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Peri-implant diseases and metabolic syndrome components: a systematic review

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Abstract. – OBJECTIVE: Metabolic syndrome (MetS) is defined as a spectrum of conditions associated with an increased risk of developing CVD and type 2 diabetes.

MetS include: hyperglycemia, hypertension, visceral obesity, dyslipidemia with elevated values of triglycerides (TG) and low levels of HDL.

The aim of this review is to provide current knowledge of the relationship between MetS, its components and peri-implant diseases.

MATERIALS AND METHODS: An electronic literature search was conducted in the English language in several databases.

The Newcastle-Ottawa Scale was used for quality assessment of cohort and cross-sectional studies; while systematic reviews were evaluated through AMSTAR; results were reported according to the PRISMA Statement.

RESULTS: A total of 272 records were identified through database searching, six studies were included for qualitative analysis. No study directly related to MetS was found, there was inconsistent and controversial evidence regarding association with cardiovascular disease. A higher risk of peri-implantitis was detected in people with hyperglycemia.

CONCLUSIONS: Future research should be orientated in assessing the risk of peri-implant diseases, evaluating patient's therapeutic response, analyzing directionality of the relationship between MetS, its components and biologic implant complications.

Key Words
Peri-implantitis, Mucositis, Peri-implant diseases, Metabolic syndrome, Cardiovascular disease, Hyperglycemia.

Introduction

High life expectancy and demographic trends, as well as widespread diffusion and reliability of modern implant dentistry, are all factors that have contributed to the increased number of dental implants in elderly patients (age > 65 years)[1-3].

Compton et al[2], in 2017, retrospectively reviewed a cohort of 245 geriatric patients and reported an implant survival rate of 92.9%, with marginal bone loss present in 23.3% of implants.

Schimmel et al[3], in 2017, concluded that placement of dental implants in elderly patients had become routine practice and clinicians should carefully take into account coexisting systemic risk factors.

Geriatric patients usually report, in their medical history, several comorbidities, with the most common ones as cardiovascular disease (CVD), hypertension, diabetes mellitus, hyperglycemia, osteoporosis and consequent assumption of anti-resorptive medications, dyslipidaemia and temporomandibular disorders[2-7].

Several authors[8-11] referred a positive correlation and a direct relationship between periodontitis and systemic diseases over the years: CVD, hypertension, dyslipidaemia and mostly diabetes mellitus and hyperglycemia.

Shimazaki et al[12] and D'Aiuto et al[13] reported, for the first time, a correlation between metabolic syndrome and periodontal disease in two cross-sectional studies.

Overview of the Metabolic Syndrome

The Metabolic syndrome (MetS) is defined as a spectrum of conditions associated with an increased risk of developing CVD and type II diabetes[14,15].

MetS include: hyperglycemia, hypertension, visceral obesity, dyslipidemia with elevated values of triglycerides (TG) and low levels of HDL.

Prevalence of metabolic syndrome has been reported steadily rising over last decade: according to the most recent survey of the National Health and Nutrition Examination Survey

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(NHANES) its prevalence is estimated around 34.7% in the American population, while in Europe is considered to be around 30% in elderly population[16].

Over the years, several diagnostic criteria have been suggested by different health organizations: National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III), the International Diabetes Federation (IDF), the World Health Organization (WHO) and the American Heart Association and National Hearth, Lung, and Blood Institute (AHA/ NHLBI)[17-20].

In a recent systematic review, Nibali et al[21] suggested that evaluation of periodontal parameters should become part of routine diagnostic procedures for patients affected by metabolic syndrome.

Authors[22,23,24] highlighted how the prevalence of periodontal disease in patients affected by MetS was almost double, compared to those without Mets (OR=1.7-2.1).

Systemic oxidative stress and up-regulation of inflammatory cytokines (IL-1, IL-6, TNF-α) were hypothesized as a possible cause of reduced insulin sensitivity, a key aspect in MetS development[22-24].

However, in a recent critical review, the literature on the possible association between periodontitis and metabolic syndrome has been judged as "biased", due to the heterogeneity of cross-sectional studies[21].

Overview of Peri-Implantitis

The massive use of dental implants in EU Population over the last decades has also developed a combination of "man-made" diseases known as "peri-implant diseases"[25].

Peri-implantitis has been defined as a chronic inflammatory lesion, characterized by peri-implant bone loss, bleeding at probing and suppuration[25,26].

Mucositis was defined as a plaque-related inflammatory soft tissue infiltrate with no concomitant loss of supporting bone[27].

Sanz and Chapple[28] highlighted how lack of consensus on definition and diagnosis may affect peri-implantitis prevalence.

They founded eight different definitions of peri-implants, based on the combination of several marginal bone loss (MBL) values and probing pocket depth (PPD) considered as thresholds.

Its prevalence, therefore, remains controversial and relatively unknown, depending mostly on study design and population: Derks and Tomasi reported 43% of dental implants affected by mucositis and 22% by peri-implantitis after a mean follow-up of 9 years in a Swedish population[29].

Hence, peri-implantitis represent an emerging disease and, like periodontitis, occurs mainly as a result of an overwhelming bacterial insult and subsequent host immune response, with a spontaneous progression if left untreated[30-32].

In particular, several authors[33,34] 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).*

Furthermore, pro-inflammatory cytokines (IL-1, IL-6, IL-8 and TNF- α) are up-regulated in peri-implantitis[35].

According to Salvi et al[36], even if peri-implantitis and periodontitis share similarities in pathogenic mechanisms and clinical features, they have to be considered as different histopathologic entities.

History of periodontitis has been considered as a risk factor for implant patients. However, a direct relationship between implant loss and periodontal disease has never been demonstrated.

Over the years, just a few papers have focused their attention on coexisting medical conditions and peri-implantitis[1,5].

The aim of this review is to provide current knowledge of the relationship between MetS, its components and peri-implant diseases.

Material and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[37].

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 metabolic syndrome (MetS) or one/more of its components presenting a higher occurrence of peri-implant diseases compared to healthy subjects?

- Population: Patients with osseointegrated dental implants.
- Exposure: patients affected by metabolic syndrome (MetS) or one/more of its components

(Hypertension, cardiovascular disease, hyperglycemia, diabetes, dyslipidaemia, obesity).
- 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 independently by two authors (PP, DR) for reports published up to 1st June 2017 in English language in several databases: Pubmed library, Web of Science (Thomson Reuters), 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 diabetes OR obesity OR metabolic syndrome

OR hyperglycemia OR hypertension OR dyslipidaemia) 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

Studies were included if they presented data on patients with a diagnosis of peri-implantitis or peri-implant mucositis, affected by metabolic syndrome or one/more of its components.

Systematic reviews of human *in vivo* studies, 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.
- Implants with at least 1 year follow-up since delivery of definitive prosthetic restoration.
- Studies published in English.

Outcome Definitions

Only studies reporting definitions of peri-implantitis and peri-implant mucositis in accordance with the European peri-implant disease case definitions[28] were included in this review.

The 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.

Metabolic syndrome is considered as a spectrum of conditions including hyperglycemia, hypertension, visceral obesity, dyslipidaemia with elevated values of triglycerides (TG) and low levels of HDL.

Presence of three or more of the following diagnostic criteria, as defined by NCEP ATP III, was needed to establish a diagnosis of MetS:
- Waist circumference >102 cm (M) or >88 cm (F).
- Triglyceridemia > 150 mg/dL.
- HDL-cholesterol <40 mg/dL (M) or < 50 mg/dL (F).
- Blood pressure > 130/85 mmHg.
- Fasting glucose > 110 mg/dL.

Studies reporting data on one or more of the following components of MetS and peri-implant diseases were included in this review:
- Hypertension.
- 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.
- Obesity
- Dyslipidemia.
- Hyperglycemia .
- Diabetes mellitus.

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[38].

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.

Evaluation of cross-sectional studies was made according to NOS modified by Borgnakke et al[39], including three sections: selection (four items), comparability (two items) and outcome (one item), with a maximum of one star for each item, excluding comparability with two stars.

The MeaSurement Tool to Assess Systematic Reviews (AMSTAR), an 11-items questionnaire, was performed to assess systematic reviews included[40].

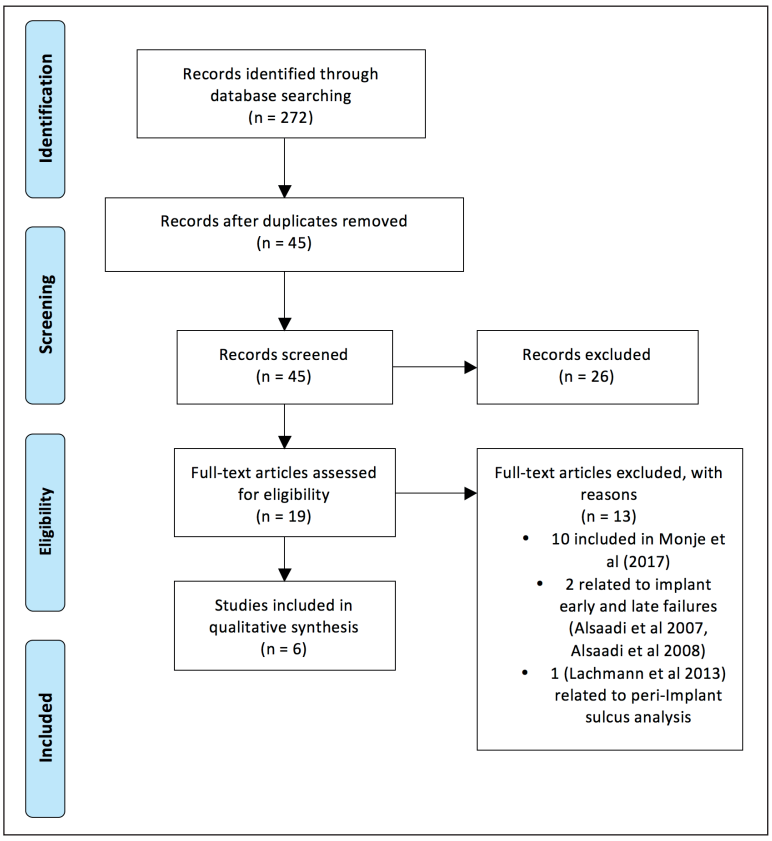

Chart 1. I PRISMA "search and selection" flow-chart.

Data extraction and analysis

Two reviewers (PP, DR), independently from each other, extracted pertinent data (year; study design; systemic condition; biologic implant complication; number of patients; number of implants; outcome) from selected studies in order to perform a meta-analysis.

However, due to heterogeneity of study designs and outcome variables, data were reported narratively and, therefore, no meta-analysis was performed.

Results

A total of 272 records were identified through database searching.

After removal of duplicates, forty-five studies were selected for title and abstract analyses, with 19 articles considered for detailed screening (Chart I).

Six studies were included for qualitative analysis: a systematic review with meta-analysis, three cohort studies (one prospective and two retrospectives) and two cross-sectional studies (Table I).

Reasons for exclusion are detailed in Chart I.

The kappa agreement between reviewers was 0.85.

No study related to metabolic syndrome was identified and, as for its components: five articles reported data on hypertension and cardiovascular disease, whereas the systematic review included twelve studies on hyperglycemia and diabetes.

Two articles[41,42] both reported data on CVD and diabetes and were included in the systematic review[43].

As for the qualitative analysis, according to AMSTAR, risk of bias was very low for Monje et al[43]; while the mean NOS score was 5 for cross-sectional studies and 7.33 for cohort studies (Table II, Table III).

Cardiovascular Disease

In a retrospective study[41], authors found a history of CVD in 27.3% of individuals with peri-implantitis, while CVD was present just in 3% of individuals in the implant health/peri-implant mucositis group.

They concluded that a 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 $p < 0.006$).

Table I. Characteristics of the studies included in the qualitative syntheses.

Study Design	Study condition	Systemic related	Implant-patients biologic complication	No. of implants	No. of	Outcome
Koldsland et al[44]	Cross-sectional study	Cardiovascular disease	Peri-implantitis Peri-implant bone loss Mucositis	109 CVD: 17	374 NR	No statistical association reported
De Souza et al[45]	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[41]	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[46]	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[42]	Cross-sectional study	Cardiovascular disease	Peri-implantitis	183 CVD: 11	938 61	8/61 implants *p*-value: 0.012
Monje et al[43]	Systematic review with meta-analysis	Hyperglicemia Diabetes	Peri-implantitis Mucositis	1955 DM: 480	2892 NR	Peri-implantitis RR=1.46 (95% CI: 1.21-1.77) OR = 1.89; (95% CI: 1.31-2.46) Mucositis RR = 0.92 (95% CI: 0.72-1.16) OR = 1.06 (95% CI: 0.84-1.27)

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

Table II. 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[45]	*	*	*		*	*	*	*	7
Renvert et al[41]	*		*		*	*	*	*	6
Krennmair et al[46]	*	*	*	*	**	*	*	*	9

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

Table III. NOS for quality assessment of cross-sectional studies.

Study	Selection (Max. 4 Stars)				Compra-bility	Outcome (Max. 1 Stars)	Total
	Representa-tiveness of the exposed subjects (Max 1 Star)	Selection of non exposed subjects (Max 1 Star)	Ascertain-ment of exposure (Max 1 Star)	Demonstra-tion 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)	
Koldsland et al[44]	*	*	*		*	*	5
Dalago et al[42]	*	*	*		*	*	5

Koldsland et al[44] evaluated, in a cross-sectional study, the association between selected risk factors and peri-implantitis in a population of 109 patients.

Fourteen individuals reported history of CVD and results of multi-level regression analysis showed no statistically significant association between variable and peri-implantitis.

De Souza et al[45] investigated a cohort of 193 patients retrospectively 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); however, no systemic factor showed influence on peri-implant bone loss.

Krenmair et al[46] conducted a prospective cohort study with 3 years follow-up, evaluating peri-implant bone loss in patients with fully edentulous mandibles rehabilitated with four dental implants.

Their results highlighted that 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[42], in a cross-sectional study, collected data on 183 patients and 916 dental implants: according to the authors, heart disorders showed no correlation with peri-implantitis.

Hyperglicemia

In a recent systematic review with meta-analysis, Monje et al[43] evaluated current literature available regarding the association between diabetes mellitus/ hyperglycemia and peri-implant diseases.

After electronic literature searching, twelve articles were considered eligible for qualitative analysis, while just seven of them for quantitative.

Meta-analysis reported a 50% higher risk of detecting peri-implantitis in subjects with diabetes/hyperglycemia compared to non-diabetes patients (RR = 1.46; 95% CI: 1.21-1.77 and OR = 1.89; 95% CI:1.31-2.46; $p < .001$).

Diabetes patients no-smokers showed a 3.39 higher risk for peri-implantitis compared to normoglycaemia subjects, therefore suggesting that smoking, contrary to what hypothesized in literature, had no leading role in development of peri-implant diseases compared to diabetes.

Dyslipidemia

No studies evaluating correlation between peri-implant diseases and dyslipidemia were found in literature.

Discussion

To the best of the authors' knowledge, this is the first systematic review to report data regarding MetS, its components and their relationship with peri-implant diseases.

Therefore, there are no previous reviews to which our findings can be compared.

MetS is a spectrum of conditions with a five-fold increased risk of diabetes and two-fold risk of developing CVD[14,15].

In the literature, only a narrative review authored by Darby et al[47] in 2015 mentioned metabolic syndrome as a possible key factor in management of periodontal elderly patients.

According to the authors, a multidisciplinary team approach with medical colleagues to best manage these patients should be implemented.

Over the years, just a few authors have investigated the possible comorbidity between cardiovascular disease (CVD) and peri-implant diseases.

In two different studies, Alsaadi et al[48,49] evaluated association between local and systemic factors and early and late implant failure, reporting no statistically significant correlation with CVD.

Lachmann et al[50], in a cross-sectional study, 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.

All the positive subjects for *Prevotella intermedia (Pi)* (n=6/74) exhibited CVD. Therefore, the cohort of cardiovascular disease patients showed statistically significant higher mean Pi load.

These results were not judged "surprising" by authors, as an association between Pi and other that bacterial species linked with periodontitis was reported by several authors[51-53].

However, for the first time, this association between periodontal pathogens and CVD was reported in the peri-implant sulcus.

Three articles included in our review showed no possible correlation with CVD, whereas two of them[41,46] reported an increased risk of developing peri-implant diseases, with OR ranging from 5.72 to 8.7.

According to Krennmair et al[46], 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[54,55].

More data is available on literature regarding possible links between hyperglycemia and diabetes and biologic and mechanical complications related to dental implants[39,56,57].

According to several authors, elevated glycemic values seem to be associated with higher rates of peri-implantitis and peri-implant bone loss[43,56].

Peri-implantitis, as well as periodontitis, is considered sensitive to factors inducing tissue inflammation (smoking, poor plaque control, hyperglycemia), which can usually be found in the same population[58-61].

According to Monje et al[43], non-smokers patients affected by hyperglycemia reported a threefold higher risk of peri-implantitis, hence smoking was not a key factor in enhancing effects of hyperglycemia.

Limitations

The aim of this review was to assess, in a systematic manner, metabolic syndrome and its components as possible risk factors 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.

No study directly related to MetS was found; therefore, only articles related to its components were selected.

Only two articles reported data on hypertension, while the other three referred to the broader category of cardiovascular disease, which include many other cardiac conditions.

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

On the contrary, MetS represent a spectrum of different conditions and elderly subjects are usually affected by multiple medical disorders.

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

MetS and periodontitis have recently been correlated by several cross-sectional studies; however, the body of scientific evidence is still immature.

On the contrary, it is reported in literature that periodontal disease is a condition that increases risk of CVD[62] and may negatively affect glycemic control of diabetic patients[57,63].

Another important limitation is represented by lack of standard, globally accepted definitions of peri-implant diseases, which may influence their prevalence.

Conclusions

The following conclusions can cautiously be drawn:

- There are no articles in literature analyzing possible correlation between Mets and peri-implant diseases.
- There is inconsistent and controversial evidence regarding association of cardiovascular disease and biologic implant complications.
- A higher risk of peri-implantitis was detected in people with hyperglycemia compared to those with normal blood glucose levels.

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

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

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Conflict of Interest:

The authors declare that they have no conflicts of interest. This study was self-funded by the authors and their institutions. Ethical approval was not required

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