The Impact of Smokeless Tobacco on Oral Health: Pathogenesis of Oral Mucosal Lesions and Malignancy

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Abstract

Smokeless tobacco (SLT) products-encompassing chewing tobacco, snuff, gutka, khaini, mawa, betel quid, and pan masala-represent a significant and often underestimated public health crisis, particularly in South and Southeast Asia. Unlike smoked tobacco, SLT is placed directly in contact with the oral mucosa, exposing epithelial tissues to a concentrated mixture of over 3,000 chemical compounds, including at least 28 known carcinogens. This prolonged mucosal contact initiates a cascade of pathological events culminating in a spectrum of oral mucosal lesions, including leukoplakia, oral submucous fibrosis (OSMF), nicotinic stomatitis, erythroplakia, and ultimately oral squamous cell carcinoma (OSCC). This review comprehensively examines the constituents of SLT, the molecular and cellular mechanisms of mucosal pathogenesis, the clinical spectrum of SLT-associated oral lesions, their malignant transformation potential, and current strategies for prevention and management. The review underscores the urgent need for enhanced clinician awareness, community-level education, and robust public health policy to mitigate the oral health burden of smokeless tobacco use.

Keywords: Smokeless tobacco, oral submucous fibrosis, leukoplakia, oral squamous cell carcinoma, betel quid, gutka, oral mucosal lesions, carcinogenesis.

Introduction

Tobacco use in its smokeless form is one of the oldest and most widespread habits practiced across cultures worldwide. Smokeless tobacco (SLT) refers to tobacco products that are used without burning and include a diverse range of preparations that are chewed, sucked, or placed in the oral cavity. Products such as chewing tobacco, moist and dry snuff, gutka, khaini, mawa, zarda, and betel quid with tobacco are consumed by an estimated 300 million people globally, with the highest burden concentrated in the South Asian subcontinent[(1)].

India bears a disproportionate share of this global burden, with approximately 199.4 million tobacco users—the majority of whom use smokeless forms. According to the Global Adult Tobacco Survey India (GATS-2, 2016–17), nearly 21.4% of all adults in India used SLT products, with significantly higher rates reported in rural areas and among lower socioeconomic groups[(2)]. The social acceptance of SLT use, low cost, easy availability, and cultural integration of betel chewing practices have made cessation efforts particularly challenging.

The oral cavity serves as the primary site of SLT exposure, placing the buccal mucosa, gingiva, palate, tongue, and floor of mouth in direct and sustained contact with a complex mixture of carcinogens, toxins, and irritants. This chronic mucosal insult results in a well-documented spectrum of pathological changes ranging from benign inflammatory and reactive lesions to potentially malignant disorders (PMDs) and frank malignancy[(3)].

The importance of this topic to dental professionals cannot be overstated. Dentists and dental students are uniquely positioned to detect early mucosal changes, provide cessation counselling, and refer patients for timely management. This review aims to consolidate current knowledge on the pathogenesis of SLT-induced oral lesions, their malignant potential, and evidence-based management strategies.

Constituents of Smokeless Tobacco and their Biological Effects

SLT products contain over 3,000 identified chemical compounds, the majority of which exert cytotoxic, genotoxic, or carcinogenic effects on oral epithelial tissues[(4)]. Key components include:

Tobacco-Specific Nitrosamines (TSNAs)

TSNAs-including N'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoanabasine (NAB), and N'-nitrosoanatabine (NAT) - are considered the most potent carcinogens in SLT.[4] They are formed during the fermentation and curing of tobacco leaves through nitrosation of tobacco alkaloids. TSNAs induce DNA adduct formation, particularly O6-methylguanine and O4-methylthymidine adducts, leading to guanine-to-adenine transitions in critical tumour suppressor genes such as TP53 and CDKN2A (p16).

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs such as benzo[a]pyrene are powerful procarcinogens present in SLT. They are metabolically activated by cytochrome P450 enzymes (CYP1A1, CYP1B1) to form reactive epoxide intermediates that form bulky DNA adducts, disrupting normal replication and predisposing cells to malignant transformation[5].

Nicotine

While nicotine itself is not a direct carcinogen, it plays an important auxiliary role in SLT-associated pathogenesis. Nicotine stimulates angiogenesis, promotes cell survival by inhibiting apoptosis, and upregulates matrix metalloproteinases (MMPs) that degrade the extracellular matrix-facilitating tumour invasion[5]. Nicotine also contributes to vasoconstriction in the gingival tissues, masking signs of periodontal inflammation.

Areca Nut Alkaloids

Areca nut (Areca catechu), a common additive in South Asian SLT preparations such as gutka, pan masala, and betel quid, contains the alkaloids arecoline, arecaidine, guvacine, and guvacoline[6]. Arecoline is the most biologically active; it acts as a muscarinic receptor agonist and stimulates fibroblast proliferation while inhibiting fibroblast phagocytosis of collagen-a central mechanism in the pathogenesis of oral submucous fibrosis (OSMF). Arecoline also promotes reactive oxygen species (ROS) generation, lipid peroxidation, and DNA strand breaks.

Heavy Metals and Other Toxins

SLT products contain trace amounts of heavy metals including cadmium, lead, chromium, and arsenic. These metals act as co-carcinogens by inhibiting DNA repair enzymes, promoting oxidative stress, and altering epigenetic regulation through DNA methylation and histone modification[4]. Aldehydes and volatile N-nitrosamines present in SLT further contribute to mucosal cytotoxicity.

Molecular Pathogenesis of Slt-induced Oral Mucosal Changes

The carcinogenic and pathological effects of SLT on oral mucosa are mediated through multiple interconnected molecular mechanisms:

DNA Damage and Mutagenesis

TSNAs and PAHs form DNA adducts that, if not repaired, lead to permanent mutations. The most commonly mutated genes in SLT-associated OSCC include TP53 (tumour protein p53), CDKN2A (p16), PTEN, and NOTCH1[7]. TP53 mutations disrupt the cell cycle checkpoint at G1/S, allowing replication of damaged DNA and accumulation of genetic errors. Loss of heterozygosity (LOH) at chromosomal loci 3p, 9p, 11q, and 17p is frequently observed in SLT-associated dysplasia and carcinoma.

Oxidative Stress

SLT exposure generates excess reactive oxygen species (ROS) through arecoline metabolism, heavy metal redox cycling, and activated inflammatory cells. ROS cause direct oxidative DNA damage (8-hydroxydeoxyguanosine, 8-OHdG), lipid peroxidation, and protein oxidation. Chronic oxidative stress depletes endogenous antioxidant defences (superoxide dismutase, glutathione peroxidase), creating a pro-carcinogenic redox environment[5].

Epigenetic Modifications

SLT carcinogens alter epigenetic regulation through aberrant DNA methylation (silencing of tumour suppressor genes via promoter hypermethylation), histone deacetylation, and dysregulation of microRNAs[7]. Silencing of genes such as DAPK, MGMT, and RASSF1A by promoter methylation has been documented in SLT-associated oral cancers. These epigenetic changes are potentially reversible and represent therapeutic targets.

Inflammatory Pathways

Chronic mucosal irritation by SLT activates NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), a master transcription factor that upregulates pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), cyclo-oxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS)[6]. Persistent inflammation promotes epithelial proliferation, inhibits apoptosis, and supports tumour microenvironment formation. Elevated prostaglandin E2 (PGE2), a COX-2 product, suppresses anti-tumour immune responses and enhances angiogenesis.

Fibrogenesis in OSMF

In oral submucous fibrosis, arecoline-stimulated fibroblasts overproduce type I and type III collagen while concurrently downregulating collagenolytic activity. Transforming growth factor-beta (TGF-β) plays a pivotal role by promoting fibroblast-to-myofibroblast differentiation, driving progressive submucosal fibrosis and mucosal rigidity[6]. Hypoxia-inducible factors (HIF-1α) upregulated in the ischaemic fibrotic tissue further promote angiogenesis and malignant transformation.

Clinical spectrum of Slt-associated Oral Mucosal Lesions

Tobacco Pouch Keratosis (Smokeless Tobacco Keratosis)

This is the most common and direct consequence of SLT use, occurring at the habitual placement site of tobacco-typically the mandibular buccal vestibule. It presents as a white, wrinkled, or corrugated plaque with a translucent or opaque appearance[3]. Lesions are usually asymptomatic and may

regress upon cessation of the habit. Histologically, hyperkeratosis, acanthosis, and mild chronic inflammation are observed, with dysplasia being uncommon in pure smokeless tobacco keratosis without areca nut.

Oral Leukoplakia

Leukoplakia is defined by the WHO as a white plaque of questionable risk having excluded other known diseases or disorders. SLT use is a well-established aetiological factor[8]. It may present as homogeneous (flat, uniformly white), non-homogeneous (speckled, nodular, or verrucous), or erythroleukoplakia. The non-homogeneous variants carry a significantly higher malignant transformation rate (up to 18%). Lesions on the floor of the mouth and lateral tongue carry greater risk.

Oral Submucous Fibrosis (OSMF)

OSMF is a chronic, insidious, potentially malignant disorder strongly associated with areca nut and betel quid use. It is characterised by progressive fibrosis of the oral submucosa, juxta-epithelial inflammatory reaction, and atrophic epithelial changes[6]. Clinically, patients present with burning sensation on consuming spicy food, progressive trismus (restricted mouth opening), blanching and fibrous bands in the buccal mucosa, and depapillation of the tongue. OSMF is classified into grades based on mouth opening and mucosal changes (Grade I: >35 mm; Grade II: 26–35 mm; Grade III: 15–25 mm; Grade IV: <15 mm). The malignant transformation rate of OSMF ranges from 7% to 13%.

Nicotinic Stomatitis

Though classically associated with pipe smoking, nicotinic stomatitis can occur with heavy SLT use, particularly reverse smoking or tobacco application to the palate. The hard palate shows diffuse grey-white keratosis with red, inflamed ductal orifices of minor salivary glands, giving a characteristic 'cobblestone' appearance. It is generally considered a benign reactive lesion that resolves with habit cessation.

Erythroplakia

Erythroplakia-a fiery red velvety plaque that cannot be attributed to any other condition-carries the highest malignant transformation potential of all oral potentially malignant disorders, with dysplasia or carcinoma in situ found in over 90% of lesions on histopathology[8]. SLT use is an important aetiological cofactor. It may coexist with leukoplakic areas as erythroleukoplakia.

Periodontal Changes

SLT causes significant periodontal damage including gingival recession at the placement site, attachment loss, and increased pocket depth. Nicotine-induced vasoconstriction masks clinical signs of inflammation while the toxic components cause direct gingival injury. Altered neutrophil function and impaired wound healing further exacerbate periodontal disease in SLT users[9].

Other Changes

Additional oral manifestations of SLT use include dental staining (brown-black discolouration), dental attrition (abrasion from tobacco grit), halitosis, reduced taste sensation, and salivary gland changes. Increased calculus formation has been reported in SLT users due to altered salivary composition.

Malignant Transformation and Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies and ranks among the ten most common cancers worldwide. In India, it constitutes approximately 30% of all cancers, reflecting the high burden of tobacco use[10]. SLT use is an independent and well-established risk factor for OSCC, with risk increasing proportionally with duration and frequency of use.

The multistep progression from normal epithelium to carcinoma involves sequential accumulation of genetic alterations driven by SLT carcinogens. The widely accepted model of oral carcinogenesis follows the sequence: normal mucosa → hyperplasia → dysplasia (mild → moderate → severe) → carcinoma in situ → invasive carcinoma. The degree of epithelial dysplasia-characterised by features such as increased nuclear-cytoplasmic ratio, loss of polarity, abnormal mitoses, and individual cell keratinisation-is the most important histopathological predictor of malignant transformation[7].

Key molecular events in SLT-associated OSCC include activation of oncogenes (EGFR, CCND1, PIK3CA), inactivation of tumour suppressor genes (TP53, CDKN2A, RB1), telomerase reactivation, and upregulation of angiogenic factors (VEGF). Loss of E-cadherin expression facilitates epithelial-to-mesenchymal transition (EMT), a critical step in tumour invasion and metastasis[7].

Clinically, OSCC may arise de novo or from pre-existing potentially malignant disorders. Common sites include the buccal mucosa (particularly relevant in SLT users), lateral border of tongue, floor of mouth, and soft palate. Early lesions may present as painless white or red patches, ulcers with indurated margins, or exophytic growths. Advanced disease presents with pain, dysphagia, cervical lymphadenopathy, and trismus.

Diagnosis and Clinical Assessment

Clinical Examination

A thorough history of SLT use-including type, frequency, duration, quantity, and placement site-is essential. Complete oral mucosal examination under adequate illumination, using

a mouth mirror and gauze for tissue manipulation, should be performed systematically. The ICDAS (International Caries Detection and Assessment System) framework may be adapted for lesion recording.

Adjunctive Diagnostic Aids

Several adjunctive methods enhance detection of mucosal changes:

- Toluidine blue (tolonium chloride) vital staining: Selectively stains nucleic acids in dysplastic and malignant cells, aiding biopsy site selection.
- Chemiluminescence (ViziLite, MicroLux): Identifies subtle mucosal abnormalities through differential light reflectance.
- Autofluorescence (VELscope): Detects loss of tissue fluorescence in dysplastic areas, improving sensitivity for early lesion detection.
- Brush biopsy (OralCDx): Non-invasive transepithelial sampling for cytological analysis.
- Incisional biopsy: The gold standard for definitive diagnosis; mandatory for any suspicious lesion.

Histopathological Grading

The WHO grading system classifies epithelial dysplasia as mild, moderate, or severe based on the extent of architectural and cytological abnormalities. The binary Ljubljana classification (SIN grading) categorises lesions as simple hyperplasia, abnormal hyperplasia, risky epithelium (atypical hyperplasia), or carcinoma in situ[8]. Molecular markers such as Ki-67, p53, p16, and survivin expression patterns may aid prognostication.

Prevention of Slt-associated Oral Disease

Primary Prevention

Primary prevention targets non-users, particularly adolescents, through school-based oral health education, community awareness campaigns, and mass media initiatives. Legislation limiting SLT marketing, restricting sale to minors, and mandating pictorial health warnings on packaging are essential public health measures[1].

Tobacco Cessation Counselling

The '5A' framework (Ask, Advise, Assess, Assist, Arrange) provides a structured approach for cessation counselling in clinical settings[2]. Motivational interviewing techniques have shown efficacy in enhancing cessation readiness. Brief cessation advice by a dental professional during routine dental visits has documented impact on quit rates.

Pharmacotherapy

Pharmacological aids for SLT cessation include:

- Nicotine Replacement Therapy (NRT): Patches, gum, lozenges, and nasal sprays reduce withdrawal symptoms and craving.
- Varenicline (Champix): A partial nicotinic receptor agonist that reduces craving and withdrawal; considered the most effective single pharmacotherapy for tobacco cessation.
- Bupropion SR: An atypical antidepressant that reduces craving through noradrenaline and dopamine reuptake inhibition.
- Cytisine: A plant-derived partial nicotinic agonist with emerging evidence for SLT cessation, particularly in low-resource settings.

Policy and Legislative Measures

The Government of India has implemented several legislative measures including the Cigarettes and Other Tobacco Products Act (COTPA) 2003, ban on gutka and pan masala (Food Safety and Standards Authority of India, 2012), and the National Tobacco Control Programme (NTCP)[2]. Enforcement of these regulations, however, remains inconsistent across states.

Management of Slt-associated Oral Lesions

Management of Tobacco Pouch Keratosis

Cessation of the tobacco habit is the primary intervention. Most lesions show significant regression within 6–8 weeks of habit cessation. Lesions persisting beyond this period require biopsy and histopathological evaluation.

Management of Oral Leukoplakia

Management depends on the degree of dysplasia. Non-dysplastic or mildly dysplastic lesions may be managed conservatively with tobacco cessation and 6-monthly follow-up. Moderate to severe dysplasia warrants surgical excision by scalpel, CO2 laser, or cryotherapy[8]. Chemoprevention with systemic retinoids (isotretinoin, etretinate), beta-carotene, and lycopene has shown partial response but is limited by side effects and high relapse rates. Photodynamic therapy (PDT) is an emerging modality for non-dysplastic and mildly dysplastic lesions.

Management of OSMF

Management of OSMF is directed at arresting progression, improving mouth opening, and monitoring for malignant transformation. Conservative management includes:

- Intralesional corticosteroid injections (dexamethasone, triamcinolone acetonide): Reduce inflammation and fibrosis.
- Intralesional placental extracts (Placentrex): Promote tissue vasodilation and have anti-fibrotic properties.

- Intralesional hyaluronidase: Enhances diffusion of injected agents and softens fibrous bands.
- Pentoxifylline: A xanthine derivative that improves tissue oxygenation and has anti-fibrotic effects.
- Micronutrient supplementation: Iron, B-complex vitamins, antioxidants (lycopene, spirulina) are used adjunctively.

Surgical management is indicated in advanced OSMF (Grade III/IV) with severe trismus and includes fibrotomy and release of fibrous bands, followed by reconstruction with buccal fat pad, skin grafts, or temporalis muscle flaps. Physiotherapy (mouth opening exercises) is a critical adjunct to surgical management[6].

Management of OSCC

Treatment of OSCC depends on the TNM stage and includes surgery (wide local excision, neck dissection), radiation therapy, chemotherapy, or a combination. Targeted therapies (cetuximab targeting EGFR) and immunotherapy (pembrolizumab, nivolumab targeting PD-1/PD-L1) have shown promise in advanced and recurrent OSCC[10]. Early-stage OSCC (Stages I–II) carries a five-year survival rate of approximately 70–80%, which drops significantly in advanced disease, underscoring the critical importance of early detection.

Discussion

The relationship between smokeless tobacco and oral disease is well-established yet remains a daily clinical reality for dental practitioners in India and across South Asia. The unique challenge posed by SLT lies in its cultural normalisation-betel quid, gutka, and khaini are deeply embedded in social and ceremonial contexts, making cessation efforts psychologically and culturally complex.

The molecular understanding of SLT carcinogenesis has advanced significantly over the past two decades. The identification of specific TSNA-induced TP53 mutations, the epigenetic silencing of tumour suppressors, and the role of arecoline in fibrogenesis have provided actionable targets for chemoprevention and early biomarker detection. Salivary biomarkers-including elevated IL-8, S100P, and specific microRNAs-are under investigation as non-invasive screening tools for early mucosal dysplasia in SLT users.

The role of the dental practitioner extends beyond clinical management. Routine oral cancer screening during every dental visit, coupled with brief tobacco cessation advice, represents an evidence-based, cost-effective public health intervention. The integration of tobacco cessation services into dental education and practice remains suboptimal in many institutions and warrants curricular reinforcement.

Digital health technologies including mobile health (mHealth) applications, teledentistry platforms, and AI-assisted image analysis for oral lesion screening offer promising avenues for extending early detection and cessation support to underserved populations in rural India.

Conclusion

Smokeless tobacco use is a major and modifiable risk factor for a broad spectrum of oral mucosal lesions, potentially malignant disorders, and oral squamous cell carcinoma. The pathogenesis is complex, involving direct genotoxic damage from TSNAs and PAHs, oxidative stress, epigenetic reprogramming, chronic inflammation, and arecoline-driven fibrogenesis. Dental professionals occupy a frontline role in the identification, monitoring, and management of SLT-induced oral lesions, as well as in motivating and supporting tobacco cessation.

A multipronged approach integrating clinical vigilance, patient education, pharmacotherapy, and strong public health policy is essential to reduce the oral health burden of smokeless tobacco in India and globally. Increased emphasis on tobacco cessation counselling within dental curricula and practice guidelines will be critical to translating existing knowledge into measurable improvements in oral cancer outcomes.

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