Association between Acute Myocardial Infarction and Periodontitis: A Review of the Literature

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Abstract

Background: Cardiovascular disease (CVD), particularly acute myocardial infarction (AMI), is the leading cause of death worldwide. In India, myocardial events are expected to be the fastest growing cause of death between 2005 and 2015. Thus, in order to prevent and manage the onset of the prevailing AMI epidemic, there is a crucial need to explore different dependent and independent risk factors of AMI, as well as its relationship with other systemic diseases and ill health conditions. One such possible relationship could be an association between AMI and periodontal diseases.

Objective and methodology: The aim of this study was to review the existing literature to assess the strength of association between AMI and periodontitis in the context of Indian, particularly North Indian, populations and to outline key knowledge gaps in this field.

Findings: Review of the literature clearly indicates that evidence on the association between periodontitis and AMI in Indian populations, as well as other populations worldwide, is limited. The number of studies done so far is relatively low. Further, inadequate sample size, retrospective data analyses, potential residual confounding factors, inconsistent definitions of exposure and outcome variables, and reported diversity in results, are some of the other key limitations.

Conclusion: Insufficient evidence is available to justify that periodontal interventions can prevent the onset or progression of acute myocardial events. More longitudinal clinical trials and case-control studies with well controlled confounding factors and valid outcome and exposure measures are needed for determining the true association between the conditions.

Key words: Cardiovascular diseases, acute myocardial infarction, periodontitis

Introduction

Cardiovascular disease (CVD), particularly acute myocardial infarction (AMI), is the leading cause of death worldwide. Annually, more people in the world die of CVDs, particularly AMI and stroke, than any other form of illness (Anand, 2001; WHO, 2011). Further, this impact is disproportionate between low-middle income countries and high-income countries. More than 80% of CVD mortalities take place in low-middle income countries such as India (WHO, 2011; WHO, 2013). In India, myocardial events are expected to be the fastest growing cause of deaths between 2005 and 2015 (WHO, 2011). Regarding the etiology of the disease, epidemiologic and pathologic studies suggest that only about 56-66% of cardiovascular risk is explained by classic risk factors (Yusuf *et al.*, 2004) and indicates the presence of a number of additional and unknown underlying social and pathophysiological determinants, or "the causes of the causes." Thus, in order to prevent and manage the onset of the huge AMI epidemic, there is a crucial need to explore different dependent and independent risk factors of AMI as well as its relationship with other systemic diseases and ill health conditions. One such possible relationship could be an association between AMI and periodontal diseases. A large body of literature indicates a possibility of this association (Ziebolz *et al.*, 2011; Machuca *et al.*, 2012). Periodontitis shares some common risk factors with CVDs, such as tobacco use, diabetes, an unhealthy diet high in sugar and fats, and heavy alcohol consumption. This is suspected to be the reason behind an observed association between the two conditions (Armitage, 2000). However, the question as to what extent the relationship is explained by the common risk factors is still unanswered.

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Further, the strength and degree of association and cause to effect relationship is also being researched and is yet to be established.

Studies conducted so far have involved diverse population groups and have come up with distinctive results, extending from the presence of a significant relationship between AMI and periodontitis to a lack of any possible association between these two conditions. Seven meta-analyses and systematic reviews available so far show noteworthy heterogeneity in the relationship between periodontitis and AMI, proposing the requirement for further studies including distinctive population subgroups (Madianos *et al.,* 2002; Janket *et al.,* 2003; Humagain *et al.*, 2006; Blaizot *et al.,* 2007; Ford *et al.,* 2007; Guiglia *et al.,* 2007; Lockhart *et al.*, 2012). Therefore, in order to serve this cause, the aim of this study was to review the existing literature to assess the strength of this association in the context of the North Indian population and to outline key knowledge gaps in this field.

Methodology

To identify previous literature pertinent to the issue of linkages between periodontal diseases and cardiovascular diseases, particularly periodontitis and AMI, an electronic search of Pub Med, MEDLINE, and Canadian Best Practices Portal was conducted. The search strategy applied was as follows: periodontitis AND (cardiovascular diseases) OR (myocardial infarction) OR (acute myocardial infarction) OR (coronary heart diseases) OR (South Asia) OR (India) OR (North India). In addition, the reference lists given in the articles were also considered. An initial screening was based on the title and the abstract. The final screening consisted of an evaluation of full-text reports and assessment of studies that met the inclusion criteria**.**

Inclusion and exclusion criteria

Research reports, literature reviews and meta-analyses were included. The studies were not limited to any specific type, but were done with adult populations only. Data from various cross sectional, case control, and cohort studies were included for review. Selected studies were not restricted to any particular geographic area or country, but included data from numerous researches conducted worldwide in various countries. However, specific attention was paid to literature from South Asian countries, specifically India. Only reports published in English were included in the study.

Results

Link between periodontal diseases and acute myocardial infarction

Despite the presence of a large body of literature investigating the link between oral and cardiovascular diseases, only a few studies investigated the particular link between periodontal diseases and AMI. For the first time, in the late 1980s, a case control study by Mattila *et al.* (1989) reported a highly significant positive association between poor dental health and AMI. The observed association was independent of the traditional risk factors for heart disease. Following the investigation by Mattila *et al.* (1989) the link between oral infection and periodontal diseases, with particular emphasis on periodontitis and AMI, has been addressed in many studies.

On the one hand, various studies conducted with different populations have suggested that atherosclerosis and the occurrence of AMI could be linked to periodontal infections (Arbes *et al.*, 1999; Buhlin *et al.*, 2002; Hujoel *et al.*, 2000; Rutger *et al.*, 2003). Data from these studies indicates the role of periodontal infection with respect to the etiology of AMI. The study conducted by Ajwani *et al.* (2003) showed a significant relationship between dental health and AMI even after adjusting for age, social class, hypertension, serum lipid and lipoprotein concentrations, smoking, presence of diabetes, and serum C peptide concentration. Further, various case control studies (Andriankaja *et al.*, 2007; Cueto *et al.*, 2005; López *et al.*, 2002) also provided evidence of an association between periodontitis and AMI, even after adjusting for well-established risk factors for AMI including smoking and gender.

However, several recent studies and meta-analyses have failed to identify any association between these two conditions (Malthaner *et al.*, 2002; Tuominen *et al.*, 2003; Humphrey *et al.*, 2008; Blaizot *et al.*, 2009; Bokhari *et al.*, 2009; Renvert *et al.*, 2010; Bokhari *et al.*, 2011; Rivas-Tumanyan *et al.*, 2012). After accounting for factors common to both periodontal disease and cardiovascular diseases, these studies found no significant association between periodontal disease and cardiovascular diseases, including AMI. Several researchers thoroughly evaluated the possibility of an association between periodontitis and AMI independent of the effect of mutual risk factors (i.e., diabetes, body mass index, smoking or dietary habits, alcohol consumption and socioeconomic status) and reported that the observed association between these two conditions was due to confounding risk factors, for example, smoking (Hujoel *et al.*, 2000; Muller, 2001; Tuominen *et al.*, 2003; Fadel, 2012). Not only the cross-sectional studies but also the various important longitudinal cohort and follow-up studies failed to identify any association between AMI and periodontitis. For instance, the health professionals' follow-up study and the physicians' health study found no association between periodontal diseases and coronary heart diseases, including AMI (Howell *et al.*, 2001). In addition, as mentioned earlier, the first National Health and Nutrition Examination Survey Epidemiologic follow-up study done by Hujoel *et al.* (2002) also indicated a negative association between periodontitis and resultant coronary heart diseases,

including AMI. Nevertheless, a 12-year follow-up study done by Tuominen *et al.* (2003) also reported that the association between periodontitis and congestive heart disease (CHD), including AMI, is mostly explained by confounding factors, particularly those relating to oral and general health behavior. The study reported that after adjusting for the established CHD risk factors, association between these two conditions was reduced to a statistically non-significant level. The study design, methodology and large sample size of the above mentioned studies add to the significance and validity of the study findings and suggest we rethink before drawing any conclusions.

Thus, the literature so far presents ambiguous results and is inconclusive. A review of literature conducted by Bokhari *et al.* (2009) also reported "the findings of epidemiologic studies conducted on the relationship of periodontal disease to cardiovascular disease are inconsistent and lead to conservative conclusions." According to this literature review, studies done so far do not prove any causal relationship between periodontitis and AMI and show lack of control over confounding variables. Bokhari *et al.* (2009) indicated that the observed varied associations between these two conditions could be due to the residual confounding and over-control of confounders.

Table 1 outlines the studies that have particularly addressed the issue of association between periodontitis and AMI (in India and worldwide), and outlines the factors considered as confounders and adjusted for in the data analysis process. The studies are organized according to the year of publication.

Link between periodontitis and acute myocardial infarction - South Asian and Indian populations

In contrast to the developed world, not much research has been done in developing countries, particularly the South Asian countries of Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan and Sri Lanka. (Kaisare *et al.*, 2007; Zamirian *et al.*, 2008; Bokhari *et al.*, 2009; Sikka *et al.*, 2011; Chopra *et al.*, 2012; Parkar *et al.*, 2013; Khosravi Samani *et al.*, 2013). Of these studies, only four studies (two with Iranian populations and two with Indian populations) particularly addressed the issue of a possible association between periodontitis and AMI (Kaisare *et al.*, 2007; Zamirian *et al.*, 2008; Parkar *et al.*, 2013; Khosravi Samani *et al.*, 2013). Moreover, all these studies are done with Iranian, South-West Indian and Eastern Indian populations. There is not even a single study involving a North Indian population, a population of around 543,937,430 spread over an area of 1,420,540 km^2.

In India, the first study was done in 2007 (Kaisare *et al.*, 2007) and was a case-control study with Goans. Its aim was to investigate the possible association between periodontal health and AMI. A total of 500 subjects, 250 with AMI disease and 250 with coronary heart disease were included in the study. Even though the study results indicated that periodontal diseases might be associated with AMI, the study had several limitations. There was no social or financial homogeneity between the case and control groups. Several possible risk factors, such as genetics, body mass index, alcohol consumption, and oral and general health care awareness level were not included in the study. Though the study adjusted for the potential confounding effect of smoking, it did not take into consideration the use of smoke-free tobacco. The research indicates the possibilities of potential negative effects of smokeless tobacco use on one's cardiovascular health (Critchley *et al.*, 2003; Subramanian *et al.*, 2004; Ali *et al.*, 2011). Hence, the possibility of confounded results (tobacco use as main confounding factor) cannot be neglected.

In contrast to the findings of the above study, another case-control study in the context of an Indian population (Sikka *et al.*, 2011) showed non-significant differences in dental caries between the case and control groups, and a minor increase in a mild form of periodontitis in cases with coronary heart disease as compared to cardiovascular healthy controls. However, these non-significant results may be due to a selection bias, as the control subjects in this study were those who visited the clinic for dental screening and may be regarded generally as a health conscious group. Further, subjects with a previous history of AMI were not included in this study. Additionally, the study design is such that it does not establish the temporality of the relationship between coronary heart disease and periodontal disease. The study design does not exclude the possibility that the changes in periodontal parameters might have resulted from, rather than causing, the coronary heart disease. The findings of this study were in contrast with the study findings of Khosravi Samani *et al.* (2013), who conducted a case-control study with an Iranian population and indicated that patients with higher DMFT scores (decayed, missing or filled teeth > 10) were at greater risk for AMI (OR = 2.73). Another similar case-control study with an Iranian population (Zamirian *et al.*, 2008) also reported a significant association between periodontitis and AMI, even after adjusting for conventional risk factors for AMI.

In light of the limited data and ambiguous findings of the previous studies, the issue of an association between periodontitis and AMI was addressed again by Parkar *et al.* (2013) with a more rigorous study design but a smaller sample size. The study produced evidence that patients who had experienced AMI exhibited poor periodontal conditions in comparison to the healthy subjects, and suggested an association between chronic oral infection and AMI. However, this study had several limitations: it was performed in one hospital and completed with a very small sample (total 60 subjects, 30 in each group) that did not adequately represent the AMI population.

Table 1. Literature on the association between periodontitis and AMI.

Author and Year	Study Methodology	Sample Size	Oral Assessment	Adjusted For	Conclusion
Kodovazenitis G, *et al.*, 2014	Case-control	204	Number of missing teeth, probing depth, clinical attachment loss	Gender, high-density lipoprotein, smoking	The association between periodontitis and acute myocardial infarction was consistent across different measurements and/or definitions of periodontitis. The strength of the association increased concomitantly with the robustness of the criteria used to define periodontitis
Parkar SM, 2013	Case-control	60	Simplified oral hygiene index, community periodontal index, loss of attachment	Age, gender, smoking, body mass index, hypertension, diabetes mellitus	The study results showed evidence that those patients who have experienced myocardial infarction exhibit poor periodontal conditions in comparison to healthy subjects and suggested an association between chronic oral infections and myocardial infarction
Khosravi Samani M, *et al.*, 2013	Case-control	123	Ramfjord periodontal diseases index, number of missing teeth	Age, gender, blood pressure, diabetes, smoking	The results showed significant relation between periodontitis and myocardial infarction
Chopra R, *et al.*, 2012	Case-control	240	Alveolar bone loss, C-reactive protein	Age, gender, smoking, hypertension, C-reactive protein level, periodontal disease severity	Periodontitis was found to be associated with increased systemic inflammatory response
Gundala R, *et al.*, 2012	Case-control	120	Plaque index, gingival index, probing depth, clinical attachment loss	Age, gender, smoking, body mass index	Elevated serum leptin concentration was found to be associated with increased BMI, chronic periodontitis and acute myocardial infarction
Ohki T, *et al.*, 2012	Lab-based experimental study	81	Polymerized chain reaction	Age, gender, diabetes, smoking, hypertension, hypercholesterolemia	Three species of periodontal bacteria were detected in the thrombi of patients with acute myocardial infarction
Buduneli E, *et al.*, 2011	Case-control	481	Plaque accumulation, clinical attachment loss, salivary analysis	Gender, age, smoking, bleeding on probing (%), probing depth	The saliva of patients with acute myocardial infarction and periodontitis had a significant trend for the highest elastase activities among the study groups

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Holmlund A, *et al.*, 2011	Case-control	200	Periodontal bone loss, number of deepened pockets, bleeding on probing, number of teeth present	Age, gender, smoking, diabetes, hypertension, total cholesterol, triglycerides, body mass index	Patients with myocardial infarction had an impaired oral health compared to controls
Kodovazenitis G, *et al.*, 2011	Case-control	87	Missing teeth, mean pocket probing depth, clinical attachment loss, bleeding on probing	Age, gender, body mass index, hypertension	Periodontitis was found to contribute to elevated C-reactive protein levels in non-diabetic, non-smoking acute myocardial infarction patients, independently of other confounding factors
Nakamura Y, *et al.*, 2011	Case-control study	209	Number of missing teeth, periodontal pocket depth, loss of attachment, bleeding on probing	Age, gender, diseased valve, history of smoking, type of surgery	The study found no evidence that receipt and timing of dental treatment affected surgical success rates and postoperative course
Sikka M, *et al.*, 2011	Case-control	200	Decayed, missing and filled teeth index, community periodontal index, loss of attachment	Age, gender, smoking, body mass index, hypertension, diabetes mellitus	The study showed a slight increase in the level of mild periodontal disease in coronary heart disease patients as compared to controls, with a non-significant difference in level of dental caries
Renvert S, *et al.*, 2010	Case-control	324	Probing depth, bleeding on probing	Age, gender, socioeconomic status (marital status, education), smoking	The study reported that evidence of bone loss around several teeth can predictably be identified as a risk factor for future acute myocardial infarction
Offenbacher S, *et al.*, 2009	Periodontitis and Vascular Events (PAVE) pilot study	303	Periodontal pocket depth, loss of attachment, bleeding on probing	Smoking, marital status and gender	Provision of periodontal scaling and root planing treatment was not found to be associated with improved cardiovascular health
Stein JM, *et al.*, 2009a	Case-control	104	Dental status, plaque index, gingival inflammation, periodontal screening index, attachment loss	Age, gender, smoking, body mass index, hypertension, plaque index, statin intake, ratio of cholesterol to high-density lipoprotein	The results of this study confirmed an association between periodontitis and acute myocardial infarction
Stein JM, *et al.*, 2009b	Case-control	104	Probing depth, clinical attachment loss, alveolar bone loss	Age, gender, smoking	The results confirmed an association between periodontitis and AMI but failed to detect a modifying impact of the composite IL-1 genotype

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Willershausen B, *et al.*, 2009	Case-control	250	Number of teeth, endodontically treated teeth, periodontal screening index, clinical attachment level, radiographic apical lesions	Age, gender, smoking	This study suggested an association between chronic oral infections and myocardial infarction
Zamirian M, *et al.*, 2008	Case-control	160	Plaque index, gingival index, pocket depth, clinical attachment loss, bleeding on probing	Hypertension, diabetes	The study found significant association between periodontitis and acute myocardial infarction, even after adjusting for conventional risk factors for acute myocardial infarction
Andriankaja OM, *et al.*, 2007	Case-control	1461	Clinical attachment loss	Age, gender, body mass index, physical activity, hypertension, cholesterol, diabetes, total pack-years of cigarette smoking	Study provided evidence of an association between probing depth and incident myocardial infarction in both genders. This association appears to be independent from the possible confounding effect of smoking
Kaisare S, *et al.*, 2007	Case-control	500	Decayed, missing or filled teeth, probing depth, simplified oral hygiene index, bleeding on probing	Age, gender, smoking, body mass index, hypertension, diabetes mellitus	The results of this study indicated that periodontal disease may be associated with acute myocardial infarction
Holmlund A, *et al.*, 2006	Case-control	200	Probing depth, bleeding on probing, plaque index, number of teeth, radiographic, bone loss used to categorize periodontitis as none, mild, moderate or severe	Age, gender, smoking	There was a significant dose-response association between number of teeth (whole sample), periodontitis (in subjects aged 40-59 years) and myocardial infarction with odds ratio 1.3-1.5. Hypertension was associated with periodontitis and number of periodontal pockets, but not with number of teeth
Karhunen V, *et al.*, 2006	Case-control	300	Number of teeth and panoramic tomography index (sum of number of residual roots, vertical bone pockets, periapical infections, furcations, caries and pericoronitis lesions seen on radiographic pictures)	Age, body mass index, smoking, diabetes, hypertension, educational level	Number of teeth was significantly associated with sudden cardiac death due to myocardial events

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Cueto A, *et al.*, 2005	Case-control	149	Periodontitis was measured as the percentage of sites with clinical attachment loss greater than 3 mm	Sex, age, tobacco habit, hypertension, diabetes, hypercholesterolemia, regular exercise, hypertension, diabetes	There was evidence of an association between periodontitis and acute myocardial infarction after adjusting for well-known risk factors for acute myocardial infarction
Rutger Persson G, *et al.*, 2003	Case-control	160	Severity of periodontitis was categorized as 10%, 20%, 30%, 40%, 50% and 60% of teeth with bone loss ≥ 4 mm measured from the cementoenamel junction to the alveolar bone	Age, sex, smoking, ethnicity, cholesterol, triglycerides, diabetes	Periodontitis was significantly associated with acute myocardial infarction with an odds ratio varying between 9.1-14.1, expressing the highest odds ratio when bone loss ≥ 4 mm was present in 50% of the sites
Tuominen R, *et al.*, 2003	12-year follow-up study	6527	Caries, periodontal and dental plaque status, pocket depth, presence of remaining teeth, various types of dentures	Age, smoking, low socioeconomic status	Adjustment for the established coronary heart disease risk factors reduced the association to statistical non-significance. Study reported that the associations between oral health indicators and coronary heart disease are mostly explained by confounding factors
Hujoel PP, *et al.*, 2000	First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study.	8032	Comparison of subjects with periodontitis (PD ≥ 4 mm for any teeth) and subjects with edentulism	All kinds of cardiovascular disease risk factors, including age and smoking	It was concluded that periodontitis or gingivitis does not elevate risk of coronary heart disease among individuals with a prior heart attack or self-reported preexisting cardiovascular disease
Malthaner SC, *et al.*, 2002	Case-control	100	Clinical attachment loss, number of sites with radiographic bone loss	Age and previous smoking history, factors common to both diseases	The study reported that there is no significant association between periodontal disease and chronic coronary artery disease, including acute myocardial infarction
Howell HT, *et al.*, 2001	Randomized, double-blind, placebo-controlled trial	2653	Self-reported presence or absence of periodontal disease at study entry	All kinds of cardiovascular disease risk factors, including age and smoking	These prospective data suggested that self-reported periodontal disease is not an independent predictor of subsequent cardiovascular disease in middle-aged to elderly men
Emingil G, *et al.*, 2000	Case-control	120	Missing teeth, restorations, probing depth, bleeding on probing	Age, gender, smoking, hypertension, diabetes	The results of this study indicate that periodontal disease may be associated with acute myocardial infarction

Additionally, in this study no radiographic diagnostic measure was used for the identification of periodontitis. Further, in order to estimate the periodontal disease severity a partial mouth recording protocol was utilized by this study. Such a protocol can only be precise in measuring the mean periodontal indices and could possibly introduce error in estimation of the prevalence of periodontal disease.

To explain the possible mechanism underlying this association, Chopra and colleagues (2012) compared two major forms of periodontitis (chronic and aggressive periodontitis) with regard to cardiovascular disease risk. This study compared the C-reactive protein (CRP) levels in chronic and aggressive periodontitis patients. A total of 240 systemically healthy subjects was divided equally into three groups (80 each): 1) generalized aggressive periodontitis, 2) chronic generalized periodontitis, and 3) no periodontitis (NP, controls). Samples of venous blood were collected and a quantitative CRP analysis was performed utilizing a turbid metric immunoassay. The findings of this study indicated that "periodontitis should be of particular concern in younger individuals where elevated levels of CRP may contribute to early or more rapid cardiovascular disease in susceptible patients" (Chopra *et al.*, 2012). However, later on, Gundala *et al.* (2014) in their cross-sectional clinical study reported that elevated serum leptin concentration was associated with "increased in body mass index, chronic periodontitis and AMI" and indicated that it should be considered as a risk factor for both AMI and periodontitis. Similarly, in another cross-sectional study, Gangadhar *et al.* (2011) indicated the possibility of an association between gingival leptin concentration and the risk of developing cardiovascular diseases. Thus, a wide ambiguity exists not only in the findings of studies exploring the strength of association between periodontitis and AMI, but also in the studies exploring the possible underlying etiopathological mechanisms linking these two conditions.

Discussion

A review of the literature indicates that studies related to AMI and periodontitis have been published with vague results. In spite of the rapid growth in the number of studies on the possible etiological role of periodontal disease in systemic diseases, the issue has not been resolved. Many questions remain unanswered, and the pathophysiological mechanisms underlying these associations remain unclear. Moreover, it is difficult to interpret the reported associations. From one viewpoint, the associations could be inferred as causal, recommending that decreasing periodontal diseases' prevalence by early interventions and treatments may be beneficial in lessening the risk of future CVD events. However, these findings could be considered erroneous due to the biases introduced by various confounding variables. Further, the literature review on the association between periodontitis and AMI in the context of North Indian populations clearly indicates the crucial need for well controlled longitudinal and case-control studies with valid outcome and exposure measures for determining the true association between the conditions.

Potential reasons for the observed diversity in findings

Use of different diagnostic criteria for periodontitis

The reasons for such diverse findings may solely reflect an inadequate definition of periodontitis. A recent study done by Kodovazenitis *et al.* (2014) reported that the strength of the association between periodontitis and AMI increased concomitantly with the robustness of the criteria used to define periodontitis. Further, there is a large variation in the outcome measures used in the studies conducted so far. The studies used varying diagnostic criteria for defining and measuring the periodontitis disease status, such as plaque index (PI), community periodontal index (CPI), community periodontal index of treatment needs (CPITN), and the Russell's periodontal index. Review of the literature indicates that in order to measure the periodontal health status, only a small number of studies utilized the methodologies and indices specified by the World Health Organization (WHO). This indicates that a standardized approach is required for the significant, but so far under-examined, issue of prevalence and severity of periodontitis among AMI patients. Additionally, the effect of non-differential misclassification stemming from the use of questionnaires and self-reporting of periodontal disease, instead of clinical examinations, can further lead to under/over estimation of the strength of association between AMI and periodontitis.

Incomplete adjustment for the confounding variables

Incomplete accounting for proper control subjects and matching for potential confounding variables may also be responsible for the observed divergence in findings. As discussed previously, periodontitis and myocardial disease have several mutual risk factors, for instance, age, body mass index, diabetes, smoking habits, alcohol consumption and stress; therefore, the possibility of confounding factors is considerable. Incomplete adjustment and matching for these factors may lead to residual confounding, which is responsible for the observed weak associations.

Varying individual immunological responses

Moreover, the observed ambiguity in the association between these two conditions can be due to different individual immunological responses that determine the onset and progression of periodontitis. Inflammatory immune response is a key factor in pathophysiology and can be altered or modified by certain host factors.

In vitro, it has been found that individual responses are affected by genetic signaling pathways that influence the expression of inflammatory mediators in response to periodontal bacterial lipopolysaccharides (Preshaw *et al.*, 2004; Divaris *et al.*, 2013). Therefore, the strength of the relationship between AMI and periodontitis may vary among populations with different genetic backgrounds. Thus, in order to confirm an association between AMI and periodontitis, it is crucial to study different populations with different genetic backgrounds.

Key knowledge gaps

The key gaps in knowledge about an association between AMI and periodontitis with regard to the Indian population are as follows: the number of research studies carried out with this population group is inadequate (no published study to date involving North Indian subjects), and studies done in other parts of the world cannot be 100% extrapolated to populations owing to the varying environmental, racial and genetic factors. Further, in studies done so far with Indian populations, some of the significant confounding variables were not taken into consideration. For example, none of the studies done with this population subgroup accounted for genetic factors and use of smokeless tobacco as potential confounding factors. Also, the findings of various studies are not consistent enough to firmly support the association between periodontitis and AMI. Further, none of the studies done so far used identical methodology and clinical data collection procedures. Hence, the results have never been verified. Moreover, the studies done with the South Asian populations, including Indian populations, used older and outdated indices to measure periodontitis and oral health, such as the Ramfjord periodontal index. These indices have several drawbacks and are no longer used for periodontitis diagnosis. Therefore, the measurement of independent variables in these studies is questionable. This measurement bias might have resulted in a biased odds ratio leading to an incorrect estimation of the strength of association between periodontitis and AMI. In line with the above-mentioned fact, most of the case-control studies with South Asian populations used some irrelevant indices, such as the oral hygiene index, to measure the participants' periodontal health. Indices such as the oral hygiene index should not be considered, as the score may be affected by subjects' duration of stay in the hospital and the cases could show worse scores due to time spent in intensive care units as well as longer hospital stays.

Conclusions

Evidence on the association between periodontitis and AMI in the context of Indian, particularly North Indian, populations is limited. The number of studies done so far is relatively low. Although various studies have demonstrated an association between different parameters of periodontitis and AMI, the studies are inconsistent in defining the independent and dependent variables. In this manner, no relationship between these two conditions has been precisely recreated or verified, and therefore insufficient evidence is available to justify that periodontal interventions can eliminate the onset or progression of acute myocardial events.

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