DR. FERNANDO SUÁREZ-LÓPEZ DEL AMO (Orcid ID : 0000-0002-0416-7380)
DR. CRISTIANE HELENA SQUARIZE (Orcid ID : 0000-0002-6782-3429)

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Dental Implants-Associated Release of Titanium Particles: A Systematic Review

Fernando Suárez-López del Amo DDS, MS [1,2], Carlos Garaicoa-Pazmiño DDS, MS [1,4], Tobias Fretwurst DDS[1,3], Rogerio M. Castilho DDS, MS, PhD [1,4], Cristiane H. Squarize DDS, MS, PhD [1,4]

1 Laboratory of Epithelial Biology, Department of Periodontics and Oral Medicine, University of Michigan School, Ann Arbor, MI, USA.

2 Department of Periodontics, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

3 Department of Oral and Craniomaxillofacial Surgery, Center for Dental Medicine, University Medical Center Freiburg, Freiburg, Germany.

4 Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA.

Corresponding author:

Cristiane H. Squarize DDS, MS, PhD

Laboratory of Epithelial Biology

Department of Periodontics and Oral Medicine.

University of Michigan

1011 N University Ave

Ann Arbor, MI

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48109-1078
Phone: 734-615-3406
e-mail: csquariz@umich.edu
Laboratory of Epithelial Biology
Department of Periodontics and Oral Medicine
University of Michigan
1011 N University Ave, Room 2029C
Ann Arbor, MI
48109-1078
Phone: (734) 615-3406
e-mail: rcastilh@umich.edu
Laboratory of Epithelial Biology
Department of Periodontics and Oral Medicine
University of Michigan
1011 N University Ave, Room 2029C
Ann Arbor, MI
48109-1078
Phone: (734) 615-3406
e-mail: rcastilh@umich.edu

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Abstract

Objectives: The presence of Titanium (Ti) particles around dental implants has been reported in the literature for decades. The prospective presence of Ti debris on soft tissues surrounding dental implants has not been systematically investigated and remains to be explored. Hence, this review aimed to evaluate the origin, presence, characteristics, and location of Ti particles in relation to dental implants.

Material and methods: Literature searches were conducted by two reviewers independently based on the PRISMA guidelines. The systematic review identified studies on Ti particles derived from dental implants. We evaluated several parameters, including anatomical location, and the suspected methods of Ti particles release.

Results: The search resulted in 141 articles, of which 26 were eligible and included in the systematic review of the literature. The investigations reported Ti and metal-like particles in the soft (i.e., epithelial cells, connective tissue, and inflammatory cells) and hard (bone crest and bone marrow) tissues around the dental implants. Shape and size of the particles varied. The current literature reported a size range from 100 nm to 54 μm identified by multiple particles identification methods.

Conclusion: Ti particles surrounding peri-implant tissues is a common finding. Peri-implantitis sites presented a higher number of particles compared to healthy implants. The particles were mostly around the implants and inside epithelial cells, connective tissue, macrophages, and bone. Various mechanisms were described as causes of Ti release, including friction during implant insertion, corrosion of the implant surface, friction at the implant-abutment interface, implantoplasty, and several methods used for implant surface detoxification.

Introduction

Since their introduction in 1960's, dental implants have progressively evolved and completely revolutionized the field of oral rehabilitation and aesthetics. While initially

developed for specific applications, today dental implants are used as the standard of care for numerous clinical scenarios. Backed up by decades of clinical investigations, dental implants have demonstrated to be reliable and predictable, and also provide long-term stability. (Buser et al., 2012; Hjalmarsson, Gheisarifar, & Jemt, 2016; Knofler, Barth, Graul, & Krampe, 2016; Rokn, Bassir, Rasouli Ghahroudi, Kharazifard, & Manesheof, 2016). Consequently, the use of dental implants continues to rise worldwide, being considered now a day the gold standard for replacing the missing dentition. Nonetheless, these implantable devices are not exempt from limitations and complications; and as such, biological, surgical and mechanical complications have been extensively described in the literature resulting in peri-implant diseases (Lang, Wilson, & Corbet, 2000; M. S. Schwarz, 2000). Indeed, peri-implant diseases represent one of the leading areas of interest and research in the periodontal field.

One of the significant successes of current implant technology advents from the use of the type 4 Ti alloy, which is known to provide enhanced biocompatibility with bone tissues and surrounding dental structures, but Ti can release particles and ions. Emerging investigations are demonstrating that those particles and ions are not entirely bioinert material. These observations elute to the prominent need for better understanding the biological implications of free Ti and metal-like particles surrounding peri-implant tissues. Multiple studies suggested the contribution of the Ti particles to the development and progression of peri-implantitis (Cadosch et al., 2010; Liu et al., 2013; Nishimura et al., 2014; Pettersson et al., 2017). These particles are associated with the activation of the inflammatory response and release of pro-inflammatory cytokines, such as TNF-α, IL-1β, and RANKL (Cadosch et al., 2010; Liu et al., 2013; Nishimura et al., 2014; Pettersson et al., 2017). Similarly, Ti particles were associated with the reduced viability of bone marrow stem cells (Meng, Chen, Guo, Ye, & Liang, 2009), and disruption of epithelial homeostasis, increasing DNA damage response, and potentially compromising the oral epithelial barrier (Suarez-Lopez Del Amo et al., 2017).

The study of metal elements in the peri-implant tissues is not new to the periodontal and implant fields (Ferguson, Laing, & Hodge, 1960). Numerous studies reported the presence of Ti particles in the peri-implant tissues (Halperin-Sternfeld, Sabo, & Akrish, 2016; He et al., 2016; D. G. Olmedo, Nalli, Verdu, Paparella, & Cabrini, 2013; Wilson et

al., 2015); however, the different hypothesis for the presence and release of Ti and metal-like particles in the surrounding peri-implant has not been systematically studied. The aim of this systematic review was to assess the current knowledge on the origin, presence, characteristics, and location of Ti particles surrounding dental implants. Therefore, studies on root form dental implants were evaluated on the present investigation.

Materials and Methods

Information Sources

An electronic and manual search in dental literature was performed by two independent reviewers (FSLA and CG) in three databases (i.e., PubMed, Web of Science, and Cochrane Central Register of Controlled Trials databases) published in the English language up to March 2017.

Review question

This review aimed to systematically search the currently available evidence related to the presence of Ti particles surrounding dental implants and the potential mechanisms of release.

Screening process

The search was conducted in three major electronic databases: PubMed, Web of Science, and Cochrane Central Register of Controlled Trials databases. The PRISMA (transparent reporting of systematic reviews and meta-analyses) guidelines were used to prepare the manuscript. It consisted of a checklist and a flow diagram. For the PubMed database, the combinations of terms used, where “[mh]” represented the MeSH terms and “[tiab]” represented the titles and abstracts search, were as follows: ("implant"[all] OR "dental implants"[mh] OR “dental implant”[tiab] OR “dental implantation” [tiab] OR “dental implantation, endosseous"[mh]) AND (“foreign body”[tiab] OR “foreign bodies”[tiab] OR “foreign substance”[tiab] OR “reactive lesion”[tiab] OR “reactive

lesions”[tiab] OR “titanium particle”[all] OR “titanium particles”[all] OR “metal element”[all] OR "metal elements"[all]) AND ("dental"[tiab] OR "oral"[tiab] OR "tooth"[tiab] OR "teeth"[tiab]). For the other databases, the keywords used in the search included “dental implant”, “foreign body”, “reactive lesion”, “titanium particle”, and “metal element”.

We also searched for the references of the selected papers and review articles. A hand search was carried out from January 2016 to March 2017 by two reviewers (FSLA and CG) in related dental journals, which included: the *Journal of Oral and Maxillofacial Implants, Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, Implant Dentistry, European Journal of Oral Implantology, Journal of Oral Implantology, International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, Journal of Dental Research, International Journal of Prosthodontics, Journal of Prosthetic Dentistry, Journal of Clinical Periodontology, Journal of Periodontology, and The International Journal of Periodontics and Restorative Dentistry*. For the search of the grey literature, Google Scholar was used to identifying any articles not included in the databases above.

Eligibility criteria

Articles were included if they evaluated the presence and/or debridement of Ti or metal-like particles released from dental implants in human tissues, animal models, or in vitro. Investigations were selected if at least one method for particles identification was carried out to detect Ti or metal-like particles. Articles were excluded if: (I) implants other than dental implants were investigated. Consequently, studies reporting on the presence of particles related to artificial joint replacement, plates for maxillofacial rehabilitation and other implants outside the oral cavity for purposes other than dental restorations were excluded. We also excluded studies on (II) metal-like particles and reactive lesions in patients that did not have dental implants except for the control group. (III) Published materials that were review articles, letters, personal opinions, book chapters, conference abstracts, and (IV) articles published in a language other than English were also excluded.

Data extraction & analyses

The same two authors (FSLA and CG) independently reviewed all full-text articles. Discussions between the two authors initially resolved any disagreements. If the two authors did not reach an agreement, a third author (CHS) made the final decision. The primary outcome considered was the histologic outcomes of peri-implant tissues. Due to the observational nature and reported outcomes of the included investigations, only a qualitative descriptive analysis was performed and systematically reviewed using tables. Significant heterogeneity was found preventing a quantitative synthesis of the included studies; therefore, the meta-analysis was precluded. This report adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement.

Risk of bias and quality assessment and of selected studies

Assessment of study quality and bias was performed for the included studies using the Cochrane review guidelines. The human non-randomized cohorts and case-control studies were assessed using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2011). The criteria for the quality assessment of case reports case series, case reports and cross-sectional studies was from the Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data (The Joanna Briggs Institute, 2017) (Supplementary Table 1-3). Currently, no quality assessment method has been developed for analysis of in vitro studies. Animal research was assessed according to ARRIVE guidelines for *in vivo* experiments and assigned predefined grades (Kilkenny et al., 2010; F. Schwarz et al., 2012) (Supplementary Table 4). Two authors (FS and CGP) independently evaluated the included studies. Next, any disagreements were resolved by discussion, and the final scores were formed. Summary assessments of the risk of bias for outcomes (across domains or criteria for the quality assessment used) within and across studies are represented in risk of bias graphics following Cochrane review guidelines. In summary, a low risk of bias was estimated when plausible bias is unlikely to seriously alter the results, or the risk of bias was low in all key domains. The unclear risk of bias was estimated when plausible bias that raises some doubt about the results or risk of bias was in one or more key domains; and the high risk of bias was estimated when plausible bias that seriously weakens confidence in the results or risk of bias was in one or more key domains (Higgins & Green, 2011).

Results

Study selection

Initial screening of electronic databases yielded a total of 151 articles, and manual search identified 34 publications. After elimination of duplicated studies, 141 titles and abstract were further evaluated. The screening of titles and abstracts resulted in 43 potentially relevant articles to be selected. The full text of the relevant studies was obtained and thoroughly evaluated. Next, 17 investigations were excluded due to the lack of investigation on dental implants and Ti presence or release (Supplementary Table 5). Overall, 26 studies fulfilled the inclusion and exclusion criteria and were assessed in this systematic review (Figure 1).

Characteristics of included investigations

- Human studies

Eleven articles evaluated the presence of Ti, metal-like particles, and other foreign bodies within peri-implant human biopsies. Included investigations were case reports/series, and retrospective and prospective studies (Table 1) (Flatebo et al., 2011; Flatebo et al., 2006; Fretwurst et al., 2016; Halperin-Sternfeld et al., 2016; He et al., 2016; D. Olmedo, Fernandez, Guglielmotti, & Cabrini, 2003; D. G. Olmedo et al., 2013; D. G. Olmedo, Paparella, Brandizzi, & Cabrini, 2010; D. G. Olmedo et al., 2012; Safioti, Kotsakis, Pozhitkov, Chung, & Daubert, 2017; Wilson et al., 2015). As such, the size of Ti particles ranged from 100 nM (or 0.1μm) to 12 μm identified at both healthy and diseased peri-implant sites (Flatebo et al., 2011; Flatebo et al., 2006; Halperin-Sternfeld et al., 2016; He et al., 2016; D. Olmedo et al., 2003; D. G. Olmedo et al., 2013; D. G. Olmedo et al., 2010; D. G. Olmedo et al., 2012; Wilson et al., 2015). Additionally, two studies reported metal-like particles with wider ranges (0.5 to 54 μm) (He et al., 2016; Wilson et al., 2015). Particle shape and description varied from round to elongated and leaf-like appearance. Higher Ti content was confirmed with post-implant placement when compared to their preoperative counterparts (Flatebo et al., 2011; Flatebo et al., 2006; He et al., 2016). Notably, significant concentrations of Ti were noted around diseased implants compared to healthy ones (D. G. Olmedo et al., 2013; Safioti et al., 2017). Wilson and coworkers

identified foreign bodies in 94% of the samples collected around dental implants, and 7 out of 36 samples displayed traces of Ti (Wilson et al., 2015). Similarly, another study reported the existence of Ti and the associated occurrence of iron in 75% of the hard and soft tissue biopsies of implants with peri-implantitis (Fretwurst et al., 2016).

The most common mechanisms of Ti release to the peri-implant tissues discussed in the articles were corrosion of the implant surface and frictional wear during implant placement and the implant-abutment interphase. Additional feasible methods of particle release were reported, such as implant surface debridement during maintenance recalls and exogenous sources (e.g., diet and dental products) (D. G. Olmedo et al., 2013; Wilson et al., 2015).

Ti particles were abundant close to the implant and or adjacent to the cover screw. Those particles were mostly found in the soft tissue, particularly inside and outside of epithelial cells, in addition to the connective tissue and inflammatory cells (i.e., macrophages) (Table 1). For example, Flatebo and colleagues demonstrated deeper deposition of particles within epithelial cells and connective tissue level after implant installation compared to the superficial deposition of Ti found preoperatively, which also correlate with the superficial deposition of Ti particles from exogenous sources (Flatebo et al., 2011). Notably, Ti particles were located inside the cytoplasm of macrophages and epithelium cells from peri-implantitis tissue (D. Olmedo et al., 2003). Alterations of basic cell mechanisms may occur in cells with phagocytized Ti particles and might lead to reactive lesions, such as pyogenic granuloma and peripheral giant cell granulomas (Halperin-Sternfeld et al., 2016; D. G. Olmedo et al., 2010). Ti particles were also reported in bone marrow (He et al., 2016).

As summarized in Table 1, the methods employed for the detections of the metal particles harvested soft and hard tissue biopsies were spectroscopy methods, in addition to optic emission spectroscopy with inductively coupled plasma (ICP-OES), inductively coupled plasma mass spectroscopy (ICP-MS), and laser ablation with ICP-MS (LA-ICP-MS).

- *In vivo* studies

A total of 12 *in vivo* studies were examined using animal models (Table 2) (Deppe, Greim, Brill, & Wagenpfeil, 2002; Franchi et al., 2004; Franchi et al., 2007; Frisken,

Dandie, Lugowski, & Jordan, 2002; Martini et al., 2003; Meyer et al., 2006; Schliephake, Reiss, Urban, Neukam, & Guckel, 1993; Tanaka, Ichinose, Kimijima, & Mimura, 2000; Weingart et al., 1994; Wennerberg, Albrektsson, & Lausmaa, 1996; Wennerberg et al., 2004; Wennerberg, Jimbo, Allard, Skarnemark, & Andersson, 2011). Aligned with the human studies, Ti ions and Ti particles with varying sizes and morphologies were described among the peri-implant biopsies. The Ti particle sizes ranged mostly from 0.1 to 45 μm.

The release of Ti particles after treatment of peri-implantitis was studied in vivo (Deppe et al., 2002). The in vivo studies also focused in models studying the release of Ti particles due to corrosion of the implant surface and frictional wear during implant site preparation and placement, and analyses were restricted to bone (i.e., maxilla, mandible) and distant organs. Notably, Ti particles were found on the implant site (bone surface and bone marrow) as well as in the blood, lymph nodes, and distant organs such as lung, liver, and kidneys (Deppe et al., 2002; Frisken et al., 2002; Schliephake et al., 1993; Weingart et al., 1994; Wennerberg et al., 2011). Higher levels of Ti in the lungs and regional lymph nodes were in animals with failed implants (Frisken et al., 2002). Surgical contamination (e.g., aspiration, ingestion) was proposed as a reason for the detection of the particles in distant parts of the body; nonetheless, Deppe and coworkers found high Ti concentrations, despite performing the surgeries with endotracheal intubation (Deppe et al., 2002). Other authors attributed the transportation of these particles to visceral organs to the immune-related cleaning mechanisms (Weingart et al., 1994; Wennerberg et al., 2011), which aligns with the presence of Ti particle in macrophages from humans. Such finding could explain the reduction of Ti particles after five months of dental implant placement (Schliephake et al., 1993). Occasionally, Ti ions were found despite the absence of clinically detectable signs (Deppe et al., 2002). Methods of detection included similar spectroscopy methods including Energy Dispersive X-ray Spectroscopy (EDS), Back-Scattered Electron (BSE), Secondary Electron (SE) probes, Synchrotron Radiation X-Ray Fluorescence (SRXRF), Flameless Atomic Absorption Spectroscopy (FAAS), Secondary Ions Mass Spectroscopy (SIMS), Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES), and Vibrational Raman and Infrared Spectroscopies (Table 2).

- In vitro studies

Four articles using in vitro assays were reviewed (Table 3) (Mints, Elias, Funkenbusch, & Meirelles, 2014; Senna, Antoninha Del Bel Cury, Kates, & Meirelles, 2015; Sridhar et al., 2016; Wennerberg et al., 2004). Studies also showed implant surface damage in addition to detection of Ti particles after implant insertion, particularly at the osteotomy walls and at the implant-bone interphase, with a higher prevalence at the crestal bone regions. One study specified the Ti particle size which ranged from 10nm to 20 μm (Senna et al., 2015). The presence of Ti particles was confirmed by various methods including Scanning Electron Microscopy (SEM) and different spectroscopy methods including EDS and BSE probe.

Quality assessment of included human and animal studies

The quality assessment of all reviewed articles followed the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, Green, 2011) (Supplementary Tables 6-8). The evaluations for risk of bias are shown in Figure 2. The assessment of cross-sectional and case-control studies resulted in a lower risk of bias. Issues were identified with case-series and case-reports studies (Fig. 2A). Some of the non-randomized studies lacked information on the cohorts' follow-up, and it is also possible that longer studies could affect the outcome; therefore, the risk of bias was unclear. Except for the items mentioned above, most aspects were considered satisfying, particularly the ones assessed on cohort studies, case-control studies, and cross-sectional studies (Fig. 2A-B). Animal study assessment had numerous criteria and required specific information to be available in the papers. Most studies satisfactorily included animal numbers, species, and ethical statement; but lack information on animal source, strain, sex, age, allocation concealment, randomization, approval number, welfare-related assessment, statistical methods used. Consequently, most in vivo studies were classified as unclear risk of bias (Fig. 2C).

Discussion

Peri-implantitis is described as an inflammatory process of the peri-implant soft tissues with the presence of progressive loss of supporting bone beyond natural bone remodeling ("Peri-implant mucositis and peri-implantitis: a current understanding of their diagnoses and clinical implications," 2013; Sanz, Chapple, & Working Group 4 of the, 2012). Recent studies have reported conflicting results regarding the prevalence of peri-

implantitis. While a low percentage (~2%) of disease have been reported (Buser et al., 2012), systematic reviews indicated the prevalence of peri-implant mucositis and peri-implantitis as 43% and 22% respectively. (Derks & Tomasi, 2015). Although peri-implantitis was initially considered a periodontitis-like lesion; it is well established now that it represents a more complex entity with numerous etiologic and contributory factors (Dalago, Schuldt Filho, Rodrigues, Renvert, & Bianchini, 2017; Derks et al., 2016; Suarez-Lopez Del Amo et al., 2017). Bacterial plaque, imbalance between the implant and the host altering the foreign body equilibrium and other causes were proposed as mechanisms for marginal bone loss and peri-implantitis (Trindade, Albrektsson, Tengvall, & Wennerberg, 2016). Thus, the influence of different implant surfaces and systems on the incidence, severity, and treatment outcomes for peri-implantitis has been investigated (Albouy, Abrahamsson, Persson, & Berglundh, 2011; Derks et al., 2015; Fickl, Kebschull, Calvo-Guirado, Hurzeler, & Zuhr, 2015). These studies demonstrated high variability among the different implant systems. While the present systematic review was not able to compare the Ti particles surrounding different implant systems, the reviewed studies on healthy and peri-implantitis sites reported higher concentration of Ti particles around the peri-implantitis (D. G. Olmedo et al., 2013; Safioti et al., 2017).

The substitution of turned surface implants for implants with moderately rough and rough surfaces decades ago is of paramount importance and aimed at providing faster and greater osseointegration and preservation of the marginal bone levels, among others biological benefits. Nonetheless, while presenting with numerous advantages, the utilization of these newer surfaces also led to potential disadvantages and complications. Some studies showed that surfaces presenting a higher degree of roughness might experience more bone loss once peri-implantitis occurred, while turned surface implants responded more favorably to treatment. (Albouy, Abrahamsson, & Berglundh, 2012; Albouy et al., 2011; Berglundh, Gotfredsen, Zitzmann, Lang, & Lindhe, 2007). Moreover, rougher implants with higher peaks were related with an increased number of particles released at the bone-implant interface during insertion (Schliephake et al., 1993; Senna et al., 2015).

While Ti alloys with several other metals are commonly used in implantable devices such as screws and plates, commercially pure Ti and the Ti-6Al-4V alloy are primary

materials used on endosseous implants (Elias, Lima, Valiev, & Meyers, 2008). Ti and its alloys are the most widely employed material for dental and medical applications (Elias et al., 2008). Many advantages can be attributed to the use of Ti in dental implants including strength and biocompatibility (Sykaras, Iacopino, Marker, Triplett, & Woody, 2000). Despite the excellent properties of the Ti, the local and systemic accumulation of Ti particles has been reported. The reports indicated that it might a result of implant surface corrosion (Flatebo et al., 2011; Flatebo et al., 2006; D. G. Olmedo et al., 2010), although Ti and Ti alloys were initially considered capable of withstanding corrosion (Solar, Pollack, & Korostoff, 1979). Exogenous sources and other dental products were proposed as possible sources. Multiple investigators also associated the cause of the Ti release to the insertion and friction of the implant into the osteotomy site. (Flatebo et al., 2006; He et al., 2016; Martini et al., 2003; Schliephake et al., 1993; Tanaka et al., 2000). The in vivo studies confirmed that Ti particles could be released during implant insertion and corrosion, while in vitro investigations mainly focused on the insertion process. Once Ti particles detached from the implant surface, they can remain embedded in the peri-implant tissues or be transported to other body sites such as lymphatic nodes, lungs, kidneys, and liver by macrophages. (D. Olmedo, Guglielmotti, & Cabrini, 2002; D. G. Olmedo, Tasat, Guglielmotti, & Cabrini, 2003; D. G. Olmedo, Tasat, Guglielmotti, & Cabrini, 2008; Schliephake et al., 1993).

Multiple reviewed studies reported on the higher prevalence of the particles around diseased implants depicting a strong association between Ti particles and peri-implant disease (Fretwurst et al., 2016; Safioti et al., 2017). The reports of Ti particles sizes in the nanometer (nm) and micrometer (μm) range are of paramount importance for this topic. The tested implants originated particles ranging from 15nm to 45 μm in the animal model studies, while similar the size particles were found in human samples. The Ti particles found in human tissues ranged from 100 nm to 54 μm. Interestingly, particles of similar sizes were used to investigate the inflammatory response, cytotoxicity, and DNA damage response caused by the Ti (Cadosch et al., 2010; Liu et al., 2013; Meng et al., 2009; Nishimura et al., 2014; Pettersson et al., 2017).

The results from this systematic review indicated that Ti particles are a common finding around the dental implants. This observation aligns with the findings related to

orthodontic mini-implants and Ti devices for maxillofacial purposes, which also release Ti particles (de Morais et al., 2009; Nautiyal, Mittal, Agarwal, & Pandey, 2013). Additionally, the release of Ti particles was reported in the medical field after joint replacement (Abu-Amer, Darwech, & Clohisy, 2007; Case et al., 1994; Grosse et al., 2015). The total joint replacement has a high long-term success rate, although it requires frequent revisions due to aseptic loosening caused by wear debris (Marshall, Ries, Paprosky, & Implant Wear Symposium Clinical Work, 2008). The Ti particles were found in multiple locations. Similar to particle from the dental implants, their range is in the nanometer and micrometer units, although some reports even described particles in the millimeter range (Bitar & Parvizi, 2015; Grosse et al., 2015).

The most common methods of Ti particle release discussed in the reviewed papers were the implant corrosion, insertion, implant-abutment friction, and wear during debridement, implantoplasty and other decontamination methods (Figure 3). An example of Ti release into the peri-implant tissue due to implantoplasty is depicted in Figure 4.

Based on the data presented in this review, possible clinical measures could potentially reduce the release of Ti and metal-like particles into the peri-implant tissues. First, the precise installation of the fixture without excessive pressure against the osteotomy site could significantly reduce the detachment of particles. The utilization of turned surface implants could diminish the presence of such particles after insertion (Goodman, Davidson, Song, Martial, & Fornasier, 1996; Scarano et al., 2003); yet, turned surface implants also present with disadvantages and limitations (Smeets et al., 2016). The careful manipulation of the implant surface during maintenance could also limit the damage to the superficial aspect of the fixture and the release of particles. Similarly, the utilization of different barriers methods during implantoplasty could reduce the impregnation of the surrounding tissues.

Limitations of the present investigation include the risk of bias. Several studies were restricted to the analyses of implant affected by peri-implantitis or reactive lesions. Lack of randomization and healthy controls was commonly observed. Similarly, studies often employed different methods of investigation for particles identification at one specific time point, which may affect the determination of the exact origin of the particles and potentially

leading to inaccurate assumptions. Lastly, the biological impact of Ti particles on cells around the implant and in different organs needs to be further elucidated.

Conclusion

While additional studies are necessary to further elucidate the effects of Ti particles on the tissue around the implant, several conclusions can be drawn from the present review. First, the prevalence of Ti particles around diseased implants is higher than surrounding healthy fixtures. Similarly, more particles can be found in sites and patients with the dental implant than in patients without fixtures. Second, the current literature presents four main theories or explanations to the presence of Ti particles and metal-like particles surrounding dental implants (i.e., implant insertion; friction of abutment-implant platform; implant surface decontamination, namely implantoplasty and debridement procedures; and corrosion). Notably, the potential detrimental effect of such particles in different cell populations remains to be further explored. These Ti and metal-like particles were found locally and systemically and vary in size and shape. Further considerations are the enhancement of the installation procedures to avoid excessive friction on the osteotomy site, and precise and delicate maintenance and surgical procedures around implants. Lastly, the employment of turned surface implants would be a consideration for decreasing the detachment of particles.

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Figures:

Figure 1: PRISMA flowchart of the screening process in the different databases

Figure 2: Assessment of quality and risk of bias of included studies

Figure 3: Mechanisms for titanium and metal particles release around the dental implants

Figure 4: Example of TI release in the peri-implant tissue.

Tables:

Table 1: Human studies reporting on the presence of Ti and metal particles

Table 2: In vivo studies reporting on the presence of Ti and metal particles

Table 3: In vitro studies reporting on the presence of Ti and metal particles

Supplementary information:

Supplementary table 1: Criteria for quality assessment of human case reports

Supplementary table 2: Criteria for quality assessment of human case series

Supplementary table 3: Criteria for quality assessment of human cross-sectional studies

Supplementary table 4: Criteria for quality assessment of animal studies

Supplementary table 5: Excluded investigations and justification

Supplementary table 6: Quality assessment of human non-randomized studies based on the Newcastle-Ottawa Scale (NOS)

Supplementary table 7: Quality assessment of human case reports, case series and cross-sectional studies based on The Joanna Briggs Institute (JBI) critical appraisal checklist

Supplementary table 8: Quality assessment of animal research based on predefined grading scores.

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	Type of Study	Description/ Condition of Sites	Type of implant	Prevalence/Location of Particles		Method for particles identification	Particles description	Suspected method for release of particles
Olmedo et al. 2003	Case series	10 biopsies from 10 failed implants **Analysis:** Peri-implant tissues **FU:** N/A	N/A	Presence of granulation tissue in all samples with diffuse macrophage distribution (range: 3-302 macrophages) and more abundant when closer to implant surface. Macrophages cytoplasm presented Ti particles.		LM, SEM, EDS	Round 1-3 μm particles	Corrosion of implant surface
Flatebø et al. 2006	Prospective	**Test:** 13 post-operative biopsies from 13 patients **Control:** 13 Pre-operative biopsies from same 13 patients **Analysis:** Oral epithelium, Peri-implant tissues **FU:** Pre-operative and 6 months post-surgery	Nobel Biocare*	**Control**	**Test**	LM	Dense and minute (<10 μm) particles	Corrosion of implant surface, Implant insertion
				No traces of foreign bodies within examined tissues	Scattered dense particles within epithelial and connective tissue located in proximity with cover screw surfaces. Mean number of particles between 2.04-13.74.			
Olmedo	Case report	2 peri-implant biopsies	Case 1: Ti	**Case 1**	**Case 2**	Histology,	**Case 1:** Multiple	Corrosion of

et al. 2010		from reactive lesions. **Analysis:** Peri-implant tissues **FU:** 2 months (Case 1) and 12 years (Case 2) post-surgery.	Grade 4, acid etched surface (Titantec*) Case 2: N/A	Metal-like particles noted and no details regarding location. No Ti identified with ICP-OES due to reduced sample volume. Histopathological diagnosis was pyogenic granuloma	Metal-like particles noted with no details regarding location. Histopathological diagnosis was peripheral giant cell granuloma	LM, ICP-OES (only Case 1)	granular, blackish, metal-like particles. **Case 2:** Isolated, free, blackish, metal-like particles.	implant surface
Flatebø et al. 2011	Prospective	**Test:** 6 biopsies of post-operative of implant sites from 6 patients **Control:** 6 biopsies of pre-operative from same 6 patients **Analysis:** Peri-implant tissues **FU:** Pre-operative and 6 months post-surgery	Pure Ti (Branemark System, Nobel Biocare*)	**Control**: Ti signals detected in most superficial surfaces of oral mucosa (Range: 0.30-0.94 mg/kg). No particles were identified with EDS	**Test**: Higher Ti signals in connective tissue adjacent to cover screw. Few larger particles detected with EDS	High-resolution optical darkfield microscopy, SEM, LA-ICP-MS, EDS	Particles size ranged between 100-5000 nm for control and 140-2300 nm for test biopsies	Corrosion of implant surface, Implant insertion

Olmedo et al. 2012	Cross-sectional	153 biopsies during Implant Stage 2 procedures from 153 patients with single, healthy, uncovered implants **Analysis:** Peri-implant tissues after 6 months of implant placement	Nobel Biocare*, Federa*, Straumann*	Despite the absence of clinical signs of metallosis, 41% of the biopsies showed Ti particles located at the connective tissue in proximity to the cover screw. These were found outside cell cytoplasm and/or phagocytized by cells.		IHC, SEM, EDS	Varying in number (460-550 particles in a 12.0 μm2) and additional sizes (0.9-3 μm2).	Corrosion of implant surface, Implant insertion
				Control	**Test**			
Olmedo et al. 2013	Prospective	**Test:** 15 biopsies from failing implants (peri-implantitis) harvested from 15 patients. **Control:** 15 biopsies from healthy implants harvested from 15 patients **Analysis:** Peri-implant tissues, Cytology **FU:** N/A	Ti Grade IV (Odontit*, Rosterdent*, B&W*)	Cytologic smears revealed metal-like particles not corresponded to Ti. Concentration of Ti samples was 0.41-0.88 ppb. No metal-like particles or traces of Ti signals by ICP-MS	Cytologic smears showed metal-like particles not corresponded to Ti. Higher concentration of Ti (2.02-2.44 ppb) compared to control sites. Separated or clustered particles present inside and/or outside epithelial cells and macrophages.	Cytologic smears. LM, ICP-MS	Varying in quantity, shape, and size.	Corrosion of implant surface, Placement/removal of prosthetic pieces (abutment/copping post), Exogenous sources (i.e. diet, dental products)

Wilson et al. 2015	Retrospective	36 biopsies of diseased implants harvested from 31 patients **Analysis:** Peri-implant tissues **FU:** N/A	N/A	Radiopaque foreign particles were identified in 34 of 36 biopsies. Predominant foreign bodies were Ti in 7 samples with concentrations ranging from 2%-43% and cement-related elements (Zr, Si, Al) in 19 samples.	LM, SEM, EDS	Diameter: 9-54 μm	Implant insertion, Wear during debridement or previous surgical attempt to arrest bone loss, corrosion of the implant surface, friction Implant-abutment
				Control	**Test**		
He et al. 2016	Case series	**Test:** 7 biopsies from 10 cadaveric jawbones with implants **Control:** 6 biopsies from same 6 jawbones without implants **Analysis:** Peri-implant hard and soft tissues **FU:** N/A	N/A (n=3), Astra Tech* (n=2), Straumann* (n=2)	Average Ti content was 634 ± 58 μg/kg-bone weight. No Ti particles were identify	From all investigated elements (Ti, Al, Cd, Cr, Co, Cu, Fe, Mn, Mo, Ni and V), only Ti content was significantly higher (1940 ± 469 μg/kg-bone weight) compared to control sites and increased at upper half of bone crest. Ti particles identified in bone marrow area at 60-700 nm from implant	LM, SEM, EDS, ICP-MS, LA-ICP-MS	0.5-40 μm	Implant insertion Implant-abutment wear

					surface.			
Fretwurst et al. 2016	Prospective	**Test:** Hard (n=7) and soft (n= 5) biopsies from 12 patients with diseased implants. **Control:** 1 ceramic implant **Analysis:** Peri-implant hard tissue biopsies **FU:** N/A	Ti Grade 4 (Camlog*, Straumann*, SteriOss* and Nobel Biocare*)	**Control** No presence of Ti or Iron	**Test** Ti and Iron elements noted in 9/12 (75%) of the samples. High Ti concentrations observed mainly in soft tissues ($7.53x10^5$ count)	SRXRF, Polarized LM	N/A	Implant-abutment wear
				Control	**Test**			

Halperin-Sternfeld et al. 2016	Retrospective	**Test:** 28 biopsies from I-RL, I-PG and I-PGCG **Control:** 88 biopsies from T-RL, T-PG and T-PGCG **Analysis:** Peri-implant and gingival tissues **FU:** N/A	N/A	Similar histologic features between T-RL and I-RL, and T-PGCG and I-PGCG. 18 out of 44 biopsies revealed foreign bodies and located within connective tissue stroma	Significantly lower values of multinucleated giant cell count, lower density of mesenchymal cells and more diffuse stromal morphology on I-PGCG. 13 out of the 14 samples were associated with foreign bodies and located within connective tissue stroma	Polarized LM	Black, crystalline or colorless structures with a fragment and needle-like shape	N/A
Safioti et al. 2017	Case control	**Test:** 20 samples from diseased implants **Control:** 20 samples collected from healthy implants **Analysis:** Submucosal peri-implant plaque **FU:** N/A	N/A	**Control** Mean Ti levels were 0.07 ± 0.19ng/µl	**Test** Mean Ti levels significantly higher in diseased (0.85 ± 2.47 ng/µl) compared to control samples	ICP-MS	N/A	Corrosion of the implant surface

Table 1: Human studies reporting on the presence of Ti and/or metal particles

Abbreviations - Ti: Titanium; SEM: Scanning electron microscopy; LM: Light microscopy; IHC: Immunohistochemistry; EDS: Energy dispersive X-ray spectroscopy or EDX; ppb: Parts per billion; ICP-MS: Inductively coupled plasma mass spectroscopy; LA-ICP-MS: Laser ablation

inductively coupled plasma mass spectroscopy; ICP-OES: Optic emission spectroscopy with inductively coupled plasma; SRXRF: Synchrotron radiation X-ray fluorescence spectroscopy; Al: Aluminum; Cr: Chromium; Cd: Cadmium; Co: Cobalt; Cu: Copper; Fe: Iron; Mn: Manganese; Mo: Molybdenum; Ni: Nickel; V: Vanadium, I-RL: Peri-implant soft tissue reactive lesions, T-RL: Tooth-associated reactive lesions; I-PG: Peri-implant pyogenic granuloma, I-PGCG: Peri-implant giant cell granuloma, T-PG: Tooth-associated pyogenic granuloma, T-PGCG: Tooth-associated giant cell granuloma, *: Implant brand name and surface reported on the original article.

Author/ Year	Description/Condition of Sites	Type of implant	Prevalence/Location of Particles	Method for particles identification	Particles description	Suspected method for release of particles
Schliephake al. 1993	**Test:** 12 implants (n= 2 per mini-pig) placed in mandibles of 6 mini-pigs. **Control:** 9 mini-pigs with no implants **Analysis:** Implant surface, peri-implant tissues and parenchymal organs **FU:** Immediately and 5 months post-surgery.	Titanium fixtures (Nobelpharma AB*)	TI particles embedded in peri-implant bone after implant placement. No traces of particles after 5 months at implant sites. Significant Ti concentrations found in lungs, liver and kidneys of test group compared to control group.	SEM, BSE probe, EDS, FAAS	Round solid (15x30 µm) and thin leaf-like 10x10x0.5 µm)	Implant site preparation, Implant insertion
Weingart et al. 1994	**Test:** 12 implants placed in maxillae and mandibles of 19 beagle dogs. **Control:** 5 animals with no implants. **Analysis:** Submandibular and deeper cervical lymph nodes, cerebrum, cerebellum, spleen, kidneys, lungs and liver **FU:** 9 months post-surgery	Plasma-coated Ti implants (Bonefit 3.3*)	Iron-free metallic pigment was found in lymph nodes of 12/19 animals of test group. Ti levels ranged between 0.16-9.0 µg/g in lymph nodes and 0.01-0.21 µg/g for visceral organs.	LM, SEM, EDS, FAAS	N/A	Implant insertion, Transport of Ti particles by phagocytes to regional lymph nodes

Wennerberg et al. 1996	**Test:** 60 implants placed in tibiae and femur of 10 New Zealand white rabbits **Control:** N/A **Analysis:** Peri-implant tissues and implant surface **FU:** 12 weeks post-surgery	Screw-shaped Ti Implants with a 25 µm (n= 30) and 75 µm (n= 30) a coating of Al^2O^3 particles	Slight smoother texture in 75um blasted implants after insertion. Particulates noted under SEM speculated to be Al^2O^3 blasting medium as their source of origin. Also, Al signaling detected via spectroscopy in areas with no visible particles. No negative effects of bone were found.	LM, SEM, Auger electron spectroscopy	N/A	Corrosion of implant surface
Tanaka et al. 2000	**Test:** 18 implants (n=6 per dog) placed in 3 beagle dog mandibles. **Control:** N/A **Analysis:** Peri-implant tissues **FU:** 3 weeks post-surgery	Pure titanium cylinder with Ti sprayed coating. (Nikon*)	Traces of granular-like components (HA and Titanium) at bone surface and rarely found beyond the implant-bone interface	LM, SEM, X-ray microanalyzer, TEM, Electron diffraction	Granular-like components with a 1.8-3.2 µm diameter	Implant insertion
Deppe et al. 2002	**Test:** 60 implants irradiated with CO^2 laser placed in 6 beagle dog mandibles (n= 10 per dog). Treatment of ligature-induced peri-implantitis (3 months) with either air-powder abrasive, laser therapy and Air-powder plus laser therapy. **Control:** N/A **Analysis:** Peri-implant tissues, spleen, liver, regional lymph nodes,	Plasma spray-coated Frialit-2 titanium implants (Friadent AG*)	No clinically detectable titanium related pigment found in peri-implant tissues. Titanium ions identified in all examined organs. Mean Ti concentration of 1.83 µg/g Fresh Weight in oral mucosa and ranged between 1-30-4.14 µg/g within the examined organs. No correlation between titanium concentration in local tissues and method of treatment.	ICP-AES	N/A	Corrosion of Implant surface

	lungs, kidneys **FU:** 4 months post-surgery.						
Frisken et al. 2002	**Test:** 12 implants inserted in mandibles of 12 sheep. **Control:** 4 sheep with no implants. **Analysis:** Lymph nodes, lungs, spleen and liver. **FU:** 1, 4, 8 and 12 weeks post-surgery	Smooth surface self-tap Mark II implants (Nobel Biocare*)	**Control** No differences in levels of Ti in any of the examined organs when compared to test sites.	**Test** Higher Ti concentration in animal tissues with failed implants.	Atomic absorption spectrophotometer	N/A	N/A
Martini et al. 2003	**Test:** 12 implants placed in 2 mongrel sheep femur and tibia diaphysis with a TPS + FHA-Ti coating. **Control:** 12 implants with a TPS coating alone. **Analysis:** Peri-implant tissues **FU:** 12 weeks post-surgery	Tapered cylindrical implants (Biocoating*)	**Control** TPS-coated implants revealed Ti particles found at implant surfaces and inside the newly formed bone within 200–250 nm or greater distance. Ti debris detectable in the bone	**Test** FHA particles found in medullary spaces near implant surfaces with a broader distribution and located at greater distances than TPS-coated implants. The greater the distance, the smaller the particles.	LM, SEM, SE and BSE probes, EDS, Vibrational Raman and Infrared spectroscopies	N/A	Implant insertion

			medullary spaces.				
Wennerberg et al. 2004	**Test:** 14 of 38 implants with an Al^2O^3 blasted coating of 25 µm, 75 µm and 250 µm particles placed in proximal tibiae of New Zealand white rabbits. **Control:** 2 of the 14 implants had one-sided turned surface **Analysis:** Peri-implant tissues **FU:** 12 weeks and 1-year post-surgery	Commercially Pure Ti (Grade I)	**Control** Lesser Ti release from turned implants when compared to rough implants.	**Test** Ti was concentrated more in bone marrow than cortex. Gradual Ti ion release extended up to 400 µm from implant surfaces and concentration ranged between 20-100 wt.ppm	SRXRF, SIMS	N/A	Corrosion of implant surface
Franchi et al. 2004	**Test:** 28 implants inserted into femoral and tibial diaphysis of 2 mongrel sheep. **Control:** N/A **Analysis:** Peri-implant tissues **FU:** Immediately and 14 days post-surgery	Conic screws with STi, TPS, alumina oxide SLA, zirconium oxide SLA surfaces (Or-Vit*)	Only TPS implants showed Ti granules at the bone-implant interface immediately and 14 days after implant placement		LM, SEM, SE and BSE probes	9-45 µm	Implant insertion
Meyer et al. 2006	**Test:** 4 implants with a 0.4 µm surface roughness installed in the mandible of 2 Gottinger mini-pigs.	Cylindrical screw-type implants with	**Control** Ti contamination along peri-implant bone as in	**Test** Ti more frequently observed at crestal part	SEM, EDS	Small angular or round elongated particles next to	Implant insertion

	Control: 8 implants with a 1.5µm (SLA) and 2.2 µm (TPS) surface roughness (n=4 per surface) **Analysis:** Peri-implant tissues **FU:** 1 day post-surgery.	SLA and TPS coating (Straumann*) and a novel conical-type turned surface implant	test sites. Highest amount of Ti observed with TPS, followed by SLA surfaces	of the block samples. Less Ti amount than TPS and SLA surfaces		SLA and ILI implants. Large and oval-shaped particles around TPS implants. Nano-sized particles (up to 10 nm) were also noted	
Franchi et al. 2007	**Test:** 24 implants placed in tibia diaphysis of 2 sheep. **Control:** N/A **Analysis:** Peri-implant tissues **FU:** 14 and 90 days post-surgery	TPS implants	Ti detectable at bone trabeculae, bone marrow and tibia diaphysis canal. Higher concentrations in marrow tissue than bone matrix. Significant overall particle reduction by 66.4% between 14 days and 90 days. Smaller particles (<250 μm^2) were reduced by 81.5% while larger particles did not showed variations. Particles extended up to 500 µm away from implant surface	LM, SEM, SE and BSE probes, EDS	Small Ti particles of different sizes (<250 μm^2 and 251-2000 μm^2) within peri-implant environment.	Implant insertion
Wennerberg et al. 2011	**Test:** 20 implants with nanometer-sized HA placed in tibiae among 10 Sprague-Dawley rats. 16 of 20 implants had an additional Calcium coating (^{45}Ca). **Control:** N/A **Analysis:** Peri-implant tissues,	Commercially pure (Grade 4) turned implants	Particles deposited and aligned along implant surface. Gradual decrease of the Calcium coating overtime in peri-implant tissues and blood. Increased ^{45}Ca levels was noted only in the liver	Autoradiography, SEM, Powder X-ray diffraction	Crystalline particles with an apatite crystal structure. Distinct, needle-shaped nanoparticles of 15x100 nm.	Corrosion of Implant surface, Transport of Ti particles to other organs due

	brain, liver, thymus, kidney, blood **FU:** 1, 2, 4 and 8 weeks post-surgery	to biologic cleaning system

Table 2: In vivo studies reporting on the presence of Ti and/or metal particles

Abbreviations - Wt.ppm: Weight.Parts-per-million; FU: Follow-up; Ti: Titanium; Al: Aluminum; SEM: Scanning electron microscopy; TEM: Transmission electron microscopy; LM: Light microscopy; TPS: Titanium plasma sprayed; HA: Hydroxyapatite; FHA-Ti: Fluorohydroxyapatite coating; SLA: Sand-blasted, large grit, acid-etched; STi: Smooth Titanium; EDS: Energy dispersive X-ray spectroscopy; SRXRF: Synchrotron radiation X-ray fluorescence spectroscopy; ICP-AES: Inductively coupled plasma atomic emission spectroscopy; SIMS: Secondary ions mass spectroscopy; SE: Secondary electron; BSE: Back-scattered electron; FAAS: Flameless atomic absorption spectroscopy; N/A: Not available; *: Implant brand name and surface reported on the original article.

Author/Year	Type of Study	Description/Condition of Sites	Type of implant	Prevalence/Location of Particles	Method for particles identification	Particles description	Suspected method for release of particles
Wennerberg et al. 2004	N/A	**Test:** 24 of 38 implants immersed in 10ml of 1% lactic acid aqueous solution **Control:** Implants immersed in 10ml of 0.1mol/l PBS **Analysis:** Ions in aqueous media **FU:** a month post-immersion	Commercially Pure Ti (Grade I) turned or sandblasted	Ti ions released into aqueous media with no difference between both control and test implants	SRXRF, SIMS	N/A	Corrosion of Implant surface
Senna et al. 2013	N/A	**Test:** 18 implants (n=6 per group) **Control:** N/A **Analysis:** Cow rib bone blocks **FU:** Immediately post-placement	TiUniteTM MkIII (Nobel Biocare*), OsseoSpeedTM TX (Astra Tech*), and SLActive® (Straumann AG*).	All implant sites showed Ti particles mostly at crestal bone level. More particles noted with Astra implants at micro-thread region. Straumann also showed alumina particles	SEM, BSE probe, EDS	Size: 10nm to 20µm. Up to 0.5 mg of particles from reduced implant volume	Implant insertion
Mints et al. 2014	N/A	**Test:** 9 implants (n=3 per examined surface)	Turned, acid-etched, and	1 PFB per group was evaluated. Only anodized implants revealed	SEM, EDS	Nano- to micro- Ti	Implant insertion

		Control: N/A **Analysis:** PFB blocks **FU:** Immediately post-placement	anodized implants with commercially pure Ti grade 3	particles along osteotomy site. Smaller and larger particles noted at crest and mid-apical regions, respectively		particles along block with the anodized implant	
Sridhar et al. 2016	N/A	**Test:** 16 implants (n=8 per block density) **Control:** N/A **Analysis:** PFB blocks of 10, 12, 30 and 40 PCF **FU:** Immediately post-placement	Standard SLA Tissue Level Implants (Straumann*)	Exfoliated material within osteotomy walls of the PFB	Digital optical microscopy and Powder X-ray diffraction	Non-metallic exfoliated material (polyuretheane debris)	Implant insertion/removal

Table 3: In vitro studies reporting on the presence of Ti and/or metal particles

Abbreviations - FU: Follow-up; PCF: Per cubic foot; SLA: Sand-blasted, large grit and acid-etched; Ti: Titanium, PBS: Phosphate buffered solution; PFB: Polyurethane foam blocks; SEM: Scanning electron microscope; EDS: Energy dispersive X-ray spectroscopy; SIMS: Secondary ions mass spectroscopy; SRXRF: Synchrotron radiation X-ray fluorescence spectroscopy; BSE: Back-scattered electron; N/A: Not available; *: *: Implant brand name and surface reported on the original article.

Figure 1

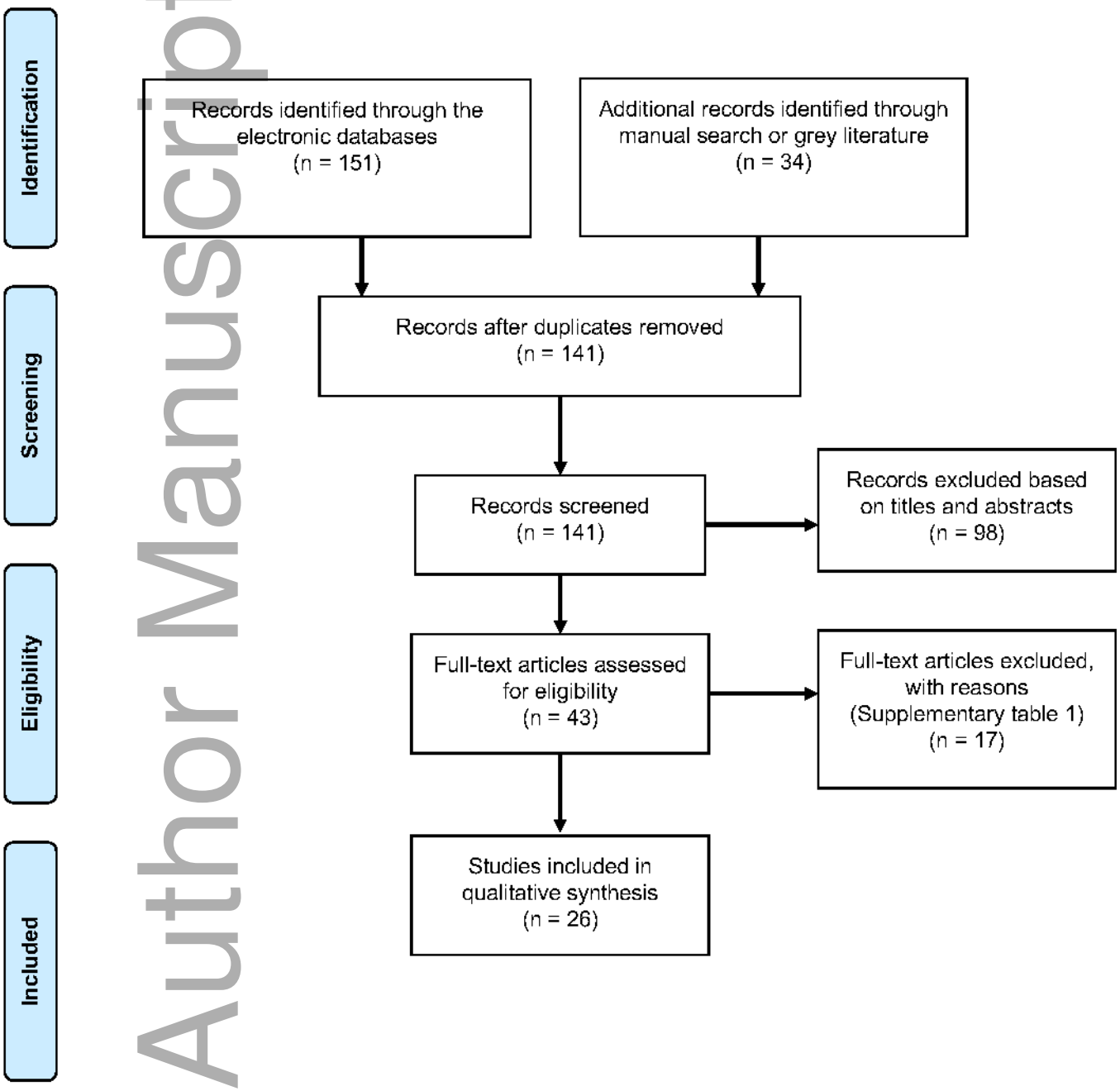

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Figure 2

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Figure 3

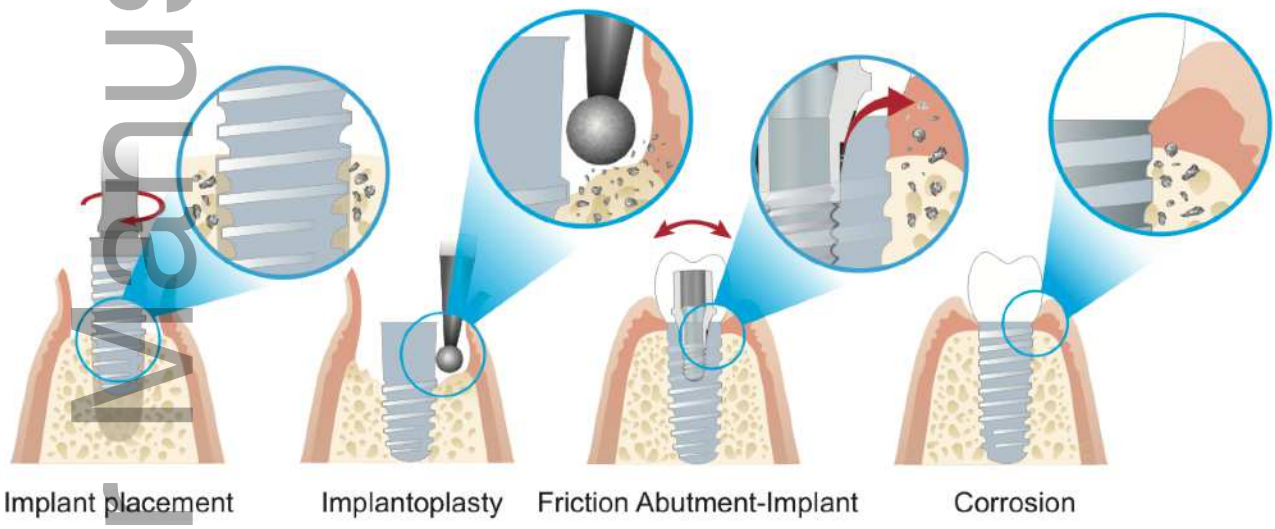

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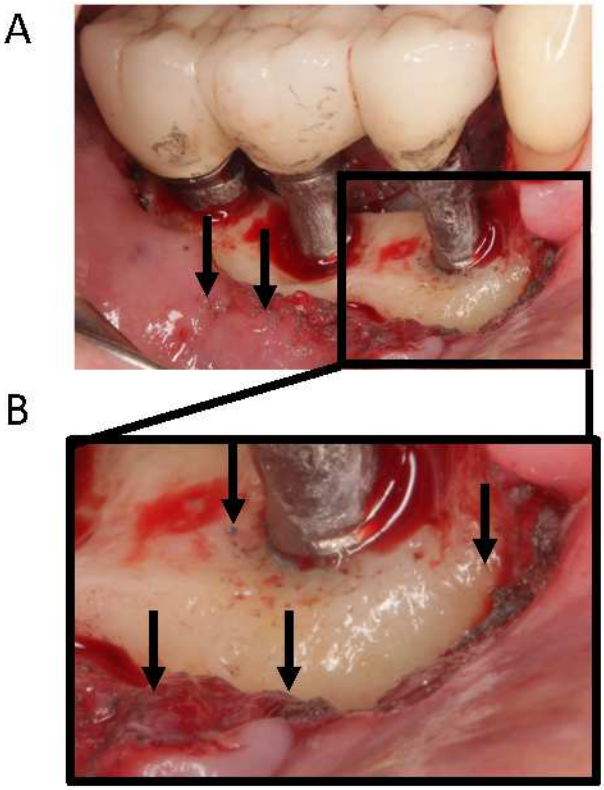
Figure 4



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