Review

Biological responses to pediatric stainless steel crowns

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Abstract: A systematic review was conducted to identify the biological responses, allergic reaction, hypersensitivity, toxicity, and ion release profile associated with pediatric stainless steel crowns (SSCs) in the existing literature. A systematic search was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. The inclusion criteria consisted of patients younger than 20 years of age with SSC placement on primary or permanent teeth in vitro and in vivo exposure to SSCs. Outcomes measures included adverse oral/mucosal effects; removal/failure/replacement of the SSC; type of allergic reaction; nickel (Ni) or other ion levels in bodily fluids, cellular, genotoxic, mutagenic or carcinogenic effects related to the SSC. After an initial search of 764 studies in the database, 17 articles were included in the analysis. Evidence of allergic reactions to SSCs in children is limited and obtained from mostly low-quality research. Some studies showed that the amount of Ni detected was less than the amount ingested in the daily diet. In contrast, other studies reported a significantly higher release of Ni occurred into the saliva in acidic environments. There is some concern about the leaching of metal ions such as Ni from SSCs in children at high risk for caries. Further long-term studies are required to investigate this phenomenon.

Keywords; biological response, children, hypersensitivity, nickel release, stainless steel crown

Introduction

Dental caries is considered the most prevalent chronic disease in children [1]. Over time, various restorative materials have been introduced in pediatric dentistry in an attempt to maintain the primary teeth in the arch prior to the eruption of the permanent successors [2,3]. One of the most durable, retentive, and relatively inexpensive restorative materials available today is the stainless steel crown (SSCs). SSCs, also known as chrome steel crowns or preformed metal crowns, are metallic restorations that have shown good long-term retention and significant clinical success in the restoration of larger carious lesions on primary molars [2,4,5]. First introduced by the Rocky Mountain Company in 1947 and later popularized in 1950 by Engel and Humphrey, SSCs remain an integral part of pediatric dental care [6,7].

The average maximum number of SSCs placed in the mouths of pediatric patients at high risk for caries receiving treatment under general anesthesia is up to eight or more, as some clinicians tend to use them on anterior teeth as well. These restorations are expected to remain in the oral environment for extended periods of time, ideally coinciding with the time of primary tooth exfoliation; thus, on average, they are in place for a maximum of eight to nine years, depending on the age at which the child receives their crowns [8]. Studies have suggested that SSCs exhibit lower failure rates relative to other primary restoration types such as amalgam, glass ionomer, composite, and componer restorations [4,9]. SSCs, therefore, are considered to be a reliable long-term primary tooth restoration modality.

Chemically, SSCs are manufactured from type 303 austenitic alloy with the chemical composition of iron (Fe: 69%), chromium (Cr: 18.4%), nickel (Ni: 9.1%), magnesium (Mg: 1.5%), silicon (Si: 1%), and other elements, including aluminum (Al: 0.6%) and molybdenum (Mo: 0.4%) [10]. Ni is a trace mineral or micronutrient that plays an important role in overall health in small doses, aiding in Fe absorption as well as glucose metabolism. However, at higher doses, Ni has been found to be harmful [11,12]. Ni has been reported as the most frequent cause of allergic contact dermatitis (ACD) worldwide; such was first recorded at the end of the 19th century among workers in the Ni plating industry and was recognized as an allergic reaction in 1925[13]. Allergy to Ni is found more frequently among women (10%-17%) than men (1%-3%) [14-17]. Ni hypersensitivity reactions are serious medical conditions that can be life-threatening and require the removal of the stimulus to prevent further sensitization [18]. A study by Elshahawy et al. documented fibroblast cell cytotoxicity induced by metal salt solutions representing ions found in stainless steel alloys [19]. Specifically, their study demonstrated that zinc (Zn), copper (Cu), and Ni salt solutions have high cytotoxic effects on fibroblast cell cultures in an in vitro experiment. Other studies have reported Ni carcinogenicity and mutagenicity [20,21]. Elsewhere, Feasby et al. reported an increased Ni-positive patch test result in children eight to 12 years of age treated with old-generation SSCs (72% Ni content) [22].

The oral environment that SSCs are most often deployed usually exhibits a significant caries risk, higher salivary acidity, and greater plaque retention [23]. There have been several articles reporting hypersensitivity reactions from Ni that leached out from orthodontic appliances [24-27]. However, a lack of significant research considering biological and hypersensitivity responses to SSCs, despite the more strenuous environment they are placed under in the pediatric population, remains. Additionally, SSCs must withstand high occluding forces while being present in a patient’s mouth for prolonged periods of time. For these reasons, further investigation into this area is necessary to improve the understanding of the characteristics of SSCs and, most importantly, assess their safe use in pediatric patients. The aim of this systematic review was, therefore, to analyze studies focused on biological kinetics, hypersensitivity responses, allergic/toxic reactions, and the release of ions (mainly Ni) associated with pediatric SSCs.

Materials and Methods

Data sources

This systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [28]. A comprehensive literature search was carried out using databases such as MEDLINE (via EBSCOhost), CINAHL (via EbscoHost), EMBASE (via ScienceDirect), and SCOPUS. The search was conducted using the keyword combinations: (“hall crown*” or “hall technique*” or “metal crown*” or “stainless steel crown*” or “nickel chrome crown*” or “chrome steel crown*” or “prefabricated crowns*” or “prefabricated crowns*”) AND (“primary molar*” or “primary teeth*” or “primary diention*” or “permanent molars*”) AND (child* or pediatric* or paediatric* or “in vitro”) without any language restriction. All published studies covering pediatric SSCs and allergy/hypersensitivity were identified. The initial screening process consisted of reviewing the titles and abstracts, while the reasons for exclusions were determined. Hand-searches using the aforementioned keywords were also performed, and the reference lists of selected studies were reviewed for any additional relevant studies. The listed databases were searched from the earliest available date to March 20,
The quality of included studies was determined using the mixed methods appraisal tool (MMAT) [29]. The MMAT is designed for application to systematic reviews that include qualitative, quantitative, and mixed methods studies. The quality of each study was assessed by responding to screening questions with either “yes,” “no,” or “can’t tell.” The calculation of an overall score is discouraged when using the MMAT, which provides a more detailed presentation of the ratings of each criterion to better inform on the quality of the assessed studies.

Results

Literature search
The search returned 764 papers, with nine additional papers included after hand-searching appropriate journal publication sites and reference lists, for a total of 773 articles. After titles and abstracts were screened, 386 papers were thought to be appropriate, and 387 papers were excluded. A further of 364 papers were excluded as they did not match the inclusion criteria. Following a review of 22 papers retrieved for full-text evaluation, an additional five studies failed to meet the inclusion criteria; therefore, 17 papers were finally included in the review. A PRISMA flowchart describing the number of studies included and excluded at the first and second levels, as well as the reasons for their exclusion at the second level of selection, is presented in Fig. 1.

Inter-rater reliability agreement
The inter-rater reliability agreement between the two assessors was 95.4% (768/773 studies), 96.7% (385/387 studies), 93.8% (19/21 studies), and 100% (17/17 studies) at the identification, screening, eligibility, and inclusion stages, respectively. Any discrepancies were resolved through discussion.

Resources selection
Studies were imported into the EndNote software (Clarivate Analytics, Philadelphia, PA, USA), and duplicate articles were removed. Two assessors (S. Z. and A. S.) performed a first-level selection based on titles and abstracts by following the inclusion and exclusion criteria independently. Population, intervention, comparison, and outcome (PICO) inclusion criteria were adopted in this study (Table 1). Studies were excluded according to the exclusion criteria listed in Table 1.

Next, the full texts of all included or potentially relevant articles were imported into the EndNote. Then, a second-level selection among these articles was performed by the same two assessors independently by reading the full texts of the articles and following the same inclusion and exclusion criteria. Any discrepancies between the assessors were resolved by discussion.

Review

Inter-rater reliability agreement
Inter-rater reliability was calculated between the two independent assessors during the data extraction (identification, screening, eligibility, and inclusion) stage (%). Inter-rater reliability agreement for the three stages (selection, comparability, and outcome) was evaluated using Cohen’s kappa in the Statistical Package for the Social Sciences version 24.0 software program (IBM Corp., Armonk, NY, USA).

Quality of included studies
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Table 1  The inclusion and exclusion criteria adopted in the literature search

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>P: Participants: any gender, up to 20 years old</td>
<td>Reviews, letters to the editor, editorials</td>
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<tr>
<td>E: Interventions: SSC placement on primary or permanent teeth, in vivo and in vitro exposure to SSC</td>
<td>Participants: adults (older than 20 years); patients with any systemic disease or who are taking medications that effect dermal/mucosal health</td>
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<tr>
<td>C: Comparison: Ni/SSC/chromium allergy or biological or hypersensitivity reaction in relation to SSC; Ni release from SSC</td>
<td>Interventions: cast metal crowns, zirconia crowns, orthodontic appliances placed in the mouth with no comparison to SSCs, patients with oral piercings (or other Ni exposure)</td>
</tr>
<tr>
<td>O: Outcomes: adverse oral/mucosal effects; removal/failure of SSC; type of allergic reaction; Ni or other ion levels in bodily fluids; any cellular, genotoxic, cytotoxic, mutagenic, or carcinogenic effects</td>
<td>Outcome: known Ni allergy</td>
</tr>
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</table>

Fig. 1  PRISMA (preferred reporting items for systematic reviews and meta-analysis) flowchart of studies.
reactions to dental materials, while allergic reactions related to SSCs were caused by stresses [32,33]. The literature search identified a previous systematic review by Kodaira et al. [46]. Similar results have been released by other researchers [45,46]. Morán-Martínez et al. reported that ni-sensitivity skin reactions to Ni include stomatitis, papula pert-oral rash, a loss of taste sensation or metallic taste, numbness, burning sensation, tongue soreness, angular cheilitis, severe gingivitis (in the absence of plaque), lichen planus, mucosal ulcers, toxicity on the cellular level, and the alteration of cell function [13,39,40]. Extraoral symptoms include edema of the eyelids, swollen lips, and fissured lips, and chronic eczema of the cheeks and palms [13,39]. In high doses, Ni provokes an allergic response through a type IV delayed hypersensitivity immune reaction [11,41,42].

Discussion

Traditionally, the SSC has been the most commonly used restorative option for primary teeth due to its durability and longevity [2,30]. The optimal placement of SSCs on primary teeth requires a “snap-fit,” with the margins of the crown coming into contact with the surrounding tissues, including the gingiva and the alveolar bone. There is limited research regarding the biocompatibility of SSCs in the oral environment as a reliable long-term restoration approach. The hostile oral environment can often induce electrochemical corrosion, and metals can be degraded under enzymatic, microbiological, thermal, and occlusal stresses [11,31]. Research into orthodontic appliances has demonstrated that a critical ion of interest is Ni, which has been shown to be released from these appliances under various stresses [32,33]. The literature search identified a previous systematic review by Syed et al.; however, the focus of their review was on allergic reactions to dental materials, while allergic reactions related to SSCs were only briefly discussed [34]. Hypersensitive reactions, allergic reactions, and potential adverse reactions related to SSCs in children have not been previously evaluated in any systematic research. The present study revealed two case reports of Ni hypersensitivity reactions in children. In the first, a 13-year-old patient presented with perioral skin eruptions following placement of the SSC. Ni hypersensitivity was diagnosed by a patch test, and the lesions resolved following the removal and replacement of the SSC with another material [35]. The second case reported the severe occurrence of ulcerative contact gingivitis in a two-year-old boy following placement of SSCs that resolved following crown removal and replacement with composite resin crowns [36]. Ni allergy can induce different clinical and morphological patterns, but more commonly, involves a localized cutaneous reaction at the site of contact with the metal known as ACD or, in a minority of patients, a systemic reaction referred to as Ni allergy syndrome (SNAS) [37]. ACD is characterized by itching, pompholyx, maculopapular exanthema, flexural eczema, urticarial, and vasculitis-like lesions [37]. SNAS is a condition characterized by contact dermatitis in association with systemic symptoms, including diarrhea, vomiting, fever, arthralgia, asthma, headache, and malaise [38]. Intra-oral reactions to Ni include stomatitis, papula pert-oral rash, a loss of taste sensation or metallic taste, numbness, burning sensation, tongue soreness, angular cheilitis, severe gingivitis (in the absence of plaque), lichen planus, mucosal ulcers, toxicity on the cellular level, and the alteration of cell function [13,39,40]. Extraoral symptoms include edema of the eyelids, swollen and fissured lips, and chronic eczema of the cheeks and palms [13,39]. In high doses, Ni provokes an allergic response through a type IV delayed hypersensitivity immune reaction [11,41,42].

The presence of the Ni-chromium crowns was confirmed by atomic absorption analysis of saliva. The maximum amounts of released Ni and Cr were below toxic health levels. There was a positive correlation between the number of SSCs and Ni release. However, the levels of Fe, Cr, and Ni released were below toxic health levels. The results of this study are consistent with previous research, which have shown that Ni release from SSCs is not significant when compared to other dental materials [36,38]. The authors concluded that SSCs can be used safely in children without the need for special precautions. The study also highlighted the importance of further research on Ni release from SSCs and its potential effects on the oral health of children. The results of this study are consistent with previous research, which have shown that Ni release from SSCs is not significant when compared to other dental materials [36,38]. The authors concluded that SSCs can be used safely in children without the need for special precautions. The study also highlighted the importance of further research on Ni release from SSCs and its potential effects on the oral health of children.

Table 2 Characteristics of the included human studies

<table>
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<th>Author</th>
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<th>Interventions</th>
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<th>Time</th>
<th>Key findings</th>
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<td>Basir et al. 2019 [46]</td>
<td>NRT</td>
<td>Children</td>
<td>SSC placement</td>
<td>After 2 months</td>
<td>Atomic absorption in saliva</td>
<td>Salivary Ni and chromium concentrations increased after placement of SSC; similarly, salivary pH also increased. Ion levels were not correlated with pH except for Cr during follow-up. Ni increase (but not Cr) was correlated with pH increase. Statistically significant differences were found in Ni release after 1 week and after 1 month following crowns placement. There was a positive correlation between the number of crowns and Ni release. However, the levels of Fe, Cr, and Ni released were below toxic health levels.</td>
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<tr>
<td>Hernández-Martínez et al. 2018 [61]</td>
<td>NRT</td>
<td>Children</td>
<td>SSC placement</td>
<td>At baseline, after 1 week, and after 1 month</td>
<td>Metal levels in saliva</td>
<td>Salivary pH</td>
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</tr>
<tr>
<td>Mohamed et al. 2013 [62]</td>
<td>NRT</td>
<td>Children</td>
<td>SSC placement</td>
<td>At baseline and after 1, 3, and 6 months</td>
<td>Saliva atomic absorption</td>
<td>The levels of salivary Ni and Cr released after lingual arch space maintainer placement were more than those after SSC placement. The maximum amounts of released Ni and Cr were much lower than the dietary intake and were not capable of causing any toxicity.</td>
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<tr>
<td>Kodaira et al. 2013 [50]</td>
<td>NRT</td>
<td>Children</td>
<td>SSC placement</td>
<td>After 3 months</td>
<td>Hair mineral analysis</td>
<td>Analysis of hair samples showed a significant difference in the level of the trace element Cr between the crown and control groups, but no significant differences were noted in the Fe or Ni levels. Levels of the trace elements Ni, Cr, and Fe were within allowable ranges, indicating that these minerals were not likely to be harmful.</td>
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<tr>
<td>Morán-Martínez et al. 2013 [47]</td>
<td>NRT</td>
<td>Children</td>
<td>SSC placement</td>
<td>At 1, 15, and 45 days after crown placement</td>
<td>Micronucleus assay</td>
<td>Odontological exposure to metal crowns resulted in genotoxic damage at the cellular level of the oral mucosa and an increase in the urinary excretion of Ni within 45 days of exposure.</td>
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<tr>
<td>Yilmaz et al. 2012 [35]</td>
<td>DS</td>
<td>Child</td>
<td>SSC placement</td>
<td>After 1 week</td>
<td>Skin allergy patch test</td>
<td>Delayed hypersensitivity reaction was triggered by the Ni in the SSC. The eruptions completely healed within one week after removal of the SSC and the tooth was restored with a bis-acryl crown and bridge. The patient was followed for six months thereafter with no further allergic reactions.</td>
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<tr>
<td>Barcet et al. 1997 [36]</td>
<td>DS</td>
<td>Child</td>
<td>SSC placement</td>
<td>After 1 month</td>
<td>Skin allergy patch test</td>
<td>The SSCs were replaced with composite resin crowns, and the patient tolerated the replacement procedure well and did not report any problems at follow-up visits.</td>
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<tr>
<td>Feasby et al. 1988 [22]</td>
<td>NRT</td>
<td>Children</td>
<td>Ni-containing intra-oral devices including SSC</td>
<td>NA</td>
<td>Ni-sensitivity skin patch test</td>
<td>No significant correlation was found between children with and without Ni-containing intraoral devices. A statistically significant correlation was found with the positive patch test readings and the presence of Ni-chromium crowns (old formulation of 72% Ni). There was a significant correlation between the presence of the Ni-chromium crowns and a positive patch test.</td>
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NRT: quantitative non-randomized trial; DS, descriptive qualitative study.
eight SSCs) of Ni in vitro [42]. In contrast with the above studies, however, some research contended that the amount of Ni detected in body fluids was less than the typical nutritional intake of Ni and is therefore below the level of a toxic dose for humans [11,42,48-50]. While the quantity of Ni ions required to produce sensitivity differs with the individual, even a low concentration of 40 µg of Ni per day can trigger a delayed hypersensitivity reaction [35,51]. Although this, indeed, is below the normal daily intake level, concentrations of less than 0.05 mg Ni/kg/day are considered safe [35,52].

The oral environment that SSCs are most often deployed in usually boasts a high concentration of Ni, chromium, and iron [47]. Ni and Cr, reaching the maximum level at the end of seven days, significantly contributed to Ni ion release. The amount of Ni released was below the toxic level and did not exceed the dietary intake. The amount of Ni released was below the toxic level and did not exceed the dietary intake.

The present systematic review revealed several adverse effects of the SSCs in children at the cellular and genetic levels. One study investigated genotoxic carcinogens and cell structural lesions caused by Ni released from SSCs and suggested that the ion release from these crowns caused genotoxic damage at the cellular level of the oral mucosa [47]. It has been found that the Ni component of stainless steel orthodontic appliances may produce a burning sensation as the most frequent symptom, along with gingivitis, gingival hyperplasia, periodontitis, metallic taste, erythema, and angular cheilitis [24-27]. Furthermore, patients with conventional braces experience more changes in the periodontium relative to those receiving Ni-free braces and often experience gingival overgrowth even without plaque accumulation around the orthodontic appliances [58]. This overgrowth has been shown to be the result of the impact of Ni on gingival epithelial cells and, even at low concentrations, Ni promotes epithelial cell proliferation [41,59]. Similarly, the existence of titanium hypersensitivity in an oral environment has also been reported in the literature [60]. On the other hand, there is a lack of significant research done on SSC materials despite being placed under a strenuous environment. The oral environment that SSCs are most often deployed in usually boasts a high concentration of Ni, chromium, and iron [47]. Ni and Cr, reaching the maximum level at the end of seven days, significantly contributed to Ni ion release.

The present systematic review revealed several adverse effects of the SSCs in children, ranging from induction of local inflammation/allergic reaction to the systematic distribution of the ions, and also touched upon cytotoxic or genotoxic effects. However, the scientific evidence concerning the use of SSCs in the pediatric population is not yet adequately established, as inadequate research prevents the conclusion of whether SSCs could potentially be responsible for any adverse cellular and allergic/hypersensitive reactions in the pediatric population. Most evidence comes from in vitro and in vivo studies that typically investigated the short-term effects of SSCs. Further research investigating the long-term release of these ions in in vitro and in vivo settings is necessary for aiding

<table>
<thead>
<tr>
<th>Author</th>
<th>Experimental design</th>
<th>Sample size</th>
<th>Time</th>
<th>Measure</th>
<th>Key findings</th>
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<tbody>
<tr>
<td>Amanna et al. 2019 [63]</td>
<td>Evaluation of ion release from SSCs in artificial saliva</td>
<td>SSCs (n = 30)</td>
<td>At 1, 7, 14, and 28 days</td>
<td>Release of metal ions in artificial saliva using atomic absorption spectrophotometry</td>
<td>A measurable release of Ni and Cr was observed at each time point, with both reaching the maximum level at the end of 28 days; however, both remained below the toxic level. The concentration of released Ni decreased with trimming of margins and increased when the temperature rose. Time and pH had no significant effect on Ni release.</td>
</tr>
<tr>
<td>Basir et al. 2018 [64]</td>
<td>Evaluation of Ni release from SSCs with crown trimming</td>
<td>SSCs (n = 18)</td>
<td>At 1, 7, and 21 days</td>
<td>pH (3.5, 5.0, and 6.7) and oral temperature (27°C, 37°C, and 47°C)</td>
<td>A significantly higher amount of Ni ions was released at a pH of 4.3, while the pH of artificial saliva was inversely related to Ni ion release.</td>
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<tr>
<td>Tiwari et al. 2016 [43]</td>
<td>Effect of pH on Ni ion release from SSCs</td>
<td>SSCs (n = 45)</td>
<td>At 15 days</td>
<td>Artificial saliva of pH (4.3, 5.5, and 6.3) using atomic absorption spectrophotometry</td>
<td>A significantly higher amount of Ni ions was released at a pH of 4.3, while the pH of artificial saliva was inversely related to Ni ion release.</td>
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<tr>
<td>Kulkarni et al. 2016 [45]</td>
<td>Biodegradation (leaching effect) of space maintainers and SSCs in the artificial saliva using atomic absorption spectrophotometer</td>
<td>SSCs (n = 45) and space maintainers (n = 45)</td>
<td>At 1,7 and 21 days</td>
<td>Atomic absorption spectrophotometer</td>
<td>A measurable release of Ni was observed and reached the maximum level at the end of seven days, which was statistically significant (P &lt; 0.05).</td>
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<td>Ramzan et al. 2014 [42]</td>
<td>Assessment of Ni release from SSCs</td>
<td>SSC (n = 270)</td>
<td>At 1, 7, 14, and 28 days</td>
<td>Amount of Ni release in artificial saliva using an atomic absorption spectrophotometer</td>
<td>The amount of Ni released was below the toxic level and did not exceed the dietary intake.</td>
</tr>
<tr>
<td>Menek et al. 2012 [49]</td>
<td>Investigation of Ni ion release from SSCs in saliva</td>
<td>SSC (n = 120)</td>
<td>At 1, 7, 14, 21, and 28 days</td>
<td>Ion release in saliva from SSCs by square wave voltammetry</td>
<td>Metal ions released in this experimental condition were well below the critical value needed to induce allergy and below the daily dietary intake level.</td>
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<tr>
<td>Keinan et al. 2010 [48]</td>
<td>Comparison of absorption of Ni, chromium, and iron by the root surface of primary molars covered with SSCs versus normal intact molars</td>
<td>SSCs (n = 17)</td>
<td>Present in the mouth for at least 24 months</td>
<td>Energy dispersive X-ray spectrometry chemical analysis</td>
<td>Significantly (P &lt; 0.001) higher amounts of Ni, chromium, and iron (five- to sixfold) were found in the cementum of molars covered with SSCs as compared to intact molars.</td>
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<tr>
<td>Bhaskar and Reddy, 2010 [11]</td>
<td>Biodegradation (leaching effect) of space maintainers made out of stainless steel band materials (Dantau, Usetek, SSC wire, solder and flux) in artificial saliva</td>
<td>SS band space maintainers (n = 20)</td>
<td>At 1, 7, 14, and 28 days</td>
<td>Atomic absorption spectrophotometer</td>
<td>Results showed that there was measurable release of both Ni and Cr, reaching the maximum level at the end of seven days, which was statistically significant (P &lt; 0.05). However, levels remained below the dietary average intake for all four bands used and were not capable of causing any toxicity.</td>
</tr>
<tr>
<td>Gagneja, 2007 [65]</td>
<td>Measure the Ni ion release from conventional SSCs and compare with the Ni ion release from the SSCs coated with a proprietary material</td>
<td>Specimens of conventional SSCs (n = 9), and SSCs coated with proprietary layer (n = 9)</td>
<td>Immersion times of 1, 10, 100, and 1,000 hours</td>
<td>Optically missioned spectrometry</td>
<td>There was a measurable release of Ni elements in the nominal compositions of a SSC alloy and a coated SSC alloy. The use of stainless steel coated with a proprietary material for the fabrication of crowns may decrease the ion release and perhaps prevent various health hazards in children.</td>
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the understanding of SSC and, most importantly, assessing their safe use in children.

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Conflict of interest

None.

References