Oral Manifestations of Diabetes

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David Dean and Beatrice Gandara

Abstract

The classic pathophysiologic features of diabetes mellitus (DM), including immune dysregulation, vasculopathy, and neuropathy, predispose diabetic individuals to numerous oral complications. Individuals with diabetes are at increased risk for periodontal disease, salivary gland dysfunction, dental caries, mucosal abnormalities, and oral burning, all of which can negatively impact patient quality of life. The bidirectional relationship between diabetes and periodontal disease is of particular importance due to the negative effect of periodontitis on glycemic control and the potential benefit of periodontal therapy on glycemic control. Emerging evidence has also identified decreased healthcare costs in diabetic individuals receiving regular periodontal therapy. Unfortunately, despite the numerous oral manifestations of diabetes and their potential impact on systemic health, many diabetic individuals are not fully aware of the relationship between their diabetes and oral health. Close collaboration between the medical and dental team can positively benefit the diabetic population through early diagnosis and management of the oral complications of diabetes.

Keywords

Diabetes • Periodontitis • Hyperglycemia • Diabetes complications • Candidiasis • Dental caries • Stomatitis • Salivary dysfunction

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D. Dean (✉) • B. Gandara
Department of Oral Medicine, University of Washington School of Dentistry, Seattle, WA, USA
e-mail: ddean2@uw.edu

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Diabetes and Periodontal Diseases

Periodontal disease is the most widely recognized oral complication of diabetes mellitus. The robust body of literature connecting the two conditions has led periodontitis to be recognized as the sixth complication of diabetes [1, 2]. Periodontal disease represents a spectrum of diseases ranging from reversible gingival inflammation to advanced periodontitis, in which the prognosis of teeth is compromised through the irreversible loss of bone and connective tissue support.

Gingivitis

In health, gingival tissues lie directly adjacent to teeth and appear firm in consistency. Tissue color ranges from pink in light-skinned individuals to brown in those with darker skin tones. Gingival health is compromised by the accumulation of bacterial plaque and mineralized calculus on the surfaces of the teeth which triggers a local immune response. Bacterial by-products activate monocytes and macrophages within the gingival tissues which release inflammatory mediators such as cytokines and prostaglandins. Clinically, gingival inflammation produces characteristic tissue changes including erythema, edema, and altered gingival contour. Gingivitis is generally asymptomatic; however, manipulation of the gingiva through brushing, flossing, or periodontal probing will often produce bleeding. Effective removal of dental plaque and/or calculus will resolve gingivitis with no long-term complications (Fig. 1) [3, 4].

Observational studies have consistently shown greater prevalence of gingivitis in patients with type 1 and 2 diabetes when compared to control subjects [5–8]. There is also evidence to suggest that the severity of gingival inflammation varies with glycemic control [5, 9, 10]. A clinical study of experimentally induced gingivitis in individuals with type 1 diabetes (and HbA1c >8.1%) identified higher incidence, greater severity, and earlier onset of gingival inflammation than that seen in age–gender-matched controls [10]. Prospective studies in children and adolescents have demonstrated greater incidence of gingivitis in subjects with poor glycemic control independent of oral hygiene effectiveness [6, 8, 11].

Periodontitis

In contrast to gingivitis, periodontitis results in irreversible loss of a tooth's foundational support and is the leading cause of tooth loss in the United States [12]. Gingivitis always precedes periodontitis; however, gingivitis will only progress to periodontitis in susceptible individuals [3, 13]. Susceptibility is multifactorial and is influenced by personal, environmental, and physiological factors, including age, smoking, diabetes, and genetic predisposition [3, 14–17].

In susceptible individuals, prostaglandins and pro-inflammatory cytokines initiate a cascade of inflammatory events which result in damage to host tissues. In early periodontitis, chemokines recruit polymorphonuclear leukocytes (PMNs), primarily neutrophils, to the periodontium in response to a bacterial challenge. Neutrophils attempt to eliminate bacteria through phagocytosis, release of noxious antimicrobial molecules, and amplification of the host inflammatory response. Unfortunately, chronic inflammation produces collateral damage to nearby tissues. Increased secretion of proteolytic enzymes known as matrix metalloproteinases (MMPs) causes breakdown of the alveolar bone and connective tissue fibers that surround the roots of the teeth. The loss of these structures creates a "periodontal pocket" which cannot be effectively cleaned without a professional dental cleaning. If left untreated, the microbial population within these pockets will transition to a more virulent group of anaerobic periodontal pathogens which can also cause tissue damage. Clinical

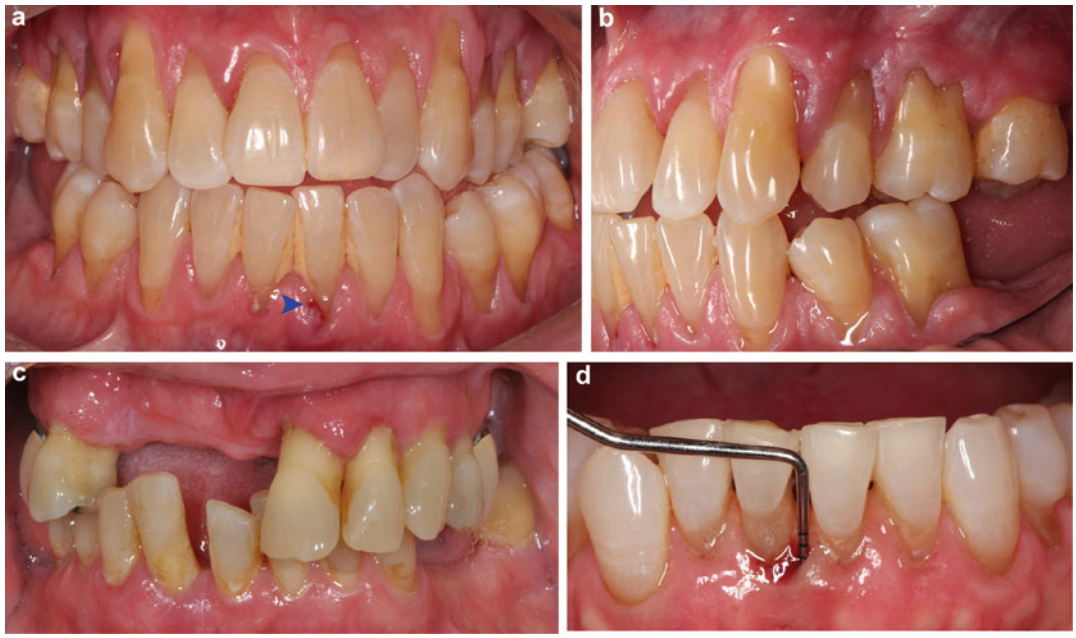

Fig. 1 Periodontitis. Clinical signs of periodontitis. (**a**) Gingival recession and root exposure. Note localized gingival bleeding in areas of calculus accumulation (*blue arrow*). (**b**) Anterior and posterior gingival recession with blunting of the interproximal papillae. (**c**) Generalized periodontal bone loss with spacing, rotation, and partial edentulism. (**d**) A 10 mm periodontal probing depth identified using a WHO probe (healthy tissues generally exhibit measurements <3 mm). Bleeding on probing indicates active inflammation (Photographs courtesy of Dr. Russell Johnson)

manifestations of this disease process include swollen/boggy gingiva, gingival recession, root exposure, tooth mobility, and ultimately tooth loss (Fig. 1) [18]. Early recognition of periodontitis, and referral to a dental professional for appropriate management, can help to minimize the oral and potential systemic consequences of the disease.

Diabetes and Periodontitis

Periodontal disease, like diabetes, is highly prevalent in the United States. The Centers for Disease Control and Prevention estimates that periodontitis affects 47.2% of adults over age 30 and 70.1% of adults over age 65 in the general population [19, 20]. Diabetes has long been recognized as a risk factor for periodontal disease and the relationship between the two conditions appears to be bidirectional. The literature in this area has previously been examined in numerous narrative reviews [21–25], systematic reviews [26, 27], and meta-analyses [28, 29]. Studies have consistently demonstrated a negative effect of moderate-to-severe periodontitis on glycemic control [24–27, 30–32]. One of the most well-known studies in this area examined individuals from the Gila River Indian Community in Arizona. In this population, subjects with diabetes and severe periodontal disease had a six times greater risk of poor glycemic control (HbA1c >9%) than diabetic subjects without severe periodontal disease [33]. Similarly, a study in nondiabetic individuals identified a 1.47 prevalence ratio for prediabetes (HbA1c = 5.7–6.4%) in subjects with moderate-to-severe periodontitis when compared to those with healthier periodontal tissues [34]. Reciprocally, diabetes has been associated with numerous measurements of periodontitis including alveolar bone loss [35–38], clinical attachment loss [28, 29, 39, 40], and increased periodontal probing

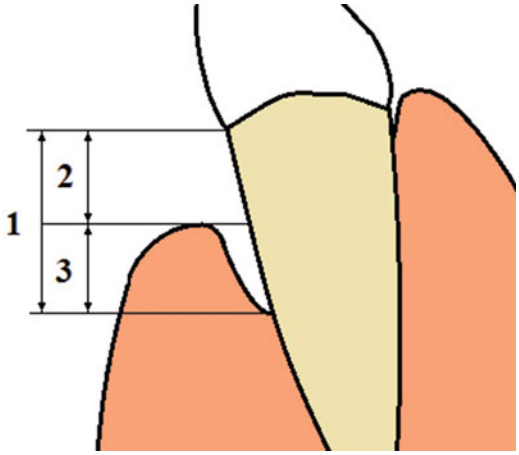

Fig. 2 Clinical measurements of periodontitis. (*1*) Clinical attachment loss (*CAL*) is the distance from the cementoenamel junction (*CEJ*) to the base of the gingival sulcus. Measurements >3 mm are indicative of periodontal disease and are termed "periodontal pockets." (*2*) Gingival recession is the distance from the CEJ to the crest of the gingiva. (*3*) Periodontal probing depth (*PPD*) is the distance from the crest of the gingiva to the base of the gingival sulcus (Illustration courtesy of Wikimedia Commons)

depth (Fig. 2) [28, 29, 39]. In contrast, individuals with quality glycemic control appear to have lower prevalence of severe periodontitis [39].

The association between periodontal disease and gestational diabetes is less clear and is discussed in depth in the "Diabetes, Pregnancy, and Oral Health" section later in this chapter.

Potential Physiologic Impact of Diabetes on Periodontal Disease

The pathophysiology of diabetes mellitus includes multiple factors which may impact the periodontium, most notably compromised immune defenses [41–51] and aberrant host inflammatory responses [18, 52, 53].

Compromised immune defenses in patients with diabetes negatively impact the periodontium, via the action of PMNs as outlined in detail earlier in this chapter [3, 54]. PMNs, particularly neutrophils, are the predominant cell type involved in the elimination of periodontal pathogens. Studies in humans and animal models have confirmed decreased chemotaxis and altered bactericidal function of PMNs in patients with diabetes [45, 48–50, 55]. Diabetic rats exposed to a microbial challenge have demonstrated decreased migration of neutrophils to the periodontium when compared to nondiabetic animals [56]. This suggests that diabetes negatively affects the host's ability to effectively mobilize antimicrobial defenses. Furthermore, PMNs isolated from patients with diabetes and periodontitis have been shown to be less effective in eliminating periodontal pathogens than PMNs isolated from individuals with normal glycemic control [47]. Taken together these results suggest a higher risk for progressive infection due to altered immune function. Additionally, diabetes alters the function of PMNs, resulting in the production of higher levels of superoxide radicals, neutrophil extracellular traps (NETs), and inflammatory cytokines which in turn compromise wound healing and increase damage to host tissues [47, 51, 55].

Numerous clinical and laboratory studies have examined the effects of inflammatory cytokines in diabetes-related periodontitis [57, 58]. Experiments in murine and rat models have identified elevated production of inflammatory cytokines, altered bony metabolism, and exaggerated periodontal bone loss in diabetic model organisms with ligature-induced periodontitis [53, 59–61]. Diabetic rats inoculated with the periodontal pathogen *Aggregatibacter actinomycetemcomitans* have been shown to produce higher levels of tumor necrosis factor (TNF)-alpha (a pro-inflammatory cytokine) in the gingival and periodontal tissues compared to nondiabetic controls. In the same study, diabetic animals exhibited more than twice the periodontal cell death and 1.7 times the alveolar bone loss when compared to their nondiabetic counterparts [62]. Inversely, inhibition of TNF-alpha (a pro-inflammatory cytokine) has been shown to enhance bone repair and increase bone formation in rats with type 2 diabetes [53].

The pathogenesis of diabetes also appears to be closely related to the formation of advanced glycation end products (AGEs). Comprehensive reviews by Lalla and Papapanou [30] and Taylor, Graves, and Lamster [63] discuss the potential

influence of AGEs on the progression of periodontitis. Briefly, laboratory studies have identified a negative effect of AGEs on fibroblast function and survival [64–66] which are necessary for the maintenance of gingival and periodontal ligament fibers. Investigators have also demonstrated a dose-dependent decrease in bacterial-induced periodontal bone loss in a diabetic murine model after administering an agent to block AGE-RAGE signaling [57]. Preservation of bone and connective tissue structure is of paramount importance in maintaining periodontal health, suggesting an important role of glycation end products in the pathophysiology of periodontal disease.

Bacterial pathogens are necessary to induce periodontal disease. Most studies have identified similar microbial species in subjects with and without diabetes [10, 22, 32, 63, 67, 68]; however, several studies using more sophisticated laboratory techniques have identified elevated levels of periodontal pathogens in diabetic individuals [69, 70]. A more virulent microbial community would imply an even greater indication for periodontal therapy in patients with diabetes.

Periodontal Therapy and Glycemic Control

A large body of evidence supports the conclusion that chronic periodontitis has a detrimental effect on glycemic control in individuals with diabetes and prediabetes [26, 34, 71]. As a result, there has been a significant scientific interest in the potential effect of periodontal therapy on glycemic control. Meta-analyses have consistently shown an approximately −0.4% change in glycosylated hemoglobin following periodontal scaling for up to 4 months following therapy. The average improvement in meta-analyses has ranged between −0.29% and −0.79% [72–79]. The recent joint consensus report from the European Federation of Periodontology and American Academy of Periodontology noted that a 0.4% reduction in HbA1c has "...a clinical impact equivalent to adding a second drug to a pharmacologic regime for diabetes" [31, 80]. In contrast to these findings, a recent multicenter randomized control trial published in *JAMA* did not show improvement in glycemic control in type 2 diabetic individuals following periodontal scaling [81].

Periodontal Disease and Incident Diabetes

Researchers have also questioned whether the presence of periodontal disease can predict incident diabetes, though studies in this area are limited. A recent epidemiologic study in South Korea identified impaired beta cell function in patients with periodontal disease regardless of diabetic status. The authors questioned whether the periodontitis may predispose to impaired glycemic control [82]. In this vein, multiple prospective studies have identified increased risk of incident hyperglycemia in subjects with deep periodontal probing depths at baseline [26, 83–85]. The largest included over nine thousand subjects screened as part of the National Health and Nutrition Survey (NHANES I). Subjects with periodontal disease at baseline had an odds ratio of 2.32 for incident type 2 diabetes developing $\geq$ 10 years after baseline examination (after controlling for age, sex, race, and education level [83]. Conversely, a Japanese study of 5848 individuals failed to show a relationship between periodontitis and incident diabetes after adjusting for confounding factors [86]. A second Japanese study examined the results of glucose tolerance tests administered to a subgroup of 591 adults at baseline and again at 10-year follow-up. Individuals with normal oral glucose tolerance at baseline who were found to have impaired tolerance on repeat testing were more likely to have deeper periodontal pockets at the follow-up examination (OR = 2.6). Periodontal data were not obtained at baseline [87].

Periodontal Disease and Metabolic Syndrome

Metabolic syndrome is a clinical entity defined by the co-occurrence of diabetes/elevated fasting

plasma glucose, hyperlipidemia, hypertension, and abdominal obesity [88]. Researchers have examined the potential association between periodontitis and metabolic syndrome. A recent meta-analysis by Nibali and colleagues identified studies from Europe, Asia, and North and South America associating periodontitis and metabolic syndrome. As part of their analysis, the authors applied strict periodontal disease classification criteria in attempts to reach a more accurate conclusion about the potential association between periodontitis and metabolic syndrome. When these "secure" criteria were applied, they detected an odds ratio of 2.09 for metabolic syndrome in subjects with periodontal disease. The vast majority of studies in the meta-analysis were case–control and cross-sectional studies. A single longitudinal study was conducted in Japan by Morita and colleagues [89]. The researchers examined laboratory values involved in the diagnosis of metabolic syndrome to determine whether periodontal status at baseline was associated with the development of metabolic syndrome at 4-year follow-up. The presence of deep periodontal probing depths at baseline was significantly associated with elevation in blood pressure (OR = 1.5; 1.0–2.3, $p < 0.05$) and blood lipids (OR = 1.9; 1.1–3.2) at follow-up. Hyperglycemia narrowly missed statistical significance (OR = 1.4; 1.0–2.1; <0.056).

Smoking and Periodontitis

Periodontal intervention is especially important in diabetic individuals who are active smokers. Literature in periodontal risk assessment suggests that smoking and diabetes are "the most significant factors in modifying the host's response to biofilm infection [90]."

Smoking has a dose-dependent relationship with periodontal disease and is the most important modifiable risk factor in the development and progression of periodontitis [17, 90, 91].

Periodontal literature evaluating the effect of smoking in the diabetic population is limited but appears to show a synergistic effect on periodontal breakdown. A Finnish study of 149 insulin-dependent diabetic subjects found a relative risk (RR) for periodontitis of 12.34 in smokers with HbA1c > 8.5% (compared to RR of 4.15 in the smokers regardless of glycemic control). Similarly, a study in Turkey evaluating subjects with periodontal disease found smokers with type 2 diabetes mellitus to have greater periodontal attachment loss than nonsmokers regardless of diabetic status [92].

Smoking may also influence an individual's response to periodontal therapy. Smokers with periodontal disease appear more resistant to therapy than nonsmokers [90, 91]. This is especially important in the diabetic population, as both diabetes and smoking negatively impact the healing capacity of the periodontium [93]. Though data are limited, prospective studies indicate that patients who are able to successfully eliminate tobacco use show better response to periodontal therapy over a 12-month period [94–96].

Periodontal Disease and Diabetes Complications

Periodontal disease may also place individuals at higher risk for systemic complications of diabetes [26]. A prospective study examining Japanese adults with diabetes detected the highest rate of hospital admission for subjects with severe periodontal disease at baseline. As a group, diabetic subjects with severe periodontal disease incurred a 21% greater health expenditure than those with healthier periodontal status over a 3.5-year period [97].

Major health complications were also reported by Saremi and colleagues. In a prospective study of Pima Indians with type 2 diabetes, all-cause mortality was found to be proportional to severity of periodontitis at baseline. Individuals with severe periodontal disease had a mortality rate of 28.4 deaths per 1000 person-years compared to 19.6 in subjects with moderate periodontal disease and 3.7 in those with no disease to mild disease on initial exam. Periodontal disease was statistically associated with death due to ischemic heart disease and diabetic nephropathy [98]. A second study examining individuals from the same

community concluded that the severity of periodontal disease at baseline was predictive for the development of end-stage renal disease (ESRD), with odds ratios of 2.0 (moderate periodontitis), 2.1 (severe periodontitis), and 2.6 (edentulism) [99]; however, the definition of periodontitis employed in the study has been questioned [100].

Additional studies have reported a relationship between periodontitis and the cardiovascular and renal complications of diabetes. A Swedish case–control study examining adults with insulin-dependent diabetes found a statistical relationship between baseline periodontitis and numerous cardiac and renal complications of diabetes including angina, myocardial infarction, stroke, and proteinuria [101]. Southerland and colleagues found an increased risk for coronary artery disease (OR = 2.6), intimal-medial thickening of the carotid (OR = 2.2), and acoustic shadowing (OR = 2.6) in patients with concurrent diabetes and severe periodontitis when compared to subjects without either condition. Finally, a recent study of a geriatric cohort in the United States detected elevated cardiovascular disease mortality (OR = 2.16) in subjects with clinical attachment loss consistent with periodontitis at baseline (>3 mm).

The potential association between diabetic retinopathy and periodontal disease has also been assessed in several studies. A study in India identified greater periodontal probing depth and clinical attachment loss in diabetic patients with retinopathy; however periodontal measures were not predictive of the severity of retinal disease [102]. In contrast, a Japanese group concluded that the degree of periodontal disease was predictive of retinal complications. Specifically, the authors reported an elevated risk for proliferative diabetic retinopathy in subjects with periodontal disease (OR = 2.80). They also identified a correlation between the severity of periodontitis and levels of the inflammatory cytokine IL-6 in the vitreous fluid of the eye [103], though the definition of periodontitis in the study was unclear.

Observational studies have also shown an association between diabetic peripheral neuropathy and periodontal disease. Borgnakke and colleagues recently published a detailed review of this literature and proposed a physiologic connection between hyperglycemia, chronic inflammation, and the effects on these distant target tissues [104].

A single study has also reported podiatric complications in diabetic individuals with periodontal disease. In the study subjects with diabetes and moderate-to-severe periodontal disease had an adjusted odds ratio of 6.6 for the development of diabetes mellitus-associated neuropathic foot ulcerations [105].

Diabetes, Pregnancy, and Oral Health

The reproductive hormone changes that occur during normal pregnancy can have a profound effect on periodontal tissues. As discussed earlier, diabetes mellitus is also associated with inflammation of the gingiva and periodontitis. Therefore the likelihood of a combined effect of pregnancy and diabetes on the periodontium is very high.

During pregnancy the gingiva becomes much more reactive to plaque resulting in an accentuated inflammatory response compared to that seen in the nonpregnant state [106–108]. This is manifested in conditions such as pregnancy gingivitis (Fig. 3), which occurs in about 25–75% of women, and pregnancy granulomas of the gingiva, which occur in about 5% of pregnant women [109, 110]. These conditions normally regress in the few months after delivery when the hormone levels return to normal.

The pregnant state also exacerbates the inflammatory processes in periodontal disease, which results in more serious outcomes. Substantial evidence exists to support the association of periodontitis with adverse pregnancy outcomes such as preterm birth, low birth weight infants, and preeclampsia. This relationship was brought to light in a case–control study of 124 pregnant subjects by Offenbacher et al. in 1996, which showed that severe periodontal disease was associated with a sevenfold increase in risk of low birth weight, after controlling for smoking, alcohol use, age, race nutrition, and genitourinary disease [111].

Several mechanisms for this association have been proposed based on the discovery of

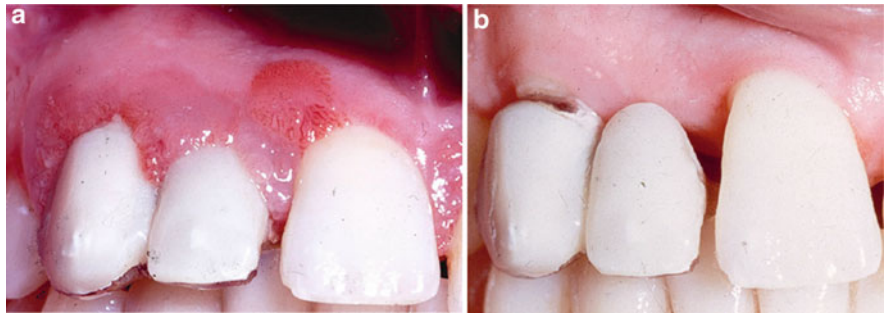

Fig. 3 Gingivitis. Gingivitis is characterized by erythema and edema of the gingival tissues. Gingival inflammation is most often a result of the cellular response against accumulation of bacterial plaque and calculus. (**a**) *Pretreatment*: Hormonal changes during pregnancy exacerbate preexisting inflammation. Note the "boggy" appearance of the tissues in the pretreatment photograph. (**b**) *Posttreatment*: Removal of plaque and calculus by scaling and root planing has led to resolution of inflammation. The tissue appears as a healthy *pink* color. Note that the tissues appear "tight" and are no longer overlapping the cervical region of the teeth (Photograph courtesy of Dr. Beatrice Gandara)

periodontal pathogens such as *Fusobacterium nucleatum*, *Campylobacter rectus*, *Porphyromonas gingivalis*, and *Bergeyella* sp. in the fetal–placental unit [112]. One possible mechanism is by direct bacterial challenge with contamination of the fetal–placental unit by hematogenous dissemination of oral microorganisms. Another possible mechanism is the transport of inflammatory mediators such as interleukins, prostaglandins, tumor necrosis factor, or lipopolysaccharides from the inflamed periodontium via circulation to the fetal–placental unit [112–114]. This can lead to placental inflammation and oxidative stress that result in placental damage, initiation of preterm delivery, low birth weight infants, or preeclampsia [115].

Despite the recognized bidirectional relationship between diabetes and periodontal disease, relatively few studies have focused on the impact of periodontitis in the pregnant patient with preexisting diabetes. In one such study of 30 pregnant women with diabetes (type not specified) and 33 pregnant women without diabetes, the diabetic group had increased indices of caries activity, plaque formation, gingivitis, and periodontitis compared to the control group. Saliva from the diabetic pregnant women had increased concentrations of inflammatory cytokines, chemokines, and cytokine receptors [116].

The majority of studies involving diabetic pregnant women have investigated the relationship of gestational diabetes mellitus (GDM) and periodontitis. Two studies utilizing large data sets collected in the NHANES III study found that pregnant women who had GDM and DM were more likely to have periodontal disease than the GDM-negative groups [117, 118]. In two smaller case–control studies, one found that 77.4% of pregnant women with GDM had periodontitis versus 57.5% of non-GDM pregnant women [119]. The other study found that 50% percent of the pregnant women with GDM had periodontitis compared to 26% of the controls [120].

In an investigation to monitor the interactions of gingivitis and GDM with respect to oral infection and the systemic inflammatory burden, GDM was associated with increased infection with oral pathogens (all $p < 0.05$). Additionally, gingivitis during pregnancy led to a 325% increase in systemic CRP (mean, 2495 vs. 8116 ng/ml, $p < 0.01$) [121]. In other studies, periodontal disease occurred more frequently in GDM patients but this difference failed to reach statistical significance [122–125].

Despite the amount of scientific evidence that supports a connection between periodontitis and adverse pregnancy outcomes, well-conducted intervention studies of nonsurgical periodontal therapy delivered during the second trimester have not consistently shown a significant effect on pregnancy outcomes. In a large study of

pregnant women with preexisting periodontal disease, who received either nonsurgical periodontal therapy during the second trimester or no treatment, there were no significant differences in rates of preterm birth or low birth weight infants. The study also found significant improvement in clinical measures of periodontal disease resulting from nonsurgical therapy during pregnancy while not increasing risk of adverse medical events [126].

One possible explanation for the lack of effect of periodontal therapy on adverse pregnancy outcomes may be that the complex risk factors relating periodontal disease and adverse outcomes cannot be solely addressed without other concurrent interventions. Additionally, studies examining periodontitis and birth outcomes have not always addressed preexisting diabetes as a confounder [114]. Another possibility is that periodontal therapy is being delivered too late in pregnancy to have a positive effect on pregnancy outcomes. Clearly, more studies are necessary that take into account preexisting diabetes and periodontal disease and other risk factors such as maternal age, obesity, race, and smoking history [114, 126, 127].

Diabetes mellitus in itself is associated with increased incidence of negative oral changes such as stomatitis, candidiasis, decrease in salivary flow and buffering capacity, neuropathic burning mouth sensations, caries, and periodontitis. These are thought to be caused by pathophysiologic mechanisms of diabetes such as chronic inflammation, oxidative stress, compromised immune function, neuropathy of the salivary glands and mucosa, and vasculopathy. Pregnancy also increases the risk for negative oral changes such as gingivitis and decrease in salivary flow and buffering capacity, thought to be caused by sex hormone alterations during pregnancy that impact the immune host response and vasculature of the periodontium and salivary glands. Diabetes and pregnancy together may potentiate greater oral problems, placing the pregnant diabetic patient at particularly increased risk for oral disease and adverse pregnancy outcomes. Therefore, coordinated management of oral healthcare by dental and perinatal healthcare providers is recommended for the diabetic pregnant patient.

Diabetes and Salivary Gland Function

Salivary Glands and Their Function

Saliva is an aqueous fluid produced by the three major paired salivary glands (parotid, submandibular, and sublingual) and hundreds of minor salivary glands embedded in the mucosa of the lips, areas of the buccal and lingual mucosa, and the soft palate. Saliva is a filtrate of blood that is modified by the secretory units (acini) and the ducts prior to secretion into the oral cavity. It contains a complex mix of immune and nonimmune factors that provide protection for the soft and hard tissues of the oral cavity against harmful bacteria, fungi, and viruses [128, 129].

Saliva also contains glycoproteins, lipids, and minerals that protect and replenish the surfaces of the teeth and oral mucosa. It not only protects the oral cavity but also has an important role in esophageal and gastric cell health and digestion. Its physical properties aid in lubrication of soft tissues, swallowing, talking, and the ability to taste [130].

Xerostomia is a subjective term that describes the sensation of oral dryness and is distinct from the actual decrease from normal salivary flow rates, though the terms are often used interchangeably (therefore, inaccurately) [131]. The distinction is important because an individual with true decrease in salivary production may or may not complain of dry mouth. Conversely, a person with normal salivary flow rate may complain of oral dryness, when the sensation is caused by other oral conditions common in diabetic individuals, such as oral lichen planus.

Both type 1 and type 2 diabetes affect gland morphology, innervation of secretory activity, and composition of the saliva [132–134]. A possible mechanism includes a decrease in extracellular fluid due to polyuria or diuresis, which in turn impacts salivary flow [135]. Another possible mechanism is microvascular alterations as a result of autonomic dysregulation that affect the salivary

glands' ability to respond to neural or hormonal stimulation [136].

In addition, medications used to treat conditions associated with diabetes, such as antihypertensive or antidepressant medications, can directly cause a decrease in salivary flow rate by altering neurotransmitter receptivity in the autonomic control of salivary secretion [137]. Regardless of cause, a decrease in salivary flow rate can severely impact the health of the oral cavity and oropharynx by causing increased risk for mucosal trauma and infections, periodontal disease, and caries [138, 139].

Morphological Changes of the Salivary Glands Due to Diabetes

Sialosis (also termed sialadenosis) is the most common type of change in the structure of the salivary glands caused by diabetes. Sialosis is a bilateral enlargement of the salivary glands that most commonly involves the parotid glands. It is painless and noninflammatory in nature. The size of the glands does not fluctuate and the gland consistency feels normal to palpation. However, the enlargement can result in noticeable facial changes that are cosmetic in nature [140, 141].

The condition is not unique to DM, as it is also associated with alcoholism, malnutrition, and bulimia or can be idiopathic in nature [140]. The underlying pathophysiology appears to be an autonomic neuropathy that consists of demyelination of parasympathetic and sympathetic nerve fibers to the acini or secreting units of the salivary glands. This can cause alterations in secretion and protein production, which results in accumulation of secretory components such as zymogen granules within the acinar cells. This development, in turn, results in cellular enlargement that can increase from its normal range of 30–56 um to 75–100 um in diameter [142–144].

Myoepithelial cells, which are contractile cells that mechanically support the acini, also show degenerative changes in diabetic sialosis [142]. The decrease in this support is hypothesized to allow increase in size of the acini [145]. These changes lead to eventual visible enlargement of the salivary glands.

In a study of 200 patients with DM, Russotto and colleagues reported a 24% occurrence of sialosis affecting the parotid glands [146]. Another study of 35 cases of sialosis resulting from various causes showed that one of the most common underlying disorders was DM [147]. Carda and colleagues studied samples of parotid glands of diabetic patients and individuals with a history of alcoholism and found that the acini in the diabetic patient samples were small with a bigger number of lipid intracytoplasmic droplets compared to those with a history of chronic alcohol intake and cirrhosis. There was also an increase in adipose infiltration of the stroma of the samples in the diabetic group [135].

Not all changes in the salivary glands are as apparent as sialosis. In recent studies by Lilliu et al. 2015, morphometry of submandibular salivary glands of diabetic individuals with controlled type 2 diabetes who did not have xerostomia revealed ultrastructural alterations consisting of enlargement of the secretory granules and acinar size and intracellular lipid accumulation [148]. In another study by the same group, parotid gland samples of type 2 diabetic individuals, also without xerostomia, did not show increased acinar size or granule area but had ultrastructural changes of acinar surfaces corresponding to altered secretory function. The differences in changes found in the two major glands likely reflect the inherent differences in the structures of the glands [149].

Salivary flow in individuals with diabetic sialosis has been reported to be both decreased [150] and increased [151]. This is in contrast to the always-decreased flow rate associated with similarly enlarged glands as seen in Sjögren's syndrome, an autoimmune disease in which the salivary (and lacrimal) glands are infiltrated with lymphocytes [152]. The enlargement does not seem to be related to the level of hyperglycemia nor duration of disease. There is no effective treatment. Surgical reduction of parotid glands affected by sialosis has risks that far outweigh the cosmetic benefits of such treatment.

Salivary Changes Due to Diabetes

The more consequential impact of DM on the salivary glands is a decrease in flow rate. As mentioned previously, saliva is an important secretion that provides numerous protective factors for the soft and hard tissues in the oral cavity [153]. Salivation is commonly impaired in both type 1 and type 2 diabetes.

In a study of children and adolescents with type 1 diabetes, stimulated salivary flow rate (from combination of all salivary glands) was found to be decreased in groups with poor glycemic control with concomitant increase in frequency of caries and gingivitis [154]. In three case–control studies, unstimulated combined salivary flow rate was determined to be significantly lower in children with type 1 diabetes compared to the controls [155–157]. In one of these [155], the diabetic children had a higher incidence of dental caries, while in the others [156, 157], the children had less caries incidence. Both adults and adolescents with type 1 diabetes have been found to have significantly decreased unstimulated combined salivary flow rates and increased complaints of xerostomia compared to controls [132, 133, 158].

Studies evaluating salivary flow rate in type 2 diabetes generally involve adult patients, thus introducing a greater chance that coexisting diseases and the medications used to treat them may also negatively impact salivary flow. The various protocols for salivary collection and variation in subject inclusion and exclusion criteria also contribute to inconsistencies in studies of salivary function. Most commonly, whole saliva is collected in graduated cylinders or pre-weighed test tubes over a defined time period, during either a resting or chewing-stimulated state. Whole saliva is a term that describes combined secretions from all three major salivary glands and hundreds of minor salivary glands and may include contributions from gingival crevicular fluid and oral cavity contaminants such as food remnants, plaque, and shed mucosal epithelial cells.

In general, the findings of the studies of salivary flow rate in type 2 diabetic individuals support the finding that resting (unstimulated) and/or stimulated (by chewing paraffin wax or other unflavored materials) whole salivary flow rates are significantly lower in diabetic individuals than nondiabetic individuals [134, 159–163].

Other studies have not found a relationship between salivary flow rate levels and type 2 diabetes status [164–166]. In one study, no difference was seen in resting and stimulated whole salivary flow rates between the patients with and without diabetes. However, effects of medications with known side effects of xerostomia were greater in diabetic patients than control patients [166].

Reduced salivary flow has significant impact on oral health as it greatly increases the risk of caries; mucosal infections, such as candidiasis; and mucosal trauma due to lack of lubrication. Salivary hypofunction also affects quality of life since inadequate amounts make it difficult to chew and swallow foods or to talk [139].

Many studies have investigated the salivary composition in diabetic individuals. Of these, the most relevant factor is the concentration of salivary glucose, due to its role in dental caries and oral mucosal infection and its potential as a biomarker to aid in blood glucose monitoring and diagnosis of hyperglycemia. In a systematic review of the effect of type 2 diabetes mellitus on salivary glucose, Mascarenas and colleagues reported a significant relationship between salivary glucose concentration and associated glycemia/HbA1c values, with the strength of the association increasing for higher glycemia/HbA1c levels [167]. Mussavira and colleagues reported a very strong correlation of blood glucose levels with salivary glucose concentrations ($p < 0.001$, $r = 0.9$) [168]. These studies support the potential of salivary glucose as a noninvasive biomarker for the screening and monitoring of type 2 diabetes. Further research is needed to identify other salivary constituents that may be combined with salivary glucose to strengthen the sensitivity and specificity of this measurement as a diagnostic test.

Several studies have reported higher salivary glucose concentrations in diabetic patient groups compared to control groups [159, 164, 169, 170]. However, evaluations of salivary glucose

levels in relation to oral disease, such as caries and periodontitis, have shown inconsistent results [164, 169, 171]. More research is needed to determine if salivary glucose plays a direct role in the initiation and progression of oral disease.

Various other components of saliva have been investigated in diabetic populations, adding to the knowledge base of the effect of diabetes on salivary gland function [163, 172, 173]. Since inflammation plays an important role in the pathophysiology of oral diseases in diabetes, recent research has focused on inflammatory mediators, antioxidant capacity [116], and matrix metalloproteinases (MMPs) [174, 175] in the saliva of diabetic patients. Studies have also investigated the proteomic identification of salivary biomarkers of type 2 diabetes [176, 177].

Confirmation of the results of these studies and research that builds on them will help to further characterize the effects of diabetes on salivary gland function and their combined effects on oral health. Additionally, there is a potential that salivary glucose may serve as an effective, noninvasive biomarker for monitoring glycemic control.

Diabetes and Dental Caries

Although periodontal disease is clearly the most common oral health problem associated with diabetes, dental caries also has the potential to impact the health of a diabetic patient through tooth loss and the potential for spreading odontogenic infection. Caries, or tooth decay, is the most common chronic disease of children affecting approximately 21–58% of children and teens in the general population (depending on age group) [178]. In adults aged 20–64, 91% have had caries and approximately 27% suffer from untreated caries [178]. Almost 50% of people age 75 or older have root caries affecting at least one tooth [179].

Caries is a breakdown of tooth structure caused by bacteria (primarily *Streptococcus mutans* and *Lactobacillus* sp.) that are present in plaque adhering to tooth surfaces. Plaque is a proteinaceous film that develops on teeth that derives from saliva, food, and bacteria. If plaque has prolonged periods of contact with the tooth as occurs when an individual has inadequate oral hygiene practices, acids produced by the metabolic activity of the bacteria will demineralize the tooth surface and eventually cause loss of tooth structure [180]. This process requires sugars or fermentable carbohydrates, obtained via the individual's diet [181]. The formation of caries is accentuated by lack of adequate saliva to provide mechanical cleansing, antimicrobial action, and acid buffering. In addition, in a low-saliva environment, plaque becomes more tenacious and difficult to remove with typical oral hygiene techniques.

Successful treatment of caries requires dental professional intervention including dental cleaning, removal of carious tooth structure, and restoration of teeth with restorative materials. When untreated caries progresses to the pulp within the tooth, it causes irreversible inflammation and eventually pulpal necrosis. At this stage, root canal therapy or extraction of the tooth is required to resolve the infection. All healthcare providers can provide preventive care for caries through education about oral health and nutrition, protecting salivary gland function by minimal use of medications that impair flow, application of fluoride varnish, and early referrals to oral healthcare professionals.

Several studies examining caries incidence in subjects with and without diabetes and in individuals with different levels of glycemic control have shown contradictory findings [175, 182, 183]. The variations in study findings illustrate the complexity of caries' risk, which includes dietary factors, salivary gland health and function, medication side effects, oral hygiene practices, available tooth surfaces, and access to preventive care such as topical fluoride application. This complexity makes it difficult to compare study results [184].

Caries and Type 1 Diabetes

Studies have shown increased rates of caries with type 1 diabetes. These findings are sometimes correlated with decreased salivary flow rate, pH, or acid-buffering capacity [154, 155,

185–188]. However, other studies have identified no difference in dental caries rates between children with and without type 1 diabetes [156, 189–192]. The majority of studies have identified elevated caries rates in individuals with type 1 diabetes with poor metabolic control when compared to those with better glycemic control [154, 169, 171, 191, 193, 194]. On the other hand, some researchers did not find a correlation between HbA1c and caries incidence [156, 195, 196]. For adults with type 1 diabetes mellitus, the association between caries and glycemic control has also been inconsistent [197, 198].

Caries and Type 2 Diabetes

Type 2 diabetes more commonly affects adults, who are at higher risk for root caries than younger individuals. Root caries is a breakdown of tooth structure at the gum line of the tooth at or below the junction of the hard enamel of the crown and the softer cementum surface of the root (Fig. 4). Gingival recession secondary to periodontitis exposes more susceptible root surface as periodontitis worsens. Risk factors for caries that are also more common in adults include usage of medications that cause oral dryness (e.g., antihypertensive, antidepressant, and gastroesophageal reflux medications) and local repetitive trauma (e.g., toothbrush abrasion) [184].

Studies of caries incidence in individuals with type 2 diabetes also yield contradictory results. A study by Hintao and colleagues in 2007 showed a higher prevalence of root surface caries and decayed/filled root surfaces in type 2 diabetic individuals (40%) compared to healthy age- and sex-matched controls (18.5%, $p = 0.001$) [199]. Several other studies have reported an increased caries rate in poorly controlled type 2 diabetic patients versus those who are well controlled. However, several studies have not identified a difference between those with type 2 diabetes and control subjects [161, 184, 200–204].

Though results are contradictory, the evidence points in the direction of the importance of making oral evaluation a part of routine management of type 1 and 2 diabetes in children, adolescents, and adults. Assessment of salivary flow rate and questions related to perceived oral dryness are especially important. All healthcare providers can assure that oral health needs are met early to prevent consequences of infection and tooth loss.

Diabetes and Oral Soft Tissue Disorders

Dental and medical evaluation of the diabetic patient should also include a complete intraoral soft tissue examination to evaluate for epithelial and mucosal pathology. Several common oral mucosal conditions that require intervention or regular monitoring are more prevalent in the diabetic population, including oral candidiasis and

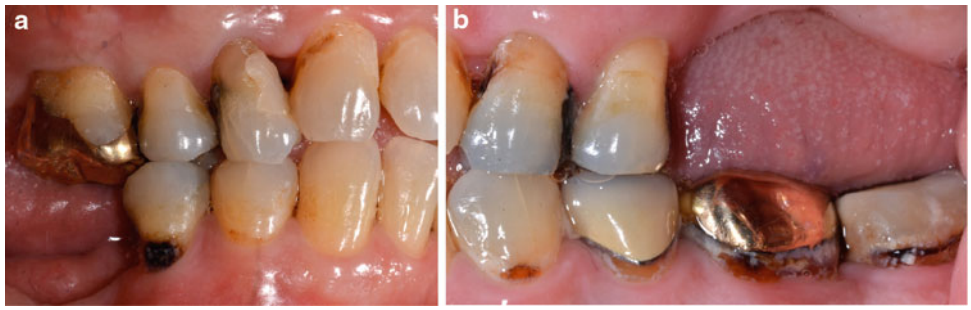

Fig. 4 Dental Caries. (**a**) Root decay is present on the facial surface of the mandibular right second premolar (evidenced by brown and distinct cavitation). (**b**) In the same patient, root caries lesions are also present on the facial surfaces of the mandibular first premolar (primary caries) and the first and second molar (recurrent decay beneath previous restorations). Note the accumulation of white dental plaque

premalignant lesions such as erythroplakia, leukoplakia, and lichen planus [205–209]. Recent literature also suggests elevated risk for oral and oropharyngeal malignancy in the diabetic population [209–211]. Susceptibility to these various conditions is believed to relate to a complex interplay between alterations in innate immunity (including decreased salivary function), systemic immune dysregulation, and compromised healing capacity [212, 213].

Oral soft tissue conditions have a range of presentations and may mimic each other. For example, lichen planus (an autoimmune-related condition) and candidiasis (an oral infection) may have similar clinical appearance. Symptom history, visual examination, manual palpation, microbial cultures, adjunctive diagnostic techniques (such as toluidine blue staining and autofluorescence visualization), and biopsy may be required to differentiate between lesions with a similar clinical appearance.

Salivary-related mucosal pathologies can generally be managed conservatively with or without pharmacologic intervention. Oral candidiasis is effectively treated with topical and/or systemic antifungal therapy and management of factors that predispose for infection (elevated blood glucose, hyposalivation, poorly fitting dentures, or inadequate denture hygiene). Premalignant and malignant conditions require multidisciplinary management unique to the severity of the disease.

Oral Candidiasis

Several species of yeast, most notably *Candida albicans*, are part of the normal oral flora. It is estimated that 30–50% of individuals are colonized by *Candida albicans* without signs or symptoms of disease [214]. Case–control studies have consistently demonstrated higher prevalence of *Candida* colonization in subjects with diabetes when compared to nondiabetic controls [205, 215–221], though others have reported no difference between groups [222]. Within the diabetic study groups, up to 87.5% of the dentate individuals [217] and 100% of edentulous subjects with denture stomatitis harbored *Candida* species [216, 218]. Prevalence of colonization in dentate and complete denture-wearing control subjects were similar to previously reported literature [214, 223, 224].

Signs and symptoms vary based on the degree of colonization and numerous host factors. Common patient complaints in symptomatic candidiasis include dysgeusia, oral burning, mucosal irritation, "coating" of the tongue, and cracking at the corners of the mouth [214, 225].

Physical manifestations of candidiasis are also commonly identified in the setting of diabetes [205, 216, 218, 225–227]. Several different mechanisms predispose patients with diabetes to *Candida* overgrowth. For example, higher levels of salivary glucose in diabetic individuals facilitate overgrowth of yeast by providing for the increasing metabolic demands of the community [219, 228, 229]. However, salivary glucose levels do not always correlate with clinical evidence of candidiasis [229]. Increased *Candida* colonization in the diabetic population is also believed to result from decreased salivary production which results in decreased microbial clearance and increased adherence of hyphae to dry mucosal tissues [230]. Saliva also contains a host of antimicrobial factors that play a role in preventing infection [231]; however, the complex interaction of salivary proteins has yet to be fully characterized [232].

The intraoral presentation of candidiasis varies based on the chronicity and depth of infection. Pseudomembranous candidiasis, or "thrush," is the most easily recognized manifestation. Clinical presentation is characterized by collections of "cottage cheese-like" debris which adheres to superficial mucosal tissues (Fig. 5). Pseudomembranous colonies can generally be removed with a tongue depressor or 2 × 2 gauze leaving an erythematous base [214]. This can be a useful way to differentiate between pseudomembranous candidiasis and other red and white mucosal lesions such as lichen planus [233] which cannot be removed in this manner.

The clinical appearance of candidiasis changes over time as hyphae enter oral tissues and trigger an immune response. Chronic infection results in thinning of tissue (atrophic candidiasis), increased

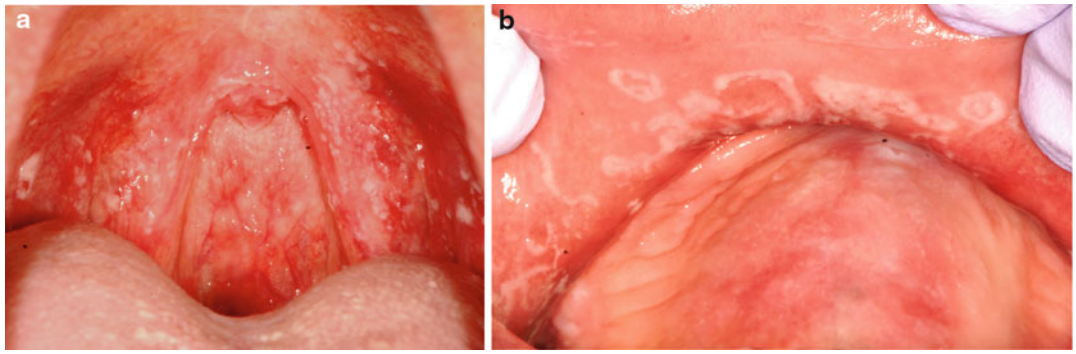

Fig. 5 Pseudomembranous candidiasis. (**a**) In the oropharynx and (**b**) maxillary labial mucosa in a patient with poorly controlled type 2 diabetes mellitus (Photograph courtesy of Dr. David Dean)

inflammation activity (erythematous candidiasis), and epithelial proliferation (hyperplastic candidiasis). Atrophic and erythematous candidiases have been reported as most common presentations in patients with diabetes (Fig. 6) [226, 227]. Additional manifestations of candidiasis, including angular cheilitis (Fig. 7), denture stomatitis (Fig. 8), and median rhomboid glossitis, are also commonly identified in diabetic populations [205, 218, 225, 234]. Finally, patients with significant immunosuppression, including poorly controlled diabetes, are at risk for invasive mucocutaneous infection [214].

Denture wear and smoking have been consistently identified as risk factors for oral candidiasis in the general and diabetic populations [205, 220, 235–238]. The relationship between glycemic control and candidiasis is less clear. There is literature to support an association between poor glycemic control, higher levels of *Candida* colonization, and higher prevalence of symptomatic candidiasis [205, 216, 225, 238, 239]. Most strikingly, subjects with severely elevated HbA1c values (>12%) had an odds ratio of 13.0 for *Candida* infection compared to those with better glycemic control [240]. Other studies have found no relationship between degree of infection and glycemic control [220, 221, 226, 235, 241].

As mentioned earlier, *Candida albicans* is the primary cause of oral candidiasis in both the diabetic and general populations [205, 222, 241, 242]. Importantly, non-albicans species, including

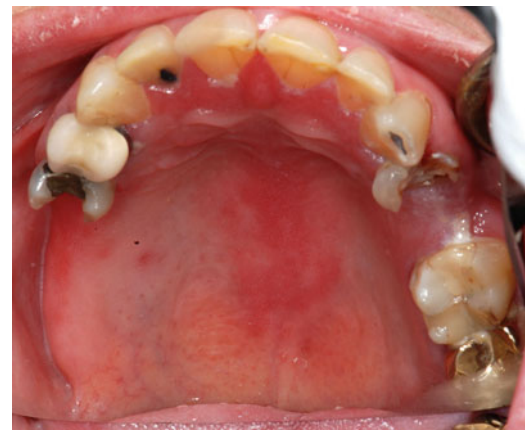

Fig. 6 Erythematous candidiasis. Erythematous candidiasis of the hard palate (Photograph courtesy of Dr. Beatrice Gandara)

Candida glabrata, *C. tropicalis*, *C. krusei*, and *C. parapsilosis*, are also commonly isolated in the diabetic population [216, 243]. Non-albicans species exhibit greater resistance to antifungal therapies [244, 245], and case–control studies have detected increased resistance to amphotericin B, fluconazole, and ketoconazole in subjects with type 1 and type 2 diabetes [215, 217, 222]. No antifungal resistance was found in control subjects. *Candida dubliniensis*, a species initially recognized in patients with severe immunosuppression [244], has also been isolated in diabetic populations [225, 246]; however, other studies have not supported these findings [247, 248].

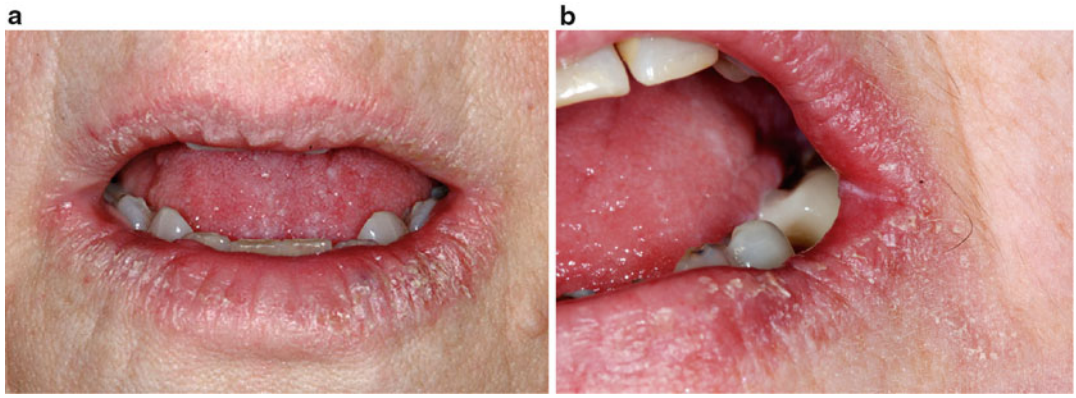

Fig. 7 Angular cheilitis. (**a**) Hyposalivation predisposes to chapped lips, furrowing, and angular cheilitis. (**b**) Angular cheilitis presents with erythema and cracking at the labial commissures, demonstrated in the close-up photograph (Photographs courtesy of Dr. Beatrice Gandara)

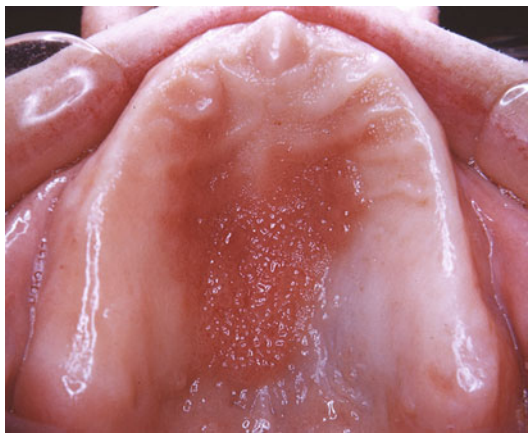

Fig. 8 Denture stomatitis. Denture stomatitis is characterized by erythema and "pebbling" of the tissue of the hard palate, also known as inflammatory papillary hyperplasia (Photograph courtesy of Dr. Kavita Shor)

Disorders of the Lingual Mucosa

Benign disorders of the tongue, including fissured tongue, migratory glossitis, and median rhomboid glossitis, are commonly identified in diabetic patients [205, 225, 249].

In normal circumstances, the majority of the dorsal surface of the tongue is covered by filiform papillae which provide the tongue with its characteristic uniform texture and appearance. Atrophy of dorsal papillae causes areas of the tongue to appear red and smooth. Generalized surface atrophy may be a sign of a vitamin B12 or iron deficiency. Patchy atrophy of the dorsal tongue in diabetic patients is strongly suggestive of atrophic candidiasis [233, 250]. Atrophy isolated to the midline of the posterior tongue is most likely to be due to median rhomboid glossitis, another form of candidiasis. Migratory glossitis should be suspected if atrophic areas are partially surrounded by raised white borders and the location of lesions changes over time [233]. Several case–control studies have reported greater prevalence of migratory glossitis in subjects with diabetes when compared to nondiabetic subjects [234, 251].

Fissuring of the dorsal tongue is also more prevalent in diabetic patients than matched controls [249, 251, 252]. Fissured tongue is characterized by the appearance of multiple grooves across the dorsal surface of the tongue (Fig. 9). It is believed to be a result of chronic lingual trauma in the setting of hyposalivation [233]. Fissuring is a qualitative indicator of oral dryness which puts patients at risk for dental caries, candidiasis, and oral burning disorders.

Oral Lichen Planus and Lichenoid Disorders

Lichen planus is a chronic autoimmune-related condition that commonly affects the oral mucosa. The

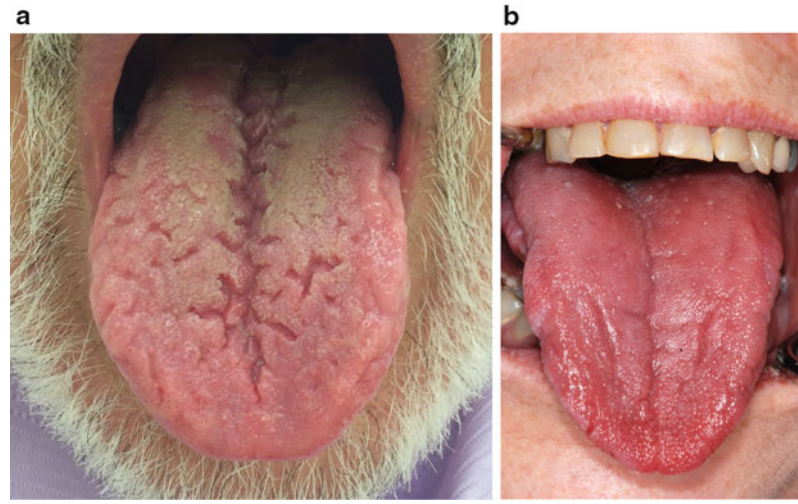

Fig. 9 Fissured tongue. (**a**) Generalized fissuring of the dorsal surface of the tongue (Photograph courtesy of Dr. Wen-Mei Lin). (**b**) Dryness of the dorsal tongue with anterior fissuring (Photograph courtesy of Dr. Beatrice Gandara)

prevalence of oral lichen planus (OLP) ranges between 0.5% and 2.2% in the general population [253]. Though the exact etiology of lichen planus remains unknown, the disorder is characterized histopathologically by infiltration of T lymphocytes beneath the epithelium that results in degeneration of the basement membrane [214, 242, 254].

Several case–control studies have indicated greater prevalence of lichen planus in patients with type 2 diabetes compared to healthy control subjects [206, 251]; however, additional research in insulin-dependent subjects found no association [249]. Case–control studies evaluating the prevalence of impaired glucose metabolism in individuals with lichen planus have shown mixed results with some studies reporting prevalence of type 2 diabetes in approximately 27% [255, 256]. However, epidemiologic work by Borghelli and colleagues found no association between the conditions [257, 258].

Lichen planus-like lesions in patients with diabetes may also be the result of lichenoid drug reaction, a condition that is indistinguishable from primary oral lichen planus upon visual examination. Oral hypoglycemic agents, including sulfonylureas and metformin [259–261] and antihypertensive medications commonly used in the diabetic population [258, 259, 262], are among the most common causes of medication-related lichenoid mucositis. Oral lichenoid lesions reported in Grinspan syndrome (a disorder characterized by the co-occurrence of diabetes mellitus, hypertension, and oral lichen planus) are now widely considered to have been the result of reactions to antihypertensive and diabetic medications used to manage diabetes [259, 261, 263].

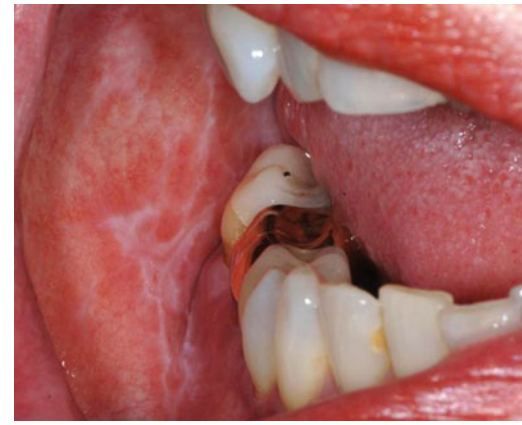

Fig. 10 Reticular lichen planus. Reticular lichen planus of the right buccal mucosa. Note the distinct striae of Wickham with surrounding erythema (Photographs courtesy of Dr. Michael Martin)

Lichen planus that appears in a reticular formation is the most common clinical presentation. It is characterized by white, "netlike" striations ("striae of Wickham") which are most commonly identified on the buccal mucosa bilaterally (Fig. 10) [214]. Patients with reticular lichen planus are generally asymptomatic and may not require pharmacologic interventions. In contrast, patients with

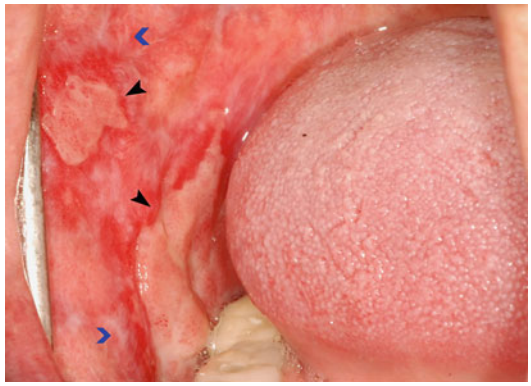

Fig. 11 Erosive lichen planus of the right buccal mucosa in a patient with poorly controlled type 2 diabetes mellitus. Note the pseudomembrane-covered ulcerations (*black arrows*) and thin peripheral lichenoid striae (*blue carets*) (Photograph courtesy of Dr. David Dean)

erosive lichen planus may develop widespread thinning and possible ulceration of the oral mucosa with symptoms of burning pain exacerbated by acidic and spicy foods. Reticular features are less prominent in erosive lichen planus though the striations can still be identified at the periphery of the lesions (Fig. 11). Erosive lichen planus cases are treated with topical and/or systemic corticosteroids or other immunomodulatory medications [264].

The World Health Organization (WHO) has recognized lichen planus as a potentially malignant disorder [265, 266]. Though considerable evidence supports the possible malignant transformation of oral lichenoid lesions [267–271], this classification has been the subject of active debate [272]. A recent systematic review indicates a lifetime transformation of 1.09% (ranging from 0% to 3.5%), which is in agreement with the preponderance of clinical data [253, 264, 265, 271]. Interestingly, several studies have reported higher transformation rates in oral lichenoid lesions than primary lichen planus [267, 271].

Lesions in erosive and "plaque-like" lichen planus have been reported to have greater risk for malignant transformation than reticular lichen planus, though squamous cell carcinoma has been described in both forms [273, 274]. An international consensus meeting concluded that there was insufficient evidence to support greater malignant transformation based on the clinical form [264]. The risk for malignant transformation underscores the importance for regular evaluation by a dental healthcare professional. Intraoral soft tissue examinations in patients with lichen planus are recommended approximately every 4 months (or at minimum once per year) [253, 275]. Others have emphasized that regular recall may place unnecessary economic burden on individuals with lichen planus, especially considering the low rate of malignant transformation. Examination costs may be decreased through opportunistic examinations by medical and dental providers during regularly scheduled appointments [276].

The ventrolateral tongue is the most common site of oral cancer and precancerous lesions [214, 277] which will be discussed in more detail below.

Malignant and Premalignant Disorders of the Head and Neck

Since the 1950s, hyperinsulinemia has been linked with abnormal cellular metabolism, increased cell proliferation, and production of reactive oxygen species, all of which are involved in the pathophysiology of cancer [278–282]. Diabetes has not traditionally been considered a risk factor for head and neck cancer; however, recent epidemiologic work suggests a modest association between altered insulin metabolism and risk for malignancy in the oral cavity, oropharynx, and upper aerodigestive tract [209–211, 283]. Upper aerodigestive tract cancers are recognized risk factors for oral and oropharyngeal carcinoma [284], most likely due to similar physical exposure to carcinogens taken in through the mouth.

A recent meta-analysis concluded that individuals with type 2 diabetes have an elevated risk of oral squamous cell carcinoma when compared to nondiabetic individuals (HR = 1.15) [209]. Two additional studies in large Taiwanese cohorts reported similar findings. A prospective cohort study of 472,979 Taiwanese subjects with type 2 diabetes found men to have an increased incidence of oral cancer over a 10-year follow-up period (standardized incidence ratio = 1.16) [211]. A second Taiwanese study of 89,089 subjects retrospectively evaluated the incidence of

head and neck cancer in newly diagnosed diabetes and control subjects (matched for age, sex, income, geographic distribution, and medical comorbidities). Subjects with newly diagnosed diabetes at baseline were found to have elevated incidence of oral cancer (adjusted hazard ratio = 1.74), oropharyngeal cancer (1.53), and nasopharyngeal carcinoma (1.40) over the study period [210]. The oral cavity was found to be the initial site of presentation in 57.1% of the diabetic cohort.

Despite this evidence, it is important to note that not all studies have reported similar findings. For example, a large case–control study completed through the United States Veterans Affairs system reported lower risk of "buccal cavity" cancer in diabetic male veterans (RR = 0.85) [285].

The prevalence of diabetes has also been examined in patients with confirmed oral and oropharyngeal cancers. Ujpal and colleagues identified a higher prevalence of diabetes in 610 patients with confirmed oral cancer than cancer-free controls (14.6% vs. 5.6%) [208]. In contrast, no difference in prevalence was detected in a study of nearly 1500 head and neck cancer patients in the Netherlands [286].

Diabetes control may also impact survival in patients being treated for head and neck cancers. The previously cited meta-analysis by Gong and colleagues reported increased oral cancer mortality in diabetic individuals when compared to those without diabetes (summary relative risk = 1.41) [209]. Similarly, a retrospective cohort study in Taiwan found patients with oral squamous cell carcinoma and concurrent diabetes to have decreased overall survival (hazard ratio = 2.22) and recurrence-free survival (HR = 2.42) compared to nondiabetic controls [287].

Leukoplakia and Erythroplakia

Early diagnosis dramatically improves survival in oral cancer, evidenced by a 5-year survival rate of 82.7% in local disease versus 60.5% in regional lymph node metastasis and 37.3% in distant metastasis [288]. Therefore, medical history taking, risk assessment, and oral examination are of paramount importance in high-risk populations. Oral premalignant lesions, such as erythroplakia and leukoplakia, are recognized precursors of oral squamous cell carcinoma [214, 242, 265, 266, 289] and have the potential to be identified prior to overt malignant transformation.

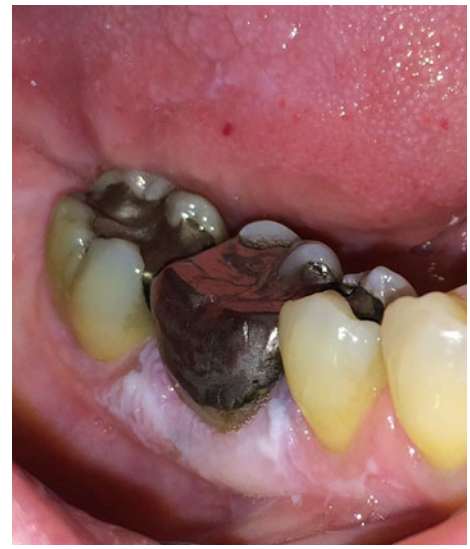

Fig. 12 Leukoplakia. A well-defined white patch on the gingiva buccal to the mandibular right first molar. Note the rough surface texture on the distal aspect of the lesion (Photograph courtesy of Dr. Thomas A. Contreras)

The terms "leukoplakia" and "erythroplakia" are clinical descriptions that do not have specific histologic characteristics. Both lesion types may occur at any age but are more common in the middle-aged and elderly [214]. Tobacco and alcohol are strongly associated with leukoplakia and are also believed to play a significant role in the pathogenesis of erythroplakia [265, 290].

Leukoplakias alone make up 85% of all oral premalignant lesions [214]. Leukoplakia presents as a well-defined white patch that will not rub away with pressure (Fig. 12). A recent WHO consensus group concluded that "the term leukoplakia should be used to recognize white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" [289]. Lesions range in appearance from thin and somewhat translucent to rough and thick. Leukoplakia that is

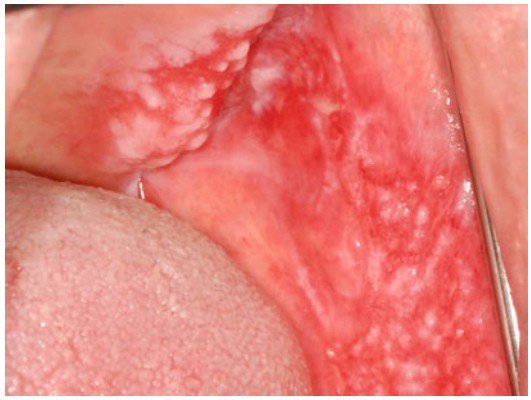

Fig. 13 Speckled leukoplakia. "Speckled" leukoplakia of the left buccal mucosa and maxillary left edentulous ridge in a patient with poorly controlled type 2 diabetes mellitus. Note the mixed *red* and *white* appearance and granular surface texture (Photograph courtesy of Dr. David Dean)

homogenous in color is less concerning for premalignancy than those that exhibit a mixed red and white color termed erythroleukoplakia or "speckled leukoplakia" (Fig. 13) [214, 289, 291]. Other signs concerning for dysplasia and carcinoma include large lesion size (>2 cm), induration, and granular/nodular surface texture [265, 291, 292]. Dysplasia or carcinoma is identified in 5–25% of leukoplakic lesions [214].

Erythroplakia generally presents as a well-defined red plaque with a velvet-like surface texture. These red patches are often isolated, helping to differentiate it from inflammatory lesions which also appear erythematous [265]. The risk of malignancy in erythroplakia is very high with up to 90% of lesions representing severe dysplasia, carcinoma in situ, or squamous cell carcinoma at the time of initial biopsy [214, 242].

Despite the modest association between oral cancer and diabetes discussed thus far, the increased incidence of oral mucosal lesions in individuals with diabetes warrants careful examination of all oral lesions. Large-scale studies in Europe and Asia have identified a high incidence of oral mucosal lesions in individuals with diabetes. Several case–control studies have identified a higher prevalence of leukoplakia and erythroplakia in diabetic individuals than nondiabetic control subjects [206–209, 293]. A population-based cohort study of nearly 50,000 subjects in Kerala, India, found an elevated odds ratios for leukoplakia (OR = 2.0) and erythroplakia (OR = 3.2) in females with diabetes. No association was found in men [207]. Data from the third National Health and Nutrition Survey (NHANES III) in the United States determined diabetes to be an independent risk factor for leukoplakia (OR = 3.03).

European studies also support these findings. A population-based study in northeast Germany associated HbA1c levels ≥6.5% with increased risk of leukoplakia (OR = 1.51), particularly among smokers (OR = 2.66) [293]. A case–control study of 200 subjects with type 1 and type 2 diabetes in Hungary identified higher prevalence of erythroplakia and/or leukoplakia in the diabetic subjects when compared to controls (8% vs. 3.2%). Odds ratios were not reported in the study.

Isolated red lesions are highly concerning for oral malignancy. Immediate biopsy or referral for biopsy is recommended to obtain a histopathologic diagnosis. Assessment is especially important if the lesion presents in a high-risk location (e.g., ventrolateral tongue, floor of the mouth, the soft palate, or tonsillar pillar area) or if the patient has a history of tobacco use.

Purely white lesions of the oral mucosa have a lower transformation potential than red or speckled red and white lesions and may have a range of contributing factors. The clinician should explore potential etiologies, including tobacco use, frictional trauma, chemical irritation, and fungal infection. Lesions that have not significantly regressed in 2–4 weeks after removal of the stimulus should be assessed histologically. White lesions with no discernable cause ("idiopathic leukoplakia") are indicated for immediate biopsy [265].

Red and white lesions on the ventral tongue or floor of the mouth are considered to be at especially high risk for malignant transformation [214]. Other high-risk sites, particularly for erythroplakia, include the soft palate and retromolar trigone [290].

Diabetes and Oral Burning

Oral burning is a common complaint among diabetic individuals [225, 294–297]. Studies reporting oral burning in diabetic populations have

commonly identified hyposalivation, candidiasis, oral lichen planus, lichenoid reaction, and benign migratory glossitis as sources of the burning sensation [225, 294, 295]. The etiology of the burning complaint must be accurately identified to achieve successful management of a patient's symptoms. Other potential causes of oral burning include vitamin deficiency, hormonal abnormalities, and lingual parafunction (i.e., tongue habits) [298].

Oral Burning Symptom

Neurologic causes of oral burning should be suspected if clinical examination and laboratory analysis fail to identify a likely etiology of burning symptoms. Primary burning mouth syndrome (BMS) is a condition characterized by burning or tingling pain most commonly affecting the anterior tongue (particularly the "tip") and the opposing hard palate. Burning symptoms are bilateral and symmetric [298, 299]. Primary BMS is a diagnosis of exclusion made after clinical examination, laboratory testing, and advanced imaging have failed to identify the underlying cause of the patient's symptoms. Histopathologic studies have identified similarities between primary BMS and diabetic small fiber neuropathy [300–302]; however, the association between diabetes and primary burning mouth syndrome remains an active debate due to the broad differential diagnosis for oral burning in the diabetic population and inconsistent inclusion criteria across studies investigating the potential relationship between the two conditions [298].

A case–control study by Moore and colleagues identified symptoms of oral burning in 5.7% of subjects with type 1 diabetes. The majority of cases could be explained by oral mucosal pathologies including fissured tongue, denture stomatitis, atrophy of the lingual papilla, and candidiasis. The prevalence of unexplained burning symptoms was similar between cases (12 of 371, 3.2%) and controls (5/233, 2.1%). Interestingly, diabetic subjects with unexplained oral burning were statistically more likely to be female and have a concurrent diabetic neuropathy. This led the authors to hypothesize a neuropathic etiology in a subset of their diabetic population [294]. Arap and colleagues further examined the potential association between diabetic peripheral neuropathy and trigeminal sensory abnormalities using quantitative sensory testing [296]. The researchers compared subjects with type 2 diabetes and painful peripheral neuropathy to age-matched subjects without diabetes or neuropathic pain. Oral burning was reported by 17.2% of those with diabetic neuropathy, and both fasting blood glucose and HbA1c were significantly correlated with sensory changes in multiple divisions of the trigeminal nerve.

Other studies have also suggested a neuropathic component for oral burning in the diabetic population. A study in an elderly Finnish population identified statistically greater prevalence of glossodynia (18% vs. 6%), diabetic neuropathy (42% vs. 0%), and parasympathetic dysfunction (54% vs. 31%) in subjects with type 2 diabetes compared to control subjects; however, the outcomes were unable to confirm an association between peripheral neuropathy and glossodynia [297]. A high prevalence of primary burning mouth syndrome was also reported in a cohort of previously undiagnosed diabetic patients presenting for care in an oral medicine clinic. Ten of 43 patients were diagnosed with primary BMS after assessing for hyposalivation, vitamin B deficiencies, and oral infection. The authors reported decreased symptoms with improvement in blood glucose levels [295]. Similarly, Carrington and colleagues reported a case of glossodynia in a patient with occult hyperglycemia. Symptoms resolved completely after initiating appropriate therapy for diabetes [303]. The authors proposed a relationship between the patient's symptoms and diabetic neuropathy.

Finally, in addition to the physical factors outlined above, it is also important to recognize the importance of psychologic factors in successful diagnosis and management of burning mouth syndrome. Though the conclusion that BMS is a purely psychogenic condition has been largely refuted [298], the relationship between chronic pain conditions and psychologic factors has been well established in literature [304, 305]. Elevated levels of anxiety, depression, and psychologic

distress have been reported in the BMS population [298, 306, 307], though not all studies agree with these findings [308].

Depression is a common condition in diabetes and is more prevalent in individuals with diabetes than the general population [309, 310]. Therefore psychological conditions should be investigated as potential contributing factors in oral burning. Successful management of oral burning with cognitive behavioral therapy [311] and psychoactive medications [298] supports their inclusion in the management of oral burning. A comprehensive overview of the differential diagnosis of oral burning, including appropriate diagnostic tests and therapeutic interventions, is presented in Table 1.

Additionally, depression can negatively affect treatment adherence and systemic health in the diabetic population [312, 313]. A global overview of the clinical considerations related to diabetes, depression, and oral health is included in Box 1.

Box 1 Diabetes, Depression, and Oral Health

Depression is reported to be more prevalent in persons with diabetes than those without diabetes, with odds ratios of 1.38–1.6 [309, 310, 314]. Depressed patients with diabetes have been shown to have poorer glycemic control and a higher incidence of microvascular and macrovascular complications [315].

Depression has a profound impact on oral health on multiple levels:

- Just as depression can affect the ability or desire of the patient with diabetes to adhere to exercise and dietary guidelines [312, 316], it may also impact the patient's ability to maintain oral hygiene or obtain prophylactic care at dental offices.
- Antidepressant medications frequently have a side effect of decrease in salivary flow rate, which results in increased risk of caries, periodontal disease, oral candidiasis, and mucosal atrophy [138, 317].
- Depression is a significant comorbid condition in neuropathic pain disorders of the oral mucosa, such as burning mouth syndrome, which are more common in diabetic individuals [305].
- Depression can also increase use of alcohol, tobacco, and other substances [318, 319] which in turn affect self-care [320] and the health of the oral mucosa and dentition.

Therefore, diabetic patients who are depressed warrant even greater surveillance of oral health and proactive treatment or management of salivary and oral mucosal disorders, caries, and periodontal disease. A close working relationship with a dental care provider is strongly advised to maintain good oral and systemic health.

Opportunities for Interprofessional Collaboration

Collaboration between medical and dental providers may help to reduce morbidity associated with systemic and oral manifestations of diabetes. Dentists have the advantage of seeing patients for routine follow-up appointments, which are generally recommended twice per year. Oral healthcare providers should be alert and oriented for the signs, symptoms, and risk factors related to hyperglycemia [321]. Additionally, certain oral conditions, such as recurrent candidiasis [322] and treatment refractory periodontitis [18], should raise suspicion for undiagnosed or poorly controlled diabetes. If the dentist identifies suggestive findings, he or she should contact the patient's primary care provider or help to establish a primary healthcare relationship if one is not in place.

Furthermore, studies have shown that dental offices may be an effective means of opportunistic screening for hyperglycemia. Lalla and colleagues [323] performed full-mouth periodontal assessment and chairside HbA1c testing on

Table 1 Oral burning is a common symptom in patients with diabetes and may relate to a variety of etiologic factors. The differential diagnosis, clinical features, appropriate diagnostic tests, and recommended therapeutic interventions are reviewed in the presence and absence of distinct clinical pathology (Reproduced with permission of Washington Dental Service Foundation)

Consider these diagnoses[a] when your patient says:				
"***My tongue*** (*mouth*) ***is burning!***"				
Condition	Characteristics	Associated factors	Examination/ diagnostic tests	Treatment/ management
Low salivary flow rate	High caries rate, mucosal atrophy and inflammation, angular cheilitis, fissured tongue, ropey saliva, inability to express saliva from duct orifices, difficulty eating, swallowing without liquid, difficulty with wearing dentures	Medication side effect, head and neck or total body radiation therapy, autoimmune disease (e.g., Sjögren's syndrome), diabetes, depression	Visual examination, note caries, plaque retention,salivary flow rate measurement	Adequate hydration, salivary stimulants such as sugarless candies or chewing gums, pilocarpine or cevimeline medication, caries prevention protocol (oral hygiene instruction, dietary counseling, topical fluoride application)
Medication side effect, **Sjögren's syndrome**, **Head and neck radiation (including thyroid cancer treatment)**	Mediated by low salivary flow (see above)	Medications with known side effect of decreased salivary flowMay be associated with other autoimmune diseases and/or family history of autoimmune diseaseRadiation field and dose dependent	All above, plus: Research medication side effects Blood tests for autoimmune disease (ANA, SSA, SSB, Rh factor), lip biopsy Review of radiation treatment history	All above, plus: Ask primary care to consider medications with less side effect of oral dryness See above See above
Candidiasis	Atrophic, inflamed mucosa, pseudomembranous plaques (not always present)	Dry mouth, antibiotic or steroid use, depression, immunosuppression	History of onset, visual appearance, fungal culture	Clotrimazole troches, nystatin rinse, other antifungal medications
Median rhomboid glossitis	"Bald" patch on posterior tongue dorsum with inflammation, a form of candidiasis	May have matching area of inflammation of the palate	Fungal culture	Clotrimazole troches, nystatin rinse, other antifungal medications
Mucosal atrophy	Tongue looks bald on dorsum or lateral borders	Chronic dry mouth, atrophic candidiasis	Medical history findings that support dry mouth	Treat infection if present, stimulate salivary flow
Benign migratory glossitis	Patches on the surface of the tongue with missing papillae, smooth areas are often surrounded by slightly raised borders, mild-to-moderate inflammation	Unknown cause, may be a form of psoriasis	By history	Symptomatic relief such as topical antihistamine, topical anesthetic

(*continued*)

Table 1 (continued)

Consider these diagnoses[a] when your patient says:				
"***My tongue*** (*mouth*) ***is burning!***"				
Condition	Characteristics	Associated factors	Examination/ diagnostic tests	Treatment/ management
Nutritional deficiency/ anemia	Atrophy of tongue papilla, numbness of tongue, bald tongue	History of poor diet, GI absorption problems, history of alcoholism	Blood tests, CBC, vitamins, refer to neurologist, GI workup	Dietary guidance, vitamin or mineral supplementation
Herpetic infection	Small vesicles may be present, ulcerations, generalized mucositis	Stress, immunosuppression	Viral culture	Antiviral medication (e.g., acyclovir)
Drug reaction/ allergy	Generalized inflammation, ulcerations, gingiva may be red and puffy, may be irritated easily by sharp or spicy substances	Associated with medication use	Identify drug, biopsy oral mucosa	Eliminate culprit drug use if possible
Lichen planus/ lichenoid drug reaction	Erosive, painful inflammation with large shallow ulcer formation, white striae may be present on the tongue, buccal mucosa	Stress, hypersensitivity to medications, dental materials	Biopsy	Treat with topical steroids
Tongue parafunction	Quivering or repetitive movement of the tongue beyond patients control, tissues may be traumatized by continual movement	Movement disorder may be due to medication side effect or degenerative nerve disease	Observation by self or others	Create occlusal stent to provide a barrier to the tongue, neurological evaluation by specialist
But the mouth looks normal!				
Small fiber neuropathy: Diabetic neuropathy Burning mouth syndrome	All mucosa looks entirely normal	Poorly controlled diabetes, depression Unknown etiology, trauma to nerve, anxiety, depression	History of burning sensation Assess hyperglycemic control Alleviated by chewing gum, worse at night	Hyperglycemic control Clonazepam, gabapentin, alpha lipoic acid, avoid opioids to minimize dependence risk Cognitive Behavioral Therapy
CNS lesion	All oral tissues may look normal	Headache, dizziness, cognitive changes, chemosensory changes	Imaging, neurological evaluation	Treat lesion

[a]Note: Poorly controlled diabetes will increase the risk of all conditions listed above

525 patients who presented to a university dental clinic with at least one risk factor for diabetes. All subjects with abnormal HbA1c values at initial exam were asked to return for a fasting blood glucose (FPG) examination. Nearly 95% of those with abnormal HbA1c values returned for additional laboratory testing which ultimately identified 4.2% of subjects to be potentially diabetic

(FPG $\geq$ 126 mg/dL) and 31.8% to be potentially prediabetic (FPG = 100–125 mg/dL). The researchers then used their data to create a predictive model for assessing the risk of abnormal FPG at follow-up. By combining two elements from the initial dental examination ($\geq$4 missing teeth and $\geq$26% PPD >3 mm) with the results of the point-of-care HbA1c test ($\geq$5.7%), they were able to retrospectively predict 92% of abnormal FPG cases at follow-up (FPG $\geq$100 mg/dL).

There is also evidence to suggest that diabetic individuals receiving regular dental care may have lower healthcare costs and experience fewer diabetes-related emergencies than those who are not receiving regular oral healthcare. A recent study by Nasseh and colleagues found lower total healthcare costs (−$1799) and diabetes-related healthcare costs over a 2-year period in a cohort of over 15,000 individuals with newly diagnosed type 2 diabetes [324]. Interestingly, a significant reduction in healthcare cost was isolated to those patients not concurrently managed with prescription medications for glycemic control. Similarly, a retrospective cohort analysis by Jeffcoat and colleagues investigated whether insurance subscribers receiving periodontal therapy in the first year of the study had lower healthcare costs over the following 5 years. The analysis included a subgroup of over 91,000 individuals with type 2 diabetes. Patients with type 2 diabetes who received periodontal therapy in the first year had 40.2% reduction healthcare costs and 39.4% decrease in inpatient hospitalization when compared to diabetic individuals who did not receive therapy [325]. It is of interest to note that only 1% of those in the diabetic cohort received periodontal therapy which suggests a highly underutilized method of potential reduction of morbidity and healthcare costs.

Diabetic emergencies also appear to be lower in those receiving periodontal therapy. A study by Mosen and colleagues found that diabetic patients completing two or more dental cleanings in the previous year were 39% less likely to visit the emergency department or require hospitalization due to diabetic complications in the subsequent 12 months [326]. These findings may relate to a direct effect of periodontal therapy or reflect general health-promoting behaviors in the group that received regular dental care.

Referral for comprehensive dental examination, including periodontal assessment, is recommended by the American Diabetes Association for all patients newly diagnosed with diabetes [327]; however, epidemiologic work suggests that only 67.3% of adults with diabetes received dental care in the preceding 12 months [328]. The importance of medical referral to a dental provider is underscored by the results of a national interview survey in the United States, which concluded that adults with diabetes were less likely to visit a dental provider in the preceding 12 months than to see a physician for diabetic-related care, foot care, or eye care compared to their nondiabetic counterparts [329]. Cost of care appears to be a limiting factor for many diabetic patients [330] which can have detrimental effects on health outcomes. Programs designed to provide healthcare resources to the uninsured, such as the Diabetes Healthy Outcomes Program, have helped patients with diabetes to receive appropriate dental therapy which may have positive effects on their systemic health. Unfortunately, low utilization of dental services has also reported in insured diabetic population.

Individuals with dental insurance in Washington State were found to be 26% less likely to see the dentist over a 5-year period if they had a prior diagnosis of diabetes. Diabetic patients who did seek care were more likely to require more advanced dental interventions, including periodontal therapy (OR = 1.30), tooth extraction (OR = 1.36), and removable prosthodontic care (OR = 1.36) [331]. Similar findings were reported in a French cohort of 1111 diabetic subjects, who were determined to be 47% more likely to experience dental problems and 117% more likely to be treated with removable partial dentures than their counterparts without diabetes [332].

The majority of oral complications of diabetes are preventable or manageable with early recognition and appropriate therapy. Medical providers play a vital role in the dental education of patients with diabetes. By reviewing the interrelationship between diabetes and the oral complications of

the disorder, providers can help to decrease the risk of dental decay, periodontal disease, and tooth loss in addition to numerous other diseases described in this chapter. Patients with diabetes are at higher risk of progressive orofacial infection, particularly when poorly controlled, which may lead to bacteremia and airway compromise. Diabetes compromises wound healing which may lead to complications following invasive dental treatment, such as extractions. Furthermore, in patients with diabetes, "food is medicine" and is essential for maintaining glycemic control [321]. Tooth loss and dental pain can significantly compromise the ability to chew food and limit dietary intake.

Primary care providers and healthcare delivery systems are increasingly accountable for the clinical outcomes of populations with chronic conditions such as diabetes. The integration of oral health into primary care and collaboration with dental care providers creates an opportunity for both provider types to meet the triple aim of improved patient experience, improved health of populations, and lower overall costs [333, 334].

The primary healthcare team can contribute to early detection of periodontitis and other oral diseases common in diabetes by (1) education of diabetic patients about the importance of maintaining good oral health and its connection with diabetes, (2) referring patients with poor glycemic control for regular dental visits to control oral disease, (3) making sure their diabetic patients have a dentist who oversees their oral health needs, (4) referring diabetic patients with oral infections or emergent abnormal findings for immediate dental care, (5) including screening, both visually and by validated questions, for oral disease as part of the protocol of diabetes monitoring, (6) including oral disease prevention protocols such as oral hygiene education, nutritional counseling, and fluoride varnish application in diabetes management and (7) establishing strong communication protocols with dentists so that medical and dental information about a patient is easily accessible and professional consults are facilitated [334–336].

Summary

Individuals with diabetes mellitus are at increased risk for a variety of oral conditions including periodontitis, dental caries, stomatitis, salivary dysfunction, and oral burning. Inquiring about oral symptoms during a standard review of systems can help to identify these conditions and ensure that patients receive appropriate diagnosis and management. Successful treatment of advanced dental caries, stomatitis, salivary dysfunction, and oral burning can have immediate impact on a patient's quality of life. Identification of largely asymptomatic oral infections, such as early dental caries and periodontal disease, can help to preserve a patient's dentition which aids in proper nutrition and glycemic control. Furthermore, early diagnosis of oral malignant and premalignant conditions can drastically affect an individual's ultimate prognosis. Patients with diabetes who do not have a dental home should be referred to a dentist for a complete evaluation of the dentition, periodontium, intraoral soft tissues, and structures of the head and neck. Collaboration between medical and dental professionals facilitates a holistic approach to care, which is essential to the health of the diabetic population.

References

1. Löe H. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care. 1993;16(1):329–34.
2. Klokkevold P, Mealey B. Influence of systemic conditions. In: Newman M, Takei H, Klokkevold P, Carranza F, editors. Carranza's clinical periodontology. St. Louis: Elsevier Saunders; 2015.
3. Newman MG, Takei HH, Klokkevold PR, Carranza FA. Carranza's clinical periodontology. St. Louis: Elsevier Saunders; 2015.
4. Fiorellini J, Stathopoulou P. Clinical features of gingivitis. In: Newman M, Takei H, Klokkevold P, Carranza F, editors. Carranza's clinical periodontology. St. Louis: Elsevier Saunders; 2015.
5. Ervasti T, Knuuttila M, Pohjamo L, Haukipuro K. Relation between control of diabetes and gingival bleeding. J Periodontol. 1985;56(3):154–7.
6. de Pommereau V, Dargent-Paré C, Robert JJ, Brion M. Periodontal status in insulin-dependent diabetic adolescents. J Clin Periodontol. 1992;19(9 Pt 1):628–32.

7. Cutler CW, Machen RL, Jotwani R, Iacopino AM. Heightened gingival inflammation and attachment loss in type 2 diabetics with hyperlipidemia. J Periodontol. 1999;70(11):1313–21.
8. Cianciola LJ, Park BH, Bruck E, Mosovich L, Genco RJ. Prevalence of periodontal disease in insulin-dependent diabetes mellitus (juvenile diabetes). J Am Dent Assoc. 1982;104(5):653–60.
9. Seppälä B, Seppälä M, Ainamo J. A longitudinal study on insulin-dependent diabetes mellitus and periodontal disease. J Clin Periodontol. 1993;20(3):161–5.
10. Salvi GE, Kandylaki M, Troendle A, Persson GR, Lang NP. Experimental gingivitis in type 1 diabetics: a controlled clinical and microbiological study. J Clin Periodontol. 2005;32(3):310–6.
11. Karjalainen KM, Knuuttila ML. The onset of diabetes and poor metabolic control increases gingival bleeding in children and adolescents with insulin-dependent diabetes mellitus. J Clin Periodontol. 1996;23(12):1060–7.
12. NIDCR Data and Statistics: Periodontal (Gum) Disease: National Institute of Dental and Craniofacial Research; [updated May 28, 2014]. Available from: http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/GumDisease/
13. Carranza F, Camargo P, Takei H. Bone loss and patterns of bone destruction. In: Newman M, Takei H, Klokkevold P, Carranza F, editors. Carranza's clinical periodontology. St. Louis: Elsevier Saunders; 2015.
14. American Academy of Periodontology. Position paper: epidemiology of periodontal diseases. J Periodontol. 1996;67(9):935–45.
15. Ismail AI, Burt BA, Eklund SA. Epidemiologic patterns of smoking and periodontal disease in the United States. J Am Dent Assoc. 1983;106(5):617–21.
16. Burt B. Research SiaTCotAAoP. Position paper: epidemiology of periodontal diseases. J Periodontol. 2005;76(8):1406–19.
17. Novak K, Novak MJ. Clinical risk assessment. In: Newman M, Takei H, Klokkevold P, Carranza F, editors. Carranza's clinical periodontology. St. Louis: Elsevier Saunders; 2015.
18. Persson GR. Diabetes and periodontal disease: an update for HealthCare Providers. Diabetes Spectrum. 2011;24(4):195–8.
19. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ, CDC Periodontal Disease Surveillance workgroup: James Beck (University of North Carolina CH, U. S. A.), Gordon Douglass (Past President, American Academy of Periodontology), R.y Page (University of Washin). Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res. 2012;91(10):914–20.
20. Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. J Periodontol. 2015;86(5):611–22.
21. Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol. 1996;1(1):1–36.
22. Mealey BL, Oates TW, Periodontology AAo. Diabetes mellitus and periodontal diseases. J Periodontol. 2006;77(8):1289–303.
23. Mealey BL, Rose LF. Diabetes mellitus and inflammatory periodontal diseases. Curr Opin Endocrinol Diabetes Obes. 2008;15(2):135–41.
24. Lakschevitz F, Aboodi G, Tenenbaum H, Glogauer M. Diabetes and periodontal diseases: interplay and links. Curr Diabetes Rev. 2011;7(6):433–9.
25. Chee B, Park B, Bartold PM. Periodontitis and type II diabetes: a two-way relationship. Int J Evid Based Healthc. 2013;11(4):317–29.
26. Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. J Periodontol. 2013;84 Suppl 4:S135–52.
27. Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. Ann Periodontol. 2001;6(1):99–112.
28. Chávarry NG, Vettore MV, Sansone C, Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. Oral Health Prev Dent. 2009;7(2):107–27.
29. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. J Diabetes Complications. 2006;20(1):59–68.
30. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nat Rev Endocrinol. 2011;7(12):738–48.
31. Chapple IL, Genco R, workshop wgotjEA. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol. 2013;84 Suppl 4:S106–12.
32. Taylor JJ, Preshaw PM, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. J Periodontol. 2013;84 Suppl 4:S113–34.
33. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontol. 1996;67 Suppl 10:1085–93.
34. Demmer RT, Jacobs DR, Singh R, Zuk A, Rosenbaum M, Papapanou PN, et al. Periodontal bacteria and prediabetes prevalence in ORIGINS: the oral infections, glucose intolerance, and insulin resistance study. J Dent Res. 2015;94 Suppl 9:201S–11.
35. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, et al. Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years. J Periodontol. 1998;69(1):76–83.
36. Tervonen T, Karjalainen K, Knuuttila M, Huumonen S. Alveolar bone loss in type 1 diabetic subjects. J Clin Periodontol. 2000;27(8):567–71.

37. Lalla E, Park DB, Papapanou PN, Lamster IB. Oral disease burden in northern Manhattan patients with diabetes mellitus. Am J Public Health. 2008;98 Suppl 9:S91–4.
38. Wu YY, Xiao E, Graves DT. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci. 2015;7(2):63–72.
39. Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Community Dent Oral Epidemiol. 2002;30(3):182–92.
40. Kaur G, Holtfreter B, Rathmann W, Rathmann WG, Schwahn C, Wallaschofski H, et al. Association between type 1 and type 2 diabetes with periodontal disease and tooth loss. J Clin Periodontol. 2009;36(9): 765–74.
41. Bagdade JD, Root RK, Bulger RJ. Impaired leukocyte function in patients with poorly controlled diabetes. Diabetes. 1974;23(1):9–15.
42. Molenaar DM, Palumbo PJ, Wilson WR, Ritts RE. Leukocyte chemotaxis in diabetic patients and their nondiabetic first-degree relatives. Diabetes. 1976;25 Suppl 2:880–3.
43. Bagdade JD, Stewart M, Walters E. Impaired granulocyte adherence. A reversible defect in host defense in patients with poorly controlled diabetes. Diabetes. 1978;27(6):677–81.
44. Bagdade JD, Walters E. Impaired granulocyte adherence in mildly diabetic patients: effects of tolazamide treatment. Diabetes. 1980;29(4):309–11.
45. Manouchehr-Pour M, Spagnuolo PJ, Rodman HM, Bissada NF. Comparison of neutrophil chemotactic response in diabetic patients with mild and severe periodontal disease. J Periodontol. 1981;52(8):410–5.
46. McMullen JA, Van Dyke TE, Horoszewicz HU, Genco RJ. Neutrophil chemotaxis in individuals with advanced periodontal disease and a genetic predisposition to diabetes mellitus. J Periodontol. 1981;52(4):167–73.
47. Shetty N, Thomas B, Ramesh A. Comparison of neutrophil functions in diabetic and healthy subjects with chronic generalized periodontitis. J Indian Soc Periodontol. 2008;12(2):41–4.
48. Mowat A, Baum J. Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. N Engl J Med. 1971;284(12):621–7.
49. Alba-Loureiro TC, Munhoz CD, Martins JO, Cerchiaro GA, Scavone C, Curi R, et al. Neutrophil function and metabolism in individuals with diabetes mellitus. Braz J Med Biol Res. 2007;40(8):1037–44.
50. Naghibi M, Smith RP, Baltch AL, Gates SA, Wu DH, Hammer MC, et al. The effect of diabetes mellitus on chemotactic and bactericidal activity of human polymorphonuclear leukocytes. Diabetes Res Clin Pract. 1987;4(1):27–35.
51. Wong SL, Demers M, Martinod K, Gallant M, Wang Y, Goldfine AB, et al. Diabetes primes neutrophils to undergo NETosis, which impairs wound healing. Nat Med. 2015;21(7):815–9.
52. Graves DT, Liu R, Oates TW. Diabetes-enhanced inflammation and apoptosis: impact on periodontal pathosis. Periodontol 2000. 2007;45:128–37.
53. Pacios S, Kang J, Galicia J, Gluck K, Patel H, Ovaydi-Mandel A, et al. Diabetes aggravates periodontitis by limiting repair through enhanced inflammation. FASEB J. 2012;26(4):1423–30.
54. Preshaw P. Periodontal pathogenesis. In: Newman M, Takei H, Klokkevold P, Carranza F, editors. Carranza's clinical periodontology. St. Louis: Elsevier Saunders; 2015.
55. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med. 1997;14(1): 29–34.
56. Golub LM, Nicoll GA, Iacono VJ, Ramamurthy NS. In vivo crevicular leukocyte response to a chemotactic challenge: inhibition by experimental diabetes. Infect Immun. 1982;37(3):1013–20.
57. Lalla E, Lamster IB, Feit M, Huang L, Spessot A, Qu W, et al. Blockade of RAGE suppresses periodontitis-associated bone loss in diabetic mice. J Clin Invest. 2000;105(8):1117–24.
58. Pacios S, Andriankaja O, Kang J, Alnammary M, Bae J, de Brito Bezerra B, et al. Bacterial infection increases periodontal bone loss in diabetic rats through enhanced apoptosis. Am J Pathol. 2013;183(6):1928–35.
59. Gyurko R, Siqueira CC, Caldon N, Gao L, Kantarci A, Van Dyke TE. Chronic hyperglycemia predisposes to exaggerated inflammatory response and leukocyte dysfunction in Akita mice. J Immunol. 2006;177(10):7250–6.
60. Silva JA, Lopes Ferrucci D, Peroni LA, de Paula IE, Rossa-Junior C, Carvalho HF, et al. Periodontal disease-associated compensatory expression of osteoprotegerin is lost in type 1 diabetes mellitus and correlates with alveolar bone destruction by regulating osteoclastogenesis. Cells Tissues Organs. 2012;196(2):137–50.
61. Liu R, Bal HS, Desta T, Krothapalli N, Alyassi M, Luan Q, et al. Diabetes enhances periodontal bone loss through enhanced resorption and diminished bone formation. J Dent Res. 2006;85(6):510–4.
62. Kang J, de Brito Bezerra B, Pacios S, Andriankaja O, Li Y, Tsiagbe V, et al. Aggregatibacter actinomycetemcomitans infection enhances apoptosis in vivo through a caspase-3-dependent mechanism in experimental periodontitis. Infect Immun. 2012;80(6): 2247–56.
63. Taylor G, Graves D, Lamster I. Periodontal disease as a complication of diabetes mellitus. In: Lamster I, editor. Diabetes mellitus and oral health: an interprofessional approach. Ames: Wiley Blackwell; 2014. p. 130–1.
64. Murillo J, Wang Y, Xu X, Klebe RJ, Chen Z, Zardeneta G, et al. Advanced glycation of type I

collagen and fibronectin modifies periodontal cell behavior. J Periodontol. 2008;79(11):2190–9.
65. Ren L, Fu Y, Deng Y, Qi L, Jin L. Advanced glycation end products inhibit the expression of collagens type I and III by human gingival fibroblasts. J Periodontol. 2009;80(7):1166–73.
66. Alikhani M, Alikhani Z, Graves DT. FOXO1 functions as a master switch that regulates gene expression necessary for tumor necrosis factor-induced fibroblast apoptosis. J Biol Chem. 2005;280(13):12096–102.
67. Zambon JJ, Reynolds H, Fisher JG, Shlossman M, Dunford R, Genco RJ. Microbiological and immunological studies of adult periodontitis in patients with noninsulin-dependent diabetes mellitus. J Periodontol. 1988;59(1):23–31.
68. Sbordone L, Ramaglia L, Barone A, Ciaglia RN, Iacono VJ. Periodontal status and subgingival microbiota of insulin-dependent juvenile diabetics: a 3-year longitudinal study. J Periodontol. 1998;69(2):120–8.
69. Casarin RC, Barbagallo A, Meulman T, Santos VR, Sallum EA, Nociti FH, et al. Subgingival biodiversity in subjects with uncontrolled type-2 diabetes and chronic periodontitis. J Periodontal Res. 2013;48(1):30–6.
70. Ebersole JL, Holt SC, Hansard R, Novak MJ. Microbiologic and immunologic characteristics of periodontal disease in Hispanic americans with type 2 diabetes. J Periodontol. 2008;79(4):637–46.
71. Demmer RT, Desvarieux M, Holtfreter B, Jacobs DR, Wallaschofski H, Nauck M, et al. Periodontal status and A1C change: longitudinal results from the study of health in Pomerania (SHIP). Diabetes Care. 2010;33(5):1037–43.
72. Janket SJ, Wightman A, Baird AE, Van Dyke TE, Jones JA. Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies. J Dent Res. 2005;84(12):1154–9.
73. Darré L, Vergnes JN, Gourdy P, Sixou M. Efficacy of periodontal treatment on glycaemic control in diabetic patients: a meta-analysis of interventional studies. Diabetes Metab. 2008;34(5):497–506.
74. Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of periodontal disease for glycaemic control in people with diabetes. Cochrane Database Syst Rev. 2010;5, CD004714.
75. Teeuw WJ, Gerdes VE, Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. Diabetes Care. 2010;33(2):421–7.
76. Engebretson S, Kocher T. Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis. J Periodontol. 2013;84 Suppl 4:S153–69.
77. Wang X, Han X, Guo X, Luo X, Wang D. The effect of periodontal treatment on hemoglobin a1c levels of diabetic patients: a systematic review and meta-analysis. PLoS One. 2014;9(9), e108412.
78. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, et al. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Cochrane Database Syst Rev. 2015;11, CD004714.
79. Corbella S, Francetti L, Taschieri S, De Siena F, Fabbro MD. Effect of periodontal treatment on glycemic control of patients with diabetes: a systematic review and meta-analysis. J Diabetes Investig. 2013;4(5):502–9.
80. Wolf D, Lalla E. The influence of periodontal disease on glycemic control in diabetes. In: Lamster I, editor. Diabetes mellitus and oral health: an interprofessional approach. Ames: Wiley Blackwell; 2014.
81. Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, et al. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. JAMA. 2013;310(23):2523–32.
82. Islam SA, Seo M, Lee YS, Moon SS. Association of periodontitis with insulin resistance, β-cell function, and impaired fasting glucose before onset of diabetes. Endocr J. 2015;62:981–9.
83. Demmer RT, Jacobs DR, Desvarieux M. Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. Diabetes Care. 2008;31(7):1373–9.
84. Chiu SY, Lai H, Yen AM, Fann JC, Chen LS, Chen HH. Temporal sequence of the bidirectional relationship between hyperglycemia and periodontal disease: a community-based study of 5,885 Taiwanese aged 35–44 years (KCIS No. 32). Acta Diabetol. 2015;52(1):123–31.
85. Morita I, Inagaki K, Nakamura F, Noguchi T, Matsubara T, Yoshii S, et al. Relationship between periodontal status and levels of glycated hemoglobin. J Dent Res. 2012;91(2):161–6.
86. Ide R, Hoshuyama T, Wilson D, Takahashi K, Higashi T. Periodontal disease and incident diabetes: a seven-year study. J Dent Res. 2011;90(1):41–6.
87. Saito T, Shimazaki Y, Kiyohara Y, Kato I, Kubo M, Iida M, et al. The severity of periodontal disease is associated with the development of glucose intolerance in non-diabetics: the Hisayama study. J Dent Res. 2004;83(6):485–90.
88. Alberti G, Zimmet P, Shaw J, Grundy S. Metabolic Syndrome: The IDF consensus worldwide definition of Metabolic Syndrome. In: Federation ID, editor. Brussels: IDF Communications; 2006. p. 1–24. http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf
89. Morita T, Yamazaki Y, Mita A, Takada K, Seto M, Nishinoue N, et al. A cohort study on the association between periodontal disease and the development of

metabolic syndrome. J Periodontol. 2010;81(4): 512–9.
90. Heitz-Mayfield LJ. Disease progression: identification of high-risk groups and individuals for periodontitis. J Clin Periodontol. 2005;32 Suppl 6:196–209.
91. Research, Science and Therapy Committee of the American Academy of Periodontology. Position paper: tobacco use and the periodontal patient. J Periodontol. 1999;70(11):1419–27.
92. Orbak R, Tezel A, Canakçi V, Demir T. The influence of smoking and non-insulin-dependent diabetes mellitus on periodontal disease. J Int Med Res. 2002;30(2):116–25.
93. Grossi SG, Skrepcinski FB, DeCaro T, Zambon JJ, Cummins D, Genco RJ. Response to periodontal therapy in diabetics and smokers. J Periodontol. 1996;67 Suppl 10:1094–102.
94. Preshaw PM, Heasman L, Stacey F, Steen N, McCracken GI, Heasman PA. The effect of quitting smoking on chronic periodontitis. J Clin Periodontol. 2005;32(8):869–79.
95. Preshaw P, Chambrone L, K N. Smoking and periodontal disease. In: Newman M, Takei H, Klokkevold P, Carranza F, editors. Carranza's clinical periodontology. 12th ed. St. Louis: Elsevier Saunders; 2015. p. 1 online resource (xix, 818, 136 pages).
96. Rosa EF, Corraini P, de Carvalho VF, Inoue G, Gomes EF, Lotufo JP, et al. A prospective 12-month study of the effect of smoking cessation on periodontal clinical parameters. J Clin Periodontol. 2011;38(6):562–71.
97. Ide R, Hoshuyama T, Takahashi K. The effect of periodontal disease on medical and dental costs in a middle-aged Japanese population: a longitudinal worksite study. J Periodontol. 2007;78(11):2120–6.
98. Saremi A, Nelson RG, Tulloch-Reid M, Hanson RL, Sievers ML, Taylor GW, et al. Periodontal disease and mortality in type 2 diabetes. Diabetes Care. 2005;28(1):27–32.
99. Shultis WA, Weil EJ, Looker HC, Curtis JM, Shlossman M, Genco RJ, et al. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. Diabetes Care. 2007;30(2):306–11.
100. Varon FN. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes: response to Shultis et al. Diabetes Care. 2007;30(12), e138; author reply e9.
101. Thorstensson H, Kuylenstierna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. J Clin Periodontol. 1996;23(3 Pt 1):194–202.
102. Banthia R, Raje S, Banthia P, Saral SK, Singh P, Gupta S. Evaluation of the association between periodontal disease and diabetic retinopathy. Gen Dent. 2014;62(6):e28–32.
103. Noma H, Sakamoto I, Mochizuki H, Tsukamoto H, Minamoto A, Funatsu H, et al. Relationship between periodontal disease and diabetic retinopathy. Diabetes Care. 2004;27(2):615.
104. Borgnakke WS, Anderson PF, Shannon C, Jivanescu A. Is there a relationship between oral health and diabetic neuropathy? Curr Diab Rep. 2015;15(11):93.
105. Abrao L, Chagas JK, Schmid H. Periodontal disease and risk for neuropathic foot ulceration in type 2 diabetes. Diabetes Res Clin Pract. 2010;90(1):34–9.
106. Figuero E, Carrillo-de-Albornoz A, Martín C, Tobías A, Herrera D. Effect of pregnancy on gingival inflammation in systemically healthy women: a systematic review. J Clin Periodontol. 2013;40(5):457–73.
107. Wu M, Chen SW, Jiang SY. Relationship between gingival inflammation and pregnancy. Mediators Inflamm. 2015;2015:623427.
108. Mealey BL, Moritz AJ. Hormonal influences: effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. Periodontol 2000. 2003;32:59–81.
109. Silk H, Douglass AB, Douglass JM, Silk L. Oral health during pregnancy. Am Fam Physician. 2008;77(8):1139–44.
110. Sills ES, Zegarelli DJ, Hoschander MM, Strider WE. Clinical diagnosis and management of hormonally responsive oral pregnancy tumor (pyogenic granuloma). J Reprod Med. 1996;41(7):467–70.
111. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol. 1996;67 Suppl 10:1103–13.
112. Sanz M, Kornman K, workshop WgojEA. Periodontitis and adverse pregnancy outcomes: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol. 2013;40 Suppl 14:S164–9.
113. Buduneli N, Baylas H, Buduneli E, Türkoğlu O, Köse T, Dahlen G. Periodontal infections and pre-term low birth weight: a case–control study. J Clin Periodontol. 2005;32(2):174–81.
114. Bansal M, Khatri M, Kumar A, Bhatia G. Relationship between maternal periodontal status and preterm low birth weight. Rev Obstet Gynecol. 2013;6(3–4):135–40.
115. Boggess KA, Lieff S, Murtha AP, Moss K, Beck J, Offenbacher S. Maternal periodontal disease is associated with an increased risk for preeclampsia. Obstet Gynecol. 2003;101(2):227–31.
116. Surdacka A, Ciężka E, Pioruńska-Stolzmann M, Wender-Ożegowska E, Korybalska K, Kawka E, et al. Relation of salivary antioxidant status and cytokine levels to clinical parameters of oral health in pregnant women with diabetes. Arch Oral Biol. 2011;56(5):428–36.
117. Novak KF, Taylor GW, Dawson DR, Ferguson JE, Novak MJ. Periodontitis and gestational diabetes mellitus: exploring the link in NHANES III. J Public Health Dent. 2006;66(3):163–8.

118. Xiong X, Buekens P, Vastardis S, Pridjian G. Periodontal disease and gestational diabetes mellitus. Am J Obstet Gynecol. 2006;195(4):1086–9.
119. Xiong X, Elkind-Hirsch KE, Vastardis S, Delarosa RL, Pridjian G, Buekens P. Periodontal disease is associated with gestational diabetes mellitus: a case-control study. J Periodontol. 2009;80(11): 1742–9.
120. Chokwiriyachit A, Dasanayake AP, Suwannarong W, Hormdee D, Sumanonta G, Prasertchareonsuk W, et al. Periodontitis and gestational diabetes mellitus in non-smoking females. J Periodontol. 2013;84(7): 857–62.
121. Gogeneni H, Buduneli N, Ceyhan-Öztürk B, Gümüş P, Akcali A, Zeller I, et al. Increased infection with key periodontal pathogens during gestational diabetes mellitus. J Clin Periodontol. 2015;42(6): 506–12.
122. Dasanayake AP, Chhun N, Tanner AC, Craig RG, Lee MJ, Moore AF, et al. Periodontal pathogens and gestational diabetes mellitus. J Dent Res. 2008;87(4): 328–33.
123. Esteves Lima RP, Miranda Cota LO, Costa FO. Association between periodontitis and gestational diabetes mellitus: a case-control study. J Periodontol. 2013;84(9):1257–65.
124. Esteves Lima RP, Cyrino RM, de Carvalho Dutra B, Oliveira da Silveira J, Martins CC, Miranda Cota LO, et al. Association between periodontitis and gestational diabetes mellitus: systematic review and meta-analysis. J Periodontol. 2016;87(1):48–57.
125. Xie Y, Xiong X, Elkind-Hirsch KE, Pridjian G, Maney P, Delarosa RL, et al. Prepregnancy obesity and periodontitis among pregnant females with and without gestational diabetes mellitus. J Periodontol. 2014;85(7):890–8.
126. Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, et al. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med. 2006;355(18):1885–94.
127. Hujoel PP, Lydon-Rochelle M, Robertson PB, del Aguila MA. Cessation of periodontal care during pregnancy: effect on infant birthweight. Eur J Oral Sci. 2006;114(1):2–7.
128. Amerongen AV, Veerman EC. Saliva – the defender of the oral cavity. Oral Dis. 2002;8(1):12–22.
129. Gråhn E, Tenovuo J, Lehtonen OP, Eerola E, Vilja P. Antimicrobial systems of human whole saliva in relation to dental caries, cariogenic bacteria, and gingival inflammation in young adults. Acta Odontol Scand. 1988;46(2):67–74.
130. Pedersen AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. Oral Dis. 2002;8(3):117–29.
131. Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. J Am Dent Assoc. 1987;115(4): 581–4.
132. Malicka B, Kaczmarek U, Skośkiewicz-Malinowska K. Prevalence of xerostomia and the salivary flow rate in diabetic patients. Adv Clin Exp Med. 2014;23(2): 225–33.
133. Moore PA, Guggenheimer J, Etzel KR, Weyant RJ, Orchard T. Type 1 diabetes mellitus, xerostomia, and salivary flow rates. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;92(3):281–91.
134. Mata AD, Marques D, Rocha S, Francisco H, Santos C, Mesquita MF, et al. Effects of diabetes mellitus on salivary secretion and its composition in the human. Mol Cell Biochem. 2004;261(1–2):137–42.
135. Carda C, Carranza M, Arriaga A, Díaz A, Peydró A, Gomez de Ferraris ME. Structural differences between alcoholic and diabetic parotid sialosis. Med Oral Patol Oral Cir Bucal. 2005;10(4):309–14.
136. Chavez EM, Taylor GW, Borrell LN, Ship JA. Salivary function and glycemic control in older persons with diabetes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;89(3):305–11.
137. Scully C. Drug effects on salivary glands: dry mouth. Oral Dis. 2003;9(4):165–76.
138. Aliko A, Wolff A, Dawes C, Aframian D, Proctor G, Ekström J, et al. World workshop on oral medicine VI: clinical implications of medication-induced salivary gland dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120(2):185–206.
139. Lm S. Drugs, dry mouth, and dentistry. In: Sreebny L, Vissink A, editors. Dry mouth, the malevolent symptom: a clinical guide. Ames: Wiley Blackwell; 2010. p. 89–191.
140. Mandel L, Hamele-Bena D. Alcoholic parotid sialadenosis. J Am Dent Assoc. 1997;128(10): 1411–5.
141. Chilla R. Sialadenosis of the salivary glands of the head. Studies on the physiology and pathophysiology of parotid secretion. Adv Otorhinolaryngol. 1981;26:1–38.
142. Donath K, Seifert G. Ultrastructural studies of the parotid glands in sialadenosis. Virchows Arch A Pathol Anat Histol. 1975;365(2):119–35.
143. Mandel L, Patel S. Sialadenosis associated with diabetes mellitus: a case report. J Oral Maxillofac Surg. 2002;60(6):696–8.
144. Mandel L, Khelemsky R. Asymptomatic bilateral facial swelling. J Am Dent Assoc. 2012;143(11): 1205–8.
145. Ihrler S, Rath C, Zengel P, Kirchner T, Harrison JD, Weiler C. Pathogenesis of sialadenosis: possible role of functionally deficient myoepithelial cells. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;110(2):218–23.
146. Russotto SB. Asymptomatic parotid gland enlargement in diabetes mellitus. Oral Surg Oral Med Oral Pathol. 1981;52(6):594–8.

147. Scully C, Bagán JV, Eveson JW, Barnard N, Turner FM. Sialosis: 35 cases of persistent parotid swelling from two countries. Br J Oral Maxillofac Surg. 2008;46(6):468–72.
148. Lilliu MA, Solinas P, Cossu M, Puxeddu R, Loy F, Isola R, et al. Diabetes causes morphological changes in human submandibular gland: a morphometric study. J Oral Pathol Med. 2015;44(4):291–5.
149. Lilliu MA, Loy F, Cossu M, Solinas P, Isola R, Isola M. Morphometric study of diabetes related alterations in human parotid gland and comparison with submandibular gland. Anat Rec (Hoboken). 2015;298(11):1911–8.
150. Merlo C, Bohl L, Carda C, Gómez de Ferraris ME, Carranza M. Parotid sialosis: morphometrical analysis of the glandular parenchyme and stroma among diabetic and alcoholic patients. J Oral Pathol Med. 2010;39(1):10–5.
151. Yakubov Y, Mandel L. Bilateral parotid swelling in polycystic ovarian syndrome. J Oral Maxillofac Surg. 2016;74(5):991–4. doi:10.1016/j.joms.2015.10.026.
152. Fox PC. Autoimmune diseases and Sjogren's syndrome: an autoimmune exocrinopathy. Ann N Y Acad Sci. 2007;1098:15–21.
153. Dodds MW, Johnson DA, Yeh CK. Health benefits of saliva: a review. J Dent. 2005;33(3):223–33.
154. Carneiro VL, Fraiz FC, Ferreira FM, Pintarelli TP, Oliveira AC, Boguszewski MC. The influence of glycemic control on the oral health of children and adolescents with diabetes mellitus type 1. Arch Endocrinol Metab. 2015;59(6):535–40.
155. Rai K, Hegde AM, Kamath A, Shetty S. Dental caries and salivary alterations in Type I diabetes. J Clin Pediatr Dent. 2011;36(2):181–4.
156. Siudikiene J, Machiulskiene V, Nyvad B, Tenovuo J, Nedzelskiene I. Dental caries and salivary status in children with type 1 diabetes mellitus, related to the metabolic control of the disease. Eur J Oral Sci. 2006;114(1):8–14.
157. Gupta VK, Malhotra S, Sharma V, Hiremath SS. The influence of insulin dependent diabetes mellitus on dental caries and salivary flow. Int J Chronic Dis. 2014;2014:790898.
158. Busato IM, Ignácio SA, Brancher JA, Moysés ST, Azevedo-Alanis LR. Impact of clinical status and salivary conditions on xerostomia and oral health-related quality of life of adolescents with type 1 diabetes mellitus. Community Dent Oral Epidemiol. 2012;40(1):62–9.
159. Vasconcelos AC, Soares MS, Almeida PC, Soares TC. Comparative study of the concentration of salivary and blood glucose in type 2 diabetic patients. J Oral Sci. 2010;52(2):293–8.
160. Jawed M, Khan RN, Shahid SM, Azhar A. Protective effects of salivary factors in dental caries in diabetic patients of Pakistan. Exp Diabetes Res. 2012;2012: 947304.
161. Kogawa EM, Grisi DC, Falcão DP, Amorim IA, Rezende TM, da Silva IC, et al. Salivary function impairment in type 2 Diabetes patients associated with concentration and genetic polymorphisms of chromogranin A. Clin Oral Investig. 2016;1–13. [Epub ahead of print]. PMID: 26750135.
162. Montaldo L, Montaldo P, Papa A, Caramico N, Toro G. Effects of saliva substitutes on oral status in patients with type 2 diabetes. Diabet Med. 2010;27(11):1280–3.
163. Dodds MW, Yeh CK, Johnson DA. Salivary alterations in type 2 (non-insulin-dependent) diabetes mellitus and hypertension. Community Dent Oral Epidemiol. 2000;28(5):373–81.
164. Lasisi TJ, Fasanmade AA. Comparative analysis of salivary glucose and electrolytes in diabetic individuals with periodontitis. Ann Ib Postgrad Med. 2012;10(1):25–30.
165. Malicka B, Kaczmarek U, Skośkiewicz-Malinowska K. Selected antibacterial factors in the saliva of diabetic patients. Arch Oral Biol. 2015;60(3):425–31.
166. Meurman JH, Collin HL, Niskanen L, Töyry J, Alakuijala P, Keinänen S, et al. Saliva in non-insulin-dependent diabetic patients and control subjects: the role of the autonomic nervous system. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86(1): 69–76.
167. Mascarenhas P, Fatela B, Barahona I. Effect of diabetes mellitus type 2 on salivary glucose – a systematic review and meta-analysis of observational studies. PLoS One. 2014;9(7), e101706.
168. Mussavira S, Dharmalingam M, Omana Sukumaran B. Salivary glucose and antioxidant defense markers in type II diabetes mellitus. Turk J Med Sci. 2015;45(1):141–7.
169. Twetman S, Johansson I, Birkhed D, Nederfors T. Caries incidence in young type 1 diabetes mellitus patients in relation to metabolic control and caries-associated risk factors. Caries Res. 2002;36(1):31–5.
170. Barnes VM, Kennedy AD, Panagakos F, Devizio W, Trivedi HM, Jönsson T, et al. Global metabolomic analysis of human saliva and plasma from healthy and diabetic subjects, with and without periodontal disease. PLoS One. 2014;9(8), e105181.
171. Twetman S, Nederfors T, Stahl B, Aronson S. Two--year longitudinal observations of salivary status and dental caries in children with insulin-dependent diabetes mellitus. Pediatr Dent. 1992;14(3):184–8.
172. Karjalainen KM, Knuuttila ML, Käär ML. Relationship between caries and level of metabolic balance in children and adolescents with insulin-dependent diabetes mellitus. Caries Res. 1997;31(1): 13–8.
173. Carda C, Mosquera-Lloreda N, Salom L, Gomez de Ferraris ME, Peydró A. Structural and functional salivary disorders in type 2 diabetic patients. Med Oral Patol Oral Cir Bucal. 2006;11(4):E309–14.
174. Collin HL, Sorsa T, Meurman JH, Niskanen L, Salo T, Rönkä H, et al. Salivary matrix metalloproteinase (MMP-8) levels and gelatinase (MMP-9) activities

in patients with type 2 diabetes mellitus. J Periodontal Res. 2000;35(5):259–65.
175. Lamster I. Non-periodontal oral complications of diabetes mellitus. In: Lamster I, editor. Diabetes mellitus and oral health: an interprofessional approach. Ames: Wiley Blackwell; 2014. p. 162.
176. Rao PV, Reddy AP, Lu X, Dasari S, Krishnaprasad A, Biggs E, et al. Proteomic identification of salivary biomarkers of type-2 diabetes. J Proteome Res. 2009;8(1):239–45.
177. Border MB, Schwartz S, Carlson J, Dibble CF, Kohltfarber H, Offenbacher S, et al. Exploring salivary proteomes in edentulous patients with type 2 diabetes. Mol Biosyst. 2012;8(4):1304–10.
178. Dye BA, Thornton-Evans G, Li X, Iafolla TJ. Dental caries and sealant prevalence in children and adolescents in the United States, 2011–2012. NCHS Data Brief. 2015;191:1–8. http://www.cdc.gov/nchs/products/databriefs/db191.htm.
179. National Center for Health Statistics: Third National Health and Nutrition Survey (NHANES III) reference manuals and reports. Hyattsville: NCHS, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; 1996.
180. Featherstone JD. Dental caries: a dynamic disease process. Aust Dent J. 2008;53(3):286–91.
181. Moynihan PJ, Kelly SA. Effect on caries of restricting sugars intake: systematic review to inform WHO guidelines. J Dent Res. 2014;93(1):8–18.
182. Novotna M, Podzimek S, Broukal Z, Lencova E, Duskova J. Periodontal diseases and dental caries in children with type 1 diabetes mellitus. Mediators Inflamm. 2015;2015:379626.
183. Ismail AF, McGrath CP, Yiu CK. Oral health of children with type 1 diabetes mellitus: a systematic review. Diabetes Res Clin Pract. 2015;108(3):369–81.
184. Garton BJ, Ford PJ. Root caries and diabetes: risk assessing to improve oral and systemic health outcomes. Aust Dent J. 2012;57(2):114–22.
185. Miralles L, Silvestre FJ, Hernández-Mijares A, Bautista D, Llambes F, Grau D. Dental caries in type 1 diabetics: influence of systemic factors of the disease upon the development of dental caries. Med Oral Patol Oral Cir Bucal. 2006;11(3):E256–60.
186. Miko S, Ambrus SJ, Sahafian S, Dinya E, Tamas G, Albrecht MG. Dental caries and adolescents with type 1 diabetes. Br Dent J. 2010;208(6), E12.
187. Edblad E, Lundin SA, Sjödin B, Aman J. Caries and salivary status in young adults with type 1 diabetes. Swed Dent J. 2001;25(2):53–60.
188. Jones RB, McCallum RM, Kay EJ, Kirkin V, McDonald P. Oral health and oral health behaviour in a population of diabetic outpatient clinic attenders. Community Dent Oral Epidemiol. 1992;20(4):204–7.
189. Lalla E, Cheng B, Lal S, Tucker S, Greenberg E, Goland R, et al. Periodontal changes in children and adolescents with diabetes: a case-control study. Diabetes Care. 2006;29(2):295–9.
190. Arrieta-Blanco JJ, Bartolomé-Villar B, Jiménez-Martinez E, Saavedra-Vallejo P, Arrieta-Blanco FJ. Bucco-dental problems in patients with diabetes mellitus (I): index of plaque and dental caries. Med Oral. 2003;8(2):97–109.
191. Orbak R, Simsek S, Orbak Z, Kavrut F, Colak M. The influence of type-1 diabetes mellitus on dentition and oral health in children and adolescents. Yonsei Med J. 2008;49(3):357–65.
192. Tagelsir A, Cauwels R, van Aken S, Vanobbergen J, Martens LC. Dental caries and dental care level (restorative index) in children with diabetes mellitus type 1. Int J Pediatr Dent. 2011;21(1):13–22.
193. Siudikiene J, Maciulskiene V, Nedzelskiene I. Dietary and oral hygiene habits in children with type I diabetes mellitus related to dental caries. Stomatologija. 2005;7(2):58–62.
194. Bolgül BS, Celenk S, Ayna BE, Atakul F, Uysal E. Evaluation of caries risk factors and effects of a fluoride-releasing adhesive material in children with insulin-dependent diabetes mellitus (IDDM): initial first-year results. Acta Odontol Scand. 2004;62(5):289–92.
195. Saes Busato IM, Bittencourt MS, Machado MA, Grégio AM, Azevedo-Alanis LR. Association between metabolic control and oral health in adolescents with type 1 diabetes mellitus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(3):e51–6.
196. Syrjälä AM, Niskanen MC, Ylöstalo P, Knuuttila ML. Metabolic control as a modifier of the association between salivary factors and dental caries among diabetic patients. Caries Res. 2003;37(2):142–7.
197. Moore PA, Weyant RJ, Etzel KR, Guggenheimer J, Mongelluzzo MB, Myers DE, et al. Type 1 diabetes mellitus and oral health: assessment of coronal and root caries. Community Dent Oral Epidemiol. 2001;29(3):183–94.
198. Lamster I. Non-periodontal oral complications of diabetes mellitus. In: Lamster I, editor. Diabetes mellitus and oral health: an interprofessional approach. Ames: Wiley Blackwell; 2014.
199. Hintao J, Teanpaisan R, Chongsuvivatwong V, Dahlen G, Rattarasarn C. Root surface and coronal caries in adults with type 2 diabetes mellitus. Community Dent Oral Epidemiol. 2007;35(4):302–9.
200. Lin BP, Taylor GW, Allen DJ, Ship JA. Dental caries in older adults with diabetes mellitus. Spec Care Dentist. 1999;19(1):8–14.
201. Collin HL, Uusitupa M, Niskanen L, Koivisto AM, Markkanen H, Meurman JH. Caries in patients with non-insulin-dependent diabetes mellitus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85(6):680–5.
202. Närhi TO, Meurman JH, Odont D, Ainamo A, Tilvis R. Oral health in the elderly with non-insulin-

dependent diabetes mellitus. Spec Care Dentist. 1996;16(3):116–22.
203. Tavares M, Depaola P, Soparkar P, Joshipura K. The prevalence of root caries in a diabetic population. J Dent Res. 1991;70(6):979–83.
204. Cherry-Peppers G, Ship JA. Oral health in patients with type II diabetes and impaired glucose tolerance. Diabetes Care. 1993;16(4):638–41.
205. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, et al. Insulin-dependent diabetes mellitus and oral soft tissue pathologies: II. Prevalence and characteristics of *Candida* and candidal lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;89(5):570–6.
206. Albrecht M, Bánóczy J, Dinya E, Tamás G. Occurrence of oral leukoplakia and lichen planus in diabetes mellitus. J Oral Pathol Med. 1992;21(8): 364–6.
207. Dikshit RP, Ramadas K, Hashibe M, Thomas G, Somanathan T, Sankaranarayanan R. Association between diabetes mellitus and pre-malignant oral diseases: a cross sectional study in Kerala, India. Int J Cancer. 2006;118(2):453–7.
208. Ujpál M, Matos O, Bíbok G, Somogyi A, Szabó G, Suba Z. Diabetes and oral tumors in Hungary: epidemiological correlations. Diabetes Care. 2004;27(3): 770–4.
209. Gong Y, Wei B, Yu L, Pan W. Type 2 diabetes mellitus and risk of oral cancer and precancerous lesions: a meta-analysis of observational studies. Oral Oncol. 2015;51(4):332–40.
210. Tseng KS, Lin C, Lin YS, Weng SF. Risk of head and neck cancer in patients with diabetes mellitus: a retrospective cohort study in Taiwan. JAMA Otolaryngol Head Neck Surg. 2014;140(8):746–53.
211. Lin CC, Chiang JH, Li CI, Liu CS, Lin WY, Hsieh TF, et al. Cancer risks among patients with type 2 diabetes: a 10-year follow-up study of a nationwide population-based cohort in Taiwan. BMC Cancer. 2014;14:381.
212. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol. 1999;26(3–4):259–65.
213. Negrato CA, Tarzia O. Buccal alterations in diabetes mellitus. Diabetol Metab Syndr. 2010;2:3.
214. Neville BW. Oral and maxillofacial pathology. 4th ed. St. Louis: Saunders/Elsevier; 2015.
215. Al-Attas SA, Amro SO. Candidal colonization, strain diversity, and antifungal susceptibility among adult diabetic patients. Ann Saudi Med. 2010;30(2):101–8.
216. Lotfi-Kamran MH, Jafari AA, Falah-Tafti A, Tavakoli E, Falahzadeh MH. Candida colonization on the denture of diabetic and non-diabetic patients. Dent Res J (Isfahan). 2009;6(1):23–7.
217. Premkumar J, Ramani P, Chandrasekar T, Natesan A, Premkumar P. Detection of species diversity in oral *Candida* colonization and anti-fungal susceptibility among non-oral habit adult diabetic patients. J Nat Sci Biol Med. 2014;5(1):148–54.
218. Sanitá PV, Pavarina AC, Giampaolo ET, Silva MM, Mima EG, Ribeiro DG, et al. *Candida* spp. prevalence in well controlled type 2 diabetic patients with denture stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111(6):726–33.
219. Kalapala L, Raghunath V, Reginald AB. Salivary factors, candidal colonization and strain diversity in type II diabetics. Nat J Lab Med. 2015;4(4):52–8.
220. Tapper-Jones LM, Aldred MJ, Walker DM, Hayes TM. Candidal infections and populations of *Candida albicans* in mouths of diabetics. J Clin Pathol. 1981;34(7):706–11.
221. Kumar BV, Padshetty NS, Bai KY, Rao MS. Prevalence of *Candida* in the oral cavity of diabetic subjects. J Assoc Physicians India. 2005;53: 599–602.
222. Bremenkamp RM, Caris AR, Jorge AO, Back-Brito GN, Mota AJ, Balducci I, et al. Prevalence and antifungal resistance profile of *Candida* spp. oral isolates from patients with type 1 and 2 diabetes mellitus. Arch Oral Biol. 2011;56(6):549–55.
223. Cavaleiro I, Proença L, Félix S, Salema-Oom M. Prevalence of yeast other than *Candida albicans* in denture wearers. J Prosthodont. 2013;22(5):351–7.
224. Zomorodian K, Haghighi NN, Rajaee N, Pakshir K, Tarazooie B, Vojdani M, et al. Assessment of *Candida* species colonization and denture-related stomatitis in complete denture wearers. Med Mycol. 2011;49(2): 208–11.
225. Dorocka-Bobkowska B, Zozulinska-Ziolkiewicz D, Wierusz-Wysocka B, Hedzelek W, Szumala-Kakol A, Budtz-Jörgensen E. Candida-associated denture stomatitis in type 2 diabetes mellitus. Diabetes Res Clin Pract. 2010;90(1):81–6.
226. Willis AM, Coulter WA, Fulton CR, Hayes JR, Bell PM, Lamey PJ. Oral candidal carriage and infection in insulin-treated diabetic patients. Diabet Med. 1999;16(8):675–9.
227. Vasconcelos BC, Novaes M, Sandrini FA, Maranhão Filho AW, Coimbra LS. Prevalence of oral mucosa lesions in diabetic patients: a preliminary study. Braz J Otorhinolaryngol. 2008;74(3):423–8.
228. Sashikumar R, Kannan R. Salivary glucose levels and oral candidal carriage in type II diabetics. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(5):706–11.
229. Borgnakke WS. Salivary glucose levels are unable to predict oral candidiasis or monitor diabetes. J Evid Based Dent Pract. 2010;10(4):237–40.
230. Darwazeh AM, Lamey PJ, Samaranayake LP, MacFarlane TW, Fisher BM, Macrury SM, et al. The relationship between colonisation, secretor status and in-vitro adhesion of *Candida albicans* to buccal epithelial cells from diabetics. J Med Microbiol. 1990;33(1):43–9.

231. Samaranayake LP. Host factors and Oral Candidosis. In: Samaranayake LP, MacFarlane TW, editor. Oral Candidosis. London: Wright Butterworth; 1990:66-103.
232. Hibino K, Samaranayake LP, Hägg U, Wong RW, Lee W. The role of salivary factors in persistent oral carriage of *Candida* in humans. Arch Oral Biol. 2009;54(7):678–83.
233. Gandara B, Morton T. Non-periodontal oral manifestations of diabetes: a framework for medical care providers. Diabetes Spectrum. 2011;24:199–205.
234. Saini R, Al-Maweri SA, Saini D, Ismail NM, Ismail AR. Oral mucosal lesions in non oral habit diabetic patients and association of diabetes mellitus with oral precancerous lesions. Diabetes Res Clin Pract. 2010;89(3):320–6.
235. Fisher BM, Lamey PJ, Samaranayake LP, MacFarlane TW, Frier BM. Carriage of *Candida* species in the oral cavity in diabetic patients: relationship to glycaemic control. J Oral Pathol. 1987;16(5):282–4.
236. Webb BC, Thomas CJ, Willcox MD, Harty DW, Knox KW. Candida-associated denture stomatitis. Aetiology and management: a review. Part 1. Factors influencing distribution of *Candida* species in the oral cavity. Aust Dent J. 1998;43(1):45–50.
237. Sahin I, Oksuz S, Sencan I, Gulcan A, Karabay O, Gulcan E, et al. Prevalence and risk factors for yeast colonization in adult diabetic patients. Ethiop Med J. 2005;43(2):103–9.
238. Aly FZ, Blackwell CC, Mackenzie DA, Weir DM, Clarke BF. Factors influencing oral carriage of yeasts among individuals with diabetes mellitus. Epidemiol Infect. 1992;109(3):507–18.
239. Chandler PT, Chandler SD. Pathogenic carrier rate in diabetes mellitus. Am J Med Sci. 1977;273(3): 259–65.
240. Hill LV, Tan MH, Pereira LH, Embil JA. Association of oral candidiasis with diabetic control. J Clin Pathol. 1989;42(5):502–5.
241. Belazi M, Velegraki A, Fleva A, Gidarakou I, Papanaum L, Baka D, et al. Candidal overgrowth in diabetic patients: potential predisposing factors. Mycoses. 2005;48(3):192–6.
242. Regezi JA, Sciubba JJ, Jordan RCK. Oral pathology: clinical pathologic correlations. St. Louis: Elsevier/ Saunders; 2012.
243. Manfredi M, McCullough MJ, Al-Karaawi ZM, Hurel SJ, Porter SR. The isolation, identification and molecular analysis of *Candida* spp. isolated from the oral cavities of patients with diabetes mellitus. Oral Microbiol Immunol. 2002;17(3):181–5.
244. Sullivan DJ, Westerneng TJ, Haynes KA, Bennett DE, Coleman DC. *Candida dubliniensis* sp. nov.: phenotypic and molecular characterization of a novel species associated with oral candidosis in HIV-infected individuals. Microbiology. 1995;141(Pt 7):1507–21.
245. Gonçalves RH, Miranda ET, Zaia JE, Giannini MJ. Species diversity of yeast in oral colonization of insulin-treated diabetes mellitus patients. Mycopathologia. 2006;162(2):83–9.
246. Willis AM, Coulter WA, Sullivan DJ, Coleman DC, Hayes JR, Bell PM, et al. Isolation of *C. dubliniensis* from insulin-using diabetes mellitus patients. J Oral Pathol Med. 2000;29(2):86–90.
247. Tekeli A, Dolapci I, Emral R, Cesur S. Candida carriage and *Candida dubliniensis* in oropharyngeal samples of type-1 diabetes mellitus patients. Mycoses. 2004;47(7):315–8.
248. Melton JJ, Redding SW, Kirkpatrick WR, Reasner CA, Ocampo GL, Venkatesh A, et al. Recovery of *Candida dubliniensis* and other *Candida* species from the oral cavity of subjects with periodontitis who had well-controlled and poorly controlled type 2 diabetes: a pilot study. Spec Care Dentist. 2010;30(6):230–4.
249. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, et al. Insulin-dependent diabetes mellitus and oral soft tissue pathologies. I. Prevalence and characteristics of non-candidal lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;89(5):563–9.
250. Farman A. Atrophic lesions of the tongue: a prevalence study among 176 diabetic patients. J Oral Pathol. 1976;5:255–64.
251. Bastos AS, Leite AR, Spin-Neto R, Nassar PO, Massucato EM, Orrico SR. Diabetes mellitus and oral mucosa alterations: prevalence and risk factors. Diabetes Res Clin Pract. 2011;92(1):100–5.
252. Silva MF, Barbosa KG, Pereira JV, Bento PM, Godoy GP, Gomes DQ. Prevalence of oral mucosal lesions among patients with diabetes mellitus types 1 and 2. An Bras Dermatol. 2015;90(1):49–53.
253. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(Suppl):S25.e1–12.
254. Epstein JB, Wan LS, Gorsky M, Zhang L. Oral lichen planus: progress in understanding its malignant potential and the implications for clinical management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(1):32–7.
255. Romero MA, Seoane J, Varela-Centelles P, Diz-Dios P, Garcia-Pola MJ. Prevalence of diabetes mellitus amongst oral lichen planus patients. Clinical and pathological characteristics. Med Oral. 2002;7(2): 121–9.
256. Seyhan M, Ozcan H, Sahin I, Bayram N, Karincaoğlu Y. High prevalence of glucose metabolism disturbance in patients with lichen planus. Diabetes Res Clin Pract. 2007;77(2):198–202.
257. Borghelli RF, Pettinari IL, Chuchurru JA, Stirparo MA. Oral lichen planus in patients with diabetes. An epidemiologic study. Oral Surg Oral Med Oral Pathol. 1993;75(4):498–500.

258. Van Dis ML, Parks ET. Prevalence of oral lichen planus in patients with diabetes mellitus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995;79(6):696–700.
259. Yuan A, Woo SB. Adverse drug events in the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(1):35–47.
260. Kaomongkolgit R. Oral lichenoid drug reaction associated with antihypertensive and hypoglycemic drugs. J Drugs Dermatol. 2010;9(1):73–5.
261. Scully C, Bagan JV. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med. 2004;15(4): 221–39.
262. Serrano-Sánchez P, Bagan JV, Jiménez-Soriano, Sarrión G. Drug-induced oral lichenoid reactions. A literature review. J Clin Exp Dent. 2010;2(2): e71–5.
263. Lamey PJ, Gibson J, Barclay SC, Miller S. Grinspan's syndrome: a drug-induced phenomenon? Oral Surg Oral Med Oral Pathol. 1990;70:184–5.
264. Lodi G, Scully C, Carrozzo M, Griffiths M, Sugerman PB, Thongprasom K. Current controversies in oral lichen planus: report of an international consensus meeting. Part 2. Clinical management and malignant transformation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100(2):164–78.
265. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral Oncol. 2009;45(4–5):317–23.
266. Pindborg J, Reichart P, Smith C, van der Waal I. Precancerous conditions. In: Organization WH, editor. Histological typing of cancer and precancer of the oral mucosa. 2nd ed. Berlin: Springer; 1997:1–87.
267. van der Meij EH, Mast H, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. Oral Oncol. 2007;43(8): 742–8.
268. Fitzpatrick SG, Hirsch SA, Gordon SC. The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. J Am Dent Assoc. 2014;145(1):45–56.
269. Gandolfo S, Richiardi L, Carrozzo M, Broccoletti R, Carbone M, Pagano M, et al. Risk of oral squamous cell carcinoma in 402 patients with oral lichen planus: a follow-up study in an Italian population. Oral Oncol. 2004;40(1):77–83.
270. Silverman S, Gorsky M, Lozada-Nur F. A prospective follow-up study of 570 patients with oral lichen planus: persistence, remission, and malignant association. Oral Surg Oral Med Oral Pathol. 1985;60(1): 30–4.
271. Casparis S, Borm JM, Tektas S, Kamarachev J, Locher MC, Damerau G, et al. Oral lichen planus (OLP), oral lichenoid lesions (OLL), oral dysplasia, and oral cancer: retrospective analysis of clinicopathological data from 2002–2011. Oral Maxillofac Surg. 2015;19(2):149–56.
272. Eisenberg E. Oral lichen planus: a benign lesion. J Oral Maxillofac Surg. 2000;58(11):1278–85.
273. Silverman S. Oral lichen planus: a potentially premalignant lesion. J Oral Maxillofac Surg. 2000;58(11): 1286–8.
274. Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. J Am Acad Dermatol. 2002;46(2):207–14.
275. Mignogna MD, Lo Muzio L, Lo Russo L, Fedele S, Ruoppo E, Bucci E. Clinical guidelines in early detection of oral squamous cell carcinoma arising in oral lichen planus: a 5-year experience. Oral Oncol. 2001;37(3):262–7.
276. Mattsson U, Jontell M, Holmstrup P. Oral lichen planus and malignant transformation: is a recall of patients justified? Crit Rev Oral Biol Med. 2002;13(5):390–6.
277. Dost F, Lê Cao KA, Ford PJ, Farah CS. A retrospective analysis of clinical features of oral malignant and potentially malignant disorders with and without oral epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116(6):725–33.
278. Vairaktaris E, Spyridonidou S, Goutzanis L, Vylliotis A, Lazaris A, Donta I, et al. Diabetes and oral oncogenesis. Anticancer Res. 2007;27(6B): 4185–93.
279. Onitilo AA, Engel JM, Glurich I, Stankowski RV, Williams GM, Doi SA. Diabetes and cancer II: role of diabetes medications and influence of shared risk factors. Cancer Causes Control. 2012;23(7): 991–1008.
280. Gallagher EJ, LeRoith D. Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer. Diabetes Care. 2013;36 Suppl 2:S233–9.
281. Liu CJ, Chang WJ, Chen CY, Sun FJ, Cheng HW, Chen TY, et al. Dynamic cellular and molecular modulations of diabetes mediated head and neck carcinogenesis. Oncotarget. 2015;6(30):29268–84.
282. Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, et al. Oxidative damage to DNA in diabetes mellitus. Lancet. 1996;347 (8999):444–5.
283. Valent F. Diabetes mellitus and cancer of the digestive organs: an Italian population-based cohort study. J Diabet Complications. 2015;29(8):1056–61.
284. Anantharaman D, Marron M, Lagiou P, Samoli E, Ahrens W, Pohlabeln H, et al. Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. Oral Oncol. 2011;47(8):725–31.
285. Atchison EA, Gridley G, Carreon JD, Leitzmann MF, McGlynn KA. Risk of cancer in a large cohort of U.S. veterans with diabetes. Int J Cancer. 2011;128: 635–43.
286. Landis SH, El-Hariry IA, van Herk-Sukel MP, van den Haak P, Janssen-Heijnen ML, Penning-van Beest FJ, et al. Prevalence and incidence of acute and chronic comorbidity in patients with squamous cell

carcinoma of the head and neck. Head Neck. 2012;34 (2):238–44.
287. Wu CH, Wu TY, Li CC, Lui MT, Chang KW, Kao SY. Impact of diabetes mellitus on the prognosis of patients with oral squamous cell carcinoma: a retrospective cohort study. Ann Surg Oncol. 2010;17(8): 2175–83.
288. Surveillance E, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Mortality – All COD, Aggregated With State, Total U.S. (1969–2012) < Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).
289. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36(10):575–80.
290. Reichart PA, Philipsen HP. Oral erythroplakia – a review. Oral Oncol. 2005;41(6):551–61.
291. Scully C, Paes de Almeida O, Bagan J, Diz Dios P, Mosqueda Taylor A. Oral medicine and pathology at a glance. Chichester: Wiley Blackwell; 2014.
292. Brouns E, Baart J, Karagozoglu K, Aartman I, Bloemena E, van der Waal I. Malignant transformation of oral leukoplakia in a well-defined cohort of 144 patients. Oral Dis. 2014;20(3):e19–24.
293. Meisel P, Dau M, Sümnig W, Holtfreter B, Houshmand M, Nauck M, et al. Association between glycemia, serum lipoproteins, and the risk of oral leukoplakia: the population-based Study of Health in Pomerania (SHIP). Diabetes Care. 2010;33(6):1230–2.
294. Moore PA, Guggenheimer J, Orchard T. Burning mouth syndrome and peripheral neuropathy in patients with type 1 diabetes mellitus. J Diabet Complications. 2007;21(6):397–402.
295. Gibson J, Lamey PJ, Lewis M, Frier B. Oral manifestations of previously undiagnosed non-insulin dependent diabetes mellitus. J Oral Pathol Med. 1990;19(6): 284–7.
296. Arap A, Siqueira SR, Silva CB, Teixeira MJ, Siqueira JT. Trigeminal pain and quantitative sensory testing in painful peripheral diabetic neuropathy. Arch Oral Biol. 2010;55(7):486–93.
297. Collin HL, Niskanen L, Uusitupa M, Töyry J, Collin P, Koivisto AM, et al. Oral symptoms and signs in elderly patients with type 2 diabetes mellitus. A focus on diabetic neuropathy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90(3):299–305.
298. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med. 2003;14(4):275–91.
299. Grushka M. Clinical features of burning mouth syndrome. Oral Surg Oral Med Oral Pathol. 1987;63(1): 30–6.
300. Yilmaz Z, Renton T, Yiangou Y, Zakrzewska J, Chessell IP, Bountra C, et al. Burning mouth syndrome as a trigeminal small fibre neuropathy: increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. J Clin Neurosci. 2007;14(9):864–71.
301. Jääskeläinen SK. Pathophysiology of primary burning mouth syndrome. Clin Neurophysiol. 2012;123 (1):71–7.
302. Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, Padovani A, et al. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain. 2005;115(3):332–7.
303. Carrington J, Getter L, Brown RS. Diabetic neuropathy masquerading as glossodynia. J Am Dent Assoc. 2001;132(11):1549–51.
304. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. Psychosom Med. 2002;64(5):773–86.
305. Zakrzewska JM. Multi-dimensionality of chronic pain of the oral cavity and face. J Headache Pain. 2013;14:37.
306. Patton LL, Siegel MA, Benoliel R, De Laat A. Management of burning mouth syndrome: systematic review and management recommendations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(Suppl):S39.e1–13.
307. Lamey PJ, Freeman R, Eddie SA, Pankhurst C, Rees T. Vulnerability and presenting symptoms in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99(1):48–54.
308. Carlson CR, Miller CS, Reid KI. Psychosocial profiles of patients with burning mouth syndrome. J Orofac Pain. 2000;14(1):59–64.
309. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with type 2 diabetes: a systematic review and meta-analysis. Diabet Med. 2006;23(11):1165–73.
310. Gendelman N, Snell-Bergeon JK, McFann K, Kinney G, Paul Wadwa R, Bishop F, et al. Prevalence and correlates of depression in individuals with and without type 1 diabetes. Diabetes Care. 2009;32(4):575–9.
311. Zakrzewska JM, Forssell H, Glenny AM. Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev. 2005; CD002779.
312. Sumlin LL, Garcia TJ, Brown SA, Winter MA, García AA, Brown A, et al. Depression and adherence to lifestyle changes in type 2 diabetes: a systematic review. Diabetes Educ. 2014;40(6):731–44.
313. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007;370(9590):851–8.
314. Lin EH, Von Korff M, Alonso J, Angermeyer MC, Anthony J, Bromet E, et al. Mental disorders among persons with diabetes – results from the World Mental Health Surveys. J Psychosom Res. 2008;65(6):571–80.
315. Harris MD. Psychosocial aspects of diabetes with an emphasis on depression. Curr Diab Rep. 2003;3(1): 49–55.

316. Smith KJ, Pedneault M, Schmitz N. Investigation of anxiety and depression symptom co-morbidity in a community sample with type 2 diabetes: associations with indicators of self-care. Can J Public Health. 2016;106(8):e496–501.
317. Sreebny LM, Schwartz SS. A reference guide to drugs and dry mouth – 2nd edition. Gerodontology. 1997;14(1):33–47.
318. Spangler JG, Konen JC, McGann KP. Prevalence and predictors of problem drinking among primary care diabetic patients. J Fam Pract. 1993;37(4):370–5.
319. Engler PA, Ramsey SE, Smith RJ. Alcohol use of diabetes patients: the need for assessment and intervention. Acta Diabetol. 2013;50(2):93–9.
320. Chew LD, Nelson KM, Young BA, Bradley KA. Association between alcohol consumption and diabetes preventive practices. Fam Med. 2005;37(8):589–94.
321. Mealey B. Management of the patient with diabetes mellitus in the dental office. In: Lamster I, editor. Diabetes mellitus and oral health: an interprofessional approach. Ames: Wiley Blackwell; 2014. p. 101–4.
322. Ueta E, Osaki T, Yoneda K, Yamamoto T. Prevalence of diabetes mellitus in odontogenic infections and oral candidiasis: an analysis of neutrophil suppression. J Oral Pathol Med. 1993;22(4):168–74.
323. Lalla E, Kunzel C, Burkett S, Cheng B, Lamster IB. Identification of unrecognized diabetes and pre-diabetes in a dental setting. J Dent Res. 2011;90(7):855–60.
324. Nasseh K, Vujicic M, Glick M. The relationship between periodontal interventions and healthcare costs and utilization. Evidence from an integrated dental, medical, and pharmacy commercial claims database. Health Econ. 2016. doi:10.1002/hec.3316. [Epub ahead of print]. PMID: 26799518.
325. Jeffcoat MK, Jeffcoat RL, Gladowski PA, Bramson JB, Blum JJ. Impact of periodontal therapy on general health: evidence from insurance data for five systemic conditions. Am J Prev Med. 2014;47(2):166–74.
326. Mosen DM, Pihlstrom DJ, Snyder JJ, Shuster E. Assessing the association between receipt of dental care, diabetes control measures and health care utilization. J Am Dent Assoc. 2012;143(1):20–30.
327. Cefalu W. American Diabetes Association: standards of medical care in diabetes. J Clin Appl Res Educ. 2015;38:S1–93. http://www.diabetes.teithe.gr/UsersFiles/entypa/STANDARDS%20OF%20MEDICAL%20CARE%20IN%20DIABETES%202015.pdf
328. PI E, GO T-E, GL B. Dental visits among dentate adults with diabetes – United States, 1999 and 2004. 2005. Report No.: Contract No.: 46.
329. Macek MD, Taylor GW, Tomar SL. Dental care visits among dentate adults with diabetes, United States, 2003. J Public Health Dent. 2008;68(2):102–10.
330. Moore PA, Orchard T, Guggenheimer J, Weyant RJ. Diabetes and oral health promotion: a survey of disease prevention behaviors. J Am Dent Assoc. 2000;131(9):1333–41.
331. Chaudhari M, Hubbard R, Reid RJ, Inge R, Newton KM, Spangler L, et al. Evaluating components of dental care utilization among adults with diabetes and matched controls via hurdle models. BMC Oral Health. 2012;12:20.
332. Azogui-Lévy S, Dray-Spira R. Sociodemographic factors associated with the dental health of persons with diabetes in France. Spec Care Dentist. 2012;32(4):142–9.
333. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. Health Affairs. 2008;27(3):759–69.
334. Hummel J, Phillips KE, Holt B, Hayes C. Oral health: an essential component of primary care. Seattle: Qualis Health; 2015.
335. Lalla E, Lamster IB. Assessment and management of patients with diabetes mellitus in the dental office. Dent Clin North Am. 2012;56(4):819–29.
336. Elangovan S, Hertzman-Miller R, Karimbux N, Giddon D. A framework for physician-dentist collaboration in diabetes and periodontitis. Clin Diabetes. 2014;32(4):188–92.