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review

PERI-IMPLANT DISEASES AND CARDIOVASCULAR DISEASE: A SYSTEMATIC REVIEWS

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SUMMARY

Few studies have investigated the possible relationship between systemic conditions and peri-implant diseases.

The aim of this review is to present, in a systematic manner, current evidence and knowledge regarding possible association between cardiovascular disease and implant biologic complications.

Out of the one-hundred-eighty-nine studies screened, just five studies were selected for qualitative analysis: three cohort studies (one prospective and two retrospectives) and two cross-sectional studies.

According to their results, there is inconsistent and controversial evidence regarding association of cardiovascular disease and implant biologic complications.

Future research should be orientated in conducting longitudinal studies, evaluating patients affected by cardiovascular disease rehabilitated with dental implants.

Key words: peri-implantitis, mucositis, peri-implant diseases, cardiovascular disease, hypertension.

Introduction

High life expectancy and widespread diffusion of implant dentistry are all factors that have contributed to the increased number of dental implants in elderly patients (1-3); according to Schimmel et al. (2), they have become routine practice and clinicians should carefully take into account coexisting systemic risk factors.

Geriatric patients report usually, in their medical history, several comorbidities, with the most common being cardiovascular disease (CVD) and hypertension, diabetes mellitus and hyperglycaemia, osteoporosis and consequent assumption of anti-resorptive medications, dyslipidaemia and temporomandibular disorders (TMDs) (4-8).

Several Authors (9, 10) have reported a positive correlation and a direct relationship between periodontitis and systemic diseases over the years: cardiovascular disease, hypertension, dyslipidaemia and mostly diabetes mellitus and hyperglycaemia.

In 2007, Shimazaki et al. (11) and D'Aiuto et al. (12) reported for the first time a correlation between metabolic syndrome and periodontal disease.

Few studies have investigated the possible relationship between systemic conditions and peri-implant diseases (13-16).

According to Sanz & Chapple (17) in 2012, peri-implantitis has been defined as a chronic inflammatory lesion, characterized by peri-implant bone loss, bleeding at probing and suppuration, while mucositis is as a plaque-related inflammatory soft tissue infiltrate with no concomitant loss of supporting bone.

The prevalence remains still controversial and relatively unknown, depending mostly of study design and population: Derks & Tomasi (18) reported 43% of dental implants affected by mucositis and 22% by peri-implantitis.

Several Authors (19-22) have reported that bacterial species associated with periodontitis and peri-implantitis are similar, including mainly

gram-negative anaerobes such as porphyromonas gingivalis, prevotella intermedia and aggregatibacter actinomycetemcomitans (Aa).
In addition, pro-inflammatory cytokines levels (IL-1, IL-6, IL-8, and TNF- α) are commonly found to be increased in peri-implantitis patients (23, 24).
History of periodontitis, smoking and inflammatory conditions have been generally considered as a risk factors for implant patients, however a direct relationship between implant loss and periodontal disease has never been demonstrated (25, 26).
The aim of this review is to present, in a systematic manner, current evidence and knowledge regarding possible association between cardiovascular disease and implant biologic complications.

Material and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (27).
The protocol of this systematic review was developed "*a priori*" following initial discussion between members of the research team.

Focused question

Investigators conducted a literature review in accordance with the following focused question: "Are patients affected by cardiovascular disease (CVD) presenting a higher occurrence of peri-implant diseases compared to healthy subjects?"
Population: Patients with osseointegrated dental implants.
Exposure: patients affected by cardiovascular disease.
Comparison: patients in good general health.
Outcome: implant-related biologic complications (mucositis, peri-implantitis or peri-implant bone loss).

Search strategy

An electronic literature search was conducted for articles published up to 1st December 2017 in English language in several databases: Pubmed library, SciVerse (Elsevier), MEDLINE (OVID) and through The Cochrane Database of Systematic Reviews (CDSR).
The following search strategy was performed: (diseases OR conditions OR pathologies OR cardiovascular OR hypertension) AND (peri-implantitis OR peri-implant inflammation OR peri-implant disease OR peri-implant infection OR peri-implant bone loss OR peri-implant mucositis OR mucositis) AND (risk factors).

Study selection

Prospective and retrospective cohort studies, case-control studies, cross-sectional surveys and case series were included in this literature review.
Studies were selected based on the following inclusion criteria:

- human trials with at least 10 subjects
- dental implants with at least 1 year of follow-up
- studies published in english.

Outcome definitions

Peri-implantitis was defined as presence of bleeding on probing and/or suppuration together with evidence of concomitant ≥ 2 mm radiographic marginal bone loss.
Peri-implant mucositis was defined as evidence of bleeding on probing and/or suppuration without concomitant marginal bone loss.
Peri-implant bone loss was defined as detectable radiographic bone loss without evidence of bleeding on probing and/or suppuration.
Cardiovascular disease defined as arterial hypertension and/or cardiac and/or peripheral vascular

disease; with concomitant drug therapy: including anticoagulants and/or calcium channel blockers/angiotensin-converting enzyme inhibitors/nitrosamines.

Quality and risk of bias assessment

The quality of each cohort and case-control study was evaluated according to NewCastle-Ottawa scale (NOS) for Assessing the Quality of Non-randomized Studies (28).
The NOS include three sections: selection (four items), comparability (two items), and outcome (three items). A maximum of one star for each item can be awarded within the selection and outcome categories, while two stars can be given for comparability.

Data extraction and analysis

Two reviewers (PP, GP), independently from each other, extracted pertinent data (year; study design; systemic condition; implant biologic complication; number of patients; number of implants; outcome) from selected studies.
A meta-analysis was not performed due to heterogeneity of study designs and outcome variables.

Results

A total of 189 records were identified through database searching.
After removal of duplicates, forty-five studies were selected for title and abstract analyses, with 13 articles considered for detailed screening (Figure 1).
Five studies were included for qualitative analysis: three cohort studies (one prospective and two retrospectives) and two cross-sectional studies (Table 1).
The mean NOS score was 6.4 (Table 2).
Renvert et al. (29) found a history of CVD in 27.3% of individuals with peri-implantitis, while just 3% of individuals had CVD in the implant health group.
Hence, according to their results, history of CVD had a high likelihood of comorbidity with peri-implantitis, expressing an odds ratio (OR) of 8.7 (95% CI: 1.9, 40.3 $P < 0.006$).
Koldsland et al. (30) evaluated possible association between selected risk factors and peri-implantitis in a population of 109 patients.
Fourteen individuals reported history of CVD, with no statistically significant association detected with peri-implantitis.
De Souza et al. (31) investigated 193 patients to evaluate influence of local and systemic factors on peri-implant bone loss.
Thirty-nine patients presented a diagnosis of CVD (35 hypertension and 4 cardiac diseases) and they did not found out a statistically significant association.
Krenmair et al. (32) evaluated peri-implant bone loss in patients with fully edentulous mandibles rehabilitated with overdentures supported by four dental implants.
According to their results, subjects affected by CVD (n=19/44) showed statistically significant increased peri-implant bone loss levels, expressing an OR of 5.72 (95% CI: 1.280-20.908).
Dalago et al. (33) collected data on 183 patients and 916 dental implants: showing no correlation between heart disorders and peri-implantitis.

Discussion

Over the years, just a few Authors have investigated the possible comorbidity between cardiovascular disease (CVD) and peri-implant diseases (34, 35).
In two different studies, Alsaadi et al. (36, 37) evaluated association between local and systemic factors and implant failure, reporting no statistically significant correlation with CVD.

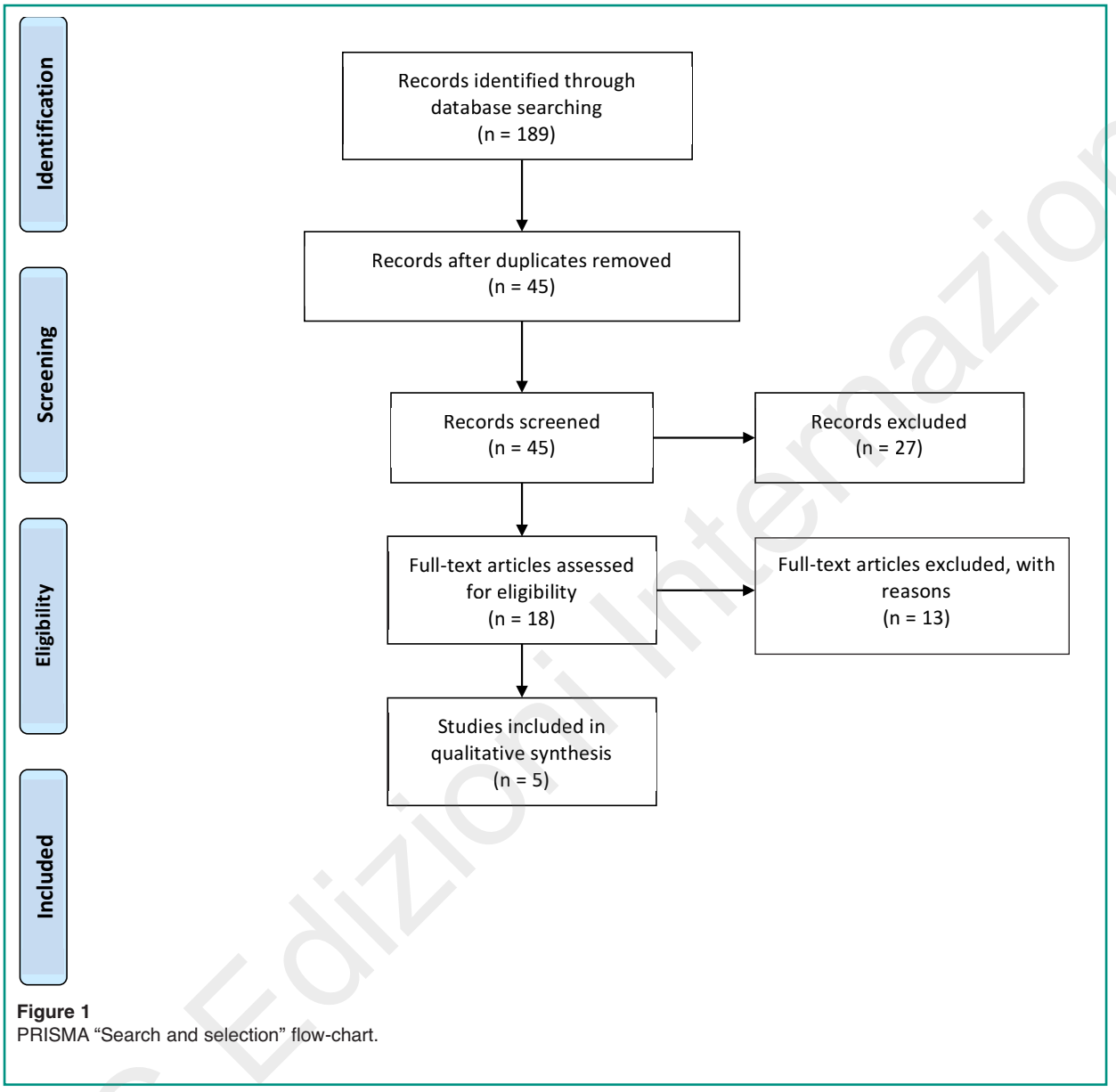

Figure 1
PRISMA "Search and selection" flow-chart.

Lachmann et al. (38), evaluated clinically and microbiologically an unselected population of seventy-four implant recall patients.
CVD was found out in twenty individuals, with hypertension (n=14) being the most common condition diagnosed.
Prevotella intermedia (Pi) (n=6/74) was found out in all subjects affected by CVD, who therefore showed statistically significant higher mean Pi load.
These results were in accordance with several Authors (39-41), who reported an association between Pi and other bacterial species linked with periodontitis.
However, for the first time, this association between periodontal pathogens and CVD was reported in the peri-implant sulcus.
In literature, Darby (42) in 2015 mentioned multidisciplinary team approach as possible key factor in management of periodontal and peri-implantitis elderly patients.
Three articles (30, 31, 33) included in our review

Table 1 - Characteristics of the studies included in the qualitative syntheses.

Study	Study Design	Systemic condition	Implant-related biologic complication	N of patients	N of implants	Outcome
Koldsland et al. (2011)	Cross-sectional study	Cardiovascular disease	Peri-implantitis Peri-implant bone loss Mucositis	109 CVD: 17	37 4NR	No statistical association reported
De Souza et al. (2013)	Retrospective cohort study	Hypertension	Peri-implant bone loss	193 CVD: 35	722 165	ABL= 63/165 implants (38.2%) P value: 0.702
Renvert et al. (2014)	Retrospective cross-sectional study	Cardiovascular disease	Peri-implantitis Mucositis	172 CVD: 47	NR NR	Peri-implantitis OR= 8.7 (95% CI: 1.9, 40.3)
Krennmair et al. (2016)	Prospective cohort study	Cardiovascular disease	Peri-implant bone loss	44 CVD: 19	176 NR	OR= 5.72 (95% CI: 1.280-20.908).
Dalago et al. (2017)	Cross-sectional study	Cardiovascular disease	Peri-implantitis	183CVD: 11	93861	8/61 implants P value: 0.012

ABL= Additional bone loss; CI= Confidence interval; CVD= Cardiovascular disease; NR= not reported; OR= Odd ratio; RR= Risk ratio

Table 2 - NOS for quality assessment of cohort studies.

Study	Selection (Max. 4 Stars)				Comparability (Max. 2 Stars)	Outcome (Max. 3 Stars)			Total
	Representativeness of the exposed cohort (Max 1 Star)	Selection of non exposed cohort (Max 1 Star)	Ascertainment of exposure (Max 1 Star)	Demonstration that outcome was not present at start of study (Max 1 Star)	Comparability of cohorts on the basis of the design or analysis (Max 2 Stars)	Assessment of outcome (Max 1 Star)	Was follow-up long enough for outcomes to occur (Max 1 Star)	Adequacy of follow-up of cohorts (Max 1 Star)	
De Souza et al. (2013)	*	*	*		*	*	*	*	7
Renvert et al. (2014)	*		*		*	*	*	*	6
Krennmair et al. (2016)	*	*	*	*	**	*	*	*	9
Koldsland et al. (2011)	*	*	*		*	*			5
Dalago et al. (2017)	*	*	*		*	*			5

showed no possible correlation with CVD, while two (29, 32) of them reported an increased risk of developing peri-implant diseases, with OR ranging from 5.72 to 8.7.

According to Krennmair et al. (32), osseointegration may be compromised and marginal bone loss improved, in CVD patients, by reduction of oxygen tension and nutrient supply caused by lower blood flow.

The aim of this review was to assess in a systematic manner cardiovascular disease as possible risk factor for peri-implant diseases.

Main limitations and source of bias were represented by absence of randomized clinical trials and by the retrospective and cross-sectional design of almost all studies included.

Different coexisting medical diseases and/or risk factors were observed in the same patient, then identification of the proper condition related to implant biologic complications could be biased.

History of periodontitis was not analysed by all studies: its relationship with peri-implant diseases is still unknown, even if they share similarities in aetiology and pathogenic mechanisms.

On the contrary, it is reported in literature that periodontal disease is a condition that increases risk of CVD and may negatively affect glycaemic control of diabetic patients (43-50).

Another important limitation is represented by lack of standard, globally accepted definitions of peri-implant diseases.

Conclusions

Within the limitations of this systematic review, the following conclusions can cautiously be drawn: there is inconsistent and controversial evidence regarding association of cardiovascular disease and implant biologic complications.

Future research should be orientated in conducting longitudinal studies, evaluating patients affected by cardiovascular disease rehabilitated with dental implants.

Goals should be to assess risk of peri-implant diseases and to evaluate patient's therapeutic response, analysing directionality of the relationship between CVD and implant biologic complications.

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