Hypersensitivity to Dental Alloys

22

Joris Muris and Cees J. Kleverlaan

22.1 Introduction

Dental elements or teeth may decay mainly due to caries or trauma. A broad variety of dental appliances can be used to restore or replace decayed or missing elements. These appliances may be made of resin-based materials, composites and ceramics, or partially or fully made of alloys. Alloys are by definition composed of more than one metal, and dental alloys usually contain at least four metals and often six or more, making them metallurgically complex [1]. These dental appliances are in use for years to decades. In this section, the different dental appliances are briefly reviewed, and the most important metals used in dentistry are discussed. Most of these metals are reviewed in detail in other chapters of this book. Finally, the path from corrosion to clinically relevant findings is discussed. Specific oral mucosal immune responses are considered in terms of the clinical picture of hypersensitivity to dental alloys.

J. Muris (✉) • C.J. Kleverlaan
Department of Dental Materials Science, Academic Centre for Dentistry Amsterdam, VU University Amsterdam and University of Amsterdam, Gustav Mahlerlaan 3004, 1081LA Amsterdam, The Netherlands
e-mail: j.muris@acta.nl

22.1.1 A Brief Overview of Dental Applications

An enormous variety of dental applications are available to restore or replace decayed dental elements. Dental applications can be categorized as dental restorations or dental fillings, fixed dental prostheses (FDP), removable dental prostheses (RDP), dental implants and orthodontic appliances.

Dental restorations or *dental fillings* are initially applied in a soft form intraorally (*direct method*). The two main filling materials used nowadays are dental amalgam and composite. The setting of amalgam occurs because of a chemical reaction between mercury (Hg) and a silver-tin-copper (Ag-Sn-Cu) alloy. The resin-based materials are cured due to a polymerization reaction, initiated by blue light in the range of 400–500 nm. The quality, in terms of mechanical properties and 'biocompatibility', of amalgam and composite restorations is to a large extent operator dependent.

Fixed Dental Prostheses (FDPs) or (partial) dental crowns and bridges are applied to teeth that are severely decayed or to replace lost and/or missing teeth. These restorations are fabricated outside the mouth (*indirect method*) and then fixed with cement onto the tooth. These constructions can also be cemented or screwed to endosseous dental implants (see below). Mostly, these constructions are made of alloys and are often veneered with porcelain. The veneers may complicate the diagnosis of adverse reactions because such restorations can be difficult to distinguish from natural

J.K. Chen, J.P. Thyssen (eds.), *Metal Allergy*, https://doi.org/10.1007/978-3-319-58503-1_22

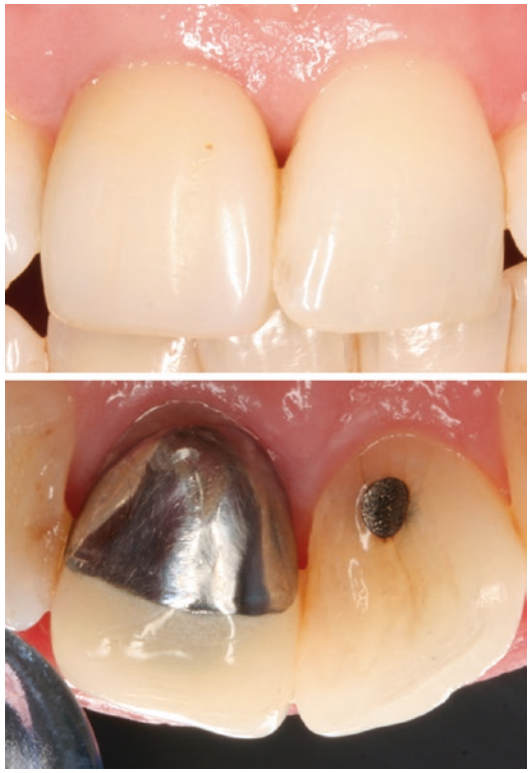

Fig. 22.1 Clinical pictures of buccal and palatal sides of front teeth. The *left element* is restored with a metal porcelain crown. The *right element* is a natural tooth with a small palatal amalgam filling. From a buccal perspective, it is not possible to distinguish the crown from the natural tooth. Of note, often also the palatal part of the crown is veneered with porcelain

teeth (Fig. 22.1). There is a huge arsenal of dental alloys available, which are roughly divided into high-noble, noble and base metals and titanium (Ti) alloys (according to the American Dental Association's revised classification system for fixed prosthodontics (2)) (Table 22.1). High-noble (or gold (Au)-based) alloys largely consist of Au and are mostly alloyed with platinum (Pt), and/or palladium (Pd). The price of these materials is high, and their use is therefore limited. Noble, predominantly Pd-based alloys are usually a composition of Pd with Au, Ag, Cu and/or gallium (Ga). This group of alloys is probably most popular, as they combine fair prices with presumed 'biocompatibility'. Base metal alloys, like stainless steel and nickel-titanium (Ni-Ti) alloys, are mainly used in orthodontics. Still, nickel-chromium (Ni-Cr) and chromium-cobalt (Cr-Co) alloys are abundantly used for FDPs due to their low prices. Ti and its alloys are considered 'biocompatible' and are mainly used for endosseous dental implants and supra-structures.

Removable Dental Prostheses (RDPs) are appliances that replace multiple lost/missing teeth. Complete RDPs (or full/complete dentures) replace all teeth in one jaw and are mostly made of resin-based materials, i.e. polymethylmethacrylate (PMMA). Partial RDPs (or partial dentures) replace one or multiple missing teeth and often consist of a metal base or core structure that is finished with PMMA. They are attached to remaining teeth and/or implants by clamps, 'click systems' or magnets. Such appliances are usually made of Cr-Co alloys (called Vitallium®) or are Ti-based to provide sufficient strength and stiffness. For parts of these constructions, such as mounting bars between implants, other alloys can be used.

Dental implants are basically Ti (alloyed with vanadium (V) and aluminium (Al)) screws anchored in the mandibular or maxillary bone (endosseous). On the implant, a so-called abutment is placed which is usually made of Ti, but other alloys or zirconium (Zr) may be used. The abutment connects the implant with the supra-structure, like a crown/bridge or removable prosthesis, which in turn can be made of a different material (Fig. 22.2).

Orthodontic appliances are used to move teeth to a more functional or aesthetic position within the jaw. Typically stainless steel (316L) is used in combination with flexible alloys like Ni-Ti. Active orthodontic appliances are usually in situ for approximately 2–3 years. However, to retain the treatment result, a retention wire is often placed behind the frontal teeth, which remains in situ for decades. These retainers are commonly made of stainless steel.

22.1.2 Metals Used in Dental Applications

While metals such as Au and Pt were used more extensively in the early twentieth century, their use has been gradually replaced with other metals and Pd, in particular, during the last decades [3]. The choice of metals depends on the purpose

Table 22.1 Classification of dental alloys based on weight percentage according to the American Dental Association (ADA) [2]. Thousands of different dental alloys exist, for which a great diversity of metals is used

Classification	Percentage of noble metals	Subgroups	Most important components
High noble	≥60% Au + Pt + Pd (>40% Au)	Au-based alloys	Au-Pt Au-Pd
		Pd-based alloys	Pd-Au (>40 Au)
Titanium (alloys)	>85% Ti	Commercially pure Ti	Ti (>99%)
		Ti alloys	
Noble	≥25% Au + Pt + Pd	Pd-based alloys	Pd-Au (<40 Au) Pd-Ag Pd-Cu
		Ag-based alloys	Ag-Pd
Base metal	≤25% Au + Pt + Pd	>20% Cr	Ni-Cr
		<20% Cr	Ni-Cr
		Cr-Co (e.g. Vitallium®)	Cr-Co
		Stainless steel[a]	Co-Cr-Ni of Cr-Ni
		Ti alloys	Ni-Ti[a]

[a]Mostly applied in orthodontics; noble metals: gold (Au), palladium (Pd), platinum (Pt); base metals: chromium (Cr), cobalt (Co), copper (Cu), nickel (Ni), silver (Ag), titanium (Ti)

(restoration, implant, orthodontics, etc.), but it also varies significantly between countries depending on the culture, health care system, demand and level of income. Metal-fused-to-porcelain crowns are still the most abundantly used type of dental crowns, although zirconium oxide-based (ceramic) crowns are gaining popularity. Overall, there seems to be an ever-increasing variety of products and alloys produced by the dental industry, and to date thousands of different alloys have been produced. The metal composition of dental work is complex and diverse. It may be difficult to ascertain the composition of dental alloys in individual patients. Consulting the patient's dentist will be helpful. The composition of intraoral alloys may be determined using scanning electron microscopy (SEM) and energy dispersive X-ray analysis (EDAX) [4]. In this so-called microanalysis, a microscopically small sample is taken from the restoration. The most important metals used for dental appliances are summarized below (Table 22.1).

Gold (*Au*) is a noble metal that, due to its soft and malleable properties, needs to be alloyed with metals like copper, platinum and/or Pd. From a dentist's point of view, Au alloys are still the first choice due to their optimal mechanical properties. Gold is one of the least reactive metals. Still, sensitization to Au is frequently observed in patients tested with metal series [5–7]; however, this is rarely relevant for ACD, and its relevance in oral disease is still unclear [8]. Nevertheless, sensitization to Au seems to be related to oral lichenoid lesions [9] and to exposure to dental Au [10].

Platinum (*Pt*) is an important strengthening component of Au alloys. Platinum rarely causes ACD but may play a role in IgE mediated allergy and adverse reactions to drugs.

Palladium (*Pd*) is a noble metal that is widely used in dentistry as a substitute for Pt and Au. Palladium is a hard metal that, like Pt, adds strength to alloys. It has a white appearance and is metallurgically compatible with Au and therefore useful in Au alloys. Dental alloys may consist up to 90 wt% Pd [11–13]. Sensitization to Pd is related to exposure to dental crowns [14] and oral disease [15].

Cobalt (*Co*) is an important constituent of Vitallium®, an alloy trademark (60% Co, 20% chromium (Cr), 5% molybdenum (Mo) and other metals) that is commonly used for metal-based removable dental prostheses. Similar to Ni-Cr alloys, Cr-Co alloys are also used for fixed dental prostheses, especially for financial reasons. Some alloys used in orthodontics may contain Co. There is an ongoing debate whether or not Co allergy has clinical relevance in oral disease [16], as allergic reactions are usually related to consumer products and occupational exposure [17].

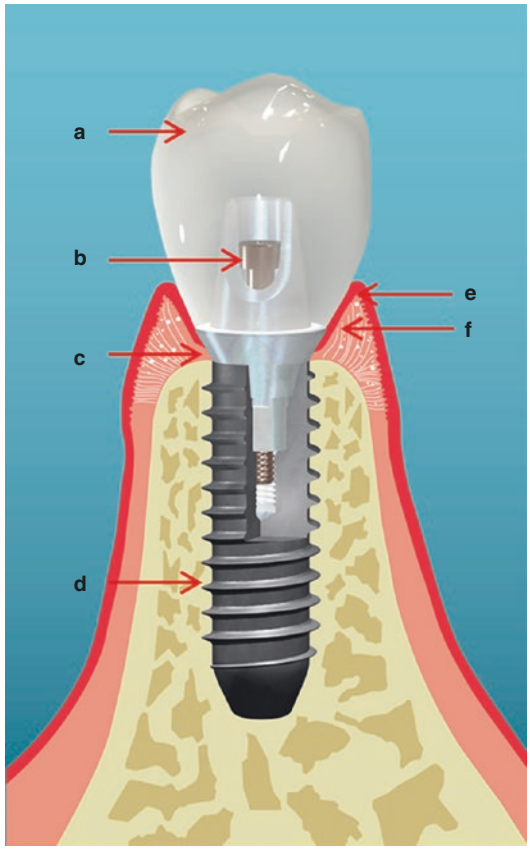

Fig. 22.2 Schematic representation of implant-crown construction in bone and gingiva. (**a**) The dental crown can be made from various materials including metals. (**b**) The abutment screw fixes the abutment to the implant (mostly made of titanium alloy). (**c**) Abutment to support the crown and to connect it to the implant (mostly made of titanium alloy). (**d**) Dental implant in the bone to replace the lost natural root. (**e**) Indicates the dental sulcus (max 1 mm). (**f**) Junctional epithelium towards the bone (1–2 mm)

Chromium (*Cr*) is a part of stainless steel (18–25%) and abundantly used in orthodontics. Furthermore, it is a constituent of Ni-Cr alloys as mentioned above, and Co-Cr-Mo alloys (Vitallium®) are typically used in fixed and removable prostheses in dentistry. Chromium easily oxidizes, resulting in a passivation layer, which prevents corrosion. Sensitization to Cr generally manifests in dermatitis from contact with leather products or occupational exposure [17].

Nickel (*Ni*), like Cr, is a component of stainless steel alloys (8–14 wt%) and is widely used in orthodontics for brackets, headgear and other parts, such as orthodontic retention wires. In contrast to the active orthodontic appliances, retention wires remain in situ for decades or even a lifetime. Nickel is well known to be prone to corrosion, especially in the aggressive oral environment [18]. It has been shown that these retention wires can release great amounts of Ni in experimental scenarios [19] and could also be responsible for extra-oral eczema even in the absence of local reactions [20]. Ni-Cr alloys are still widely used for fixed dental prostheses, especially for financial reasons [18]. Sensitization to Ni is common and clinically relevant in the oral cavity.

Titanium (*Ti*). The vast majority of endosseous dental implants are made of commercially pure Ti (>99 wt%) or its alloys like Ti6Al4V (Ti with 6 wt% aluminium and 4 wt% vanadium). Abutments, used to connect implants to the suprastructures, are also mostly made of Ti or its alloys. Titanium surfaces, even when alloyed, immediately oxidize when exposed to air. This oxidation creates a passive layer, making the metal resistant to corrosion. Still, this passive layer (10–20 nm) can be easily affected by many influences such as mechanical forces, exposure to high concentrations of fluoride and corrosion [21, 22]. Titanium allergy has rarely been identified as an allergen in oral disease using patch testing [23, 24], most probably due to the use of or instant formation of TiO_2 from other Ti test salts, which does not penetrate the skin [25, 26]. Notably, TiO_2 has been shown to penetrate the oral mucosa [27, 28]. In in vitro assays such as lymphocyte proliferation or transformation test assays, (LPT/LTT), sensitization to Ti was frequently diagnosed (4.2–42%), although the clinical relevance of these positive test results is unclear [29, 30]. Still, of 56 patients who developed health problems after dental implant insertion, half showed increased Ti-induced lymphocyte proliferation. Ti-positive patients who had their implants removed showed considerable health improvement [31]. At this time, Ti patch testing is unreliable.

22.2 Corrosion in the Oral Cavity

Corrosion is an inevitable chemical reaction between the oral environment and dental alloys. When an alloy is susceptible to corrosion, large

amounts of corrosion products, i.e. metal ions, are released in the local environment. Further distribution of the metal ions into biological tissues may lead to adverse reactions either locally or systemically. It is important to emphasize that corrosion of dental restorations differs from dental implants. Corrosion products from restorations are released into saliva and may penetrate the tissue, whereas corrosion products from dental implants are released directly into the body by definition.

A well-known example of corrosion of dental alloys is the greyish discoloration of teeth restored with dental amalgam and the marginal breakdown of amalgam restorations. Less known is the corrosion of dental cast alloys that may contain both noble and base metals, such as Ni, Pd, Cr, Co, Au, Ti and many more. Despite the nobility of certain metals, all metals will corrode (to some extent) in the aggressive oral environment [1, 32].

Notably, tarnish is a surface discoloration resulting from hard and soft tissue deposits, like sulphides and chlorides, and is easily removed by polishing. Tarnish does not cause material breakdown. In contrast, corrosion is a chemical reaction and is always accompanied by material breakdown.

The most important difference between corrosion at the skin versus the oral mucosa is the constantly wet conditions of the latter. Saliva contains multiple dissolved oxidisers like oxygen that withdraw electrons from the metal/alloy. The extraction of electrons results in a positively charged metal surface, resulting in the release of positively charged metal ions into the saliva.

Basically, two main localized wet corrosion processes occur in the oral cavity: firstly, galvanic corrosion that is driven by the electrochemical potential between two connected metals or alloys; and second, crevice corrosion that is driven by an oxygen concentration gradient within one metal or alloy. These processes may work simultaneously on one metal or alloy and are further enhanced by the hostile oral environment. Since corrosion processes are described in detail in Chap. 2, here the specific environment of the oral cavity is discussed.

22.2.1 Galvanic and Crevice Corrosion

Galvanic, bimetallic or contact corrosion occurs when two dissimilar metals or alloys are placed in direct contact in the presence of an electrolyte, like saliva or other body fluids. The driving force is the electrochemical potential between the dissimilar alloys. This results in dissolution of the metal at the anode (less noble metal). The free electron will travel through the contact area of the two metals towards the cathode (noble metal) and will there be released into the environment. Thus, the electron exchange occurs through the contact point and the metal ion exchange through the electrolyte. Notably, some alloys are called 'multiple-phase' alloys. Within these alloys, different 'phases', e.g. areas with dissimilar compositions, coexist, resulting in galvanic corrosion within the alloys itself. Obviously, these multiple-phase alloys are more prone to corrosion than single-phase alloys [1, 33]. Clinically, galvanic corrosion plays a role in many situations. Often dental alloys are in direct contact to each other; for example, when an amalgam filling is situated directly next to a gold dental crown. Also, opposing restorations may contact one another during mastication, grinding and clenching. Notably, mechanical wear accelerates corrosion processes due to the local breakdown of the passive layer [34]. Many dental constructions are an assembly of two or three different alloys. For example, a dental crown may be in contact with a core build-up or implant abutment, which again is connected to the implant itself (Figs. 22.2 and 22.3). All three alloys may be of different composition. If the alloys are not in direct contact, galvanic corrosion may still occur since the restorations are connected via the oral tissues and saliva. Of note, the presence of multiple dental alloys in one patient is very common (Fig. 22.4).

Crevice corrosion of a dental alloy occurs in the small sheltered volume of a crevice. Basically, the process is similar to pitting corrosion and is driven by an oxygen gradient between the crevice surface, i.e. a place with a low oxygen concentration, and the bulk surface of the alloy. In a crevice, unstable metal chlorides are formed that tend to hydrolyse, resulting in an increase of H^+ ions.

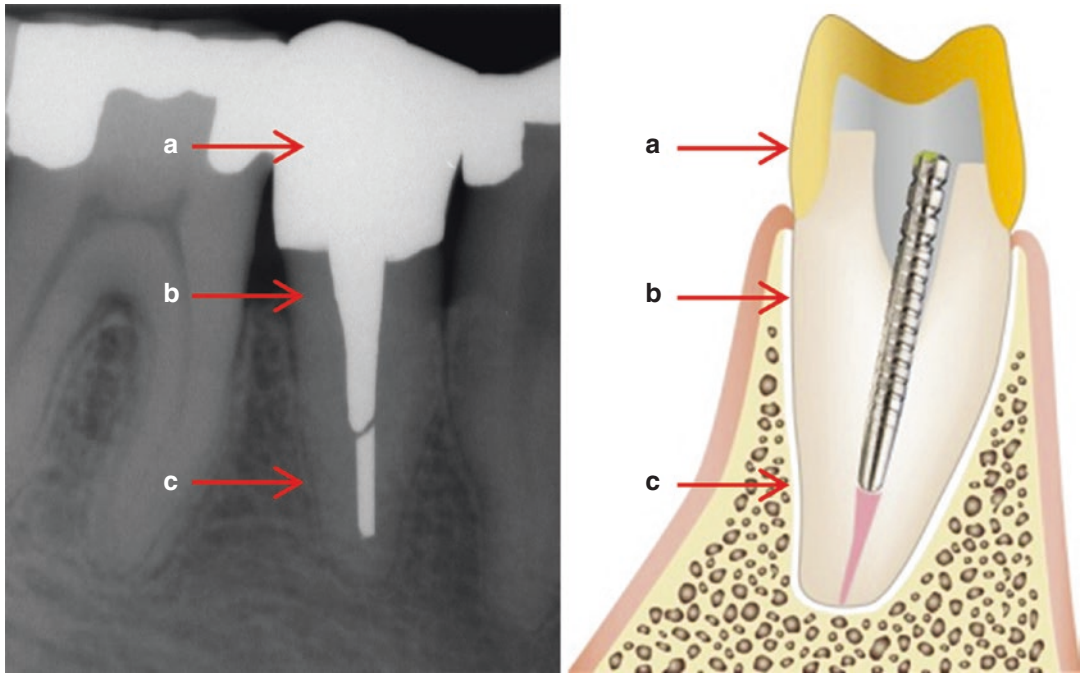

Fig. 22.3 (*Left*) X-ray picture of solitary lower premolar (with parts of neighbouring elements). (*Right*) Schematic representation of the X-ray (©ACTA – Dept. of Oral Implantology and Prosthetic Dentistry). (**a**) Metal-based crown. (**b**) Metal core structure. In some cases, the metal post may be cast onto the core (*right picture*). In that event, two different alloys are cast to each other. This is radiographically not visible. (**c**) Silver point of root canal filling

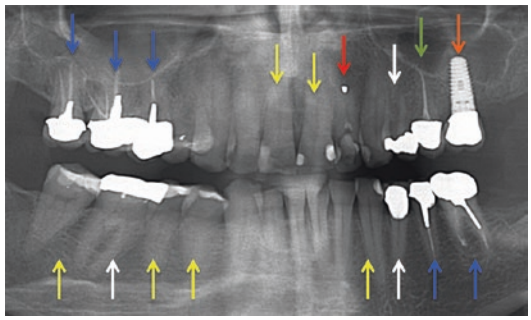

Fig. 22.4 Ortho Pantomo Graph (OPG; X-ray) showing the upper and lower jaw with teeth and molars from one patient. *Yellow arrows* indicate elements with resin composite filling. *White arrows* indicate elements with metal-based dental crowns. *Green arrow* indicates element with root canal filling and metal-based crown. *Blue arrows* indicate elements with root canal fillings, metal core and metal-based crown. *Red arrow* indicates element with retrograde root canal filling, in this case amalgam (small *white spot* at the apex of the root). Of note, theoretically all these metal structures could be composed of different alloys

This acid environment further accelerates the corrosion processes. Examples of crevices in the oral cavity are propagated pits, scratches in the alloys due to wear or insufficient finishing in the dental laboratory, interdental spaces or close contact areas between different parts of the restorative structures.

There is a specific oral microenvironment where crevice corrosion has a particular biological impact. Dental restorations or crowns often extend below the level of the gingiva into the gingival sulcus. This is a physiologically occurring sulcus or crevice. It is the interface between a tooth and the surrounding gingiva (Fig. 22.2). The oral tissues are here coated with the sulcus epithelium that has great similarity with the gingiva, being a stratified squamous keratinized epithelium. Further towards the apex of the dental root, at the base of the gingival sulcus, lies the so-called junctional epithelium (JE), providing the ultimate transition from the outside to the inside of the body. The JE maintains a tight seal against the mineralized tooth surface, i.e. enamel, with hemi-desmosomes, called the 'epithelial attachment'. It tapers off in the apical direction and consists of 15–30 cell layers coronally and only 1–3 cell layers at the cement-enamel junction [35]. It is a stratified squamous non-keratin-

ized epithelium that is made up of two strata only: a basal layer and supra-basal layer; it lacks membrane-coating granules and is therefore highly permeable and assumedly much more permeable than the floor of the mouth. As the cells are interconnected by a few desmosomes only, the intercellular spaces are relatively wide, allowing for fluid secretion and transmigration of leucocytes. These leucocytes form the basis for the crevicular fluid, which comprises the first line of peripheral host defence against the bacteria in this area. In a situation of inflammation, the epithelial attachment may be lost, or the JE may even get disrupted due to either increased fluid flow or bacterial products and leucocytes passing through [35]. The JE has been shown to be permeable to a variety of materials ranging from carbon particles [36] to proteins [37], especially when the tissue is inflamed. Importantly, the underlying connective tissue has a dense capillary network, which assumedly helps corrosion products to enter the bloodstream.

22.2.2 Patient Factors

Unlike the skin, the mouth comprises an ideal environment for corrosion processes to occur. The constant presence of saliva, with corrosive compounds like hydrogen, chloride ions, sulphide compounds, dissolved oxygen and free radicals, enhances the corrosion of dental appliances, which in turn leads to metal exposure. Consumption of foods and beverages results in constant fluctuations in acidity (pH 1.5–8.0) and temperature (0–60 °C), which also contributes to corrosion processes. Especially Ni release from dental alloys is greatly enhanced by pH values between 1–4 [32, 38]. For example, cola has a pH around 1.5, but also fruit juices are commonly acidic. The presence of proteins like serum albumin was also found to increase elemental release from dental alloys [39, 40]. Serum albumin plays a fundamental role in the distribution of transition metals, including Pd, in the human body [41].

Individual general health aspects may also play a role in corrosion processes. For example, it is well known that xerostomia, independent of its aetiology (such as Sjögren's syndrome or as an adverse effect of many pharmaceutical drugs), decreases the saliva's pH and its buffering capabilities [42]. Hypertension has also been linked to decreased pH in unstimulated saliva [43]. Oral hygiene can also enhance corrosion. For example, fluoride ions, a key element in cavity prevention, are known to attack the passive oxide layers of Ti, Cr and Co alloys in vitro, when concentrations rise above the range of 0.05–0.2% [22]. Furthermore, it has been shown that tooth brushing also increases metal ion release, especially when abrasive toothpaste is used [44–46]. Inversely, no tooth brushing also enhances corrosion as it was found that *Streptococcus mutans*, a lactic acid-producing bacteria and the primary contributor to dental decay, colonizes within 24 h Ni-Cr alloys. Due to the lactic acid production of these bacteria, the metal ion release was increased, causing cytotoxic and pro-inflammatory cell responses [47]. On top of that, accumulation of dental plaque will promote crevice corrosion due to local low oxygen availability.

22.2.3 In Vivo Ion Release and Uptake

Although the mechanisms of corrosion are theoretically well known, due to individual, clinical and alloy-production-process variables, the exact in vivo corrosion mechanisms remain complex, and it is difficult to obtain reliable figures on in vivo metal ion release. The oral tissues do not absorb most of the released ions, as they are diluted by saliva. Still, as dental restorations often extend below the level of the gingiva within the gingival sulcus, micro-environments are formed where ion concentration can reach high levels due to the absence of saliva [1]. Moreover, biologically adverse effects can be enhanced due to direct cell contact [48]. It has been clearly shown that exposure to dental amalgam is associated with increased levels of Hg in blood, plasma, urine and body organs as compared to people with no dental amalgams [49, 50] and that urinary Hg levels decreased after amalgam removal to levels similar to those of patients who never had an amalgam filling [51, 52].

Furthermore, some reports provide evidence for considerable absorption of released metal ions from high-noble or noble dental alloys. Significantly higher levels of Au and Pd were found in gingival tissues adjacent to dental cast restorations compared to control groups [53]. Cristaudo et al. found significantly higher concentrations of Pd in saliva, blood serum and urine in six patients with Pd-containing dental restorations relative to negative control groups [54]. Drasch et al. found that the Pd and especially the Au content of body fluids, i.e. resting saliva, chewing saliva, serum, whole blood, morning urine and faeces, were correlated to the number of high-noble or noble dental alloys. The calculated maximum of Au and Pd in one day's saliva of 1.38 mg and 70 μg, respectively, was found. They concluded that for Pd, the composition, rather than the number of restorations, might be the critical factor for ion release with subsequent increased concentrations of Pd in body fluids [55]. It has been calculated that exposure to Pd in the general population is mainly caused by dental restorations [56], and Pd-based dental alloys were shown to release up to 80 ng cm^{-1} per day in artificial saliva [57–59]. Likewise, for Au, the number of Au-based inlays (*indirect fillings*) is related to the concentration of Au in the blood, even after many years [55, 60]. Furthermore, it has been reported that the Au concentration in blood positively correlates to patch test reactivity [61, 62].

A final remark in this context should be made. The production process in the dental laboratory importantly influences the in vivo release of metal ions. The casting process itself has been shown to double the Pd release from Pd-Ag alloys [63]. Then, during the veneering process, corrosion resistance may further drop [64]. Also, reuse of casted alloys may be insidious to the corrosion resistance [65]. Most of the literature on corrosion resistance of dental alloys investigated the alloys that were directly obtained from the manufacturer, which can be misleading for the in vivo situation.

In summary, the complex corrosion processes occurring in the oral cavity are difficult to quantify in vitro and in vivo. Still, it is fair to say that substantial metal ion release will take place for all dental alloys, and some, including Au and Pd, will be at least partially absorbed by the body. Furthermore, corrosion is a continuous process that increases with time, especially in the case of crevice or pitting corrosion. It is well established that the release of Ni from dental casting alloys is most common.

22.3 Adverse Reactions to Dental Alloys

Norway, Sweden and the United Kingdom have national reporting systems for adverse reactions to dental materials. In the USA, such a system is executed by the Food and Drug Administration (FDA), although it is a part of MedWatch [66] and, as such, also records reports about the malfunction of dental devices [67]. An overview of the data obtained from European reporting systems showed that patients with subjective and objective complaints attributed to their dental materials were 70–80% female, and the most commonly affected age groups were 40–49 and 50–59 years of age for both men and women. Similar data was found in Tokushima, Japan [68]. The vast majority of the reports concerned dental alloys [69].

Nearly all metals used in dental alloys may cause hypersensitivity in humans; the most common ones are Ni, Cr, Co, Pd, Au, Ti and Hg. Especially for dental crowns and bridges, a huge arsenal of alloys are available on the dental market, all using different compositions. Of all metals, Au and Pd are of special interest in this context. When exposed to the skin, like in jewellery, these noble metals have good resistance to dry corrosion, and, therefore, they are well tolerated even in hypersensitive patients. In the aggressive oral environment, however, these metals will corrode, leading to possibly relevant exposure. Indeed, particularly hypersensitivity to Au and Pd has been associated with dental alloys and subsequent adverse oral reactions [10, 14, 70–74].

Palladium is known to cross-react with Ni [75–80]. When with patch testing instead of $PdCl_2$ the more sensitive test allergen (Na_2PdCl_4) is used, it becomes clear that cross-reactivity between these metals is not absolute, and about

25% of the Ni and Pd sensitized patients are mono-sensitized to both metals [81–83]. In contrast to Ni, Pd sensitization is not associated with the female gender, suggesting a different source of exposure [81]. Palladium and not Ni mono-sensitization is related to exposure to dental alloys and dental crowns in particular [14, 15, 17, 56]. Interestingly, in a European multicentre study, it was shown that from 906 dermatology patients with dental alloys (n = 496), 44% suffered from metal ACD, in comparison to only 28% of dermatology patients without dental alloys (n = 410) [14]. For those patients with dental crowns, the percentage was even higher, i.e. 52%. Perhaps exposure to dental alloys could lower the patient's threshold for elicitation via the skin, or systemic ACD could play a role. Not only is Ni widely used in dental alloys, oral Pd exposure could lower the threshold for Ni elicitation in the case of cross-reactivity.

Both local and systemic symptoms have been attributed to adverse reactions to dental alloys in the scientific literature [14, 70, 72, 84, 85]. However, none of these are specific or pathognomic manifestations [7, 86–88] nor is it clear whether these reactions result from innate immune responses or hypersensitivity to specific metals in dental alloys. Importantly, diagnostics may also be blurred by tolerogenic immune responses of the oral mucosa.

22.3.1 Innate Immune Responses

Nickel ($NiCl_2$), palladium (Na_2PdCl_4) and cobalt ($CoCl_2$) have been shown to induce innate immune responses by triggering TLR4 on human monocyte-derived dendritic (MoDC) cells measured by elevated pro-inflammatory cytokine IL-8 release [89, 90]. Gold ($Na_3Au(S_2O_3)_2.2H_2O$) was found to induce substantial IL-8 release by triggering TLR3 from MoDC, PBMC and THP-1 cells [91] on both skin- [92, 93] and gingiva-derived keratinocytes [94]. Subsequently, it was shown that ionized Au was a strong innate activator of human keratinocytes [94]. Thus, epithelial TLR3 is likely to play a key role in both skin- and mucosa-localized irritation reactions to Au.

Human MoDC and THP-1 cells were cultured on top of different dental alloy specimens (Ni-Cr, Co-Cr, Pd-Cu, Pd-Ag, Ti-6Al-4 V, amalgam, Au-alloy and stainless steel). All dental alloys induced significantly elevated IL-8 production in both MoDC and THP-1 (except for Cr-Co) cells, with Au and Pd-Cu providing the strongest stimulation. Even in 24 h alloy-exposed non-corrosive culture media, all alloys, except Ni-Cr and stainless steel, resulted in significantly elevated IL-8 production [95]. Also, Au, Pd-Cu, Pd-Ag, Ti-6Al-4 V and amalgam were effective in potentiating LPS responsiveness [95]. These findings might explain why oral exposure to Au-, Pd- and Ti-based dental alloys is associated with local non-dental plaque related inflammatory responses in the absence of hypersensitivity.

22.3.2 Tolerogenic Immune Responses of the Oral Mucosa

Oral mucosal DCs have a unique repertoire of receptors that induce tolerance rather than inflammation [96]. They express high affinity receptors for IgE that upon ligation lead to IL-10 and TGF-β production, which is necessary for the induction of Tregs [97]. Also, oral DC activation by TLR-4 (by LPS) will induce Tregs expressing FOXP3, IL-10 and TGF-β [98]. Oral DCs express constitutively more B7.H co-inhibitory molecules and thereby contribute to immune-silencing [98]; their expression is up-regulated by ligation of TLR-4 [97]. B7.H inhibits T-cell activation through binding with CD28.

The clinical outcome of these tolerogenic properties of the oral mucosae is observed in patients who had orthodontic treatment or oral exposure to Ni prior to ear piercing, resulting in decreased levels of sensitization to Ni compared to ear-pierced patients without previous orthodontic treatment [99, 100]. In a guinea pig study, it was shown that oral tolerance resulted from antigen-specific immunosuppression and was induced more effectively after direct contact with the oral mucosa (using an ointment) than via feeding [101]. In a murine study, tolerance to Ni was effectively achieved by intra-gastric feeding

of Ni [102]. Even Ni-releasing cages and drinking nipples were sufficient to induce tolerance for this metal in mice [102].

Another important factor that influences immune response is age. From studying the skin, it is known that the number of DCs decreases with age, possibly in response to UV exposure. Even though UV exposure is not likely to occur in the oral cavity, a considerable decrease in DCs was still reported in subjects older than 40 [103], which might be why oral diseases are more frequently observed in the elderly. The induction of oral tolerance was found to be less effective in older guinea pigs compared to younger animals [101].

Finally, effector T cells are strongly biased towards skin migration rather than towards mucosal surfaces [104, 105]. This may explain the systemic complaints from hypersensitivity to dental alloys in absence of local symptoms or lesions as illustrated by several case reports [20, 106–109]. One report describes a 54-year-old Taiwanese woman who suffered from full-body annular erythema for 15 years; her condition was alleviated almost immediately after one Pd-containing dental inlay was removed. No flare-up reactions occurred for 2 years following [108]. A Japanese retrospective study reported that in patients suspected of having an allergy to metal in dental alloys, pustulosis palmaris et plantaris/dyshydrotic eczema and contact dermatitis were frequently found (±30%). Also in these cases, mostly no intraoral signs of contact allergy were visible [68]. It is clear that the absence of local clinical signs of hypersensitivity to dental alloys may be a major pitfall in its diagnosis.

22.3.3 Objective Symptoms

Lichen planus is a chronic systemic disease of established (auto) immune-mediated pathogenesis. It commonly involves the oral cavity, but it may involve other sites such as the skin, vaginal mucosa, glans penis, the scalp (alopecia) and the nails [110]. Some cases have been described in which alopecia in patients with positive patch test results for Ni and Pd disappeared after the removal of Pd and/or Ni-containing dental restorations [111]. The author explained the pathogenesis by the high affinity of these metals for binding to the sulphur (-SS-) in hair follicles and referred to this phenomenon as ‘internal contact dermatitis’. Oral lesions are mostly bilateral and symmetrical, characteristically with a lace-like network of slightly raised grey-white lines (Wickham’s striae). The lesions may be reticular when Wickham’s striae are present; the plaque-like form is similar to leukoplakia. In the case of erythematous/erosive oral lichen planus (OLP), mostly the gingiva is affected. It is unlikely that sensitization to metals plays a significant role in the aetiology of OLP.

Clinically and histopathologically, OLP may be indistinguishable from oral lichenoid lesions (OLL). OLL result from contact with dental materials, as a result of drug reactions or from graft versus host disease [112]. Dental materials most commonly related to OLL are amalgam, Au and Pd [8, 9, 14, 70, 113–115]. The lesions are usually in close contact with the causative dental material(s). It is not fully clear whether or not OLL results from a type IV allergic reaction, as the value of patch testing has been debated [14, 70, 71, 88, 116–118]. From this perspective, OLL may be a manifestation of irritant contact stomatitis [94, 95, 118]. Still, a positive patch test to a metal of the dental alloy and a strong topographic association between the lesion and restorative material are positively correlated, and the lesions generally disappear after the alloy is removed [119, 120]. Other allergens, such as perfumes, cinnamaldehyde (in cinnamon), carvone (in caraway and dill) and other food additives are also related to OLL [7, 86, 88]. In the scientific literature dealing with adverse reactions to dental alloys, the distinction between OLP and OLL is often not made or not well described.

A variety of symptoms and lesions have traditionally been associated with dental alloys; however, most studies report on small numbers, making it difficult to draw definitive conclusions. Most reported lesions/complaints attributed to metals are stomatitis and gingivitis/bleeding and/or swelling of the gingiva and are similar to inflammatory responses to bacteria. Also, in the case of non-plaque-related gingivitis in direct contact to metal-containing restorations, the

diagnosis of contact hypersensitivity is very often not made [70], suggesting again innate immune responses [95].

Finally, it has been reported that referring dentists often overlook intraoral lesions, since many more lesions have been reported by specialists in the field, such as those working in adverse reaction units [121]. This could mean that general dentists and dermatologists are under-reporting oral lesions. In this context, it is noteworthy to stress that dental metal-based crowns and bridges are often difficult to distinguish from natural teeth as they are mostly veneered with porcelain.

22.3.4 Subjective Symptoms

22.3.4.1 General Complaints

Several studies report on decreased health complaints after the removal of amalgam fillings [50, 121–125]. The most commonly reported complaints that improved after restoration replacements were pain from muscles and joints, memory and concentration problems, complaints about the ear/nose/throat and fatigue. However, treatment without removing the offending amalgams was also found to significantly reduce the symptoms [124]. Furthermore, these complaints are also frequently observed in the general population, although the intensity of the complaints is lower [122, 123]. Stejskal et al. [126] studied the relation between dental alloys, various subjective complaints and lymphocyte transformation test results. They reported significantly increased Pd-, Au- and Hg-induced lymphocyte proliferation in 111 chronic fatigue-like patients compared to 116 controls. Of those 111 patients, 98 had their dental restorations removed, and 76% (n = 83) reported long-term health improvement. Interestingly, during a follow-up, 73 patients who removed their dental alloys were retested and showed dramatically reduced lymphocyte proliferation of the aforementioned metals. Of note, in these patients Ni-induced proliferation was not reduced. Several interesting cases have been described in more detail [127]. It has been suggested that ongoing chronic inflammation with subsequent increased cytokine levels may affect the hypothalamic-pituitary-adrenal axis (HPA axis), triggering non-specific somatic and psychological symptoms [126].

It may be concluded that there is only scarce evidence suggesting improvement of systemic complaints as a result of dental alloy removal and that several other factors must be taken into consideration, especially psychosomatic factors [50, 128].

22.3.4.2 Local Complaints

The most commonly reported subjective local complaints are burning mouth/tongue, metallic taste/taste disturbance and/or dry mouth [72, 122, 123]. However, there is little evidence for true associations with allergy to dental alloys, in particular, for burning sensations/burning mouth syndrome (BMS) [14, 129]. The exact aetiology of BMS remains imprecise and is likely multifactorial, including neuropsychiatric, endocrine, immunologic, nutritional, infectious and iatrogenic causes [130]. In the context of immunologic aetiologies, also food allergens can be involved [7]. Xerostomia has been related to exposure to dental alloys and to hypersensitivity to Ni and Pd [14]. However, many drugs also induce xerostomia and/or taste disturbance and may present further confounding variables [131, 132]. Metallic taste is primarily a sign of exposure due to corrosion. The lack of evidence for an association with allergy does not exclude an association with exposure. Indeed, metallic taste has been related to exposure to dental alloys [14]. Notably, burning sensation and xerostomia are probably related, since in the case of xerostomia, the mucin layer, with its important barrier and protective function, is absent, resulting in increased susceptibility to irritation/burning sensation from otherwise harmless food components and/or additives.

Another important issue to address is the possible influence of menopause on oral health. The female population within the age range of 40–60 is the largest patient group afflicted by oral disease attributed to dental materials. Periodontal disease, burning mouth syndrome and xerostomia are common manifestations in postmenopausal women [133]. The density of important immune-regulating cells was found to

be drastically reduced in gingival tissues of healthy subjects older than 40 relative to those under 40, a finding that contributes to the predisposition for oral disease in the older population [103].

References

1. Wataha JC. Biocompatibility of dental casting alloys: a review. J Prosthet Dent. 2000;83(2):223–34.
2. ADA. Revised Classification System for Alloys for Fixed Prosthodontics [01-23-2017]. Available from: http://www.ada.org/en/about-the-ada/ada-positions-policies-and-statements/revised-classification-system-for-alloys-for-fixed-prosthodontics.
3. Aberer W, Holub H, Strohal R, Slavicek R. Palladium in dental alloys--the dermatologists' responsibility to warn? Contact Dermatitis. 1993;28(3):163–5.
4. Muris J, Feilzer AJ. Micro analysis of metals in dental restorations as part of a diagnostic approach in metal allergies. Neuro Endocrinol Lett. 2006;27(Suppl 1):49–52.
5. Davis MD, Wang MZ, Yiannias JA, Keeling JH, Connolly SM, Richardson DM, et al. Patch testing with a large series of metal allergens: findings from more than 1,000 patients in one decade at Mayo Clinic. Dermatitis. 2011;22(5):256–71.
6. Kanerva L, Rantanen T, Aalto-Korte K, Estlander T, Hannuksela M, Harvima RJ, et al. A multicenter study of patch test reactions with dental screening series. Am J Contact Dermat. 2001;12(2):83–7.
7. Torgerson RR, Davis MD, Bruce AJ, Farmer SA, Rogers RS 3rd. Contact allergy in oral disease. J Am Acad Dermatol. 2007;57(2):315–21.
8. Moller H. Dental gold alloys and contact allergy. Contact Dermatitis. 2002;47(2):63–6.
9. Ahlgren C, Bruze M, Moller H, Gruvberger B, Axell T, Liedholm R, et al. Contact allergy to gold in patients with oral lichen lesions. Acta Derm Venereol. 2012;92(2):138–43.
10. Ahlgren C, Ahnlide I, Bjorkner B, Bruze M, Liedholm R, Moller H, et al. Contact allergy to gold is correlated to dental gold. Acta Derm Venereol. 2002;82(1):41–4.
11. Berzins DW, Kawashima I, Graves R, Sarkar NK. Electrochemical characteristics of high-Pd alloys in relation to Pd-allergy. Dent Mater. 2000;16(4):266–73.
12. Manaranche C, Hornberger H. A proposal for the classification of dental alloys according to their resistance to corrosion. Dent Mater. 2007;23(11):1428–37.
13. Pigatto PD, Feilzer AJ, Valentine-Thon E, Zerboni R, Guzzi G. Burning mouth syndrome associated with palladium allergy? Eur J Dermatol. 2008;18(3):356–7.
14. Muris J, Goossens A, Goncalo M, Bircher AJ, Gimenez-Arnau A, Foti C, et al. Sensitization to palladium and nickel in Europe and the relationship with oral disease and dental alloys. Contact Dermatitis. 2015;72(5):286–96.
15. Faurschou A, Menne T, Johansen JD, Thyssen JP. Metal allergen of the 21st century-a review on exposure, epidemiology and clinical manifestations of palladium allergy. Contact Dermatitis. 2011;64(4):185–95.
16. Al-Imam H, Benetti AR, Ozhayat EB, Pedersen AM, Johansen JD, Thyssen JP, et al. Cobalt release and complications resulting from the use of dental prostheses. Contact Dermatitis. 2016;75(6):377–83.
17. Thyssen JP, Menne T. Metal allergy—a review on exposures, penetration, genetics, prevalence, and clinical implications. Chem Res Toxicol. 2010;23(2):309–18.
18. Wataha JC, Drury JL, Chung WO. Nickel alloys in the oral environment. Expert Rev Med Devices. 2013;10(4):519–39.
19. Milheiro A, Kleverlaan C, Muris J, Feilzer A, Pallav P. Nickel release from orthodontic retention wires-the action of mechanical loading and pH. Dent Mater. 2012;28(5):548–53.
20. Feilzer AJ, Laeijendecker R, Kleverlaan CJ, van Schendel P, Muris J. Facial eczema because of orthodontic fixed retainer wires. Contact Dermatitis. 2008;59(2):118–20.
21. Mathew MT, Barao VA, Yuan JC, Assuncao WG, Sukotjo C, Wimmer MA. What is the role of lipopolysaccharide on the tribocorrosive behavior of titanium? J Mech Behav Biomed Mater. 2012;8:71–85.
22. Noguti J, de Oliveira F, Peres RC, Renno AC, Ribeiro DA. The role of fluoride on the process of titanium corrosion in oral cavity. Biometals. 2012;25(5):859–62.
23. Sicilia A, Cuesta S, Coma G, Arregui I, Guisasola C, Ruiz E, et al. Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. Clin Oral Implants Res. 2008;19(8):823–35.
24. Siddiqi A, Payne AG, De Silva RK, Duncan WJ. Titanium allergy: could it affect dental implant integration? Clin Oral Implants Res. 2011;22(7):673–80.
25. Fage SW, Muris J, Jakobsen SS, Thyssen JP. Titanium: a review on exposure, release, penetration, allergy, epidemiology, and clinical reactivity. Contact Dermatitis. 2016;74(6):323–45.
26. Gulson B, McCall MJ, Bowman DM, Pinheiro T. A review of critical factors for assessing the dermal absorption of metal oxide nanoparticles from sunscreens applied to humans, and a research strategy to address current deficiencies. Arch Toxicol. 2015;89(11):1909–30.
27. Roblegg E, Frohlich E, Meindl C, Teubl B, Zaversky M, Zimmer A. Evaluation of a physiological

in vitro system to study the transport of nanoparticles through the buccal mucosa. Nanotoxicology. 2012;6(4):399–413.
28. Teubl BJ, Leitinger G, Schneider M, Lehr CM, Frohlich E, Zimmer A, et al. The buccal mucosa as a route for TiO_2 nanoparticle uptake. Nanotoxicology. 2015;9(2):253–61.
29. Valentine-Thon E, Muller K, Guzzi G, Kreisel S, Ohnsorge P, Sandkamp M. LTT-MELISA (R) is clinically relevant for detecting and monitoring metal sensitivity. Neuroendocrinol Lett. 2006;27:17–24.
30. Valentine-Thon E, Schiwara HW. Validity of MELISA for metal sensitivity testing. Neuro Endocrinol Lett. 2003;24(1–2):57–64.
31. Muller K, Valentine-Thon E. Hypersensitivity to titanium: clinical and laboratory evidence. Neuro Endocrinol Lett. 2006;27(Suppl 1):31–5.
32. Geurtsen W. Biocompatibility of dental casting alloys. Crit Rev Oral Biol Med. 2002;13(1):71–84.
33. Wataha JC, Craig RG, Hanks CT. The release of elements of dental casting alloys into cell-culture medium. J Dent Res. 1991;70(6):1014–8.
34. Khan MA, Williams RL, Williams DF. Conjoint corrosion and wear in titanium alloys. Biomaterials. 1999;20(8):765–72.
35. Bosshardt DD, Lang NP. The junctional epithelium: from health to disease. J Dent Res. 2005;84(1):9–20.
36. Fine DH, Pechersky JL, McKibben DH. The penetration of human gingival sulcular tissue by carbon particles. Arch Oral Biol. 1969;14(9):1117–9.
37. Tolo KJ. A study of permeability of gingival pocket epithelium to albumin in guinea pigs and Norwegian pigs. Arch Oral Biol. 1971;16(8):881–8.
38. Wataha JC, Lockwood PE, Khajotia SS, Turner R. Effect of pH on element release from dental casting alloys. J Prosthet Dent. 1998;80(6):691–8.
39. Hedberg Y, Wang X, Hedberg J, Lundin M, Blomberg E, Wallinder IO. Surface-protein interactions on different stainless steel grades: effects of protein adsorption, surface changes and metal release. J Mater Sci Mater Med. 2013;24(4):1015–33.
40. Wataha JC, Nelson SK, Lockwood PE. Elemental release from dental casting alloys into biological media with and without protein. Dent Mater. 2001;17(5):409–14.
41. Bal W, Sokolowska M, Kurowska E, Faller P. Binding of transition metal ions to albumin: sites, affinities and rates. Biochim Biophys Acta. 2013;1830(12):5444–55.
42. Su N, Marek CL, Ching V, Grushka M. Caries prevention for patients with dry mouth. J Can Dent Assoc. 2011;77:b85.
43. Kagawa R, Ikebe K, Enoki K, Murai S, Okada T, Matsuda K, et al. Influence of hypertension on pH of saliva in older adults. Oral Dis. 2013;19(5):525–9.
44. Wataha JC, Lockwood PE, Frazier KB, Khajotia SS. Effect of toothbrushing on elemental release from dental casting alloys. J Prosthodont. 1999;8(4):245–51.
45. Wataha JC, Lockwood PE, Mettenburg D, Bouillaguet S. Toothbrushing causes elemental release from dental casting alloys over extended intervals. J Biomed Mater Res B Appl Biomater. 2003;65(1):180–5.
46. Wataha JC, Lockwood PE, Noda M, Nelson SK, Mettenburg DJ. Effect of toothbrushing on the toxicity of casting alloys. J Prosthet Dent. 2002;87(1):94–8.
47. McGinley EL, Dowling AH, Moran GP, Fleming GJ. Influence of S. Mutans on base-metal dental casting alloy toxicity. J Dent Res. 2013;92(1):92–7.
48. McGinley EL, Coleman DC, Moran GP, Fleming GJ. Effects of surface finishing conditions on the biocompatibility of a nickel-chromium dental casting alloy. Dent Mater. 2011;27(7):637–50.
49. Bjorkman L, Lundekvam BF, Laegreid T, Bertelsen BI, Morild I, Lilleng P, et al. Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. Environ Health. 2007;6:30.
50. Langworth S, Bjorkman L, Elinder CG, Jarup L, Savlin P. Multidisciplinary examination of patients with illness attributed to dental fillings. J Oral Rehabil. 2002;29(8):705–13.
51. Begerow J, Zander D, Freier I, Dunemann L. Long-term mercury excretion in urine after removal of amalgam fillings. Int Arch Occup Environ Health. 1994;66(3):209–12.
52. Molin M. Mercury release from dental amalgam in man. Influences on selenium, glutathione peroxidase and some other blood and urine components. Swed Dent J Suppl. 1990;71:1–122.
53. Garhammer P, Schmalz G, Hiller KA, Reitinger T. Metal content of biopsies adjacent to dental cast alloys. Clin Oral Investig. 2003;7(2):92–7.
54. Cristaudo A, Bordignon V, Petrucci F, Caimi S, De Rocco M, Picardo M, et al. Release of palladium from biomechanical prostheses in body fluids can induce or support PD-specific IFN gamma T cell responses and the clinical setting of a palladium hypersensitivity. Int J Immunopathol Pharmacol. 2009;22(3):605–14.
55. Drasch G, Muss C, Roider G. Gold and palladium burden from dental restoration materials. J Trace Elem Med Biol. 2000;14(2):71–5.
56. Kielhorn J, Melber C, Keller D, Mangelsdorf I. Palladium—a review of exposure and effects to human health. Int J Hyg Environ Health. 2002;205(6):417–32.
57. Begerow J, Neuendorf J, Turfeld M, Raab W, Dunemann L. Long-term urinary platinum, palladium, and gold excretion of patients after insertion of noble-metal dental alloys. Biomarkers. 1999;4(1):27–36.
58. Kratzenstein B, Sauer KH, Weber H. In-vivo corrosion phenomena of cast restorations and their interactions with the oral cavity. Dtsch Zahnarztl Z. 1988;43(3):343–8.
59. Schwickerath H. Solubility of dental alloys. Deutsche Zahnarztliche Zeitschrift. 1988;43(3):339–42.
60. Ahlgren C, Molin M, Lundh T, Nilner K. Levels of gold in plasma after dental gold inlay insertion. Acta Odontol Scand. 2007;65(6):331–4.

61. Ekqvist S, Lundh T, Svedman C, Bjork J, Moller H, Nilsson LA, et al. Does gold concentration in the blood influence the result of patch testing to gold? Br J Dermatol. 2009;160(5):1016–21.
62. Ekqvist S, Svedman C, Lundh T, Moller H, Bjork J, Bruze M. A correlation found between gold concentration in blood and patch test reactions in patients with coronary stents. Contact Dermatitis. 2008;59(3):137–42.
63. Milheiro A, Muris J, Kleverlaan CJ, Feilzer AJ. Influence of shape and finishing on the corrosion of palladium-based dental alloys. J Adv Prosthodont. 2015;7(1):56–61.
64. Berzins DW, Kawashima I, Graves R, Sarkar NK. Heat treatment effects on electrochemical corrosion parameters of high-Pd alloys. J Mater Sci Mater Med. 2008;19(1):335–41.
65. Viennot S, Lissac M, Malquarti G, Dalard F, Grosgogeat B. Influence of casting procedures on the corrosion resistance of clinical dental alloys containing palladium. Acta Biomater. 2006;2(3):321–30.
66. Kessler DA. Introducing MEDWatch. A new approach to reporting medication and device adverse effects and product problems. JAMA. 1993;269(21):2765–8.
67. Fuller J, Parmentier C. Dental device-associated problems: an analysis of FDA postmarket surveillance data. J Am Dent Assoc. 2001;132(11):1540–8.
68. Hosoki M, Bando E, Asaoka K, Takeuchi H, Nishigawa K. Assessment of allergic hypersensitivity to dental materials. Biomed Mater Eng. 2009;19(1):53–61.
69. van Noort R, Gjerdet NR, Schedle A, Bjorkman L, Berglund A. An overview of the current status of national reporting systems for adverse reactions to dental materials. J Dent. 2004;32(5):351–8.
70. Muris J, Scheper RJ, Kleverlaan CJ, Rustemeyer T, van Hoogstraten IM, von Blomberg ME, et al. Palladium-based dental alloys are associated with oral disease and palladium-induced immune responses. Contact Dermatitis. 2014;71:82–91.
71. Issa Y, Duxbury AJ, Macfarlane TV, Brunton PA. Oral lichenoid lesions related to dental restorative materials. Br Dent J. 2005;198(6):361–6. disussion 549; quiz 372
72. Marcusson JA. Contact allergies to nickel sulfate, gold sodium thiosulfate and palladium chloride in patients claiming side-effects from dental alloy components. Contact Dermatitis. 1996;34(5):320–3.
73. Vamnes JS, Morken T, Helland S, Gjerdet NR. Dental gold alloys and contact hypersensitivity. Contact Dermatitis. 2000;42(3):128–33.
74. Axell T. Hypersensitivity of the oral mucosa: clinics and pathology. Acta Odontol Scand. 2001;59(5):315–9.
75. Wahlberg JE, Boman AS. Palladium chloride—a potent sensitizer in the Guinea pig. Am J Contact Dermat. 1990;1(2):112–3.
76. Wahlberg JE, Boman AS. Cross-reactivity to palladium and nickel studied in the guinea pig. Acta Derm Venereol. 1992;72(2):95–7.
77. Wahlberg JE, Liden C. Cross-reactivity patterns of palladium and nickel studied by repeated open applications (ROATs) to the skin of guinea pigs. Contact Dermatitis. 1999;41(3):145–9.
78. Hindsen M, Spiren A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. Contact Dermatitis. 2005;53(1):2–8.
79. Moulon C, Vollmer J, Weltzien HU. Characterization of processing requirements and metal cross-reactivities in T cell clones from patients with allergic contact dermatitis to nickel. Eur J Immunol. 1995;25(12):3308–15.
80. Pistoor FH, Kapsenberg ML, Bos JD, Meinardi MM, von Blomberg ME, Scheper RJ. Cross-reactivity of human nickel-reactive T-lymphocyte clones with copper and palladium. J Invest Dermatol. 1995;105(1):92–5.
81. Muris J, Goossens A, Goncalo M, Bircher AJ, Gimenez-Arnau A, Foti C, et al. Sensitization to palladium in Europe. Contact Dermatitis. 2015;72(1):11–9.
82. Muris J, Kleverlaan CJ, Feilzer AJ, Rustemeyer T. Sodium tetrachloropalladate ($Na_2[PdCl_4]$) as an improved test salt for palladium allergy patch testing. Contact Dermatitis. 2008;58(1):42–6.
83. Muris J, Kleverlaan CJ, Rustemeyer T, von Blomberg ME, van Hoogstraten IM, Feilzer AJ, et al. Sodium tetrachloropalladate for diagnosing palladium sensitization. Contact Dermatitis. 2012;67(2):94–100.
84. Khamaysi Z, Bergman R, Weltfriend S. Positive patch test reactions to allergens of the dental series and the relation to the clinical presentations. Contact Dermatitis. 2006;55(4):216–8.
85. Raap U, Stiesch M, Reh H, Kapp A, Werfel T. Investigation of contact allergy to dental metals in 206 patients. Contact Dermatitis. 2009;60(6):339–43.
86. Wray D, Rees SR, Gibson J, Forsyth A. The role of allergy in oral mucosal diseases. QJM. 2000;93(8):507–11.
87. Shah M, Lewis FM, Gawkrodger DJ. Contact allergy in patients with oral symptoms: a study of 47 patients. Am J Contact Dermat. 1996;7(3):146–51.
88. Ahlgren C, Axell T, Moller H, Isaksson M, Liedholm R, Bruze M. Contact allergies to potential allergens in patients with oral lichen lesions. Clin Oral Investig. 2014;18(1):227–37.
89. Rachmawati D, Bontkes HJ, Verstege MI, Muris J, von Blomberg BM, Scheper RJ, et al. Transition metal sensing by toll-like receptor-4: next to nickel, cobalt and palladium are potent human dendritic cell stimulators. Contact Dermatitis. 2013;68(6):331–8.
90. Schmidt M, Raghavan B, Muller V, Vogl T, Fejer G, Tchaptchet S, et al. Crucial role for human toll-like receptor 4 in the development of contact allergy to nickel. Nat Immunol. 2010;11(9):814–9.

91. Rachmawati D, Alsalem IW, Bontkes HJ, Verstege MI, Gibbs S, von Blomberg BM, et al. Innate stimulatory capacity of high molecular weight transition metals Au (gold) and Hg (mercury). Toxicol In Vitro. 2015;29(2):363–9.
92. Kollisch G, Kalali BN, Voelcker V, Wallich R, Behrendt H, Ring J, et al. Various members of the toll-like receptor family contribute to the innate immune response of human epidermal keratinocytes. Immunology. 2005;114(4):531–41.
93. Oosterhoff D, Heusinkveld M, Lougheed SM, Kosten I, Lindstedt M, Bruijns SC, et al. Intradermal delivery of TLR agonists in a human explant skin model: preferential activation of migratory dendritic cells by polyribosinic-polyribocytidylic acid and peptidoglycans. J Immunol. 2013;190(7):3338–45.
94. Rachmawati D, Buskermolen JK, Scheper RJ, Gibbs S, von Blomberg BM, van Hoogstraten IM. Dental metal-induced innate reactivity in keratinocytes. Toxicol In Vitro. 2015;30(1 Pt B):325–30.
95. Rachmawati D, von Blomberg BM, Kleverlaan CJ, Scheper RJ, van Hoogstraten IM. Immunostimulatory capacity of dental casting alloys on endotoxin responsiveness. J Prosthet Dent. 2016;117:677–84.
96. Kosten IJ, Buskermolen JK, Spiekstra SW, de Gruijl TD, Gibbs S. Gingiva equivalents secrete negligible amounts of key chemokines involved in Langerhans cell migration compared to skin equivalents. J Immunol Res. 2015;2015:627125.
97. Novak N, Gros E, Bieber T, Allam JP. Human skin and oral mucosal dendritic cells as 'good guys' and 'bad guys' in allergic immune responses. Clin Exp Immunol. 2010;161(1):28–33.
98. Allam JP, Peng WM, Appel T, Wenghoefer M, Niederhagen B, Bieber T, et al. Toll-like receptor 4 ligation enforces tolerogenic properties of oral mucosal Langerhans cells. J Allergy Clin Immunol. 2008;121(2):368–74. e1
99. Fors R, Stenberg B, Stenlund H, Persson M. Nickel allergy in relation to piercing and orthodontic appliances—a population study. Contact Dermatitis. 2012;67(6):342–50.
100. Van Hoogstraten IM, Andersen KE, Von Blomberg BM, Boden D, Bruynzeel DP, Burrows D, et al. Reduced frequency of nickel allergy upon oral nickel contact at an early age. Clin Exp Immunol. 1991;85(3):441–5.
101. van Hoogstraten IM, Boden D, von Blomberg ME, Kraal G, Scheper RJ. Persistent immune tolerance to nickel and chromium by oral administration prior to cutaneous sensitization. J Invest Dermatol. 1992;99(5):608–16.
102. Van Hoogstraten IM, Boos C, Boden D, Von Blomberg ME, Scheper RJ, Kraal G. Oral induction of tolerance to nickel sensitization in mice. J Invest Dermatol. 1993;101(1):26–31.
103. Zavala WD, Cavicchia JC. Deterioration of the Langerhans cell network of the human gingival epithelium with aging. Arch Oral Biol. 2006;51(12):1150–5.
104. Geginat J, Paroni M, Maglie S, Alfen JS, Kastirr I, Gruarin P, et al. Plasticity of human CD4 T cell subsets. Front Immunol. 2014;5:630.
105. Islam SA, Luster AD. T cell homing to epithelial barriers in allergic disease. Nat Med. 2012;18(5):705–15.
106. Feilzer AJ, Kleverlaan CJ, Prahl C, Muris J. Systemic reactions to orally applied metal alloys. Ned Tijdschr Tandheelkd. 2013;120(6):335–41.
107. Fernandez-Redondo V, Gomez-Centeno P, Toribio J. Chronic urticaria from a dental bridge. Contact Dermatitis. 1998;38(3):178–9.
108. Hanafusa T, Yoshioka E, Azukizawa H, Itoi S, Tani M, Kira M, et al. Systemic allergic contact dermatitis to palladium inlay manifesting as annular erythema. Eur J Dermatol. 2012;22(5):697–8.
109. Van Loon LA, Nieboer C, Van Ketel WG. A case of local and systemic disorders caused by palladium hypersensitivity. Ned Tijdschr Tandheelkd. 1982;89(2):50–1.
110. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(Suppl:S25):e1–12.
111. Nakayama H. New aspects of metal allergy. Acta Dermatovenerol Croat. 2002;10(4):207–19.
112. Schlosser BJ. Lichen planus and lichenoid reactions of the oral mucosa. Dermatol Ther. 2010;23(3):251–67.
113. Koch P, Bahmer FA. Oral lesions and symptoms related to metals used in dental restorations: a clinical, allergological, and histologic study. J Am Acad Dermatol. 1999;41(3 Pt 1):422–30.
114. Laeijendecker R, Dekker SK, Burger PM, Mulder PG, Van Joost T, Neumann MH. Oral lichen planus and allergy to dental amalgam restorations. Arch Dermatol. 2004;140(12):1434–8.
115. Laeijendecker R, van Joost T. Oral manifestations of gold allergy. J Am Acad Dermatol. 1994;30(2 Pt 1):205–9.
116. Skoglund A. Value of epicutaneous patch testing in patients with oral, mucosal lesions of lichenoid character. Scand J Dent Res. 1994;102(4):216–22.
117. Dunsche A, Kastel I, Terheyden H, Springer IN, Christophers E, Brasch J. Oral lichenoid reactions associated with amalgam: improvement after amalgam removal. Br J Dermatol. 2003;148(1):70–6.
118. Wong L, Freeman S. Oral lichenoid lesions (OLL) and mercury in amalgam fillings. Contact Dermatitis. 2003;48(2):74–9.
119. Thornhill MH, Pemberton MN, Simmons RK, Theaker ED. Amalgam-contact hypersensitivity lesions and oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95(3):291–9.
120. Thornhill MH, Sankar V, Xu XJ, Barrett AW, High AS, Odell EW, et al. The role of histopathological characteristics in distinguishing amalgam-associated oral lichenoid reactions and oral lichen planus. J Oral Pathol Med. 2006;35(4):233–40.

121. Lygre GB, Gjerdet NR, Gronningsaeter AG, Bjorkman L. Reporting on adverse reactions to dental materials–intraoral observations at a clinical follow-up. Community Dent Oral Epidemiol. 2003;31(3):200–6.
122. Lygre GB, Gjerdet NR, Bjorkman L. A follow-up study of patients with subjective symptoms related to dental materials. Community Dent Oral Epidemiol. 2005;33(3):227–34.
123. Lygre GB, Sjursen TT, Svahn J, Helland V, Lundekvam BF, Dalen K, et al. Characterization of health complaints before and after removal of amalgam fillings–3-year follow-up. Acta Odontol Scand. 2013;71(3–4):560–9.
124. Melchart D, Vogt S, Kohler W, Streng A, Weidenhammer W, Kremers L, et al. Treatment of health complaints attributed to amalgam. J Dent Res. 2008;87(4):349–53.
125. Sjursen TT, Lygre GB, Dalen K, Helland V, Laegreid T, Svahn J, et al. Changes in health complaints after removal of amalgam fillings. J Oral Rehabil. 2011;38(11):835–48.
126. Stejskal VD, Danersund A, Lindvall A, Hudecek R, Nordman V, Yaqob A, et al. Metal-specific lymphocytes: biomarkers of sensitivity in man. Neuroendocrinol Lett. 1999;20(5):289–98.
127. Stejskal V, Hudecek R, Stejskal J, Sterzl I. Diagnosis and treatment of metal-induced side-effects. Neuro Endocrinol Lett. 2006;27(Suppl 1):7–16.
128. Herrstrom P, Hogstedt B. Clinical study of oral galvanism: no evidence of toxic mercury exposure but anxiety disorder an important background factor. Scand J Dent Res. 1993;101(4):232–7.
129. Marino R, Capaccio P, Pignataro L, Spadari F. Burning mouth syndrome: the role of contact hypersensitivity. Oral Dis. 2009;15(4):255–8.
130. Gurvits GE, Tan A. Burning mouth syndrome. World J Gastroenterol. 2013;19(5):665–72.
131. Scully C, Bagan JV. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med. 2004;15(4):221–39.
132. Smith RG, Burtner AP. Oral side-effects of the most frequently prescribed drugs. Spec Care Dentist. 1994;14(3):96–102.
133. Dutt P, Chaudhary S, Kumar P. Oral health and menopause: a comprehensive review on current knowledge and associated dental management. Ann Med Health Sci Res. 2013;3(3):320–3.