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Periodontal systemic associations: review of the evidence

Gerard J. Linden[1], Amy Lyons[2] and Frank A. Scannapieco[3]

[1]Centre for Public Health, School of Medicine Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, Northern Ireland, UK; [2]Health Science Library, University at Buffalo, The State University of New York, Buffalo, NY, USA; [3]Department of Oral Biology, School of Dental Medicine, University at Buffalo, The State University of New York, Buffalo, NY, USA

Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence.

Abstract

Aim: To critically appraise recent research into associations between periodontal disease and systemic diseases and conditions specifically respiratory disease, chronic kidney disease, rheumatoid arthritis, cognitive impairment, obesity, metabolic syndrome and cancer.

Methods: A MEDLINE literature search of papers published between 2002 and April 2012 was conducted. Studies that included periodontitis as an exposure were identified. Cross-sectional epidemiological investigations on large samples, prospective studies and systematic reviews formed the basis of the narrative review. A threshold set for the identification of periodontitis was used to identify those studies that contributed to the conclusions of the review.

Results: Many of the investigations were cross-sectional secondary analyses of existing data sets in particular the NHANES studies. There were a small number of systematic reviews and prospective studies. There was substantial variability in the definitions of exposure to periodontitis. A small number of studies met the threshold set for periodontitis and supported associations; however, in some of the chronic diseases there were no such studies. There was strong evidence from randomized controlled trials that interventions, which improve oral hygiene have positive effects on the prevention of nosocomial pneumonias.

Conclusions: There was substantial heterogeneity in the definitions used to identify periodontitis and very few studies met a stringent threshold for periodontitis. Published evidence supports modest associations between periodontitis and some, although not all, of the diseases and conditions reviewed. There is a need to reach a consensus on what constitutes periodontitis for future studies of putative associations with systemic diseases.

Key words: cancer; chronic kidney disease; cognitive impairment; metabolic syndrome; obesity; periodontitis; pneumonia; respiratory disease; rheumatoid arthritis

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In recent years, there has been intense interest in potential associations between periodontal disease and various chronic systemic diseases and conditions. Prospective cohort studies, which show that periodontal disease is associated with an increased risk of premature death from any cause, suggest the hypothesis that periodontitis may be a risk factor for other diseases (DeStefano et al. 1993, Garcia et al. 1998, Linden et al. 2012). A large body of research work has investigated periodontitis as an independent risk factor for atherosclerosis including stroke (Wu et al. 2000) and coronary heart disease (Bahekar et al. 2007, Humphrey et al. 2008, Friedewald et al. 2009, Kebschull et al. 2010, Buhlin et al. 2011); adverse pregnancy outcomes (Chambrone et al. 2011a,b, Matevosyan 2011); and diabetes (Demmer et al. 2008, Allen et al. 2011, Ide et al. 2011, Preshaw et al. 2012).

The purpose of this review is to assess the state of the science regarding the association of periodontitis with systemic diseases and

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conditions excluding cardiovascular disease, diabetes and adverse pregnancy outcomes, which are re-examined in a series of accompanying systematic reviews (Borgnakke et al. 2013, Dietrich et al. 2013, Ide & Papapanou 2013). The focus is on diseases and conditions that have a major impact on public health, including respiratory disease, chronic kidney disease, rheumatoid arthritis, cognitive impairment, obesity, metabolic syndrome and cancer. This narrative review is a critical appraisal of studies that have addressed potential associations with periodontitis and overall our approach is as inclusive as possible. There was a range in the quality of the published studies and a wide variation in the criteria used to classify periodontitis exposure. The term periodontal disease was often used when there was a less certain exposure to periodontitis, for example, when surrogate markers were used. In this review, we did not include epidemiological studies that used tooth loss as a surrogate measure of periodontitis exposure. To more properly assess associations with systemic diseases and conditions, particularly where no systematic reviews or prospective studies had been completed, specific criteria were applied to identify the presence of periodontitis. Although we have been inclusive in relation to the studies reviewed, the conclusions are based only on those studies in which there was exposure to periodontitis at the specified diagnostic threshold. In some cases, there were variations in the diagnostic criteria used to identify specific systemic diseases or conditions and these have been highlighted.

Studies published since 2002 form the basis of the review, but a small number of other studies that provide pivotal information are included. Prospective studies or systematic reviews are preferentially cited where these are available. Discussion of the biological mechanisms through which periodontitis could increase the risk of other diseases is beyond the scope of this review and these are discussed in detail in an accompanying paper (Van Dyke & van Winkelhoff 2013).

Method

A MEDLINE literature search was conducted, and limited to human studies in English from April of 2002 to April of 2012. The oral/dental search terms used were periodontal diseases, gingival diseases, periodontitis, tooth loss, dental plaque and oral hygiene. All terms used were exploded to assure retrieval of all items related to the specific search terms. All these terms were linked together by the use of "OR". The systemic terms used were lung diseases (chronic obstructive pulmonary disease, bronchitis, pulmonary disease, pneumonia or aspiration), kidney diseases, rheumatoid arthritis, cognitive impairment, Alzheimer's disease, obesity, metabolic syndrome and cancer, also all exploded. Studies that identified periodontitis as an exposure were identified. Cross-sectional investigations on large samples, prospective studies and systematic reviews formed the basis of the narrative review.

Assessment of periodontitis

The threshold set for the identification of periodontitis, where clinical measures were available, was the case definition outlined by Page & Eke (2007). Periodontitis equated to ≥ 2 inter-proximal sites with clinical attachment level (CAL) of ≥ 4 mm or ≥ 2 inter-proximal sites with probing pocket depth (PPD) of ≥ 5 mm (Page & Eke 2007). For studies relying on radiographic assessment alveolar bone loss (ABL) of $\geq 40\%$ was accepted as evidence of periodontitis exposure. These clinical and radiographic thresholds were used to identify studies, which contributed to conclusions reached on associations between periodontitis and the diseases and conditions studied.

Chronic Obstructive Pulmonary Disease (Appendix S1)

Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive airflow obstruction and inflammation in the airways. The airflow limitation is associated with an abnormal inflammatory response of the lung to noxious particles or gases. The main cause of COPD is smoking tobacco (Giovino et al. 2012). The worldwide prevalence is 9–10% in those aged 40 years and older and there is a striking rise in developing countries due to increased smoking rates. COPD is aggravated by exacerbations likely caused by bacterial or viral infections or both (Decramer et al. 2012).

A possible link between periodontitis and chronic respiratory disease was first suggested in several epidemiological analyses of NHANES data (Scannapieco et al. 1998, Scannapieco & Ho 2001) and data from the Veterans Administration Dental Longitudinal Study (VADLS) (Hayes et al. 1998). A later analysis of the VADLS data, after over 30 years follow-up, validated the association even after stratification for smoking (Garcia et al. 2001) suggesting that periodontitis could be a co-factor for COPD.

Following analysis of NHANES III, Hyman & Reid (2004) found an almost threefold increase in COPD among current smokers with severe periodontitis (Appendix S1). However, this was the only significant association found and was limited to 1.3% of those studied. It was concluded that adjusting for smoking as a confounder was insufficient and that it should be treated as an effect modifier in any association between periodontitis and COPD (Hyman & Reid 2004). A study of well-functioning adults aged between 70 and 79 years found an association between periodontitis and obstructive airway disease in former smokers but not in never smokers. No association was evident in current smokers; however, values of all the periodontal indices were increased in this subset regardless of pulmonary status (Katancik et al. 2005). A case-control study from a hospital population in Beijing found that in analyses stratified for smoking there was no significant association between periodontitis and COPD (Wang et al. 2009). Periodontal status was not associated with the frequency of exacerbations in patients with COPD (Liu et al. 2012).

A systematic review by Scannapieco et al. (2003) concluded that the associations reported between periodontal disease and COPD were preliminary and further studies were needed. A subsequent systematic review by Azarpazhooh & Leake (2006) concluded that there was poor evidence of a weak association between oral health and COPD.

Comment

No studies which met the threshold set for periodontitis supported an association with COPD. The studies investigating periodontitis and COPD remain preliminary and large-scale prospective epidemiological studies are needed. Adequately powered randomized clinical trials that test the efficacy of periodontal interventions on the progression of COPD are required to further investigate a role for periodontal inflammation in its pathogenesis.

Pneumonia

Pneumonia is classified on the basis of the source of infection and/or the setting in which the infection is acquired (Raghavendran et al. 2007). Community-acquired pneumonia is a lung infection in individuals who have not recently been hospitalized and is usually caused by bacteria, which reside in the oropharynx. Nosocomial hospital-acquired pneumonia (HAP) manifests 48 h after admission to a hospital. Ventilator-associated pneumonia (VAP), a subset of HAP, is defined as pneumonia developing $\geq$48 h after intubation for mechanical ventilation (Flanders et al. 2006). In VAP, placement of the endotracheal tube can transport oropharyngeal organisms into the lower airway (Safdar et al. 2005). Growth of a biofilm, resistant to host defences and antibiotics, on the surface of the tube is a further problem (Feldman et al. 1999). The oral cavity may serve as an important reservoir of infection for VAP (Paju & Scannapieco 2007). The mouth can become colonized by typical respiratory pathogens such as *Staphylococcus aureus, Pseudomonas aeruginosa* and enteric species (Scannapieco et al. 1992). It has been suggested that efforts should focus on preventing or minimizing colonization of the oral cavity by respiratory pathogens, as well as on limiting aspiration, antibiotic exposure and use of invasive devices (Craven 2006).

A systematic review and meta-analysis of five randomized controlled trials (RCTs) (four hospitals, one elderly in nursing homes) found that interventions aimed at reducing the oral microbial load produced a reduction in the risk of HAP. Those who did not have the intervention had an increased odds ratio (OR) for contracting pneumonia (OR = 3.68, 95%CI 1.89–7.16). It was concluded that oral colonization by respiratory pathogens, fostered by poor oral hygiene and periodontitis, was associated with nosocomial pneumonia (Scannapieco et al. 2003).

A further systematic review found that poor oral health was associated with HAP in prospective studies, but none of these assessed periodontal status (Azarpazhooh & Leake 2006). Periodontal pathogens in saliva or dental plaque were shown to be a risk factor for aspiration pneumonia. There were 10 (7 RCTs) intervention studies that adopted various approaches to reducing sources of infection in the mouth, including the provision of professional dental care, the application of topical antiseptics or antibiotics. The 10 studies included 1064 (range 25–270) subjects in the intervention groups. In total, 9 of the 10 studies showed reduced incidence of pneumonia with reductions in relative risk between 34% and 83%, which equated to a number needed to treat of 2–16 (Azarpazhooh & Leake 2006). The systematic review concluded that there was good evidence that improved oral hygiene and frequent professional oral health care reduced respiratory diseases among high-risk elderly adults living in nursing homes and especially those in intensive care units (Azarpazhooh & Leake 2006).

The systematic review by Sjogren et al. (2008) reported positive preventive effects of oral hygiene on pneumonia and respiratory tract infection in hospitalized elderly people and nursing home residents with an absolute risk reduction from 6.6% to 11.7%. They calculated that mechanical oral hygiene could prevent approximately one in 10 cases of death from HAP. A systematic review of antiseptic use (Labeau et al. 2011) concluded that it significantly reduced the risk of VAP (RR 0.67; 95% CI 0.50–0.88). The effect was most prominent for 2% chlorhexidine, while risk reduction was not significant for lower concentrations.

One small case-control study investigated if periodontitis was associated with nosocomial lower respiratory tract infection (Gomes-Filho et al. 2009). There was a significant association between periodontitis and HAP (OR = 3.67, 95%CI 1.01–13.53). The study was underpowered and the outcome should be treated with caution particularly given the very wide confidence intervals.

Comment

Improved oral hygiene has an important role in the prevention of pneumonia in a variety of at-risk populations. Unanswered questions remain about the effects of established chronic periodontitis in relation to any increased risk of lung infections.

Chronic Kidney Disease (Appendix S2)

Chronic kidney disease (CKD) is defined as kidney damage with decreased function (glomerular filtration rate (GFR) <60 mL/min per 1.73 m^2) for 3 months or more. CKD is a worldwide public health problem generally associated with ageing, diabetes (diabetic nephropathy), hypertension, obesity and cardiovascular disease (Levey & Coresh 2012). Kidney failure, defined as GFR <15 mL/min per 1.73^2 m, is treated by dialysis or transplantation and represents end-stage renal disease (ESRD).

The Atherosclerosis Risk In Communities (ARIC) study found that periodontitis was associated with CKD with an OR = 2.0 (95% CI 1.23–3.24) (Kshirsagar et al. 2005). A further study from ARIC found that high levels of antibodies to the periodontal pathogens *Porphyromonas gingivalis, Treponema denticola* and *Actinobacillus* Aggregatibacter) *actinomycetemcomitans* were associated with CKD with an odds ratio ranging from 1.6 to 1.8 (Kshirsagar et al. 2007). In both these studies, estimates were adjusted for a wide range of confounders including age, race, sex, smoking, hypertension, body mass index (BMI) and education.

No significant association between periodontitis and CKD was found in subjects aged $\geq$40 years in an analysis of NHANES III data,

which the authors suggested was due to underestimation of periodontitis by the partial-mouth examination protocol used in NHANES (Fisher et al. 2008). Subsequently, the same group reported that periodontitis was associated with a 60% (95% CI 7%–139%) increased odds of CKD, when data were analysed from all those aged $\geq$18 years who had a periodontal examination in NHANES III (Fisher & Taylor 2009). A further investigation confirmed the association and using structural equation modelling, suggested that periodontal disease was independently associated with CKD in a bidirectional relationship mediated by diabetes duration (Fisher et al. 2011). Ioannidou & Swede (2011) reported that after stratification by race, periodontitis was significantly associated with CKD in NHANES III only in Mexican Americans. Grubbs et al. (2011) found a 51% (95% CI 13%–102%) increased odds of CKD associated with moderate or severe periodontitis using data from NHANES (2001–2004). Those with CKD were less likely to access dental care, which may explain associations evident in these cross-sectional studies (Grubbs et al. 2012).

A prospective study in subjects with type 2 diabetes in the Gila River Indian Community of Arizona, USA found that periodontal disease, assessed by the severity of radiographic bone loss, predicted the development of overt nephropathy, as indicated by macroalbuminuria and ESRD in a dose-dependent manner (Shultis et al. 2007). In a prospective study of subjects with ESRD those who had periodontitis at baseline had an 83% (95% CI 4%–224%) increased risk of death from any cause at the 6 year follow-up (Chen et al. 2011). A prospective study of 317 (166 men, 151 women) 75 year olds, which used the periodontal inflamed surface area as a surrogate measure of exposure, found those in the highest quartile had a 124% (95% CI 5%–379%) increased risk of CKD over 2 years (Iwasaki et al. 2012). The studies of Chen et al. (2011) and Iwasaki et al. (2012) had very wide confidence intervals indicating a lack of precision in the estimates of the overall population values.

One small exploratory clinical study reported that periodontal treatment of systemically healthy individuals resulted in a slight reduction in cystatin C, a surrogate measure of GFR, consistent with a beneficial effect on renal function (Graziani et al. 2010).

Comment

Cross-sectional studies (Kshirsagar et al. 2005, Fisher & Taylor 2009, Grubbs et al. 2011, Ioannidou & Swede 2011), which met the inclusion threshold for periodontitis, reported associations between periodontitis and CKD. The complex pathogenesis of CKD and its close linkage with diabetes and other comorbid conditions makes prospective studies of a role for periodontitis challenging. Prospective studies, with measures of periodontitis that exceeded the study threshold, identified the progression of CKD in subjects with type 2 diabetes (Shultis et al. 2007) and progression of ESRD to eventual death (Chen et al. 2011).

Rheumatoid Arthritis (Appendix S3)

Rheumatoid arthritis (RA) is characterized by persistent synovial inflammation and associated damage to articular cartilage and underlying bone (Scott et al. 2010). RA affects 0.5–1% of adults in developed countries, is three times more frequent in women and is age related. The mechanisms for the development of RA have resonance with the pathogenesis of chronic periodontitis (de Pablo et al. 2009). Smoking is the dominant environmental risk factor that doubles the risk of developing RA but its effect is limited to those with antibodies to citrullinated peptides (Klareskog et al. 2009).

de Pablo et al. (2009) comprehensively reviewed studies which indicated a potential positive association between periodontitis and RA and noted that the majority were small case-control studies with their outcomes potentially seriously affected by selection bias. One of these case-control studies (Pischon et al. 2008) reported an association between periodontitis, identified on the basis of mean CAL $\geq$4 mm and RA with an odds ratio of 6.09 (95% CI 1.72–21.55). In this study, cases from a hospital Rheumatology Department were compared with controls from an outpatient general dentistry clinic and it is difficult on the basis of the information provided to rule out selection bias in the recruitment of the controls. The prevalence of osteoporosis in the RA cases (37%) was significantly higher compared with the controls (2%). The wide confidence interval suggests imprecision in the estimate of the strength of the association in this small study. There have been 3 studies with at least 100 cases of incident or prevalent RA. de Pablo et al. (2008) reported an 82% (95% CI 4%–220%) increase in RA associated with periodontitis, identified by one or more sites with CAL of $\geq$4 mm, in a cross-sectional study using data from NHANES III. There were wide confidence intervals after correction for age, sex, race and smoking which suggests an imprecise population estimate. A prospective study by Arkema et al. (2010) equated a positive exposure to periodontitis with a history of periodontal surgery in the 2 years before baseline. The history of periodontal surgery was not validated. No significant association was found with incident RA in a 12-year follow-up (Arkema et al. 2010). A further study of both prevalent and incident RA used data from NHANES I and its follow-up (Demmer et al. 2011). The baseline examination used the periodontal index (Russell 1956) to classify the periodontal condition. There were higher odds of prevalent and incident RA in those with periodontal disease but these did not reach statistical significance.

A small clinical trial found that non-surgical periodontal treatment of subjects with RA and periodontitis resulted in a reduction in the severity of RA over a 6 week period, as measured by an accepted disease activity score (Ortiz et al. 2009).

Comment

No epidemiological studies of a possible association with RA met the threshold for periodontitis. Early case-control studies, which identified associations have been questioned on methodological grounds (de Pablo et al. 2009). Studies of inci-

dent RA (Arkema et al. 2010, Demmer et al. 2011) do not provide support for a link. There is currently little published evidence that periodontitis represents a risk factor for RA. Studies that recognize the heterogenous nature of RA, particularly in relation to antibody specificity, may be informative.

Cognitive Impairment (Appendix S4)

Mild cognitive impairment (MCI) is defined as cognitive decline that is greater than expected for age and education level but which does not interfere notably with the activities of daily life (Gauthier et al. 2006). Cognitive assessment is typically conducted on the basis of tests of a limited number of functions and these can be affected by levels of understanding particularly in those with limited education. MCI with memory complaints and deficits has a high risk of progression to dementia particularly of the Alzheimer disease (AD) type. AD, an age-related disorder, is the most common form of dementia rising exponentially to affect 24–33% of those aged 85 or over in the Western world (Blennow et al. 2006). Research is focused on the search for modifiable risk factors for AD as currently only non-changing risk factors have been identified.

No significant association was found between periodontitis as categorized by Syrjala et al. (2007) and MCI in middle-aged and older Finns. In contrast, two cross-sectional studies which used data from NHANES (1999–2002) concluded that periodontitis was associated with poor cognitive function in those older than 60 years (Wu et al. 2008, Yu & Kuo 2008). A further study of data from NHANES III (Stewart et al. 2008) found an association between periodontitis, identified by the presence of sites with ≥ 3 mm CAL and cognitive function in subjects under 60 years with little evidence of modification by age. Stewart et al. (2008) suggested that later life associations did not arise purely because of adverse effects of dementia on oral health care. Noble et al. (2009), using a high serum level of IgG antibodies to *P. gingivalis* as surrogate evidence of periodontitis exposure, found this significantly predicted poorer performance on cognition tests in NHANES III. In contrast, post hoc analysis of clinical periodontitis measures found no significant associations (Noble et al. 2009). The digit symbol substitution test (DSST) was used as the cognitive measure in NHANES (III and 1999–2002). Not all those who had a periodontal examination in these NHANES studies completed the DSST. In particular, those with poor cognition were excluded because they were not able to complete the test and so were underrepresented in studies which used data from NHANES.

A study from Finland reported that patients diagnosed with dementia by a geriatrician, but excluding AD, had an increased likelihood of periodontal infections (Syrjala et al. 2012); however, the number of dentate individuals studied was small and periodontal infection was equated with the presence of pocketing of ≥ 4 mm. A further recent European study of 152 dentate 70-year-old subjects in Denmark found that those with periodontal inflammation had lower scores in tests of cognitive function (Kamer et al. 2012). Periodontal inflammation was equated with pocketing ≥ 4 mm affecting 10% of the remaining teeth and so did not meet the threshold set in the current review for periodontitis.

The prospective VADLS (Kaye et al. 2010) found that higher rates of periodontal disease progression independently predicted increased risks of low cognitive test scores over 32 years of follow-up. For each tooth that had progression of bone loss or pocketing the overall risks of low cognitive test scores increased between 3% and 4%. It may be difficult to extrapolate these results to worldwide populations, as in the VADLS only white, non-Hispanic male subjects were included.

The Biologically Resilient Adults in Neurological (BRAIN) study followed subjects who were cognitively normal at baseline over a 10-year period (Stein et al. 2012). Subjects who developed MCI and AD had significant elevations of antibody levels to *Prevotella intermedia* and *Fusobacterium nucleatum*. In addition, those who developed AD had increased levels of antibody to *T. denticola* and *P. gingivalis* at baseline compared with controls. Clinical periodontal data were not available but the authors argued that antibody levels represented a strong marker of periodontal infections and therefore were a good surrogate marker for periodontal disease (Stein et al. 2012).

Comment

Only one cross-sectional study (Yu & Kuo 2008) and one prospective study (Kaye et al. 2010) met the criteria set for periodontitis exposure. These studies reported associations with screening tests, which provide a relatively crude screening assessment of cognition, and there were limitations to generalizability due to the design of both studies. The evidence therefore from currently published studies for an association between periodontitis and MCI is weak. There is no evidence meeting the criteria set for periodontitis in relation to AD. There are no effective treatments for dementia or AD therefore the identification of modifiable risk factors for cognitive decline is of prime importance. The outcomes to date highlight the need for prospective cohort studies with detailed information on clinical measures of periodontal status and cognitive function.

Obesity (Appendix S5)

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. There is a global pandemic with 500 million obese adults worldwide (Wang et al. 2011). The rising prevalence of obesity has resulted in an increased burden from several major diseases, notably diabetes with recent evidence suggesting a possible link to periodontitis (Preshaw et al. 2012). Adiposity is generally quantified by the BMI, with a BMI >30 kg/m^2 equating to obesity (World Health Organization 2000). The BMI provides a measure of overall body fat, but not body fat distribution, and other measures such as waist circumference (WC) are required to quantify abdominal obesity.

A cross-sectional study of non-smoking US adolescents in NHANES III found older adolescents had a 5% (95% CI 1%–8%) increased odds of periodontitis for each 1 cm increase in WC (Reeves

et al. 2006). Obese young adults aged 18 and 34 years in NHANES III had a 76% (95% CI 19%–161%) increase in the prevalence of periodontitis, classified as at least one site with CAL $\geq$ 3 mm and PPD $\geq$ 4 mm, compared with normal weight subjects (Al-Zahrani et al. 2003). These studies suggest that periodontitis could be related to lifestyles associated with adiposity (Reeves et al. 2006). Cross-sectional studies in adults (Dalla Vecchia et al. 2005, Linden et al. 2007, Haffajee & Socransky 2009, Khader et al. 2009, Kongstad et al. 2009, Han et al. 2010, Shimazaki et al. 2010) have investigated a possible association between obesity and periodontitis.

A recent systematic review and meta-analysis included 28 independent studies (Chaffee & Weston 2010) and found an OR of 1.35 (95% CI 1.23–1.47) for the association between obesity and prevalent periodontitis. Summary estimates were similar whether BMI or WC was used to define obesity. A further systematic review (Suvan et al. 2011) reported a stronger association between obesity and periodontitis (OR = 1.81, 95%CI 1.42–2.30) from a meta-analysis of 19 studies.

A small prospective study in Finland (Saxlin et al. 2010) of never smokers who were free of diabetes concluded that body weight was weakly but non-significantly associated with the development of periodontal infection. Saxlin et al. (2010) stated that the results of their study should be interpreted cautiously particularly due to its small size and that the results did not provide evidence that obesity was a significant risk factor in the pathogenesis of periodontal infection. A similar, but much larger, prospective study in Japan found a significant association between obesity and overweight and the development of periodontal pocketing in women; however, in men the association was not significant in the obese but only in those who were overweight (Morita et al. 2011). These studies had a relatively short follow-up of 4 to 5 years and used the identification of pocketing ($\geq$ 4 mm), which did not meet the threshold set in the current review, to indicate periodontitis.

The VADLS who monitored non-Hispanic white men over more than 20 years (Gorman et al. 2012) showed that the hazards of experiencing progression to $\geq$ 5 mm pocketing or CAL or >40% radiographic ABL progression were 40%, 52% and 60% higher, respectively, among obese (BMI >30 kg/m$^{2)}$ men relative to ideal weight men. There was also a 41% increase in the risk of $\geq$ 5 mm CAL in men with evidence of abdominal obesity. There was a robust definition of periodontitis progression and long follow-up; however, a limitation was that only non-Hispanic white men were studied.

Comment

A modest positive association between obesity and prevalent periodontal disease is supported by the outcomes of two systematic reviews (Chaffee & Weston 2010, Suvan et al. 2011). One prospective study (Gorman et al. 2012), with criteria for periodontitis which met the threshold, supported an association with the general direction from obesity to periodontal infection; however, the generalizability of this finding can be questioned. Adiposity may be a marker of unhealthy lifestyle resulting in an increased risk of periodontitis and of other conditions such as type 2 diabetes which may confound any linkage.

Metabolic Syndrome (Appendix S6)

The metabolic syndrome (MetS) is a clustering of multiple interrelated atherosclerotic risk factors, including abdominal obesity, dyslipidaemia, hyperglycaemia and hypertension, which identifies a 5-fold increase in risk for developing type 2 diabetes (Grundy 2005). The usefulness of MetS in relation to clinical management is controversial; however, it is useful for epidemiological investigations (Gale et al. 2008).

Epidemiological studies, which have reported an association between periodontitis and MetS have been cross-sectional in nature and cannot identify the direction of any effect (Shimazaki et al. 2007, Kushiyama et al. 2009, Kwon et al. 2011, Fukui et al. 2012). In the largest population studied from NHANES III the association with severe periodontitis (two sites with CAL $\geq$ 6 mm) was not significant in the whole sample but only in those aged $\geq$ 45 years (D'Aiuto et al. 2008). In a study limited to non-diabetic, never smokers the association between MetS and periodontal infection was not significant when pocketing $\geq$ 6 mm was used to classify periodontitis (Timonen et al. 2010).

A prospective study on the effect of exposure to periodontitis ($\geq$ 1 pocket $\geq$ 4 mm at baseline) over a 4-year period reported an OR of 2.2 (95%CI 1.1–4.1) for the development of 2 or more components of MetS (Morita et al. 2010). The more accepted criterion of 3 positive components to identify MetS was not used as only 0.8% subjects were affected. Of concern in this and other studies from Japan is the modification of accepted criteria by replacing WC, a measure of abdominal obesity and insulin resistance, with a general measure of adiposity (BMI $\geq$ 25) (Kushiyama et al. 2009, Fukui et al. 2012) and the use of diabetes as an indicator of glucose intolerance (Shimazaki et al. 2007, Kushiyama et al. 2009) rather than a confounder in any association.

Comment

Currently, evidence of an association of MetS with periodontitis, which met the stated threshold, is limited to one study (D'Aiuto et al. 2008). Studies from Japan (Kushiyama et al. 2009, Fukui et al. 2012), which met the criteria for periodontitis exposure, applied modified criteria for MetS. The strongly increased risk of type 2 diabetes in those with MetS may confound any association with periodontitis.

Cancer (Appendix S7)

The higher incidence of cancer development in those with chronic inflammatory conditions (Coussens & Werb 2002) has underpinned research into possible linkages with periodontitis. Tooth loss or poor oral health have been associated with a number of cancers (Fitzpatrick & Katz 2010); however, the use of tooth loss as a surrogate for periodontitis has shortcomings as teeth may be extracted as a result of both caries and periodontal disease and indeed for non-disease associated reasons.

Data from NHANES III, in which oral tumours were defined as 'exophytic growths for which a cause cannot be identified', found periodontitis was significantly related to the presence of tumours. Stratified analysis found this association was only present in current smokers (Tezal et al. 2005). Many of the lesions identified may not have been neoplasms. Hospital based case-control studies from a US Cancer Institute found that alveolar bone loss was associated with an increase in tongue cancer (Tezal et al. 2007) and primary head and neck squamous cell carcinomas (Tezal et al. 2009). The authors accepted that they had limited data on the history of tobacco and alcohol use and oral human papilloma virus (HPV) infection (Tezal et al. 2009) which makes the determination of the association with periodontal disease problematic. A recent study, from the same centre, found that periodontitis, assessed by measurements of ABL, was associated with tumour HPV status in patients with oropharyngeal cancer (Tezal et al. 2012).

In a follow-up of subjects from NHANES I, those with periodontitis as diagnosed using the Periodontal Index (Russell 1956), had a 55% (95% CI 25%–92%) increased risk of death from any cancer (Hujoel et al. 2003). There was a significantly increased risk for lung cancer; however, this was not evident in never smokers. It was argued that periodontitis could be capturing an unmeasured aspect of smoking history and therefore the association with lung cancer was spurious (Hujoel et al. 2003).

In a large prospective cohort investigation, Michaud et al. (2007, 2008) analysed data from the Health Professionals Follow-up Study (HPFS). The participants were mainly white men in the United States (dentists 58%, veterinarians 20% pharmacists 8% optometrists 7%, others 7%). Exposure was equated with the participants reporting they had a history of periodontal disease with bone loss at baseline. The question was validated in a subsample by reviewing radiographs. There was a 64% (95% CI 19%–126%) increase in the relative risk of pancreatic cancer in those classified with periodontal disease after 16 years of follow-up (Michaud et al. 2007). The influence of self-reported periodontal disease was stronger in never smokers. A further study in the HPFS identified 5720 incident cancers over 17.7 years follow-up of 48375 men (Michaud et al. 2008). Men who reported periodontal disease had a slightly increased total cancer incidence of 14% (95% CI 7%–22%), which persisted when the analysis was limited to never smokers. There were significantly increased risks of lung, kidney, pancreatic and haematological cancers after adjustment. Interestingly, when the number of teeth was used as the exposure, the only significant association was with an increased risk of lung cancer. Limitations in the assessment of periodontal disease were accepted, but it was argued that there was good agreement between self-assessment and the radiographic validation (Michaud et al. 2008).

A prospective study in a twin registry in Sweden identified over 4000 incident cancers after median follow-up of 27 years (Arora et al. 2010). At baseline the participants were classified with periodontal disease if they reported that at least half their teeth had come loose or had fallen out on their own. Periodontal disease was associated with a 15% (95% CI 1%–32%) increased risk of all cancers. There were increased risks of digestive tract, colorectal, pancreatic and prostate cancers in men and of the corpus uteri in women associated with periodontal disease. In co-twin analyses the association was absent in monozygotic but remained in dizygotic twins. It was concluded this indicated that shared genetic risk factors could partially explain the association between periodontal disease and cancer (Arora et al. 2010); however, it also suggests the contribution of genetic factors is limited.

A recent study (Ahn et al. 2012) followed up participants in NHANES III and reported that periodontitis was associated with increased orodigestive cancer mortality (OR = 2.28, 95%CI 1.17–4.45). There was a trend for an increase in risk with increasing severity of periodontitis. They also found that after excluding those with clinically evident periodontal disease those with high levels of serum antibody to *P. gingivalis* had excess orodigestive cancer mortality (Ahn et al. 2012).

Comment

Research into possible associations between periodontitis and cancer has been hampered by the difficulty in controlling for confounders such as smoking and socioeconomic status. Furthermore, the identification of periodontitis in a number of large epidemiological studies relied on surrogate markers. Only one study (Ahn et al. 2012) clearly met the threshold criteria set for periodontitis. Despite these caveats periodontitis has been identified as a possible risk factor for orodigestive and pancreatic cancer as well as possibly other cancers. Further studies, particularly long term follow-up of cohorts, are needed.

Discussion

This review attempted to synthesize data from a large number of published studies which had investigated possible associations between chronic periodontitis and a number of chronic systemic diseases and conditions. This proved to be a difficult undertaking due to the limitations of existing studies. A striking factor was the substantial variability in the definitions of periodontitis used in the various studies. In many cases, it is doubtful whether the criteria applied could be realistically taken to unequivocally identify periodontitis, in particular where surrogate measures were used. We used the case definitions originally developed by the Centre for Disease Control (CDC) Periodontal Disease Surveillance Workgroup (Page & Eke 2007) to set a threshold for the identification of periodontitis. The application of this threshold significantly reduced the number of studies, which could be identified as evaluating possible associations.

An analysis of the totality of the evidence (Table 1) shows there were a very small number of studies that met the threshold set for periodontitis and supported an association with the diseases and conditions studied. In CKD an association was reported in independent cross-sectional studies: in ARIC (Kshirsagar et al. 2005); in NHANES III (Ioannidou & Swede 2011); and in NHANES 2001–04 (Grubbs et al. 2011). Prospective studies of peri-

odontitis and CKD were complicated by the presence of diabetes (Shultis et al. 2007) or ESRD (Chen et al. 2011). In relation to obesity the association was supported by two independent systematic reviews (Chaffee & Weston 2010, Suvan et al. 2011) and one prospective investigation in VADLS (Gorman et al. 2012). An association with MCI was supported by one cross-sectional study from NHANES 2001–02 (Yu & Kuo 2008) and outcomes from the prospective VADLS (Kaye et al. 2011). It is difficult to generalize from VADLS as it was limited to non-Hispanic white men. There was only one positive study for MetS (D'Aiuto et al. 2008) and one for cancer (Ahn et al. 2012) both representing the analysis of data from NHANES III and no confirmation in other populations. There were no studies which met the threshold set for periodontitis that reported an association with COPD or RA. There is therefore a lack of evidence to support associations between moderate or severe periodontitis and a number of the systemic diseases and conditions reviewed. In this context, it is worth remembering that absence of evidence is not evidence of absence (Altman & Bland 1995).

Many of the studies were secondary analyses of existing data sets, in particular data abstracted from the NHANES studies in the United States. The organization of the successive NHANES studies and the criteria used to identify periodontitis in these studies have been outlined by Page & Eke (2007). Recent methodological studies found that the partial-mouth periodontal examination systems used in NHANES III, 1999–2000 and 2001–2004 underestimated the prevalence of periodontitis by 50% or more, when compared with a full-mouth examination (Eke et al. 2010, 2012). The protocols used in NHANES also had low sensitivity resulting in extensive misclassification (Eke et al. 2010). This is likely to hamper studies of the strength of the associations between periodontitis and systemic diseases (Albandar 2011). Such misclassification is non-differential; however, it will reduce the size of any observed association (Dietrich & Garcia 2005, Heaton & Dietrich 2012a). Therefore, the strength of associations may be stronger than suggested by the studies reviewed. This could counteract concerns that the weak associations reported represent residual confounding by smoking or other unrecognized confounders. The studies were not able to control for all possible confounders in particular for residual confounding in relation to socio-economic status. The complex diseases and conditions reviewed are all chronic in nature, develop slowly over a number of years and may be affected by many established risk factors, in particular diabetes, which confound possible associations with other non-traditional risk factors such as periodontitis.

The heterogeneity in defining what constitutes periodontitis across and within each disease and condition is striking. Comparisons between studies and the identification of the size of any associations between periodontal disease and other diseases are therefore difficult. Many studies of possible associations used less stringent criteria for periodontitis than those outlined by Page & Eke (2007). Some, but by no means all, of these studies were small and underpowered and therefore were unable to properly deal with confounding variables particularly in relation to diseases and conditions which are aetiologically complex. Diabetes is a particular problem in such studies as it is inextricably linked with CKD, MetS and obesity. Some epidemiological studies, which did not rely on clinical measurements but used surrogate measures of periodontal disease, produced intriguing results. For example, the identification of an association between periodontal disease and pancreatic and other forms of cancer in the large data set in HPFS (Michaud et al. 2007, 2008) suggests hypotheses which can be tested. The difficulties posed by the design of future studies to investigate such hypotheses should not be underestimated. In this context, associations may be present or absent depending on the definition of periodontitis used (Manau et al. 2008) and so there is a need to reach a consensus on what thresholds should be used to define periodontitis (Tonetti & Claffey 2005, Preshaw 2009).

Causation is a difficult concept and any given disease can be caused by more than one mechanism and every causal mechanism involves the joint action of a multitude of component causes (Rothman & Greenland 2005). We may have to accept that while we may conclude

Table 1. Studies which met the case definition of periodontitis outlined by Page & Eke (2007) and reported significant positive associations between periodontitis and the systemic diseases and conditions reviewed

	Cross-sectional	Prospective studies
Chronic obstructive pulmonary disease	No	No
Chronic kidney disease	Kshirsagar et al. (2005) ARIC Fisher & Taylor (2009) NHANES III Ioannidou & Swede (2011) NHANES III Grubbs et al. (2011) NHANES 2001–04	Shultis et al. (2007) Gila River Indian Community, Arizona At baseline all had diabetes Chen et al. (2011) Taipei, Taiwan At baseline all had ESRD
Rheumatoid arthritis	No	No
Mild cognitive impairment	Yu & Kuo (2008) NHANES 2001–02	Kaye et al. (2011) VADLS
Obesity	Linden et al. (2007) Belfast, UK	Gorman et al. (2012) VADLS
Metabolic syndrome	D'Aiuto et al. (2008) NHANES III	No
Cancer	No	Ahn et al. (2012) NHANES III

that periodontal disease is associated with a certain disease this will not lead to a complete explanation or understanding of that disease; just as identifying the risk factors for falling do not provide us with a theory of gravity (Broadbent 2009). In many cases, the associations were weak and therefore might be dismissed. However, a weak association does not rule out a causal connection (Rothman & Greenland 2005). The principals of disease causation and causal theory are beyond the scope of this discussion but are clearly described by Heaton & Dietrich (2012b). There are other explanations for example common genetic factors could be associated with both susceptibility to periodontitis and other diseases. Alternatively, periodontitis may be a phenotype of low socioeconomic status reflecting factors such as smoking, poverty and low education and developing in parallel with other diseases which reflect disadvantaged lifestyle.

RCTs of interventions, which improve oral hygiene, have been shown to have positive effects on the prevention of acute infections as represented by nosocomial pneumonias (Scannapieco et al. 2003, Labeau et al. 2011). However, there are difficulties inherent in setting up RCTs to study any putative aetiological role for periodontitis in the development of other complex chronic diseases (Dietrich & Garcia 2005). Notwithstanding, intervention studies to assess the effects that periodontal treatment could have on reducing the incidence, progression and complications of conditions may be informative as has been shown in the past (Tonetti et al. 2007, Ortiz et al. 2009). Interventions may be beneficial even in the absence of a full understanding of the mechanisms underlying a particular disease or condition (Broadbent 2009).

Conclusions

A limitation in reviewing the literature was the fact that for several systemic disease states, few if any studies evaluated associations for periodontitis that met the CDC threshold (Page & Eke 2007). The heterogeneity in the definitions used to identify periodontitis in the studies reviewed was striking and there is a need to reach a consensus on what constitutes periodontitis for future studies of putative associations with systemic diseases. Since very few of the studies reviewed met a stringent threshold for periodontitis there are limited outcomes that can be used to provide support for or against possible links between periodontitis and the diseases and conditions studied. Well-designed observational studies of associations between periodontal disease and systemic disease need to remain an integral component of future research to more fully understand such associations as suggested by Dietrich & Garcia (2005). In particular, longitudinal studies that are designed to assess risk would be valuable. Concerted efforts are needed to reach agreed definitions of health and disease to ensure that future studies are meaningful.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1. Epidemiological studies of the association between periodontal disease and chronic obstructive pulmonary disease (COPD).

Appendix S2. Epidemiological studies of the association between periodontal disease and chronic kidney disease (CKD).

Appendix S3. Studies of the association between periodontal disease and rheumatoid arthritis. ACR-American College of Rheumatolog.

Appendix S4. Epidemiological studies of the association between periodontal disease and mild cognitive impairment, dementia and Alzheimer's disease.

Appendix S5. Epidemiological studies of the association between obesity and periodontal disease. Cross sectional studies selected from those judged to provide high quality population-based evidence in the systematic review completed by Chaffee and Weston (2010).

Appendix S6. Epidemiological studies of the association between periodontal disease and the metabolic syndrome (METs). * Note modification of criteria for METs in Shimazaki et al. 2007, Kushiyama et al. 2009, Morita et al. 2010 and Fukui et al. 2012.

Appendix S7. Epidemiological studies of the association between periodontal disease and various cancers.

Address:
Gerry Linden
Periodontal Department
School of Dentistry
Queen's University
Grosvenor Road
Belfast BT12 6BP
UK
E-mail: g.linden@qub.ac.uk

Clinical Relevance

Scientific rationale for the study: There have been many studies of possible linkages between periodontitis and cardiovascular disease, adverse pregnancy outcomes and diabetes. The current review critically appraised research into associations between periodontal disease and other systemic diseases and conditions.

Principal findings: The review identified reports of modest associations between chronic periodontitis and various chronic systemic diseases and conditions. There was a great variation in the criteria used for periodontitis and only a small number of studies met stringent criteria for its identification. These studies provided limited evidence to support or refute links between periodontitis and various systemic diseases and conditions. There was strong evidence that interventions that improved oral hygiene in at-risk individuals had positive effects in the prevention of nosocomial pneumonias.

Practical implications: Patients with periodontitis are increasingly aware of research into possible links between periodontal disease and other diseases. Dentists should know that there is currently limited evidence to support or refute such associations. Nevertheless, continued focus on improvements in periodontal health may also benefit general health.