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SYSTEMATIC REVIEW

Detection and sensing of oral xenobiotics in edentulous patients rehabilitated with titanium dental implants: Insights from a scoping review

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ABSTRACT

Statement of problem. Titanium has been considered the standard element in implant manufacturing. Recent studies have evaluated the role of titanium as a biological modulator of oral health. However, evidence regarding the association between the release of metal particles and peri-implantitis is lacking.

Purpose. The purpose of this scoping review was to evaluate the literature regarding the release of metal particles in peri-implant tissues correlated with the methods of detection and the local and systemic implications.

Material and methods. The study was performed in adherence with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines and was registered with the National Institute for Health Research PROSPERO (Submission No. 275576; ID: CRD42021275576). A systematic search was conducted in the Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE via PubMed, Scopus, and Web of Science bibliographic databases, complemented by a manual evaluation. Only in vivo human studies written in the English language and published between January 2000 and June 2022 were included.

Results. In total, 10 studies were included according to eligibility criteria. Different tissues and analytic techniques were reported: the characterization technique most used was inductively coupled plasma mass spectrometry. All 10 studies analyzed the release of metal particles in patients with dental implants, continuously detecting titanium. None of the studies reported a significant association between metal particles and biological effects.

Conclusions. Titanium is still considered the material of choice in implant dentistry, despite the detection of metal particles in peri-implant tissues. Further studies are necessary to evaluate the association between analytes and local health or inflammatory status. (J Prosthet Dent 2023;■:■-■)

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Clinical Implications

Although hypersensitivity reactions to metal particles and peri-implantitis have been described following implant treatment, genotoxic damage in oral mucosa cells has not been directly associated with titanium ion release. Implant-derived analytes can be detected in salivary fluids, serum, gingival crevicular fluid, and intraoral soft tissues. The methods most used for detection include biopsy of peri-implant inflammatory tissue, gingivoplasty, and brushing procedures. Further research is needed to investigate the association between dental implants, ion release, and peri-implant disease.

Implant-supported rehabilitation is a well-supported evidence-based therapeutic strategy for replacing missing teeth in partially or completely edentulous patients, with predictable long-term success rates.[1] Different materials have been used in the fabrication of dental implants; however, commercially pure titanium (Ti) is still the material of choice in implant dentistry.[2] Despite Ti implants being regarded as the standard in prosthetic dentistry over the last 20 years, Ti has been considered a biological modulator of oral health. The ions and metal particles released may alter the interior physiological oral environment and initiate peri-implantitis or trigger a peri-implantitis flare.[3]

The continuous release of chemical or physical agents and the persistence of foreign bodies have been associated with chronic inflammation.[4] Although inflammation is a crucial biological process of the human immune system, chronic inflammation can have secondary consequences such as inflammation-related diseases or disorders.[5]

Chronic inflammation is a broad topic, depending on the type of cells involved and the anatomic area. Nevertheless, typical stages of chronic inflammation are represented by ongoing stimulus, immune cell recruitment, secretion of more inflammatory mediators (free radicals), and increased inflammation.[6] Chronic inflammation and the following release of free radicals can disturb the balance between reactive oxygen species formation and endogenous antioxidant defense mechanisms by provoking oxidative stress conditions and, potentially, local or systemic disease.[7]

Remarkably, xenobiotics after biotribocorrosion may be found in saliva, in the periodontal tissue, and inside immune cells (resident macrophages).[8] Ti particles may then directly exert a cytotoxic effect on oral tissues but may also indirectly trigger or amplify oral inflammation. The degradation products increase in loco resulting in the systemic release of pro-inflammatory cytokines,[9] namely tumor necrosis factor (TNF)-α, interleukin (IL)-1β and the secretion of the receptor activator of nuclear factor kappa-B ligand (RANK-L).[1,8] Furthermore, Żukowski et al[10] demonstrated in vivo that Ti might trigger peri-implant intracytoplasmic changes in the macrophages and deregulate reactive oxygen species production and catabolism. Thus, implant-based Ti release may initiate peri-implant tissue inflammation, together with oral dysbiosis, via redox dysregulation.[10-13]

The consequent pro-inflammatory microenvironment is further altered by Ti-driven saliva chemical changes such as acidification.[8] In particular, Ti may impact oral physiology in different phases, including the surgical, prosthetic, and maintenance phase.[14,15]

Despite the growing number of studies hypothesizing the role of Ti in peri-implantitis,[16-18] evidence is still contradictory because of the heterogeneity of the study design, analytic methods of detecting Ti, and the lack of a validated protocol for ascertaining or even distinguishing the nature of the peri-implantitis (Ti accumulation versus metal allergy).[19-24]

This scoping review aimed to summarize and critically evaluate the current studies that focused on the detection of metal particles released from implant-supported prostheses and the link between such xenobiotics and peri-implantitis. The research hypothesis was that xenobiotics in the saliva and periodontal tissues of patients with dental implants would influence their oral health.

MATERIAL AND METHODS

This scoping review was performed in adherence with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines[25] and registered with the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO) with the submission No. 275576; ID: CRD42021275576. A modified population, intervention, control, outcome (PICO) model, namely a population, exposure, outcome (PEO) framework, was adopted to prepare a focused question in order to determine the association between a particular exposure and the outcomes in healthcare settings.[26,27]

Only in vivo human studies were considered. Randomized controlled and controlled clinical trials, prospective and retrospective cohort studies, and case series involving treatment of ≥5 participants were included. A separate analysis of case reports and technical notes was also conducted. Only studies written in English and published between January 2000 and June 2022 were included. Only data pertinent to the present review were considered for studies with multiple treatments.

To satisfy the primary aim of the present review, the following additional inclusion criteria were applied:

in vivo human studies, studies reporting on Ti dental implants, studies reporting on implant-derived particles released following implant insertion, studies reporting on detection of implant-derived particles in peri-implant tissues and saliva, and studies reporting on the methods used to detect and assess such particles. All studies not satisfying the inclusion criteria were excluded, including in vitro studies, in vivo animal studies, reviews, and studies reported in languages other than English.

A comprehensive literature search was conducted electronically in the Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE via PubMed, Scopus, and Web of Science bibliographic databases by 3 authors (S.B., N.O., R.G.) independently. The electronic search was supplemented by a manual evaluation of the reference lists of all selected full-text articles. The purpose was to identify all the available pertinent information on the release of metal particles in the peri-implant tissues following biotribocorrosion, including the methodology used in their analysis. The most recent search was executed on June 2, 2022.

For the electronic search, specific keywords, medical subject headings (MeSH), and other terms not indexed as MeSH were combined to search all relevant studies, fulfilling the requirements of the PEO question. As such, publications were screened according to the following search query adapted to each database: (biotribocorrosion OR bioaccumulation OR bioaccumulation OR release OR bio-concentration OR biomagnification OR biomagnification) AND dental implants AND (saliva OR periodontal tissues OR oral cavity OR periodontium OR parodontium) as either keywords or MeSH terms. Additional screening of the reference lists of pertinent articles and recent literature reviews on the topic was performed to identify further relevant studies. Online registries of clinical trials were also checked at http://clinicaltrials.gov/; http://www.centerwatch.com/clinicaltrials/ and http://www.clinicalconnection.com/.

Primary screening of the titles and abstracts was performed by adding studies of any level of evidence published in peer-reviewed journals written in English. During this step, in vitro and animal studies were detected and excluded. Duplicates, abstracts, conference presentations, literature reviews, editorials, and expert opinions were also removed. Two reviewers (N.O., M.M.) independently screened the titles and abstracts of collected papers to select eligible studies. Then, full-text publications of the selected papers were obtained and evaluated in duplicate and independently by the same examiners. After 2 weeks, eligible studies were reread to establish investigator agreement about article selection. Any disagreement was resolved through discussion between the 2 reviewers, and any controversy was resolved by a third reviewer (P.P.P.). The articles excluded and the reasons for exclusion were noted. Any incomplete, unclear, or unpublished data were checked by contacting the corresponding authors of the articles included after the screening process.

All data were extracted from the article text, tables, figures, and supplementary materials. While reviewing the publications, a spreadsheet was created and consecutively updated. According to the PEO framework, the recorded data were distributed in tables, including demographic data (first author, publication year, journal name, title, study type, sample size, implant information), xenobiotics information (type of analytes, particles size), methods of assessment (type of tissue, type of harvesting process, characterization technique, timeline of harvesting), and biological responses (peri-implant hard and soft tissues, local or systemic effects).

In view of the PEO framework adopted in the present review, with the aim of mapping the current evidence regarding the types of analytes released from Ti implants following biotribocorrosion in humans and regardless of the purpose of the individual articles or the clinical outcome of the evaluated treatments, quality assessment of the included studies was not performed. This was in accordance with the PRISMA-ScR guidelines stating that the risk of bias assessment among the studies should not be applied to scoping reviews.

RESULTS

Initially, 416 articles were identified, 186 in MEDLINE, 55 in Web of Science, 26 in SCOPUS, 128 in Embase, and 21 in the Cochrane Library. After duplicate removal, 391 articles remained for the screening phase. Following the evaluation of titles and abstracts, 311 publications were excluded. Overall, 69 articles were excluded after reading the full text because they did not meet the selection criteria. Finally, 10 studies were included after the review process[8,20-24,28-31]: 6 case-control studies,[8,21-24,29] 1 cross-sectional study,[30] 1 single-arm clinical trial,[20] 1 retrospective study,[31] and 1 prospective study.[28] The flow chart of the search strategy and workflow is shown in Figure 1. Overall, 573 participants were enrolled in the included studies. For the present review, the participants involved were divided into 2 groups: 386 participants who received dental implants (experimental group) and 203 participants without dental implants (control group). One single-arm clinical trial included the same 16 participants in the experimental and in the control group.[20] Overall, 806 samples were obtained from participants with dental implants. Table 1 describes the main features of the included studies. Two studies[30,31] had only an experimental group because of their study design.

The detection and concentration of analytes were evaluated by harvesting different tissues and using several analytic techniques. In particular, 4

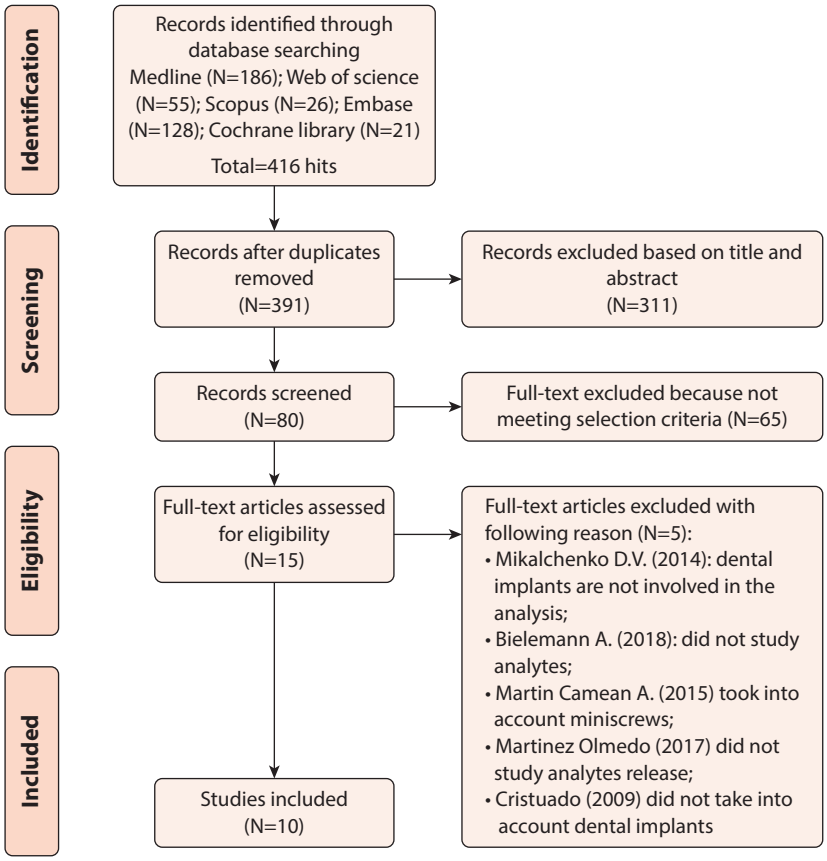

Figure 1. Flowchart of study selection process.

studies analyzed salivary fluids,[8,23,24,28] 1 study assessed serum,[28] 2 studies collected gingival crevicular fluid,[24,30] and 5 studies collected samples from intraoral soft tissues.[20-22,29,31]

Salivary fluids were collected by using calibrated microcapillaries, tubes, sterile syringes, and brushes. Papi et al[8] used an unstimulated drainage method (sterile tubes). Soft-tissue samples were collected using 3 methods: biopsy of peri-implant inflammatory tissue, exfoliative cytology of gingival samples by means of gingivoplasty, or brushing procedures.[20-22] Two research groups collected peri-implant inflammatory tissue during flap surgery.[29,31]

The characterization technique most used was inductively coupled plasma mass spectrometry (ICP-MS) in 7 of 10 studies.[8,20-23,28,30] One study used total-reflection X-ray fluorescence (TXFR) using synchrotron radiation,[24] and 3 studies used energy-dispersive spectroscopy (EDS) analyses.[20,29,31]

In total, 10 articles evaluated the distribution of metal components in participants with dental implants.[8,20-24,28-31] Nevertheless, features such as implant surface characteristics and type of connection were not considered. In general, the most investigated analyte was Ti, being the only element studied in all the articles regarding dental implants,[8,20-24,28-31] as summarized in Table 2.

Wilson et al[31] analyzed the proportions of the elements in the peri-implantitis biopsies, reporting a mean ±standard deviation percentage of Ti in the biopsies of participants with dental implants of 0.60 ±1.79%. In Abraham et al,[24] Ti concentrations in the gingival crevice fluids of participants with dental implants (22 ±7 μg/mL) showed statistically significantly higher values than in those participants without implant rehabilitations (1.3 ±0.4 μg/mL), while groups did not differ significantly in saliva (2.8 ±0.4 μg/mL and 2.5 ±0.5 μg/mL, respectively).

Similar results were reported by both Gürbüz-Urvasızoğlu et al[28] and Camacho-Alonso et al.[23] The highest Ti concentrations were found in participants with metal-ceramic fixed prostheses on dental implants + dental amalgams and in participants with metal-ceramic fixed prostheses on dental implants + metal-ceramic fixed prostheses on teeth + dental amalgams, yielding median values of 1.02 and 0.89 μg/L, respectively. Interestingly, the first group of showed a statistically higher level of genotoxicity.[23]

Similarly, other studies that collected samples from soft tissues did not reveal any significant discrepancies among the Ti concentrations in the 2 investigated

Table 1. Summary of types of population (participants), types of interventions (and comparisons), and types of outcomes

First Author	Number of Implants	Number of Participants	Experimental Group	Control Group	Inclusion Criteria	Population Characteristics	Ratio Implants:Participants
Abraham et al 2014[24]	N° implants not reported	49	23	26	> 18 y, 2 or more functional dental areas, no toothpaste for 2 d before sampling, dental implants 2 y older, underwent periodontal treatment within last year	No age and gender details were provided	N° implants not reported
Selda Mercan et al 2013[21]	20	30	20	10	Healthy, nonsmoking, single tooth edentulism	9 F, 11M; Mean age: 37,8 y; Age range: 23-52 y; Implant localization: 7 (maxilla), 13 (mandible)	1 (20:20)
Andrew Tawse-Smith et al 2017[20]	16	16	16 (participants with dental implants)	16 (same participants contralateral tooth taken into account)	Single-tooth extraction (esthetic zone), > 18 y, Adequate oral hygiene, Presence of 4-mm bone apical to socket, Stable socket walls post-extraction with 3-wall dehiscence of <4 mm, placement of implants at least 13 mm in length and 4 mm in diameter, mesial distal proximal distance at least 6 mm, implant insertion torque between 30 and 45 Ncm	/	1 (16:16)
Fabio Camacho-Alonso et al 2013[23]	180	105 participants. 15 participants excluded. Overall, 90 participants included	75	15	Age between 30 and 60 y, treatment with dental implants (with minimum time of 2 months from prosthetic rehabilitation)	105 participants (50 men and 55 women); mean age: 38 y (range 30.54 y); 70.5% of sample nonsmokers; 45.7% did not drink alcohol. Majority no systemic disease; average n° of teeth (27, range 10-32)	2 (180:90)
Lopez-Jornet et al 2014[22]	90 (average: 3 implants per participant [range 1-10])	60	30	30	> 18 y, good general health, dental implants installation with 1-y follow-up and no associated pathologies	Mean age: 50.3 ±10.41; 14 M, 16 F; Smoking: 24 no, 6 yes; Alcohol consumption: 23 no, 7 yes	3 (90:30)
Wilson et al 2015[31]	36	31	31	/	Participants with peri-implantitis and requiring surgical intervention	/	1.52 (36:31)
Papi et al 2020[8]	50	100	50 (26 healthy implants; 24 with peri-implantitis)	50	Single crown implants functioning for >1 y; No clinical signs of pathologies; ≥ 18 y; Implants clinically healthy (group A); Implants with peri-implantitis (group B); Nonsmoker; No uncontrolled systemic diseases; Not pregnant or breastfeeding; No metal reconstruction, crowns, or other prosthetic restorations present in oral cavity	Implants classified as clinically healthy (Group A): n° of participants 26, 11M e 15 F, mean age (63.13 ±17.72 y), n° of implants = 26; Implants with a diagnosis of peri-implantitis (Group B): n° of participants 24, 11M e 13F, mean age (70.52 ±8.24 y), n° of implants = 24	1 (50:50)
Gelengül Gürbüz-Urvasızoğlu et al 2022[28]	258 (5,16 implant every participant)	50	25	25	Experimental group: peri-implantitis clinically and radiologically and receiving no medication or surgical treatment	Experimental group: 11 M, 14 F; mean age 44.4 y (24-67). Control group: 11 M, 14 F; mean age 45.9 y (27-63).	5.16 (258:50)
Mia Rakic et al 2022[29]	39	70	39	31	Systemically healthy with diagnosis of either peri-implantitis or severe periodontitis	16 F, 23 M; mean age: 52.5 (24-60); 18 smokers	1 (39:39)
Eswar Kandaswamy et al 2022[30]	117	77	77	/	> 18 y; with dental implant –supported restorations ≥ 1 y in function, systemically healthy or with controlled systemic health problems	Mean age: 62 ±2 y (range 25-88); 39 M, 38 F; mean time in function: 9 ±1 y	1,52 (117:77)

groups.[20,21] Conversely, Papi et al[8] and López-Jornet et al[22] reported statistically significant differences in terms of Ti concentration.

López-Jornet et al[22] reported a higher Ti concentration in exfoliated oral mucosal cells harvested with a toothbrush in the experimental group (2.42 ±5.04 μg/L)

Table 2. Summary of Ti determination and quantitation in control groups and participants with Ti-based implant using different analytic techniques

Ref. Number	Ref.	Analytical Technique	Type of Samples		[Ti]	Significantly Different
8	Papi et al 2020	ICP-MS	Saliva	Control	136.6 ±263.2 μg/L	Yes
				Dental implant	489.6 ±227.8 μg/L	
20	Tawse-Smith et al 2017	ICP-MS	Intraoral soft tissue	Control	0.582 ±2.033[g]	No
				Dental implant	0.472 ±2.210[g]	
				Dental implant[a]	0.379 ±2.382[g]	
				Dental implant[b]	0.836 ±2.743[g]	
		EDS		Control	0.33[h]	No
				Dental implant	0.53[h]	
				Dental implant[a]	1[h]	Yes
				Dental implant[b]	0.92[h]	
21	Mercan et al 2013	ICP-MS	Intraoral soft tissue	Control	37.1 ±1.0 μg/g	No
				Dental implant	50.4 ±23.5 μg/g	
22	López-Jornet et al 2014	ICP-MS	Intraoral soft tissue	Control	0.46 ±1.13 μg/L	Yes
				Dental implant	2.42 ±5.04 μg/L	
23	Camacho-Alonso et al 2015	ICP-MS	Saliva	Control	0.00-1.39 μg/L	No
				Dental implant[c]	0.00-1.02 μg/L	
				Dental implant[d]	0.00-0.89 μg/L	
24	Abraham et al 2014	TXFR	Saliva	Control	2.5 ±0.5 μg/mL	No
				Dental implant	2.8 ±0.4 μg/mL	
			Gingival crevicular fluids	Control	1.3 ±0.4 μg/mL	Yes
				Dental implant	22 ±7 μg/mL	
29	Rakic et al 2022	EDS	Intraoral soft tissue	Control	-	NA
				Dental implant	-	
30	Kandaswamy et al 2022	ICP-MS	Gingival crevicular fluids	Control	-	No
				Dental implant	-	
31	Wilson et al 2015	EDS	Intraoral soft tissue	Dental implant	0.60 ±1.79%	NA
28	Gürbüz-Urvasızoğlu et al 2022	ICP-MS	Saliva	Control[e]	168.9 ±39.1 μg/L	No
				Dental implant[f]	146.8 ±90.8 μg/L	
			Serum	Control[e]	102.9 ±19.4 μg/L	No
				Dental implant[f]	84.2 ±27.4 μg/L	

EDS, energy-dispersive spectroscopy; ICP-MS, inductively coupled plasma mass spectrometry; NA, not applicable. [a]Implant-abutment interface. [b]Implant cervical. [c]Metal-ceramic fixed crowns on dental implants + dental amalgam. [d]Metal-ceramic fixed crowns on dental implants + metal-ceramic fixed crowns on teeth + dental amalgam. [e]Healthy osseointegrated implant. [f]Peri-implantitis. [g]Geometric means and standard deviations with comparison based linear mixed model using log-transformed data. [h]Proportion with comparisons based on logistic mixed models.

compared with the control group (0.46 ±1.13 μg/L). Nonetheless, the authors did not report any evidence regarding an increase in mutagenic and carcinogenic risks in humans with dental implants.

Similarly, Papi et al[8] reported higher levels of Ti particles in the experimental group (489.60 ±227.86 μg/L) than in the control group (136.65 ±263.28 μg/L). Furthermore, they compared Ti concentration in participants with healthy dental implants (489.60 ±227.86 μg/L) and in those with peri-implantitis (492.83 ±313.90 μg/L). They concluded that Ti content in saliva was higher in those with dental implants when compared with those without dental implants. However, no statistically significant differences were found in the Ti concentrations of participants with healthy implants or peri-implantitis.[8]

DISCUSSION

Ti dental implants are a reliable and predictable option for replacing missing teeth.[20] Although, inflammatory reactions associated with metallic particles released in peri-implant tissues have been reported,[11-13,28] a cause-and-effect relationship between Ti particles and peri-implant disease has not been verified, rejecting the research hypothesis of the study.

Suárez-López del Amo et al[16] evaluated the evidence related to the presence and the mechanisms of release of Ti particles in peri-implant tissues and concluded that higher concentrations of metal-like particles were observed in participants with dental implants and around diseased implants when compared with healthy ones. A recent study measured the trace element levels in blood serum and saliva using ICP-MS, comparing participants with diagnosed peri-implantitis with those with healthy osseointegrated implants.[28] No statistically significant difference in Ti or Al levels was found between the 2 study groups either in saliva or serum. Moreover, slightly higher concentrations of Ti were detected in saliva as compared with serum samples.[28]

Mombelli et al[19] evaluated the association between implant biocorrosion and complications, allergies, and hypersensitivity reactions, reporting insufficient

specificity to consider Ti particles the cause of biological complications. However, they suggested that Ti ion concentrations may be higher just because of inflammation.[19] Nonetheless, Noronha Oliveira et al reported that Ti and metal-like ions and particles released by the degradation of dental implants can result in adverse biological side effects by means of the production of proinflammatory cytokines, inflammatory cells, and osteoclasts activity.[1]

A recent study evaluated the inflammatory process associated with Ti particles in biopsy specimens harvested from peri-implantitis lesions by using scanning electron microscopy coupled with dispersive X-ray spectrometry.[29] Comparing peri-implantitis and periodontitis, more severe inflammation and increased vascularization were found in peri-implant tissues than in periodontal tissues.[29]

The parameters involved in unexplained implant failures have been investigated.[18,19] A connection between inexplicable failed dental implants and a positive reaction to Ti ions was hypothesized by Sicilia et al,[18] reporting that 62.5% of the participants with implants that failed for unknown reasons showed hypersensitivity to Ti.

A recent scoping review evaluated the consequences of the accumulation of Ti ions in peri-implant tissues.[17] In addition to cytotoxic and inflammatory effects, Ti particles may cause accelerated peri-implant bone loss.[29] An association between Ti dental implants and hypersensitivity reactions has been investigated[13,18]; in particular, facial eczema and multiple cutaneous fistulae have been reported.[18] The genotoxic effect of Ti particles should also be further analyzed to identify any eventual correlation between Ti and neoplasias.[18]

Limitations of this research include the heterogeneity of detection methods: different types of tissues were analyzed, biologic samples were harvested using several technologies, and different characterization techniques with distinct features were described. This heterogeneity complicated the analysis of the results from the studies included. Further studies are needed to identify the most reliable and least-invasive detection method of revealing metal particles to possibly demonstrate an association between analytes and peri-implantitis.

CONCLUSIONS

Based on the findings of this scoping review, the following conclusions were drawn.

1. Metal particles can be not infrequently found in peri-implant tissues.
2. Such analytes were mostly detected in salivary fluids, serum, gingival crevicular fluid, and intraoral soft tissues.
3. Biopsy of peri-implant inflammatory tissue and exfoliative cytology of gingival samples by means of gingivoplasty and brushing procedures were the commonly used methods of harvesting soft-tissue samples.
4. The most used characterization technique was ICP-MS, followed by EDS analysis and TXFR using synchrotron radiation.
5. Although Ti was investigated the most, a clear and direct correlation between Ti particles and peri-implantitis could not be ascertained from the results reported.

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