Evolving evidence for relationships between periodontitis and systemic diseases: Position paper from the Canadian Dental Hygienists Association

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ABSTRACT

Aim: The aim of this position paper is to investigate the current state of the evidence for proposed associations between periodontitis and rheumatoid arthritis, Alzheimer's disease, obesity, inflammatory cancers, and renal disease using a narrative review approach. This is the last of a series of 5 position papers from the Canadian Dental Hygienists Association (CDHA) on the relationship between periodontitis and systemic conditions. **Methods:** Individual literature searches were conducted for each of the 5 proposed linkages and limited to human studies, with a preference for systematic reviews (SRs) and prospective studies, in the English language, published between 2015 and 2021, focused on associations between 1) periodontitis and rheumatoid arthritis; 2) periodontitis and Alzheimer's disease/cognitive impairment; 3) periodontitis and obesity; 4) periodontitis and inflammatory cancers; and 5) periodontitis and chronic kidney disease. Databases searched were PubMed, MEDLINE/OVID, CINAHL, Scopus, Cochrane Registry of Systematic Reviews, and Web of Science. **Results:** A total of 39 papers were selected for discussion, including 6 SRs for rheumatoid arthritis; 7 SRs for Alzheimer's disease/cognitive impairment; 11 SRs, 1 meta-review of SRs, and 1 population-based cohort study for obesity; 9 SRs for inflammatory cancers; and 4 SRs for kidney disease. **Conclusions:** The evidence for the 5 proposed associations varied in strength, with obesity being most strongly associated with periodontal disease. More robust studies are recommended to clarify the exact nature of these associations.

RÉSUMÉ

Objectif : Cet exposé de position vise à utiliser une approche de revue narrative pour examiner l'état actuel de la preuve pour les associations proposées entre la parodontite et la polyarthrite rhumatoïde, la maladie d'Alzheimer, l'obésité, les cancers inflammatoires et les maladies rénales. Ce document est le dernier d'une série de 5 exposés de position de l'Association canadienne des hygiénistes dentaires (ACHD) sur la relation entre la parodontite et les affections systémiques. **Méthodologie :** Des recherches documentaires individuelles ont été menées pour chacun des 5 liens proposés et ont été limitées aux études humaines, avec une préférence pour les revues systématiques (RS) et les études prospectives en anglais, publiées entre 2015 et 2021, axées sur les associations entre 1) la parodontite et la polyarthrite rhumatoïde; 2) la parodontite et la maladie d'Alzheimer ou la déficience cognitive; 3) la parodontite et l'obésité; 4) la parodontite et les cancers inflammatoires; et 5) la parodontite et la maladie rénale chronique. Des recherches ont été effectuées dans PubMed, MEDLINE/OVID, CINAHL, Scopus, le registre de revues systématiques Cochrane, et Web of Science. **Résultats :** En tout, 39 articles ont été sélectionnés pour discussion, dont 6 RS pour la polyarthrite rhumatoïde, 7 RS pour la maladie d'Alzheimer ou la déficience cognitive, 11 RS, 1 méta-analyse de RS et 1 étude de cohorte représentative de la population sur l'obésité, 9 RS pour les cancers inflammatoires et 4 RS pour les maladies rénales. **Conclusions :** Les preuves pour les 5 associations proposées ont varié en force, l'obésité étant la plus fortement associée à la maladie parodontale. Des études plus rigoureuses sont recommandées pour clarifier la nature exacte de ces associations.

Keywords: Alzheimer's disease; cognitive decline; dementia; end-stage renal disease; gastric cancers; inflammatory cancers; kidney disease; obesity; overweight; pancreatic cancer; periodontal disease; periodontitis; renal disease; rheumatoid arthritis
CDHA Research Agenda categories: risk assessment and management; capacity building of the profession

CANADIAN DENTAL HYGIENISTS ASSOCIATION POSITION STATEMENT

The Canadian Dental Hygienists Association notes that weak associations have been found between periodontal disease and rheumatoid arthritis; kidney disease; inflammatory cancers; and cognitive impairment/Alzheimer's disease. A stronger association exists between periodontal disease and obesity for all age levels. Although the nature of these associations has yet to be determined, they are suspected to be linked to inflammation resulting from a dysbiosis of the oral microbiome.

INTRODUCTION

Evidence has been mounting over the past 30 years for the existence of relationships between oral diseases such as periodontitis and a variety of systemic diseases, often coined periodontal medicine. The more established relationships with the greatest amount of evidence published are in the form of "associations" with cardiovascular diseases, adverse pregnancy outcomes, respiratory diseases, and diabetes mellitus, which were the topics of the first 4

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position papers in this series.[1-4] In 2013, the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP) cohosted a series of workshops on these systemic associations with a primary focus on cardiovascular disease, diabetes, and adverse pregnancy outcomes.[5-8] However, Linden and colleagues[9], as a part of the same series of workshops, presented a review of the evidence of lesser known potential associations including chronic kidney disease, rheumatoid arthritis, cognitive impairment, inflammatory cancers, and obesity. Their review found some modest associations between periodontitis and obesity, but weaker associations if any with rheumatoid arthritis, cognitive impairment, and oropharyngeal cancers. They noted that study weaknesses revolved primarily around how periodontal disease was defined as well as lack of control of confounders, thus not totally ruling out the possibility of existing associations.[9] In 2016, Monsarrat and colleagues[10], in a systematic mapping of clinical trial registers on periodontal medicine, reported 57 systemic conditions currently being investigated for potential links with periodontal diseases.

A plethora of studies have been conducted since the 2013 AAP/EFP workshops and thus the purpose of this position paper is to explore the more recent literature in order to provide evidence for a position statement for the Canadian Dental Hygienists Association (CDHA) on the relationships between periodontitis and rheumatoid arthritis, cognitive impairment/Alzheimer's disease, obesity, inflammatory cancers, and chronic kidney disease. Unlike the 4 previously published position papers that focused on whether there is now sufficient evidence of a causal relationship between periodontal disease and specific systemic conditions, this paper investigates whether there is evidence of any relationship and, if so, the nature of such relationships. Thus, this paper takes the form of a narrative review rather than a scoping review, systematic review or umbrella review. With the conditions discussed in this paper, research is evolving and is still primarily in the form of case–control and cross-sectional studies, which are lower levels of evidence.

METHODS

Individual searches of the literature for each of the 5 proposed systemic disease linkages with periodontitis were limited to human studies, with a preference for systematic reviews (SRs), meta-analyses (MAs), and prospective studies in the English language, published between 2015 and 2021, and focused on associations with periodontal disease. Excluded were non-human studies, editorials, and narrative reviews. Databases searched were PubMed, Medline/OVID, CINAHL, Scopus, Cochrane Registry of Systematic Reviews, and Web of Science. Keywords used were as follows:

1. periodontitis, periodontal disease, rheumatoid arthritis, systematic reviews
2. periodontitis, periodontal disease, Alzheimer's disease, dementia, cognitive decline, systematic reviews
3. periodontitis, periodontal disease, obesity, overweight, systematic reviews
4. periodontitis, periodontal disease, pancreatic cancer, inflammatory cancers, gastric cancers, systematic reviews
5. periodontitis, periodontal disease, renal disease, end-stage renal disease, systematic reviews

RESULTS

Six (6) SRs (5 with MAs) on rheumatoid arthritis (RA) were selected for evaluation (Table 1), along with 7 SRs (4 with MAs) on cognitive impairments/Alzheimer's disease (CI/AD) (Table 2), 11 SRs (7 with MAs), 1 meta-review of SRs, and 1 population-based cohort study on obesity (OB) (Table 3), 9 SRs (6 with MAs) on inflammatory cancers (IC) (Table 4), and 4 SRs all with MAs on chronic kidney disease (CKD) (Table 5). Some animal or laboratory studies were referenced for historical purposes, rather than discussion and analysis. There were 2 systematic reviews that did contain a few animal studies but were included since the majority of studies within their review were human studies.

Positive associations were found, to varying degrees, between periodontitis and all 5 conditions under investigation. Results were mixed for RA, CKD, IC, and CI/AD; there was a stronger association between AD and the risk for periodontitis rather than the other way around. Associations between gastrointestinal (GI) cancers and periodontitis are unclear but appear to involve a variety of periodontal pathogens. Which periodontal pathogens are associated with specific cancers have yet to be clarified. It has been determined, however, that they differ between upper and lower GI tract cancers. The strongest association exists between obesity and periodontal disease for all age levels, although there is insufficient evidence at this time to examine whether a cause-and-effect relationship exists. In all instances, most of the studies were either case–control (retrospective studies) or cross-sectional studies, which do not provide a high level of evidence and do not qualify as a measure of causality. More robust studies are recommended by the SR/MA authors to clarify the exact nature of these associations. Table 6 identifies and describes the measurements used in the systematic reviews to improve the readers' understanding of the results.

Table 1. Study findings for rheumatoid arthritis associated with periodontitis

Reference	Study type(s)	Outcome	Strength of evidence
Kaur et al. 2013[14]	**SR:** 16 case–control studies 3 experimental studies	Association between RA & tooth loss, CAL & ESR CRP, IL-1β & other markers Some evidence of positive outcome of SRP on RA	Good Moderate Weak
Kaur et al. 2014[15]	SR & MA: 4 RCTs/1 CT	Effects of NSPT on various biochemical markers Statistically significant reductions only for ESR (but not CRP)	Weak
Cerqueira Calderaro et al. 2017[16]	SR & MA: Same 4 RCTs as Kaur et al.[15]	No significant reductions in ESR but statistically significant reductions in DAS28 Results conflicted with Kaur et al.[15]	Strong for DAS28
Tang et al. 2017[17]	SR & MA: 8 case–control studies	Statistically significant association Higher prevalence of periodontitis in those with RA. OR: 4.68 (95% CI, 3.11–7.05) Higher levels of *P. gingivalis* IG-G in RA patients	Strong (*but studies lower level*)
de Oliveira Ferreira et al. 2019[18]	SR & MA: 2 cohort studies 7 cross-sectional studies	Included those with and without periodontitis; used RA as an outcome 7 of the 9 studies reported associations but only 3 studies were used in MA; results were inconclusive	Inconclusive Higher level studies required
Hussein et al. 2020[19]	SR & MA: 8 case–control studies but 2 eliminated due to high risk of bias	Explored if a bidirectional relationship exists No significant effects of RA on periodontitis Reported significantly worse RA disease activity in those with periodontitis ($p < 0.001$)	None

Table 2. Study findings for Alzheimer's disease/cognitive impairment associated with periodontitis

Reference	Study type(s)	Outcome	Strength of evidence
Dioguardi et al. 2020[31]	**SR:** 15 studies (6 animal, 1 post-mortem, 4 observational, 1 clinical, 1 case–control, 2 database)	Investigated whether inflammation from periodontal microbes played a role in the onset & progression of AD Evidence exists for an association but mostly from animal studies rather than human trials Mixed results from observational studies and negative result from clinical trial	Weak (*primarily from animal studies*)
Leira et al. 2017[32]	SR & MA: 5 studies (2 cross-sectional, 2 case–control, 1 cohort)	Significant association between periodontal disease and AD (OR 1.69; 95% CI, 1.21–2.35); higher for those with more severe disease. Individuals with AD are less capable of performing oral hygiene (confounding factor if not controlled for in study)	Strong (*for those with AD having periodontal disease but weak for the reverse*)
Foley et al. 2017[33]	SR & MA: 28 studies but only 1 controlled for oral hygiene	Negative influence of dementia on oral health status in persons with dementia (argued for causality, i.e., dementia causes periodontal disease)	Weak (*only 1 study explored ability of those with AD to perform oral hygiene)*

Table 2. (*continued*)

Reference	Study type(s)	Outcome	Strength of evidence
Gusman et al. 2018[35]	SR & MA: 14 studies (varying types)	Assessed severity of periodontal disease in those with dementia No association found between dementia/AD and severity of periodontal disease	No evidence
Nadim et al. 2020[36]	SR & MA: 5 cohort and 7 case–control studies	11 studies reported a positive association between periodontal disease and dementia risk RR of dementia related to periodontal disease was only 1.38 (95% CI, 1.01–1.90)	Weak (*borderline meaningful*)
Alvarenga et al. 2021[37]	SR: 12 studies (8 case–control, 3 cross-sectional, 1 cohort)	Associations found but results were mixed with other neurodegenerative diseases	Weak
Hu et al. 2021[38]	SR & MA: 5 studies for AD; 5 studies for MCI Combination of cross-sectional, case–control, and 2 cohort	Results for AD risk compared with non-periodontitis patients was OR 1.78 (95% CI, 1.15–2.76) while risk for MCI was OR 1.60 (95% CI, 1.24–2.06)	Weak

Table 3. Study findings for obesity associated with periodontitis

Reference	Study type(s)	Outcome	Strength of evidence
Suvan et al. 2018[43] (Includes refs 48-56)	Meta-review of SRs: 14 SRs reporting on prevalence, incidence, response to periodontal therapy, and biomarkers	Prevalence: obese individuals compared to those with normal weight are more likely to have some form of periodontal disease Incidence: Studies consistent with findings that obesity places individuals at higher risk for periodontal disease Response to periodontal therapy: Of 6 SRs, 2 reported no differences[49,53], while 4 had mixed results[50,51,54,55]	Strong Strong Inconsistent
Khan et al. 2018[57]	SR: 25 studies	Explored whether overweight or obesity was a risk factor for periodontal disease in young adults & adolescents Obesity was positively associated with periodontal disease in 17 of 25 studies, with ORs ranging from 1.1 to 4.5.	Moderate to strong
Chen et al. 2021[59]	13-year longitudinal population-based cohort study: Obese cohort: 4,140 Non-obese cohort: 8,280	Those who were obese were at slightly higher risk for periodontal disease (HR 1.12; 95% CI, 1.01–1.25) After subgroup analysis, obese individuals older than 65 years had a much higher risk for periodontal disease (HR 1.98; 95% CI, 1.22–3.22)	Weak Moderate to strong (*based on cohort size and study length*)
Gonçalves da Silva et al. 2021[58]	SR & MA: 90 studies (82 of which were cross-sectional/clinical trials)	Focus on gingival inflammation Majority of studies found no significant differences between obese & non-obese in gingival inflammation MA revealed higher levels of gingival inflammation in those with periodontitis compared with non-obese individuals **This could suggest a dose-response relationship*	No evidence

Table 4. Study findings for inflammatory cancers associated with periodontitis

Reference	Study type(s)	Outcome	Strength of evidence
Corbella et al. 2018[63]	SR & MA: 8 prospective studies (6 in MA)	Explored whether humans with periodontal disease were at higher risk than those without; explored various cancers (esophageal, liver, pancreatic, gastric, colorectal, prostate, hemopoietic) Low statistically significant associations for all included cancers but used HRs not ORs **Interpret with caution*	Weak
Chen et al. 2019[65]	SR: 17 case–control studies	Reported on potential association between oral microbes and various GI cancers (colorectal, pancreatic, gastric, esophageal, liver) Associations found with *P. gingivalis, T. forsythia* & *P. intermedia* but with differences in microbes for upper and lower GI cancers No MA	Not assessed
Xiao et al. 2020[66]	SR & MA: 18 articles (including 39 studies)	Effects of periodontal bacteria on incidence & prognosis of a variety of cancers Bacterial infection increased overall incidence of cancer (OR 1.25) & was associated with poor overall survival (HR 1.75) Subgroup analysis revealed associations with *P. gingivalis* (OR 2.16; 95% CI, 1.34–3.47) & *P. intermedia* (OR 1.28; 95% CI, 1.01–1.63)	Strong (*P. gingivalis)* Weak (*P. intermedia*)
Reitano et al. 2021[67]	SR: 28 studies (26 case–control; 2 cohort)	Variety of digestive cancers Findings in contrast with Xiao et al.[66] *P. gingivalis* and *F. nucleatum* appeared to be associated with colorectal cancer No quantitative analysis	Weak (*due to study types and high levels of heterogeneity in studies*)
Maisonneuve et al. 2017[68]	SR & MA: 8 studies (7 were cohort studies)	Explored relationship between periodontal disease, edentulism & pancreatic cancer Results support a relationship between periodontal disease & pancreatic cancer (RR 1.74; 95% CI, 1.41–2.15) For edentulism & pancreatic cancer (RR 1.54; 95% CI, 1.16–2.05)	Moderate Weak
Sun et al. 2021[69]	SR & MA: 14 studies (incidence) 3 (mortality)	Focused on incidence & mortality of colorectal cancer being associated with periodontal disease Incidence RR 1.179 (95% CI, 1.036–1.342), $p < 0.013$	Weak
Wei al. 2021[74]	SR & MA: 7 studies (4 prospective cohort studies; 3 retrospective cohort studies)	Explored association between periodontal disease & prostate cancer Revealed a significant association (RR 1.17; 95% CI, 1.07–1.27; $p < 0.000$)	Weak
Wu et al. 2020[75]	SR & MA: 6 studies (4 cohort, 1 case–control, 1 retrospective cohort)	Investigated relationship between periodontal disease & hematopoietic & lymphatic cancers Significant association between both types of cancers but stronger for lymphatic (RR 1.17; 95% CI, 1.07–1.27; $p < 0.001$)	Weak

Table 5. Study findings for chronic kidney disease associated with periodontitis

Reference	Study type(s)	Outcome	Strength of evidence
Zhao et al. 2018[81]	SR & MA: 2 cohort studies (for directionality) 3 cross-sectional studies and 1 case–control study (for relationship analysis)	Results were inconclusive for directionality For the non-directional relationship, individuals with periodontal disease had significantly higher odds of CKD (OR 3.54; 95% CI, 2.17–5.77; $p < 0.001$)	Strong (*treat with caution due to lower-level study types*)
Kapellas et al. 2019[79]	SR & MA: 17 observational studies	Evaluated association between periodontal disease and CKD from both directions Only statistically significant association was for those with periodontal disease developing CKD (OR 1.60; 95% CI, 1.44–1.79)	Weak (*due to low level of evidence based on studies*)
Deschamps-Lenhardt et al. 2019[82]	SR & MA: 17 studies assessing association (MA) 2 RCTs assessing treatment impact (no MA)	Explored association between periodontal disease & CKD and investigated if periodontal treatment could have an influence on CKD Association found (OR 2.39 95% CI, 1.70–3.36) Conflicting results for treatment assessment	Moderate for association
Zhao et al. 2020[80]	SR & MA: 4 case series studies (109 participants) 1 RCT (97 participants)	Insufficient evidence to state whether NSPT has a beneficial effect on CKD	No evidence

Table 6. Interpretation of common measurements used in research studies

Measurement	Use	Limitations	Magnitude of association[a]
Odds ratio (OR)	Determines the association between 2 variables (exposure to outcome)	Can be used in any study type but not always useful as it exaggerates the risk	OR 1.0 to 1.5 (further research required) OR 1.5 < 2.0 (worth further investigation) OR 2 < 4 (possibly important) OR 4.0 (pretty strong)
Risk ratio/Relative risk (RR)	Determines risk of the incidence of an exposure to the incidence without the exposure	Study design must be representative of the population; cannot be used on case–control studies *Note: RR is a more accurate and preferable measure of risk*	RR 1.0 to 1.5 (further research required) RR 1.5 < 2.0 (worth further investigation) RR 2.0 < 4.0 (possibly important) RR 4.0 (pretty strong)
Hazard ratio (HR)	Determines how 1 group changes over another; based on rate of change between 2 hazards; typically used in survival studies	Usefulness based on consistency in the rate of change within 2 groups; used to measure certain "points in time"; does not measure "means" over time	HR 1 (no association) HR 1.5 < 2.0 (weak association) HR 2.5 < 3.5 (moderate association) HR 3.5 (strong association)
Confidence interval (CI)	Intervals in which the population statistic could lie; typically uses a 95% confidence interval as the threshold for significant results. (Provides a range of values between which the results lie)	N/A	Range of values will be based on the OR, RR or HR measured and thus interpreted according to the above scales The narrower the CI, the more precise the estimate

Table 6. (*continued*)

Measurement	Use	Limitations	Magnitude of association[a]
P value	Reports the probability that the sample statistic was produced from random sampling of a population Significance values are determined by the researchers prior to commencement of the study set at a minimum of <0.05 (<5% probability that results are due to chance)	N/A	Significance based on what the researchers determined at the beginning of the study; no higher than $p < 0.05$

Table adapted from George A, Stead TS, Ganti L. What's the risk: differentiating risk ratios, odds ratios and hazard ratios? *Cureus*. 2020;12(8):e10047.
[a]Magnitude of association adapted from http://utstat.utoronto.ca/reid/odds.pdf and http://onbiostatistics.blogspot.com

DISCUSSION

Rheumatoid arthritis

Rheumatoid arthritis (RA), classified as an autoimmune disease, is considered the most common chronic inflammatory joint disease globally as well as the leading cause of disability.[11] In Canada, RA affects approximately 1.2% of the population (374,000 persons) annually with an incidence rate of 0.8 per 1,000 persons per year.[11] This disease is manifested by the immune system mistakenly attacking the lining of the joints as well as other surrounding tissues. The resulting inflammation causes pain, swelling, stiffness and, ultimately, if left untreated, damage to the joints.[11] RA is more prevalent in women with increasing incidence with age.[11]

Animal studies have supported a relationship between RA and periodontitis[12,13] along with a plethora of human studies, primarily in the form of case–control studies. In order to capture the greatest number of human studies, 6 recent systematic reviews were evaluated.[14-19] Three hypotheses kept recurring in these reviews for the potential nature of the relationship between RA and periodontitis. The first was the "two-hit model" proposed by Golub and colleagues in 2006,[20] which suggests that periodontitis appears first then leads to rheumatoid arthritis. The second hypothesis, originally proposed by Rosenstein et al.,[21] appeared to be more commonly represented, and is based on the appearance of anticyclic citrullinated peptide autoantibodies (ACPA) during the development of RA. They suggest that, since *P. gingivalis* has the propensity to citrullinate proteins and induce autoantibodies, these autoantibodies may be responsible for the initiation of RA.[21] The third hypothesis, described by Bartold and colleagues in 2005,[22] suggests a shared common molecular pathway between the 2 diseases within the RANK/OPG/TRAIL axis (receptor activator of nuclear factor kappa/osteoprotegerin/tumour necrosis factor-related apoptosis inducing ligand axis) whereby a decrease in OPG may lead to a reduction in vascular protection.

The first systematic review conducted by Kaur et al.[14] in 2013, included 16 case–control studies along with 3 experimental studies. They found good evidence of an association between periodontitis and RA regarding tooth loss, clinical attachment loss (CAL), and erythrocyte sedimentation rate (ESR) which, if high, would be an indication of inflammation or infection. There was, however, only moderate evidence for other parameters measured such as C-reactive protein (CRP), interleukin-1β (IL-1β), and other biochemical markers. Based on the 3 included clinical trials (2 of which were randomized controlled trials), the authors did find some evidence of a positive outcome of periodontal treatment on RA. However, these studies had very small sample sizes. Their conclusions suggest that common risk factors and common pathological processes are more likely responsible for the association between RA and periodontitis. More rigorous and higher level studies are required to substantiate this relationship.[14] A second systematic review published by the same lead author author the following year focused on whether periodontal treatment had an effect on clinical and biochemical measures for RA.[15] Four randomized controlled clinical trials (RCTs) and one clinical trial without randomization were included, testing the effects of non-surgical periodontal therapy (NSPT) on a variety of biochemical measures including tumour necrosis factor-alpha (TNFα), interleukin-6 (IL-6), CRP, ESR, ACPA, and disease activity score (DAS28). Similar to their previous findings, there were statistically significant reductions in ESR, suggesting a reduction of systemic inflammation. Surprisingly, however, there was no reduction in CRP which is known to be a non-specific marker of systemic inflammation. Interestingly, of the 5 included studies, 3 had been included in their 2013 systematic review.[14] Once again, the authors concluded that studies had low participant numbers and were of short duration thus indicating the need for more rigorous studies with larger sample sizes and of longer duration to determine whether NSPT has a positive effect on reducing the disease activity for individuals with RA.[15]

Calderaro and colleagues[16] in 2017 examined the same 4 RCTs that Kaur et al.[15] had included in their 2014

publication, but reported conflicting meta-analysis results. Unlike Kaur et al., they found no significant reductions in ESR. However, they did find statistically significant reductions in DAS28 scores.[16] This is an important finding as DAS28 is a validated score commonly used by clinicians to monitor disease activity in 28 selected joints subsequently used to guide treatment decisions.[23] Calderaro et al. suspected this difference in results was due to Kaur et al.'s inclusion of 1 study that used a different RA activity score to measure the DAS28. This measure, which included the CRP rather than ESR, has been shown to underestimate disease activity when compared with DAS28, thus Calderaro and colleagues excluded this study from their meta-analysis.[16,23]

Tang and colleagues,[17] in a more recent systematic review and meta-analysis of 8 case–control studies, reported a statistically significant association between periodontitis and RA, finding a higher prevalence of periodontitis in individuals with RA in all included studies ranging from 15.5% to 100%.[17] Their meta-analysis using a fixed effects model revealed a pooled odds ratio for periodontitis of 4.68 (95% CI, 3.11–7.05) when compared with healthy controls. Of particular interest is that, within the studies evaluated in this systematic review, several reported RA patients had significantly higher levels of anti-*P. gingivalis* immunoglobulin G than non-RA patients. This finding is noteworthy as higher levels of anti-*P. gingivalis* IgG have been associated with higher serum concentrations of ACPA, which is a specific marker of RA.[17] This finding lends support to the hypothesis that oral bacteria, especially *P. gingivalis,* could induce citrullination of peptides and thus be the link between periodontitis and RA.[21]

de Oliveira Ferreira and colleagues,[18] in a continuation of the quest to determine if periodontal disease is a risk factor for RA, included studies that only compared individuals with and without periodontal disease and examined RA as the outcome. Their systematic review included 2 cohort studies and 7 cross-sectional studies with 7 of the 9 reporting associations. Six of the studies were assessed as low risk of bias, while 3 were found to have high risk of bias. Only 3 of the studies could be included in their meta-analysis (MA) which was repeated a second time removing one of the studies due to high heterogeneity. The results were highly conflicting, with the first MA showing a strong correlation with RA for the periodontal disease group while the second MA showed a higher correlation with the non-periodontal disease group.[18] With these inconclusive results, they determined that higher level studies with larger sample sizes and better exclusion criteria are required. They did, however, suggest that a genetic link may be responsible as one of the alleles on the human leukocyte antigen gene (HLA-DRBI) found on chromosome 6 has been shown to be responsible for 25% to 50% vulnerability to RA and has also been recently identified as a mass producer of cyclic citrullinated autoantibody peptides.[18,24] This is of importance as these macromolecules have been shown to provoke autoimmune activity in the joints.[18]

The most recent systematic review and meta-analysis was published by Hussein and colleagues[19] in 2020, which explored whether a bidirectional relationship exists between RA and periodontal disease. Eight case control studies were analysed but 2 were eliminated due to a high risk of bias. Results from the MA did not reveal any significant effects of RA on periodontal disease based on periodontal pocket depth and CAL measurements. However, the authors reported a high level of heterogeneity. In contrast, they reported significantly worse RA disease activity ($p < 0.001$), as measured by DAS28 score, in those with periodontal disease. The authors concluded their findings did not support a bidirectional relationship, although they did emphasize that periodontal disease appeared to have a negative impact on RA disease activity.

Despite not having very clear answers at this time regarding the nature of the relationship between RA and periodontitis, it is evident that some type of association does exist. It would be prudent to carefully and regularly monitor the periodontal status of individuals living with RA. Collaboration between oral health professionals and rheumatologists is paramount to understanding the link between these 2 diseases in order to provide patient care that would result in better clinical outcomes.

Cognitive impairment/Alzheimer's disease

As human life expectancy continues to increase, so too has the incidence of cognitive decline in the elderly. There are numerous conditions associated with cognitive impairment (CI) or dementia, with the most common being Alzheimer's disease (AD). In Canada, between April 2017 and March 2018, there were 452,000 people over the age of 65 living with dementia and approximately 85,000 people newly diagnosed.[25] Of these numbers, 60% to 70% were diagnosed with AD. Dementia is a term used to describe a set of symptoms affecting brain function that is chronic and progressive over time. There are many forms of dementia, such as Alzheimer's disease, vascular dementia, Lewy body disease, mixed dementia, frontotemporal dementia, and Korsakoff dementia.[25] Various hypotheses exist regarding the etiology and pathogenesis of Alzheimer's disease. What is generally accepted is that amyloid precipitation, caused by an abnormal overproduction of amyloid peptides in the brain, results in lesions such as neurofibrillary tangles (tau protein), alterations of senile plaques (Aβ protein), and neural or glial cells.[26] However, it is unknown what causes this overproduction of amyloid peptides.

Over the past 10 years, research has progressed substantially, demonstrating that the once thought impermeable blood-brain-barrier (BBB) can be rendered more permeable by systemic inflammatory mediators enabling transmigration of activated macrophages and dendritic cells across the BBB.[27] This finding has led

researchers to explore the possibility of periodontal pathogens, such as *P. gingivalis,* translocating through the BBB and being one potential source of inflammation that could lead to dementia.[28] Researchers have recently confirmed the presence of *P. gingivalis* in the brains of patients with AD, along with gingipains which are toxic proteases associated with the bacterium.[29] One common feature of CI/AD is the presence of inflammation. Thus, the hypothesis that inflammation in the brain reflects the spread of systemic inflammation triggered by periodontitis is plausible. Another hypothesis is that the cytokine storm produced during periodontal inflammation elevates systemic inflammation through the release of inflammatory markers such as IL-1β, IL-6, CRP, and TNFα and could play a role in increasing neuroinflammation.[30,31]

To capture the most current literature on the relationship between periodontitis and CI/AD, findings from 7 systematic reviews,[31–33,35–38] 4 of which included meta-analyses[32,35,36,38] published between 2017 and 2021 are discussed in this position paper. Dioguardi and colleagues[31] conducted a systematic review exploring whether inflammation induced by periodontal microbes played a role in the onset and progression of Alzheimer's disease. Their analysis included 15 studies, 6 of which were animal studies, 1 was a post-mortem study, 4 were observational studies, 1 was clinical study, 1 a case–control study, and 2 were database studies. This review indicated that, although some evidence does exist for a relationship between periodontal disease and AD, most comes from animal studies rather than human trials. Mixed results were found in the observational studies, and the 1 clinical trial did not support their hypothesis that periodontal disease is a risk factor for AD.[31] Although 6 of the studies in this SR were animal studies, the author of this current position paper chose to include this SR[31] since 9 of the studies within the review were human.

Leira and colleagues[32] conducted a systematic review with a meta-analysis in 2017 to explore whether a relationship between AD and periodontal disease exists. In their analysis, they included 2 cross-sectional studies, 2 case–control studies, and 1 cohort study. Their results revealed a significant association between the 2 conditions (OR 1.69; 95% CI, 1.21–2.35) overall and particularly for those with more severe disease (OR 2.98; 95% CI, 1.58–5.62). This finding is not surprising as one could argue that individuals with CI/AD are less capable of performing oral hygiene, particularly those in institutional settings. This could be a major confounding factor if their ability to perform oral hygiene is not controlled for in the study. Authors of a Canadian systematic review published in the same year[33] examined the oral health status of persons with dementia. In their review, they found a negative influence of dementia on oral health. They indicated that the case for AD leading to the development of periodontal disease is obvious due to the well-documented lack of attention to oral hygiene among individuals living with dementia. Unfortunately, of the 28 studies included in their SR, only 1 study explored the ability of those with AD to perform oral care.[33] The authors raised an interesting point, that it is unclear whether individuals with AD living in institutionalized settings have worse oral health than other individuals in the same setting with other psychiatric conditions. The provision of daily oral hygiene care for nursing home residents by caregiver staff overall has been reported to be problematic. A 6-week RCT conducted in a nursing home in Canada, which measured caregiver staff's adherence through self-reporting to the provision of daily oral care with either an electric toothbrush or usual care, found that at the end of the 6 weeks, their overall adherence to both interventions had dropped from 46.6% in week 1 to 36.0% by week 6.[34]

Similarly, in 2018, Gusman et al.[35] published a systematic review and meta-analysis to assess the severity of periodontitis in individuals with dementia and found most of the 14 studies reported higher levels of periodontal disease in those with dementia. Interestingly, the meta-analysis was conducted twice; once with and once without the lone cross-sectional study. The MA that included the cross-sectional study reported a significant association between dementia and periodontitis, while no difference was found when the study was removed. Thus, the authors concluded that the MA did not support an association between dementia and the severity of periodontal disease. They explained these findings to be due to high heterogeneity among the studies, which were of varying types.[35]

In 2020, Nadim and colleagues[36] published a systematic review and meta-analysis investigating the influence of periodontal disease on dementia. They included 5 cohort and 7 case–control studies in their analysis. Of the 12 studies, 11 reported a positive association between periodontal disease and dementia risk, with 10 being statistically significant. Results of their MA including all studies revealed a relative risk (RR) of dementia related to periodontal disease at 1.38 (95% CI, 1.01–1.90) which is borderline meaningful. Interestingly, although typical for the study types, results were much higher for the case–control studies (2.25 [1.48–3.42]) versus the lower scores for the cohort studies (1.18 [1.06–1.31]). Of interest, the authors of this study also assessed the results against the Bradford Hill criteria for causation, indicating that all criteria were met. However, several of the criteria were misinterpreted, particularly the use of animal studies as fulfilling the criterion of experiment. Experimental human studies are required, preferably randomized controlled trials or at the very least, prospective cohort trials. Additionally, they indicated that strength of the evidence was fulfilled with a pooled RR of 1.38, which included all study types. The cohort studies came in at a much lower pooled figure (RR 1.18). In epidemiological interpretations,

typically anything below a RR of 2.0 is not considered strong. Lastly, the interpretation of temporality was not shown as, by definition, the exposure (periodontal disease) would need to have preceded the outcome (dementia or Alzheimer's disease). The only exposure that preceded the outcome would have been those with dementia who then developed periodontal disease. As previously discussed, that is more realistic. Before assessments of causality are made, further studies are required, such as interventional trials to test whether elimination of oral inflammation results in less severe progression or even improvements in dementia.

The most recent systematic reviews were published in 2021 by Alvarenga and colleagues[37] and by Hu et al.[38] whose review also included a meta-analysis. Both SRs reported associations between CI/AD and periodontal disease. However, the review by Alvarenga et al.[37] differed because, apart from evaluating AD studies, it also included other neurodegenerative diseases such as Parkinson's disease and multiple sclerosis. Of the 12 included studies, 8 were case–control studies, 3 were cross-sectional studies, and 1 was a cohort study. Despite reporting associations between the neurodegenerative diseases, they classified the evidence as very low.[37] In contrast, the Hu et al. SR[38] included 5 studies on AD and 5 studies on mild cognitive impairment (MCI). The studies were once again a combination of cross-sectional and case-control studies along with 2 cohort studies. In the MA for AD risk compared with non-periodontal patients, the OR was 1.78 (95% CI, 1.15–2.76), while risk for MCI was reported as OR = 1.60 (95% CI, 1.24–2.06). The authors reported several limitations, including heterogeneity of studies and diversity in diagnostic definitions for periodontal disease and MCI.

The conclusions that can be drawn regarding the association between periodontitis and CI/AD from these 7 systematic reviews is that there may be some sort of association, especially where individuals with dementia have compromised oral health. However, it remains unclear as to whether periodontal disease actually presents a risk for the development of dementia. Furthermore, comprehensive higher level studies are required to determine the exact nature of this relationship. Certainly, there is biological plausibility for such a relationship based on the hypothesis of inflammation.

Obesity

Obesity and overweight have become worldwide problems in epidemic proportions and are now considered chronic inflammatory diseases by health experts. The National Institutes of Health (NIH) defines obesity as a "complex multifactorial chronic disease"[39] while the World Health Organization (WHO) refers to obesity as a "chronic disease"[40]. WHO has reported significant increases worldwide in obesity rates among all age groups since 1975.[41] The statistics in Canada are painfully high with 64% of adults over 18 years of age classified as overweight or obese in 2017, representing a 15% increase since 1978.[42] Health Canada recognizes obesity as a major risk factor for several chronic diseases such as coronary heart disease, Type 2 diabetes, stroke, hypertension, some cancers, and osteoarthritis.[42]

Although causes of obesity and overweight are fundamentally cited as being an "energy imbalance between calories consumed and calories expended"[40] it is now understood that the causes of weight gain are much more complex than previously believed, involving both environmental and genetic factors.[43]

For over 20 years, oral health researchers have been investigating the potential relationship between obesity and periodontal disease. Several possible mechanisms for this connection have been revealed, particularly involving the inflammatory cascade. Both animal and human trials have confirmed that obese individuals have an exaggerated host immune response[44,45] in addition to differences in the oral microbiome.[46] Adipose tissue cells (adipocytes) are inflammatory in nature and have been shown to secrete proinflammatory cytokines, similar to those produced in periodontal disease, and thus capable of an exaggerated host response.[47] Additionally, other potential mechanisms being explored are TNFα, production of reactive oxygen species resulting in oxidative stress, the role of leptin which is secreted by adipose tissue and thought to play a role in inflammation, dyslipidemia, and alterations in the secretion of the hormone ghrelin in the stomach which plays a role in energy balance.[43] Findings from these research endeavors have confirmed a biological plausibility for a relationship between periodontal disease and obesity.

A search of the most current literature on the nature of the relationship between periodontitis and obesity (OB) revealed 11 systematic reviews published between 2015 and 2021[48-58] and 1 meta-review (umbrella review) of SRs published in 2018 by Suvan and colleagues[43], which included 9[48-56] of these 11 SRs. The deluge of literature on this topic is overwhelming. Thus, the analysis in this paper has been limited to findings from these systematic reviews and the meta-review. Suvan and colleagues in their meta-review[43] organized their findings in terms of "prevalence, incidence, response to periodontal therapy, and biomarkers". Nine of the 14 SRs within their meta-review reported results on prevalence and were all in agreement that obese individuals compared with those of normal weight are more likely to have some form of periodontal disease.[43] Those SRs within the meta-review reporting on incidence, some of which included children and adolescents, were also consistent in their findings. Thus the authors concluded that overweight or obesity places individuals at higher risk for periodontal disease.[43] Furthermore, Khan et al.[57] published a SR in 2018 exploring more specifically whether overweight or obesity was a risk factor for periodontitis in young adults and

adolescents. The results of their review found obesity to be positively associated with periodontitis in 17 of 25 studies analysed, with ORs ranging from 1.1 to 4.5.[57] These overall conclusions are supported by findings from a recent 13-year longitudinal population-based cohort study in Taiwan, published in 2021, that included cohorts of 4,140 obese individuals and 8,280 non-obese individuals.[59] The study authors reported that those who were obese were at slightly higher risk for periodontitis (HR 1.12; 95% CI, 1.01–1.25) than those of normal weight. Of interest, after completing a subgroup analysis, the authors found a much higher risk for periodontal complications in obese individuals older than 65 years (HR 1.98; 95% CI, 1.22–3.22).[59] These longitudinal findings are significant due to the size of the cohort and overall length of the study.

Earlier studies investigating the relationship between periodontitis and OB were primarily in the form of animal studies, cross-sectional, case–control or cohort studies. However, more recent intervention studies have begun to surface. Six SRs[49-51,53-55] that included intervention studies were analysed in the meta-review[43]. No clear answers emerged as results of these studies were mixed. For example, in one SR by Gerber et al.,[51] 3 included studies did not demonstrate any differences in outcomes of NSPT between the obese and normal weight groups, while 5 studies included in the same SR revealed better outcomes for those who were of regular weight. Unfortunately, due to the heterogeneity of these studies, a meta-analysis was not possible. Of the 6 SRs, 2[49,53] reported no differences in clinical outcomes between study groups, while 4[50,51,54,55] had mixed results. Some of the SRs that included intervention studies evaluated in the meta-review included measures of various biomarkers in response to NSPT. The variety of biomarkers measured as well as where samples were collected (i.e., gingival crevicular fluid, saliva, plasma) was inconsistent which most likely explains the mixed results. Overall, a tendency towards higher levels of CRP and other proinflammatory cytokines was noted. However, there were inconsistencies across studies in whether these levels were reduced following NSPT.[43]

A systematic review and meta-analysis published in mid-2021 by Gonçalves da Silva and colleagues[58] investigated whether an association between clinical measures of gingival inflammation and obesity exists. This SR/MA differs from previous reviews as it focused on gingival inflammation rather than periodontitis. It included 90 studies, 82 of which were cross-sectional/clinical trials. Interestingly, the majority of studies did not find significant differences between obese and non-obese individuals in overall gingival inflammation. However, the MA revealed higher levels of gingival inflammation in individuals diagnosed with periodontitis who were obese compared with non-obese individuals.[58] This finding could suggest a dose-response relationship, but further studies will be required to substantiate it.

The authors also noted variations in the measurement of obesity, although the majority of studies used body mass index (BMI) as their unit of measurement. Some studies used waist–hip ratio (WHR) and waist circumference (WC) and, interestingly, reported significantly higher levels of gingival inflammation in those with higher WHR and WC.[58] More consistency in the use of measurement tools in future studies will be required to prevent heterogeneity.

It is clear from these SRs and MAs that a positive association exists between obesity and periodontitis in all age levels although determination of a cause–effect relationship is premature at this time. Better quality prospective study designs with larger sample sizes and more homogenous measures are required to examine the responses to NSPT for those who are overweight or obese compared to non-obese individuals. Additionally, more robust studies are required to determine the exact mechanisms and magnitude of this relationship. It has been suggested that oral health professionals increase client awareness of the impact that overweight and obesity may have as a potential risk factor for the development of periodontitis.[43,60] In this age of personalized or precision medicine, it would be prudent as part of routine risk assessment to include the measurement of body mass index (BMI) and to educate clients about the complex nature and multi-organ involvement of obesity. Communication with endocrinologists, dietitians, and other specialists is warranted to best manage those clients dealing with obesity.[43,60]

Inflammatory cancers

According to Canadian Cancer Society statistics published in 2019, cancers were found to be the leading cause of death in Canada, representing 28.2% of all deaths.[61] The society reported the top 4 cancers to be prostate, lung, breast, and colorectal cancers, accounting for 20%, 13%, 25%, and 11% of all new cases, respectively.[61] Although the causes of all cancers have yet to be determined, numerous risk factors have been proposed. More recently, some types of cancers have been thought to be inflammatory in nature, such as the orodigestive cancers that include oropharyngeal, esophageal, gastric, pancreatic, and colorectal cancers. Given the high prevalence of periodontal disease worldwide, along with its well-established associations with other systemic diseases such as cardiovascular disease, respiratory microbes, and diabetes,[1,3,4] researchers have begun to explore the possibility of these cancers being associated with specific periodontal microbes. One of the first prospective studies of a nationally representative population sample (N = 7,852) to report an association between orodigestive cancer mortality and periodontal disease was conducted in 2012 by Ahn and colleagues.[62] In addition to finding an association between periodontal disease and orodigestive cancer mortality (RR = 2.28), these authors identified the presence of *P. gingivalis* suggesting it could potentially be

an independent biomarker for orodigestive cancer risk.[62] This finding lead to a plethora of studies investigating the various periodontal microbes and their potential associations with more specific oropharyngeal cancers. Results of these studies have been mixed, with some reporting the presence of specific microbes for specific cancers, while others had conflicting results.

This position paper assesses the most current literature on the nature of these potential relationships, namely 9 systematic reviews[63,65-72] (6 with MAs) published between the years 2017 and 2021. These SRs/MAs reported on a variety of cancers, including esophageal, liver, pancreatic, gastric, colorectal, prostate, and hemopoietic cancer. Corbella and colleagues[63] published a SR and MA in 2018 with the intent of assessing if humans with periodontitis were at higher risk for cancer compared with those without periodontitis. Of the 8 included papers, 2 were deemed to be of low quality and thus not included in their MA. Results of their quantitative analysis using hazard ratios (HR) revealed statistically significant associations for all included cancers. Of interest was their use of HRs rather than odds ratios (OR) for their MA calculations. HRs are typically used as indicators of a causal relationship between 2 conditions representing a point estimate, whereas ORs are used, more appropriately, to measure the association between an exposure and an outcome.[64] The authors noted this as a limitation and explained that the majority of the included studies had used HRs whereas only a few had used ORs, thus precluding the use of ORs in their MA calculations as the 2 different outcomes could not be pooled.[63] This major limitation reduced the number of papers that could be used in the various MA analyses. Thus, despite the statistically significant results, the correlations reported in their SR/MA require further substantiation with more rigorous studies with larger sample sizes and better methodology.

Three more recent SRs have reported overall results for various types of cancers in relation to the presence of oral microbes. In 2019, Chen et al.[65] reported on the potential of oral microbes being associated with various gastrointestinal cancers, including colorectal, pancreatic, gastric, esophageal, and liver cancers. From the qualitative evaluation of the 17 included studies, they reported an association with several periodontal microbes, including *P. gingivalis*, *T. forsythia,* and *P. intermedia*, regardless of the type of cancer.[65] Interestingly, microbial differences were found between upper digestive cancers and colorectal cancers suggesting a different mechanism due to anatomical and physiological differences. Of importance was the validation of the use of saliva sampling as the preferred method for the collection of microbial DNA samples, which could become future in-office practice as a screening method for cancers.

Another mixed SR/MA was conducted by Xiao et al. in 2020.[66] Their study explored the effects of periodontal bacteria on incidence and prognosis of cancer, revealing that periodontal bacterial infection increased the overall incidence of cancer and was associated with poor overall survival, disease-free survival, and cancer-specific survival. In addition, their subgroup analysis revealed associations between 2 periodontal bacteria and cancer risk: *Porphyromonas gingivalis* (Pg) (OR 2.16; 95% CI, 1.34–3.47) and to a lesser extent, *Prevotella intermedia* (Pi) (OR 1.28; 95% CI, 1.01–1.63) but not *Tannerella forsythia* (Tf), *Treponema denticola* (Td), *Aggregatibacter actinomycetemcomitans* (Aa) or *Fusobacterium nucleatum* (Fn).[66]

The third mixed SR that included a variety of digestive cancers was published in 2021 by Reitano and colleagues.[67] Although their SR did not include a MA, their qualitative analysis was extensive, reporting on 28 studies (26 case–control and 2 cohort studies). Their investigation of the composition of the microbes in a variety of digestive cancers included esophageal squamous cell carcinoma, gastric cancer, colorectal cancer, liver carcinoma, and pancreatic cancer. Their overall results found a difference in bacterial composition between those with and those without cancer in the majority of the 28 studies. In particular, one key finding was that *F. nucleatum* and *P. gingivalis* appeared to be associated with colorectal cancers.[67] This is in contrast to the findings of Xiao and colleagues who found no association with *F. nucleatum*.[66] The authors of this SR[67] suggested the oral microbiota is different in individuals with and without digestive cancers, and recommended further studies to confirm which microbes are related to which form of cancer. They also suggested a future role for the screening of oral microbial biomarkers to detect specific cancers once the specific microbes have been confirmed.

In addition to these SRs and MAs that investigated a variety of digestive cancers, 5 other SRs (4 of which included MAs) each investigated a specific type of cancer. Maisonneuve and colleagues[68] from Italy published a SR/MA in 2017 on the relationship between periodontal disease, edentulism, and pancreatic cancer. Their MA included 8 studies, and focused on the examination of risk of pancreatic cancer related to periodontal disease. As 7 of the 8 studies were cohort studies, they were able to calculate the relative risk (RR), a more robust measure compared to the odds ratio (OR). Their results revealed RR = 1.74 for pancreatic cancer (95% CI, 1.41–2.15) and RR = 1.54 for edentulism (95% CI, 1.16–2.05).[68] The authors reported no evidence of heterogeneity or publication bias and indicated most of the studies had been adjusted for numerous variables previously associated with pancreatic cancer.[68]

Interestingly, these findings are almost identical to those of Corbella et al.[63] with the exception that Corbella and colleagues calculated the outcome as an HR rather than a RR (HR 1.74; CI 95%, 1.21–2.52). Although the SR by Maisonneuve et al.[68] did not evaluate the relationship between periodontal pathogens and pancreatic cancer, it

cited numerous studies that support a positive relationship between the presence of *P. gingivalis* and pancreatic cancer, which is in agreement with the SRs published by Chen et al.[65] and Xiao et al.[66] The authors concluded their MA supports the hypothesis of a relationship between periodontal disease and pancreatic cancer and suggested the association was generalizable due to the inclusion of studies from 3 continents.[68]

The Canadian Cancer Society estimated in 2019 that colorectal cancer accounted for 11% of all new cases in Canada, labelling it as one of the 4 most common cancers.[61] Although colorectal cancer incidence was included in systematic reviews discussed earlier in this paper, a meta-analysis specific to colorectal cancer was published in 2020 by Sun et al.[69] as a conference abstract. Their MA evaluated the relationship between periodontal disease and both the incidence and mortality of colorectal cancer with data from 14 studies focused on incidence and 3 on mortality. The results of their pooled analysis for incidence reported a RR = 1.179 (95% CI, 1.036–1.342; $p = 0.013$; $I^2 = 84.7\%$). While these numbers are low yet still significant, their subanalysis of studies by region and size showed slightly higher numbers. Their analysis of the impact of periodontal disease on mortality related to colorectal cancer was non-significant. The systematic review by Reitano et al.[67], previously discussed, reported *F. nucleatum* and *P. gingivalis* to be associated with colorectal cancers. Similarly, numerous individual studies[70-72] have reported associations between *F. nucleatum* and colorectal cancer. However, these findings have been inconsistent based on the analyses of both Chen et al.[65] and Xiao et al[66]. One possible explanation suggested by Chen and colleagues, based on microbial species differences between upper and lower digestive tract cancer, was that different sampling methods may be required for lower digestive tract cancers for better accuracy.[65]

Although some of the mixed SRs included liver cancer as part of their analysis,[65,67,73] the number of studies included were small and analyses were combined with other cancers. In addition, studies were deemed to be of low quality given numerous methodological flaws, mixed findings, and substantial heterogeneity. Authors of these studies concluded that, although there may be a link between periodontal disease and liver cancer risk, more robust studies are required to explore this proposed association.[65,67,73]

Two other cancers that are not specifically related to digestive cancers have been explored in SR/MAs related to periodontitis risk. Wei et al.[74] published a SR/MA in 2021 exploring the association between periodontal disease and prostate cancer while Wu and colleagues[75] conducted a SR/MA in 2020 investigating the association between periodontitis and hematopoietic and lymphatic cancers. Findings from the Wei et al.[74] SR/MA revealed a significant association between periodontal disease and prostate cancer through the pooled results of 7 studies. (RR 1.17; 95% CI, 1.07–1.27; $p = 0.001$). Interestingly, the association was significant for both Asian and European populations, but not among American populations.[74] Further exploration of this potential association is warranted, particularly with a North American population.

Results of the Wu study[75] found a significant association between both types of cancers (RR 1.17; 95% CI, 1.07–1.27; $p = 0$) with a stronger association with lymphatic cancers. It is noteworthy that, in their stratified analysis, they determined that never smokers as well as the American population appeared to be at higher risk. The authors concluded that larger, more robust studies that adjust for confounders such as age, gender, race, and smoking are required.[75]

The evidence for a link between periodontal disease and a variety of cancers, particularly those that are orodigestive, appears to support some sort of association. However, both the mechanism and nature of such associations require further investigation. Of interest is the proposed relationship between the digestive cancers and specific periodontal pathogens. Once research has confirmed the more specific microbes associated with the various types of cancers, in concert with the concept of personalized/precision medicine, oral health professionals may have an opportunity for future in-office screening for salivary biomarkers to determine risk for these cancers.

Renal disease or chronic kidney disease

Chronic kidney disease (CKD) has been identified as one of the major global chronic noncommunicable diseases that is increasing at a rapid rate.[76,77] The Canadian Institute of Health Information (CIHI) reported in 2019 that the number of Canadians starting renal replacement therapy (dialysis) had nearly doubled over the past 20 years and the number of kidney transplants performed had increased by 41% between 2010 and 2019.[78] These are serious increases that place a significant burden on the Canadian health care system both financially and resource wise. Identification and modification of risk factors for CKD are paramount to addressing this growing global disease.

Numerous risk factors for CKD have been identified, such as hypertension, smoking, age, poorly managed diabetes, racial background, and systemic inflammation.[79] Two of these risk factors are shared with periodontal disease: smoking and diabetes. Systemic inflammation has been proposed as the mechanism for the association between CKD and periodontal disease since it has been well established that periodontitis releases numerous inflammatory cytokines resulting in elevation of C-reactive protein systemically. It has been suggested that this increase in systemic inflammation could have a negative impact on renal function.[79,80]

Only 4 systematic reviews addressing a possible association between periodontitis and CKD,[79-82] all with meta-analyses and published between 2018 and 2020, were identified as suitable for inclusion. Evidence appears

to be more limited on this proposed linkage as the majority of the studies contained in these reviews were either cross-sectional or case–control studies and often with small sample sizes. In 2018, Zhao et al.[81] conducted a SR/MA of observational studies to explore the nature of the association between periodontitis and CKD in terms of directionality. The results of their analysis were inconclusive as only 2 cohort studies were included, and results were conflicting. To assess the non-directional relationship, they included 3 cross-sectional studies and 1 case–control study, which showed that individuals with periodontitis had significantly higher odds of having CKD (OR 3.54; 95% CI, 2.17–5.77; $p < 0.001$) than those without periodontitis. The authors concluded that there was evidence to support a non-directional association between periodontitis and CKD, but suggested further studies were required to assess the presence of periodontitis as a risk factor for CKD.[81] Although the reported results in this study are strong , the findings should be treated with caution as the evidence is at a low level.[81] Case–control studies are retrospective in nature and typically result in higher ORs than cohort or prospective studies.

Kapellas and colleagues[79] followed in 2019 with a SR/MA also evaluating the association from both directions using 9 observational studies with periodontal disease as the exposure and CKD as the outcome, and 8 studies with CKD as the exposure and periodontal disease as the outcome. Although both analyses showed positive associations, only the association between individuals with periodontal disease having higher odds of developing CKD was statistically significant (OR 1.60; 95% CI, 1.44–1.79).[79] These findings are similar to those of Zhao et al.[81] However, the odds calculated by Kapellas and colleagues are much lower than those reported in the Zhao study, which is most likely due to the larger number of studies analysed in the Kapellas study. The authors concluded that, although the methodological quality of the studies was high, all studies were observational and had inconsistencies in defining periodontal disease, so the level of evidence should be considered low.[79]

In 2019, Deschamps-Lenhardt and colleagues[82] conducted a SR/MA to explore the association between periodontitis and CKD. They also included an investigation of the potential influence of periodontal treatment in patients with CKD. The results of their MA assessing the association between periodontitis and CKD in 17 studies revealed an OR of 2.39 (CI, 1.70–3.36), which fell between the results of the 2 previously discussed studies.[79,81] Their assessment of the effects of periodontal treatment was only qualitative due to the lack of RCTs making it impossible to conduct a MA. Of the 2 RCTs that were included, results were contradictory. The authors concluded that more RCTs would be required to assess the impact of periodontal treatment on the outcome of CKD.

Finally, in 2020, Zhao et al.[80] conducted a SR/MA of the effects of NSPT on renal function in those with CKD and periodontitis. As indicated by Deschamps-Lenhardt and colleagues,[82] the number of interventional trials was limited. Zhao located and included 4 case series studies with a total of 109 participants and 1 RCT with 97 participants. Although they conducted 2 MAs, 1 on eGFR (glomerular filtration rate) and 1 on serum creatinine, neither revealed significant results. They concluded there was insufficient evidence to state whether NSPT has a beneficial effect or not on CKD.

It appears from the results of these 4 SR/MAs that some evidence exists of an association between periodontitis and CKD, but the nature of the association has yet to be confirmed. The dearth of intervention trials makes it impossible to determine whether periodontal treatment would be of significant benefit to those with CKD.

CONCLUSION

Based on the assessment of the evidence in this position paper, it is clear that there are associations, varying in strength, between periodontitis and the 5 conditions discussed. The strongest association appears to be between periodontal disease and obesity with a plethora of evidence in support of the relationship for all age categories. The second largest amount of evidence supports a relationship between dementia/AD and periodontal disease, particularly in terms of increased odds of periodontal disease in individuals with dementia or AD. What is of importance is that periodontal disease and these 5 conditions seem to have a common connection: systemic inflammation. It appears that these linkages may be due to the inflammatory burden that results from a dysbiosis of the oral microbiome. More rigorous and higher-level studies with more consistent parameters for the measurement of periodontal disease are required to further define the nature of these relationships. In the meantime, dental hygienists should be made aware of these associations, however strong or weak, in order to educate their clients about the potentially far-reaching systemic effects of inflammatory periodontal disease and the importance of maintaining good oral health.

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CONFLICTS OF INTEREST

The author has declared no conflicts of interest.

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