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Periodontal disease and metabolic syndrome: A qualitative critical review of their association

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Abstract

Background—Metabolic syndrome (MetS) is a conglomerate of several physical conditions/diseases that, as a group, increases the risk of mortality resulting from development of T2DM and cardiovascular diseases (CVD). These conditions/diseases include glucose intolerance/insulin resistance, hypertension, obesity, and dyslipidemia. The results from epidemiological studies suggest that there is an association between metabolic syndrome (MetS) and periodontitis, it is therefore important to understand the current status of the association and a possible contribution of periodontitis to MetS.

Objective—This review will qualitatively analyze published papers on the association of MetS and periodontitis/periodontal disease to clarify the current status of the association and suggest future directions for studies which may unravel the causal relationship between them.

Results—Of 309 papers related to MetS and periodontitis, 26 are original research papers that investigated the relationship/association between periodontal disease and MetS. Criteria used to assess periodontitis and MetS as well as overall study designs and patient recruitment criteria varied greatly among these studies.

Conclusion—All these studies demonstrated a positive association between periodontal disease and MetS. However, due to the heterogeneity of criteria to assess periodontitis and MetS and also paucity of longitudinal studies, it is difficult to determine the relative contribution of periodontitis to MetS. Age and the number of positive components of MetS appear to strengthen the relationship, however, incidence of each disease entity increases with ageing. Thus, mechanistic studies are also necessary to unravel the inter-relationship between periodontitis and MetS. In this regard, a use of animal models will be helpful as they are more uniform in regards to genetic background and have minimum confounding factors. Finally, development of accurate,

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.archoralbio.2014.05.003>.

Competing interests

None declared.

Ethical approval

Not applicable.

quantitative assessment of gingival inflammation are necessary in order to determine the influence of periodontal disease on the development of MetS and its components.

Keywords

Periodontitis; Metabolic syndrome; Qualitative review; Criteria

1. Introduction

Metabolic syndrome (MetS) is a combination of derangements including obesity, insulin resistance or glucose intolerance, hypertension, and dyslipidemia which collectively increase the risk of development of T2DM and cardiovascular diseases. The consequences in terms of T2DM alone are severe as evidenced by the 2–4 fold increase in mortality in T2DM patients relative to non-diabetic individuals.^{1,2} Furthermore, subjects with cardiovascular disease have the highest mortality rate in the US.³ Thus, subjects with MetS have a high risk of having or developing T2DM and cardiovascular diseases,^{4,5} and thus may increase mortality rates.⁶ The results from cross-sectional studies indicate that there is an association between MetS and periodontitis although the defining criteria for MetS and the means of assessing periodontitis have varied over time. However, the extent to which the association is bidirectional as well as underlying mechanisms for this association are not well understood.

PubMed, SCOPUS, and Cochrane Library searches were performed using the combination of keywords: periodontal disease; periodontitis; pocket depth; periodontal pocket; periodontal pocketing; attachment loss; clinical attachment loss; Metabolic syndrome and syndrome X. All publications pertaining to this topic written in English up to December 2013 were selected. Two hundred and twenty four papers out of 250 results from SCOPUS search and 31 papers out of 57 results from PubMed search were manually excluded as these either did not focus on association/interrelation between MetS and periodontal diseases; or were review papers,⁷⁻¹⁰ or were studies/reviews focused on cytokines and other biomarkers.¹⁰⁻¹⁶ Two papers from the Cochrane Library search matched with those from the SCOPUS search (Appendix 2). In addition a number of studies reported on the association between periodontal disease and one or two components of MetS.¹⁷⁻²⁴

Although most studies indicate that the association between periodontitis and MetS exists, there is variation in the reported degree of association between periodontitis and MetS. This variation may be due to the fact that many variables were involved in assessing the association between periodontitis and MetS. These variables include different methodology/criteria used to assess periodontitis, definitions of MetS, and criteria used for subject recruitment. In addition, there are several different approaches to determine the association between these two diseases/conditions: determining co-morbidity, odds ratios for subjects with MetS who have periodontitis and vice versa, case-control studies, and longitudinal studies. These differences further complicate the comparison of these studies.

In this review, we will discuss the variables involved in determining the association between periodontal disease and MetS and suggest future studies that will unravel the causal nature of the relationship and its underlying mechanisms.

2. Critical factors involved in assessing the association between periodontitis and MetS

2.1. Criteria used to assess periodontal disease

The terms “periodontal disease” and “periodontitis” are frequently used interchangeably in the literature, however these terms are not synonymous as “periodontal disease” refers to periodontitis or gingivitis or both. Thus, a necessary consideration is to clarify if a study reports on the association between periodontitis and MetS or gingivitis and MetS or the combination of the two.

Criteria for assessing periodontitis, gingivitis, and oral hygiene status are all relevant and should be carefully considered. Measurements and indices used to determine the periodontal condition in the studies reviewed varied greatly. These include probing or pocket depths (PD) with different cutoff values for periodontitis^{11,25-30} clinical attachment loss (CAL) with different cutoff values,^{11,25,27,28,31,32} Community Periodontal Index (CPI),³³⁻³⁹ and bone loss between the CEJ and the crest of alveolar bone using panoramic radiographs⁴⁰ or bite wing radiographs.⁴¹ Some studies used Plaque Index⁴² and Gingival Index⁴³ for clinical evaluation, and some used Ramfjord’s Periodontal Disease Index.^{31,32,44} Other variations include the number of teeth and sites on teeth examined.^{25-32,39,44-47} A few studies used self-evaluation of the periodontal condition^{48,49} or tooth mobility and a non-specified index of gingival inflammation⁵⁰ (Tables 1 and 2).

2.1.1. Pocket/probing depth—Among the studies that used PD to determine the presence of periodontitis, one study used a mean PD greater than 2 mm²⁵ to define periodontitis and a PD greater than 2.5 mm²⁶ to define moderate–severe periodontitis. Other studies used a PD of 4–5 mm (or CPI 3) and PD ≥ 6 mm (CPI 4) to define periodontitis,^{33-36,38,51} or two or more inter-proximal sites with PD ≥ 5 mm, not on the same tooth⁵² to define periodontitis. Subjects with a mean PD of ≥ 2 mm could potentially have no attachment loss and no gingival inflammation and therefore have healthy gingiva or alternatively gingivitis using this criterion. A PD of 4 mm may also be due to gingivitis.

2.1.2. Clinical attachment level or attachment loss (CAL)—Studies that used clinical attachment loss for assessing periodontitis also varied greatly in terms of cutoff values. For example, mean CAL ≥ 3 mm^{11,30,32} or a CAL of ≥ 4 mm in 2 or more sites, but not on the same tooth have been used in diagnosing periodontitis.^{27,28} In some studies, moderate periodontitis was diagnosed as two sites, not on the same tooth, with a CAL ≥ 4 mm or one site with PD (defined as “gingival probing depth” by the investigators) > 4 mm, and severe periodontitis was diagnosed by combining CAL and PD assessment, i.e., if two sites, not on the same tooth, with a CAL ≥ 6 mm and at least one site with a PD ≥ 4 mm.²⁷

In one study healthy gingiva was defined as no CAL or bleeding on probing (BOP), early periodontitis as CAL ≥ 1 mm on at least 2 teeth, moderate periodontitis as 3 sites with CAL ≥ 4 mm and at least 2 sites with PD ≥ 3 mm, and severe periodontitis as CAL ≥ 6 mm in at least 2 teeth and PD ≥ 5 mm in at least one site.⁴⁴

2.1.3. Number of sites and surface/site of tooth examined—In addition to the cutoff values for assessing periodontitis based on either PD or CAL, there is also variability in the number of sites examined. In some studies investigators examined the full dentition with assessment at 4 or 6 sites per tooth^{11,43} but most studies used only partial dentition for measurements.^{25-27,33-35,37,38} For example, in one study probing was performed on 4 surfaces of each tooth and investigators used the deepest site on each tooth as the basis for assigning subjects a different severity of periodontitis.²⁹ In another study, 2 randomly selected quadrants per subject were examined.²⁵ In the case of CPI, only the highest code (CPI 4) for a designated sextant is recorded. Once a Code 4 has been assessed, there is no need to continue assessing the remaining teeth of the sextant. Thus, it is not certain if the extent of periodontitis is represented by this system. CPI also does not reflect attachment loss.

Besides the number of sites examined, some studies restricted sites for assessing PD and CAL measurements to certain sites of a tooth. For example, in two studies, measurements were taken at mesio-buccal and mid-buccal sites for two randomly selected quadrants.^{25,26} CAL measurements at mid buccal sites were discouraged as attachment loss might have resulted from tooth brushing trauma and not from periodontal disease.⁴⁵ Thus, it should be considered that inclusion of measurements at mid-buccal sites may reduce the average PD.

2.1.4. Radiographic examination of bone loss—Radiographic evaluation of alveolar bone loss was determined by measuring the distance between the CEJ and the crest of alveolar bone and the level of bone loss was categorized as follows: none or slight bone loss (1–2 mm), moderate bone loss (3–4 mm), or severe bone loss (≥ 5 mm) in panoramic radiographs.⁴⁰ In another study, greater than 6 mm between the CEJ and the alveolar bone crest at one or more sites in bitewing radiographs was defined as periodontitis.⁴¹ However, radiographic bone loss at one site may not represent the overall periodontal condition of a subject.

2.2. Burden of inflammation

It has been suggested that the common denominator between periodontitis and MetS is inflammation.^{53,54} One biologically plausible basis that periodontitis may be a risk factor for MetS is that locally produced inflammatory cytokines or periodontal pathogens/LPS in the periodontium enter the systemic circulation and thus influence other sites of the body to accelerate or induce development of MetS. Thus, a critical issue is to determine definitively if periodontal conditions might increase the systemic inflammatory burden.

To this end the determination of severity and extent of gingival inflammation is of importance. CAL, PD or radiographic evidence of bone loss may represent the extent of past tissue destruction due to inflammation, but may not represent present inflammation. In one study, the extent of periodontitis was assessed by % sites with CAL ≥ 3 mm and % sites with PD ≥ 3 mm and the severity of periodontitis was assessed based on an average CAL and PD.³² Of interest is another study which demonstrated that severe CAL (≥ 6 mm) without severe PD (≥ 4 mm) was not significantly associated with MetS.⁴⁵ Thus, a deep PD

may cause a greater inflammatory burden which in turn influences the development of MetS.

One clinical measure which reflects the presence of inflammation is BOP. It has been reported that a 10% increase in the number of sites with BOP is associated with increased diagnosis of MetS.²⁷ In addition, in children age 8–10 years with at least one obese biological parent, males with MetS had a significantly higher number of sites with BOP.⁵⁵ Thus, optimally, index/clinical measures that assess the current extent of gingival inflammation should be included. These include the number of sites which bleed on probing (BOP), extent of bleeding and gingival index.

A method to estimate the inflamed surface area of periodontal pockets was proposed by Nesse et al.⁵⁶ This method combines BOP, CAL and gingival recession. Use of this method may very well reflect inflammatory burden due to periodontitis.

In addition to current inflammatory status, the duration of inflammation associated with periodontal disease may be important in assessing the association between periodontal disease and MetS. For example, older patients with chronic periodontitis may have a prolonged duration of chronic inflammatory burden compared to younger subjects with a shorter period of chronic periodontitis if the amount of inflammation in both populations is similar. In support of this hypothesis, studies have demonstrated that the association between periodontitis and MetS³⁴ as well as periodontitis–MetS co-morbidity³³ is higher among older compared with younger age groups.

One way to focus on the burden of inflammation is to exclude or separately analyze data from subjects who had periodontal treatment or regular maintenance for the final analyses, since these subjects may have attachment loss, but exhibit a minimal amount of inflammation. Thus, criteria for patient recruitment or exclusion of certain subjects with previous periodontal therapies may be of value.

In summary, a number of different criteria to assess the presence of periodontal disease have been used in epidemiological/cross-sectional studies to determine the association between periodontitis and MetS. Although all of these measurements are used frequently in epidemiological studies, they are, for the most part, only indirect indicators of the inflammatory burden which is thought to be the link in the association between periodontitis and MetS. A new method to assess the inflammatory burden will be necessary to understand the possible causal relationship between these two conditions.

2.3. Definition of metabolic syndrome

The impetus for defining MetS by the medical community is that some metabolic disorders such as obesity, insulin resistance or glucose intolerance, hypertension, and dyslipidemia are comorbid more often than by chance and are also considered as risk factors for cardiovascular disease (CVD).

Historically, several different definitions of MetS have existed, including those by Reaven,⁵⁷ Kaplan,⁵⁸ Alberti and Zimmet,⁵⁹ Hauner,⁶⁰ Groop and Orho-Melander,⁶¹ and by organizations including the WHO,⁵⁹ the National Cholesterol Education Program

(NCEP),^{62,63} and the American Association of Clinical Endocrinologists (AACE).⁶⁴ It should be noted that earlier studies may have used definitions of MetS that differed in regards to criterion for one or more components of MetS. In 2009 a unified definition of MetS was established through a joint effort by the International Diabetes Federation (IDF), American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI), World Heart Federation, International Atherosclerosis Society and the International Association for the Study of Obesity.⁶⁵ Among the components of MetS, the definition of obesity and cutoff value for fasting glucose level have historically varied most. For example, BMI > 30,⁶⁶ BMI > 25,³³ or various waist circumferences^{25,31,33-35,37,66} and fasting glucose levels including IR^{11,28,31,32,39} have been used by different investigators (Table 2).

In the unified definition of MetS, it was agreed that a single set of cutoff points would be used for all components of MetS except that waist circumference could differ depending on the population and would therefore be country specific.⁶⁵

At present, a clinical diagnosis of MetS is made by fulfilment of 3 of the following 5 criteria:

1. Increased waist circumference: population and country specific definition can be used.
2. Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator): 150 mg/dL (1.7 mmol/L).
3. Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator): <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females.
4. Elevated blood pressure (anti-hypertensive drug treatment in a patient with a history of hypertension is an alternate indicator): systolic 130 mmHg and/or diastolic 85 mmHg.
5. Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator): 100 mg/dL.

2.4. Study designs

2.4.1. Types of studies—The majority of studies reviewed to assess the association of periodontitis and MetS were cross-sectional in which the prevalence of periodontitis and MetS were ascertained at a single point and time and therefore a temporal sequence or cause and effect cannot be determined.⁶⁷ However, some of these studies identified the exposure (explanatory or independent) and outcome variables^{25,30,32,34,36,44-46,48,51} with directionality (Tables 1 and 2). For other studies which did not identify the exposure and outcome variables,^{31,33,35,37,38,40,41,44,47,50} we interpreted directionality based on the authors' description. There are only a few case control studies^{30,32,36} and longitudinal studies are available.^{39,68}

There are significant differences in the percentages of co-morbidities as well as odds ratios in studies determining the level of association between periodontitis and MetS. For example,

the prevalence of subjects co-morbid with MetS and Periodontitis varies from 2% to 25%.^{25,26,28,33,34}

A considerable variation in OR (1.52–4.7) is evident in subjects with MetS in regards to having/developing periodontitis.^{25,26,28-30,32-34,37,38,44,46,51} The most frequent variable influencing this directionality and association is the increased number of positive components of MetS.^{25,26,33,34,37,51} Among the components of MetS, central obesity (large waist circumference),^{25,26,29,33,44} impaired fasting glucose levels (insulin resistance or hyperglycemia),^{25,28,29,34,41} hypertension,^{34,45} low HDL (dyslipidemia)^{25,33} appear to influence the OR of having/developing periodontitis. Besides the components of MetS, other factors such as gender, i.e., female,^{26,46,50} smoking,³⁸ age^{34,38,48} also influence this relationship. Many studies adjusted for typical confounding factors such as smoking and age for calculating ORs.^{27,28,30,31,34,38-40,44,51}

OR for subjects with periodontitis who have/develop MetS varies from 1.04 to 2.73.^{27,36,40} Factors which influence this directionality/association are severity of periodontitis or bone loss,^{27,40} frequency of tooth brushing,^{45,68} gingival inflammation and plaque score,³¹ age,^{27,36} and gender, i.e., female.⁵⁰

Other studies which examined the relationship between MetS and periodontitis were longitudinal by design.^{39,68} In the study of Morita et al.,³⁹ subjects with periodontitis without any components of MetS at baseline were monitored for 4 years and the components of MetS were re-assessed. The result indicates that the presence of periodontal pocket at baseline was associated with a positive conversion of 2 (blood pressure and dyslipidemia) or more components of MetS. This suggests that periodontitis influences the development of some of the components of MetS. In a recent longitudinal study, Kobayashi et al.,⁶⁸ investigated the frequency of toothbrushing and its relation to MetS over a period of 3 years. The results indicate that the more frequently subjects brush their teeth, the lower the incidence of MetS is. This study outcome is very interesting since it suggests that the amount of plaque may be critical in inducing some of the components of MetS. There has been no study which investigated the reverse situation, i.e., examined subjects with MetS with no periodontitis at baseline and monitored for the development of periodontitis. However, in the study by Lopez et al.,¹¹ subjects co-morbid with MetS and periodontitis were followed for one year following supragingival cleaning (control group) or scaling and root planning in conjunction with antibiotics (experimental group) and neither group had an improvement in terms of MetS components (see Table 3).

2.4.2. Study population/subjects—There are a number of variables which may impact the association between periodontitis and MetS including ethnicity/geography and age which, for the most part, have not been studied.

There are several variables involved in study population/subjects.

(a) Different populations-ethnicity/geography: It is not clear if the association between periodontitis and MetS exists for all populations since a cross-sectional study comparing different populations using the same criteria for MetS and periodontitis has not been

performed. There are two independent studies which used the same target population but different age groups and criteria for periodontitis.^{26,27} These two papers report comorbidity of 26% (26) and 34–37% with moderate and severe periodontitis.⁶⁹

(b) Age of population: One critical factor affecting the association of MetS and Periodontitis appears to be the age of the patients.^{27,34,36,38,48} For example, in a cross-sectional study in which the age of study population was 24–60 years old,³³ the co-morbidity of MetS and periodontitis was 8.2% (based on our calculation using their data). However, when these subjects are grouped by age (24–39 years, and 40–59 years), the co-morbidity was 2.3% in the 24–39 age group and 11.6% in the 40–59 age group, showing the effect of age. In a cross-sectional study which examined co-morbidity in a population with an age range of 18–84 years, co-morbidity was higher in subjects older than 65 years old.³⁴ The data support the contention that age is a critical factor influencing co-morbidity.

2.4.3. Components of MetS in recruited subjects—A certain combination of components that make up MetS is reported to be significantly associated with deep PD. For example, high BP (median systolic BP of 130 mmHg⁻¹) and low HDL defined by NCEP/ATPIII is significantly associated with CPI 4.³⁷ In addition, the combination of dyslipidemia and hyperglycemia was associated with CPI 3.³⁸ In another study, a combination of high glucose levels including insulin resistance (IR) defined by impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) by WHO and hypertension showed a higher association in subjects older than 65 years.³⁴ Severe periodontitis is associated with subjects with IR determined by homeostatic model assessment (HOMA).²⁸ In addition to this study, subjects with impaired fasting glucose levels have a higher prevalence of bone loss assessed by radiographs compared with subjects with normoglycemia.⁴¹

Other components such as central obesity^{26,41} and dyslipidemia (low HDL-cholesterol) appear to be associated with deeper PD, CAL²⁵ or bone loss.⁴¹ In addition to certain components of MetS, the number of components also appears to increase the association between MetS and Periodontal disease. For example, OR of having deep pocket defined as PD > 4 mm or CPI 3 increases as the number of positive components of MetS increases in patients in their 40 s and 50 s compared with patients in their 20 s and 30 s.³³ A longitudinal study³⁹ which monitored the development of components of MetS⁷⁰ in subjects with CPI 4 and CPI 2 determined that the development of hypertension and lipidemia were strongly associated with the presence of periodontal pockets defined as PD 4 mm or CPI 3 PD at the beginning of the study.

It is not clear why different combinations of components of MetS are significantly associated with periodontitis or periodontal disease in different studies. However, the one component that is most frequently associated with periodontitis/disease is impaired glucose levels or IR.^{28,29,34,41,71,72}

2.4.4. Other factors/confounding factors—Smoking is a well-known risk factor for periodontitis⁷³ but the effect of smoking on the association between periodontitis and MetS is not clear. When age and gender are adjusted between smokers and non-smokers, the OR of having periodontal pocket depths increases as the number of positive components of

MetS increases, regardless of smoking habits.³³ This is in contrast to the results from another study³⁴ which reported that smokers age 65 or older have a stronger association between periodontal disease and MetS relative to non-smokers. Since smoking is known to increase the incidence of CVD,⁷⁴ one might expect to see increased MetS and periodontitis association among smokers. Therefore, in recruiting subjects, smoking habits must be ascertained. Another factor which influences the OR of subjects with MetS to have/develop periodontitis is gender. Three studies^{26,46,50} show that females have the higher OR of having/develop MetS whereas one study³⁴ indicates that males have a higher OR. Another study³⁸ indicates that there is no difference based on gender.

Another factor which might influence data interpretation in these studies is that many of the definitions of MetS allow for inclusion of subjects on medication to treat components of MetS, i.e., subjects with hypertension, dyslipidemia, T2DM. The effect of these medications on systemic inflammation is not known, however, it is known that thiazolidinediones which include pioglitazone and rosiglitazone have anti-inflammatory functions and thus subjects with a long term use of these medications might have reduced gingival inflammation or less severe periodontitis.

3. Discussion

Based on the papers we reviewed, there is an interrelationship between periodontitis and MetS. However, analysis/comparison of ORs using data from cross-sectional studies is problematic due to the different criteria used to define both MetS and periodontitis across studies. This variation in criteria also makes it difficult to assess the relative contribution or association of periodontitis to individual MetS components.

As mentioned, one challenge in interpreting the results of epidemiological/cross-sectional studies that investigate the relationship between periodontal disease (either gingivitis and/or periodontitis) and its systemic implications such as MetS is the use of indices which do not differentiate the extent of periodontal inflammation and severity of periodontitis. This is a critical issue in terms of assessing the systemic burden from oral inflammation/infection.

IR is associated with the number of sites with periodontitis²⁸ as well as alveolar bone loss.⁴¹ IR may lead to dysregulated blood pressure, dyslipidemia, and CVD which are components of the Insulin Resistant Syndrome⁶⁴ or Syndrome X.⁵⁷ Therefore, intervention to prevent development of IR may be the best prevention for the development of MetS and subsequent development of T2DM.

Finally, systematic reviews are considered to be the most acceptable review at present, however, systematic reviews can give different perspectives due to the arbitrarily set criteria used to systematically screen and categorize studies and this aspect is well discussed by Nibali et al.⁹

Taken together, diagnosis of periodontitis and extent of gingival inflammation may need to be reconsidered in epidemiological/cross-sectional studies which investigate systemic inflammatory burden originating from an oral environment and its relationship with other systemic conditions.

4. Conclusion

Although there is an association between periodontitis and MetS, due to the heterogeneity of criteria to assess periodontitis and MetS and paucity of longitudinal studies, it is not possible to determine (a) if periodontitis predisposes subjects to MetS, i.e., periodontitis is a risk factor for MetS, or (b) subjects with MetS tend to develop periodontitis. The following studies and issues may help clarify these interrelationships.

1. Studies to develop accurate, quantitative assessment of gingival inflammation are necessary to understand the systemic inflammatory burden originating from periodontium and thus how this may influence the development of MetS and its components. Bleeding on probing can indicate the presence of inflammation, but not the severity of inflammation of the site. It is also helpful to determine the duration of chronic inflammation. Possible effect of bacterial plaque on the development of MetS cannot be ignored. In this context, re-assessment of currently used clinical parameters are necessary in epidemiological/cross-sectional studies which investigate the relationship between periodontal disease and systemic conditions.
2. Longitudinal studies using re-assessed parameters to determine if periodontitis influences the development of some or all of the components of MetS, or vice versa.
3. For all human studies, appropriate subgroup analysis or stratified analysis must be a part of the analyses. This is due to the heterogeneous characteristics of recruited subjects.
4. Prospective studies to ascertain the potential of existing therapies to affect co-development of MetS and periodontitis.
5. Animal studies are necessary to determine mechanisms by which periodontitis impacts the development of MetS and how MetS impacts susceptibility to periodontitis. Advantages of animal studies include the limited individual variability in genetic and dietary components. Furthermore, initial therapeutic targets will be clearly identified due to the minimum number of confounders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Cross-sectional and case control studies.

Name	Population	Age range (years)	Criteria for periodontitis	Criteria for MetS	Odds ratio (OR)	Directionality	Modifying/ contributing factors and comments
<i>Cross-sectional</i>							
Shimazaki et al. (2007) ²⁵	Hisayama, Japan. 584 all females	40–79, mean 55.7 ± 8.8	Subjects divided into 2 groups: (1) mean pocket depth (PD) <2 mm and (2) mean clinical attachment loss < 3 mm. PD and CAL measured at MB, MdB in two randomly selected quadrants, one maxillary and one mandibular. Subjects had at least 10 teeth	NCEP ATP III	3.3 [1.2–8.8], $p < 0.05$	MetS to Pits	The more components of MetS, the higher the OR of having greater PD and CAL. Modifying factors: Large waist circumference. Low HDL, high fasting glucose level enhances the strength of the association
Morita et al. (2009) ³³	Tokyo, Japan. 2478 subjects. Employees in a household product company. 2,028 males and 450 females	24–60, mean 43.3	WHO CPI. Examined 10 teeth in six sextants. Subjects divided into two groups: (1) no periodontal pocket; CPI 2, and (2) periodontal pocket: at least one sextant with CPI 3	Matsuzawa (2005)	2.4 [1.7–2.7], $p < 0.01$	No direction specified	OR of the presence of periodontal pockets 2.4 when having 3 positive components of MetS regardless of smoking habit. Modifying factors: BMI, BP, TG, fasting glucose level and HbA1c increase in subjects with PD 4 mm
Han et al. (2010) ³⁴	Shiwha-Banwol, Korea. 1046 subjects. 457 male, 589 female	18–84, mean 42.3 ± 12.2	WHO CPI (CPI: CPI 0–2 as healthy – Gingivitis, CPI 3–4 for periodontitis)	Joint/unified classification (population and country specific): 90 cm in male, 85 cm in female, FGL > 110 mg/dL	# of positive components of MetS and periodontitis (CPI 3–4) OR 1.7 [1.22–2.37], $p = 0.002$	MetS to Pits	If 3 positive components, OR of having Periodontitis 1.53 [1.05–2.23], if 4 or 5 positive components, OR 2.20 [1.28–3.78] ($p = 0.004$), showing dose effect relationship. Age influence $p < 0.001$, frequency of tooth brushing <0.001. The more components, a higher association. If fasting glucose >110 mg/dL and hypertension, OR 2.19 [1.23–3.90]. Modifying factors: age 65, male,

Name	Population	Age range (years)	Criteria for periodontitis	Criteria for MetS	Odds ratio (OR)	Directionality	Modifying/ contributing factors and comments
Andriankaja et al. (2010) ²⁶	NHANES III (1988–1994), 7431 subjects	20	Examined one randomly selected maxillary and one mandibular quadrant. PD measured MF and Mdf. No or mild Periodontitis: mean PD <2.5 mm. Moderate–severe periodontitis: mean PD 2.5 mm	NCEP ATP III	4.7 [2.0–11.2] ($p < 0.001$), only in females	MetS and components to PtiS	smoking, high glucose and high blood pressure. In females, if 2 or more MetS, the higher OR of having periodontal disease. Modifying factors: abdominal obesity was highest contributing factor for assoc. between MetS and periodontal disease in both males and females
D'Aiuto et al. (2008) ²⁷	United States. NHANES III (1988–1994). 13,994 men and women, cross-sectional survey	17	Moderate Periodontitis: two sites, not on the same tooth, with CAL 4 mm, or one site with PD (defined as “gingival probing depth”) >4 mm. Severe Periodontitis: if two sites, not on the same tooth, had CAL 6 mm and at least one site had PD 4 mm. (Page and Eke, 2007). Examined randomly selected half mouth	NCEP ATP III	Severe periodontitis and MetS assoc. 1.74 [1.10–2.76], ($p < 0.05$) if age >44 years	PtiS to MetS	Prevalence of MetS 18% [16–19] if no to mild periodontitis, 34% [29–38] if moderate periodontitis, 37% [28–48] if severe periodontitis. After adjusting age, if 45 years old with periodontitis, 2.31 × greater chance to have MetS [1.13–4.73]. Modifying factor: age
Benguigui et al. (2010) ²⁸	Toulouse, France. 255 participants, sub-sample of subjects included in the MONA LISA survey. 2006 and 2007	35–74, mean 58	Page and Eke (2007). (GI, PI–no references for these indices) Examined 4 sites/tooth for entire dentition	NCEP ATP III plus HOMA-IR	$p = 0.05$	MetS to PtiS	41% subjects had moderate periodontitis, 39% severe periodontitis. After adjusting confounders, only HOMA index remain assoc. with severe periodontitis. Modifying factors: increase in % of periodontal pockets and gingival bleeding. IR
Kushiyama et al. (2009) ³⁷	Miyazaki City, Japan. 1070 residents	40–70, median 60	CPI in subjects with more than 10 teeth. Subjects divided into 2 groups based on CPI: Low (code 3) and High (code 4)	NCEP ATP III	3 positive components, 2.13 [1.22–3.7] ($p = 0.008$), 4–5 positive components, 2.34	No direction specified	2.34 [1.08–5.08] $p = 0.032$ compared to subjects with no components. Modifying factors: hypertension and low HDL

Name	Population	Age range (years)	Criteria for periodontitis	Criteria for MetS	Odds ratio (OR)	Directionality	Modifying/ contributing factors and comments
Timonen et al. (2010) ²⁹	Finland. 2050 subjects. Dentate, non-diabetic individuals from the National Institute for Health and Welfare	30–64	Presence of deepened periodontal pockets: (1) 4 mm PD < 6 mm, (2) PD 6 mm. 4 sites/tooth but only recorded deepest site on each tooth	EGIR	RR 1.5 [0.96–2.36] in PD 6 mm group	MetS to PtiS	If PD 4 mm, RR of association with MetS 1.19 [1.01–1.42], if PD 6 mm, RR 1.5 [0.96–2.36], no <i>p</i> -value listed. Modifying factors: IR, central obesity and PD 6 mm
Nesbitt et al. (2010) ⁴⁰	United States. 200 subjects. Data from Baltimore Longitudinal Study of Aging	Mean 56.8 ± 12.7	Distance between CEJ and crest of alveolar bone measured on panoramic radiograph. None or slight bone loss: 1–2 mm, moderate: 3–4 mm, or severe 5 mm	Modification of NCEP ATP III: 2 or more rather than 3 or more of the criteria outlined in NCEP ATP III	Moderate to severe bone loss assoc. 2.61 [1.1–6.1] (<i>p</i> < 0.05)	No direction specified	Moderate to severe bone loss significantly more associated with MetS
Chen et al. (2011) ³¹	Taiwan. 253 subjects undergoing hemodialysis	58.8 ± 0.8	PI (Silness and Loe) ⁴² , GI (Loe and Silness) ⁴³ , Ramfjord Periodontal Disease Index ⁷⁵ . Gingival inflammation designated: no inflammation (PDI 0), mild gingivitis (PDI 1), moderate gingivitis (PDI 2), and advanced gingivitis (PDI 3). Attachment loss 0–2 mm (PDI 4), 3–6 mm (PDI 5), and >6 mm (PDI 6).	NCEP ATP III with the Asian cutoff points for waist circumference (80 cm in women and 90 cm in men)	If Moderate to severe Periodontitis OR 2.73 [1.29–5.79] (<i>p</i> = 0.008)	No direction specified	Moderate to severe periodontitis assoc. with fasting plasma glucose > 110 mg/dL (<i>p</i> = 0.004), hypertriglyceridemia (<i>p</i> = 0.001). Modifying factors: gingival inflammation and amount of plaque
Chomkhakhai et al. (2009) ³⁵	Thailand. 369 subjects from the Endocrine Clinic of the King Chulalongkorn Memorial Hospital. 94 male, 275 female with MetS	32–88, mean 63.9 ± 10.4	CPI around 6 teeth (one permanent molar, in each quadrant, one max central incisor and one man central incisor)	The International Diabetes Federation (IDF) except waist circumference cutoff point 90 cm in male, 80 cm in female	No <i>p</i> value	Co-morbidity	52% of subjects with MetS had periodontitis, 45% had gingivitis, and 3% healthy gingiva. Modifying factors: age 40, female, smoking
Zadik et al. (2010) ⁴¹	815 Israel Defence Forces personnel. Non-diabetic male adults	Mean 38.1 ± 7.0	Periodontitis: distance between CEJ and alveolar bone crest 6 mm at one or more sites. Determined using bitewing radiographs	Impaired fasting glucose levels (100 mg/dL to <126 mg/dL). BMI 25, serum triglyceride 200 mg/dL, total cholesterol 200 mg/dL, and LDL-cholesterol 130 mg/dL. Excluded diabetics (fasting glucose 126 mg/dL)	Assoc. with each component examined	No direction specified	Bone loss is associated with age, IFG 100–125 mg/dL (<i>p</i> = 0.032); BMI 25 (<i>p</i> = 0.025), TG 200 mg/dL (<i>p</i> = 0.01), TCH 200 mg/dL (<i>p</i> = 0.001), LDL 130 mg/dL (<i>p</i> = 0.009)

Name	Population	Age range (years)	Criteria for periodontitis	Criteria for MetS	Odds ratio (OR)	Directionality	Modifying/ contributing factors and comments
Kwon et al. (2011) ³⁸	Korea. 6520 subjects participating in the Korean NHANES (KNHANES)	19	Periodontitis: CPI code 3	NCEP ATP III except abdominal obesity cutoff was based on the Korean Society for the Study of Obesity (190 cm for males, 85 cm for females)	No <i>p</i> value, OR 1.55 [1.32–1.83] between MetS and PDI ₃	No direction specified	If <40 years, 1.3 [0.91–1.86]. MetS is not assoc. with Periodontitis. If >40 years old, sig. assoc. 1.47 [1.23–1.76]. No difference in gender. Modifying factors: age but not BMI or BP
Sora et al. (2013) ⁴⁴	Gulla African American in South Carolina. Periodontitis with MetS with T2DM. Hypertension 85%, large waist circumference 84%	55 ± 11	Data extracted from previous cross-sectional study. PD, CAL, BOP, PI (reference not listed). Severe Periodontitis: CAL 6 mm in at least 2 teeth and PD 5 mm in at least one site	NCEP ATP III	Severe Periodontitis and Met S, RR 2.77 (<i>p</i> = 0.03)	MetS to PtiS	MetS associated with extent of severe Periodontitis in Gullah population with T2DM. Modifying factors: waist circumference, HbA1c 7.5
Tu et al. (2013) ⁵⁰	Taiwan. 33,740 Taiwanese	Control: female, 49.96 ± 12.43, male, 50.55 ± 12.93, Gingivitis: female 48.57 ± 11.48, male 47.06 ± 11.78, Periodontitis: female 54.15 ± 11.08, male 53.22 ± 11.15	Periodontal disease defined as combination of the following: tooth mobility, gingival inflammation, periodontal pocketing (no specific values were given)	NCEP ATP III except waist circumference was modified for cutoff values for Asians (90 cm in male, 80 cm in female) or BMI ₂₇	MetS assoc. with periodontitis in females: 1.52 [1.41–1.63] (<i>p</i> < 0.001), males: 1.04 [0.96–1.12] (<i>p</i> = 0.317) non-significant	No direction specified	Females but not males show weak assoc. between MetS and Periodontitis. Modifying factor: gender (female)
Bensley et al. (2011) ⁴⁸	Washington State, US. Washington Adult Health Survey, cross-sectional study. 2006–2007. Non-Hispanic white	456, 25	Severe periodontitis: history of S/R or loose teeth; mild/moderate periodontitis: self evaluation of own gum condition; no periodontal disease: self evaluation of having excellent or good gums	AHA/NHLBI, glucose and lipid analysis and BP	1.5× more likely to have MetS if severe periodontitis is present, no <i>p</i> value	PtiS to MetS	Subjects with severe Periodontal disease were 1.5× more likely to have MetS compared with subjects without Periodontal disease. Modifying factor: age
Fukui et al. (2012) ⁴⁵	Japan. 6421 Japanese (4944 males, 1477 females)	34–77	PD and CAL measured at MB sites: none/mild if 3 mm, moderate if 4–5 mm, severe if 6 mm. Subjects with minimum of 20 teeth examined	NCEP ATP III excluding waist circumferences (used BMI ₂₅ kg/m ²)	Severe periodontitis assoc. with MetS 1.35 [1.03–1.77] (<i>p</i> < 0.05)	PtiS to MetS	Severe PD and severe CAL or moderate PD and moderate CAL had significantly higher ORs for MetS. But severe CAL without severe PD was not significantly assoc. with MetS, i.e., PD more critical. PD >4 mm assoc. with MetS. 1.44

Watamabe and Cho

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Table 2

Longitudinal studies.

Name	Population	Age range (years)	Criteria for periodontitis	Criteria for MetS	Odds ratio OR	Directionality	Modifying/contributing factors and comments
Morita et al. (2010) ⁵⁹	Tokyo, Japan. Longitudinal study. 1023 company employees without MetS but with Periodontal disease at the start of the study. Monitored for 4 years. 727 males and 296 females	Mean 37.3	Healthy: CPI 2. Periodontal disease: CPI 3 (PD 4 mm) at least one sextant	Matsuzawa (2005) plus waist circumference (>85 cm in males and >90 cm in females)	If 2 or more positive components, 2.2 [1.1–1.4], $p < 0.05$	Pts to MetS components	Presence of periodontal pockets at baseline associated with a positive conversion of 2 or more components of MetS in 4 years. If only one positive component, OR 1.4 [1.0–2.1] and no Stat sig. If 2 or more positive components, OR 2.2 [1.1–4.1] ($p < 0.05$). If CPI 3 then more positive components. BP and lipid index sig. assoc. with presence of periodontal pockets (CPI 3)
Kobayashi et al. (2012) ⁶⁸	Japan. Cross-sectional study (925), 3 year longitudinal study (685) 2008–2011, Japan	Brushing freq: 1/day, median age 45; 2/day, median age 43; 3/day, median age 43	Self assessment of tooth brushing frequency	AHA/NHLBI except waist circumferences (90 cm in male, 80 cm in female)	MetS prevalence: cross-sectional: 15.7%. OR of having MetS: if brush 2/day, 0.71 [0.48–1.05], if 3/day, 0.47 [0.24–0.92]	Frequency of tooth brushing to MetS components	Longitudinal study: baseline excluded subjects with MetS. After 3 years, 99 out of 985 developed MetS, i.e., incidence of 14.5%. If brush 2/day, OR 0.8 [0.49–1.31] (p trend < 0.05), 3/day, 0.43 [0.19–0.97] ($p < 0.05$). Increase in frequency of brushing, decrease in TG (P for trend is $p < 0.05$). Modifying factor: frequency of tooth brushing

Table 3

Classifications and criteria for metabolic syndrome.

Components	Syndrome X ⁵⁷	Deadly quartet ⁵⁸	World Health Organization ⁵⁹	European Group for the Study of Insulin Resistance ⁷⁶	National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) ⁶²	American Association of Clinical Endocrinologists (AAACE) ⁶⁴	Matsuzawa ⁷⁰	International Diabetes Federation (IDF) ⁶⁶	American Heart Association/ National Heart, Lung and Blood Institute (AHA/NHLBI) ⁶³	Joint/unified classification ⁶⁵
Insulin resistance	IR underlying cause; but by itself is not sufficient to produce full syndrome	Glucose intolerance and		hyperinsulinemia	IR (1 of the following): type 2 diabetes; impaired fasting glucose (IFG); impaired glucose tolerance (IGT), or for those with normal fasting glucose values <110 mg/dL, a glucose uptake below the lowest quartile for background population under hyperinsulin	IR (defined as hyper-insulinaemia – top 25% of fasting insulin values among the non-diabetic population). Plus 2 of the following (below)	Impaired fasting glucose 110–125 mg/dL, glucose intolerance	Refers to MetS as “Insulin Resistance Syndrome”. Impaired glucose tolerance or impaired fasting glucose	N/A	N/A
IR included	N/A									
Blood pressure	Hypertension	Blood pressure above 140/90 mmHg	140/90 mmHg or use of antihypertensive therapy	140/90 mmHg or use of antihypertensive therapy	130/85 mmHg	130/85 mmHg	130/85 mmHg	130/85 mmHg or use of antihypertensive therapy	130/85 mmHg or use of antihypertensive therapy	130/85 mmHg or documented use of antihypertensive therapy
Fasting blood glucose	Hyperglycemia = risk factor	N/A	Impaired glucose tolerance, impaired fasting glucose, or type 2 diabetes mellitus. No specifications	6.1 mmol/L	110 mg/dL	>110 mg/dL. Fasting glucose between 110 and 126 mg/dL, IGT or IFG.	110 mg/dL	100 mg/dL or previously diagnosed T2DM	100 mg/dL or drug treatment	100 mg/dL or use of hyperglycemia drug therapy
BMI	N/A	N/A	>30 kg/m ²	N/A	N/A	25 kg/m ²	25 kg/m ²	>30 kg/m ²	30 kg/m ²	N/A
Waist circumference	N/A	Obesity: body weight more than 20% above the ideal weight. Male: Waist-to-hip girth ratio	Waist:hip ratio >0.9 in men, >0.85 in women	94 cm for men and 80 cm for women	102 cm for men and 88 cm for women. There are	>102 cm in males, >88 cm in females	>85 cm for men and 80 cm for women	Prerequisite for diagnosis of MetS, 94 cm for Europid men	102 cm for men and 88 cm for women	Population- and country-specific definitions