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SYSTEMIC DISEASES (M BARTOLD, SECTION EDITOR)

Modifiable Risk Factors for Periodontitis and Diabetes

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Abstract This review describes the evidence published from January 2013 through March 2016 for modifiable risk factors for chronic periodontitis and diabetes mellitus. Risk factors are factors that increase the chance of developing the disease. Modifiable risk factors for both these chronic, inflammation-related diseases include the following: hyperglycemia; microbial overgrowth, infection, and inflammation (virus, poor oral hygiene, gut microbiome); overweight and obesity; metabolic syndrome; hyperlipidemia; medication; unhealthy diet (added sugar; alcohol and other non-sugary carbohydrates, fat, and meat; nutrition, minerals (including zinc), and vitamins); current tobacco smoking (including environmental tobacco smoke); sedentary lifestyle; sleep disturbances; stress, depression, anxiety, poor coping skills, and allostatic load; low health literacy; and the environment and pollution.Given the similarity between the inflammatory mechanisms underlying chronic periodontitis and diabetes mellitus, one can wonder: Could these diseases both be somewhat different manifestations of inflammatory response-based overload? Could both periodontitis and diabetes even be regarded as autoimmune diseases that are manifested due to poor biologic and psychologic coping skills in response to the micro- and macro-level stressors that cause inflammation?Any successful intervention must include more measures than clinical medical/dental care can provide and hence might benefit from active participation of all parties, first and foremost the patient, in a patient-centered, interprofessional health care (not merely disease care) collaboration for the benefit of the mutual patient.But first, it is necessary to be aware of the risk factors that can be modified to pose less risk, a goal toward which this review hopefully will be helpful.

Keywords Added sugar · Hyperglycemia · Hyperlipidemia · Inflammation · Lifestyle · Oral-systemic health

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Introduction

Chronic periodontitis and diabetes mellitus are both complex, multifactorial, cumulative, chronic, and inflammation-based diseases [1•].

This review will focus on reports published between January 1, 2013, and March 31, 2016, to present the current scientific evidence for *modifiable* risk factors for periodontitis and diabetes, whereas a companion review concerns the "*non-modifiable*" factors [1•]. That complementary paper introduces the definition of risk factor used, the inability to disentangle individual risk factors as several always exist simultaneously and interact, and the type of studies described [1•].

It is currently believed that the host inflammatory responses overall constitute the main mechanism underlying most of the modifiable risk factors for both periodontitis and diabetes. Gregor and Hotamisligil introduced in 2011 the term "metaflammation" for "a chronic, low-grade inflammatory response initiated by excess nutrients in metabolic cells" [2••], partly based on the then recently discovered function of adipose tissue as a dynamic, endocrine organ that expresses many pro-inflammatory cytokines. With metaflammation

being the hallmark of obesity, insulin resistance, and type 2 diabetes (*T2D*), it should be pointed out that the cytokines expressed in metaflammation are also expressed in periodontitis [3].

Periodontitis

Chronic periodontitis is initiated by dysbiosis (microbial imbalance) among the members (bacteria, fungi, virus, and archaea) of the community of microbes referred to as the microbiome or microbiota in dental plaque (biofilm) that, in especially susceptible individuals, can lead to hyperinflammation and breakdown of the soft and hard tissues surrounding the teeth [4••, 5]. This hyperinflammatory response includes swelling of the soft tissues and will therefore lead to deepening periodontal sulci/pockets, thus favoring the disproportionate growth of anaerobe members of the subgingival microbiome. Their increasing abundance will lead to continued inflammation-related breakdown of periodontal tissues in a vicious cycle that, in the absence of intervention, may lead to tooth loss. Traditional risk factors for periodontitis were reviewed in the past [6], so whereas their evidence will be updated, non-traditional, novel modifiable risk factors will be emphasized in this review.

Diabetes Mellitus/Hyperglycemia

Diabetes mellitus is a group of metabolic disorders particularly manifested by hyperglycemia (elevated blood glucose levels) resulting from impairment of insulin secretion or action or both, and its major categories are as follows: type 1 diabetes (*T1D*), type 2 diabetes (T2D), prediabetes (*preDM*, increased risk for developing overt T2D in individuals with impaired fasting glucose (*IFG*) levels and/or impaired glucose tolerance (*IGT*)), and gestational diabetes (*GDM*). Glycated hemoglobin (HbA1c) concentration expresses the degree of irreversible binding of glucose to hemoglobin and is a measure of blood glucose control over the previous 3 months (the lifespan of the red blood cells), weighted toward the recent few weeks.

Table 1 provides an overview of the identified modifiable risk factors for periodontitis and diabetes, respectively.

Hyperglycemia/Diabetes

Periodontitis A multitude of studies of various designs and in different populations supports the adverse effect of *hyperglycemia* as a risk factor for periodontitis prevalence, severity, extent, incidence, and progression, often in a dose-response manner [6, 7, 117].

Importantly, it has rather recently been demonstrated that it is the *level of hyperglycemia*, not diabetes type or etiology or diagnosis per se, that is associated with incident periodontitis [8••], as clinical attachment loss (CAL) is strongly associated *with poorly controlled DM*, but not with preDM or well-controlled DM [7].

Among 7042 National Health and Examination Survey (NHANES) 2009–2012 participants, severity and extent of CDC/AAP defined periodontitis [118] increased by glycated hemoglobin (HbA1c) level, with odds for having periodontitis increasing by 18 % per each percentage point HbA1c [9]. Hyperglycemia also affects the composition of subgingival plaque [10].

Two rare, large, population-based longitudinal studies among Japanese [11] and Taiwanese [12], respectively, demonstrate the bi-directional links between periodontitis and hyperglycemia/T2D.

Increasing T1D severity, duration, and presence of complications significantly and negatively affect the periodontal health status [13].

GDM exacerbates both local and systemic inflammatory responses [16] and is significantly associated with periodontitis; blood lipids and glucose [17]; local and systemic levels of pro-inflammatory cytokines in gingivo-crevicular fluid (GCF), saliva, and serum [16]; and concentration of C-reactive protein (CRP), a general acute-phase inflammatory marker, which is more than tripled in GDM. Nevertheless, pre-pregnancy obesity can mask any difference in periodontitis prevalence between those with and without GDM [18], and a 2015 meta-analysis deemed the studies too heterogenic for a firm conclusion [19].

Diabetes In the Korean Healthy Twin Study, baseline blood glucose level (preDM) was demonstrated to be a risk factor for developing T2D [14], and almost 60 % of Asians with initial preDM progressed to manifest T2D over 10 years in a study among 1376 Asian Indians with normal glucose tolerance (NGT) or preDM at baseline [15].

Pregnancy is a maternal stressor that causes low-grade inflammation and hence can cause GDM or bring out overt T2D [20, 21••].

Bariatric Surgery

Periodontitis and Diabetes Although *bariatric surgery* can prevent incident T2D or induce its remission [23], accompanying periodontal health status is usually poor and does not seem to improve despite reduced levels of hyperglycemia after bariatric surgery. Rather, severity and extent of periodontitis increase post-surgery [22].

Table 1 Modifiable risk factors for chronic periodontitis and diabetes mellitus: citations [reference number]

Modifiable factors	Periodontitis	Diabetes
Hyperglycemia	[7, 8••, 9–13]	[14, 15] Risk for preDM
Current gestational diabetes (GDM)	[16–19]	[20, 21••] Risk for GDM
Bariatric surgery	[22]	[23]
Microbial overgrowth/infection/inflammation	[4••, 24, 25•, 26–30]	[9, 11, 12, 31•, 32–34]
		[19] Risk for GDM
Virus	[35, 36]	[35, 37] Risk for T1D
Poor oral hygiene	[38•]	[39, 40]
Gut microbiome	[41]	[42–44]
Overweight/obesity	[45–47]	[48] Risk for preDM
		[49] Risk for T2D
		[50•] Risk for T1D
Adipokines	[51, 52]	[51, 52]
Metabolic syndrome	[53, 54]	[14, 55]
Hyperlipidemia	[56•, 57, 58, 59••]	[14, 59••]
Medications	[60, 61]	[62–64]
Unhealthy diet		
Added sugar	[65, 66]	[65••, 67–77]
Alcohol/other non-sugary carbohydrates, fat, meat	[78]	[79, 80••, 81–83]
Nutrition, minerals, vitamins	[84]	[85–89]
Zinc	[90]	[90]
Current smoking	[91, 92]	[93–95]
Environmental tobacco smoke	[96]	[93]
Sedentary lifestyle	[97]	[98]
Sleep disturbances	[39, 99–102]	[103]
Stress, depression, anxiety, poor coping skills, allostatic load	[104, 105]	[21••, 106–108]
Low (oral) health literacy	[109]	[110, 111]
Environment, pollution	[112]	[113–116]

preDM prediabetes, *T2D* type 2 diabetes, *T1D* type 1 diabetes

Microbial Overgrowth/Infection (Bacteria, Virus, Microbiome dysbiosis)/Inflammation

Periodontitis There is no doubt that microbes in the dental plaque initiate local inflammatory cascades as described by Bartold and van Dyke [4••], whereas the host response will determine the degree of periodontal breakdown [4••, 24]. This explains why no evidence exists for clear, direct causal links between specific, individual periodontal microbes and periodontitis initiation and progression [25•]. When provided with extraordinarily favorable growth conditions, commensal microbiome members create dysbiosis [5, 26], and some multiply in abundance and "turn pathogen," as described by Han regarding *Porphyromonas gingivalis* [27] and explained in general by Hajishengallis and Lamont [28].

A novel discovery is the potentially important role of *microbial nucleic acid sensing* by pattern recognition receptors, such as toll-like receptors (TLRs) [29].

Metaflammation is a risk factor for periodontitis, as shown in an 11-year-long cohort study among 1784 adult Germans, in whom the inflammatory markers *fibrinogen* and *white blood cell counts* significantly affected all measures of periodontal health status [30].

Diabetes Periodontitis encompasses both microbial overgrowth, infection, and inflammation and hence will be used as an example of such a risk factor. The only systematic review of non-interventional studies suggests that periodontal disease adversely affects diabetes outcomes, namely *incident hyperglycemia* in persons without diabetes, *incident* T2D, *poorer glycemic control in T2D*, *complications of T1D* and *T2D*, and possibly GDM [31•]. Even in persons without manifest diabetes, elevated HbA1c is seen in those with chronic periodontitis compared to those without periodontitis [32] and localized, acute gingival inflammation also modifies insulin/glucose metabolism [33].

Metaflammation is a risk factor for development of insulin insensitivity and eventually manifests T2D with periodontal bacteria and their by-products contributing as illustrated elsewhere in a conceptual model [34, 117].

Among 6125 initially diabetes-free Japanese, those with baseline periodontitis had 2.5–3.5 times greater risk of incident T2D 5 years later [11]. A similar study among 34–44-year-old 5885 Taiwanese reported an adjusted 33 % increased risk for incident hyperglycemia (including manifest T2D) 5 years later in those with baseline periodontitis [12].

The most recent NHANES 2009–2012 data from 7042 participants show that people with periodontitis have significantly higher mean HbA1c level than those without periodontitis [9].

A meta-analysis of three case-control studies calculated that women with periodontitis had about twice the risk for developing GDM compared to periodontitis-free pregnant women [19].

Virus

Periodontitis Viruses are both transient and commensal members of the oral microbiome, contribute to the development of periodontitis in dysbiotic situations, and may be able to stimulate the overgrowth of bacteria seen with periodontitis [35, 36].

Herpesviruses are frequent inhabitants of periodontitis lesions, and based on 26 recent studies in 15 countries, Slots reported that subgingival *cytomegalovirus*, *Epstein-Barr virus*, and *herpes simplex virus type 1*, respectively, yielded median prevalences of 40, 32, and 45 % in chronic periodontitis versus 3, 7, and 12 % in healthy perodontia [35].

Diabetes Transient or commensal viral members of the periodontal microbiome are suspected to be involved in incident *DM1*, such as *enteroviruses* [37] and *herpes viruses* (cytomegaloviruses, Epstein-Barr virus, and herpes simplex virus type 1) [35].

Poor Oral Hygiene

Periodontitis Logically, *poor oral hygiene* that leads to plaque buildup would be a risk factor for gingivitis/periodontitis. Since the 1965 publication by Löe, Theilade, and Jensen [119], it has been accepted that plaque is a necessary factor for periodontitis, and 50 years later, a meta-analysis confirmed that infrequent tooth brushing is significantly associated with severe periodontitis [38•].

Diabetes Persons with diabetes generally exhibit poor dental hygiene [120]. In persons with T2D, gingivitis indicated by bleeding during tooth brushing is associated with elevated HbA1c levels [39]. Host responses to dental plaque due to ineffective oral hygiene contribute to the metaflammation that is a risk factor for incident T2D, as concluded by a meta-analysis of longitudinal studies calculating 31 and 26 % higherT2D risk for elevated levels of the inflammatory markers *IL-6* and *CRP*, respectively, even after adjustment for adiposity and hyperglycemia [40].

Gut Microbiome

Periodontitis Dental plaque and the periodontal pocket function as a reservoir not only for more than 700 different species of commensal periodontal microbes, but also for transient microbes that ordinarily inhabit only the guts [121] and stomach, such as *Helicobacter pylori* [122, 123] that is abundant in Chinese, especially in those with periodontitis [124], and may be a risk factor for periodontitis [41].

Diabetes The discovery of important roles of the gut microbiome in the development of the host immune system has lately attracted much attention, and evidence is accumulating for novel, substantial roles of the gut microbiome in the development of metabolic disorders such as obesity, obesity-associated inflammation and insulin resistance, and eventually T2D [42].

Presence of *H. pylori* was found associated with HbA1c in a dose-response manner among Indians [43], and gastric *H. pylori* infection was associated with manifest diabetes, but not with preDM, in Taiwanese [44].

As well, gut microbiota may influence the development of T1D that is an autoimmune disease mediated by T cells and anti-islet cell autoantibodies are developed. Reduced gut microbiota diversity is seen in individuals with autoimmune diseases such as T1D who lack the great diversity of the gut microbiome and thereby do not possess the strong adaptive immune response required to prevent such diseases [125].

Overweight/Obesity

Recently, obesity was officially declared a disease, and adipose tissue is now recognized as a complex endocrine organ that secretes bioactive molecules, such as pro-inflammatory adipokines [2••, 3].

Periodontitis Risk for periodontitis is associated with increasing BMI in a dose-dependent manner [45], and a longitudinal study found *weight gain* among initially normal weight persons to be associated with elevated risks of 13 and 33 % for incident periodontitis in individuals becoming overweight or obese, respectively [46]. Two meta-analyses [47, 126] reported direct associations between overweight and obesity, respectively, and incident periodontitis with 13 % increased risk for periodontitis for each standard deviation BMI increase [126].

In morbidly obese individuals, the severity of periodontitis is found associated with *orosomucoid* (alpha-1-acid glycoprotein), an acute phase protein reactant [52].

Diabetes Obesity is a traditional risk factor for incident T2D. The metaflammation caused by the omnipresent adipose tissue has been regarded as the main mechanism, but recently, attention has been drawn to the effects of the accompanying *dyslipidemia* (described as a separate risk factor).

General obesity was found significantly associated with preDM only in women in one study [48], whereas a *high birth weight* significantly increased the risk of T2D in males in another study among 759,999 Swedes aged 28–38 years [49].

March 2016 saw the publication of novel findings regarding growth/size in the first 4 years of life in children at genetic risk of T1D [50•]. Greater weight in the first years of life, particularly at 12 months and less than 3 months of exclusive breast feeding with *early introduction of gluten-containing food*, was associated with an increased risk of development of islet autoimmunity and development of multiple islet autoantibodies [50•], and in an estimated 70 % of children, the latter will progress to diabetes within 10 years.

Periodontitis and Diabetes *Adipokines* (*adipocytokines*)—such as *resistin*, *adiponectin*, *leptin*, and *adiponutrin*—may illustrate inflammatory mechanisms linking obesity, diabetes, and periodontitis. Resistin is reportedly expressed in GCF in all persons with both periodontitis and diabetes [127], whereas obese individuals have elevated levels of circulating leptin and GCF *TNF-α* [51]. Periodontal bacteria regulate and periodontal tissue cells express adipokines (*visfatin*, leptin, and adiponectin), so obesity may modulate levels of local GCF and systemic adipokines toward a pro-inflammatory state [51, 52], which promotes both diabetes and periodontitis incidence and severity.

Metabolic Syndrome

Metabolic syndrome (MetS) is diagnosed when at least three of the following five conditions are satisfied: (1) abdominal obesity, (2) hypertriglyceridemia, (3) decreased fasting high-density lipoprotein (HDL) cholesterol level, (4) hypertension, or (5) hyperglycemia [>100 mg/dl (5.6 mmol/L or HbA1c >5.6 %)]; 100–125 mg/dl or HbA1c 5.7–6.4 % is defined as "preDM" and ≥126 mg/dl or HbA1c ≥5.7 % as manifest (overt) diabetes.

Periodontitis *MetS* was reported to be a risk factor for incident periodontitis after 4 years among initially 75-year-old periodontitis-free Japanese [53], and a meta-analysis reported a strong association between the prevalence of MetS and periodontitis [128]. However, the study designs of 26 studies included in another review prevented determination of the direction of any effect [129].

The association between periodontitis and MetS seems to be similar in GDM and non-pregnant women [17], and *visceral adiposity* was associated with greater periodontitis risk in another study [54].

Diabetes *Abdominal obesity* is strongly associated with preDM in both sexes and was the strongest predictor for preDM in a comprehensive prediction model using NHANES 2001–2006 data from 2230 adults ≥50 years without manifest diabetes [55].

A *large waist circumference* is also shown to independently and significantly predict incident T2D in the Korean Healthy Twin Study, independently of BMI [14].

Hyperlipidemia

Periodontitis It has recently been proposed that hyperlipidemia (elevated blood level of one or more lipids: lipoproteins, triglyceride, fatty acids) plays a direct role in the development of periodontitis, independently of MetS. Cutler's team reported almost 20 years ago that poor glycemic control leads to elevated levels of serum triglycerides with adverse effects on every clinical measure of periodontal health [56•], which went largely unnoticed until lately.

Among 18,210 adult subjects in the Fourth Korea National Health and Nutrition Examination Survey (KNHANES), dyslipidemia in the forms of *hypertriglyceridemia* and *hypo-HDL* was associated with periodontitis overall [57].

Kalsi and colleagues propose a triangular link between hyperglycemia, *periodontitis*, and T2D [58] as they observed increasing hyperlipidemia with worsening oral glucose tolerance and poorer clinical periodontal health. Excess plasma levels of the free fatty acid *palmitate* induce inflammatory responses, such as secretion of cytokines and chemokines, as well as amplify *P. gingivalis*-induced chemokine secretion in human gingival fibroblasts in vivo. As well, hyperlipidemia contributes to periodontitis pathogenesis with the diet's specific content of *fatty acids* being more important than weight gain or obesity in rodent models.

Diabetes *Hyperlipidemia* is increasingly recognized as a major, independent, risk factor for incident T2D, not only as part of MetS. Hypertriglyceridemia, but not HDL or LDL levels, was found to significantly predict incident T2D in originally healthy Korean twins [14].

Periodontitis and Diabetes In 2015, Zhou and colleagues proposed a model that includes important roles of hyperlipidemia both in the development of diseases periodontitis and diabetes, respectively, and in their two-way interactions, mostly by enhancing expression of pro-inflammatory cytokines like TNF-α and *IL-1-β* [59••], also suggesting that periodontitis and diabetes each contribute to elevate blood lipid levels. With confirmation of this novel concept of hyperlipidemia being able to activate the immune response, mechanisms

underlying the links between periodontitis and diabetes/hyperglycemia need updating [130].

Medications

Periodontitis All major groups of the most commonly used pharmaceuticals have the propensity to lead to hyposalivation with dry mouth, which invariably causes buildup of dental plaque. Notably, persons with diabetes usually have several co-morbidities requiring medicine in addition to any antidiabetic drugs. Specific medications may also be associated with higher periodontitis risk due to other mechanisms, such as *aromatase inhibitors* causing low estrogen levels in breast cancer survivors [60] and gingival overgrowth due to the antihypertensive drugs *calcium channel blockers* (*nifedipine*, *diltiazem*, and *amlodipine*) combined with poor oral hygiene [61].

Diabetes A noteworthy side effect of several pharmaceuticals is elevation of blood glucose levels and, ultimately, incident T2D as well as higher diabetes complication rates. Importantly, this could be the case with the widely used *statins* [62], although currently disputed [131]. *Niacin* is associated with incident T2D, independently of statin regimen [63]. Moreover, a meta-analysis recently concluded that incident T2D risk is higher in youth taking *antipsychotic medications* compared to other psychiatric diseases and healthy controls [64].

Unhealthy Diet

Added Sugar

Only recently has evidence surfaced for consumption of added sugar—especially the high-fructose corn syrup that gradually has displaced cane and beet sugar as an inexpensive sweetener added to soft drinks, candy, and processed foods—may induce a *hyperinflammatory state*, possibly metaflammation. This chronic inflammatory state leads to *abdominal adiposity*, dyslipidemia, and *insulin resistance* [65••] in addition to general obesity and hence could represent a link between inflammation-related chronic diseases, including periodontitis and T2D. NHANES data show that *high-sugar-sweetened beverage* (*SSB*) consumption increases *oxidative stress* and *systemic inflammation* and is independently associated with biomarkers of inflammation-related chronic disease risk (CRP; total, HDL, and LDL cholesterol) [132]. Adult SSB intake is prevalent in up to half the adults and most common in 18–24 year olds and among lower SES groups [133].

Additionally, vapor from *e-cigarettes* contains unknown types and quantities of sugar and its effects need further investigation as a novel, increasingly popular source of hidden sugar.

Periodontitis A 2014 analysis of NHANES III data from 18 to 25 year olds reported high-frequency consumption of added sugars to be independently associated with bleeding on probing and periodontal probing depth 3+ mm [65••].

Culturing human periodontal ligament stem cells (PDLSCs) in media with four different glycemic concentrations showed that PDLSC proliferation and differentiation into osteoblasts were inhibited while gene expression of the pro-inflammatory cytokines IL-6 and *IL-8* increased in the high glucose concentrations [66].

Diabetes Mean sugar consumption is found to be independently associated with diabetes prevalence, and it is becoming evident that SSB intake not only does pose a risk for incident T2D via increased obesity, but also is a significant, independent risk, as concluded by two meta-analyses [67, 68] of which one reported a dose–response relationship [67]. Analyses of data from 175 countries calculated that every 150 kcal/person/day increase in sugar availability (~1 can of soda/day) was associated with 1.1 % increase in diabetes prevalence [69].

Prospective cohort studies agree that SSB consumption is associated with weight gain and causes metabolic risks [70]. Surprisingly, a longitudinal study of UK children specifically showed that *both artificially* and *sugar-sweetened* beverages were associated with increases in percentage body fat and BMI [71]. Unlike glucose, fructose is metabolized almost exclusively by the liver, leading to lipogenesis, non-alcohol fatty liver disease, and accumulation of visceral and ectopic fat that also increase T2D risk directly [72], although consuming too many calories overall plays a much greater role in the obesity epidemic [134].

A 2-year study of 564 Caucasian Canadian children with at least one obese parent showed no changes in obesity measures (fat mass, BMI, waist circumference) due to added sugar in liquid or solid form, whereas such sugar was a risk factor for incident *impaired glucose homeostasis* and insulin resistance [135].

Among 1893 children, total sugar intake was associated with T1D development only in children with the strongest T1D genetic risk [136].

Artificial Sweeteners

Periodontitis and Diabetes *Non-caloric artificial sweeteners* (NAS)—also called non-nutritive sweeteners (NNS) or artificially sweetened beverages (ASB)—are not found to be investigated in relation to periodontitis during the period under review. However, NAS turn out to change the composition and function of the *gut microbiome* and thus can cause *glucose intolerance* and *metabolic inefficiency* [74–76] and lead to increases in percentage body fat and BMI in children [71]. A meta-

analysis of longitudinal studies ($N = 191,686$) calculated a significant 28 % increase of incident T2D in those drinking *sugar-sweetened fruit juice* [77], contrary to no increased T2D risk for persons drinking *100 % fruit juice* in a similar meta-analysis ($N = 137,663$).

NAS may also interfere with learned responses regulating glucose control and energy homeostasis, as well as with *sweet taste receptors* expressed throughout the digestive system that play a role in glucose absorption and trigger insulin secretion [75]. Finally, NAS stimulates insulin secretion, which may explain the greater *adiposity* associated with NAS [76].

Alcohol and Other Non-Sugary Carbohydrates, Fat, and Meat

Periodontitis A 2016 meta-analysis including 18 observational studies concluded that alcohol consumption is associated significantly with increased periodontitis risk in both sexes [78]. However, women are especially susceptible, with those consuming alcohol having more than double the risk for periodontitis versus a 25 % increased risk for men. There was a linear dose-response relationship, with the risk of periodontitis significantly increasing by 0.4 % for each 1 g/day increment in alcohol consumption [78].

Diabetes A novel danger is posed by the increasingly popular habit of inhaling the hot vapor from smoke-free e-cigarettes that contain unknown and varying concentrations of *alcohol*.

Eating *potatoes*, particularly French fries, independently increased T2D risk in an analysis of three cohort studies of initially diabetes-free US health professionals totaling 3,988,007 person-years of follow-up, with a 4 % increased risk of incident T2D for each three servings per week increment over 4 years [80••]. As well, pre-pregnancy consumption of potatoes was independently associated with first GDM occurrence among 15,632 nurses [81].

Periodontitis and Diabetes Intake of meat, especially *red meat*, is included as an item in the "unhealthy diet" that has high inflammatory potential scored by the "Dietary Inflammatory Index (DII)" and hence may enhance incident *periodontitis* and T2D. Processed meat consumption was associated with elevated fasting plasma glucose (FPG), and unprocessed red meat was associated with both elevated FPG and FI levels only before controlling for BMI among 50,345 diabetes-free participants in 14 studies [83].

Nutrition, Minerals, and Vitamins

Periodontitis A healthy diet is declared important for a healthy periodontium [84], and several reports pertain to potential roles in human periodontal health of various individual nutrition components. Nonetheless, a 2014 systematic review found insufficient evidence to support the link between nutritional status and periodontal inflammation, although "*vitamin E, zinc, lycopene and vitamin B complex may have useful adjunct benefits*" [137].

Diabetes An abundance of reports pertains to the important roles of *diet* and *nutrition* in human insulin resistance and hyperglycemia/diabetes, for example: quantity and quality of *rice, resveratrol* supplements, *higher fiber* intake and lower *starch to fiber* ratio, *lignan metabolites* (especially *enterolactone*), *fruits* and *vegetables* (serum carotenoid concentrations), specific *whole fruits* (particularly blueberries, grapes, and apples), and *100 % natural fruit juice*.

Of special importance for *meat* eaters is the consistently reported increased risk of incident hyperglycemia due to dietary heme *iron* intake, in addition to eliciting inflammation [85]. Iron plays a catalytic role in forming hydroxyl radicals, which are powerful pro-oxidants that can severely damage pancreatic beta-cells that are particularly vulnerable to oxidative stress.

Additionally, overall *food insecurity* (limited or uncertain availability of nutritionally adequate and safe foods) in persons with T2D of low SES is shown to be associated with lower adherence to healthy lifestyle recommendations and poorer glycemic control [87].

Diet early in life may play a role in the development of T1D, with infants breastfeed for at least 12 months having lower risk of islet autoimmunity progressing to T1D, even in genetically predisposed children [88]. Furthermore, *attending daycare before age 2 years* increases the risk of T1D, whereas breastfeeding ameliorates this risk.

A 2015 hypothesis points to soil-derived *zinc* as the most important trigger for T1D in Finland that has the world's highest T1D incidence, followed by the Italian island Sardinia whose soil is similar to the Finnish [89].

Periodontitis and Diabetes Zinc is a component of insulin (a peptide hormone) and zinc deficiency—that, for instance, may be created when zinc is moving from serum into the liver during stress—can lower the bioavailability of ingested nutrients, and cause several metabolic problems, such as oxidative stress and impaired wound healing. Zinc deficiency is hypothesized to promote insulin resistance, T2D, *diabetes complications*, and periodontitis and is thought to mediate the relationship between periodontitis and T2D also by interfering with *vitamin C* levels and collagen formation [90].

Current Smoking

Periodontitis Cigarette smoking is the strongest independent risk factor for incident periodontitis and is estimated to cause about 20 % of all periodontitis cases in US adults 30+ years [91]. These representative population-based findings confirm those from a multitude of smaller studies in many population subgroups in many countries.

Smokers have *lower IgG antibodies* to oral bacteria, indicative of a compromised humoral immune response and higher levels of inflammatory markers such as salivary *IL-1β* and IL-6. As well, cigarette smoking affects the composition of the subgingival microbiome to include less bacterial diversity.

The use of alternative nicotine delivery modes is rapidly increasing, such as e-cigarettes with "vaping" thousands of different concoctions of unknown ingredients, often in addition to nicotine. Regardless of e-cigarette vapor nicotine content, e-cigarette vapor is cytotoxic to epithelial cell lines and causes breaks in DNA strands [92], also in human gingival fibroblasts.

Diabetes A 2015 meta-analysis of 84 cohort studies (N = 5,853,952) calculated that initially diabetes-free smokers had 37 % higher risk for developing T2D than never smokers in a dose-dependent relationship [93]. For instance, data from current, former, and never smokers of European ancestry found cigarette smoking to cause larger waist circumferences for a given BMI, and the mean HbA1c level was related to smoking in a dose-dependent manner, that is, by decreasing HbA1c from current smoking via former smoking to never smoking. Importantly, current smoking is found related to decreased *pancreatic beta-cell function* in a dose-dependent manner [94, 95].

Environmental Tobacco Smoke

Periodontitis In lifetime nonsmokers, high exposure to environmental tobacco smoke (ETS), also known as secondhand or passive smoke, predicts periodontitis risk and the prevalence of moderate/severe periodontitis increased with ETS in a dose-response manner [96]. Nonetheless, a 2014 systematic review concluded the ETS-periodontitis association is still debatable [138].

Diabetes A 2015 meta-analysis of seven prospective studies (N = 156,439) concluded that never smokers exposed to ETS had a 22 % higher risk for incident T2D [93].

Sedentary Lifestyle

Periodontitis Among sedentary men aged 45 to 65 years, low levels of *cardiorespiratory fitness* were independently associated with moderate and severe periodontitis [97].

Diabetes *Lack of physical activity* is a traditional risk factor for hyperglycemia and other adverse metabolic conditions [139], with five systematic reviews of longitudinal studies agreeing that sedentary behavior is a significant risk factor for T2D [98].

Sleep Disturbances

Periodontitis In NHANES 2009–2012 (N = 3,740), an unadjusted association between *usually sleeping less than 7 h* and periodontitis was reported [99], and among US Hispanics (N = 12,469), Sanders' team found *disordered breathing during sleep* to be independently associated with severe periodontitis [100].

In 2009, an Australian team identified the novel, strong association between *obstructive sleep apnea* (*OSA*) and periodontitis [101], a finding that is confirmed in studies in several countries and subgroups. OSA risk is found associated with moderate/severe periodontitis [102] and gingival bleeding during brushing [39].

Diabetes As recently as in 1999, it was surprisingly, but scientifically, discovered that *sleep deprivation* strongly affects metabolic and endocrine function similarly to normal aging [140] and may even increase the incidence of chronic diseases such as obesity and diabetes [141] due to influencing stress-related gene expression, increased systemic inflammation, and metabolic imbalance.

Categories of sleep disturbances that contribute to obesity and its glycemic co-morbidities include [142]: alterations of sleep duration, including chronic sleep restriction and excessive sleep; alterations in sleep architecture; sleep fragmentation; circadian rhythm disorders and disruption (i.e., shift work); and OSA.

A 2016 study of 133,353initially healthy nurses followed over 10 years reported incident T2D to be significantly associated with *sleeping difficulty* [103]. Women suffering simultaneously from sleeping difficulty, *frequent snoring*, *sleep duration ≤6 h*, and *sleep apnea or rotating shift work* had more than four times the likelihood of developing T2D.

Stress, Depression, Anxiety, Poor Coping Skills, and Allostatic Load

Periodontitis The concept *allostatic load* refers to physiologic consequences of neural, neuroendocrine, and immune reactions ("wear and tear on the body") by chronic or repeated exposure to stress [143] and has been linked to poorer periodontal health in minorities. Among Peruvian 30–65 year olds, higher salivary levels of the stress marker *cortisol* were seen with moderate periodontitis compared to mild periodontitis, and periodontitis was fourfold more likely in high-cortisol-level participants [105]. Nonetheless, even though studies report associations

between *stress* and periodontitis or *depression level* and severity of periodontitis, even in a dose-response manner [104], a 2016 meta-analysis failed to demonstrate a significant association between depression and periodontitis [144].

Diabetes In the entire Swedish national cohort of 1,534,425 initially diabetes-free military conscripts followed up to age 62 years (39.4 million person-years), incident T2D was strongly and independently associated with low *stress resilience* [106].

Demmer's team analyzed data from two large US cohort studies among adults and reported *depression* to be predictive of T2D only in women [107]. Results from national surveys about 12 years apart of the same 3604 Germans initially aged 18–79 years demonstrated that people who lived on extremely busy roads (increasing levels of stress and its subsequent allostatic load) had twice the risk for incident T2D compared to those living on moderately busy side streets [108].

Pregnancy is a *stressor* for the pregnant woman and is a risk factor for GDM and incident T2DM [21••].

Low (Oral) Health Literacy

Low *literacy* rates, lower *health* literacy rates, and even lower *oral* health literacy rates and their resulting low knowledge and understanding of the diseases and their treatment are, in general, grossly overlooked as risk factors for health and health care processes and outcomes. In the US National Assessment of Adult Literacy (NAAL), less than half scored at the *proficient* level [145]. Among the questions were a subset specifically designed to assess health literacy, defined as "The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" [146••]. One in seven (14 %) possessed *below basic*, 22 % *basic*, 53 % *intermediate*, and 12 % proficient health literacy [146••]. The only 12 % scoring at the proficient level leaves 88 %—nearly 9 in 10—with less than proficient health literacy. Over a quarter (27 %) of persons receiving Medicare health insurance for adults 65+ years and 30 % of persons in receipt of Medicaid (health insurance for low-income individuals) had below basic health literacy [146••].

Periodontitis Lower oral health literacy was significantly associated with periodontitis severity in 121 highly educated persons in North Carolina [109].

Diabetes A 2013 systematic review of health literacy and health outcomes in diabetes concluded that poorer *knowledge of diabetes* was consistently seen with low health literacy [110]. For instance, poor understanding of the evidence-based concepts of their disease even upon explanatory interventions is reported among people with T2D and unintentional *non-adherence* to diabetes medications in T2D was associated with limited health literacy. Finally, a 2016 meta-analysis of 98 studies concluded that *health literacy* and *health beliefs* significantly affected *adherence to glucose-lowering medication* [111]. Such poor comprehension and non-adherence may facilitate the development as well as increase the severity of disease.

Environment, Pollution

Periodontitis A Korean study reported that serum concentrations of the hazardous heavy metals *cadmium* and *lead* were significantly associated with periodontitis [112], presumably due to increased oxidative stress and inflammation.

Diabetes Understanding the role of *endocrine-disrupting chemicals* in causing diabetes by altering *insulin production* is developing [113]. Human pancreatic beta-cells were exposed for 1 month to three concentrations of the still prevalent pesticide dichlorodiphenyltrichloroethane (DDT), an endocrine disruptor banned in 1970 in the developed world. Several proteins were downregulated and hence stressing protein expression in pancreatic beta cells similarly to exposure to palmitate, hyperglycemia, *imidazoline derivative*, and *cytokines*, all of which cause *diminished insulin production* [113]. Environmental pollutants may also cause insulin resistance.

A 2013 systematic review of 29 epidemiologic studies of *environmental chemicals* found suggestive evidence for associations between diabetes and *arsenic* and *persistent organic pollutants*, respectively, but insufficient evidence for such links to *mercury*, *phthalates*, and *bisphenol A* and no evidence for cadmium [114]. For example, examination of biomarkers of diabetes and systemic inflammation as well as persistent organic pollutants (*POPs*) in consumers of the US Great Lakes sport caught fish revealed that odds of incident T2D were elevated with exposure to *p,p-dichlorodiphenyldichloroethylene*(*DDE*) and *polychlorinated biphenyls* (*PCBs*), with POPs possibly affecting more strongly individuals at risk for diabetes.

A 2014 meta-analysis of 23 studies on *organochlorine pollutants* (*OCPs*) concluded that OCP exposure is associated with heightened risk for T2D development [115].

Probably illustrating the importance of *lifestyle*, *environment*, and *SES combined*, a meta-analysis including six studies among 75,498 couples concluded that *spousal diabetes history* was associated with a 26 % increase in diabetes risk [116].

Conclusion

Modifiable risk factors for chronic periodontitis and diabetes mellitus are largely identical and can be regarded as lifestyle factors that are intrinsically intertwined and inseparable. Lifestyle is not solely behavioral in nature but has biologic consequences as seen in the allostatic load. The Healthy Lifestyle Score (HLS) introduced in 2015 includes the five lifestyle components: (1) diet, (2) physical activity and sedentary behaviors, (3) smoking, (4) social support and network, and (5) sleep [147]. The HLS is associated with risk for MetS, allostatic load, and cardiometabolic and neuroendocrine factors and is associated with the inflammatory markers IL-6, TNF-α, and CRP [148]. As well, prior psychological distress is recently suggested to impact health risks later in life, despite the stress having subsided [149], and repeated stressful experiences with chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system cause epigenetic mutations, neuroendocrinologic alterations, impaired immune system function and lipid metabolism, hypertension, and depression [150].

Elevation of blood glucose levels is a normal, biologic part of the host immune response's inflammatory cascade responding to microbes in the periodontal pockets from which they also may travel around the body [122] and contribute to the cumulative bacterial load in the body. Any surplus glucose will eventually be converted into adipose tissue that, in itself, functions as an organ that contributes to the metaflammation, which in turn causes metabolic changes, in a vicious cycle.

When taking into account all the non-modifiable [1] and modifiable risk factors reviewed, it is becoming increasingly tempting to speculate that all the chronic inflammation-based conditions are part of the same cluster of cumulative, age-related, chronic diseases that are related to a compromised immune system weakened by an unhealthy lifestyle and environmental stressors. Might there exist an inflammation-based periodontitis-insulin resistance-adiposity-hyperglycemia-renal disease-atherosclerotic cardiovascular disease-rheumatoid arthritis-impaired cognition ("brain diabetes")-cancers axis, which several individual diagnoses each reflect parts of? One wonders: *Could periodontitis and T2D both be considered inflammatory* (*potentially even autoimmune as T1D?*) *diseases that are manifested over time due to poor biologic and psychologic coping skills in response to micro- and macro-level stressors?*

Regardless of any terminology used for the underlying processes, the enlightened dental care professional (who is aware of the multifactorial nature and interactions of risk factors for periodontitis and diabetes mellitus) is well positioned to contribute—in a patient-centered, interprofessional health care team approach—to the betterment of the oral health, general health, and, ultimately, the quality of life of the population.

Compliance with Ethical Standards

Conflict of Interest Wenche S. Borgnakke declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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education level. Yet, proper patient communication is imperative for health professionals who must adjust their messages according to the patient's comprehension level.

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