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*Review*

# Evaluation of the effect of mouthwashes on titanium alloy miniscrews: a systematic review

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**Abstract:** Orthodontic miniscrews (MSs) are increasingly used in orthodontics, providing good treatment results, particularly Ti-6Al-4V MSs. Sometimes, after placing the MSs, orthodontists prescribe mouthwashes to avoid risk of infection, thus ensuring good stability and optimizing the final treatment result. The aim of this review is to analyze the effects of chlorhexidine (CHX) and sodium fluoride (NaF) mouthwashes on the surface of titanium alloy MSs and to analyze the cytotoxicity, corrosion and ion release caused. The search was carried out in the PubMed, ScienceDirect and Google Scholar databases for articles published between January 2011 and December 2023. For the study, ten articles were selected, based on exclusion and inclusion criteria. Numerous studies show that NaF seems to have more negative effects than CHX, in terms of the quantity of ions released and in terms of alteration of the surface layer, with greater corrosion and destruction of the surface microstructure. In conclusion, mouthwash with NaF alters the surface layer, causing corrosion and release of ions. Mouthwash with CHX gives good results because it causes minimal alteration of the surface layer of the MSs and minimal release of contained ions.

**Keywords:** dental implants; Orthodontic Anchorage Procedures; chlorhexidine; sodium fluoride; corrosion; ions

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## Introduction

Orthodontics is a specialized field of dentistry that deals with the diagnosis, prevention, and correction of dental and facial irregularities. Its main aim is to improve the aesthetics as well as the dental function of the patient [1]. Orthodontics is a broad field that includes different types of treatment and understanding the needs of each patient is extremely important [2].

In more complex cases, simple orthodontic treatment is not enough because the teeth need more complex forces to achieve the desired result [3,4]. This is where, in recent years, the introduction of skeletal anchorage with miniscrews (MSs) has come into play to provide additional anchorage [4].

In dentistry, anchorage refers to the resistance that teeth or appliances offer to support and control tooth movement during orthodontic treatment [5,6]. According to Newton's third law, "for every action there is a corresponding reaction of equal intensity and opposite direction". Anchorage therefore obeys this law. Among anchorage devices, there are non-skeletal and skeletal anchorage devices [7].

For more complex treatments, the use of skeletal anchorage systems will be more appropriate with MSs, which are increasingly used in orthodontics due to their many advantages, including low cost and ease of insertion and surgical removal [4]. These devices allow teeth to be moved more precisely and efficiently and are able to provide absolute anchorage [8,9].

Titanium (Ti) alloys with aluminum (Al) and vanadium (V) are widely used, have a low modulus of elasticity and a high level of corrosion resistance thanks to their protective Ti oxide layer, which forms in contact with oxygen [9-13]. The Al and V incorporated into Ti will produce a stronger alloy and increase MSs resistance to fracture [2].

For good efficacy, MSs must have good biocompatibility [8]. However, complications can occur after MSs placement, related to peri-implant inflammation and infection due to poor oral hygiene at the MSs, for example [10,12]. These complications can contribute to the loss of stability of orthodontic MSs [3]. It is therefore recommended to use chlorhexidine (CHX), which has fungicidal and bactericidal properties, as a mouthwash after placing MSs, to avoid or reduce these complications [3,9,11,14,15]. In addition to CHX, sodium fluoride (NaF) mouthwashes are also used, which are important for preventing caries in patients undergoing orthodontic treatment [16]. Despite their widespread use and effectiveness as antimicrobial agents in dentistry, CHX and NaF are likely to cause changes to the surface of MSs and the release of ions that can be toxic at a certain threshold [11]: an oral exposure to less than 0.01 mg V/kg/day (minimal risk level) would have health effects [5], and Al has a tolerable daily intake of 1 mg/kg body weight/day [9]. After high-dose Ti oral administration (5 mg/kg body weight), liver and kidney lesions have been observed in some studies [17]. Al and V ions can be released into the tissues and cause health effects [2]. For example, V can cause stomach cramps with diarrhea [18]. As for Al, it is recognized as a neurotoxin, notably through its association with Alzheimer's disease as an environmental factor: an increase in the aggregation and amyloid deposition, characteristic of the disease, would be observed at high concentrations of Al. Al is also associated with Parkinson's disease: it is thought to be at the root of altered iron metabolism, leading to the accumulation of high levels of iron in neurons [19]. It is also likely that the NaF contained in mouthwash attacks the protective layer of Ti alloy MSs [16]. These changes can be very problematic because they can increase the roughness of the MSs surfaces and biofilm formation within the porosities [10]. It is therefore important to analyze the effect of these mouthwashes on the properties of orthodontic MSs to identify the one that provides an antimicrobial function without greatly altering the characteristics of the dental implant surface [15].

The aim of this systematic review is to evaluate the changes on the surface of the Ti MSs and to analyze cytotoxicity, corrosion and the release of ions caused by the two mouthwashes (CHX and NaF), since orthodontists are sometimes unaware of this influence.

## Materials and Methods

### Review guidelines

This systematic review was conducted from September 2023 to December 2023, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A search was carried out in the PubMed, ScienceDirect and Google Scholar databases for articles published between January 2011 and December 2023, using the following keywords: "dental implants", "Orthodontic Anchorage Procedures", "chlorhexidine", "sodium fluoride", "corrosion" and "ions". This systematic review was registered in PROSPERO (CRD42024521845).

### Eligibility criteria

The guide question was defined according to the PICO strategy: Population characteristics, Intervention type, Comparison parameters and Outcomes, as presented in Table 1. The search question defined by the PICO strategy is also represented in Table 1.

**Table 1.** PICO strategy.

| **Patient** | Ti alloy MSs or disks |
|---|---|
| **Intervention** | Immersion of the MSs or disks in different mouthwashes |
| **Comparison** | Compare the different surface changes according to the mouthwash used |
| **Outcome** | Analyze cytotoxicity, ion release and corrosion |
| | What is the effect of mouthwashes on the surface of Ti MSs? |

The inclusion criteria corresponding to the PICO's questions were: complete and accessible articles, articles related to the topic and whose abstract is relevant, articles published between January 2011 and December 2023, *in vitro* studies, studies using MSs or Ti alloy disks and articles in Portuguese or English.

The exclusion criteria were: articles not related to the topic, articles published before January 2011, articles in languages other than English or Portuguese, studies excluding Ti MSs and studies that do not specify the percentage of CHX or NaF.

### Search strategy

The literature search was made using the PubMed, ScienceDirect and Google Scholar databases. The MeSH terms used for the search were: "Dental Implants"[Mesh], "Orthodontic Anchorage Procedures"[Mesh], "Chlorhexidine"[Mesh]), "Sodium Fluoride"[Mesh], "Corrosion"[Mesh], "Ions"[Mesh]. The search strategies are detailed in Table 2.

**Table 2.** Search sequence of keywords.

| Sequence of keywords<br>(PubMed, ScienceDirect and Google Scholar) | Articles identified | Reports excluded | Total articles selected |
|---|---|---|---|
| ((dental implants) OR (orthodontic anchorage procedures)) AND ((corrosion) OR (ions)) | 201 | 36 duplicated<br>161 excluded after reading title and abstract | 4 |
| ((dental implants) OR (orthodontic anchorage procedures)) AND ((chlorhexidine) OR (sodium fluoride)) | 87 | 83 excluded after reading title and abstract<br>2 excluded after full reading | 2 |
| (dental implants (OR) orthodontic anchorage procedures) (AND) (sodium fluoride) OR (chlorhexidine)) AND ((corrosion) OR (ions)) | 46 | 12 duplicated<br>17 excluded after reading title and abstract<br>2 excluded after full reading<br>9 excluded for not meeting language criteria<br>2 did not provide relevant information | 4 |

### Selection of articles and data collection

***Preliminary selection.*** Advanced searches were carried out using the keywords in the databases in different combinations. Searches were carried out in PubMed, ScienceDirect and Google Scholar, after applying the inclusion criteria and removing duplicate articles using the Zotero tool. The exclusion criteria were applied, and a preliminary analysis of the titles and abstracts was carried out to determine whether the articles met the aim of the study. ***In-depth selection.*** Potentially eligible studies were fully read and assessed. ***Final selection.*** A full evaluation of the articles was completed. The data was extracted and organized. Finally, ten *in vitro* studies were included in this systematic review, the characteristics of which are presented in Table 3.

### Quality assessment of data

The ROBINS-I tool was used to assess the methodological quality of the studies, as all the studies approved in this analysis were non-randomized. Three authors (LES, ACO and CS) independently evaluated the quality of the selected articles based on seven bias domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, selection of the reported results and overall bias. Three studies were considered to have low risk of bias. Most of the studies had a moderate risk of bias (Table 4).

## Results

### Selection of articles

In total, three hundred and thirty-four articles were initially identified. After eliminating duplicates, we carried out a full-text analysis: two hundred and eighty-six articles were initially selected, two hundred and seventy were excluded based on exclusion criteria, two did not provide relevant information and four were excluded after full reading. The flow chart is shown in Figure 1.

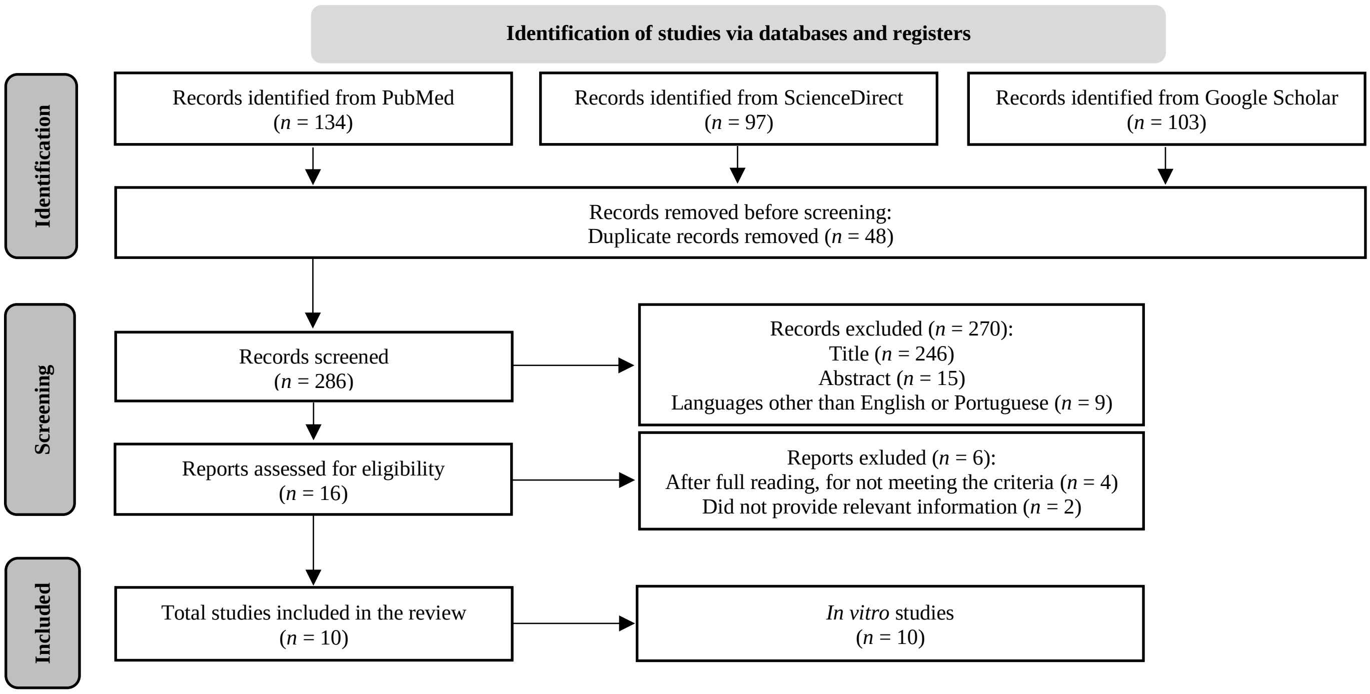


**Figure 1.** PRISMA 2020 flow diagram for new systematic reviews. From [20].

**Table 3.** Data and outcomes from articles.

| Title and Authors | Miniscrews/disks Ti-6Al-4V | Population | Aims | Results | Conclusion |
|---|---|---|---|---|---|
| Cytotoxicity effect of orthodontic miniscrew-implant in different types of mouthwash: an In-vitro study – Utami *et al.* (2022) [8] | 28 samples of Ti-6Al-4V MSs immersed in 4 groups: 7 MSs in each group | Human gingival fibroblasts in cultures in contact with mouthwash for 28 days: comparison of cell viability between the "eluate" group with MSs and the "solution" group of each mouthwash | Evaluate the cytotoxicity of MSs in contact with four different mouthwashes (using human gingival fibroblasts in cultures): 0.2% digluconate mouthwash (MINOSEP®), 0.2% NaF mouthwash (Pepsodent Pro Complete), 1% chitosan with 0.25% acetic acid (KITOBE™), and aquadest (distilled water, Aqua Pro Injection Sterile) | Aquadest and 1.5% chitosan: Minor toxicity: <30% in the "solution" group<br>No statistically significant difference in cell viability between the "eluate" and "solution" groups ($p$>0,05)<br><br>Solution of 0.2% CHX and 1.5% fluoride (NaF 0.2%): High toxicity with cell viability <30% in the "solution" group<br>Statistically significant difference in cell viability between the "eluate" and "solution" groups ($p$<0,05) | The MSs contribute by increasing the cytotoxicity of 0.2% CHX mouthwash and 0.2% NaF, but do not increase the toxicity of aquadest and chitosan mouthwash<br><br>The dissolution of the protective layer of Ti MSs caused by CHX and NaF mouthwashes can decrease cell viability |
| Ions release evaluation and corrosion of titanium mini-implant surface in response to Orthokin®, Oral B® and chlorhexidine mouthwashes – Alavi *et al.* (2021) [9] | 40 Ti-6Al-4V MSs: 10 MSs in each group | MSs immersed in three different mouthwashes and artificial saliva (control group – Kin Hidrat spray, Spain) for 21 days | Evaluate the release of Al, Ti and V ions from MSs in contact with different mouthwashes: Orthokin® (0.06% CHX digluconate, 0.34% zinc acetate, with 500 ppm F⁻), Oral-B® (CC, with 250 ppm F⁻), CHX (with 0 ppm F⁻ in its composition) | Al ions: statistically significant ↑ release with Orthokin® and Oral-B® difference compared with the control group with a peak between 1st-7th day. Slight ↑ with CHX but no statistically significant difference from control group<br><br>Ti ions: ↑ concentration with Oral B®. Peak: 1st-7th day. Statistically significant difference compared with the control group. Slight ↑ with Orthokin® and CHX compared with artificial saliva, but statistically significant<br><br>V ions: Very slight ↑ without statistically significant difference from the control group | The release of Al and Ti ions is dependent on the exposure time and type of mouthwash<br><br>The values do not exceed the toxicity values and do not appear to cause a toxic effect on the health of the patient or the oral cavity |
| Corrosion resistance of titanium alloy orthodontic mini-implants immersed in chlorhexidine, fluoride, and chitosan mouthwashes – Putri *et al.* (2021) [11] | 28 Ti-6Al-4V MSs: 7 MSs in each group | 4 groups immersed for 28 days in four different mouthwashes and distilled water (control group) | Examine the surface of MSs in contact with 0.2% CHX gluconate (MINOSEP®), 0.2% NaF (Pepsodent Expert Protection Pro Complete), 1.5% chitosan (KITOBE™), and distilled water (Aqua Pro Injection Sterile) to assess resistance to corrosion in their presence | Distilled water group: No signs of corrosion<br><br>1.5% Chitosan group: more samples with smooth surfaces but not statistically significant<br><br>0.2% CHX, 0.2% NaF: rougher surfaces. No signs of cracking or corrosion.<br>Significant difference in the percentage of release of Al and Ti ions between the chitosan and NaF groups, with a higher percentage in the chitosan group<br><br>No statistically significant difference in surface topography between groups | Chitosan: ↑ corrosion resistance of MSs by ↑ composition of Ti and Al → protective layer<br><br>Corrosion resistance of MSs in mouthwashes containing CHX, 0,2% NaF and 1.5% chitosan |
| Dynamic action of mouthwashes affects the electrochemical behavior of Ti-6Al-4V alloy – Sousa *et al.* (2021) [12] | 20 Ti-6Al-4V alloy disks: 5 in each group | Soak 3 times a day for 1 minute in each mouthwash, using AS as a control group. The corrosion, roughness and surface of the Ti-6Al-4V disks were tested at baseline and after 7 and 14 days of dynamic action of the mouthwashes | Evaluate the kinetic corrosion of the Ti-6Al-4V alloy under the influence of the dynamic action of 0.12% CHX, 0.053% CC and 3% HP mouthwashes | HP: formation of a less protective oxide layer/deterioration of the oxide layer with a statistically significant difference from the other groups<br><br>CC: stronger, more protective oxide film formed on the metal surface, with a significant difference from the other groups<br><br>CC and CHX: significantly improved corrosion potential of Ti alloy compared with AS<br><br>All groups: No major differences in topography between the groups, except for the HP group, with the presence of pitting corrosion | HP alters the corrosion resistance of the Ti-6Al-4V MSs<br><br>CC offers passive film stability in contact with this solution<br><br>Adsorption of molecules from CC and CHX solutions would be likely to block reactive sites on the surface of MSs and inhibit corrosion by forming a protective layer |
| Corrosion of dental alloys used for mini implants in simulated oral environment – Curkovic *et al.* (2021) [21] | 316 stainless steel and Ti-6Al-4V MSs | MSs in AS (control group, pH = 5.1) and two different solutions: A (0.05% CHX with 0,05% NaF, 500 ppm F⁻ + AS, pH = 6.1) and B (probiotic + AS) | Evaluate the general and pitting corrosion resistance of stainless steel and titanium-based orthodontic MSs in different oral environments | Solution A: ↓ in corrosion resistance, but the difference between the passivation and repassivation potential of the protective layer is not significant compared with artificial saliva alone for both implant materials<br><br>Solution B: For both implant materials, ↓ corrosion and passivation compared with artificial saliva alone | Presence of an antiseptic: corrosion activity of both MSs altered → effects of presence of fluoride ion + pH<br><br>Probiotic: beneficial effect on the barrier properties<br><br>Ti-6Al-4V MSs: more resistant to corrosion than stainless steel implants |

| | | | | | |
|---|---|---|---|---|---|
| Do chlorhexidine and probiotics solutions provoke corrosion of orthodontic mini-implants? An In vitro study – Pavlic *et al.* (2019) [10] | 316 stainless steel and grade 5 and grade 23 Ti-6Al-4V MSs: a size of 5 samples per group was reached | MSs immersed in AS (control group), saliva with probiotics and saliva with CHX for 28 days | Evaluate the roughness and microhardness of MSs immersed in AS, saliva with probiotics and saliva with 0.05% CHX | ↑: Roughness of grade 5 Ti-6Al-4V MSs after immersion in probiotics statistically significant ($p$<0,005) compared with the control; roughness in CHX for stainless steel MSs more significant than in probiotics<br><br>↓: Microhardness of the stainless-steel MSs in contact with CHX. No significant changes for Ti alloys<br><br>Greatest corrosion for the grade 5 Ti-6Al-4V in the group with probiotics. Least significant corrosion for the grade 23 Ti-6Al-4V group in the presence of CHX | <u>Stainless steel MSs</u>: ↑ roughness and ↓ microhardness when in contact with CHX.<br>CHX: no significant effect on Ti alloy MSs<br><br><u>Probiotics</u>: ↑ roughness of Ti alloy MSs, which allows for ↑ partial osseointegration and ↑ plaque accumulation |
| Analysis of two different orthodontic mini-implants immersed in fluoridated mouthwashes using scanning electron microscopy (SEM) – Abboodi *et al.* (2018) [13] | 15 Ti-6Al-4V MSs (3 subgroups with 5 MSs in each subgroup) and 15 stainless steel MSs (3 subgroups with 5 MSs in each subgroup) | MSs immersed in artificial saliva (AS) (control group)<br>and fluoride mouthwash for 28 days | Evaluate the effect of fluoride mouthwash (Lacalut White® mouthwash: sodium fluoride and chlorhexidine digluconate, with 153 ppm $F^-$, pH = 5.5; and Kin B5® mouthwash: cetylpyridinium chloride, with 226 ppm $F^-$, pH = 6) and immersion time on the corrosion behavior and microscopic surface of Ti and stainless steel orthodontic MSs | <u>AS group (pH 6.75)</u>:<br>Less corrosivity and surface roughness than mouthwash<br><br><u>Lacalut-White® group (pH 5.5)</u>:<br>Ti-6Al-4V MSs: less pitting and cracking than Kin-B5®<br><br><u>Kin B5 MW® group (pH 6.5)</u>:<br>MSs Ti-6Al-4V: more roughness and more pitting corrosion than those of artificial saliva or Lacalut-White® | The results of the microscopic examination revealed that signs of corrosion in the form of cracks and pitting were detected in all groups: Kin-B5® > Lacalut-white® > artificial saliva |
| Assessment of metal ions released from orthodontic mini-implants in fluoridated mouthwashes – Abboodi *et al.* (2018) [22] | 15 MSs Ti-6Al-4V: 3 subgroups with 5 MSs in each subgroup | MSs immersed separately in AS (control group) and two different mouthwashes for 28 days | Evaluate the effect of fluoride mouthwashes and immersion time on the amount of metal ions released of Lacalut White® mouthwash (NaF and CHX digluconate, with 153 ppm $F^-$, pH = 5.5) and Kin B5® mouthwash (CC, with 226 ppm $F^-$, pH = 6) | Release: Al > Ti > V<br><br><u>Ti ions</u>: Lacalut White® > Kin-B5® > AS. ↑ release between the 1st and 7th days<br><br><u>Al ions</u>: ↑ release between the 7th and 14th days<br><br><u>V ions</u>: ↑ between the 15th and 28th days in AS, but between the 1st and 7th in mouthwashes | The ↑ amount of release was in Lacalut White (contains more fluoride), followed by Kin-B5® and AS (more acidic pH and the presence of $F^-$).<br>The total amounts of ions released was ↓ than the toxicity limits |
| The effect of fluoride-containing oral rinses on the corrosion resistance of titanium alloy (Ti-6Al-4V) – Huang *et al.* (2017) [23] | 25 Ti-6Al-4V alloy disks: 5 in each group | Immersed in four different mouthwashes containing fluoride. The saline solution was used as a control | Evaluate the effect of fluoride-containing mouthwashes on the corrosion behavior of Ti alloys: solution A, pH 4.46/260 ppm $F^-$; solution B, pH 4.41/178 ppm $F^-$; solution C, pH 6.30/117 ppm $F^-$; and solution D, pH 4.17/3.92 ppm $F^-$) | <u>Solution A group</u>: more defects, statistically significant crevice and pitting corrosion<br><br><u>Solution B group</u>: not as many defects and pitting as the sample in solution A<br><br><u>Solution C, D and saline solution groups</u>: ↓ pitting corrosion than the samples in solutions A and B<br><br><u>Increased fluoride content</u>: ↑ tendency for the corrosion potential to decrease (except for solution D). Statistically significant ↓ in corrosion resistance in the presence of $F^-$ | 2 parameters influence the corrosion resistance of Ti-6Al-4V MSs: pH and fluoride concentration.<br>↑ fluoride concentration and ↓ pH → ↓ corrosion resistance |
| Corrosion kinetics and topography analysis of Ti–6Al–4V alloy subjected to different mouthwash solutions – Faverani *et al.* (2014) [15] | 20 Ti-6Al-4V alloy disks: 5 in each group | Corrosion kinetics and surface topography were analyzed at baseline and after 7 and 14 days of dynamic action of the mouthwash.<br>EIS was used to study the electrochemical formation.<br>The disks were analyzed with a SEM | Evaluate the corrosion kinetics and surface topography of the Ti-6Al-4V alloys exposed to mouthwash solutions (0.12% CHX, 0.053% CC and 3% HP) compared with AS (control group, pH 6.5) | <u>HP group</u>: ↑ in roughness surface. Statistically significant ↑ weight loss of Ti-6Al-4V compared with all other solutions.<br>Statistically significant ↓ metal's ability to resist ion exchange with the electrolytic environment<br><br><u>CHX and CC groups</u>: ↑ roughness values after 14 days compared with the control group with no statistically significant change in the corrosion kinetics | 3% HP reduced the corrosion resistance of the Ti-6Al-4V alloy; to be avoided for post-operative treatment<br><br>0.12% CHX and 0.053% CC: favorable for post-operative treatment; non-significantly alter corrosion kinetics |

Al: aluminum; AS: artificial saliva; CC: cetylpyridinium chloride; CHX: chlorhexidine; EIS: electrochemical impedance; HP: hydrogen peroxide; MSs: miniscrews; NaF: sodium fluoride; SEM: scanning electron microscope; Ti: titanium; V: vanadium; ↑: increase(d); ↓: decrease(d)

**Quality assessment of data**

**Table 4.** Assessment according to the ROBINS-I tool [24].

| Reference | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall bias |
|---|---|---|---|---|---|---|---|---|
| Utami *et al.* (2022) [8] | L | L | M | M | L | L | N | L |
| Alavi *et al.* (2021) [9] | L | M | M | M | L | M | N | M |
| Putri *et al.* (2021) [11] | L | L | L | N | L | M | N | L |
| Sousa *et al.* (2021) [12] | L | M | M | L | L | S | N | M |
| Curkovic *et al.* (2021) [21] | M | M | L | M | L | M | N | M |
| Pavlic *et al.* (2019) [10] | L | S | M | L | L | M | N | M |
| Abboodi *et al.* (2018) [13] | L | M | M | N | L | M | N | M |
| Abboodi *et al.* (2018) [22] | L | M | M | N | L | M | N | M |
| Huang *et al.* (2017) [23] | L | L | M | L | L | L | N | L |
| Faverani *et al.* (2014) [15] | M | M | M | L | L | M | N | M |

L: low risk of bias; M: moderate risk of bias; S: serious risk of bias; N: no information.

## Discussion

This systematic review assessed the effects of two mouthwashes on the surface of Ti alloy MSs and analyzed the cytotoxicity, corrosion and release of ions caused. For orthodontic treatments, there are two types of Ti alloys: grade 5 Ti (Ti-6Al-4V) and grade 23 Ti [Ti-6Al-4V ELI (which stands for Extra Low Interstitial)], both of which have the advantage of greater mechanical and fatigue resistance than pure Ti alloys [10]. For this systematic review, the focus is grade 5 Ti, which is the most widely used [25,26].

One of the main characteristics of Ti is the spontaneous formation of a passive layer on its surface when it meets water, air or biofluids [12]. The oxide layer that forms makes it biocompatible [26]. This biocompatibility can be compromised by the release of toxic Al and V ions from the Ti alloy of the MSs [27]. However, when this protective layer breaks down or disappears, Ti-6Al-4V is more susceptible to corrosion.

Corrosion can be defined as the loss of metal ions directly into solution or the progressive dissolution of a surface film, usually an oxide or sulphate. Corrosion will lead to the degradation of orthodontic MSs, which can be detrimental to them, as they will lose their structural integrity, increasing the roughness of the head and thus facilitating the formation of biofilm and its accumulation in the recesses. All this can contribute to inflammation around the MSs and to their loss [10].

In orthodontics, most patients do not always have adequate oral hygiene, due to the difficulty of properly cleaning their teeth because of the orthodontic brackets or attachments. For this reason, it is recommended to use NaF mouthwash, which is also effective in reducing dental caries and white spot lesions [22]. NaF mouthwashes are also important in cases of enamel demineralization, which is a problem that can occur after the installation of fixed orthodontic appliances [16].

However, according to several previous studies that evaluated the effects of different mouthwashes on Ti alloy MSs, it was demonstrated that fluoride-containing mouthwashes have a detrimental effect on their surface, as fluoride affected the integrity of the passive protective layer. This is because of fluoride ($F^-$) ions in fluorinated acid solutions, which combine with $H^+$ to form hydrofluoric acid (HF) and can destroy the oxide layer of Ti and its alloys [28].

These results are in line with the study by Alavi *et al.* (2021), in which it was reported that fluoride ions increase the release of ions from Ti-6Al-4V MSs, causing corrosion and discoloration. The authors found that the mouthwashes with higher fluoride concentrations proved to be more corrosive, confirming the effects of the combination of $F^-$ and $H^+$ found in other studies [9]. This suggests that the effect of NaF-containing mouthwashes is linked to the amount of fluoride present. According to Putri *et al.* (2021), this corrosion phenomenon is explained by the formation of an ionic Ti-fluoride complex, leading to a reduction in the strength of the protective Ti oxide, and modifying the surface topography of Ti-6Al-4V MSs by increasing their surface roughness [11].

This change of surface topography caused by the presence and quantity of fluoride encountered in mouthwashes is also described by different types of surface corrosion, which can be observed with scanning electron microscopy (SEM), as in a study from Abboodi *et al.* (2018), who found pitting and crevice corrosion on the surfaces of MSs after immersion in two mouthwashes containing NaF [13]. This surface corrosion was also observed in another study, that of Huang *et al.* (2017), who also observed pitting or crevice corrosion defects, which were more significant in mouthwashes containing higher concentrations and with more acidic pH values [23]. From these studies, we can therefore see that it is important to observe the surface topography of MSs, which can give us a clue to the effect of mouthwashes on MSs and is a sign of corrosion of these MSs.

This corrosion is related to the quantity of fluoride ions present in the mouthwash, but also to the pH [23]. It is therefore essential to take these two important parameters into account when choosing which mouthwash to prescribe. Curkovic *et al.* (2021) have identified these two important parameters as increasing the porosity of the protective layer and therefore increasing the risk of corrosion. A lower pH and a higher percentage of fluoride lead to more corrosion, which is undesirable. The ideal would be therefore to use a mouthwash with adequate fluoride concentrations and a pH above 3.5 [21]. This is supported by the Alavi *et al.* (2021) study, which showed that a higher fluoride concentration (500 ppm $F^-$) was responsible for a higher concentration of ions contained in the surface of MSs compared with a lower concentration (250 ppm $F^-$) or no concentration (0 ppm $F^-$) [9].

These two parameters are also highlighted in the study by Abboodi *et al.* (2018), in which the concentration of fluoride ions, as well as the decrease in pH, influenced the release of Ti, Al and V ions, resulting in an increase compared with artificial saliva [22]: the increase in corrosion at low pH is due to the presence of a greater quantity of halogens (anions) that will be incorporated into the passive film formed in the biological solution [27].

Most recently, Utami *et al.* (2022) performed a study to analyze the cytotoxicity of 0.2% NaF in contact with MSs on gingival fibroblasts, with a cell viability of less than 30% after immersion. The results of this study showed that there is a statistically significant difference ($p<0.05$) in cell viability between the fluoride eluate (without MSs) and the fluoride solution containing MSs [8]. Indeed, the viability of L929 and MC3T3-E1 cells could be reduced at certain concentrations of Al ions ranging from 0.2 to 0.5 ppm and V ions ranging from 0.002 to 0.2 ppm. The lower toxicity threshold of V ions means that V ions are more toxic at low doses than Al ions. As for Ti ions, a higher toxicity threshold of 11 ppm was observed [8].

Understanding and studying the effect of NaF mouthwashes is therefore essential, but it is not the only mouthwash we need to consider in this study. CHX is a commonly used mouthwash [29], being an antibacterial agent, effective against bacteria (Gram-positive and Gram-negative bacteria), yeasts and fungi [3,29]. CHX has a broad bactericidal and bacteriostatic spectrum due to its binding properties and demonstrates its antiseptic activity by precipitating phosphate-containing molecules from the bacterial cell membrane [14,29].

The systemic toxicity of CHX is considered low because it is poorly absorbed from the gastrointestinal tract. The use of 0.2% CHX mouthwash, rinsed twice a day, has proven to be effective in preventing the accumulation of plaque and the development of gingivitis, and consequently allows for a reduction in infectious complications around the MSs [3,9,14]. In current practice, CHX is considered the benchmark of oral antiseptics and in the chemical control of biofilms [9,10].

However, despite these remarkable qualities, CHX can increase the corrosiveness of the Ti material by increasing the dissolution of the protective Ti oxide layer, which will cause the release of the ions that make up the oxide layer of MSs [8]. In contrast to NaF mouthwashes, the effects of CHX on surface topography, corrosion and ion release are less significant than those of NaF. In fact, Alavi *et al.* (2022) found that the release of Ti ions and Al ions increased for MSs in contact with CHX (without fluor) with a non-statistically significant difference, while the concentration of these two ions increases with statistically significant difference for NaF mouthwashes (Orthokin® – 500 ppm; and OralB® – 250 ppm), compared with artificial saliva (control group) [9]. The authors state that these results can be explained by the fact that CHX mouthwash does not contain fluoride, which once again highlights the effect on the protective layer of Ti-6Al-4V MSs.

Alavi *et al.* (2022) therefore reported in their study that CHX caused minimal corrosion [9]. This is in line with the study by Faverani *et al.* (2014), who found, in comparison with artificial saliva, that there was no statically significant difference in the change in corrosion kinetics of Ti alloy MSs immersed in CHX [15]. These studies thus give a favorable opinion on the post-operative use of CHX mouthwash treatments [9,15].

Other studies have also observed the surface roughness of MSs in contact with mouthwashes. Putri *et al.* (2021) observed that MSs became rougher after immersion in CHX but showed no signs of corrosion. The authors suggest that this roughness is due to the presence of chloride ions, which can destabilize the Ti oxide protective layer of the Ti-6Al-4V MSs, thus modifying the layer's repassivation capacity and making it rougher [11]. Pavlic *et al.* (2019), by having also studied this change in surface roughness, reported that CHX at 0.05% did not cause a significant increase in roughness on the surface of Ti-6Al-4V MSs when compared with the probiotic, which showed a significant increase in roughness. The Ti-6Al-4V MSs also showed no change in microhardness [10]. In comparison with the effects of NaF mouthwashes found in the above studies, the majority of studies show that CHX mouthwashes do not appear to cause significant corrosion on Ti alloy MSs, which Sousa *et al.* (2021) explained by the fact that CHX solutions likely block reactive sites on the surface of MSs and inhibit corrosion by forming a protective layer [12]. The Sousa *et al.* (2021) study is one of the few available that moves the samples 3 times a day for 1 minute in order to reproduce the reliability of the results as closely as possible, making this study more representative. The authors even demonstrated that CHX was responsible for a significant improvement in the corrosion potential of Ti alloy MSs compared with artificial saliva [12]. Comparing NaF mouthwashes with those containing CHX and those containing chitosan, Putri *et al.* (2021) found a statistically significant difference ($p<0.05$) between the fluoride and chitosan groups, which was not found comparing CHX with chitosan groups. This suggests a more damaging effect of fluoride mouthwash than the one with CHX on Ti-6Al-4V MSs [11].

Although CHX mouthwashes have less significant effects than NaF mouthwashes, it is important to consider the release of Ti, Al and V ions that both mouthwashes can cause, to study the effects these ions can have on the patient's health. Ananthanarayanan *et al.* (2016) observed that Al and V ions have toxic effects [5]. Al and V ions are also associated with local inflammation, allergic reactions, carcinogenic effects, and neurological disorders [18,19,22]. In fact, Al ions have dose-dependent cytotoxicity in human bronchoalveolar cancer cells at doses of 5 to 25 mg/L, increased association with the development of Alzheimer's disease, detection at the osteoid-calcified matrix interface in the bone of patients with chronic renal failure, which interferes with mineralization leading to osteomalacia [5]. All the data presented in these various studies are therefore very important to consider, to enable the orthodontist to avoid adversely affecting the patient's health. The toxic effect of Al cytotoxicity was also highlighted in the study by Utami *et al.* (2022), in which the authors observed that the Al ion affected the metabolic activity of osteoblasts, preventing their proliferation and differentiation [8]. Metal ions can affect various types of cells in the human body, in particular osteoclasts [30]. This is because the MSs, when placed in bone, cause the osteoclasts and osteoclast precursors to be exposed to metal ions contained in Ti-6Al-4V MSs [30]. The role of osteoclasts is very important during MSs implantation because, as they are bone resorption cells, they will consequently be involved in implant stability. Therefore, any disturbance in osteoclast activity may be associated with a failure in MSs stability [30].

The World Health Organization (WHO) has recommended that the tolerable daily dose of Al should be 1 mg/kg body weight/day [9]. The V ion is considered more toxic than Al, due to its ability to bind transport proteins ferritin and transferrin, and therefore to be distributed throughout the body [5]. In addition to its high toxic effect, V has also been reported to inhibit the mitotic index, which subsequently causes chromosomal aberrations. Oral exposure of less than 0.01 mg/kg/day (minimum risk level) has been shown to have effects on human health [5]. However, V is the least released ion: as V is not present in the oxide layer of the Ti-6Al-4V surface, Ti and Al are the metal ions most likely to be released from the Ti-6Al-4V surface [9,22].

According to Alavi *et al*. (2021), the ions released can be the cause of oxidative stress, causing damage not only to cells, but also to proteins, lipids, and nucleic acids. All this can lead to cancer, causing oxidative stress that damages human cells. Oxidative stress seems to affect proteins, lipids and nucleic acids, causing tissue damage and the progression of cancer [9]. All these studies highlight the fact that metal ions can be toxic to cells and tissues in the environment where Ti-6Al-4V MSs were found. However, it seems that, to have significant effects, the dose of metal ions must be quite high. In most studies, it has been found that minimal doses of metal ions do not cause significant adverse effects that could harm the patient's health.

Although fluoride solutions are important for preventing dental caries in orthodontic patients, their use can lead to corrosion of Ti-6Al-4V MSs and, consequently, to their fracture [16].

**Limitations of the study**

Most of the studies found for the basis of this systematic review were *in vitro* studies and were not carried out in patients. The authors tried to reproduce conditions as close as possible to a patient's oral environment. However, many factors, such as individuals and the presence of saliva, were not considered in the results presented.

In only one study did the authors regularly agitate the mouthwash to achieve the closest possible reproducibility.

In addition, more metal could be released in real life due to the fluidity of saliva in the mouth and the fact that oxide layers are removed by brushing the teeth.

The number of studies is limited. Given the small number of studies carried out on this subject, it would be interesting to carry out an experimental study in patients undergoing orthodontic treatment with Ti-6Al-4V MSs and using a CHX mouthwash and a NaF mouthwash.

**Clinical relevance**

As orthodontic MSs are frequently used in treatment, the study of mouthwash selection and its impact on the surface area of Ti-6AL-4V alloy MSs is clinically relevant for an orthodontist. Indeed, it can provide valuable information for understanding and limiting induced ion release, preventing corrosion, managing inflammation and infection, and maintaining the stability of orthodontic MSs.

It is essential for the orthodontist to prescribe the most appropriate mouthwash so that there is no change to the surface of the MSs used as a treatment aid in patients.

## Conclusions

After analyzing several studies in this systemic review, we can conclude that: (1) Mouthwash containing NaF is not the better choice because it causes corrosion of the MSs and releases ions that can be harmful to health when released in large quantities; (2) Mouthwash containing CHX seems to alter the MSs very little. The release of contained ions in contact with CHX also appears to be minimal. CHX seems to have a positive effect on reducing the risk of infection after the placement of MSs; (3) We can therefore consider mouthwashes with CHX to be more beneficial than mouthwashes with NaF.

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## Author Contributions

LES planned the overall design, conceived and designed the work, acquired, analyzed and interpreted the data, drafted, substantially revised and was the main author of the present manuscript. ACO and SSS substantially revised the manuscript. CSS revised the manuscript. PSS was responsible for the idea for the study, conceived and designed the work, analyzed the data, drafted and substantially revised the manuscript. All authors read and approved the final manuscript.

## Conflicts of interest

The authors declare no competing interests.

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