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Systematic Review

Inflammatory, Reactive, and Hypersensitivity Lesions Potentially Due to Metal Nanoparticles from Dental Implants and Supported Restorations: An Umbrella Review

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Abstract: The present umbrella review aimed to assess the prevalence of cases diagnosed with lesions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations, characterizing lesions' macroscopic, imaging, and microscopic features. Secondary aims were to categorize the reported lesions as resembling or ascribable to peri-implant mucositis and peri-implantitis, reactive lesions of the peri-implant mucosa, or hypersensitivity reactions, and to evaluate their relationship with cases', dental implants, and implant-supported restorations' characteristics, and with the evidence of Titanium allergy. The study protocol, developed in advance and compliant with the PRISMA statement, was registered on PROSPERO (CRD42022354676). Systematic reviews were searched through the Web of Science, Scopus, MEDLINE/PubMed, Cochrane library databases, and the PROSPERO register until 19 August 2022; reference lists were also screened. Data from four systematic reviews of critically low/low quality (AMSTAR 2), one including a meta-analysis, were analyzed qualitatively. An overall prevalence of 16.9% of cases was estimated. Reported lesions resembled or were ascribable to peri-implant mucositis and peri-implantitis (55.17%), reactive lesions (17.22%), and hypersensitivity reactions (24.12%); no oral contact lichenoid lesions were described. Titanium allergy was hardly and heterogeneously investigated. Due to the severely incomplete data, no definitive conclusions could be drawn on the potential role of cases' and implant characteristics and Titanium allergy on lesions onset, development, and treatment responsiveness.

Keywords: oral; periodontal; peri-implant; lesions; reactions; nanoparticles; dental implant; hypersensitivity; Titanium; alloy

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1. Introduction

Dental implants have been increasingly used in the last decades to restore function and aesthetics in partial and total edentulism [1–7], thus improving the quality of life for dental patients [8,9]. Dental implant design and surface topography have been continuously ameliorated according to peri-implant outer and inner tissue biology [10–12]. Titanium is the leading material employed for dental implant fixtures, mainly owing to its biocompatibility, corrosion resistance, and high tensile strength, likely accounting for their long-term stability and recorded survival rates [13]. As a counterpart, a complex interplay between biofilm adhesion, chemical contact, and mechanical wear [9] has been proposed to be involved in dental implant surface degradation [14], more recently characterized as "tribocorrosion", which may determine the release of metal ions and particles within the surrounding tissues [15]. Considering that commercially pure titanium grade II and

grade IV are the most employed materials for dental implant fixtures, and a Titanium alloy (Ti6Al4V) is the most used for the abutment and prosthetic structures, tribocorrosive processes may lead to Titanium and, to a minor extent, Aluminium and Vanadium particles release [15].

Such metal nanoparticles have been presumably implied, in conjunction with foreign bodies (i.e., cementum), chronic irritation and biofilm accumulation due to complex and improper oral hygiene maintenance, especially in case of implant exposure [16], in the onset of reactive exophytic lesions of the peri-implant mucosa [17]. Such lesions, mainly represented by pyogenic granuloma and peripheral giant cell granuloma, are characterized by high recurrence rates, electively requiring excision and curettage and leading to dental implants explantation in about 41% of the cases [17]

Moreover, Titanium nanoparticles released by dental implant degradation are considered a common finding in peri-implant soft and hard tissues [18] and have been detected in peri-implant submucosal biofilm [9]. In detail, larger amounts of Titanium nanoparticles were found in peri-implant mucosa [13,19] and the submucosal biofilm [20] of peri-implantitis sites compared to healthy ones. Thus, such nanoparticles have been somehow implied in peri-implant disease pathogenesis [21], raising further concerns about dental implant degradation and inflammation [9] of the outer and inner peri-implant tissues [10,11].

Furthermore, similar to mucocutaneous and boney hypersensitivity reactions from Titanium alloys of medical devices, including pacemakers, stents, orthopedic prostheses, and others [21,22], also those suspected to be related to Titanium nanoparticles from dental implants were first described in 2008 [20] and recognized as putative epiphenomena of underlying immune-inflammatory allergic disorders. Indeed, T-cell-mediated delayed hypersensitivity immune reactions to Titanium alloy nanoparticles from dental implants have been proposed to be responsible, in genetically susceptible and sensitized subjects [23], for the genesis of heterogeneous lesions that constitute the spectrum of allergic contact stomatitis. Thus, localized edema and aspecific erythematous maculae, vesicles, or erosive-ulcerative lesions, as well as white hyperkeratotic plaques, which are generally identified as oral lichenoid contact reactions [24], similar to those known to be causatively related to dental amalgam [25], metals from removable prostheses, and teeth-/implant-supported restorations [24], have been related to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations.

Considering that metal nanoparticles from dental implants may be involved in peri-implant mucositis and peri-implantitis pathogenesis and in the development of peripheral giant cell granuloma and pyogenic granuloma, and taking into account that the most common hypersensitivity reactions to dental materials are induced by metals [26], with T-cell-mediated delayed metal sensitivity approximately affecting 15% of the general population [27], the present umbrella review aimed to assess the prevalence of cases diagnosed with lesions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations, characterizing lesions' macroscopic, imaging, and microscopic features. Secondary aims were to categorize the reported lesions as lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, reactive lesions of the peri-implant mucosa, and orofacial, periodontal, and peri-implant hypersensitivity reactions, and to evaluate their relationship with cases' history of allergies, comorbidities and ongoing pharmacological therapies, dental implants, and implant-supported restorations' characteristics, and evidence of Titanium allergy.

2. Materials and Methods

2.1. Study Protocol

The study protocol was developed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [28] before the literature search, data extraction, and analysis and was registered on PROSPERO systematic review register (CRD42022354676).

Question formulation records search and study selection strategies were based on the PEO (Population-Exposure-Outcome) [29] model, a modified version of the PICO one [30]. The research question [31] was focused on the prevalence, macroscopic, imaging, and microscopic features of lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, of peri-implant reactive lesions and of orofacial, periodontal, and peri-implant hypersensitivity reactions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations, specifically:

P—Population: subjects with dental implants and implant-supported restoration(s);

E—Exposure: lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, peri-implant reactive lesions, and orofacial, periodontal, and peri-implant hypersensitivity reactions potentially due to the release of Titanium (alloy) or other metal nanoparticles from dental implants and implant-supported restorations;

O—Outcomes: definitive diagnosis, diagnostic procedure(s), pharmacological therapy, treatments, resolution/progression of the lesions, and evidence of titanium allergy.

2.2. Search Strategy

Systematic reviews (with or without meta-analysis) published in the English language concerning orofacial, periodontal, and peri-implant inflammatory, reactive, and hypersensitivity lesions potentially related to metal nanoparticles released from dental implants were electronically searched without date restrictions till 19 August 2022 across the PROSPERO register and Web of Science (Core Collection), Scopus, MEDLINE/PubMed and Cochrane Library databases, by two independent reviewers (F.D.S., M.P.D.P.), combining the following keywords with Boolean operators:

1. Titanium OR titaniums OR titanium alloy

   And

2. hypersensitivity OR sensitivity OR sensitive OR sensitivities OR sensitives OR sensitivity AND reaction OR reactions OR hypersensitivity AND reaction OR reactions

   And

3. dental implants OR dental AND implants OR dental implant.

The following filters were applied: "Review (English) and "refine: systematic review" on the Web of Science database; "Review (English)" on the Scopus database; "Systematic Review (English)" on the MEDLINE/PubMed database; "Keywords" on the Cochrane library; no filters were employed on the PROSPERO register.

2.3. Study Selection and Eligibility Criteria

Collected citations were recorded, duplicates were eliminated through EndNote™ (Clarivate) reference management tool, and the remaining titles were screened by two independent reviewers (F.D.S., M.P.D.P.). The two same reviewers independently screened potentially relevant title abstracts of systematic reviews with or without meta-analysis. Full texts of those records compliant with the eligibility criteria and ambiguous title-abstracts were obtained, also contacting study authors in case unavailable full texts, and full texts were independently reviewed by the same authors (F.D.S., M.P.D.P.). Any disagreement was solved by discussing till consensus with a third author (F.D.) when necessary.

Reference lists of potentially eligible/included articles were also screened for relevant titles, and the subsequent study screening was performed as already described.

Inclusion criteria were systematic reviews, with or without meta-analysis, published in the English language, concerning lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, peri-implant reactive lesions, and orofacial, periodontal and peri-implant hypersensitivity reactions potentially due to Titanium (alloy) or other metal nanoparticles released from dental implants and implant-supported restorations. No restrictions regarding the date of publication, number of studies, and study design included in each systematic review, number of diagnosed cases, dental implants and implant-supported

restorations' characteristics, definitive diagnosis, diagnostic procedures, and lesions therapies/treatments were applied.

Data concerning orthopedic implants, likely pre-existing and self-diagnosed oral lesions, as well as lesions of the oral mucosa related to previously identified mucous, mucocutaneous, and systemic diseases and disorders, were currently excluded.

2.4. Data Extraction and Collection

Data were independently extracted in duplicate by two authors (F.D.S. and M.P.D.P.) on a standardized data extraction form developed from the models proposed for intervention reviews on RCTs and non-RCTs [31] before data extraction; a third author (F.D.) was involved in case of disagreement.

From each systematic review (with or without meta-analysis) included in the present umbrella review, the following data criteria were recorded:

- First author, year, journal, funding, quality of the study;
- Number and design of studies included in each systematic review;
- Sample size, gender ratio, and mean age of the study population of each review;
- Cases' number, gender ratio, mean age, history of allergies (any), comorbidities, ongoing pharmacological therapies, smoking habit, Plaque Index [32];
- Dental implants number, position, general characteristics, and survival;
- Implant-supported restoration types and materials;
- Macroscopic (number, distribution, location), imaging (description) and microscopic (description) features, and time to onset of the lesions described, categorized as resembling or ascribable to peri-implant mucositis and peri-implantitis, peri-implant reactive lesions, and orofacial, periodontal and peri-implant hypersensitivity reactions;
- Definitive diagnosis, diagnostic procedure(s), pharmacological therapy, treatment, resolution/progression of those lesions potentially related to Titanium (alloy) or other metal nanoparticles released from dental implants and implant-supported restorations, and evidence of titanium allergy.

2.5. Data Synthesis

A narrative synthesis of the data concerning the investigated population, exposure, and outcomes was conducted.

Data from included studies were qualitatively synthesized through descriptive statistical analysis using the Microsoft Excel software 2019 (Microsoft Corporation, Redmond, WA, USA):

- To assess the prevalence of cases diagnosed with lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, peri-implant reactive lesions, and orofacial, periodontal, and peri-implant hypersensitivity reactions potentially due to Titanium (alloy) or other metal nanoparticles released from dental implants and implant-supported restorations;
- To characterize reported lesions based on macroscopic, imaging, and microscopic features;
- To assess the frequency of reported lesions, categorized as lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, peri-implant reactive lesions, and orofacial, periodontal and peri-implant hypersensitivity reactions;
- To relate the reported lesions with cases' history of allergies, comorbidities, and related ongoing therapies;
- To relate the reported lesions with implants' characteristics;
- To relate the reported lesions with Titanium allergy evidence.

2.6. Quality Assessment

The quality assessment of the systematic reviews presently included was performed through the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2 tool,

accessed online (https://amstar.ca) on 19 August 2022, evaluating for quality the systematic reviews of randomized and/or nonrandomized studies [33].

3. Results

3.1. Study Selection

A total of 2509 records were identified from the electronic search, specifically 64 from Web of Science (Core collection), 216 from Scopus, 2053 from MEDLINE/PubMed, 174 from the Cochrane library databases, and 2 from the PROSPERO register. In total, 281 duplicates were eliminated, 2228 title abstracts were screened, and 2217 were excluded. Of the 11 abstracts relevant to and compliant with the eligibility criteria of the present systematic review, full texts were screened, and seven articles were furtherly excluded, specifically because: (n = 2) not relevant; (n = 1) narrative and (n = 1) scoping reviews; (n = 1) cross-sectional study; (n = 2) not describing orofacial lesions. A total of four systematic reviews were finally included in the present umbrella review; no relevant records were retrieved from the subsequent screening of the reference lists.

Figure 1 illustrates the study selection flowchart for electronically retrieved records.

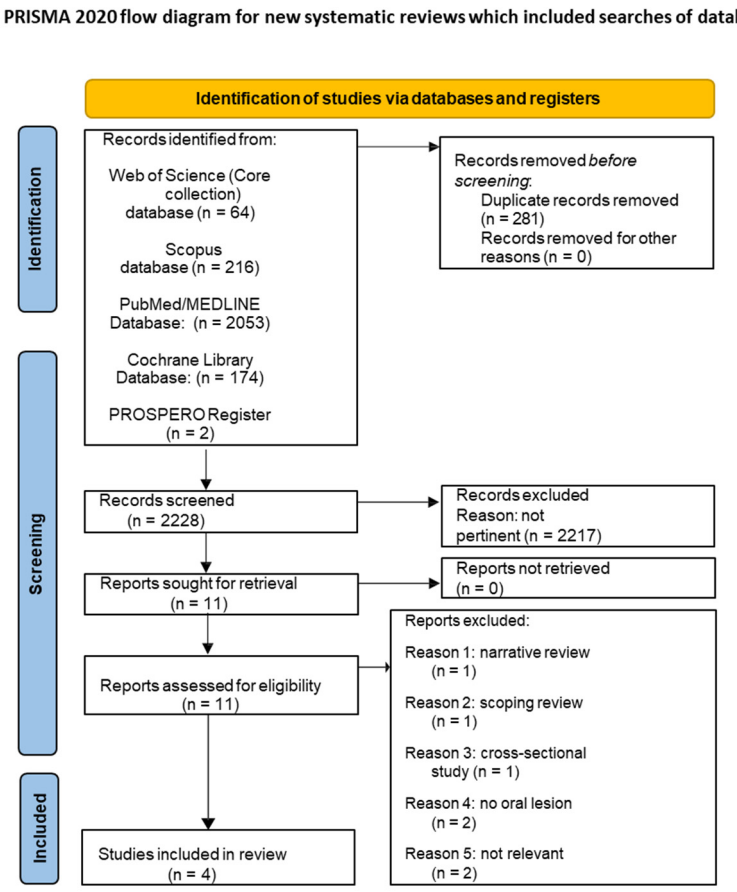

Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only.

3.2. Study Characteristics and Qualitative Synthesis

Of the four systematic reviews presently considered [34–37], one also included meta-analysis [37], all full texts were available, and no authors declared funding. Three studies were of a critically low [34,36,37] and one of a low [35] quality, based on the AMSTAR 2 tool evaluation. All the systematic reviews [34–37] analyzed results from clinical (cross-sectional and/or retrospective and/or prospective) studies, along with case reports and case series.

Data were extracted and collected based on eligibility criteria from seven cohort, four case-control, six undefined clinical studies, one prospective and one retrospective study,

and from five case reports and three case series, overall involving 3277 participants. Age and gender ratio were recorded for 509 participants, specifically 149 males and 360 females, with a mean age of 52.74 (Table 1).

Table 1. Data extracted and collected from the studies included in the present systematic review. Source: First Author, year, reference, journal of publication, meta-analysis, assessed quality, and funding (if any). Studies of the systematic reviews included in the present umbrella review: design and number. The population of the systematic reviews included in the present umbrella review: sample size (n.), number of subjects with Titanium allergy, mean age (y.o.), and gender ratio (M/F). Cases diagnosed with lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, peri-implant reactive lesions, of orofacial, periodontal, and peri-implant hypersensitivity reactions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations: sample size (n.), number of subjects with Titanium allergy, mean age (y.o.), gender ratio (M/F), history of allergies, other comorbidities, ongoing pharmacological therapies, smoking habit, Plaque Index [32]. Dental implants: number, position, characteristics, survival (months/years). Implant-supported restorations: type, materials. Reported lesions and hypersensitivity reactions: macroscopic features (number, distribution, location); imaging features; microscopic features, time to onset. Definitive diagnoses, treatments, and progression; evidence of titanium allergy.

Source	Studies and Population	Cases	Dental Implants Implant-Supported Restorations	Reported Lesions and Hypersensitivity Reactions	Diagnosis, Therapy, and Progression Evidence of Titanium Allergy
Javed, 2013 [34] CIDRR No meta-analysis Critically Low quality	Studies: n.7 CR (n.2) CS (n.1) RS (n.1) PS (n.1) Clinical (n.1) Experimental (n.1) Sample size: n.127 (n.32, 25.2% with Ti allergy) Mean age: 46 y.o. (14.3–84.1 y.o.) Gender ratio: 34M/74F/19MD	Cases n.113 n.30 (38.45%) with Ti allergy Mean age: 46.9 y.o. Gender ratio: 33M/71F/19MD **History of allergies:** MD **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: MD Position: MD Characteristics: MD Survival: MD; or 6 months or more than 6 months **Restorations** Type: MD Materials: MD	**Macroscopic features:** MD Number: MD Distribution: MD Location: MD **Imaging features:** MD **Microscopic features:** MD **Time to onset:** MD	All Cases **Definitive diagnosis**: MD **Diagnostic procedure(s):** MD **Pharmacological Therapy:** MD **Treatment:** MD **Resolution/Progression:** MD **Evidence of Titanium allergy:** MD
		Case n.1 n.0 (0%) with Ti allergy Mean age: 50 y.o. Gender ratio: 1F **History of allergies:** MD; **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: 2 Position: MD Characteristics: MD Survival: 2 years **Restorations** Type: MD Materials: MD	**Macroscopic features:** "Chronic inflammatory response with fibrosis" Number: MD Distribution: MD Location: peri-implants tissues **Imaging features:** MD **Microscopic features:** MD **Time to onset:** MD	

Table 1. *Cont.*

Source	Studies and Population	Cases	Dental Implants Implant-Supported Restorations	Reported Lesions and Hypersensitivity Reactions	Diagnosis, Therapy, and Progression Evidence of Titanium Allergy
		Case n.1 n.0 (0%) with Ti allergy Mean age: 49 y.o. Gender ratio: 1F **History of allergies:** MD **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: 6 Position: MD Characteristics: MD Survival: 1 week **Restorations** Type: MD Materials: MD	**Macroscopic features:** Swelling and hyperemia (with pain) Number: MD Distribution: MD Location: MD **Imaging features:** MD **Microscopic features:** MD **Time to onset:** MD	
		Cases n.2 n.2 (100%) with Ti allergy Mean age: 46.5 y.o. (44–49 y.o.) Gender ratio: 1M/1F **History of allergies:** MD **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: 8 Position: MD Characteristics: MD Survival: n.4 implants for 2 weeks; n.4 implants for 3.5 months **Restorations** Type: MD Materials: MD	**Macroscopic features:** Peri-implant mucosa and gingival overgrowth ("hyperplasia") Number: MD Distribution: MD Location: gingival tissues **Imaging features:** MD **Microscopic features:** MD **Time to onset:** MD	
Müller-Heupt, 2022 **[35]** Int J Impl Dent No mea-analysis Low quality	Studies: n.10 CS (n.1) Clinical unspecified study (n.2) Cohort study (n.7) Sample size: n.1951; (n.70, 3.6% with Ti allergy) Mean age: MD Gender ratio: MD	Cases n.2 N/D with Ti allergy Mean age: MD Gender ratio: MD **History of allergies:** MD **Other comorbidities:** v1 case with psoriasis or seborrheic eczema; Other cases MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: MD Position: MD Characteristics: MD Survival: MD **Restorations** Type: MD Materials: MD	**Macroscopic features:** MD Number: MD Distribution: MD Location: MD **Imaging features:** MD **Microscopic features:** MD **Time to onset:** MD	**Definitive diagnosis:** MD **Diagnostic procedure(s):** Positive patch test reactions for: Ti in 35/511 (6.9%) sbjs Ti dioxide in 7/599 (1.2%) sbjs Ti (IV) isopropoxide in 8/272 (2.9%) sbjs Ti (IV) oxalate in 17/216 (7.9%) sbjs Ti lactate in 2/45 (4.4%) sbjs Ti citrate in 1/45 (2.2%) sbjs Negative patch test reactions for: Ti chloride tested in 207 sbjs Ti(IV) oxid tested in 56 sbjs **Pharmacological Therapy:** MD **Treatment:** MD **Resolution/Progression:** MD **Evidence of Titanium allergy:** Positive Patch test result(s)

Table 1. *Cont.*

Source	Studies and Population	Cases	Dental Implants Implant-Supported Restorations	Reported Lesions and Hypersensitivity Reactions	Diagnosis, Therapy, and Progression Evidence of Titanium Allergy
Poli, 2021 [36] Materials No meta-analysis Critically low quality	Studies: n.7 CR (n.3) CS (n.1) CC (n.1) Clinical study (n.1) Clinical and Experimental (n.1) Sample size: n.401; Mean age: 67.1 y.o. Gender ratio: 106M/295F	Case n.1 N/D with Ti allergy Mean age: 56 y.o. Gender ratio: F **History of allergies:** MD **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: 4 Multiple Position: mandible (43–44–45–46) Characteristics: MD Survival: 9 months **Restorations** Type: MD Materials: MD	**Macroscopic features:** Swelling and redness, bleeding and a probing depth of 6 mm, buccally and 5 mm lingually, high mucosal "hypersensitivity" and implant exposure" Number: N/D Distribution: N/D Location: all peri-implant tissues **Imaging features:** Bony defect with a crater-like shape around the first molar implant and cervical decay on teeth and vertical bone loss involved the new implants, and the process of external resorption affected the teeth up to the canine **Microscopic features:** Absence of any kind of bone lesion or disease **Time to onset:** MD	**Definitive diagnosis:** MD **Diagnostic procedure(s):** Biopsy of cortical and medullary bone (see microscopic features) Blood tests = increased number of eosinophils Bacterial culture = negative MELISA test = titanium hypersensitivity **Pharmacological Therapy:** MD **Treatment:** Implant removal + Placement of five one-piece zirconia implants (4 in the anterior jaw and 1 in the right molar region) **Resolution/Progression:** Healed **Evidence of Titanium allergy:** Positive MELISA test result(s)
		Case n.1 N/D with Ti allergy Mean age: 49 Gender ratio: F **History of allergies:** MD **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: 6 Multiple Position: mandible Characteristics: n.2 cylindrical implants (GMI, Southern Implants–Pty- Ltd., Centurion, South Africa) Survival: MD **Restorations** Type: MD Materials: MD	**Macroscopic features:** Swelling and hyperemia (no pus and no necrosis); lip crease Number: MD Distribution: MD Location: peri-implant tissues, submental region, lip **Imaging features:** Irregular radiolucent areas at the apex and sides of the implants **Microscopic features:** Foci of subacute and moderate chronic inflammation, granulation tissue, and giant cells **Time to onset:** MD	**Definitive diagnosis:** Type IV hypersensitivity **Diagnostic procedure(s):** Biopsy of peri-implant tissues **Pharmacological Therapy:** Metronidazole 400 mg **Treatment:** Peri-implant debridement and implant removal + Amoxicillin 500 mg and Ibuprofen 400 mg **Resolution/Progression:** MD **Evidence of Titanium allergy:** MD

Table 1. *Cont.*

Source	Studies and Population	Cases	Dental Implants Implant-Supported Restorations	Reported Lesions and Hypersensitivity Reactions	Diagnosis, Therapy, and Progression Evidence of Titanium Allergy
		Cases n.2 N/D with Ti allergy Mean age: 69.5 Gender ratio: 2F **History of allergies:** MD **Other comorbidities:** MD Ongoing pharmacological therapies: MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: 3 Single/2Multiple Position: n.1 mandible; n.2 maxilla (22–23) Characteristics: n.1 Ti grade 4 acid-etched surface (Titantec, Proaltec S.A., Buenos Aires, Argentina); n.2 Branemark-like designed implant. Survival: MD **Restorations** Type: MD Materials: MD	**Macroscopic features:** Proliferative lesion (n.1: 1 × 1 × 0.6 cm) with a smooth and bright red surface bleeding on palpation; Distal vestibular sessile red and irregular lesion (n.1: 0.6 × 0.5 × 0.4 cm). Number: 2 Distribution: Single Location: n.1 implant 22 **Imaging features:** n.1 lesion with no bone loss; n.1 lesion with cup-shaded bone loss **Microscopic features:** Intense vascular proliferation, mixed inflammatory infiltrate, and abundant macrophages. Numerous "metal-like particles", inclusions within macrophages, perivascular region **Time to onset:** MD	**Definitive diagnosis:** Pyogenic granuloma (n.1) Peripheral giant cell granuloma (n.1) **Diagnostic procedure(s):** MD **Pharmacological Therapy:** MD **Treatment:** Surgical removal of the lesion and curettage + Chlorhexidine 2% gel **Resolution/Progression:** No recurrence **Evidence of Titanium allergy:** MD
		Cases n.70 N/D with Ti allergy Mean age: 48.9 y.o. Gender ratio: 36M/34F **History of allergies:** n.19 unspecified allergen **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: MD Position: MD Characteristics: MD Survival: MD **Restorations** Type: MD Materials: MD	**Macroscopic features:** "Clinical symptoms and/or implant loss" (n.16) Number: MD Distribution: MD Location: MD **Imaging features:** MD; no changes in 1 case **Microscopic features:** MD **Time to onset:** MD	**Definitive diagnosis:** MD **Diagnostic procedure(s):** Cutaneous and epicutaneous test for Ti: Test: 9 positive (25.7%) MELISA test: 13 positive (37.5%) for Ti and 3 (21.4%) for Ni Control: 0 positive (0%) **Pharmacological Therapy:** MD **Treatment:** MD **Resolution/Progression:** MD **Evidence of Titanium allergy:** Positive N/D test result(s)

Table 1. *Cont.*

Source	Studies and Population	Cases	Dental Implants Implant-Supported Restorations	Reported Lesions and Hypersensitivity Reactions	Diagnosis, Therapy, and Progression Evidence of Titanium Allergy
		Cases n.327 N/D with Ti allergy Mean age: 58.9 y.o. Gender ratio: 79M/248F **History of allergies:** MD **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: MD or 2 Position: MD or right lower molars Characteristics: n.2 implants with a rough surface (TiOblast) Fixture MicroThread system (AstraTech Implant System, Mölndal, Sweden) Survival: MD **Restorations** Type: MD Materials: MD	**Macroscopic features:** Facial eczema and unspecified local reactions (n.4) Facial eczema only (n.1); Others MD Number: MD Distribution: MD Location: MD **Imaging features:** MD **Microscopic features:** MD **Time to onset:** 2 years	**Definitive diagnosis:** MD **Diagnostic procedure(s):** MELISA test and Patch test: the presence of lymphoblasts and Ti inclusions within the macrophages 218 Patch test for 28 metal types: 1 positive to Ti induced by orthopedic surgery; 217 (80.4%) positive to at least one metal; 4 positive to Ti and 11 positive to other metals among the 16 cases with allergy signs **Pharmacological Therapy:** MD **Treatment:** MD **Resolution/Progression:** MD **Evidence of Titanium allergy:** Positive MELISA or Patch Test result(s)
Singh, 2021 [37] J Pharm Bioallied Sci Meta-analysis Critically low quality	Studies: n.3 CC (n.3) (Original sample size n.798) Sbjs with dental implants: n.299; n.35 (11.7%) with Ti allergy Mean age: MD Gender ratio: MD	Cases n.35 N/D with Ti allergy Mean age: MD Gender ratio: MD **History of allergies:** MD **Other comorbidities:** MD **Ongoing pharmacological therapies:** MD **Smoking habit:** MD **Plaque Index:** MD	**Dental Implants** Number: MD Position: MD Characteristics: MD Survival: MD **Restorations** Type: MD Materials: MD	**Macroscopic features:** MD Number: MD Distribution: MD Location: MD **Imaging features:** MD **Microscopic features:** MD **Time to onset:** MD	**Definitive diagnosis:** MD **Diagnostic procedure(s):** Patch test for Ti dioxide in 248 sbjs with dental implants: 22 positive (8.9%); Patch test for Ti in 16 sbjs with dental implants: 4 positives (25%); Both cutaneous and epicutaneous tests for Ti dioxide in 35 sbjs with dental implants: 9 positive (25.7%) **Pharmacological Therapy:** MD Treatment: MD **Resolution/Progression:** MD **Evidence of Titanium allergy:** Positive patch test or cutaneous and epicutaneous tests result(s)

Abbreviations: Case Report, "CR"; Case Series, "CS"; Case-Control, "CC"; Retrospective Study, "RS"; Prospective Study, "PS"; male, "M"; female, "F"; years old, "y.o."; number, "n"; subject(s), "sbj(s)"; missing data, "MD"; not defined, "N/D"; titanium, "Ti"; Memory Lymphocyte Immonostimulation Assay, "MELISA".

Findings from 555 cases, accounting for 16.9% of the overall study population, diagnosed with lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, peri-implant reactive lesions, and orofacial, periodontal, and peri-implant hypersensitivity reactions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations, were obtained. Cases history of

allergies was reported in 19 cases [36]; allergens were not specified. Cases comorbidities described in two cases [35] were psoriasis and seborrheic eczema, and related therapies were not detailed.

Data on 31 dental implants [34,36,37] were currently retrieved. Dental implants' position was specified for two fixtures placed in maxillary [36] and eleven in mandibular [36] dental arches. Implant-supported restorations were never specified. Dental implant survival was noticed in five cases [34,36] in a time range between 1 week and 2 years.

The clinical appearance of the reported lesions was recorded in 29 (5.22%) cases, describing: (58.64%, n = 16) macroscopic features likely resembling peri-implant mucositis and peri-implantitis with or without implant loss (n = 2),defined as "clinical symptoms and/or implant loss" [36] and (3.44%, n = 1) swelling, erythema, bleeding of the peri-implant mucosa and a deep probing depth [36]; (6.89%, n = 2) exophytic lesions of the peri-implant mucosa, identified as Pyogenic granuloma and Peripheral giant cell granuloma [36], (6.89%, n = 2) gingival overgrowth (defined as "gingival hyperplasia") [34], and (3.44%, n = 1) a not better-defined peri-implant chronic inflammatory response with fibrosis [34], likely identifiable as reactive lesions of the peri-implant mucosa (17.24%, n = 5); (17.24%, n = 5) facial eczema and/or unspecified local reactions [36], (3.44%, n = 1) swelling and hyperemia [34], and (3.44%, n = 1) orofacial erythema, swelling and lip crease [36], ascribable to orofacial, periodontal and peri-implant hypersensitivity reactions (24.12%, n = 7) (Figure 2).

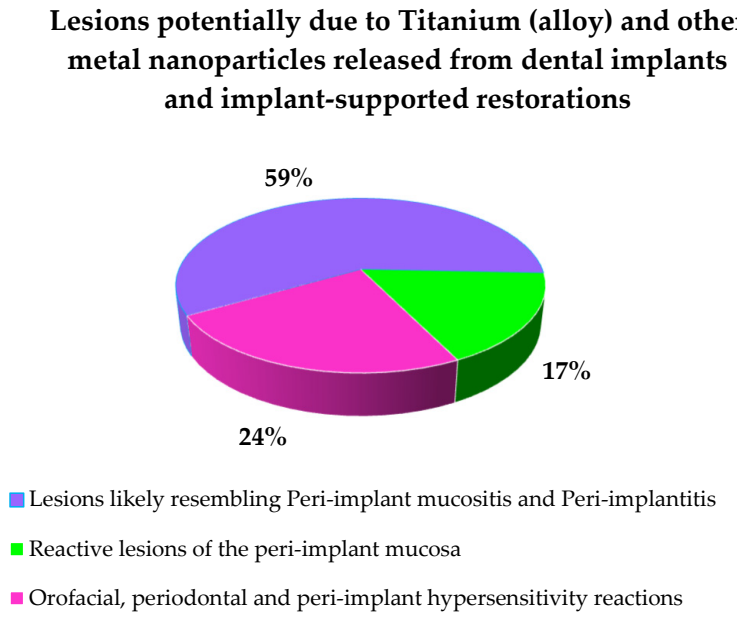

Figure 2. Frequency of described lesions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations, categorized as those likely resembling peri-implant mucositis and peri-implantitis, reactive lesions of the peri-implant mucosa and orofacial, periodontal and peri-implant hypersensitivity reactions.

The imaging features were illustrated in five cases [36], with images suggestive of peri-implant bone loss in two cases and showing an irregular radiolucent area in one case; no bone loss was observed in the remaining two cases [36]. Microscopic features were depicted in four cases, describing an inflammatory infiltrate and/or "metal-like" particle inclusions within macrophages in three cases [36]; no histopathological alterations were found in one case [36]. The time to lesion onset was delineated in one case diagnosed with facial eczema, occurring two years after implant placement [36].

Definitive diagnoses, reported in three cases, were (n = 1) type IV hypersensitivity ("orofacial erythema, swelling and lip crease") [36], (n = 1) pyogenic granuloma [36], and (n = 1) peripheral giant cell granuloma [36].

Diagnostic procedure(s) performed were: (n = 3.059) Patch Test reactions [35–37]; (n = 2) biopsy [36]; (n = 1) bacterial culture [36]; (n = 1) blood test [36]; (n = 86) epicutaneous tests [36,37]; (n = 37) MELISA tests [36,37].

The prescribed pharmacological therapy following lesions detection and diagnosis was specified in one case [36] with Metronidazole administration. In two cases [36], post-operatively administered Amoxicillin and Ibuprofen, or Chlorhexidine 2%, were reported. Lesions treatments were discussed in four cases [36] and comprised (n = 2) lesion excisional biopsy and curettage [36] and (n = 2) dental implant removal; in one case, the removed implant was replaced with a zirconia implant [36].

Lesion resolution was noticed in two cases [36] that underwent excisional biopsy.

The overall evidence of Titanium (alloy) or other metal allergies overall recorded in reported cases is shown in Figure 3.

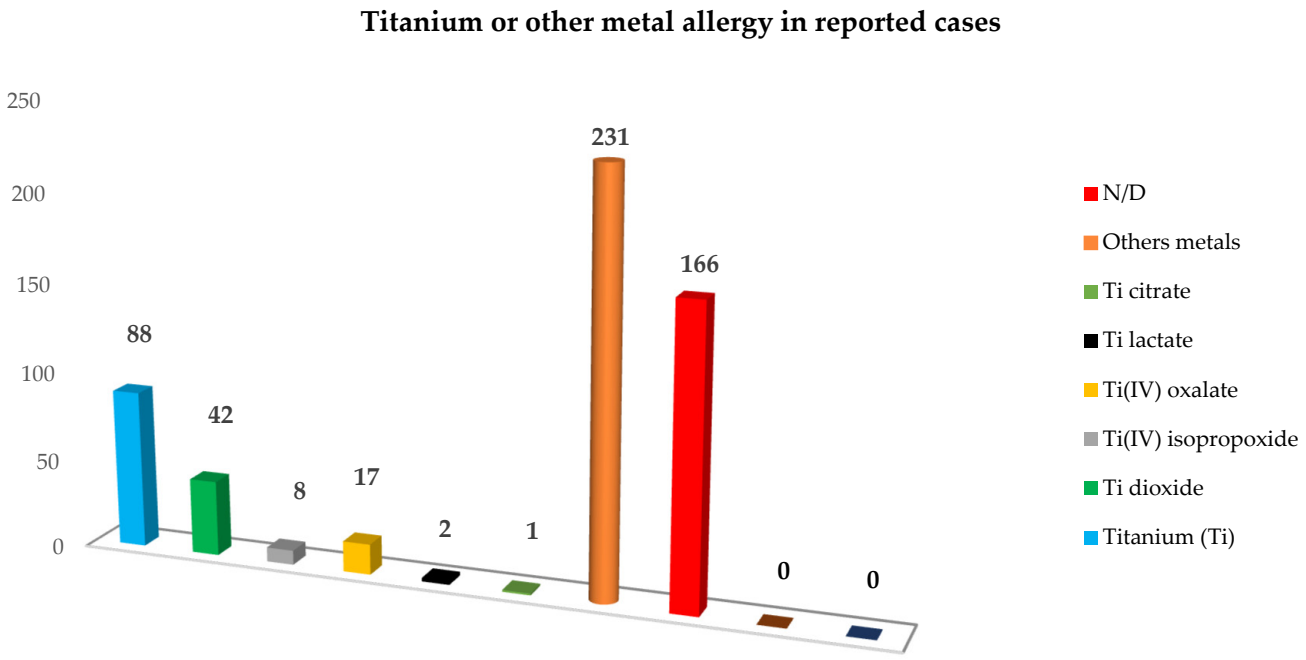

Figure 3. Titanium or other metal allergies in reported cases diagnosed with lesions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations.

Specifically, Titanium allergy was detected through MELISA testing in 1 case [36] and N/D tests in 16 cases [36], diagnosed with lesions likely resembling peri-implant mucositis and peri-implantitis (77.27%), respectively, and through both MELISA and Patch tests in five cases with orofacial, periodontal and peri-implant hypersensitivity reactions (22.72%), while no evidence of Titanium allergy was retrieved for reactive lesions (Figure 4).

3.3. Quality Assessment

Most of the studies were judged of critically low [34,36,37] or low [35] quality through the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2 tool [33], as illustrated in Table 1.

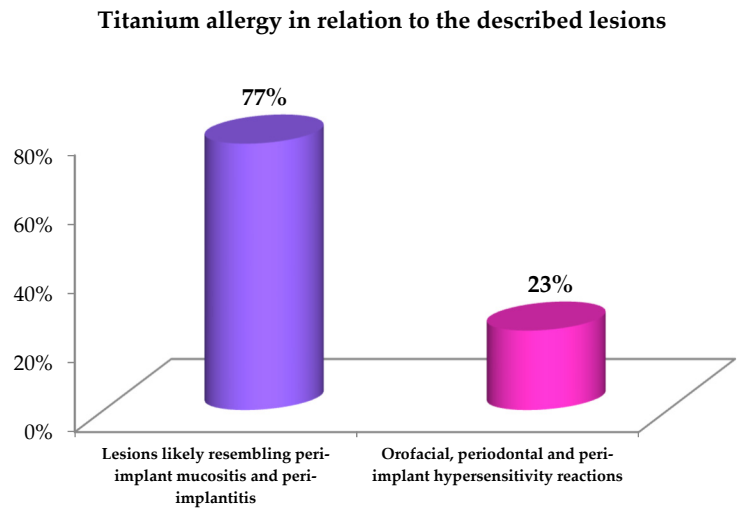

Figure 4. Frequency of Titanium allergy in relation to the described lesions, categorized as those likely resembling peri-implant mucositis and peri-implantitis, reactive lesions of the peri-implant mucosa, and orofacial, periodontal, and peri-implant hypersensitivity reactions.

4. Discussion

Four systematic reviews [34–37] were included in the present umbrella review, aiming to assess the prevalence of cases with lesions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations. Despite the greatly inclusive eligibility criteria, such a low number of studies included may be attributable to the little attention to the topic, which may be secondary to the fact that Titanium has long been regarded as a highly biocompatible, resistant, and excellent osseointegration material [13]. Coherently, the publication dates of the included studies were all extremely recent and consistent with the rising evidence and knowledge on the tribocorrosion phenomenon, which, brought to light only in recent years [9,15], has indirectly drawn attention to the possible effects that nanoparticles from dental implants may generate within peri-implant, periodontal and oral tissues, as well as in distant organs and systems [38,39].

A total of 555 cases, accounting for 16.9% of the overall population involved in the systematic reviews, were identified and may, fortunately, appear few, especially compared to the estimates of Titanium dental implants placed annually. Even so, cases' prevalence may be biased by underdiagnosed, misdiagnosed, or underreported lesions.

Recorded lesions were presently categorized as per their macroscopic features, described in only 29 (5.22%) out of 555 reported cases, as lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, peri-implant reactive lesions, and orofacial, periodontal and peri-implant hypersensitivity reactions.

4.1. Lesions Resembling or Ascribable to Peri-Implant Mucositis and Peri-Implantitis

Lesions likely resembling peri-implant mucositis and peri-implantitis, with or without implant loss [36], were recorded in 58.61% (n = 16) of the overall cases, corroborated by the radiographic finding of peri-implant bone loss in 6.89% (n = 2) of the cases [36]. In detail, dental implants were lost within one week to 2 years [34].

Coherently, it has been proposed that the immune-inflammatory reaction to Titanium could contribute to implant failure since bone resorption may be directly affected by the Titanium particles released. In detail, Titanium particles within 20 µm could induce the release of Tumor Necrosis Factor-alfa (TNF-a) and Interleukin (IL)-6 from fibroblasts in vitro [40], whereas those between 0.25 and 7 µm could increase PGE2 and IL-6 production by osteoblasts in vitro [41,42] and induce the expression of IL-6, TNF-a, and IL-1b in macrophages [43]. Consequently, IL-1b released by macrophages may induce the expression of RANKL [44], activating, in turn, osteoclasts and thus determining bone resorption [45].

Notably, evidence of Titanium allergy was reported in most cases (77.27%) with lesions resembling or ascribable to peri-implantitis [34,36]. Therefore, it may also be hypothesized that an altered bone turnover, combined with a possible hypersensitivity reaction to Titanium, further triggering the local inflammatory process, may cause implant failure.

Furthermore, attention should be paid to lesions potentially mimicking peri-implantitis in early stages, underlying, instead, primary or secondary malignancies [46].

4.2. Reactive Lesions of the Peri-Implant Mucosa

Reactive lesions, reported in 17.24% (n = 5) of the cases, mainly affected the peri-implant mucosa but also the gingiva [34] and appeared to be slightly more frequent in females, contrary to Quesada et al. findings [17].

Such lesions were described as gingival overgrowth, "gingival hyperplasia"(6.89%, n = 2) [34], not better-defined peri-implant chronic inflammatory responses with fibrosis (3.44%, n = 1), and reactive exophytic lesions (6.89%, n = 2), specifically diagnosed as peripheral giant cell granuloma and pyogenic granuloma [36]. In detail, the last two definitive diagnoses were in accord with the results of a retrospective study on 65 peri-implant tissue samples [46], revealing that peripheral giant cell granuloma and pyogenic granuloma accounted for 24.6% and 23% of all biopsy reports, respectively, thus being among the most frequent peri-implant lesions. Conversely, no fibro-epithelial hyperplasia, estimated to constitute 30.7% of the overall peri-implant lesions diagnoses [46], was recorded.

Imaging features, potentially highlighting the local aggressiveness of some reactive exophytic lesions [46], were only reported in one case and depicted boney defects [36].

Similarly, lesions recurrency, not specified in the systematic reviews, should also be taken into account since it has been recorded in 12.3% of peripheral giant cell granulomas and 6% of pyogenic granulomas [46], thus suggesting that excision and curettage of the lesion should be preferred to the resection surgical approach alone [17].

4.3. Orofacial, Periodontal, and Peri-Implant Hypersensitivity Reactions

Hypersensitivity reactions were reported in 24.12% (n = 7) cases, heterogeneously manifesting as (17.24%) facial eczema and/or unspecified local reactions [36], (3.44%) swelling and hyperemia [34], and (3.44%) orofacial erythema, swelling and lip crease [36].

Lesions' macroscopic features overlapped with the previously noticed clinical appearance of mucocutaneous hypersensitivity reactions to Titanium and comprised erythema [47,48], edema [49], urticaria [49], atopic dermatitis [50], facial eczema [51], and non-keratinized edematous proliferative hyperplasia [52]. Noteworthy, no oral contact lichenoid lesions, despite being the epiphenomenon of delayed type IV hypersensitivity reactions and commonly described in association with dental materials, especially metals from prosthetic rehabilitation [24], were recorded.

Similarly, imaging features closely resembled those described for bone hypersensitivity reactions to Titanium and encompassed impaired fracture healing [53], pain, necrosis, and weakening of orthopedic implants [54].

Microscopic features [36] consisted of intense vascular proliferation, mixed inflammatory infiltrates with abundant macrophages, foci of subacute and moderate chronic inflammation, granulation tissue, and giant cells; conversely, B lymphocytes were never detected. Numerous "metal-like" particle inclusions within macrophages have also been described. Accordingly, Titanium particles unexpectedly exhibited significant biological reactivity and have been demonstrated capable of inducing the immune-inflammatory response, increasing IL-1b, IL-6, prostaglandins, TNF-a, and granulocyte-macrophage colony-stimulating factor (GM-CSF) levels, with the consequent recruitment and activation of monocyte/macrophage lineage cells and T lymphocytes [55,56].

Moreover, since Titanium is used for producing various everyday goods beyond plastic and orthopedic surgery devices and dental implants [19], it may be inferred that the rapid spread of titanium-containing products, increasing the population's exposure to this metal, may result in an increased risk of latent sensitization. Such sensitization may be

crucial in susceptible individuals [19,57] and potentially determine an increase in orofacial, periodontal, and peri-implant hypersensitivity reactions also due to nanoparticles from dental implants.

Furthermore, Titanium nanoparticles have also been traced in distant lymph nodes and organs [38,39], including the liver, lungs, spleen, and kidney, where plasma proteins might probably convey them and phagocytic cells through the systemic bloodstream [58–60], so driving the attention to the possible occurrence of hypersensitivity reactions, elicited by nanoparticles released by dental implants, in distant organs.

4.4. Cases' Characteristics

No predilection for cases' age was presently found, similar to Neville et al.'s results [61,62].

The female gender, generally more prone to immune-inflammatory dysregulation and abnormal immune system reactions [63], mainly attributable to hormonal and immune factors [64], was found even more inclined to the development of reactive lesions of the peri-implant mucosa, as previously described for the gingival ones [65]. Noteworthy, a higher frequency of lesions resembling peri-implant mucositis and peri-implantitis was recorded in females, contrary to prevalence rates reported for the general population [66,67]. Females were also more inclined to orofacial, periodontal, and peri-implant hypersensitivity reactions (M/F = 139:368), as also suggested by Feller et al. [23]. Compared to males, the last finding may be partially explained by prolonged contact with cosmetic products containing various metals, including Nickel and Titanium. Indeed, overt lesions manifesting hypersensitivity reactions develop after repeated exposures in weeks or months to the antigen/allergen at sub-threshold concentration [68].

Nonetheless, a history of allergies was reported in only 19 cases [36], and the allergens were not specified. Such a datum, resulting largely missing, could be particularly relevant for hypersensitivity reactions, which are well known to occur against single or multiple antigens/allergens in genetically susceptible individuals [23,69], especially considering that some Titanium dental implants may contain minute traces of Nichel [70], a highly sensitizing allergen in the general population. The paucity of data on cases' pre-existing allergic diathesis has also precluded the possibility of hypothesizing on a possible cross-reactivity with other antigens/allergens underlying hypersensitivity lesions, although a definitive causative role of systemic allergens for oral hypersensitivity reactions has not been confirmed [23].

Analogously, comorbidities and systemic conditions potentially affecting oral, periodontal, and peri-implant mucosa [71,72] were only reported in one case with psoriasis and seborrheic eczema [35]. Such finding may be explained by the evidence that certain diseases such as connective tissue disease (e.g., systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis) are notoriously associated with an increased frequency of delayed hypersensitivity reactions to mercury, palladium, silver, nickel, and titanium [70]. Nevertheless, the predisposing or contributing role of autoimmune and dysimmune systemic disorders, such as Oral Lichen Planus, in periodontitis remains controversial [73]. Moreover, it is well known that, during pregnancy, periodontal and, presumably, peri-implant vasculature, immune cells, and microbiome [74] undergo typical modifications due to the higher sex hormones levels, thus enhancing tissue reactivity and promoting the development of exophytic reactive lesions [75–77]. However, given the paucity of retrieved data concerning cases' comorbidities, it could not be speculated on the putative predisposing or contributing role of systemic conditions, disorders, and related therapies on lesions development, progression, and treatment responsiveness.

Furthermore, the lack of data concerning ongoing pharmacological therapies would have also prevented differentiating oral lichenoid lesions, frequently linked to systemically administered medicaments, from oral lichenoid contact lesions, topographically related to the causative material [24,69], in any case not presently recorded.

No data were retrieved concerning smoking habit and plaque index, whose role in peri-implantitis is defined by a medium level of evidence [62]. In addition, biofilm accumu-

lation has long been reported among low-grade irritants, along with ill-fitting appliances, cervical cavities, and grossly carious teeth, concurring in developing reactive lesions [75]. Analogously, it may be proposed that biofilm and calculus accumulation may contribute to tissue inflammation in orofacial, periodontal, and peri-implant hypersensitivity reactions, thus precipitating their onset or favoring their worsening.

4.5. Dental Implant and Implant-Supported Restoration Characteristics

Data on 31 dental implants [34,36,37] were retrieved, although related characteristics were rarely detailed [36]; two Titanium dental implants [36] were removed, and one was replaced by a zirconia dental implant, with clinical lesion healing [36].

Indeed, Titanium dental implant surfaces could be a resource for releasing nanoparticles and microparticles with still ignored biological effects and biodistribution within the organism. In detail, nanoparticles were demonstrated to be capable of activating the host immune-inflammatory response [55,56] and supposed to be more biologically reactogenic, thus more harmful, than microparticles [78] due to the larger surface area-to-volume ratio [55,56]. In addition, nanoparticle aggregation may determine an unanticipated reduction of the immune-inflammatory response against them [79]. Furthermore, given the degenerative alterations of macrophages and neutrophils phagocytosing Titanium particles and the mutations in human cells cultured in a medium containing Titanium nanoparticles, nanoparticles may exert cytotoxic and genotoxic effects on peri-implant tissues, probably related to their physicochemical properties and concentration [48]. Coherently, dental implant survival, specified in only five cases [34,36], nonetheless ranged from 1 week to 2 years.

Degradation of the implant-abutment connection induces implant instability, material loss, micro-gap formation, and release of nanoparticles into the peri-implant tissues [79]. Considering that implant-abutment connections are exposed to corrosion and abrasion secondary to contact with the oral environment and chewing forces [43,79], a Morse taper implant-abutment connection may incur less deterioration of the coils compared to an external hex connection. Therefore, considering the fewer nanoparticles released from the implant and stimulating the immune system, such implant-abutment connections may be better tolerated by subjects predisposed to hypersensitivity reactions [22].

According to Tsushima et al. [69] and Olms et al. [26], approximately 40% of the lesions should likely be the epiphenomenon of hypersensitivity reactions to not better-defined implant-supported restoration materials, rather than Titanium; however, implant-supported restorations characteristics were never specified. Coherently, the metals employed in implant-supported rehabilitations, especially Nickel and Cobalt-based alloys, widely employed for prosthetic reconstructions [34], are known to be potentially responsible for allergic reactions, followed by Palladium [69]. Moreover, nickel is considered the allergen with the highest incidence of contact hypersensitivity, reaching 11.4% in the general population [80]. However, since the time to lesions onset following dental implant placement, as well as prosthetic rehabilitation, was not specified, the potential effect of metal nanoparticles from implant-supported restorations could not be safely ascertained.

4.6. Evidence of Titanium Allergy

Most allergy tests (41.6%) were positive for other metals, while 15.9% of cases tested positive for Titanium and 7.2% for Titanium dioxide. Coherently, commercially pure Titanium, when exposed to an aqueous medium or air, forms a passive oxide surface film that creates a high resistance to corrosion induced by acids, chlorides, and wet environments, with low elution of the Titanium ions [22]. However, disruption of the oxide layer can lead to metal corrosion and subsequent biocompatibility reduction [22]. This mechanism could explain the higher incidence found in the present study of allergy to pure Titanium compared to Titanium dioxide or others, which have been rarely detected—3.1% for titanium(IV) oxalate; 1.4% for titanium(IV) isopropoxide; 0.4% for titanium lactate; 0.2% to titanium citrate. Evidence of Titanium (IV) oxide or Titanium chloride sensitivity was never

recorded, and in almost 30% of cases, the type of metal involved in the hypersensitivity reactions was not specified.

Several tests are currently available to identify metal allergies. The Epicutaneous Patch Test is one of the most diffuse tests for metal allergy [22], although capable of only detecting about 75% of type IV metal allergies [81] and lacking standardization. Accordingly, 3145 epicutaneous Patch Tests [35–37] were recorded. The other diagnostic procedure most commonly conducted to identify the allergen responsible for the hypersensitivity reactions was Memory Lymphocyte Immuno-Stimulation Assay (MELISA) tests [36,37] in 37 cases. The MELISA test is a modified form of the lymphocyte transformation test (LTT) used to analyze the local and systemic effects of mucosal-sensitizing allergens in vitro [22]. Celebrant et al. [82] compared the Patch Test, MELISA test, and conventional LTT and pointed out that the MELISA test is accompanied by a high number of false positives, whereas the Patch Test should be considered the gold standard for investigating the presence of metal allergy. Oral mucosa patch tests may be introduced to assess Titanium allergy, as previously proposed for dietary Nickel [83].

Titanium allergy was detected through MELISA testing in 1 case [36] and N/D tests in 16 cases [36], diagnosed with lesions likely resembling peri-implant mucositis and peri-implantitis (77.27%), respectively, and through both MELISA and Patch tests in five cases with orofacial, periodontal and peri-implant hypersensitivity reactions (22.72%). In contrast, no evidence of Titanium allergy was retrieved for reactive lesions (Figure 4).

The main limitation of the present umbrella review may rely on the few systematic reviews retrieved, despite the very inclusive eligibility criteria. Consequently, the presently computed prevalence of cases diagnosed with inflammatory, reactive, and hypersensitivity lesions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations may have been biased by underreporting, underdiagnosis and misdiagnosis.

The incomplete data recorded on lesions' macroscopic, imaging, and microscopic features may have led to an inaccurate categorization of lesions resembling or ascribable to peri-implant mucositis and peri-implantitis, of peri-implant reactive lesions, and of orofacial, periodontal, and peri-implant hypersensitivity reactions. However, lacking data may be presumably due to the fact that Titanium has long been regarded as highly biocompatible, that the phenomenon of dental implant degradation has been only recently disclosed, and that, contrary to other orofacial conditions and disorders [84,85], investigated lesions may be asymptomatic.

For the same reasons, no definitive conclusions could be drawn on the potential role of cases' and implant characteristics, as well as of Titanium allergy, on lesions onset, development, and treatment responsiveness, thus highlighting the need for further investigations on the topic.

Nonetheless, this umbrella review may be the first study jointly estimating the overall prevalence of cases diagnosed with lesions potentially due to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations and categorizing lesions as those resembling or ascribable to peri-implant mucositis and peri-implantitis, reactive lesions of the peri-implant mucosa, and orofacial, periodontal, and peri-implant hypersensitivity reactions. Moreover, the present study may be considered the first to evaluate those lesions in relation to cases' history of allergies, comorbidities and related therapies, dental implants and implant-supported restorations' characteristics, and Titanium allergy, thus providing preliminary data for future research and consistent clinical implications.

Indeed, future studies should evaluate metal nanoparticle release from dental implants also in conjunction with bone regenerative materials [3,85] and in view of patients' systemic conditions and disorders [86,87]. In addition, synthesized data may provide the bases for preventive strategies. A higher clinicians' awareness of nanoparticles released from dental implants and potential local and systemic effects [88–90], the identification of high-risk

subjects through Titanium (alloy) allergy testing, and the related individualized medical decision-making choosing alternative materials may be encouraged [27,86,91].

5. Conclusions

The present umbrella review included only four systematic reviews, highlighting the need for further investigations on Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations.

An overall prevalence of 16.9% of cases was estimated based on data reported in the systematic reviews, although potentially biased by underdiagnosis, misdiagnosis, or underreporting.

Lesions' macroscopic features likely resembled peri-implant mucositis, peri-implantitis, and/or implant loss in more than half (55.17%) cases. Reactive exophytic lesions of the peri-implant mucosa were described in 17.22% of the cases. Hypersensitivity reactions with facial eczema and/or unspecified local reactions erythema, swelling, and lip crease, although Titanium allergy was heterogeneously investigated, and the related evidence was severely lacking, were noticed in 24.12% of the cases. Notably, no oral contact lichenoid lesions were reported. Imaging features were detailed only for suspected peri-implantitis, while cyto/histopathology was rarely recorded, mainly for clinically evident reactive exophytic lesions, although some locally aggressive lesions may clinically mimic peri-implantitis.

Due to the severely incomplete data reported, no definitive conclusions could be drawn on the potential role of cases' and implant characteristics, as well as Titanium allergy, on lesions onset, development, and treatment responsiveness.

Future studies should deepen the knowledge of dental implant surface degradation, metal nanoparticle release, toxicity, biodistribution, and local and distant biological effects. Highlighting the etiopathogenic mechanisms underlying reactive exophytic lesions genesis and inducing hypersensitivity reactions to Titanium (alloy) and other metal nanoparticles released from dental implants and implant-supported restorations, along with identifying the most effective and sensitive allergy tests for dental applications, may aid in identifying subjects at high risk of lesions development and guide clinical choices better fitting patients' individual needs in both primary and secondary prevention strategies, also considering alternatives to Titanium alloys, if needed.

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