Oral diseases and conditions throughout the lifespan. II. Systemic diseases

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Oral diseases may affect general health and many systemic disorders have oral manifestations and implications for dental treatment. This article reviews examples of the oral manifestations of systemic diseases, including oral cancer, diabetes mellitus, and infection from HIV. In addition, the plausible link between periconceptional use of folic acid by the mother and the risk of facial clefts is reviewed. The possible associations between oral infections, specifically periodontal diseases, and both cardiovascular disease and the delivery of preterm low birthweight infants also are reviewed.

These and other associations present challenges to dentists, who must evaluate the scientific evidence supporting the associations or alleged causality and select effective treatment options. Both of these challenges require in-depth knowledge of the scientific method, criteria to establish causality, and evaluation of the merit of possible treatment options; in turn, these requirements identify dentists as medical professionals who utilize prevention as the first option in health care, use oral tissues and saliva to diagnose systemic diseases, rely on medical facilities to order laboratory tests, and diagnose and treat patients in close collaboration with their medical colleagues.

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In a previous article, the authors described the most common oral diseases and conditions throughout a person’s lifespan, concluding that dental caries, periodontal diseases, and dental injuries are directly associated with tooth loss. Scientific evidence shows that oral diseases may affect general health and many systemic disorders have oral manifestations and implications for treatment; these conditions were identified as systemic diseases. This review article describes three such conditions: oral cancer, a disease that affects general health and could lead to death, and diabetes mellitus and HIV infection, two conditions that have oral manifestations with clear implications for treatment. This article also reviews the possible association between the periconceptional use of folic acid to prevent facial clefts and intraoral infection (specifically periodontal diseases), with cardiovascular diseases and preterm low birth weight as outcomes. These diseases and conditions are detailed in Figure 1; colored lines denote established associations while white lines denote associations with studies showing both positive and negative results.

Oral cancer

Oral and pharyngeal cancer also is known as buccopharyngeal cancer and collectively as oral cancer. More than 95% of all oral cancers are squamous cell carcinomas (also known as epidermoid carcinomas). Sometimes the term oral cancer is used to identify only cancers of the tongue, floor of the mouth, palate, gingiva, alveolar mucosa, buccal mucosa, and oropharynx, excluding cancers of the lip, salivary glands, and nasopharynx.

The terms precancer and premalignancy are used to identify specific histological changes that appear clinically as red or white lesions; these lesions may experience malignant transformation over time. This group includes leukoplakia (white lesions), erythroplasia (red lesions), and leich planus (particularly the erosive type). Tobacco usage is the main risk factor for the development of leukoplakia. These lesions are asymptomatic and may experience complete regression.

According to the Surgeon General’s report on oral health, approximately 30,000 cases of oral cancer are diagnosed in the United States each year (2.4–3.5% of all cancers). Approximately 8,000 Americans die each year from oral cancer; only 50% or so survive five years after diagnosis. There are important differences in incidence and mortality based on sex and race. The age-adjusted incidence and mortality rates are higher among men than women, while black men have higher age-adjusted rates than white men. A follow-up analysis of 23 years of data showed a significant reduction in cancer incidence among white men between 1973 and 1996. An analysis of black Americans from 1973–1992 suggests a trend toward lower incidence that began in the early 1980s and an overall reduction in mortality rates among both races and both sexes. However, survival rates have not changed. This finding is consistent with the fact that many oral cancers are diagnosed late, when regional or distant metastasis occurs.

Oral cancer presents dentists with important management issues. Because most cancers and precancers show up as white, red, or ulcerative lesions on the oral mucosa, the dentist should conduct a thorough extraoral and intraoral soft-tissue examination, especially if the patient has risk factors. The dentist should document the information obtained by the patient’s history and clinical examination and consult with the patient’s physician. Any suspicious lesion with a duration longer than 10–15 days should be biopsied or the patient
should be referred for such a procedure. Biopsies should include all representative areas or the lesion, especially any red areas, in addition to normal tissue. If the biopsy tests positive for malignant transformation, the dentist, in cooperation with the patient’s physician, should refer the patient to an oncologist or cancer center for final diagnosis and treatment. Any dental treatment should be coordinated with the oncologist with the goal of maximizing oral health before and after surgical treatment. Finally, the patient should receive preventive care to avoid dental caries, as xerostomia is a side effect of radiation therapy.

Diabetes mellitus and periodontal diseases
Diabetes mellitus is a serious and costly disease that is characterized by abnormal amounts of glucose in the plasma, leading to hyperglycemia. The CDC estimates that 17 million Americans have diabetes mellitus and that more than 200,000 diabetics die each year from related complications. Nearly six million Americans are unaware they have diabetes mellitus, a disease associated with heart disease, stroke, blindness, kidney failure, leg and foot amputations, pregnancy complications, and deaths related to influenza and pneumonia.17

There are two main types of diabetes. Type 1, previously known as insulin-dependent diabetes mellitus (IDDM), generally appears during childhood or adolescence. Type 2, previously known as non-insulin-dependent diabetes mellitus (NIDDM), represents approximately 90–95% of people with diabetes, usually appearing among those age 40 or older. In addition, 2.0–5.0% of all pregnant women develop gestational diabetes.18

While there is scientific support for the theory that diabetes is a risk indicator for periodontal diseases, the evidence does not establish causality.19 Good metabolic control reduces the risk of periodontal complications.16 One national objective of the U.S. Healthy People 2010 is to increase (from 58% to 75%) the proportion of persons with diagnosed diabetes (aged 2 and older) who undergo at least an annual dental examination.19 There also is increasing evidence that periodontal infection can affect the glycemic control in persons with Type 2 diabetes.20-22

Two proposed mechanisms can explain the association between diabetes and periodontal diseases. One is based on effects similar to those seen in other complications resulting from diabetes mellitus; the other is based on independent effects via glycation of body proteins.14,23,24

Conventional dental treatment is suitable for people with diabetes mellitus.22,23 Non-emergency surgical procedures for poorly controlled Type 1 or Type 2 patients should be postponed until the metabolic process is under control; emergency treatment should be provided with antibiotic prophylaxis.24 For well-controlled patients, antibiotic prophylaxis should be the same as for patients without diabetes.

HIV infection
The importance of the oral cavity in the diagnosis of HIV infection has been recognized since this disease’s first cases were reported in 1981.25 A variety of books and publications are available regarding the clinical appearance, diagnosis, and treatment of the oral manifestations of HIV infection.26-36 Oral candidiasis may be the first sign of HIV infection, is the most common manifestation of pediatric HIV infection, and is inversely related to the level of CD4 lymphocytes.36-38 Both candidiasis and hairy leukoplakia have been related to the diagnosis, staging, and prognosis of AIDS.37,38

HIV/AIDS affect at least two dimensions of clinical dentistry: infection control and patient care. Every dentist needs to follow the principle of universal precautions, in which all patients are considered
potentially infectious. Barriers such as gloves, masks, and glasses are used to limit the risk of infection between patient and dentist; at the same time, equipment, instruments, and materials should be handled and recycled in a manner that will avoid contamination and cross-infection. In the late 1980s and early 1990s, many organizations prepared extensive and detailed recommendations for infection control. In December 2003, the CDC published an updated set of recommendations incorporating the standard precautions principle. This principle includes the major features of universal precautions in that they are designed for the care of all patients, regardless of their diagnosis or presumed infection status, but also includes all body fluids as potentially infectious.

HIV-infected patients need dental care not only to restore dental function but also to prevent intraoral infections that could overload their weakened immune system; dental treatment also could improve the well-being and self-esteem of HIV/AIDS patients. The evidence indicates that HIV-seropositive patients could receive the same dental procedures as seronegatives; in fact, denying dental treatment to HIV-positive patients solely on the basis of their serostatus could have negative effects that may outweigh any risk of infection to the health care provider. The CDC series of recommendations incorporating the standard precautions principle includes the major features of universal precautions that are designed for the care of all patients, regardless of their diagnosis or presumed infection status, but also includes all body fluids as potentially infectious.

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Various publications have documented the specifics of dental treatment of HIV-infected persons. There are no contraindications to orthodontic, endodontic, or prosthetic treatment (including implants) or to using local anesthetics and other materials commonly used in dental treatment. There is no indication for antibiotic use prior to treatment unless the patient has neutropenia (< 500 cells/mm³).

Dentists performing extractions should try to minimize trauma, inflammatory reaction, and chance of infection. Because an HIV infection could produce thrombocytopenia, patients with a history of bleeding must have their hemostatic function evaluated. There is no difference between the frequency of postoperative complications for HIV-seropositive and HIV-seronegative patients.

There is no contraindication for dental treatment of HIV-seropositive children. Some studies have reported high levels of dental caries among these children, a finding that emphasizes the need to institute appropriate fluoride therapies. Fluoride varnishes appear to be an appropriate fluoride delivery choice for this group. Oral surgery is a possibility for children with severe dental disease who are unable to cope with long and repetitive appointments.

Periconceptional use of folic acid and craniofacial clefts

Unilateral or bilateral cleft lip results from the medial nasal and the maxillary processes failing to fuse during the sixth week of embryonic life. Cleft palate occurs when the lateral palatine processes fail to fuse between weeks 8 and 12 of gestation. This review refers to both conditions as craniofacial clefts. Clinically, clefts can appear isolated or together and may show different degrees of anatomical involvement.

Worldwide, the incidence of cleft palate ranges from 5–12 cases per 10,000 live births while the incidence of cleft lip ranges from 6–16 per 10,000. In the U.S., the incidence of craniofacial clefts is 8 per 10,000 live births. In an analysis of nearly 800,000 births in California and metropolitan Atlanta from 1983–1988, blacks had a lower prevalence of clefts than whites. The etiology of craniofacial clefts is complex. Syndromic clefts are those associated with other congenital malformations, such as Pierre Robin syndrome; more than 300 syndromes that include facial clefting have been reported. Non-syndromic clefts are multifactorial. Some are genetic in origin; approximately 20 genes have been suggested as candidates. Environmental factors such as exposure to certain drugs and maternal smoking have been implicated, either independently or in association with genetic factors.

There has been increased interest recently in determining whether daily supplementation with folic acid (pteroyl-mono-glutamic acid) in women prevents craniofacial clefts in their offspring. It has been shown that consumption of folic acid around the time of conception reduces the incidence of neural tube defects such as spina bifida. The body transforms folic acid into tetrahydrofolate, a molecule that is involved in the synthesis and metabolism of amino acids. Of particular interest, tetrahydrofolate provides the methyl group (-CH₃) that transforms homocysteine into the essential amino acid methionine, reducing homocysteine plasma concentrations as a result.

At least two studies have shown a positive association between the periconceptual use of folic acid and lower incidence of craniofacial clefts; however, these studies measured folic acid consumption as part of multivitamin supplementation, meaning the benefit could be attributed to other vitamins. A 1996 case-control study found no such association. Multicenter randomized clinical trials are needed to determine the potential benefit of folic acid consumption in the reduction of craniofacial clefts.

Women who are planning to conceive should supplement their diet with folic acid to reduce the risk of having an offspring with a neural tube defect. This is especially important for women with a
previous history of a neural tube defect. To reduce the risk of spina bifida, a dose of 400 µg/day is recommended. Synthetic folic acid is more active biologically than the natural salt folate. The FDA has issued regulations requiring that all cereal grains be enriched with a concentration of 1.4 mg of folic acid/kg of grain. This dosage is equivalent to approximately 100 µg/day (less than the recommended daily dosage); as a result, women who wish to use folic acid to prevent neural tube defects should supplement their cereal consumption. Treatment of craniofacial clefts requires a multidisciplinary team approach including multiple surgeries; psychological and speech therapy; and dental, orthodontic, and prosthodontic treatments. Timing for surgical closure of the palate is still a matter of discussion; improved speech and hearing must be weighed against undisturbed facial growth. Little epidemiological information exists to characterize the dental and periodontal needs of patients with craniofacial clefts.

**Cardiovascular diseases, preterm low birthweight, and periodontal diseases**

Since 1996, interest has increased regarding the possible association between periodontal diseases as a source of focal infection and the risk of systemic problems, such as cardiovascular diseases, strokes, and the risk of delivering a preterm low birthweight (PLBW) infant. This interest is nothing new: during the first part of the 20th century, teeth sometimes were extracted because they were thought to be the source of local and distant infection; this theory was later discredited when symptoms were not relieved following extraction. Manipulating dental tissues (for example, the simple mechanical process of brushing) increases the risk of bacteremia. The American Heart Association’s recommendations for antibiotic prophylaxis are based on concerns about bacteremia and the risk of bacterial endocarditis. A summary review of the literature regarding cardiovascular diseases and periodontal diseases from 1996–2003 revealed 24 articles that presented epidemiological data, 34 that presented personal opinions on the topic, and more than 50 literature reviews. The medical literature contains reviews by the same authors published in different periodicals, articles regarding legal implications, and pieces with such suggestive titles as “Focal infection: Back with a bang!” and “Floss or die…” Some authors forecast a new subspecialty within periodontology; that is, periodontal medicine or a new paradigm. The basis for an association between periodontal diseases and cardiovascular diseases can be summarized by the following two statements: first, not all cases of cardiovascular diseases can be explained by known risk factors (high cholesterol, low density lipoproteins, hypertension, smoking, and diabetes); second, atheromatosis (the anatomical manifestation of cardiovascular diseases) appears to be a hyperactive response mediated by inflammatory cells and molecules that also are involved in the pathogenesis of periodontal diseases. While other laboratory and experimental pathology evidence makes the link plausible, epidemiological evidence of causality remains inconclusive.

Since Matilla’s original case-control study, 24 publications have incorporated a vast array of study designs, from cross-sectional to follow-up and cohort studies. These studies have used varied outcome measures, including alterations in the electrocardiogram, and prevalence or incidence of atherosclerosis, myocardial infarction, coronary heart disease, peripheral vascular disease, and stroke/cerebrovascular disease. Measures of exposure included a “total dental index” (that is, the number of clinical and radiographic sites showing signs of caries, periodontal disease, or their sequelae), Russell’s periodontal index, pocket depth, loss of attachment, and the Community Periodontal Index of Treatment Needs (CPITN). These studies included many sets of co-variates and different levels of control for epidemiological confounding. A confounding variable is associated with both exposure and disease and can either cause spurious associations or cover up real associations, depending on the direction of its association with exposure and disease. For example, tobacco use is strongly associated with both cardiovascular diseases and intraoral infection, especially periodontal diseases; as a result, it is possible that a statistically significant association between periodontal diseases and cardiovascular diseases could result mostly from tobacco use. To avoid confounding, researchers control for that variable by using multivariate statistical models; however, such control could be incomplete if the variable measuring the confounding factor is not valid and precise. For example, tobacco use could be measured by such variables as levels of cotin—in—a metabolite of nicotine—in blood (a valid, precise measurement) or as a simple self-reported measure of tobacco use (this method is less precise and potentially invalid if behavior is not reported accurately).

Some studies have shown positive associations while others have been negative. Among those yielding positive associations, the measure of such strength—either the odds ratio or the relative risk—generally has been below 2.0, suggesting a weak association. At present, it would be fair to conclude that the data suggest a plausible association (but not causality) and that more scientifically rigorous prospective studies are needed. This weak association may be the effect of epidemiological confounding. A recent cross-sectional study reported that smoking was a necessary co-factor in the association between periodontal diseases and cardiovascular disease.

Another proposed link for periodontal diseases involves preterm birth, preterm delivery, low birthweight, and preterm low birthweight. Per international standards, a preterm birth or preterm delivery occurs before the 37th gestational week, while low birthweight occurs among infants who weigh less than 2,500 g at birth. Preterm low birthweight (also known as spontaneous preterm birth) is the combination of preterm birth and low birthweight. In the United States, the ratio of children born with preterm low birthweight is 1:10.

A 1985 Institute of Medicine committee on the prevention of low birthweight listed the following risk factors: maternal age (below 17 and over 34), African-American race, low socioeconomic status, inadequate prenatal care, drug abuse, alcohol and tobacco use, hypertension, genitourinary tract infections, diabetes, multiple pregnancies, and history of a previous preterm low birthweight offspring. Some cases of preterm low birthweight show no identifiable cause and children are born with preterm low birthweight after their mothers had re-
ceived interventions to eliminate or ameliorate some risk factors. Because inflammatory factors are associated in the pathogenesis of preterm low birthweight, a plausible connection exists between periodontal diseases and preterm low birthweight, mediated by the elements of the inflammatory process.\textsuperscript{127,128}

Direct evidence to support an association between periodontal diseases and preterm low birthweight is scarce. Four epidemiological studies have been published since Offenbacher et al published the first case-control study in 1996, which reported odds ratios between 7.5–8.0.\textsuperscript{127} One study, conducted among white and Bengali women living in East London, showed no association.\textsuperscript{129,130} The other three were conducted among women from Thailand, China, Chile, and Senegal and showed positive associations but none from Thailand, China, Chile, and Senegal.\textsuperscript{3} Three were conducted among women not to be isolated from the rest of the body overreaching because the oral cavity can’t be associated in the way dentistry is practiced: the most common type of dental practice in the U.S. is the single-owner practice, while most physicians work in explicit association with other physicians.\textsuperscript{131} Clearly, dental and medical students are trained and later practice in entirely different milieus.\textsuperscript{127}

**Conclusion**

As discussed in a previous article, a new type of dental graduate is needed, a professionally integrated with other health care professionals and focused on the prevention and care of the oral cavity as integral part of the human body. The examples presented in this review illustrate such a need. Future dentists could be primary care specialists who use prevention as the first option in health care, use oral tissues and saliva to diagnose systemic disease, rely on medical facilities to order laboratory tests, and diagnose and treat patients in close collaboration with their medical colleagues.

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