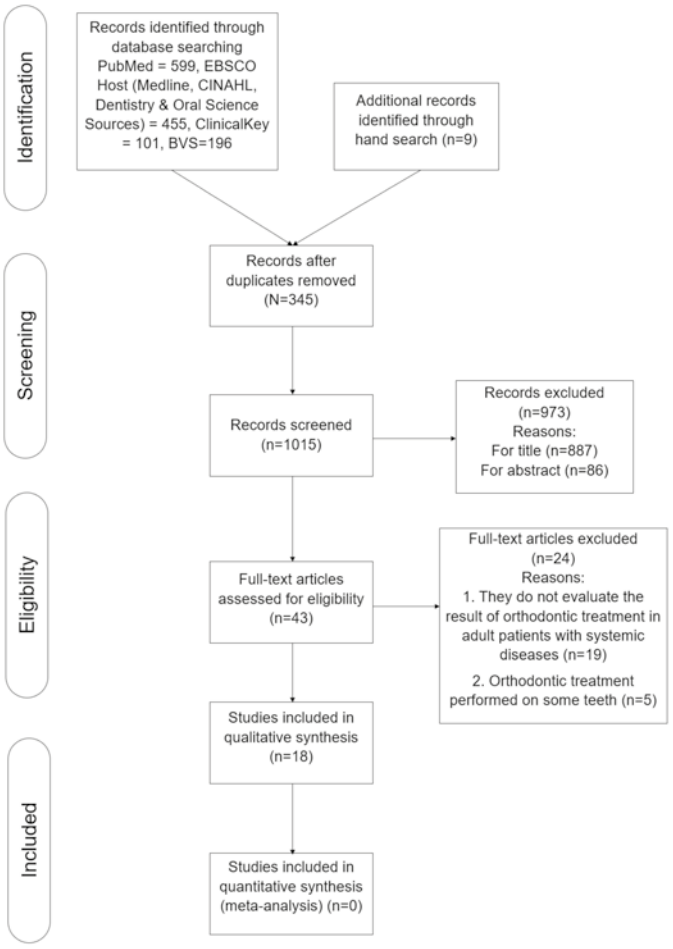

Figure 1. *The flow of information illustrating the systematic selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.*

Risk of bias within studies: In Figure 2 and 3 present a summary of the risk of bias assessment for RTCs and NRS. Supplementary Table III shows the full summary of the risk of bias analyses for systematic reviews, cross-sectional studies, case-control studies, case series studies, and before-after studies. Only one study showed a low risk of bias, 7 studies showed a moderate risk of bias, and 10 studies showed a high risk of bias, including all RCTs analyzed. The main cause of the risk of bias that was repeated in most of the studies was the lack of blinding.

Furthermore, of the 18 papers, 14 studies do not indicate the source of funding[2,7,21-32] and only 4 studies indicate it [33-36], of which only one did not receive external funding.[34] Of the other 3 studies, one received funding from the educational institution [36], another from Wuxi Young Medical Talent [35], and another from the Korean government research fund.[33] On the other hand, 2 studies do not indicate the presence or absence of conflicts of interest of the authors.[21,25] Not including the source of financing and, furthermore, not declaring possible conflicts of interest, indicates that the results obtained should be taken with caution.

Table 2. *Articles excluded from this review and reason for exclusion.*

Study	Reason for exclusion
De Couto Nascimento et al (2016)[1]	It only evaluated the difference in the patients' self-esteem before and after orthodontic treatment.
Gorbunkova et al (2016)[3]	The study only reports characteristics of patients with orthodontic treatment.
Gracco et al (2016)[4]	Study carried out in a patient without systemic or oral diseases.
Hirschfeld et al (2019)[5]	The study evaluated the interest of patients to undergo orthodontic treatment.
Lee et al (2018)[6]	The study only looked at the level of satisfaction with orthodontic treatment.
Subhiksha et al (2020)[8]	Describes the importance of orthodontics in multidisciplinary dental treatments.
Yuvaraj et al (2020)[9]	The study only describes the characteristics of adult orthodontic patient.
Salehi et al (2019)[10]	The study analyzed the facial attractiveness of different profile silhouettes.
Antoun et al (2017)[11]	It only reports the effects and complications of orthodontic treatment of patients with periodontal disease, as well as some studies carried out in animals.
Brämswig et al (2020)[12]	It relates the contribution of digital orthodontics.
Wong et al (2018)[14]	It only evaluated the degree of satisfaction of the patients with the orthodontic treatment in public and private services.
Arn et al (2020)[41]	The study evaluated the effect on periodontal tissues of two types of fixed lingual retainers.
Barbosa et al (2018)[37]	The study looked at factors related to bracket failure.
Elkordy et al (2019)[43]	The study did not evaluate adult patients.
Hwang et al (2016)[38]	It only evaluated the effect of orthodontic treatment on anterior teeth.
Jiang et al (2017)[46]	The study evaluated the effect of orthodontic treatment only on canines.
Knaup et al (2019)[42]	The study evaluated the effect on periodontal tissues of a fixed CAD/CAM lingual retainer.
Lewkowicz (2019)[49]	Only orthopedic treatments were performed.
Luchian et al (2016)[50]	The study does not indicate the age of the participants.
Maeda et al (2018)[26]	It only evaluated the effect of orthodontic intrusion of upper molars with mini implants.
Morita et al (2017)[45]	The study only performed orthodontic treatment for the dental intrusion of the upper left first premolar (2.5).
Palomo (2019)[51]	Describes the importance of orthodontics in multidisciplinary dental treatments.
Puttaravuttiporn et al (2018)[47]	It only evaluated the effect of orthodontic treatment on upper incisors.
Wu et al (2020)[44]	The population included in the studies only evaluated the adolescents population.

Results of individual studies

Gingival Crevicular Fluid (GCF)

Zhang et al.[32] examined 117 patients, 67 men and 50 women, between 22 and 46 years, with mild to severe periodontal disease, randomly assigned to the periodontal treatment only and periodontal treatment combined with the orthodontic treatment groups, along with 52 patients healthy that were used as a control group, collecting GCF samples from all groups. The age distribution between the groups was similar. In the periodontal treatment combined with the orthodontic treatment group achieved periodontal indices (PD, PI, CAL, BI) without significant differences with the control group; furthermore, the GCF showed that the levels of inflammatory cytokines were gradually reduced to achieve levels similar to the control group and much faster than the group treated only with periodontal

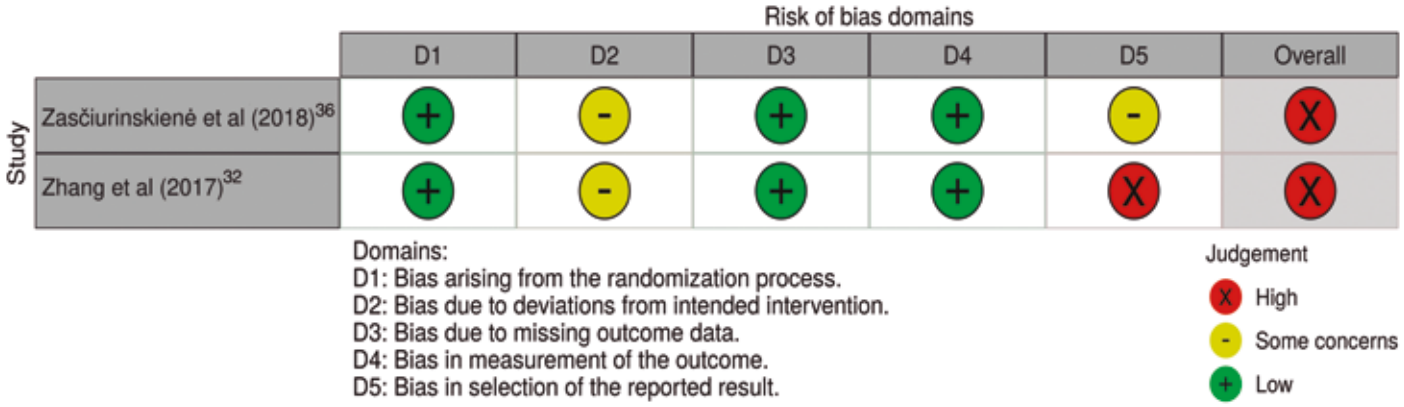

Figure 2. *Robvis tool to visualize assessment of risk of bias in RCTs with the RoB 2.0 tool.*

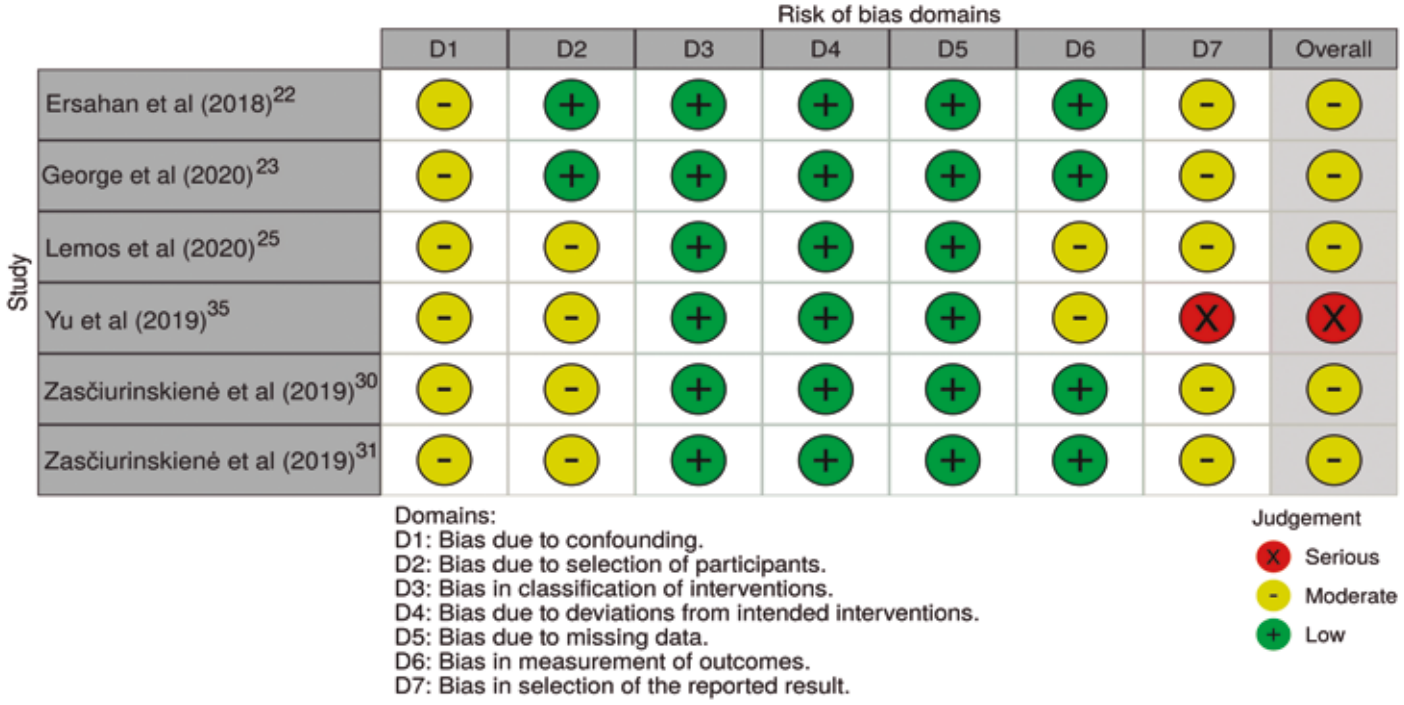

Figure 3. *Robvis tool to visualize risk of bias assessment in NRS with ROBINS-I tool.*

treatment, indicating that the periodontal state recovers more quickly when combined with orthodontic treatment in adult patients. Yu et al.[35] studied 60 middle-aged adult patients with chronic periodontitis and compared them with 32 periodontally healthy patients, finding that the periodontal indices (PI, BI, PD, CAL) and HMGB1 and NLRP3 biomarkers of GCF before treatment were significantly higher in the group with periodontal disease, values that decreased after periodontal and orthodontic treatment obtaining a positive correlation between these biomarkers and periodontal indices.

The systematic review by Schubert et al.[13] compared the concentration of biomarkers (PGE2, IL-1β, IL-6, IL-1 receptor antagonist, receptor activator of nuclear factor-kappa-B ligand, osteoprotegerin (OPG), granulocyte-macrophage colony-stimulating factor, pentraxin 3 (PTX-3), matrix metallo-proteinase 9 (MMP-9)) in GCF during orthodontic treatment among adolescents (<16 years) and adults (16 - 43 years), although the included studies had a significant range of magnitude of applied force and different techniques making their comparison difficult. Adults showed a lower rate of bone turnover, fewer progenitor cells, vessel formation, and fibroblast density. Furthermore, baseline PGE2 levels were significantly higher in adults, but after orthodontic activation they increased in both groups without significant differences between them. IL-1 levels did not differ between the two groups, but the average was slightly higher in adolescents showing a positive correlation with OTM speed. RANKL levels increased significantly in both age groups 24 hours after applying orthodontic force and OPG decreased simultaneously, although both biomarkers were significantly lower in the adult group compared to adolescents. MMP-9 levels did not vary in any age group. The level of PTX-3 increased 2.5 times in adolescents and 2 times in adults with the peak at 24 hours of application of orthodontic force

returning to the baseline level in 2 weeks in adolescents and 1 week in adults, showing an increase in the rate of OTM in adolescents. Most studies indicated that tooth movements are slower and with a later initial response to orthodontic force in adults compared to adolescents, which increases the total treatment time. Light and continuous orthodontic forces induce longer-lasting levels of cytokines during OTM, while strong and decreasing orthodontic forces create fluctuating cytokine levels and increase the risk of root resorption and hyalinization. It seems that adolescents have a higher rate of OTM than adults, but this prediction is not accurate given the high interindividual variability, genetics, and complexity of bone remodeling induced by OTM. Pharmacological agents for the prevention or treatment of diseases, including analgesics and dietary supplements, were observed to alter the rate of OTM. Fluctuation of estrogens during menopause or the female reproductive period, vitamin D3 supplementation, and even dietary calcium intake plays an important role in the RANK/RANKL/OPG signaling pathway that affects the rate of OTM. It is essential to maintain good oral hygiene during orthodontic treatment since gingival inflammation influences the expression of IL-1 and IL-1β. The follow-up periods of the included studies were short, which can lead to misleading conclusions.

A similar study compared 110 women in premenopausal and postmenopausal groups to evaluate the effect on GCF during menopause due to altered estrogen levels, analyzing RANKL and osteopontin (OPN) levels. GCF measurement was only performed 24 hours after orthodontic activation because previous studies showed that biomarkers changes occur 24 hours after orthodontic activation. Although baseline RANKL levels were significantly higher and OPN levels were significantly lower in premenopausal women, both biomarkers increased significantly at 24 hours in premenopausal and postmenopausal women without showing statistically significant differences between the two groups, demonstrating that postmenopausal women have a profile bone turnover different from premenopausal women, but the response to orthodontic activation is similar.[7]

Radiographic changes

Bone changes recorded with periapical radiographs have shown that even elderly patients with sequelae of periodontal disease can benefit from orthodontic treatment. In studies by Jang et al.[24] and Tsai et al.[28] evaluated 55-year-old adult patients undergoing periodontal treatment with bone regeneration followed by orthodontic treatment showed a considerable improvement in infrabony defects and their periodontal indices (PD, PI, CAL, REC) especially if the treated orthodontics is performed after bone regeneration, after controlling periodontal disease, results evidenced during a follow-up of 1 year and 2 years after periodontal and orthodontic treatment, in each study respectively. In another study of 14,693 patients of different ages, when analyzing patients undergoing orthodontics treatment a lower prevalence of periodontitis was observed (9%), being present in older, overweight people and not associated with oral hygiene technique; Moreover, in the groups without orthodontic treatment a higher prevalence of periodontitis (44%) and chronic systemic diseases was observed, providing a positive association regarding the fact that orthodontic treatment can reduce the prevalence of periodontitis.[27] On the other hand, Han et al.[33] analyzed periapical radiographs prior to and after orthodontic treatment of young adults (19 to 30 years) and middle-aged adults (older than 40 years), identifying that occlusal and periodontal conditions were more severe in adults middle-aged. However, at the end of the orthodontic treatment the bone and periodontal response was similar in both groups without finding a greater risk of root resorption or marginal bone tissue in the older population, showing a good tolerance to orthodontic treatment, even when the initial conditions were most unfavorable.

Zasčiurinskienė et al.[31] evaluated 50 adults (mean age 45.4 years) with periodontal disease using CBCT before and after periodontal and orthodontic treatment, observing external apical root resorption (EARR) after treatment in 80.7% of single-rooted teeth with a mean of 1.2mm, although in 82.3% of the cases it was ≤2mm. The magnitude of the intrusion and inclination of the central incisors influence the extension of the EARR, and this was greater when orthodontic treatment was longer than 18 months. There are no significant differences in EARR if orthodontic treatment is performed after (84.2%) or simultaneously (80%) with periodontal treatment. Age and sex did not influence the prevalence and extent of EARR. In another study by Zasčiurinskienė et al.[30] where they used the same population and time interval, they evaluated the changes in the alveolar bone level (ABL) before and after periodontal and orthodontic treatment without finding differences in ABL between both time periods were in a 69 % of the surfaces was no changes in ABL, in 15.6% there was the gain of ABL and in 15.1% there was a loss of ABL, finding a significant loss of ABL in the buccal and lingual surfaces compared to the mesial and distal surfaces. The same happened in the maxillary incisors that were not intruded with respect to those that did. Those maxillary incisors that were retroclined by more than 8.6° and were intruded more than 1.6 mm showed a significant gain in ABL compared to those that did it in smaller magnitudes. Changes in ABL after orthodontic-periodontal treatment in patients with periodontal disease were small. Greater orthodontic movements of the upper incisors influenced a greater ABL gain. No differences were found in ABL before and after orthodontic treatment between upper and lower teeth, or between anterior and posterior teeth; however, a significant difference was found in the posterior maxillary teeth between the two time periods. Age, sex, duration of orthodontic treatment, type of malocclusion, and type of anchorage did not correlate with changes in ABL. Severe ABL loss (> 6mm) after treatment in areas that had a normal baseline bone level before treatment (<3mm) only occurred in 1% of the studied surfaces.

On the other hand, Lemos et al.[25] analyzed the effect of fixed containment in 17 adults (mean age 38.3 years) using CBCT and bacterial analysis, comparing the start of orthodontic treatment and 12 months later, finding that biofilm levels increased, but not

evidenced significant loss of marginal bone tissue. PD and CAL improved significantly, only increasing in 3% of the periodontal sites examined. The concentration of *Actinomyces Sp* decreased, the orange group increased, and the red group remained the same, without affecting the periodontal indices.

Clinical manifestations

In the RCT of Zasčiurinskienė et al.[36] 50 patients older than 25 years with periodontal disease and undergoing orthodontic treatment in different phases were studied according to the group to which they were randomly assigned, showing that the periodontal indices (PD, CAL, REC) improved without significant differences when the Orthodontic treatment is performed simultaneously with surgical periodontal treatment or subsequently. However, in this study, the duration of treatment was significantly longer in the group in which orthodontic treatment was performed after completing the surgical and non-surgical periodontal treatment. These same results were observed in a case report by Capelli Júnior et al.[21] where a 50-year-old patient with malocclusion, moderate chronic periodontitis with vertical bone defects and tooth loss underwent periodontal treatment followed by orthodontic and prosthodontic treatment, observing periodontal health and bone stability during a 30-month follow-up demonstrating the importance of achieving appropriate mechanical systems, although the tissue response be slower compared to young patients. These results and improvement in periodontal indices (PD, PI, BI, CAL, REC) after orthodontic treatment were also observed in the studies by González et al.2 and Yu et al.[35] Watahiki et al.[29] treated two patients with marginal bone resorption using periodontal regeneration treatment with the O-PRO technique and orthodontic treatment simultaneously, showing that, even after 4 years of orthodontic treatment, bone tissue levels remain stable. This shows that an initial alignment and leveling can improve the dental position and blood flow of the periodontal membrane, facilitating regeneration maneuvers.

Orsini et al.[34] analyzed the periodontal indices (PI, GI, PD, CAL) in 19 adult patients between 30 and 52 years underwent orthodontic treatment three months after the end of periodontal treatment, together with free gingival grafts in areas with minimal keratinized tissue (≤1 mm) three months after starting orthodontic treatment. Periodontal indices worsened after periodontal treatment and before starting orthodontic treatment, however, these improved after free gingival graft surgery with a follow-up of up to 15 months, indicating that the treatment of areas with little keratinized tissue during orthodontic treatment with fixed appliances can improve periodontal indices.

On the other hand, when comparing pulp blood flow (PBF) between young adults (mean age 20.3 years) and middle-aged adults (mean age 47.6 years) undergoing orthodontic treatment, it was observed that the PBF is significantly higher in young patients compared to middle-aged adults in all measurements made at 24 hours, 72 hours, 1 week, 3 weeks and 1 month after orthodontic activation. In addition, a greater decrease in PBF was observed in the anterior teeth compared to the posterior ones in both groups.[22]

George et al.[23] analyzed periodontal ligament cells (PDLC) and periodontal biomarkers (PGE2, IL-1β, acid phosphatase (ACP), alkaline phosphatase (ALP), RANKL, OPG, bone gamma-carboxyglutamate protein (BGLAP)) from extracted premolars before the application of orthodontic force, and at 7, 14, 28 days after the application of orthodontic force in adolescents (mean age 16.4 years) and adults (mean age 40.9 years). PDLC levels were higher in adults, with a peak at 7 days, reaching similar values in both groups at day 28 indicating positive and productive changes of PDLC in adults. PGE2 levels were significantly higher in adults, and in both groups at day 28 the values were significantly higher compared to day 7. For IL-1β the values were significantly higher in adults than in adolescents in all measurements, similar values for ACP. When analyzing ALP values, it was observed that this increase progressively in both groups from day 7 to 28, being significantly higher in adolescents on day 28, similar results when analyzing RANKL. In the case of OPG at 7 days the values were statistically higher in adolescents compared to adults, a trend that was maintained on day 14 although not significantly, results that were reversed on day 28 when they were significantly higher in adults. The BGLAP values increased in all measurements in both groups without significant differences, although in adults the increase was lower. A progressive reduction in the effects of aging is observed in PDLC as the days progress from the application of force with a large initial increase in these effects at day 7 and decreasing over time (day 28). A greater catabolic and inflammatory change is observed together with a less productive bone response in adults, while in adolescents PDLCs have a rapid recovery from initial inflammation with a productive anabolic response 28 days after the application of force. The PGE2 and IL-1β response was 2 and 3 times greater, respectively, in adults indicating cellular sensitivity and increased inflammatory response to forces as we age, producing more catabolic than anabolic changes. ACP indicates bone resorption and the results suggest that this begins much earlier in adults and continues at a high level until day 28, while in adolescents their immune system counteracts it (due to the low inflammation due to the values of PGE2 and IL-1β) starting at a slow pace. ALP is associated with bone formation and is minimally expressed in adults compared to adolescents. BGLAP is released only by osteoblasts related to bone mineralization, being lower in adults, although they are similar to adolescents on day 7, on day 14 they fall correlating with the higher level of ACP on day 14 in adults, showing that on this day there is greater inflammation-causing greater resorption than bone apposition; However, on day 28 they increase to be comparable to that of adolescents correlated with the increase in OPG, which prevents osteoclastogenesis by joining RANKL, promoting bone formation.

Risk of bias across studies

Due to the methodology of the studies, it was not possible to

determine selection, performance, or attrition bias, although significant signs of these biases were observed; especially in a study that indicated that it did not include 3 patients for "other reasons" without explaining what reasons they were and that, in addition, it replaced a patient who withdrew from the study without indicating the characteristics of the new patient who replaced it, which could affect the sample.[36] Other studies did not indicate the teeth that were used to collect the samples or did not explain why they selected specific teeth for measurements[7,23,33,35] On the other hand, the absence of a blind was found in all the studies analyzed. Furthermore, randomization was only possible in two studies,[32,36] although the examiners and/or operators were not blinded.

DISCUSSION

Summary of evidence

This review included various types of studies among which we found 1 systematic review, 2 RCTs, 6 NRSs, 1 Cross-sectional study, 2 Case-control studies, 1 case series, and 5 Case reports that investigated the response of orthodontic treatment in adults and adolescents of both sexes evaluating clinical, GCF and radiographic parameters. In the literature there are many studies regarding the response to orthodontic treatment in adolescents, however, the evidence regarding healthy adults and/or with oral or systemic disease, as well as the effect of physiological alterations, such as in the case of postmenopausal women, they are scarcer.[7] During this review, great heterogeneity was observed between the studies analyzed.

Adults increasingly seek orthodontic treatments to improve their functional and/or aesthetic alterations with orthodontics being an effective alternative to improve these conditions, deliver a psychosocial benefit, and help to increase their self-esteem and quality of life.[1,3-9,11,12,33] Although the perception of aesthetics is subjective, multifactorial, and changes over time, it is still important to achieve an adequate facial profile. [10] For this reason, it is essential to carry out multidisciplinary treatments in adult patients [1,3,4,8,12,31], together with effective communication to adequately determine their objectives since, generally, they seek shorter treatments, appliances and results more aesthetic, and are concerned about costs, being factors that can influence the satisfaction of orthodontic treatment and affect the decision to want to be treated [6,9,13,14], a situation in which it is possible to lean on technology through digital orthodontics to facilitate this communication and understanding by the patient.[12] In addition, adults have been seen to be more cooperative, committed, and careful with their treatment, even with lower rates of bracket failure.[37] However, each case should always be carefully analyzed and the consumption of medications such as NSAIDs, bisphosphonates, insulin, metformin, vitamin D, eicosanoids, and some dietary supplements should be evaluated as they alter the rate of OTM which can modify the planning, prognosis, and duration of treatment. [9,12,13]

Several studies have concluded that orthodontic treatment provides satisfactory results in patients undergoing surgical and/or non-surgical periodontal treatment, allowing the improvement of periodontal indices as well as bone defects and the presence of malocclusions, [2,5,21,24,27,28,35,38] but they are studies with a low level of evidence and almost all have a high or moderate risk of bias.[39] Periodontal regeneration techniques have even been proposed that are more effective when complemented with orthodontic treatment, such as the case of O-PRO, showing superior results compared to conventional methods, although it requires further investigation.[29] Some studies with a higher level of evidence, such as RCT, also showed this improvement in periodontal indices in patients with biofilm-induced periodontitis of varying severity when supplemented with orthodontic treatment, [32,36] although they also present a high or moderate risk of bias, mainly for lack of blindness in its methodology, which can compromise its results. However, multiple studies agree that an adequate analysis, diagnosis, and planning is required at the beginning of treatment since, for example, the periodontal biotype and the amount of attached gingiva are important factors when determining the effect of orthodontic treatment on periodontal tissues.[3] The study by Orsini et al.[34] the only one with a low risk of bias in this review, indicated that in cases with bands of keratinized tissue ≤1mm and that undergo free gingival grafts, they show less accumulation of biofilm and gingival inflammation, so it is essential to perform an adequate general and oral diagnosis, including the periodontal tissues, to minimize the possible adverse effects of fixed appliances.

Biomarker studies show a greater inflammatory response and bone resorption evident in adults due to the increase in PGE2, ILB1 and ACP compared to adolescents who showed a progressive increase in these molecules, indicating controlled bone resorption. In addition, adolescents have bone formation controlled by an increase in ALP and the balance between RANKL/OPG, since in adults this relationship was lower on days 7 and 14, but on day 28 OPG increased significantly, showing an active defensive mechanism against reabsorption by binding of OPG to RANKL23 added to a positive and statistically significant correlation between RANKL levels in the GCF and increasing age.40 These elements indicate that adults can show a more marked catabolic response than adolescents, but this difference tends to decrease over time, which again gives importance to correct diagnosis and planning since this more delayed initial response and a lower rate of bone turnover should be considered in adults during orthodontic forces compared to adolescents, elements that help define the orthodontic activation intervals and the possible extension of the orthodontic treatment period in adults,[2,13] a situation that it is not a contraindication for orthodontic treatment.

On the other hand, when analyzing the levels of RANKL and OPN in the GCF after orthodontic force, no significant

differences were observed between premenopausal and postmenopausal women, giving security in their orthodontic treatment,[7] although Schubert et al.[13] indicated that menopause can affect the rate of OTM, which is why more studies are lacking to confirm it. In any case, this is a precedent that gives security to orthodontic treatment and shows that there are no adverse effects associated with age or physiological condition itself, reducing everything to an adequate diagnosis and planning.

Furthermore, it is possible to question the use of fixed appliances in adults considering their higher prevalence of periodontal disease, given that this appliance can increase the accumulation of biofilm and worsen their periodontal condition. However, studies have shown that although fixed retainers increase the amount of biofilm and mean gingivitis values, they do not affect periodontal indices (PD, BI),[40,41] nor marginal bone tissue in adults by accurately measuring with CBCT.41 In addition, the types of retainers have been analyzed, finding that those developed by CAD/CAM made of nitinol are more beneficial for gingival tissues compared to conventional flexible coil wires.[42] Studies suggest that there are no differences in periodontal tissues between conventional plain or braided fixed retainers, although this is a controversial issue with a lack of quality studies.[41] For this reason, these are factors to consider in the use of fixed orthodontic appliances, especially in adults, which is why improvement in hygiene techniques and awareness of oral care in patients should be encouraged. On the other hand, a meta-analysis and a systematic review not included in our study found that periodontal indices (PD, PI, CAL, REC, gingival index) worsened with the use of fixed appliances compared to removable appliances,[43,44] and some have even declared that there is a loss of marginal bone tissue, although these studies were carried out in adolescents and evaluated with bitewing and periapical radiographs, together with showing poor hygiene habits in the population studied,[25] which may affect the analysis by not using a more standardized and precise method such as CBCT, recognizing that it is not a routine method given its higher radiation and cost, because these studies do not indicate the use of positioners to standardize the intraoral radiographic taking, only standardizing the angulation in 10° and that the central beam is perpendicular to the mesial surface of the first molar (which has a degree of subjectivity and variability between each radiographic taking) without commenting on the position of the patient's head or his possible movements during the X-ray, not being a completely objective and standardized X-ray.[25,39]

Orthodontic treatment in adults can go even further. This is reflected in a case report by Morita et al.[45] not included in this review, who performed orthodontic traction, rather than extraction, in a patient at high risk of osteoradionecrosis (ORN) and bisphosphonate osteonecrosis (MRONJ) with successful results and bone tissue formation, without infections, ORN or MRONJ with a follow-up of 2.5 years. This case invites us to continue with these investigations to improve the scientific evidence regarding orthodontic treatment in adults and under different systemic conditions that may occur in this population.

In response to the objectives of this review, the evidence indicates that adults tolerate orthodontic treatments in a similar way to adolescents, even if their initial periodontal condition is unfavorable, without observing a greater risk of root resorption or serious bone loss with increasing age,[33] even evaluated with CBCT,[30,31] although care must be taken in the intensity of orthodontic forces, type of movement used, or some IL-1β phenotypes, as is the case of polymorphisms in the IL-1β gene rs1143634, which confers a higher risk of EARR, although it is difficult to assess routinely and which, likewise, are important factors to consider in the young population without being exclusive to adults.[11,23,46,47] Some studies even used mini implants as a complement to orthodontic treatment and showed beneficial results without damaging teeth or bone tissue, although knowing the possible risks if they are not used and indicated appropriately, such as root resorption or damage due to proximity to tissues surrounding areas, being an alternative to consider for more predictable orthodontic treatments in adults with loss of anchorage due to sequelae of periodontal disease and/or dental loss, improving their prognosis and response to treatment.[11,26] In other words, the response of various biomarkers present in the GCF may show less encouraging results in adults compared to adolescents, and even mean that the treatment period in adults may be longer, but in clinical practice the adult population responds in a way satisfactory compared to orthodontic forces, even if they present sequelae of periodontal disease, without showing significantly higher risks on bone and dental tissue compared to adolescents, results that are replicated when observing that there are no differences between sex and, even, between premenopausal and postmenopausal women who have a different basal bone metabolism, but who respond similarly to orthodontic treatment.

Limitations

This review reported a high risk of bias in most of the included studies, with the main cause being the absence of blinding in all studies. This can cause the results and interventions to have been influenced by the knowledge of the condition and treatment assigned to each patient. On the other hand, two studies did not report the presence or absence of a conflict of interest, which is a serious fault, being an indicator of a potential risk of bias because all decisions and professional judgment regarding a primary interest should not be unduly influenced for a secondary interest, something that is not known by not declaring it. Furthermore, 14 studies did not disclose the source of funding, which may contribute to a conflict of interest or bias as secondary interests may be economic or non-economic.48 Due to these inaccuracies and potential severe risks of bias, added to the bias results obtained with the tools used previously, it determines that these results are analyzed with caution.

Moreover, another major limitation that causes us to be cautious

with the results is the incorporation of studies with levels of evidence that provide lower quality evidence, as in the case of case report or case-control compared to studies with higher levels of evidence such as systematic reviews, for example. However, it is essential not to assume that studies with level 1 evidence are always a guarantee of quality research and the best option to answer the research question and objectives.[39] In addition, the number of existing studies that address the subject of this study are scarce, which is why it was decided to incorporate studies with levels of evidence with lower quality of evidence, being aware and assuming the limitations that this causes, to set a precedent and invite future clinical investigations with a higher quality of evidence.

Finally, another limitation present in this review was the use of studies published in English and Spanish, excluding potential studies in other languages, along with limiting the search with studies with a maximum of 5 years old.

CONCLUSION

The evidence from the studies included in this review indicates that orthodontic treatments do not present substantial differences in the response to treatment between adults and adolescents, in addition to not having differences by sex and showing a positive response to orthodontic treatment in patients with periodontal disease, verifying the proposed null hypothesis. However, there is great heterogeneity among the included studies and there is evidence of a high and moderate risk of bias in most of the included studies. Furthermore, studies with a low level of evidence were incorporated, which is why these results should be analyzed with caution.

Due to this, it is necessary to carry out more clinical studies of higher quality and with less bias on this subject, as well as to incorporate patients with systemic diseases and/or physiological alterations to have a better understanding of the treatment of an adult population that is increasingly prevalent in orthodontics.

A relevant area to deepen is the impact of active and retention fixed orthodontic appliances on long-term periodontal tissues due to the subclinical inflammatory state that is observed when analyzing GCF biomarkers. In addition, the impact of orthodontic treatment in patients under treatment with antiresorptive, such as bisphosphonates, should be studied in greater depth, since many postmenopausal women consume them and are the ones who increasingly seek orthodontic treatment, deepening the existing clinical report that did not show osteonecrosis in a 2.5-year follow-up, which needs to be studied with higher quality studies.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors of the present article declare no conflicts of interest.

Supplementary Table I. *Overview of systematic review.*

Study	Design	Included studies	Younger group age range {mean age ± DS} (size group) [M/F]	Older group age range {mean age ± DS} (size group) [M/F]	Control/ test group distribution	Health status and inclusion criteria	Oral hygiene regimes and periodontal	Observation period	Response to orthodontic treatment	Complementary exams
Schubert et al (2020)[13]	SR	10 prospective CT	10.5y - 15y	16y – 43y	382/382 (Same treatment in all patients. Control group was the baseline or opposite and/ or contralateral tooth, test group were teeth subjected to OTM)	Healthy. No consumption of antibiotics and anti-inflammatories	Three studies with periodontal screening, CHX mouth rinse and supragingival oral prophylaxis before treatment orthodontic.	28d (baseline) to 20w	Variable in each study. in general, adults respond less to OTM and with a more delayed initial response than adolescents but with limited quality evidence.	GCF collection in six studies
			{NA}	{NA}			One study with only periodontal screening.			
			(206)	(176)			Four studies with periodontal screening and IHO.			
			[111/95]	[88/88]			One study with periodontal screening, supragingival oral prophylaxis and IHO.			

SR = Systematic Reviews, CT = Controlled Trial, RCTs = Randomized Controlled Trials, DS = Deviation Standard, M/F = Male/Female distribution, y = years, NA = Not applicable, CHX = Chlorhexidine, d = days, w= weeks, OHI = Oral Hygiene Instruction, OTM = Orthodontic Tooth Movement

Supplementary Table 2. *Overview of RCTs, NRS, Cross-Sectional study, case-control study, and case reports.*

Study	Design	age range {mean age ± DS} (size group) [M/F]	Control group /test group	Health status and inclusion criteria	Oral hygiene regimes and periodontal screening	Duration of study	Response to orthodontic treatment	Complementary exams	Adjuvant treatments
Zasčiurinskienė et al (2018)[36]	RCT	<25y (50) [15/35]	25/25 (Groups were randomly determined. The test group received surgical periodontal treatment after alignment and leveling with orthodontics. The control group received surgical periodontal treatment prior to orthodontic treatment)	Healthy patients, except for periodontal disease without the use of medication that would influence treatment and pregnant or lactating women	Periodontal screening, OHI, oral prophylaxis, CHX mouth rinse	20 months	Both groups improved CAL and a decrease in sites with PD ≥4mm without significant differences between them. There are no differences in the development of REC between the groups. The orthodontic treatment time was significantly longer in the control group. Orthodontic treatment is suggested simultaneously with periodontal treatment routinely in cases of biofilm-induced periodontitis	NA	Surgical periodontal treatment in all patients
Zhang et al (2017)[32]	RCT	22y – 46y {35.9 ± 5.9y} [104/65]	117/52 (patients with periodontal disease versus healthy patients. Patients with periodontal disease were randomly assigned to non-surgical periodontal treatment or surgical + non-surgical periodontal treatment)	Healthy patients, except for periodontal disease, without the use of antibiotics or NSAIDs in the last month and without the use of mouth rinse.	Periodontal screening, OHI, oral prophylaxis	2y	All periodontal indices improved significantly in the orthodontic treatment group with surgical + non-surgical periodontal treatment, without differences with the group of healthy patients, showing a greater periodontal recovery compared to the orthodontic treatment group with non-surgical periodontal treatment. The levels of inflammatory cytokines in the GCF decreased significantly in 6 months in the orthodontic treatment group with surgical + non-surgical periodontal treatment. The age distribution was similar in the 3 groups.	GCF collection	Surgical + non-surgical periodontal treatment in 59 randomly chosen patients
Ersahan et al (2018)[22]	NRS	18y – 55y (28)	14/14	Healthy patients	Periodontal screening	1 month	Measurements were made at 24 hours, 3 days, 7 days, 21 days and 1 month. Mean pulp blood flow values were significantly higher in the youngest group in all measurements. The severe decrease in blood flow in the older group in the face of orthodontic forces can be associated with age-related arteriosclerotic changes in the pulp, which has been reported in several histological studies. Orthodontic tooth movement caused a significant reduction in PBF in the experimental teeth in both groups.	Laser Doppler flowmetry to measure pulpal blood flow	NA
George et al (2020)[23]	NRS	12y – 50y {28.7 ± 3.39y} (40)	20/20	Healthy patients and without drug use	Periodontal screening	28 days	A greater activity of the adult PDLC was observed compared to the young ones. The PGE2 inflammatory response was statistically significantly higher in adults with significantly higher levels on day 28 than on day 7 after orthodontic force application. ILB1 was also statistically significantly higher in adults. RANKL increased throughout the follow-up in both groups without significant variations, although in adults the variation and levels were lower and significantly compared to the young on day 28. A progressive reduction of the aging effects of PDLC is observed at as the days go by since the application of orthodontic force, a more catabolic and inflammatory response is observed along with a lower bone production response, unlike in adolescents.	GCF collection	NA
Lemos et al (2020)[25]	NRS	{38.3 ± 6.3} (17) [7/10]	NA	Healthy patients	Periodontal screening, OHI, non-surgical periodontal treatment. The use of mouth rinses was prohibited	12 months	Visible biofilm sites increased, but there was no statistically significant loss of marginal bone. Mean PD decreased and CAL improved significantly. The concentrations of Actinomyces sp decreased and the bacterial species of the orange group increased, the red group remained the same.	CBCT	NA
Yu et al (2019)[35]	NRS	{42 ± 13y} (92) [52/40]	32/60	Healthy patients, except for periodontal disease in the test group	Periodontal screening, OHI, non-surgical periodontal treatment	1 month	The initial periodontal parameters and levels of HMGB1 and NLRP3 from the GCF collection were higher in patients with periodontal disease than in healthy patients, but after 6 months of orthodontic treatment these levels decreased, although they continued to be higher than in healthy patients. A significant positive correlation was observed between levels of HMGB1 and NLRP3 with the periodontal parameters. (PI, BI, PD, CAL)	GCF collection	NA

Continued on next page ➡

SR = Systematic Reviews, CT = Controlled Trial, RCTs = Randomized Controlled Trials, DS = Deviation Standard, M/F = Male/Female distribution, y = years, NA = Not applicable, CHX = Chlorhexidine, d = days, w= weeks, OHI = Oral Hygiene Instruction, OTM = Orthodontic Tooth Movement

Supplementary Table 2. *Overview of RCTs, NRS, Cross-Sectional study, case-control study, and case reports.*

Study	Design	age range {mean age ± DS} (size group) [M/F]	Control group /test group	Health status and inclusion criteria	Oral hygiene regimes and periodontal screening	Duration of study	Response to orthodontic treatment	Complementary exams	Adjuvant treatments
Zasčiurinskienė et al (2019)[30]	NRS	{45.5 ± 1.94} (50) [15/35]	25/25 (control group performed periodontal treatment before orthodontic treatment / test group performed periodontal treatment simultaneous orthodontic alignment and leveling)	Healthy patient, except for periodontal disease	Periodontal screening, OHI, non-surgical periodontal treatment	6 years	Changes in ABL after orthodontic-periodontal treatment in patients with periodontal disease were small. The ABL gain applies more to the mesial and distal surfaces and the ABL loss to the buccal and lingual surfaces. Larger orthodontic movements of the upper incisors influenced ABL gain.	CBCT	Surgical periodontal treatment in sites with PD greater than 6mm after orthodontic alignment and leveling. Use of mini implants or osseointegrated implants for greater anchorage in orthodontic movements when needed.
Zasčiurinskienė et al (2019)[31]	NRS	{45.4 ± 1.95y} (50) [15/35]	25/25 (control group performed periodontal treatment before orthodontic treatment / test group performed periodontal treatment after orthodontic alignment and leveling)	Healthy patient, except for periodontal disease	Periodontal screening, OHI, non-surgical periodontal treatment	6 years	80.7% of the single-rooted teeth presented an average EARR of 1.2mm, and in 82.3% of these cases the EARR was ≤2mm. Severe EARR was found in 8% of the cases (> 4mm). The amount of intrusion and the change in the angle of inclination of the steeper upper central incisor influenced the extent of the EARR. The mean EARR was significantly higher when orthodontic treatment lasted more than 18 months. There were no differences in the EARR between the test and control groups. Age and sex did not influence the EARR. If the retroinclination was greater than 8.6°, a higher EARR is observed. It can be concluded that the average EARR is not higher in patients with periodontal disease compared to healthy patients.	CBCT	Surgical periodontal treatment in sites with PD greater than 6mm after orthodontic alignment and leveling. Use of mini implants or osseointegrated implants for greater anchorage in orthodontic movements when needed.
Sim et al (2017)[27]	Cross-sectional study	>19y {41.92 ± 0.57y} (14,693) [7,295/7,398]	13,909/784	Patients with orthodontics (test group) and without orthodontics (control group) were included. Smokers and drinkers, with periodontal disease and systemic diseases (diabetes, hypertension, metabolic syndrome) were included.	Only periodontal screening	NA	The prevalence of periodontitis was lower in the orthodontic treatment group. In the test group, the subjects with periodontitis did not show a higher prevalence of diabetes.	Blood tests, BMI, waist circumference	NA
Han et al (2019)[33]	Case – Control Study	19 - ≥40y {38 ± 5.43y} (39) (15/24)	Dec-27	NA	Periodontal screening, OHI	NA	The discrepancy index was significantly in the older group, although CRE was similar in both groups. The duration of treatment was longer for the older group. Even though the older group had worse periodontal and occlusal conditions, the periodontal results after orthodontic treatment were similar to the young group, so that the increase in age does not negatively affect the result of orthodontic treatment, although studies are lacking long-term.	Periapical radiography	NA
Orsini et al (2020)[34]	Case series	30y – 52y (19) [8/11]	NA	Healthy patients, except for periodontal disease. smoking patients were excluded	Periodontal screening, OHI, non-surgical periodontal treatment	15 months	After IHO at the beginning of non-surgical periodontal treatment, hygiene was not reinforced again, even during orthodontic treatment, with the intention of evaluating changes in periodontal parameters with free gingival grafts. Increasing the thickness of the keratinized gum, as the only treatment, favors the improvement of GI and PI during orthodontic treatment, justifying its use in patients with little or no keratinized gum, poor plaque control, and/or in progressive gingival recessions, although considering the limitations of the study	NA	Free gingival grafts to enhance the band of keratinized tissue during orthodontic treatment
Capelli Júnior et al (2016)[21]	Case report	50y (1) All female	Only test group	Chronic periodontitis	Periodontal screening, OHI, non-surgical periodontal treatment	30 months	Orthodontic treatment of an adult periodontal patient can be an important component of interdisciplinary care. This case report demonstrates that appropriate biomechanical systems and ancillary units are critical to the success of such orthodontic treatment and should be planned from the beginning.	NA	NA
Jang et al (2019)[24]	Case report	55y (1) All female	Only test group	Sequelae of periodontal disease, angle class II malocclusion with anterior spacing, and pathological migration of incisors without systemic diseases	Only periodontal screening	1y after orthodontic treatment	Bone defects and periodontal parameters improved considerably after the application of EMD and synthetic bone together with orthodontic treatment. The orthodontic treatment produced a synergistic effect, improving periodontal parameters. After 1 year the orthodontic and periodontal results were successfully maintained.	Control with periapical radiographs every 3 months.	Mixture of Emdogain (EMD) and Synthetic bone for vertical bone defects before orthodontic treatment

Continued on next page ➡

Supplementary Table 2. *Overview of RCTs, NRS, Cross-Sectional study, case-control study, and case reports.*

Study	Design	age range {mean age ± DS} (size group) [M/F]	Control group /test group	Health status and inclusion criteria	Oral hygiene regimes and periodontal screening	Duration of study	Response to orthodontic treatment	Complementary exams	Adjuvant treatments
Tsai et al (2017)[28]	Case report	55y (1) All Female	Only test group	Angle type 2 malocclusion with multiple missing teeth. Systematically healthy	Periodontal screening, OHI.	1.5y after orthodontic treatment	New bone formation was evidenced at 8 months in the regenerated area. 1.5 years after the end of the orthodontic treatment, it was observed that the regenerated bone was maintained. This result supports the opportune moment to move the teeth after regenerative surgery if the periodontal condition is controlled.	CBCT	Small-granule bone graft material was added in edentulous areas and areas with thin bony cortices. Regional acceleratory phenomenon (RAP) is performed to decrease OTM times.
Watahiki et al (2020)[29]	Case report	35y – 47y (2) [1/1]	NA	Healthy patients	Periodontal screening	7 years	The O-PRO approach was developed to regenerate periodontal tissues with poor bone quality in an optimized way for orthodontic movements by restarting orthodontic movement 2 weeks after the O-PRO procedure. The conditions of the malocclusion and recessions improved, remaining stable throughout the follow-up	NA	O-PRO with demineralized bovine bone matrix and demineralized lyophilized bone graft, covered with a collagen matrix
González et al (2019)[2]	Case report	41y (1) All female	NA	Healthy patient, except for periodontal disease	Periodontal screening, OHI, non-surgical periodontal treatment	30 months after orthodontic treatment	It is possible to perform periodontal treatment in adult patients but maintaining adequate control of periodontal disease and considering age, which, without being a contraindication, must be considered that the response of the tissues is slower than in adolescents.	NA	NA
Smuthkochorn et al (2017)[7]	Case-control study	23y – 80y (28) All women	16/12/2021 (control group were premenopausal women/test group postmenopausal women. Both groups had a similar malocclusion discrepancy rate)	Healthy patients without consumption of NSAIDs, corticosteroids or other anti-inflammatory, without hormone replacement therapy or bone fixation, without periodontal disease and with a plaque index less than 30%	NA	24 hours	A difference is observed between the baseline GCF biomarkers between both groups, evidencing the differences in the bone turnover profile in postmenopausal women, but, in the absence of periodontal disease, 24 hours after orthodontic activation, the response was similar in both groups, delivering a level of safety in treatment in postmenopausal women. It is not known whether this result is similar in longer terms, but it has been observed that biomarker changes occur 24 hours after orthodontic activation and not at any other time.	GCF collection	NA

RCTs = Randomized Controlled Trials, NRS = Non-Randomized controlled Study, NA = Not Applicable, y = year, OHI = Oral Hygiene Instruction, CBCT = Cone Beam Computed Tomography, OTM = Orthodontic Tooth Movement, CAL = Clinical Attachment Level, PD = Pocket Depth, REC = Gingival Recession, CRE = Cast-Radiograph Evaluation, PBF = Pulpal Blood Flow, PI = Plaque Index; BI = Bleeding Index, PDLC = Periodontal Ligament Cells, O-PRO = Optimized Periodontal Regeneration for Orthodontics, EARR = External Apical Root Resorption ABL= Alveolar Bone Level

Supplementary Table 3. *Summary of the risk of bias assessment for systematic reviews, cross-sectional studies, case-control studies, case series studies, and before-after studies.*

Assessment of risk of bias of systematic reviews with the AMSTAR-2 tool.																	
	Domains/Item																Confidence
Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Schubert et al (2020)[13]	Yes	Yes	No	Partial yes	Yes	Yes	Yes	Yes	Partial Yes	No	NA	NA	Yes	Yes	NA	Yes	Moderate

Assessment of risk of bias of cross-sectional studies with the NIH tool.																
	Major Components														Quality Rating	Reasons
Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Sim et al (2017)[27]	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	NA	Yes	No	No	Yes	Fair	Mainly due to the absence of blind and follow-up.

Assessment of risk of bias of case – control studies with the NIH tool.														
	Major Components												Quality Rating	Reasons
Study	1	2	3	4	5	6	7	8	9	10	11	12		
Smuthkochorn et al (2017)[7]	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	No	Poor	Mainly due to the absence of a blind and randomization, a follow-up was not performed longer than 24 hours.
Han et al (2019)[33]	Yes	No	No	No	NA	Yes	Yes	No	Yes	No	No	Yes	Poor	Mainly due to the absence of a blind, the study population was not clearly defined, the sample size was not justified, the exposure was applied in different periods in the different groups.

Assessment of risk of bias of case series studies with the NIH tool.										
	Major Components									Quality Rating
Study	1	2	3	4	5	6	7	8	9	
Orsini et al (2020)[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Assessment of risk of bias of Before-After (Pre-Post) Studies with No Control Group with the NIH tool.														
	Major Components												Quality Rating	Reasons
Study	1	2	3	4	5	6	7	8	9	10	11	12		
González et al (2019)[2]	Yes	No	No	Yes	No	Yes	No	Yes	Yes	No	No	No	Poor	Non-representative sample of the population, absence of blind, without good analysis of results, absence of statistical analysis.
Capelli Júnior et al (2016)[21]	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Poor	Non-representative sample of the population, absence of blind, without statistical analysis
Jang et al (2019)[24]	No	No	No	Yes	No	Yes	Yes	No	Yes	No	No	No	Poor	Absence of blind, no statistical analysis, non-representative sample of the population, and the absence of a clear definition of the objective of the study.
Tsai et al (2017)[28]	No	No	No	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Poor	The study objective was not clearly defined, the sample is not representative of the population, absence of a blind.
Watahiki et al (2020)[29]	No	No	No	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Poor	Absence of clear study objective, non-representative sample of the population, absence of blind, absence of statistical analysis.

NA = Not Applicable

REFERENCES

1. De Couto Nascimento V, de Castro Ferreira Conti AC, de Almeida Cardoso M, Valarelli DP, de Almeida-Pedrin RR. Impact of orthodontic treatment on self-esteem and quality of life of adult patients requiring oral rehabilitation. Angle Orthod. 2016; 86: 839–45.
2. González R, Llanes R, Fernández P. Tratamiento ortodóncico en paciente adulta con Periodontitis crónica controlada. Rev habanera cienc médi. 2019; 18: 741–51.
3. Gorbunkova A, Pagni G, Brizhak A, Farronato G, Rasperini G. Impact of Orthodontic Treatment on Periodontal Tissues: A Narrative Review of Multidisciplinary Literature. Int J Dent. 2016; 2016: 1–9.
4. Gracco A, Siviero L, de Stefani A, Bruno G, Stellini E. Anterior open-bite orthodontic treatment in an adult patient: A clinical case report. Int Orthod. 2016; 14: 171–83.
5. Hirschfeld J, Reichardt E, Sharma P, Hilber A, Meyer-Marcotty P, Stellzig-Eisenhauer A, et al. Interest in orthodontic tooth alignment in adult patients affected by periodontitis: A questionnaire-based cross-sectional pilot study. J Periodontol. 2019; 90: 957–65.
6. Lee R, Hwang S, Lim H, Cha JY, Kim KH, Chung CJ. Treatment satisfaction and its influencing factors among adult orthodontic patients. Am J Orthod Dentofacial Orthop. 2018; 153: 808–17.
7. Smuthkochorn S, Palomo JM, Hans MG, Jones CS, Palomo L. Gingival crevicular fluid bone turnover biomarkers: How postmenopausal women respond to orthodontic activation. Am J Orthod Dentofacial Orthop. 2017; 152: 33–7.
8. Subhiksha K, Saravanan, Sabapthy K. Limitations of adult orthodontics - a review. Eur j mol. 2020; 7: 1737–41.
9. Yuvaraj S, Kumar N. Adult Orthodontics - A literature review. Int j multidiscip res. 2020; 7: 5607–10.
10. Salehi P, Azadeh N, Beige N, Farzin M. Influence of Age on Perception of Best Esthetical Profile. J Dent (Shiraz). 2019; 20: 16–23.
11. Antoun JS, Mei L, Gibbs K, Farella M. Effect of orthodontic treatment on the periodontal tissues. Periodontol 2000. 2017; 74: 140–57.
12. Brämswig L, Pollak T, Richter MT, Knaup I, Wolf M. Orthodontics for adults-current innovations and interdisciplinary possibilities. Dtsch zahnärztl Z. 2020; 2: 174–80.
13. Schubert A, Jäger F, Maltha JC, Bartzela TN. Age effect on orthodontic tooth movement rate and the composition of gingival crevicular fluid. J Orofac Orthop. 2020; 81: 113–25.
14. Wong L, Ryan FS, Christensen LR, Cunningham SJ. Factors influencing satisfaction with the process of orthodontic treatment in adult patients. Am J Orthod Dentofacial Orthop. 2018; 153: 362–70.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med. 2009; 6: e1000100.
16. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017; 358: j4008.
17. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016; 355: i4919.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366: l4898.
19. The National Institute of Health. Study Quality Assessment Tools [Internet]. Health Topics [updated n.d.; cited 2021 March 17]. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
20. McHugh M. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012; 22: 276–82.
21. Capelli Junior J, Cosendey V, Frossard W, Feu D. Treatment of Chronic Adult Periodontitis in a Patient with Negative Overjet and Multiple Tooth Loss. J Clin Orthod. 2016; 50: 239–49.
22. Ersahan S, Sabuncuoglu FA. Effect of age on pulpal blood flow in human teeth during orthodontic movement. J Oral Sci. 2018; 60: 446–52.
23. George P, George JK, Krishnan V, Vijayaraghavan N, Rajendran SR, Chandran BM, et al. Periodontal ligament cells in adolescents and adults: Genetic level responses to orthodontic forces. Am J Orthod Dentofacial Orthop. 2020; 158: 816–23.
24. Jang I, Lee JK, Song GS, Choi DS, Yozgatian J, Cha BK. Application of Enamel Matrix Derivative and Intrusive Orthodontic Movement in the Treatment of Vertical Bony Defects: A Case Report. Int J Periodontics Restorative Dent. 2019; 39: 73–81.
25. Lemos M, Cattaneo P, Melsen B, Faveri M, Feres M, Figueiredo L. Impact of Treatment with Full-fixed Orthodontic Appliances on the Periodontium and the Composition of the Subgingival Microbiota. J Int Acad Periodontol. 2020; 22: 174–81.
26. Maeda S, Nakaya M. A Case History Report on Use of Orthodontic Intrusion in a Partially Edentulous Patient. Int J Prosthodont. 2018 ; 31: 540–2.
27. Sim HY, Kim HS, Jung DU, Lee H, Lee JW, Han K, et al. Association between orthodontic treatment and periodontal diseases: Results from a national survey. Angle Orthod. 2017; 87: 651–7.
28. Tsai HC, Yao CC, Wong MY. Early Orthodontic Tooth Movement into Regenerative Bony Defects: A Case Report. Int J Periodontics Restorative Dent. 2017; 37: 581–9.
29. Watahiki J, Ono R, Maeda M, Hiranuma T, Naito S. Optimized Periodontal Regeneration for Orthodontics (O-PRO): A Case Series. Int J Periodontics Restorative Dent. 2020; 40: 835–42.
30. Zasčiurinskienė E, Lund H, Lindsten R, Jansson H, Bjerklin K. Outcome of periodontal–orthodontic treatment in subjects with periodontal disease. Part II: a CBCT study of alveolar bone level changes. Eur J Orthod. 2019; 41: 565–74.
31. Zasčiurinskienė E, Lund H, Lindsten R, Jansson H, Bjerklin K. Outcome of orthodontic treatment in subjects with periodontal disease. Part III: a CBCT study of external apical root resorption. Eur J Orthod. 2019; 41: 575–82.
32. Zhang J, Zhang AM, Zhang ZM, Jia JL, Sui XX, Yu LR, et al. Efficacy of combined orthodontic-periodontic treatment for patients with periodontitis and its effect on inflammatory cytokines: A comparative study. Am J Orthod Dentofacial Orthop. 2017; 152: 494–500.
33. Han J, Hwang S, Nguyen T, Proffit WR, Soma K, Choi YJ, et al. Periodontal and root changes after orthodontic treatment in middle-aged adults are similar to those in young adults. Am J Orthod Dentofacial Orthop. 2019; 155: 650-655.e2.
34. Orsini M, Benlloch D, Aranda Macera JJ, Flores K, Ríos-Santos JV, Pedruelo FJ, et al. Improvement of Periodontal Parameters with the Sole Use of Free Gingival Grafts in Orthodontic Patients: Correlation with Periodontal Indices. A 15-Month Clinical Study. Int J Environ Res Public Health. 2020; 17: 6578.
35. Yu L, Zhou C, Wei Z, Shi Z. Effect of combined periodontal-orthodontic treatment on NOD-like receptor protein 3 and high mobility group box-1 expressions in patients with periodontitis and its clinical significance. Medicine. 2019; 98: e17724.
36. Zasčiurinskienė E, Basevičienė N, Lindsten R, Slotte C, Jansson H, Bjerklin K. Orthodontic treatment simultaneous to or after periodontal cause-related treatment in periodontitis susceptible patients. Part I: Clinical outcome. A randomized clinical trial. J Clin Periodontol. 2018; 45: 213–24.
37. Barbosa IV, Ladewig VM, Almeida-Pedrin RR, Cardoso MA, Santiago Junior JF, Conti AC. The association between patient's compliance and age with the bonding failure of orthodontic brackets: a cross-sectional study. Prog Orthod. 2018; 19: 11.
38. Hwang H, Jeon H, Lee K, Boyd RL. Use of a Minitube Appliance in Periodontally Compromised Adult Patients with Severely Displaced Incisors. J Clin Orthod. 2016; 50: 533–42.
39. Burns PB, Rohrich RJ, Chung KC. The Levels of Evidence and Their Role in Evidence-Based Medicine. Plast Reconstr Surg. 2011; 128: 305–10.
40. Rody WJ, Elmaraghy S, McNeight AM, Chamberlain CA, Antal D, Dolce C, et al. Effects of different orthodontic retention protocols on the periodontal health of mandibular incisors. Orthod Craniofac Res. 2016; 19: 198–208.
41. Arn ML, Dritsas K, Pandis N, Kloukos D. The effects of fixed orthodontic retainers on periodontal health: A systematic review. Am J Orthod Dentofacial Orthop. 2020; 157: 156-164.e17.
42. Knaup I, Wagner Y, Wego J, Fritz U, Jäger A, Wolf M. Potential impact of lingual retainers on oral health: comparison between conventional twistflex retainers and CAD/CAM fabricated nitinol retainers. J Orofac Orthop. 2019; 80: 88–96.
43. Elkordy SA, Palomo L, Palomo JM, Mostafa YA. Do fixed orthodontic appliances adversely affect the periodontium? A systematic review of systematic reviews. Semin Orthod. 2019; 25: 130–57.
44. Wu Y, Cao L, Cong J. The periodontal status of removable appliances vs fixed appliances. Medicine. 2020; 99: e23165.
45. Morita H, Imai Y, Yoneda M, Hirofuji T. Applying orthodontic tooth extrusion in a patient treated with bisphosphonate and irradiation: a case report. Spec Care Dentist. 2017; 37: 43–6.
46. Jiang F, Chen J, Kula K, Gu H, Du Y, Eckert G. Root resorptions associated with canine retraction treatment. Am J Orthod Dentofacial Orthop. 2017; 152: 348–54.
47. Puttaravuttiporn P, Wongsuwanlert M, Charoemratrote C, Leethanakul C. Volumetric evaluation of root resorption on the upper incisors using cone beam computed tomography after 1 year of orthodontic treatment in adult patients with marginal bone loss. Angle Orthod. 2018; 88: 710–8.
48. Norris SL, Holmer HK, Ogden LA, Burda BU. Conflict of Interest in Clinical Practice Guideline Development: A Systematic Review. PLoS One. 2011; 6: e25153.
49. Lewkowicz B. Link Between Oral Health and Healthy Aging. Contribution of orthodontics-orthopedics to the oral health of older adults part 2. RAOO. 2019;61:41–50.
50. Luchian I, Martu I, Ioanid N, Goriuc A, Vata I, Hurjui L, et al. Salivary IL-1 β: A Biochemical Marker that Predicts Periodontal Disease in Orthodontic Treatment. Rev de Chim. 2016;67: 2479–83.
51. Palomo L. Orthodontic treatment in the age of periodontal risk management. Semin Orthod. 2019;25: 09.