Original Article

In Vivo Aging of Orthodontic Alloys: Implications for Corrosion Potential, Nickel Release, and Biocompatibility

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Abstract: Despite the large number of studies investigating nickel release from orthodontic stainless steel and nickel-titanium alloys, there is a lack of conclusive evidence with respect to the composition and kinetics of the corrosive products released. The objective of this review is to address the critical issues of corrosion potential and nickel leaching from alloys by investigating the effect of intraoral conditions on the surface reactivity of the materials. After an overview of fundamentals of metallurgical structure of orthodontic alloys, we provide an analysis of corrosion processes occurring in vivo. We present recent evidence suggesting the formation of a proteinaceous biofilm on retrieved orthodontic materials that later undergoes calcification. We illustrate the vastly irrelevant surface structure of in vivo– vs in vitro–aged alloys and discuss the potential implications of this pattern in the reactivity of the materials. Finally, we present a comprehensive review of the issue of nickel release, based on three perspectives: its biologic effects, the methods used for studying its release, and nickel-induced hypersensitivity in orthodontic patients. (*Angle Orthod* 2002;72:222–237.)

Key Words: Nickel; Nickel release; Corrosion potential; Orthodontic alloy; Biocompatibility

INTRODUCTION

Nickel (Ni)-containing alloys are present in a substantial number and wide variety of appliances, auxiliaries, and utilities used in orthodontics and thus become an integral part of almost every routine orthodontic intervention. Table 1 lists the Ni-containing alloy applications, which to a great extent pertain to stainless steel alloys used in bracket and archwire manufacturing. The ''hidden'' as well as the Ni-free alternative applications are also included in this table. Nickel-titanium (NiTi) archwires contain 47%–50% Ni[1] and are the richest source of Ni in the intraoral environment of the average orthodontic patient. Recent evidence has attributed carcinogenic,[2] mutagenic,[3] cytotoxic,[4] and allergenic[5–7] actions to Ni in various forms and compounds. In addition, there is a trend for state laws to increasingly take into account the possibility for adverse reactions to Ni and to emphasize the necessity for patient awareness of possible undesirable sequelae.[8]

Nonetheless, there is a lack of data in the relevant literature to support an increased prevalence of clinical adverse effects of Ni. For example, studies have failed to confirm that patients receiving artificial joints containing Ni are at a greater risk for developing pathologic entities linked to Ni[9]; however, a slightly higher incidence of tumors has been associated with the implantation of metallic components.[10]

The orthodontic applications of Ni alloys are unique in that the alloy element is not implanted into the tissue, but is placed in an open cavity. Therefore, tests involving implantation of Ni-containing alloys that are frequently used in other medical fields bear no relevance to the clinical use of the material in orthodontics. Although the implantation procedure may be considered more invasive than the intraoral placement of the Ni-containing alloys, the reactivity of the implanted material is decreased because of the formation of a connective tissue capsule surrounding the foreign body.[11,12] In contrast, intraorally placed materials (ie, wires, brackets) exhibit a pattern of continuous reaction with the environmental factors present in the open oral cavity.

Investigators have recognized the potential biological implications of Ni release, focusing on the fate of corrosive products of alloys used in orthodontics.[13–29] However, most studies have adopted in vitro approaches, which have proved methodologically unreliable and clinically irrelevant because of the largely different nature of in vitro media and the oral cavity. Moreover, the results of these studies are

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TABLE 1. Nickel-Containing Orthodontic Materials and the Corresponding Nickel-Free Substitutes [a]

Category	Material	Ni-Free Substitute and Modifications
Standard appliances	Brackets	Ni-free stainless steel, ceramic, plastic, Ti, gold-plated, or coated with other precious metals (Pd, Pt) brackets
	Bands	Gold-plated bands
Treatment utilities	Stainless steel archwires	No alternative currently available; development of polymeric wires in progress
	NiTi archwires	β-Ti (TMA) archwires; nitride- or epoxy-coated NiTi archwires; α-Ti archwires
	CoCrNi archwires (Elgiloy)	No alternative currently available
Mechanics auxiliaries	Sliding yokes, transpalatal and lingual arches	β-Ti (TMA), plastic, or inert metal (gold) coating of wire segments
Miscellaneous auxiliaries	Stainless steel ligatures	Teflon-coated ligatures
	Kobayashi hooks	Teflon-coated Kobayashi hooks; Ni-free brackets with hooks
	Coil springs	Elastomeric ligatures
Fixed expansion appliances	Stainless steel appliances (Quad-Helix, Rapid Palatal Expander)	β-Ti (TMA) wires for Quad-Helix
	Stainless steel headgear	Teflon-coated stainless steel facebow
	NiTi spring screws	No alternative currently available
Removable appliances	Stainless steel components of Hawley appliance and variations	Plastic or elastic retainers; elastic positioners or acrylic splints Invisalign™ technique
Complex therapeutic interventions	Orthognathic surgery lag screws and plates	Resorbable polylactic-polyglycolic lag screws and plates
	Distraction osteogenesis apparatus	No alternative currently available

[a] TMA indicates titanium molybdenum alloy.

inconclusive with respect to the composition of released products as well as the description of the release kinetics. Recent evidence on the actual in vivo aging pattern of NiTi and stainless steel alloys has provided new insight on the processes accompanying the placement of the alloys in the oral cavity for extended periods of time.[30–32]

This article has the following aims:

- To provide an overview of the fundamentals of metallurgy and corrosion resistance for stainless steel and NiTi alloys
- To discuss the corrosion process in Ni-containing orthodontic alloys in vitro and intraorally
- To review the composition and fate of leaching products and to summarize the biologic effects of Ni
- To assess the clinical relevance and scientific coherence of protocols employed to evaluate Ni leaching in light of new evidence describing in vivo–induced material surface alterations
- To address the issue of Ni-induced hypersensitivity in the orthodontic patient

METALLURGY OF STAINLESS STEEL AND Ni-CONTAINING ORTHODONTIC ALLOYS

Knowledge of the basic metallurgic structures of the orthodontic alloys and the reactions occurring intraorally are necessary for understanding the events preceding Ni leaching and the nature of the compounds released. The latter may be instrumental in assessing the biologic effects of the alloys.

Stainless steel

Stainless steel alloys represent a group of corrosion-resistant alloys that incorporate iron (Fe) and chromium (Cr). This group may be divided into 5 families based on the predominant phase constituent of the alloys' microstructure. The first four families are the martensitic, ferritic, austenitic, and duplex (austenitic plus ferritic) families.[9] The fifth family is the precipitation-hardened stainless steels, which is derived by heat treatment. The austenitic stainless steels generally have the greater corrosion resistance compared with other microstructures. Austenitic steels that contain Ni as the primary austenite stabilizer include the 316L type (the *L* designation denotes a low carbon content) that is the stainless steel most commonly used for implantation applications. Although addition of Cr has the greatest effect on corrosion resistance, other alloying elements are used to enhance corrosion behavior. Among the most important alloying elements are carbon, nickel, molybdenum (Mo), and nitrogen. Because the Ni atoms are not strongly bonded to form some intermetallic compound, the likelihood of in vivo slow Ni ion release from the alloy surface is increased, which may have implications for the biocompatibility of these alloys.[1]

There have been some potentially alarming reports on the corrosion potential and Ni release of the AISI type 316L austenitic stainless steel alloy currently used for bracket manufacturing.[33] Thus, a 2205 stainless steel alloy that contains half the amount of Ni found in the 316L alloy has recently been proposed as an alternative for orthodontic brackets.[34] This alloy has a duplex microstructure consisting

of austenitic and delta-ferritic phases and is harder than the 316L alloy. Moreover, the 2205 alloy demonstrates substantially less crevice corrosion than the 316L alloy when coupled with NiTi, β-Ti, or stainless steel archwires in vitro.[33]

The use of the 2205 stainless steel alloy for bracket fabrication follows recent research that reported on the microhardness of metallic brackets, which was studied to obtain information concerning the relative strength of the bracket alloys.[35] It was found that the 316L alloy has a much lower hardness compared with the precipitation-hardening (PH) 17-4 stainless steel bracket alloy, although the former has a significantly greater corrosion resistance.

Some recently reported evidence on the feasibility of manufacturing Ti brackets by metal injection molding might contribute to the introduction of alternative forms of stainless steel alloys (Table 1). Titanium brackets were found to exhibit mechanical properties, corrosion resistance, and bond strength equivalent to or better than that of their stainless steel counterparts.[36] There is no ''Ti coating'' on brackets. There are coatings such as titanium nitride (poor protection against Ni leaching), gold, and other precious metals (palladium, platinum), but none really works as the Ti brackets per se.

NiTi alloys

The NiTi wires contain approximately equiatomic proportions of Ni and Ti and are based on the intermetallic compound NiTi. Examination of the binary phase diagram reveals that often there is some deviation from stoichiometry for NiTi.[1] Particles with dimensions typically less than 1–2 μm and containing a large atomic fraction of Ti have been found on the surfaces and in cross-sections of NiTi wire samples.[1] There are two major NiTi phases in the NiTi wires:

The *austenitic* phase has an ordered base-centered cubic (bcc, cesium chloride type) structure, which occurs at high temperatures and low stresses.

The *martensitic* phase NiTi has been reported to have a distorted monoclinic, triclinic, or hexagonal structure and forms at low temperatures and high stresses.[1]

CORROSION RESISTANCE OF ORTHODONTIC ALLOYS

The "stainless" of stainless steel

Stainless steel owes its corrosion resistance property to chromium, a highly reactive base metal. The alloy's corrosion resistance depends on its passive film, which spontaneously forms (passivation) and reforms (repassivation) in air and under most tissue fluid conditions.[9] Oxygen is necessary to form and maintain the film, whereas acidity and chloride ions can be particularly detrimental to it. Increasing the content of Cr results in a reduction in the passive current density, raises the breakdown and pitting potentials, and lowers the critical current density and potential necessary for passivation. Nickel is added to decrease the critical current density, whereas Mo has a strong effect on lowering the critical current density and raising the pitting potential.[1,9]

Studies have shown that the film formed by Cr complexes also contains Fe, Ni, and Mo. In an aqueous environment, this film consists of an inner oxide layer and an outer hydroxide layer. The oxide of nonimplanted and implanted materials consists mainly of chromium oxide with precipitation of calcium, phosphorous, and sulfur.[37] The addition of Mo to the 316L stainless steel alloy provides further protection from crevice and pitting corrosion. The chromium oxide passive films are not as stable as their titanium oxide counterparts and thus contribute to the inferior corrosion resistance of stainless steel relative to Ti alloys.[1] Furthermore, several other materials are known to promote corrosion in the event that stainless steel is sensitized as a consequence of improper handling.[37] A similar mechanism of corrosion resistance is postulated to occur for the cobalt-chromium-nickel (CoCrNi) (Elgiloy) orthodontic wire alloys.

NiTi alloys: titanium oxides and corrosion resistance

The corrosion resistance feature of NiTi wires is largely due to the presence of a large proportion of Ti (48%–54%). Titanium forms several oxides (TiO_2, TiO, Ti_2O_5). The TiO_2 oxide is the most common and most stable one and is found in three crystalline forms: the tetragonal anatase, the rutile, and the orthorhombic brookite. The latter presents the highest dielectric constant among the three forms. Actually, the composition of the oxide layer has not been clearly defined, and it is unlikely that it would correspond to the stoichiometric composition and, therefore, TiO_x describes more accurately the oxide form. Evidence shows that the ready formation of TiO_2 in the air might be due to the low free energy value of the reaction

$Ti + O_2 \rightarrow TiO_2$ which has a ΔG of -203.8 kcal/mol (-856 kJ/mol), making the formation of TiO_2 entropically favorable.[37] However, a considerable dispute exists concerning the pattern, kinetics, and direction of oxide growth. Although some reports suggest that the oxide thickness is increased as a log function of immersion time in electrolytes, others have noted different directions of growth and steady-state levels of TiO_2.[38]

When Ti is exposed to water, TiO_2 is expected to form according to the reaction

$Ti + 2H_2O \rightarrow TiO_2 + 2H_2$ with a ΔG of 82.9 kcal/mol (348 kJ/mol). Because passivation initiates further oxidation via a decrease in the free energy of the above reaction, the oxide's formation is favored thermodynamically. In electrolyte solutions, anions adsorbed on the oxide surface

generate a sufficiently high electric field to facilitate migration of metal (oxide) anions through the film to the oxide-electrolyte interface. During this reaction, H^+ ions are produced, increasing the pH. The resulting OH^- anions are adsorbed on the surface, where they create an electrical field for ion migration and subsequent oxide growth. In aqueous solutions, the high rate of initial thickening when the oxide possesses an amorphous structure diminishes as crystallization sets in. This process is in accordance with theoretical models proposing that reactivity in solids increases with increasing extent of structural disorder.

CORROSION OF ORTHODONTIC ALLOYS

It is known that corrosion of orthodontic alloys occurs in the intraoral environment, regardless of the alloys' metallurgic structure, and it is also known that the extent of manufacturing defects may accelerate the process.[33] Although there is an abundance of relevant information on corrosion of stainless steel, very little is known about the corrosion of NiTi alloys.

There are several different forms of corrosion that may affect orthodontic alloys.

Uniform attack

Uniform attack is the most common type of corrosion, occurring with all metals at different rates. The process arises from the interaction of metals with the environment and the subsequent formation of hydroxides or organometallic compounds. Uniform attack may not be detectable before large amounts of metal are dissolved.

Pitting corrosion

Corrosion in the form of pitting has been identified in brackets and wires. A pit is considered as a pore with a depth equal to its width. Interestingly, initiation of the process may take place before intraoral placement since excessively porous surfaces have been found on as-received products.[39] The surfaces of as-received stainless steel and NiTi wire specimens (Figures 1a and 1b, respectively) exhibit crevices and pores. These pores may give rise to attack since they represent sites susceptible to corrosion.

Potentiodynamic polarization experiments and scanning electron microscopic observations of archwires composed of stainless steel, CoCr, NiCr, NiTi, and β-Ti exposed to electrochemical corrosion in artificial saliva have shown evidence of pitting corrosion formed on the wire surfaces.[22] Electrochemical studies have also indicated that pitting corrosion of NiTi archwires occurs in a 1% saline solution. However, surface irregularities observed in NiTi archwires, which are sites susceptible to selective dissolution of Ni, may arise from the manufacturing process.[1]

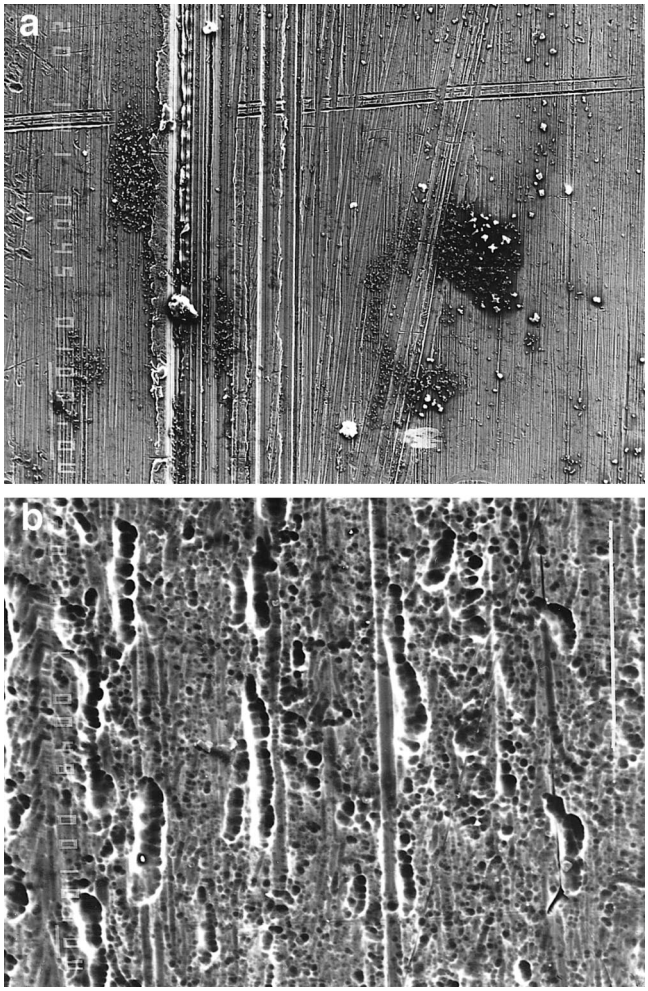


FIGURE 1. Secondary electron images of as-received wires. Note excessively porous surfaces with a high susceptibility to pitting corrosion, which is attributed to manufacturing defects. (a) Stainless steel wire (original magnification ×180, bar = 100 μm). (b) NiTi wire (original magnification ×600, bar = 100 μm).

Crevice corrosion

Crevice corrosion (or gasket corrosion) occurs in loci exposed to corrosive environments, often through the application of nonmetallic parts on a metal (ie, elastomeric ligatures on a bracket) and arises from differences in metal ion or oxygen concentration between the crevice and its vicinity. Figure 2 shows the face surface of a bracket before (Figure 2a) and after (Figure 2b) one year of intraoral exposure. Severe disintegration on the surface of the bracket is evident, with the formation of craters, deep fissures, and excessive pores. In clinically derived material, the depth of the crevice can reach 2–5 mm, perforating the base in one-piece brackets, and the amount of metal dissolved can reach high levels. The attack may be attributed to the lack of oxygen associated with plaque formation and the byproducts of microbial flora, which deplete the oxygen disturbing the regeneration of the passive layer of chromium oxides.[40,41]

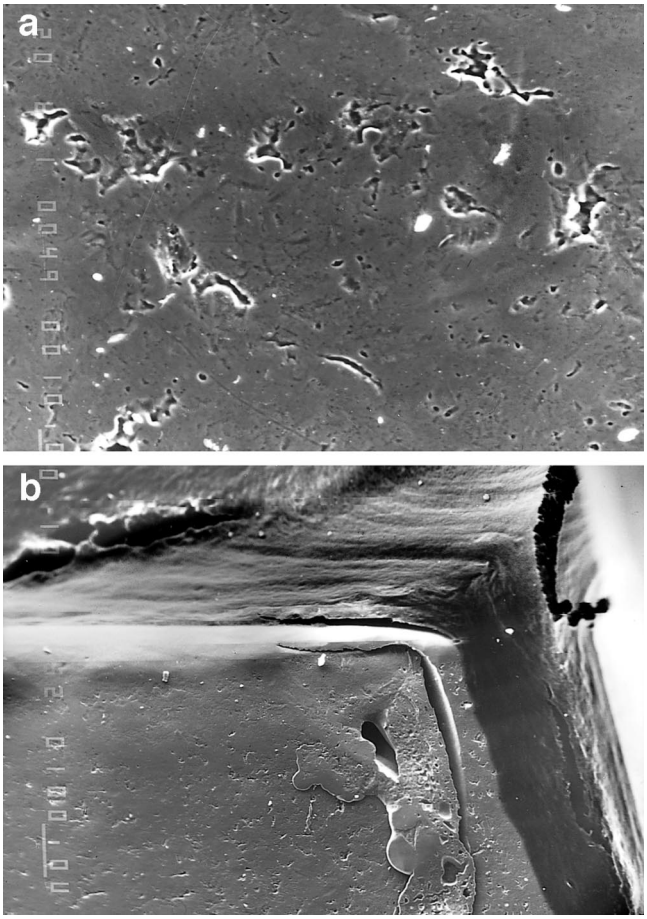


FIGURE 2. Secondary electron images of the surfaces of an as-received stainless steel bracket (a) and a retrieved stainless steel bracket (b). A portion of the face of the bracket is shown. Note the excessive craters, deterioration, and porous surface (original magnification ×60, bar = 100 μm).

Galvanic corrosion

When different metals (or even the same alloy, subjected to different treatments) are joined, a combined process of oxidation and dissolution takes place. The less noble metal is oxidized and becomes anodic and, as some of its atoms release electrons, the resulting ions dissolve and become soluble ions.[42] The nobler metal becomes cathodic and more corrosion resistant with respect to the less noble metal. Stainless steel is characterized by a passive-active behavior depending on the environmental conditions in which the protective chromium oxide layer may be eliminated (active form) or regenerated (passive form). Thus, galvanic corrosion may take place depending on the status of the stainless steel (contact with metals arising from brazing). Nonetheless, this type of corrosion is more common in the broader dental applications of materials.[43]

Intergranular corrosion

Stainless steel brackets subjected to a range of temperatures, known as sensitization temperatures, undergo an alteration of their microstructure. The phenomenon is due to a precipitation of chromium carbide at the boundaries of the grains.[9] In contrast to the uniform or pitting corrosion patterns involving dissolution of a part of the metal, intergranular corrosion affects mainly the solubility of chromium carbide.

Fretting corrosion

Fretting corrosion refers to the process occurring in contact areas of materials under load and finds its analogue in the bracket's slot-archwire interface. Figure 3 shows the surface appearance of a longitudinally sectioned, metallographically polished NiTi wire specimen after its intraoral exposure for a period of nine months.[30] Crevices and increased porosity are apparent together with signs of delamination (Figure 3a), probably due to friction created during movement. In the same figure, the notable destruction of grain arrangement (Figure 3b) along with a reduction in the grain size of the intraorally exposed wire contrasts with the intact structure of an as-received sample (Figure 3c). It is interesting to note that this appearance is much different from that of the typical wire surface shown after in vitro aging through the application of electrolyte or artificial saliva solutions. The underlying mechanism involves the cold welding at the interfaces under pressure, which results in rupturing of the contact points (wear-oxidation pattern). Alternatively (oxidation-wear pattern), most materials are covered by a thin layer of oxides that is disturbed and producing oxide debris that leads to accelerated oxidation.

Microbiologically influenced corrosion

While the effect of alloy exposure to certain species has been recognized in the literature, Matasa[44] was the first to show evidence of microbial attack on adhesives in the orthodontic field. The effect of enzymatic activity and degradation of composite resins has been reported earlier.[45] Occurrence of these phenomena in brackets results in the formation of craters in the bracket base.

Stress corrosion

When archwires are engaged to brackets bonded to crowded teeth, the reactivity status of the alloy increases. The increased reactivity results from the generation of tensile and compressive stresses developed locally because of the multiaxial, three-dimensional loading of the wire. Thus, an electrochemical potential difference occurs with specific sites acting as anodes and other surfaces acting as cathodes.

Corrosion fatigue

A highly important process for the aging of orthodontic alloys is the tendency of a metal to fracture under repeated cyclic stressing. This process (fatigue) is accelerated by the reduction in fatigue resistance induced by exposure to a

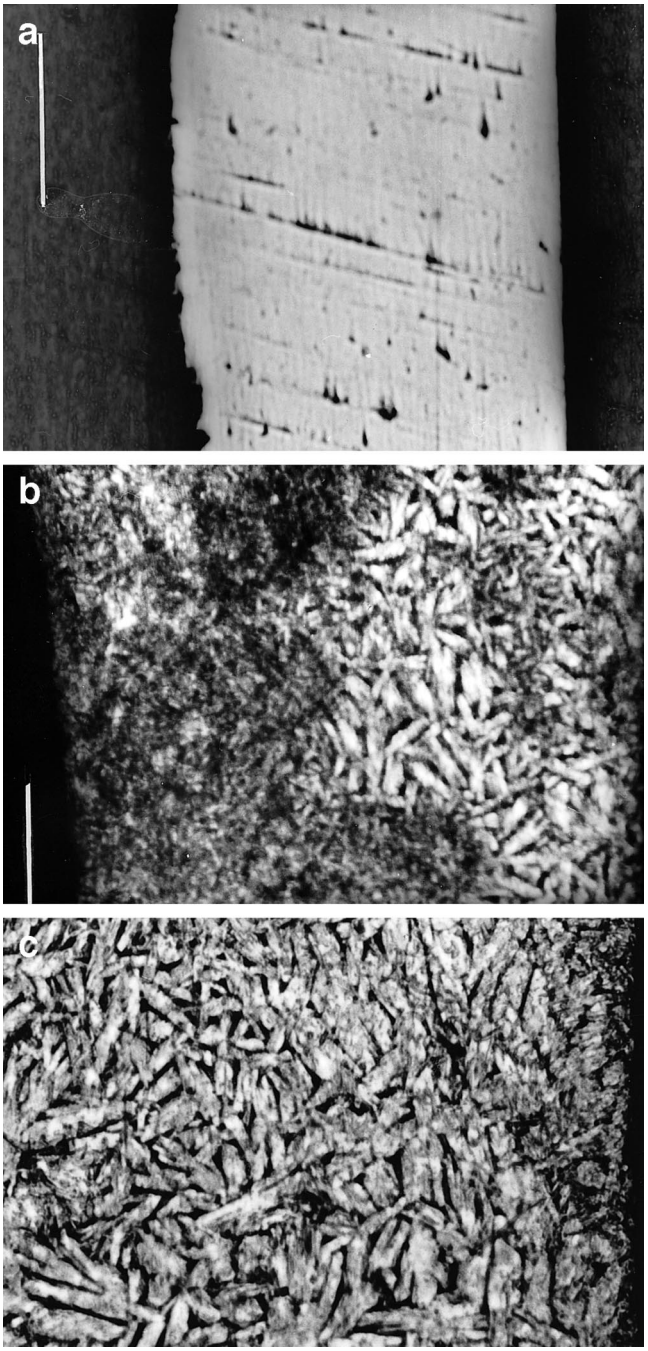


FIGURE 3. Reflected light image of a longitudinally sectioned and metallographically polished nickel-titanium wire specimen. (a) Surface demonstrating delamination, pitting, and crevice corrosion. This surface was engaged to the bracket slot. (Original magnification ×160, bar = 1 mm.) (b) Destruction of the grain arrangement of the region engaged to the bracket (left). (Original magnification ×50, bar = 100 μm.) (c) As-received wire demonstrating a crystallographically intact structure. (Original magnification ×50, bar = 400 μm.)

corrosive medium such as saliva (corrosion fatigue). The process occurs frequently in wires left in the intraoral environment for extended periods of time under load, and in general, it is characterized by the smoothness of the fractured areas, which also include a site of increased roughness and crystalline appearance (Figure 4). Also, fracture incidents of headgear facebow wires, especially in the inner arch located at the wire segment entering the buccal tube, may be due to corrosion fatigue. Unfortunately, fatigue tests are only scarcely present in the relevant orthodontic materials literature.[46]

FIGURE 4. Secondary electron image of an intraorally fractured inner facebow wire. Fracture plane demonstrating three distinct zones: the radiant zone (low), the ductile zone (medium), and the shear lip zone (original magnification ×75).

IN VIVO AGING OF ORTHODONTIC ALLOYS

In vitro vs in vivo conditions

A major concern for investigators in the past decade has been the performance of alloys in the environment in which they are intended to function, namely, the oral cavity. This concern arose because it was recognized that storage media, consisting of electrolyte or acidic solutions employed in vitro, cannot reliably simulate the intraoral environment. A number of factors and variables are responsible for this difference and may include the following:

- An absence of extreme variations in a set of parameters affecting the corrosion potential and reactivity of the alloy (pH, temperature, stress). It is known that the corrosion potential of stainless steel is increased in acidic environments.[22]
- An absence of the simulation of bracket-archwire ligation. Both components are moving elements, which may induce fretting corrosion.[47]
- An absence of the complex intraoral flora and accumulation of plaque and its byproducts. This is the most important difference.
- The use of nonagitated storage solutions, which has given false evidence. The release of Ni from the wires results in rapid attainment of equilibrium in the solution and, therefore, the long-term release is not taken into account.

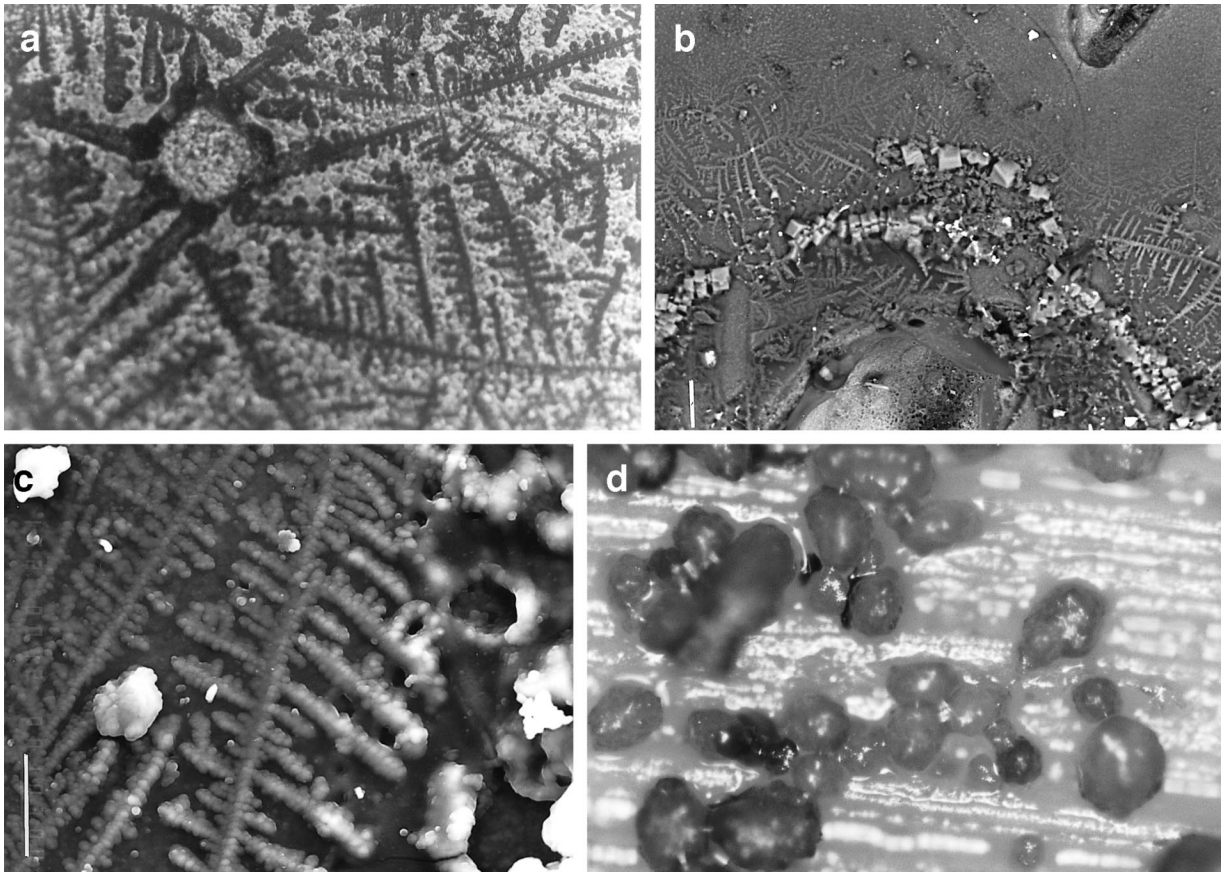


FIGURE 5. Microbial colonization of a retrieved dental material. (a) Radial pattern of colonization on an adhesive (optical polarized light microscopy, bright field, original magnification ×50). (b) Secondary electron image of a composite showing the microbial colonization and precipitation of crystalline complexes (cubic structures) (original magnification ×60, bar = 100 μm). (c) Higher magnification of a portion of the area depicted in (b) illustrating clearly the crystalline nature of the white formations corresponding to elements of high atomic number (original magnification ×300, bar = 100 μm). (d) Optical polarized light image of streptococcal species precipitated on a retrieved elastomeric module after staining (bright field, original magnification ×50).

It is known that fatigue of the alloys results in acceleration of release rates and disintegration reactions.[47]

Orthodontic alloys are in contact with a variety of substances that impose potent effects on their reactive status and surface integrity, including the following substances:

- Saliva, which may contain acid arising from the degradation and decomposition of food.
- Environmental factors including several parameters related to the surroundings, such as air. It has been estimated that an urban mouth-breather inhales in two hours approximately a cubic meter of air with a potential sulfur dioxide intake of up to 2.3 mg.[40]
- Oral flora and its byproducts. Figure 5 shows the organization of colonies on a composite adhesive material. The extent of colonization and the simultaneous precipitation of crystalline formations presumably composed of calcium-phosphorus complexes are also shown. The presence of streptococcal species on a elastomeric ligature after intraoral exposure is shown in the same figure.

The action of microbial colonization is twofold: (1) certain species can take up and metabolize metals from alloys and (2) microbial byproducts and the metabolic processes may alter the conditions of the microenvironment (ie, decreasing the pH, thereby contributing to the initiation of the corrosion process). The metal uptake capacity of microbes has been long known and applied to the problem of metal waste management. Other species, including the sulfate-reducing Bacteriodes corrodens, the sulfur oxidizer Thiobaccilum ferroxidans, and the acid-producing Streptococcus mutans, may adversely affect the surface structure of dental alloys.[48] The implication of bacterial metabolism in the surface alterations of alloys has been reported for dental alloys[48] and endodontic silver points[49] among other materials. It is known that sulfate-reducing and nitrate-reducing bacteria are aggressive and inflammatory to the hosting tissues, and that these bacteria also affect the corrosion processes of various alloys.[49]

Corrosive products may be adsorbed by enamel, as evidenced by the incidence of tooth staining that occurs by

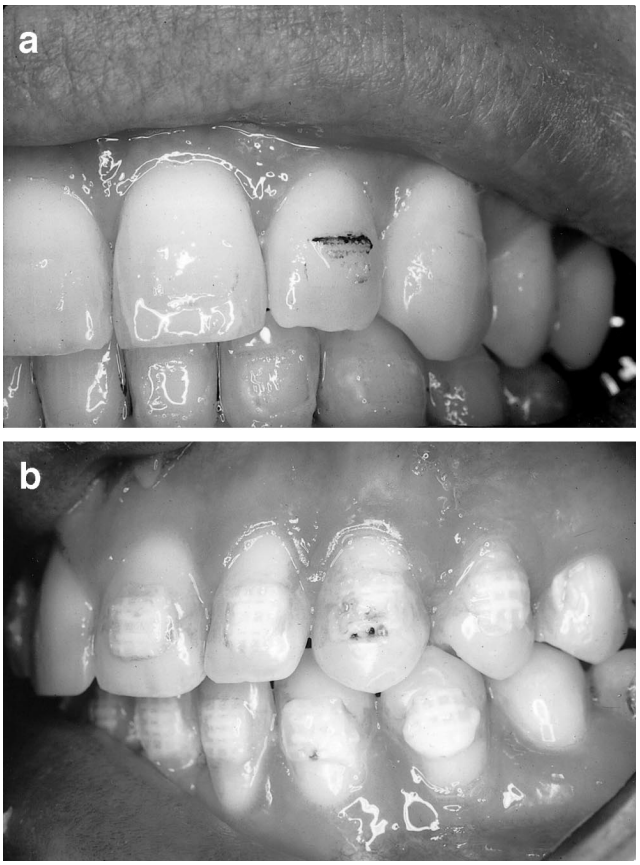


FIGURE 6. Enamel appearance after debonding and before resin grinding of a metallic bracket (a) and a plastic bracket (b). Discoloration of the adhesive layer may be attributed to diffusion of corrosive products from the metallic bracket base or the stainless steel wire used, respectively.

diffusion through the adhesive layer. Figure 6a shows the enamel appearance after debonding of a stainless steel bracket but before resin grinding. Metallosis (the diffusion of metallic particles generated by reactions occurring in the bracket) that has extended to the adhesive layer is evident.[16] Figure 6b shows the corresponding clinical appearance after debonding of a plastic bracket. The discoloration in this case may derive from corrosive products of the wire. A portion of the corrosive product mass may be moved to the gastrointestinal track during normal swallowing. This possibility emphasizes the importance of clarifying the kinetics of release when examining the potential for ion passage to the body.

Retrieval studies

One approach used to study the alteration of material properties that occurs in vivo is the study of used or retrieved materials. The wide range of orthodontic auxiliaries, utilities, and appliances used as an integral part of orthodontic therapy comprise the body of materials used by the clinician in everyday practice. These materials present an ideal model for the study of material alterations occurring in vivo because the majority of materials (with the exception of brackets) may be removed and studied during the regular treatment visits of patients with no implications in the advancement of treatment. Most of the wires, elastomers, and other utilities are only periodically used during therapy. In contrast, for some appliances such as brackets and bands, collection of used materials can only take place after the end of treatment owing to ethical concerns and technical problems arising from the intentional debonding and rebonding of the appliance.

Recent studies have focused on the alterations of NiTi wires and inner archwire of stainless steel facebows.[30,31] It was found that the material surfaces are coated by intraorally formed proteinaceous integuments that mask the alloy surface topography to an extent dependent on an individual patient's oral environmental conditions and on the intraoral exposure period (Figures 7a through 7d). The organic constituents of the film acquired on the alloy surface were amide, alcohol, and carbonate, whereas the predominating elemental species were sodium, potassium, chloride, calcium, and phosphorus. The elemental distribution of the biofilm complies with the formation of sodium chloride, potassium chloride, and calcium phosphate crystalline precipitates on wire surfaces, as confirmed by the X-ray microanalysis images depicted in Figures 7c and 7d. Mineralized regions may provide a protective effect over the alloy substrate, especially under low pH conditions under which the corrosion rate of stainless steel and NiTi wires is increased.

The morphology of the free wire surfaces differed distinctly between the retrieved and reference specimens.[30] Surface smoothening and increased pitting were the main findings. Although pitting corrosion occurs on retrieved NiTi wire surfaces, no major effects on the mechanical properties of the wires have been identified clinically. This absence of major effects occurs despite the obvious alteration of the surface of the alloy involving a notably high increase in roughness, as evidenced from the atomic force microscope images shown in Figure 8. Further research should address potential alteration in the fatigue properties of retrieved wires relative to that in as-received or in vitro–aged wires to assess the effect of intraoral aging on mechanical properties of the material.

Crevice corrosion and selective Ni dissolution from the near-surface region has also been documented on NiTi wires in vitro.[21] However, such compositional changes have been reported in crevices of both as-received and used NiTi archwires, implying the possibility of manufacturing defects. Several important differences were noted in the surface profile morphology of the longitudinally sectioned and polished wires relative to the as-received wires. Surface regions engaged to the bracket slot showed surfaces demonstrating excessive wear, and characteristic patterns of delamination were observed. The enhanced deterioration of this specific region may be attributed to compressive forces

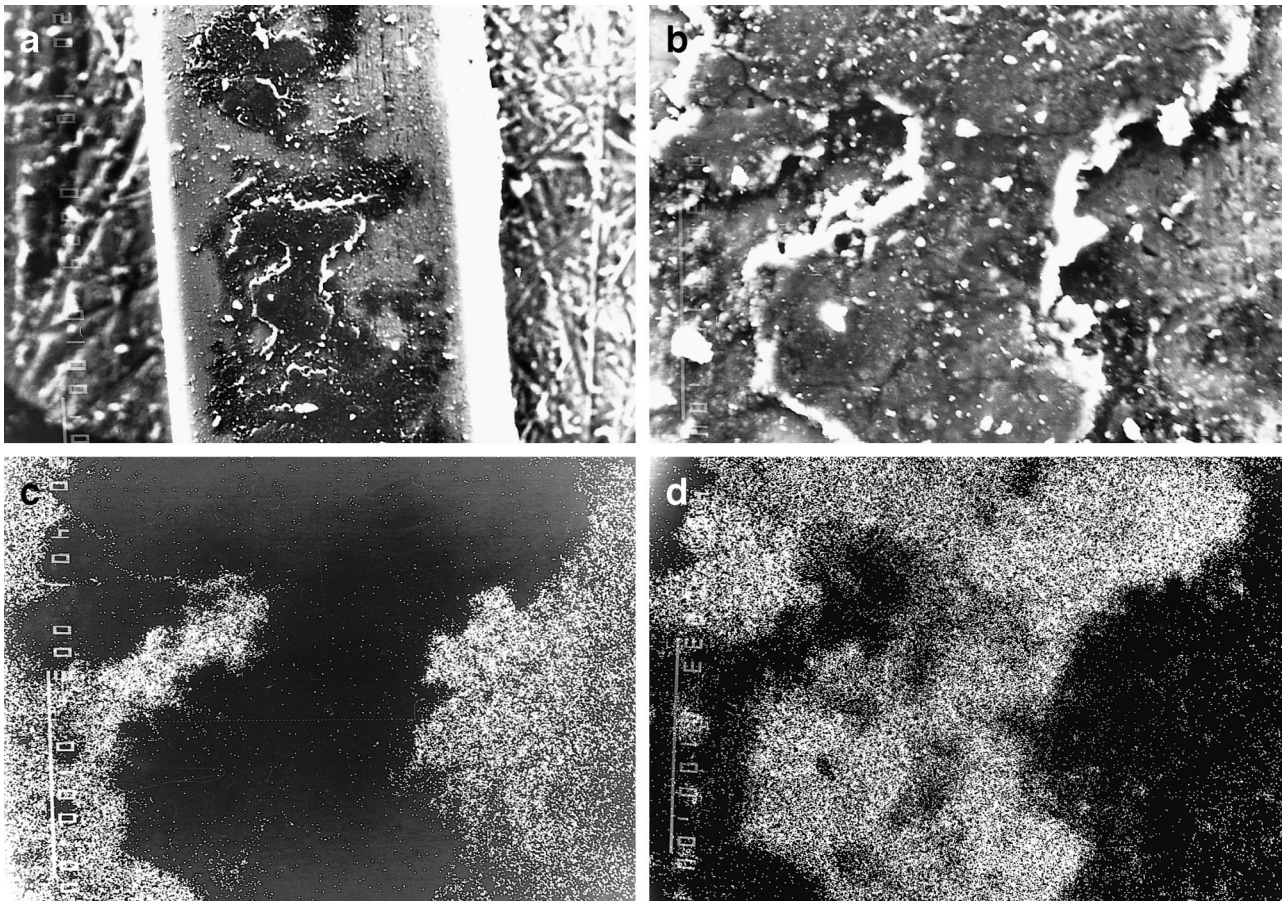


FIGURE 7. Scanning Electron Microscope-Wavelength Dispersive (SEM-WDS) X-ray microanalysis of a nickel-titanium wire specimen after nine months of intraoral exposure. (a) Secondary electron image, SEI (original magnification ×100, bar = 100 μm). (b) SEI (original magnification ×400, bar = 100 μm). (c) X-ray image of nickel. An identical distribution was observed for titanium. Note the absence of nickel distribution presumably due to covering of the alloy wire surface by precipitants. (d) X-ray image of calcium. The distributions of phosphorus showed a pattern identical to that of calcium.

accompanying wire activation through ligation and possible frictional damage produced inside the slot. An identical pattern has been found for the stainless steel inner facebow arches after exposure to the intraoral environment of patients for a period of six to nine months (Figure 9).

Recent evidence also suggests that some notching occurs on the wire surface during treatment as a result of masticatory loads. This effect has a wide range of severity depending on the bracket-archwire combination, with the ceramic brackets presenting the most pronounced alterations on the wire surface.[49,50]

It is worth noting that the evidence presented has not been taken into consideration in several in vitro approaches typically employed to simulate the intraoral environment, thus precluding the extrapolation of clinically meaningful conclusions. The clinical significance of the in vivo–induced alterations identified in the foregoing studies relates to the biological performance of the alloy. Biofilm adsorption and calcification may provide a protective inert film, thereby reducing the incidence of host immune response because of the decreased exposure of the alloy surface to the oral environment. Alternatively, the intraoral aging process described in this study involves adsorption of ions. The associated reactions can possibly accelerate corrosion and disintegration phenomena in the oral cavity, which is widely considered to be a severe environment. Currently, there is a lack of evidence about the contributory role of intraoral aging on the extent and kinetics of Ni release.[31]

Ni LEACHING

Importance and biologic effects

The fate of particulate masses of foreign bodies implanted or placed in open cavities of the human body has attracted the interest of investigators because of the apparent clinical importance of the information. However, the models proposed to study the phenomenon vary significantly because of the extreme variation in applications coupled with the different metabolic and excretory potential of individual elements in the animal models used.

In general, released particles of various sizes are phagocytized by a variety of cells, with the uptake capacity vary-

ing as a function of particle size. Usually, an approximate 10-fold increase in the size of particles induces a 200-fold decrease in the ability of cells to incorporate these particles into their cytoskeleton.[51] The uptake and transport of particles are described by complex mechanisms involving kinetic models, which vary among species.

The major corrosion products of stainless steel are Fe, Cr, and Ni. Although all three elements potentially have adverse effects, Ni and Cr have received the most attention because of their reported potential for producing allergic, toxic, or carcinogenic effects.[52] Caution should be used in interpreting these findings, since documented toxicities generally apply to the soluble forms of these elements. These toxicities may not be relevant to implant corrosion products.[9] For orthopedic implants, any association between release of metal and any metabolic, bacteriologic, immunologic, or carcinogenic toxicity is considered as conjectural, since cause and effect have not been demonstrated in humans. Nevertheless, investigations continue to indicate concern for short-term and long-term exposures to stainless steel corrosion products. Moreover, it is unlikely that the same pattern characterizes the orthodontic application of alloys.

Generally, solutions of Ni (0.05 mol/L) and Co (0.01 mol/L) have been found to impair the phagocytosis of bacteria by human polymorphonuclear leukocytes in vitro.[53] Nickel ions may affect the chemotaxis of leukocytes, which is mediated by a change in shape. These ions stimulate neutrophils to become aspherical and to move more slowly, and they inhibit calcium ion–dependent contractile activity by depolarizing the neutrophil cell membrane.[54] Also, Ni has been shown to inhibit chemotaxis at a concentration of 2.5–50 ppm.[54,55] Nickel concentrations within the range of that released from dental alloys have been shown to activate monocytes and endothelial cells and to suppress or promote the expression of intercellular adhesion molecule 1 by endothelial cells.[56,57] The latter depends on the concentration of Ni. Most of the relevant literature indicates that the presence of Ni poses a risk of promoting inflammatory response in soft tissues.

Nickel complexes in the form of arsenides and sulfides are known carcinogens, allergens, and mutagens (Table 2). Furst, as cited by Black,[51] has proposed strict criteria for investigating the carcinogenicity of metals. Although most of the studies have examined the metals in the implantable form, which is irrelevant to the orthodontic use, Ni was found to fulfill all criteria since it had carcinogenic action both, in pure form and in compounds (with chloride and sulfide formulations).

There is an abundance of evidence supporting the carcinogenic and mutagenic actions of Ni in cell cultures. However, the actual mediation of its effect remains to be elucidated. A number of studies have indicated that Ni may mimic hypoxia, with a pattern involving up-regulation of Cap43, a hypoxia-regulated gene.[58,59] A different route leading to the same conclusion has been presented; according to this proposed mechanism, oxidative stress caused by exposure to metals and specifically Ni is mediated by induction of lactate dehydrogenase,[60] lipid peroxidation, and induction of the Fenton reaction.[61] The latter process involves the reaction of O_2^- with an oxidative trace metal and generation of O_2, which in turn reacts with hydroxy peroxide to form the hydroxy radical and OH^-. An additional hypothesis for the oxidative stress involves the induction of acetaldehyde formation by Ni.[62] Furthermore, the evidence of oxidative action is illustrated in the increase of lactoferrin receptors after exposure of cell populations to Ni. The latter constitutes an effort to diminish the active metals.[63]

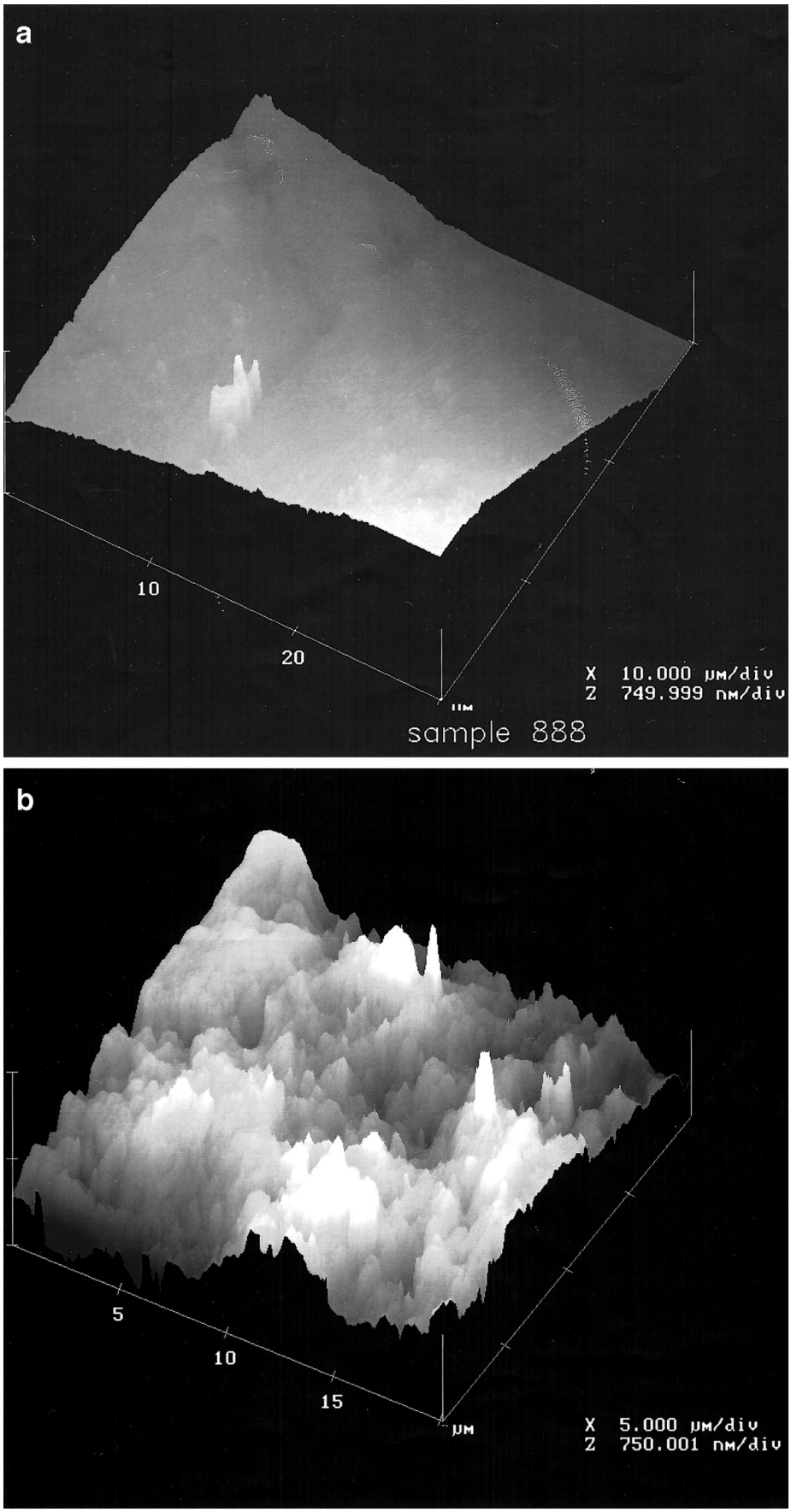
A plethora of studies have also established that Ni at nontoxic concentrations induces DNA damage by base damage and DNA strand scission (single strand breaks) that are site specific.[64] The implication of nuclear factor kappa B (NFκB) and AP-1 transcription factors has been also illustrated through studies showing that Ni-resistant cells have reduced binding of these two factors to their DNA sequences.[59] Nickel-mediated DNA damage may also be inflicted indirectly by inhibition of enzymes that repair DNA breaks, such as 8-oxo-2′-deoxyguanosine and 5′-triphosphate pyrosphosphatases.[65] At nontoxic concentrations, Ni promotes microsatellite mutations, inhibits nucleotide excision repair, and increases total genomic methylation, thus contributing to the genetic instability that has been incriminated as a cause of its carcinogenic action.[66,67]

Estimation of ionic release from Ni-containing alloys

For implanted Ni-containing alloys (ie, those used in orthopedic surgery for arthroplasty applications), the rate of Ni release may range from 0.81–0.0081 μg/h per kilogram body weight totaling 5–500 mg/y for a 70-kg individual.[51] The wide variation present in the estimated values cannot be overlooked. Moreover, the irrelevance for orthodontic applications of a model that involves implantation of the biomedical device must be considered. Orthodontic application of alloys presents a unique pattern for alloy aging and release that is dissimilar to that studied in associated biomedical applications, hence, the striking scarcity of information is the field.

The results of the rare studies of Ni release from orthodontic materials show that full-mouth orthodontic appliance exposed to 0.05% saline release Ni and Cr ions amounting to about 40 μg Ni and 36 μg Cr per day.[68] Similar findings have been reported for sets of standard fixed appliances for the maxillary arch immersed in artificial saliva.[66]

Table 3 presents a classification and critique of the protocols adopted for investigating Ni leaching associated with orthodontic alloys. These studies can be classified into three major categories based on the environment used, namely,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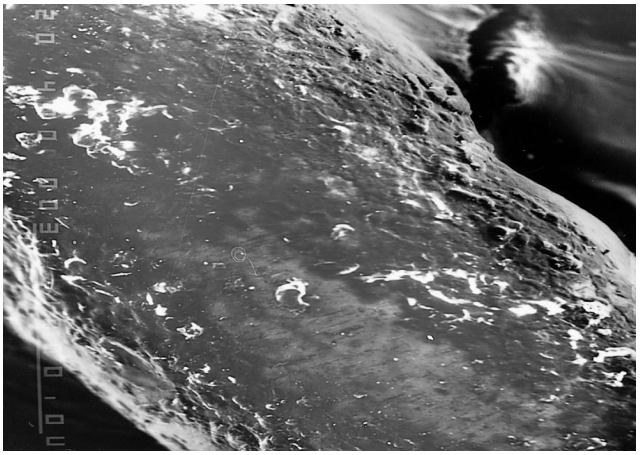

FIGURE 9. Secondary electron image of the inner bow of a retrieved facebow (area shown corresponds to the molar region). Note the precipitation build up (original magnification ×100, bar = 100 μm).

in vitro, retrieval (ex vivo investigation of in vivo–aged samples), and in vivo.

In vitro studies present several flaws, which are pertinent to their lack of clinical relevance and overwhelming simplifications. Specifically, weighing the appliance before and after exposure to various organic acids or other potent factors and attributing the weight difference to leached Ni can only lead to inconclusive evidence with respect to the composition and kinetics of the eluted substances as well as the reactive status of the leached species (Table 3). This may be of critical importance since Ni in particulate forms presents almost a fraction of the side effects of its counterpart in a soluble condition.[58]

Estimation of ionic release through the use of storage media composed of nonagitated, nonreplenished solutions cannot withstand any scrutiny with respect to the methodologic soundness of the approach. By adopting such a setup, the release rate is *forced* to rapidly reach a plateau because of the establishment of an equilibrium between the metal ions present in the solution and the metal ions at the metal-solution interface. This phenomenon leads to the false conclusion that the release rate is accelerated initially and remains steady later, an observation that opposes the findings of most studies showing that the aging of the alloys in the form of fatigue or corrosion enhances ionic release.[47]

Retrieval analyses of used samples are most reliable and present almost no ethical concerns. However, in these studies, the issue examined is investigated from the materials perspective, and an inference to the processes occurring in vivo is made.

The most clinically relevant methods involve the estimation of Ni in biological fluids (saliva, serum, and urine). Saliva is the first diluting pool of Ni, and the results have direct association with the amount of the metal leached. Urine and serum metal concentrations, however, are dependent on the excretory rate of Ni, which is a highly individualized parameter and species specific. This factor is derived from mathematic modeling of the infusion and excretion rate of a metal by an organism.[51] Thus, equations to predict the total body metal content do not take into account the presence of multicompartment components in the organism and the selective binding of metals to organs. For example, in rabbits, Ni shows a high affinity for the kidneys, whereas Mo is selectively accumulated in the spleen.[51] Therefore, the observation that Ni levels in the blood of orthodontic patients are not different from those in untreated individuals cannot rule out the possibility that Ni has been accumulated in an organ.

Ni leaching from orthodontic alloys

In vivo investigations have indicated an increased salivary concentration of Ni and Fe three weeks after the insertion of fixed orthodontic appliances. However, large individual variations deriving from the high variability in the number of bands and brackets of each participant precluded the detection of statistically significant differences in Ni concentrations.[27] Similarly, study of Ni and Cr levels in saliva did not reveal an increased concentration of these ions in a period ranging from one day to one month after insertion of fixed appliances relative to concentrations before insertion.[28] On the other hand, other investigations have indicated that the Ni released from orthodontic appliances might not be measurable in saliva or blood after one week.[29]

It must be noted, however, that the foregoing investigations did not examine the *potential* of Ni release; rather, they aimed at estimating the release occurring under specific conditions that were far from being close to the routine clinical situation. The time periods employed for the in vivo aging of materials were substantially short, and this factor may account for the lack of significant release rates shown. In addition, the saliva sampling periods adopted did not exceed one month, a time interval almost 20 times shorter than the typical duration of treatment. As a result, the effect of corrosion processes and mechanical phenomena such as wear and fatigue on the release of Ni could not be elucidated.[68]

Saliva sampling in those studies was performed at discrete time points, resulting in a notable lack of continuous and cumulative data extending over a wide time period.[27,28]

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FIGURE 8. Tapping-mode three-dimensional atomic force microscopic images of nickel-titanium archwires (x and y directions: 20 μm per division; z direction: 0.75 μm per division). (a) As-received wires. (b) Wires retrieved after six months of intraoral exposure. Note the rough topography of the retrieved wire illustrated.

TABLE 2. Classification and Hypothesized Mediation of Nickel's Biologic Effects [a]

Oxidative Stress Mechanisms	DNA Damage Mechanisms
Induction of Cap43 (hypoxia-regulated gene)	Promotion of DNA strand scission (single strand breaks)
Induction of HIF	Induction of p53 and K-Ras alterations
Elevation of lipid peroxidation	Inhibition of DNA repair enzymes (eg, 8-oxo-2′-deoxyguanosine)
Release of lactate dehydrogenase	Increase in DNA methylation
Increased acetaldehyde formation	Induction of silent gene expression by chromatin condensation, incorporation of critical genes into heterochromatin, and methylation of DNA, resulting in silencing genetic activity necessary for the maintenance of normal cellular functions
Possible implication of oxidative stress factors (Ni-resistant cells show reduced binding to NFκB and AP-1)	
Histone hydrolosis and inhibition of histone H_4 acetylation	

[a] HIF indicates hypoxia-inducible factor; NFκB, nuclear factor kappa B.

TABLE 3. Methods for Studying Nickel Release From Nickel Containing Alloys

Environment	Method	Reliability and Clinical Relevance
In vitro	Weighing before and after immersion in solvent solutions or acids (HCl, lactic acid)	''Blind'' method; no information on what is actually released; no information on mechanism; lacks clinical relevance (oral flora, plaque, and calcification processes are not integrated in the model)
	Same as above, but the Ni is detected in solution by spectroscopic methods	Lacks clinical relevance; no information on the status of released Ni (free vs compounds) which largely affects its reactivity
	Estimation of Ni leached from alloys in nonagitated, nonreplenished storage media	The Ni leached rapidly reaches a plateau level because of the establishment of equilibrium between ions present in the solution and the alloy-solution interface; false description of release kinetics; lacks clinical relevance
Retrieval (ex vivo study of in vivo–aged specimens)	Elemental mapping of Ni content in specimens retrieved after intraoral placement and in as-received specimens	It is hypothesized that the missing Ni has been leached; no information on mechanism; clinically relevant
In vivo	Measurement of salivary Ni levels in patients before and after initiation of treatment or comparison of levels with those in a control population	Provides information about Ni levels in the first ''diluting pool'' of the human body; sample must be followed in treatment for extended period of time to collect cumulative data and allow an estimate of the effect of material aging and fatigue on Ni release; clinically meaningful
	Measurement of urinary or serum Ni levels in patients before and after initiation of treatment or comparison of levels with those in a control population	Provides information about Ni levels after excretory clearance; decreased values may be mistakenly attributed to low release levels and not to low Ni excretory clearance associated with accumulation in an organ

Moreover, the protocol for saliva collection, which involved stimulation though chewing on a piece of paraffin wax or gum, inevitably restricted the collection of saliva to that secreted almost directly from the salivary gland. This effect arose from the lack of saliva wetting of the oral cavity, including teeth, limiting the exposure of appliances to salivary flow. A final comment concerning this type of study may relate to the fact that short-term release patterns have proven to have poor predictive value for the long-term release potential. Recent evidence has shown that for multiple-phase alloys, long-term release may be higher than that occurring within the first week, whereas single-phase alloys present various release patterns with increasing or decreasing rates depending on the element released.[69] Therefore, the results of studies employing time intervals within the one-month range for the investigation of ionic release should be treated with skepticism.[70]

Ni HYPERSENSITIVITY IN THE ORTHODONTIC PATIENT

The issue of Ni hypersensitivity reactions in orthodontic patients has been reviewed in the literature during the last 10 years.[71–85] However, the majority of evidence on this adverse effect associated with conventional orthodontic appliances has been derived from scarce case report types of articles. These individualized reports have indicated that insertion of NiTi wire alloys may occasionally lead to formation of rashes, swelling, and painful erythematous lesions in the oral and labial mucosae (Figure 10).[5–7] Other case reports have implicated Ni, Co, and Cr. However, case reports may be misleading owing to the individual variability frequently found among different populations.

Most of our knowledge about the Ni-induced hypersensitivity reactions on a larger scale originates from studies by several authors that have exhaustively examined the is-

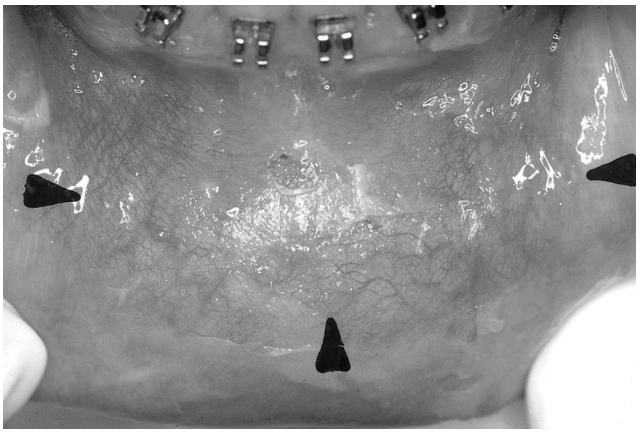

FIGURE 10. Erythematous swelling of the anterior region of the lower lip of a patient after bonding of stainless steel brackets and insertion of a nickel-titanium wire alloy. For this patient, recommended management consists of bonding with titanium, nonnickel stainless steel, or nonmetallic (plastic or ceramic) brackets along with the use of β-titanium (titanium molybdenum alloy) wires.

sue of hypersensitivity to metals in relation to dentistry for both patients and operators.[21,27,28,32,68,71,76,77] A survey among Norwegian orthodontists showed that dermal reactions such as redness, itching, eczema, fissuring, and desquamation most often could be attributed to metal parts of extraoral appliances and that such reactions were more frequent than intraoral reactions.[69–74] The general frequency of patient reactions was estimated to about one in 100; however, the authors projected a lower prevalence for patients and personnel because of material improvements such as the coating of extraoral metal parts.[72,73]

The same authors have also noted that the relationship between sensitization by a potential allergen at an early age and the reaction obtained after a new contact is not always straightforward. Many observations indicate that early contact with potential allergens may actually lead to a diminished probability for allergic reactions later in life.[73,74] In orthodontics, the tolerance concept has been introduced to explain observations associated with Ni reactions. Nickel-containing jewelry worn at an early age may induce sensitization of prospective orthodontic patients.[82] Ear piercing, which is very common among adolescent girls, may enhance the prevalence of these sequelae.[76] However, there are indications that orthodontic treatment with Ni-containing metallic appliances before sensitization to Ni (ie, ear piercing) may lower the incidence of Ni hypersensitivity.[75,81,85] The study of the medical histories of a more than 1000 female orthodontic patients receiving treatment showed no Ni allergic reaction of the oral mucosa.[81] The majority of the girls with nonspecific mucosal reactions and skin lesions had atopy with chronic dermatitis.

Nonetheless, the tolerance concept does not exclude the possibility of allergic reactions after orthodontic treatment after a previous sensitizing contact with Ni has occurred.[74,79] However, the current consensus about the issue of orthodontics-derived Ni as a sensitizing agent is that the risk is extremely low for patients who are not Ni hypersensitive at the start of orthodontic treatment.[73,76–79] Tolerance to Ni in these individuals may be related to its slow long-term release from orthodontic appliances.[72]

Currently, there is a lack of data linking directly the prevalence of Ni-induced side effects in nonsensitized individuals with the insertion of orthodontic materials. However, for patients who have a history of hypersensitivity, we suggest the use of the Ni-free alloy substitutes or Ni alternatives listed in Table 1.[23,82,83] In general, the clinical manifestations of Ni hypersensitivity are easy to diagnose, and extraoral or intraoral appliances containing Ni must be removed after the development of dermal or mucosal signs in the form of rashes or swelling. Administration of cortisone-based substances to counteract hypersensitivity has been shown to affect the tooth movement process, reducing the movement rate, and this administration should be avoided if the symptoms are not severe.[80,84–86]

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