



REVIEW ARTICLE

Global burden of oral diseases: emerging concepts, management and interplay with systemic health

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OBJECTIVES: This study presents the global burden of major oral diseases with an exegetical commentary on their current profiles, the critical issues in oral health-care and future perspectives.

METHODS: A narrative overview of current literature was undertaken to synthesise the contexts with critical elaboration and commentary.

RESULTS: Oral disease is one of the most common public health issues worldwide with significant socio-economic impacts, and yet it is frequently neglected in public health policy. The oral data extracted from the Global Burden of Disease Study in 2010 (Murray *et al*, 2012) show that caries, periodontal disease, edentulism, oral cancer and cleft lip/palate collectively accounted for 18 814 000 disability-adjusted life-years; and the global burden of periodontal disease, oral cancer and caries increased markedly by an average of 45.6% from 1990 to 2010 in parallel with the major non-communicable diseases like diabetes by 69.0%. Oral diseases and non-communicable diseases are closely interlinked through sharing common risk factors (e.g. excess sugar consumption and tobacco use) and underlying infection/inflammatory pathways.

CONCLUSIONS: Oral disease remains a major public health burden worldwide. It is of great importance to integrate oral health into global health agenda via the common risk factor approach. The long-term sustainable strategy for global oral health should focus on health promotion and disease prevention through effective multidisciplinary teamwork.

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disease; edentulism; oral cancer; oral mucosal diseases; cleft lip/palate

Introduction

A healthy mouth is a unique and invaluable asset, and yet an integrated component of general health and quality of life; it can also be regarded as a basic human right (Glick *et al*, 2012; Sgan-Cohen *et al*, 2013). Furthermore, the mouth is a critical point of contact with the external environment such as speech, mastication, swallowing and digestion of food that begins there and, on a truly human perspective, the mouth is crucial to sound integration and an individual's appearance. However, oral health is frequently affected on a daily basis by various forms of oral diseases, mainly dental caries and periodontal disease, and occasionally by oral cancer, lesions in HIV/AIDS, mucosal and salivary gland diseases, and orofacial pain and clefts. These oral disorders are collectively the commonest chronic diseases in mankind with great impacts on vital oral functions, self-esteem, quality of life and overall health and well-being. It is currently recognised that oral diseases are worldwide epidemic and a major public health problem (Petersen *et al*, 2005; Beaglehole *et al*, 2009) that affects almost everyone throughout their life courses. Yet, oral health is often neglected in general health (Lancet 2009). Oral cancer is the eighth most common cancer globally, while dental caries and periodontal disease are the most prevalent, with severe periodontal disease (periodontitis) being a leading cause of multiple tooth loss and edentulism in adults, and caries being the most common chronic disease of childhood (Petersen *et al*, 2005; Pihlstrom *et al*, 2005; Beaglehole *et al*, 2009; Lancet 2009; Benjamin, 2010; Jin *et al*, 2011).

Because of the high prevalence and recurrent cumulative nature of caries and periodontal disease, the mouth is among the most expensive parts of the body to treat in some countries such as Japan, Australia and Germany

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(Ministry of Health, Labour & Welfare, Japan 2008; Robert Koch-Institut, Berlin, Germany 2009; Rogers, 2011). In the European Union, the annual spending on oral care is about 79 billion Euros (€) (average yearly expenditure 2008–2012) and, if trends continue, that figure may go up to 93 billion in 2020 (Patel, 2012). These European costs on oral diseases (€79.0B) exceed expenditures on neuromuscular disorders (€7.7B), multiple sclerosis (€14.6B), stroke (€38.0B), cancer (€51.0B), respiratory diseases (€55.0B) and Alzheimer's disease (€71.1B), respectively (Listl *et al*, 2015b). In addition to the significant financial impact on government and individuals, the costs in terms of pain and suffering, discomfort, social and functional limitations and handicaps, and time lost from school and work are common problems for many people (U.S. Department of Health and Human Services, 2000; Casamassimo *et al*, 2009). The annual time lost from school, work or normal activities due to dental problems and treatment of the average Canadian was 3.5 h; for adults aged 20–69 years that equated to 4.14 million days lost (Hayes *et al*, 2013).

The topic on global burden of oral diseases may cover wide and rich contexts. The intent of this study was to provide an updated synopsis on this crucial health agenda and present in a concise manner the global burden of major oral diseases and their links to systemic diseases including non-communicable diseases (NCDs), as well as give a critical and exegetical commentary on the aetiology, clinical profile and prevalence of these diseases. This review highlights the importance of integrating oral health into the global health agenda within the framework of a common risk factor approach for optimal oral and general health.

Overview of global burden of oral diseases

An estimated 90% of the world's population suffer from some forms of oral diseases at some points in their life courses. Oral diseases are therefore recognised as a major global health burden, having huge impacts on people's daily lives and economic development, with the loss of millions of school and work hours yearly around the world (U.S. Department of Health and Human Services, 2000; Petersen *et al*, 2005; Ministry of Health, Labour & Welfare, Japan 2008; Beaglehole *et al*, 2009; Casamassimo *et al*, 2009; Lancet 2009; Robert Koch-Institut, Berlin, Germany 2009; Benjamin, 2010; Jin *et al*, 2011; Rogers, 2011; Glick *et al*, 2012; Patel, 2012; Hayes *et al*, 2013; Sgan-Cohen *et al*, 2013). Dental caries and periodontal disease are among the most common chronic diseases. In most European countries, between 13% and 36% of people aged 65–74 years have all their teeth extracted (complete edentulism) because of oral diseases (König *et al*, 2010). In the United States, 53 million people live with untreated caries of their permanent teeth, and one-quarter of adults aged 65 years and older have lost all of their teeth due to untreated oral diseases (Centers for Disease Control & Prevention, USA, 2011; National Institute of Dental and Craniofacial Research, 2015). Since the 1990s, the burden of caries and periodontal disease has increased significantly (Institute for Health Metrics and Evaluation, Seattle, USA, 2013).

The Global Burden of Diseases (GBD) Study in 2010 has well documented the global burden of premature death and morbidity, owing to 291 diseases and injuries, 1160 sequelae and 67 risk factors from 187 countries in year of 1990 and 2010 (Lim *et al*, 2012; Murray *et al*, 2012; Institute for Health Metrics and Evaluation, Seattle, USA, 2013; Marcenes *et al*, 2013), and the oral data extracted from the GBD Study indicate that dental caries, periodontal disease, edentulism, oral cancer, and cleft lip and palate collectively accounted for up to 18 814 000 disability-adjusted life-years (DALYs) in 2010, an average of 20.4% increase from 1990 (Murray *et al*, 2012; Marcenes *et al*, 2013). Surprisingly, the overall global burden of periodontal disease, oral cancer and dental caries increased markedly by an average of 45.6% (DALYs, Figure 1) from 1990 to 2010, in parallel with major NCDs (25.0%) such as diabetes mellitus (DM) (69.0%), neoplasms (27.3%) and cardiovascular disease (CVD) (22.6%), although the DALYs due to cleft lip and palate, and edentulism decreased (Murray *et al*, 2012). It is noteworthy that the prevalence of untreated caries, severe periodontitis and severe tooth loss collectively affected 3.9 billion of the world population; strikingly, untreated caries in adults was the most common disease among all 291 diseases included in the Study with an estimated prevalence of 35% globally, followed by severe periodontitis (6th), untreated caries in primary teeth (10th) and severe tooth loss (36th) with a global prevalence of 10.8%, 9.0% and 2.3%, respectively (Marcenes *et al*, 2013; Kassebaum *et al*, 2014). The report further shows that untreated caries was the major cause of DALYs in young adults below 35 years, whereas severe periodontitis and severe tooth loss emerged as the leading disease burden in those between 35 and 59 years, and the elderly above 60 years (Marcenes *et al*, 2013). In addition, traumatic dental injuries constitute another component of the oral disease burden among children and adults with an increased prevalence and high costs of treatment in both developed and developing countries (WHO, 2016). As noted above, these oral conditions do not represent the entire burden of all oral diseases. A recent study by Listl and co-workers (2015a) using an approach recommended by the World

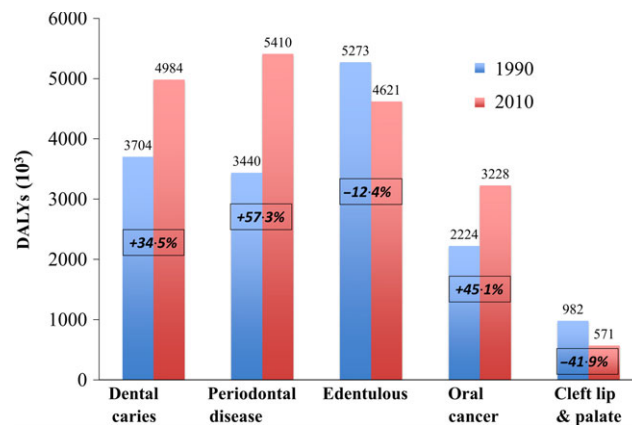


Figure 1 The global burden of major oral diseases and conditions in 1990 and 2010, measured by the disability-adjusted life-years (DALYs × 10³). Data extracted from Murray *et al* (2012)

Health Organization (WHO)'s Commission on Macroeconomics & Health indicates that the global economic impact of oral diseases amounted to US\$442 billion in 2010. Indeed, the improvements in oral health on a global scale may generate substantial economic benefits, not only in terms of reduced oral healthcare costs, but also because of fewer productivity losses in the labour market (Listl *et al*, 2015a). Conceivably, the accumulated burden of oral diseases and related healthcare costs is huge in the ageing population, especially among the medically compromised, disabled and mentally impaired subpopulation in both developed and developing countries.

Major oral diseases and conditions

Dental caries and periodontitis are the main causes of tooth loss around the world. The consequence of these common oral diseases significantly affects mastication and nutritional intake, speech, self-esteem, quality of life and social interactions (Starr and Hall, 2010; Petersen and Ogawa, 2012). Overall, the global burden of severe tooth loss remains high, with a prevalence of 10–35% among the older population in both developed and developing countries (Petersen and Ogawa, 2012), whereas the recent GBD Study (2010) and systemic review/meta-analysis show that the global age-standardised prevalence of total edentulousness decreased from 4.4% to 2.4%; however, the prevalence of severe tooth loss continued to increase with age and notably exhibited a significant increase among the elderly people over 70 years old (Kassebaum *et al*, 2015). These findings suggest that older adults would require more oral care than previous generations of seniors, and this represents an increasing oral healthcare burden in the global ageing population.

Dental caries

Dental caries is a 'ubiquitous, global, dynamic, disease process which still represents a considerable burden for many individual patients and groups in society' (Selwitz *et al*, 2007). The US Surgeon General called this disease a 'silent epidemic' (U.S. Department of Health and Human Services, 2000; Benjamin, 2010), and yet it is the major cause of tooth loss in children and can have serious health consequences, such as odontogenic infections, and even mortality. There remains a remarkable complacency about caries and its impacts, accompanied by a failure to implement effective primary and secondary prevention, while surgically biased concepts of treatment still predominate.

Caries is initiated by acids that demineralise the enamel. The acids are produced due to the ecological shifts in the microbiological composition of the plaque biofilms caused by the presence of excess free sugars. The consequent demineralisation of the enamel is also affected by salivary flow and composition, exposure to fluoride and, to a small extent, by effective cleaning of the teeth. The caries process consists of alternating phases of de- and remineralisation, and it is controlled by the balance of this de- and remineralisation over time. The disease is initially subsurface and reversible and can be halted at any stage of severity (Selwitz *et al*, 2007). The involvement of sugar

in oral and systemic diseases is crucial, particularly considering the recently issued WHO guidance for daily sugar consumption (WHO 2015). The proposal to revise this guidance was triggered by a recent systematic review on the beneficial effect of restricting sugar intake on caries prevention (Moynihan and Skelly, 2014), as well as on overall health, specifically obesity and diabetes. The WHO (2015) Guideline on sugars intake for adults and children recommends the following: i) reduced intake of free sugars throughout the life-course (strong recommendation); ii) in both adults and children, that intake of free sugars not exceed 10% of total energy (strong recommendation); and iii) further reduction to below 5% of total energy (conditional recommendation). In addition, WHO makes the comment that 'For countries with low free sugars intake, levels should not be increased' (WHO 2015).

Based on current understanding of the clinical continuum of caries, a 'new' classification (Figure 2a with examples shown in Figure 2b,c) and management matrix system was proposed to facilitate effective prevention of initial lesion and management of sepsis and pain that result from the end-stage lesion (Fisher and Glick, 2012; Pitts and Ekstrand, 2013). The untreated extensive carious lesions (e.g. Figure 2c) usually result in pulp necrosis and cause periapical infections, adding to the burden, and morbidity of caries. Caries treatment is often complex, requiring infrastructure, and trained dental professionals.

The current notions of caries prevention and management extend beyond previous views on the roles of individual cariogenic bacteria implicated previously (e.g. *Streptococcus mutans* and *Lactobacillus species*), to now move the focus to ecological shifts within the plaque biofilms associated with pH reductions at susceptible tooth surfaces. They also re-affirm the high effectiveness and benefits of primary prevention of caries though widespread use of fluorides such as water fluoridation and, in particular, fluoride toothpaste twice a day (Cochrane Library, 2014). There is strong evidence that fissure sealants are effective, but in many settings, these are often not used.

The clinical management of caries has progressed over the last 150 years through extractive, restorative and preservative phases. What is being proposed now is a more integrated preventive approach using management pathways to preserve dental tissues and promote oral health, using a wider team within and beyond dentistry (Ismail *et al*, 2013; Pitts and Ekstrand, 2013). There is a re-emphasis on prevention with tooth-preserving operative intervention only provided as a last resort to more closely align upstream, midstream and downstream efforts at caries control, while seeking to reduce health inequalities globally (Pitts *et al*, 2011). The crucial issues going forward include closing the oral health knowledge gradient and transforming health education on caries prevention/control among all healthcare professionals and the public (Richards *et al*, 2014). A recent step forward is The ICDAS Foundation's International Caries Classification & Management System (ICCMS™), which has been simplified into an implementation ICCMS™ *Guide for Practitioners and Educators* by an international group (Pitts *et al*, 2014). Other priorities include reforming payment systems to cover appropriate preventive care; responding

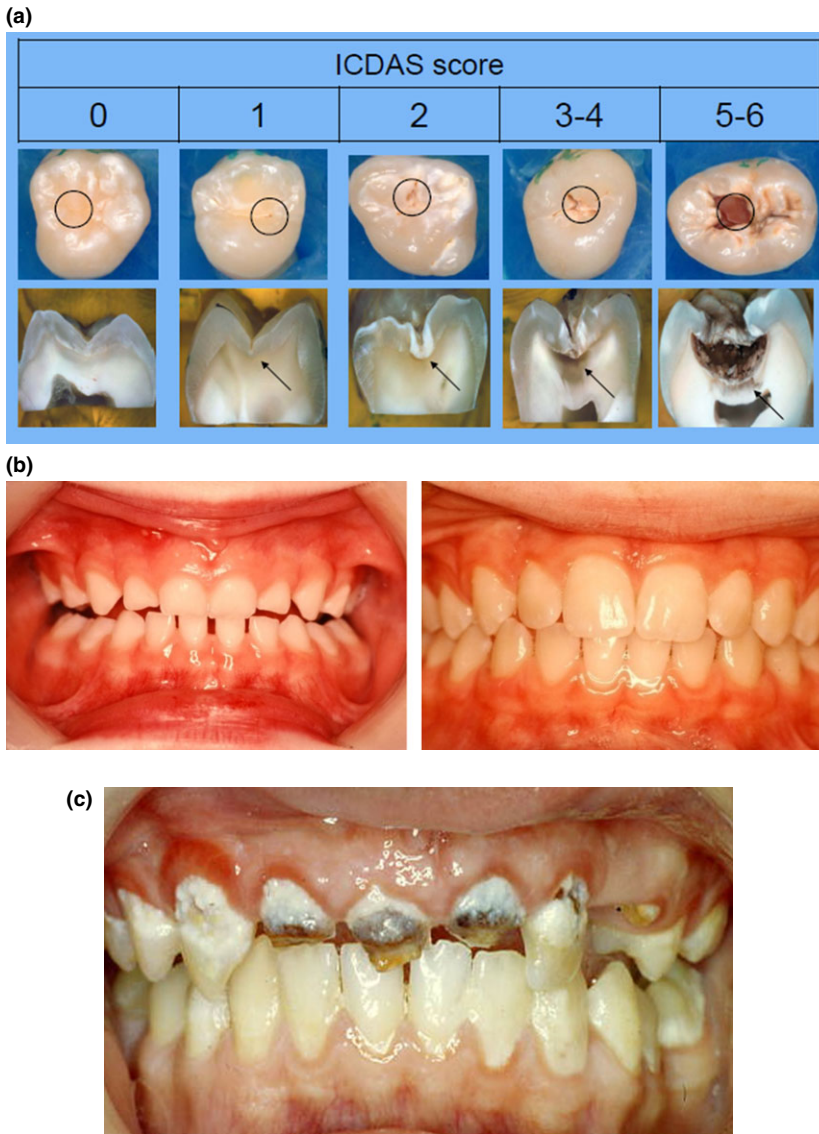


Figure 2 Staging the clinical caries continuum. (a) Comparison of visual appearance of occlusal surfaces of teeth classified according to the International Caries Detection and Assessment System (ICDAS) codes and the histological extent of caries within the tooth. Reproduced with permission from Karger Publications. (b) Examples of clinically healthy mouths in a child (left) and adult (right) with no obvious caries (Code 0). (c) Examples of a range of lesion severity (Codes 2–6) in an adult

to environmental challenges (Minamata Convention on Mercury 2013); and ensuring that new strategies work for both developed and developing countries to avoid repeating ‘high-tech’ restorative and now implant-focused models of care – at the expense of preventing – and controlling this global epidemic in concert with the parallel focus on obesity and diabetes.

Periodontal disease

Periodontal disease is a group of common, chronic immuno-inflammatory disorders affecting the tooth-supporting structures, broadly categorised as gingivitis and periodontitis (Armitage, 1999). Gingivitis is an inflammation of the gingival mucosa without loss of underlying alveolar bone, whereas periodontitis involves both inflammatory changes and resultant destruction of periodontal ligament, and supporting alveolar bone. Aggressive periodontitis is the form that advances most rapidly and seen first in adolescents and young adults. Currently, severe periodontitis remains the major cause of tooth loss in

adults (Pihlstrom *et al*, 2005; Jin *et al*, 2011). Clinically, gingivitis is characterised by oedema, erythema and bleeding during a periodontal examination. These conditions also occur in periodontitis with additional signs of increased periodontal pocket, attachment loss and alveolar bone resorption on radiographs (Figure 3), often presenting with gingival recession and associated tooth hypersensitivity, tooth mobility and drifting, and periodontal abscesses, which can eventually lead to tooth loss.

Clinical evidence of gingivitis is present in virtually all adults, but due to the lack of a universally accepted case definition, determining the prevalence of periodontitis is challenging. Based on the definition of the US Centers for Disease Control & Prevention, and the American Academy of Periodontology (Page and Eke, 2007), a recent report from the United States showed that 8.5% of adults above 30 years of age had severe periodontitis, which is in agreement with the overall prevalence of 5 to 15% worldwide (Lancet 2009; Petersen and Ogawa, 2012). Public awareness of periodontal health and the irreversible

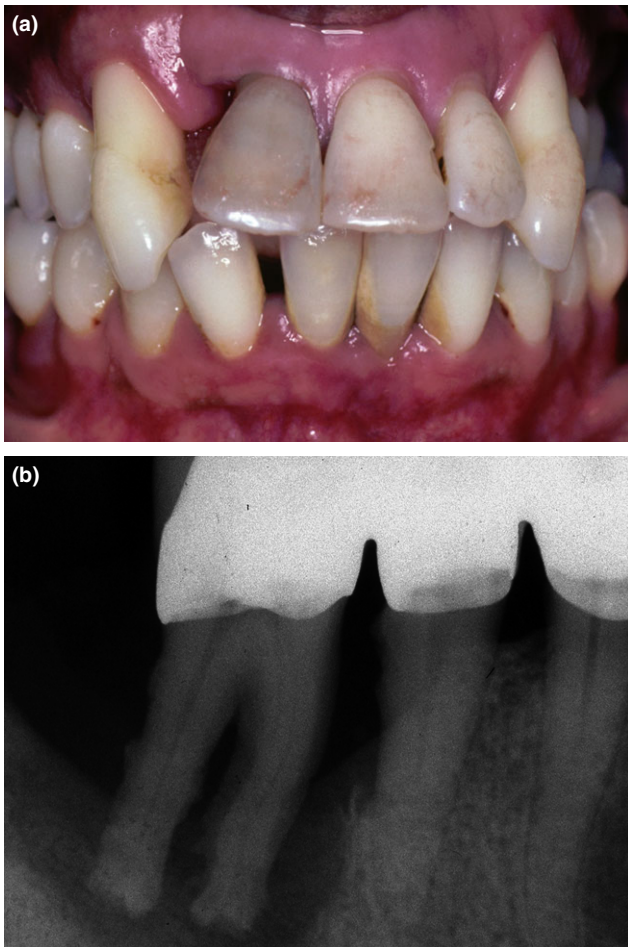


Figure 3 Severe periodontitis. (a) Uncontrolled periodontitis. (b) Severe bone loss about the mandibular right molar is evident in the radiograph

consequences of periodontitis is low, and periodontal care is often neglected especially in the early and moderate stages, due to the clinically ‘silent’ nature of disease, and the lack of a community-wide preventive care strategy (Jin *et al*, 2011; Jin, 2015).

Periodontal disease is initiated by the accumulation of plaque biofilm at the gingiva–tooth interface, which eventually extends into the subgingival niche. The primary periodontal pathogens include Gram-negative anaerobic bacteria, for example *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola* and *Aggregatibacter actinomycetemcomitans*. The extent and severity of periodontal disease are largely determined by the bacteria-initiated and dysregulated hyperimmuno-inflammatory response, modulated by various genetic, epigenetic, environmental and host factors such as tobacco use and uncontrolled DM (Page *et al*, 1997; Kornman, 2008; Cekici *et al*, 2014). This leads to the exuberant T- and B-lymphocyte activity and the influx of neutrophils and macrophages along with activation of constituent cells such as fibroblasts, producing an array of pro-inflammatory cytokines, and connective-tissue degrading enzymes that lead to periodontal destruction (Kornman, 2008). The host responses can be assessed via assay of inflammatory

mediators (e.g. IL-1 β and IL-6; and MMPs 1,3, 8 and 9) in gingival crevicular fluid and saliva (Lamster and Ahlo, 2007; Brinkmann *et al*, 2011). Risk factors for periodontitis have been well documented, for example cigarette smoking, poorly controlled DM and socio-economic determinants (Eke *et al*, 2012). A number of rare syndromes and disorders of collagen metabolism (e.g. Ehlers-Danlos syndrome) and neutrophil function (e.g. Chediak-Higashi syndrome) are strongly associated with aggressive periodontitis.

Gingivitis is eminently preventable and treatable, and periodontitis is generally manageable through control of the plaque biofilm and modifiable risk factors, effective mechanical periodontal treatment including surgical procedures and regular professional care. However, improved oral health literacy and an emphasis on prevention are key.

Oral cancer and potentially malignant disorders

Oral squamous cell cancer (OSCC) was the eleventh commonest cancer in men (2012) worldwide, accounting for around 300 000 new cases and 145 000 deaths annually (Ferlay *et al*, 2013). When oropharyngeal cancer (OPC) cases are added, the annual incidence is about half-million cases, and together, these cancers collectively occupy the eighth position (Lancet 2009). Global prevalence is estimated to be 750 000 survivors of OSCC for at least five years (Warnakulasuriya, 2010). Oral cancer remains a major cancer in the Indian subcontinent, East Asia, Eastern Europe and France, and parts of Latin America (Warnakulasuriya, 2009). OSCC generally affects middle aged and older males, while over recent decades, there has been an increased incidence of tongue cancer and OPC in both genders among young people below 45 years.

The major causes of oral cancer include tobacco use, areca nut chewing and heavy alcohol drinking (International Agency for Research on Cancer, 2012) – all modifiable risk factors. Human papillomavirus (HPV) infection is an emerging risk factor mainly in OPC. In about a quarter of young people affected by oral cancer, the absence of known aetiological factors makes it difficult to predict the susceptible individual. OSCC arises from the mucosal lining of lip, tongue, mouth floor, gingivae, palate and buccal mucosa. The most common site in high-income countries is the lateral margin of tongue. Up to 70% of cancers are preceded by oral potentially malignant disorders (OPMDs), but some do arise *de novo* from clinically normal looking mucosa. Early invasive cancer presents as a single, painless, small ulcer with rolled margins, red and nodular plaque (Figure 4a), or a new growth. A cardinal feature is the presence of induration at the base or margins of a persistent lesion. These signs can be detectable, through careful systematic visual inspection, and oral palpation (conventional oral examination). The National Institute for Health & Care Excellence (UK) (<http://guidance.nice.org.uk/csgn>) guidelines and others assist physicians and dentists to identify asymptomatic cancers and make early referral. A diagnostic biopsy should be performed to confirm malignancy and grade. Detection of OPMDs such as oral leukoplakia and erythroplakia (Figure 4b) (Warnakulasuriya *et al*, 2007), particularly ones

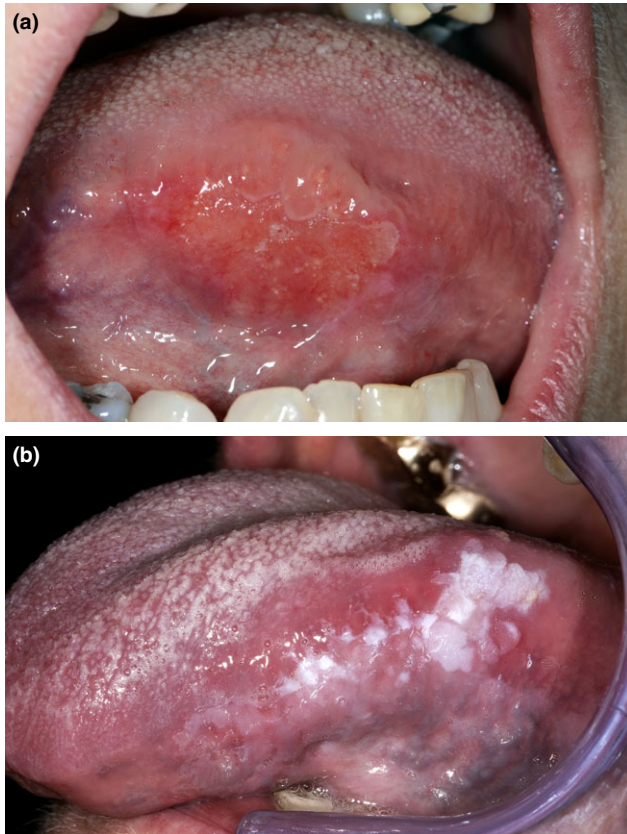


Figure 4 Oral cancer and oral potentially malignant disorder. (a) An early carcinoma on the lateral margin of tongue presenting as a raised red patch with a rolled superior margin. (b) A patch of erythroleukoplakia on the lateral margin of tongue which on biopsy shows moderate/severe dysplasia (with permission from www.oralcancerldv.org)

demonstrating dysplasia, may allow early intervention to reduce future malignant transformation. Molecular biomarkers for early detection and prognosis are available but not yet in routine use (Pitiyage *et al*, 2009). Aneuploidy and cases with loss of heterozygosity in specific chromosome loci may increase the risk for malignant transformation (Zhang *et al*, 2012; Sperandio *et al*, 2013). Research should be focused beyond contemporary methods to detect potentially malignant molecular changes in clinically suspicious mucosae (Scully, 2014).

The survival rate from tobacco- and alcohol-induced OSCC is currently among the worst of all cancers, due to its biological aggressiveness and delayed diagnosis, with the best five-year survival of 65% and a five-year survival rate approximately 50% in Europe while below 35% in India. The five-year survival for early detected, localised cancers can exceed 80% but falls to less than 20% when regional lymph nodes are involved. This demands improved public education and a key role by physicians and dentists to detect and rapidly refer any suspected malignancies. The mode of treatment and assessment of prognosis are largely based on tumour size, node and metastasis staging system. Early lesions can be effectively treated with minimal adverse effects, whereas delayed diagnosis results in serious sequelae, such as disturbances of facial appearance and oral functions, leading to poor

quality of life, and ultimate death. As this disease affects mostly people in the lower socio-economic groups (Conway *et al*, 2008), measures to improve equity, healthy living and access to health care among these underserved populations are of foremost significance (Johnson *et al*, 2011). Cessation of tobacco and betel quid use, moderation of alcohol consumption and increased consumption of fruits and vegetables can contribute to preventing oral cancer. HPV vaccination of all adolescents may confer protection. When primary prevention fails, early diagnosis through opportunistic screening and assessment as well as rapid professional intervention could significantly reduce the mortality rate (Sankaranarayanan *et al*, 2013). Web-based e-learning modules are available to improve skills of early detection and screening for oral cancer and oral potentially malignant disorders (www.oralcancerldv.org).

Oral lesions in immunocompromised people

The HIV/AIDS pandemic is now well into its fourth decade, with over 70 million people having been infected. About 36.9 million are HIV carriers and approximately 2.0 million were newly infected, and there were 1.2 million HIV/AIDS-related deaths in 2013. By March 2015, 15 million HIV-infected individuals globally had received anti-retroviral therapy (UNAIDS report 2014). Thus, HIV/AIDS has in parts of the world become predominantly a chronic condition.

Orofacial lesions have featured in the diagnosis and care of HIV/AIDS patients throughout the pandemic and remain so (Coogan *et al*, 2011). The most prominent lesions include oral and pharyngeal candidiasis (e.g. pseudomembranous as shown in Figure 5a, erythematous and angular cheilitis), hairy leukoplakia due to Epstein–Barr virus (EBV) infection (Figure 5b), herpes simplex and zoster, human papillomavirus warts, severe periodontal disease, Kaposi's sarcoma and HIV-related lymphoma. Oral lesions are seen less often in patients undergoing anti-retroviral treatment, with the exception of oral warts. Interestingly, HIV-associated oral lesions may serve as early indicators of disease progression in the untreated, and correlate with HIV load, and CD4 cell depletion. Oral healthcare professionals play crucial roles in disease identification, hence in early diagnosis, and effective management of HIV/AIDS. Studies on the aetiopathogenesis and management of the orofacial complications of HIV/AIDS are valuable in the overall approach to tackling this pandemic. Currently, saliva-based tests are increasingly used to detect HIV antibodies, and novel technologies are evolving (Chen *et al*, 2013). Similar orofacial complications can affect many of those on immunosuppressive therapy such as transplant patients.

Noma is a bacterial infection in origin, often complicating acute necrotising ulcerative gingivitis and it is a neglected but serious destructive necrosis affecting the soft tissues and bones of the mouth and adjoining orofacial areas (Enwonwu *et al*, 2006). It occurs predominantly in malnourished children, mostly but not exclusively reported in sub-Saharan Africa, where the estimated frequency varies from one to seven cases per 1000 population. The WHO estimate in 1998 showed that 500 000 people were affected, and 140 000 new cases were reported yearly

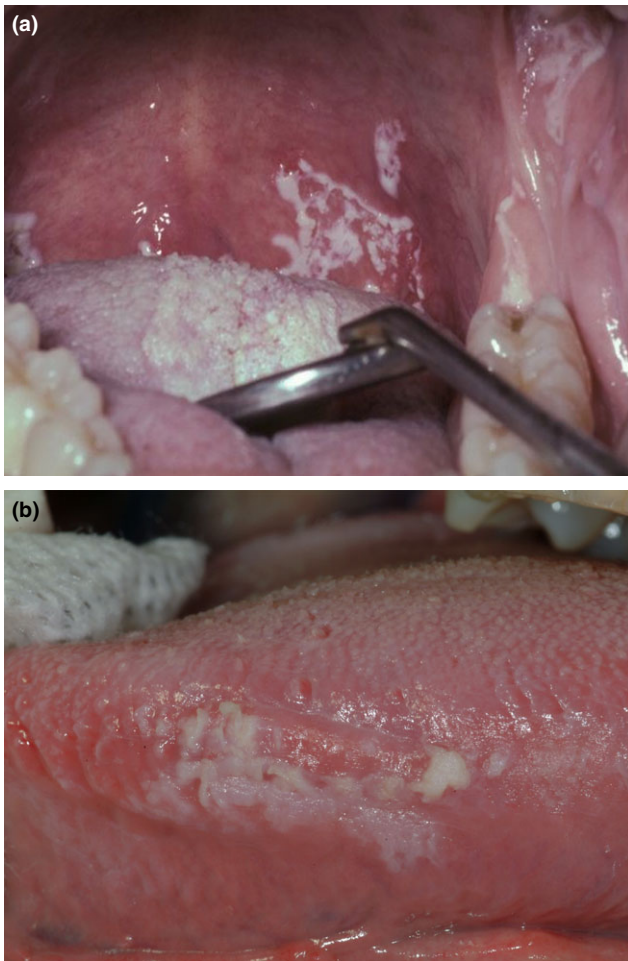


Figure 5 Candidiasis and leukoplakia. (a) Pseudomembranous candidiasis on the soft palate and tongue. (b) Hairy leukoplakia on the lateral tongue (Courtesy of Deborah Greenspan)

(Bourgeois and Leclercq, 1999). This condition often occurs after an acute illness such as measles or malaria, but it is also associated with malnutrition or HIV infection. Noma has a rapid and life-threatening course but responds in most cases to antibiotics and supportive care. When available and affordable, the treatment could be followed by plastic surgery.

Oral mucosal and salivary gland diseases

The epidemiological literature on oral mucosal diseases is sparse (Kramer *et al*, 1980), yet these disorders can be debilitating, and require effective management, often in collaboration with physicians. Biological therapies are now complementing the more traditional therapies with topical immunomodulators (Georgakopoulou and Scully, 2015).

Recurrent aphthous stomatitis manifests with multiple recurrent ulcers with first onset in childhood or adolescence with a prevalence of 5–66% (Baccaglini *et al*, 2011; Chattopadhyay and Shetty, 2011). The diagnosis is frequently misapplied to similar aphthous-like ulcers, which may be seen in immune deficiencies, Behçet syndrome, Coeliac disease, Crohn's disease and auto-inflammatory conditions (Scully, 2006).

Lichen planus affects stratified squamous epithelia – the skin, oral mucosa and genitalia – and has a prevalence of 1% (Baccaglini *et al*, 2013). Lesions clinically and histologically similar, termed 'lichenoid lesions', are sometimes caused by dental restorative materials, chronic graft-vs-host disease or hepatitis C virus. Notably, mucosal lichen planus carries a potential for malignant development about 1–3% over ten years. Much more research is required in this common but enigmatic condition.

Several other oral disorders have a more defined immunological basis, and in view of their common involvement of other tissues, these oral lesions are best managed with physicians. Vesiculobullous disorders (pemphigoid and pemphigus mainly) and salivary hypofunction in Sjogren syndrome are the main conditions. Pemphigoid is an immune-mediated subepithelial blistering disease. Special immune tests are required to separate the various phenotypes. Mucous membrane pemphigoid affects oral mucous membranes (Di Zenzo *et al*, 2014). Most patients have oral involvement only. There may be associated autoimmune disorders, and associations with parkinsonism, cerebrovascular events and disseminated sclerosis. Internal malignancy such as lymphoma may be present in some cases with anti-epiligrin (anti-laminin 322) pemphigoid, but those with antibodies to $\alpha 6$ integrin may have a reduced relative risk for developing cancer.

Pemphigus has autoantibodies against desmosomes (Cirillo *et al*, 2012). Pemphigus vulgaris, the most common variant and responsible for most oral lesions, is associated with antibodies against desmoglein 3. Pemphigus causes blisters and scabs on the skin and erosions on mucosae of the mouth, pharynx, larynx, oesophagus, nose, conjunctiva or anogenital region.

Sjögren syndrome is an autoimmune disorder producing dry mouth and eyes, affecting 0.2–3.0% of the population (Aframian *et al*, 2013; Reksten and Jonsson, 2014). A fully developed lesion in major salivary glands appears as a dense mass of lymphocytes interspersed by epithelial islands as the 'benign lymphoepithelial lesion'. The diagnosis is confirmed by history, clinical examination and investigations on salivary gland and autoantibodies against Ro (SSA) and La (SSB) autoantigens that may antedate the disease by months or years. Systemic complications including lymphomas may complicate Sjogren syndrome.

Orofacial pain

Orofacial pain is fairly common and challenging to manage due to its complex nature (Romero-Reyes and Uyanik, 2014). Most cases arise from dental diseases – notably the consequences of caries, and less common causes are psychogenic neurological, vascular or referred (Koopman *et al*, 2009).

Temporomandibular joint and muscle disorder refers to a triad of joint clicking, locking and pain, affecting 5–12% of the population mainly in younger adult women (National Institute of Dental and Craniofacial Research, USA, 2014). Its aetiopathogenesis, diagnosis and management remain controversial but may have a psychogenic basis. Diagnosis is made through clinical approaches, but it is crucial to exclude organic diseases locally or

elsewhere. Conservative therapies are adequate, although other alternative approaches may be offered when appropriate.

Burning mouth 'syndrome' could affect 4–40% population especially in older women, most frequently affecting the tongue with persistent discomfort (Ducasse *et al*, 2013). No precipitating cause can be identified in 50%, but it may appear to follow dental interventions, respiratory tract infections or drugs (e.g. ACE inhibitors) and can be psychogenic. About 20% of cases may be associated with anxiety, depression, cancerphobia or concern about possible sexually shared infections.

Trigeminal neuralgia seen mainly in the older patients presents with severe paroxysmal orofacial pain. Differential diagnosis must be undertaken to exclude organic diseases such as cerebral space-occupying and demyelinating lesions.

Orofacial clefts

Cleft lip and palate are among the most common birth defects, approximately affecting one of 600–700 live births, with roughly 220 000 new patients yearly in USA (U.S. Department of Health and Human Services, 2000; Mossey *et al*, 2011). A great variation occurs in term of the prevalence, clinical profiles with or without additional congenital defects, infant mortality and morbidity, access to professional care and resultant impacts on quality of life, among ethnic groups in different countries. The exact cause remains unclear, while the aetiological factors include tobacco use, maternal metabolic disorders, poor nutrition and cleft-related genetic loci (Beaty *et al*, 2010; Mossey *et al*, 2011). Prevention should be reinforced through health promotion and controlling common risk factors (Mossey *et al*, 2011). Multidisciplinary care is crucial and significantly improves appearance, oral function and quality of life. It is currently important to set an appropriate protocol to provide high-quality and cost-effective care, through an internationally collaborative approach.

Links between oral and systemic diseases

The epidemic of NCDs has become a health and socio-economic crisis globally (Beaglehole *et al*, 2011). CVD, DM, cancer and chronic respiratory disease collectively result in around two-thirds of mortality (Ezzati and Riboli, 2012). Over the years, the risk factors for NCDs shared with common oral diseases have been well documented, for example excess sugar consumption and alcohol intake, tobacco use, unhealthy diet containing high levels of saturated and trans fats and salt, obesity, stress and depression, genetic factors and socio-economic determinants (Pihlstrom *et al*, 2005; Beaglehole *et al*, 2011; Jin *et al*, 2011; Lim *et al*, 2012; Petersen and Ogawa, 2012). It is crucial to address these modifiable common risk factors by integration of oral health into the overall health agenda. Further, population-wide control of these risk factors is fundamentally important in disease prevention, patient management and overall health benefits (Lancet 2009; Beaglehole *et al*, 2011; Petersen and Ogawa, 2012; FDI World Dental Federation 2013a).

Furthermore, the evidence suggests, after adjustment of various confounders, a significant association of some oral diseases such as periodontal disease with major NCDs, for example CVD, DM and chronic respiratory disease (Pihlstrom *et al*, 2005; Lockhart *et al*, 2012; FDI World Dental Federation, 2013b; Tonetti and Kornman, 2013). Such an association has been explored in a range of other diseases and conditions, such as adverse pregnancy outcomes, chronic kidney disease, rheumatoid arthritis, dementia, metabolic syndrome and certain forms of cancers (Tonetti and Kornman, 2013). Various common risk factors and biological plausibility have been postulated to support the oral-systemic linkage, in line with current understanding of the aetiopathogenic mechanisms of major NCDs (Pihlstrom *et al*, 2005; Beaglehole *et al*, 2011; Jin *et al*, 2011; Lim *et al*, 2012; Lockhart *et al*, 2012; Tonetti and Kornman, 2013). Conceivably, such long-lasting but persistent periodontal infection and inflammation have a huge impact on the healthcare economy (Chapple, 2014). Uncontrolled periodontal disease may possibly contribute to the pathological pathways in CVD and DM, through direct metastatic infections (e.g. bacteraemias, endotoxaemias and vascular infection/endothelial invasion by periodontopathogens like *P. gingivalis*) and/or indirect mechanisms (e.g. systemic inflammation and molecular mimicry-induced autoimmune damage) (Pihlstrom *et al*, 2005; Parahitiyawa *et al*, 2009; Tonetti and Kornman, 2013). Interestingly, common genetic susceptibility may partially explain the comorbidity of periodontal disease and CVD (Bochenek *et al*, 2013).

Clinical studies further reveal the promising effects of effective periodontal care on reduction of systemic inflammation, and improvement of certain biomarkers of CVD and endothelial function, as well as a decrease in blood glucose level in subjects with type 2 DM (Tonetti *et al*, 2007; Lalla and Papapanou, 2011; Lockhart *et al*, 2012; Tonetti and Kornman, 2013). Nevertheless, evidence for a causal relationship has not been firmly established and further multicentre clinical trials with a sufficient sample size are required. Based on the integrated link of oral health and general well-being, common oral diseases such as periodontal disease should be subject to effective prevention, control, care and management by all healthcare professionals through a collaborative approach for overall health (FDI World Dental Federation 2013a,b and Jin, 2013).

Summary and conclusions

Oral disease represents one of the most common public health issues and remains a major global health burden, yet it has frequently been neglected in public health strategy and policy. Various oral diseases and conditions have significant socio-economic impact in terms of healthcare cost, the absence from school or work, and individual's daily lives and self-esteem. They range in severity from painful but treatable to life-threatening, such as oral cancer. Oral diseases and NCDs share risk factors, such as excess sugar/alcohol consumption and tobacco use. It is therefore crucial to incorporate oral health into general health agenda for optimal health and general well-being. The long-term sustainable strategy for global oral health

must focus on health promotion and disease prevention, through controlling the modifiable common risk factors.

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Author contributions

LJ Jin and I Lamster provided outline of the work and overall guidance on preparation of the manuscript. All authors contributed to the development of the drafts, successive revision and refinement of the manuscript. LJ Jin contributed especially to the sections on overview of global burden, and links between oral and systemic diseases; N Pitts on dental caries; I Lamster on periodontal disease; S Warnakulasuriya on oral cancer; JS Greenspan on oral lesions in HIV/AIDS; and C Scully on oral mucosal and salivary gland diseases, and orofacial pain. LJ Jin finalised the manuscript based upon comments from other authors for submission. All authors reviewed the final version of the manuscript.

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