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The Link Between Chronic Periodontitis and Head and Neck Squamous Cell Carcinoma: A Short Review

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Abstract

Chronicperiodontitis is an inflammatory condition characterised by the loss of attachment and a pocket depth >3mm. The organisms involved in pathogenesis are Tanerella Forsythia, Aggregatibacter Actinomycetemcomitans, Porphyromonas Gingivalis, Fusobacterium Nucleatum, Prevotella Intermedia, Campylobacter Rectus. These organisms release various bacterial biomarkers and increase the amount of inflammatory cytokines into the saliva. Head and neck cancer is classified as one of the top ten most commonly occurring cancers in the world. Risk factors include alcohol and tobacco consumption, genetic factors etc. Like every foreign substance, the cancer cells are susceptible to the immune system macrophages and lymphocytes, that initiate the release of inflammatory cytokines into the tumour environment and begin angiogenesis. This gives the tumour cells sufficient nutrition to proliferate. Concurrently, the periodontal pocket acts as a reservoir of many micro-organisms including HPV (human papilloma virus). The bacterial biomarkers released by these organisms lead to suppression of tumour necrotic factor, thus allowing the tumour to proliferate. Many studies have been conducted to prove the association between periodontal disease and oral cancer. From these studies, it can be concluded that periodontal disease, along with history of smoking and tobacco consumption is a significant risk factor associated with the development of oral cancer.

Keywords: Head and neck cancer, periodontal disease, inflammation

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Introduction

Chronic Periodontitis is a chronic infection caused by gram negative anaerobic bacteria [1]. It leads to loss of attachment of the teeth from the periodontium characterised clinically by presence of periodontal pockets and alveolar bone loss. Periodontitis, as a risk factorhas been linked to several systemic conditions such as diabetes, cardiovascular disorders, pregnancy complications [2-4], etc. Furthermore, it has been seen that the treatment of periodontitis has led to reduction in symptoms of various systemic conditions that are known to be associated with periodontal disease. It is seen to affect 35% of adults aged between 30 to 90 years in the USA.According to various researchers, cancer has been seen to be significantly associated with inflammatory diseases[5,6]. Recent studies also suggest a striking relationship between periodontal disease, oral health and hygiene and its association with carcinogenesis.

Head and neck cancer are one of the ten most common cancers in the world. Common sites include the larynx, pharynx, oral cavity, nasal cavity. Major risk factors include genetic factors, viral infections like human papilloma virus infection [7], smoking, sex and occupation. Inflammation caused due to periodontitis is strongly associated with tumour formation in the oral cavity and associated structures due to increased release of cytokines and other inflammatory mediators which lead to suppression of the tumour necrotic factor alpha and increased angiogenesis. This provides optimum condition for cell growth and thus leads to rapid proliferation of a tumour. Many epidemiological studies have been done, both case -control and cohort, to evaluate the relationship between inflammation and cancer. In vitro studies on tongue cancer in a clinical setting have shown the relationship.

Periodontal disease

Periodontal disease gingivitis includes (inflammation of the gingiva) and periodontitis. Periodontitis is characterised by gingival inflammation. destruction of periodontal tissues, and reduction in alveolar bone height. Periodontal diseases are defined on the basis of clinical attachment loss in minimum three teeth measuring >3mm in depth. Risk factors for periodontitis include smoking, diabetes, genetic causes, poor oral hygiene etc. Periodontal disease is caused due to a transient shift in the oral microbial environment from gram positive microorganisms to gram negative microorganisms. According to numerous studies, common bacteria involved in the pathogenesis of periodontal disease are Aggregatibacter Actinomycetemcomitans, Tanerella Forsythia, Porphyromonas Gingivalis, Prevotella Intermedia, Campylobacter Fusobacterium Rectus, Nucleatum, Treponema Denticola, These organisms lead to initiation of inflammation and increase in the amount of bacterial biomarkers into the saliva and circulation. Inflammatory mediators like cytokines released into the bloodstream are aimed at restoring homeostasis. Failure to do so, may cause organ damage due to loss of order in circulatory mechanisms. Chronic inflammation caused due to periodontal disease can have protective as well as detrimental effects on the body.

Head and neck cancer

Majority of the head and neck cancer is caused due to alcohol or tobacco consumption. Recent studies have suggested a link between inflammatory products and development of oral cancer. The risk factors include lack of consumption of fruits and vegetables, increased intake of alcohol and tobacco, greater levels of stress, genetic susceptibility and poor oral hygiene (in most cases related to periodontitis). Various animal aided studies show that in an area affected by chronic inflammation; in presence of continuous



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exposure to the inflammatory agent, a long standing tissue damage is evident followed by excessive cellular proliferation due to increased mutagenic potential. This, in certain cases can be followed by tissue repair or metaplasia (change in cell type). Another possible outcome is the presence of dysplasia or disordered cell development imparting neoplastic characteristics. A roughly translated version of cancer development is inflammation followed by metaplasia and dysplasia giving rise to carcinogenic potential by alteration of cell DNA and phenotypes by certain carcinogenic substances.

Like every foreign substance in the body, the cancer cells are also susceptible to invasion by the immune system cells like macrophages and lymphocytes. Once these cells invade the tumour, they release inflammatory mediators like cytokines which initiate angiogenesis or the production of new blood vessels in the area. Therefore, instead of destroying the cancer cells these macrophages provide a way for obtaining nutrition for survival along with increased oxygenation in the area. This provides optimum conditions for survival of cancer cells, assisting them in further proliferation in the body. Contact inhibition of proliferation is a property of a normal untransformed cell seen during organogenesis. This is characterised by downregulation of proliferation by various cell signalling pathways when the cell density in a particular region increases. This property is lost in cancer cells which aids in rapid proliferation and growth of the tumour. Another manner in which the cytokines accelerate tumour growth is by building a stroma around the tumour. In certain cases inflammation and increased blood flow may allow some cancer cells to enter the circulatory system and lymphatics, allowing the tumour cells to travel across the body and lodge in various sites setting up a new cancerous cell growth in the new site. This property is called as metastasis. This is a characteristic of malignant tumours. Benign tumours do not have the capability to metastasize.

Link between oral micro-organisms and cancer

Many mechanisms have been linked to development of oral cancer and microorganisms causing periodontitis. Α possible mechanism is attributed to the presence of Porphyromonas Gingivalis in the gingival crevice. This leads to development of resistance to death among host epithelial cells (by changing the phenotype and imbibing anti apoptotic properties to individual cells); causing uncontrolled cell growth which is histologically seen as metaplastic or dysplastic features. Viruses like the HPV (Human Papilloma Virus) which may be found in the periodontal pockets is also linked to oral cancer. Oncogenes E6 and E7 have the ability to suppress tumoursuppressors by binding to their surface, leading to tumour proliferation. In certain cases, and indirect route of tumour proliferation may be established by chronic infection. This includes activation of host cell immune responses like macrophages and neutrophils, leading to DNA damage by reactive O2 species. This produces more growth factors and cytokines, the outcome being proliferation of damaged tumour like cells. Recent studies in patients affected by carcinoma of the tongue have shown a relationship between tumour related human papilloma virus and chronic periodontitis. HPV commonly affects the cervical epithelial cells, according to many studies and the inflammatory cytokines have been found to change the proliferation of HPV leading to a modulation in expression of its oncogenes. Recently, it has been seen that the periodontal pocket or gingival sulci serves as a reservoir of high-risk human papilloma viruses. A pilot study was done to study the presence of highrisk HPV in the marginal periodontium. It consisted of samples procured by pocket scrapings in eight patientsalong with detection of E6/E7 mRNA. This was done in intact cells using flow cytometry. Four of these patients were found positive. Therefore, it was concluded that prevalence of high-risk HPV



could link periodontitis to HPV related carcinoma. Another study performed in 740 Hispanic adults diagnosed with severe periodontitis showed that oral human papilloma virus infection was strongly and positively associated with periodontitis. The odds of HPV infection was higher in individuals diagnosed with periodontal disease.

Studies linking oral cancer and periodontitis

A hospital-based study evaluating 473 subjects (266 cases and 207 controls), newly diagnosed with head and neck squamous cell carcinoma was conducted by Tezal et al. [8], in the Rosewell Park Cancer Institute. Periodontitis was assessed on the basis of loss of clinical attachment and radiographs. The loss of attachment predicted precancerous lesions and tumours. It also proved that smoking alone did not increase the risk of a precancerous lesion, as it was seen in non-smokers too. And it is associated with recent and chronic smokers, but not short term or former smokers. The greatest association was seen in the oral cavity, followed by the larynx and pharynx.

Another hospital based study consisting of 46 patients was conducted by Nitescu et al. [9], at the Clinical hospital of recovery, Romania to association between study the chronic periodontitis and head and neck squamous cell carcinoma. The cases consisted of patients diagnosed with different cancers of the head and neck region including oral cavity SCC(squamous cell carcinoma), oropharyngeal and laryngeal with well differentiated tumours of the oral cavity. The study reported that the risk of HNSCC (head and neck squamous cell carcinoma) increases four times with every millimetre increase in the loss of attachment and every patient diagnosed with SCC had a higher degree of periodontal disease, stating that periodontal disease is a major risk factor in the development of SCC. Therefore, proper periodontal treatment and good oral hygiene

may reduce the risk of development of oral cancer.

A study conducted by Pow et al. [10], to evaluate the oral health status among the Chinese population 1-4 years after radiotherapy for NPC (nasopharyngeal carcinoma) showed that the oral health was compromised as the survivors had frequent dental treatments. It was carried out on a sample size of 109 patients where 38 were NPC survivors, 40 had been recently diagnosed and 31 were healthy. Evaluation was done on the basis of amount of jaw opening, alveolar bone loss, mucositis, candidiasis along with widespread carious lesions. Hujoel et al. [11], explored the relationship between periodontitis and cancer with data procured from 11,328 adults and concluded that of all the cancers, lung cancer showed the strongest association.

In 2008 a study was conducted by Christian Abnet et at. [12], on how tooth loss along with poor oral hygiene is associated with a higher risk of oesophageal carcinoma in subjects living in a high-risk area in Iran consisted of 283 cases and 560 controls. Significant associations were found between poor oral hygiene and a high risk of oesophageal squamous cell carcinoma. Shankarapillai et al. [13], evaluated the periodontal and gingival findings in 73 subjects diagnosed with acute myeloid leukaemia and no other systemic disorders. It showed a very strong association between gingival overgrowth and periodontal findings in about three quarters of the tested young adults diagnosed with AML.

A study conducted by Michaud et al. [14], evaluated 7466 subjects of the Atherosclerosis Risk in Communities study cohort where periodontal disease was assessed along with the cancer risk. Disease severity was defined using probing depth and gingival recession. It showed an increased risk of cancerfor severe periodontitis and a strong association was observed with lung cancer and in some cases colorectal cancer. Freudenheim et al, 15-17],



conducted a study to evaluate periodontal disease and breast cancer association. There are mechanisms that explain various this association including periodontitis associated systemic inflammation and increased c reactive protein. A prospective study conducted by Manish Arora et al. [18], evaluated the genetic risks between periodontitis and cancer. 15333 Swedish twins were evaluated using a questionnaire-based record of tooth mobility this and cancer. According to study periodontitis was associated with colorectal. pancreatic and prostate cancer in monozygotic twins. In dizygotic twins, periodontitis showed an increase in cancer risk by 50%. Another prospective study carried out by Michaud et al. evaluated associations [19]. between periodontitis and pancreatic cancer among US male health professionals. It consisted of 216 subjects diagnosed with pancreatic cancer in a 16 year follow up study. It was found that all professionals with a history of periodontal disease had a 64% increased risk of pancreatic cancer. A review by Shamami et al. [20], reported that nine out of ten case control studies which showed an association between severe periodontal disease and cancer. Cohort consisted of 48375 men and the most common cancers found were colorectal, skin melanoma, lung cancer, bladder cancer and advanced prostate cancer. In never smokers, periodontitis was associated with an increase in total cancer and no relationship was noted with lung cancer in those who never smoked. A case control study conducted by Divaris et al. [21], in 2010 to evaluate head and neck squamous cell carcinoma in 46 counties in North Carolina. It consisted of 1361 subjects and oral health was evaluated based on an interview data collected on tooth loss, mobility and hygiene protocols. Self-reported history of tooth loss was associated mildly with increased HNSCC risk. A case control study was performed in Beijing on 404 subjects for evaluation of the association between dentition and risk of oral cancer. Analysis showed that a two to three-fold increase in risk for oral cancer was observed in males who reported tooth loss for females a five

to eight times increase was seen. In 2011, in study conducted by Grant et al. [22], showed the relationship between low vitamin d status and how it contributes to the link between periodontitis and breast cancer. In 1986 Felix et al. [23] reported a case that showed AML (acute monoblastic leukaemia) mainly manifests as gingival hypertrophy in the oral cavity, making oral symptoms as a chief sign of AML. In 2005, Tezal et al. [24] conducted a study on 13798 subjects 20 years of age having at least six natural teeth. The variables employed were tumour (non-specific), precancerous lesions and oral soft tissue lesion. Clinical attachment loss was measured and its effect on dependant variables was assessed and adjusted with effects of race, ethnicity, decayed and filled teeth, smoking and tobacco consumption. This study showed an association between precancerous lesion and tumours which lead to the hypothesis about a plausible relation between periodontitis and oral cancer. A retrospective study involving radiographical evaluation of bone loss was carried out by Moergel et al. [25], where cases consisted of individuals diagnosed with oral squamous cell carcinoma. Controls consisted of individuals who were not diagnosed by a malignant tumour. Data collection was done using a telephone survey and a questionnaire regarding the individual's oral hygiene, presence of any deleterious habits, use of dental prosthesis, presence or absence of gingival bleeding and halitosis, along with personal data. The evaluation of periodontal disease was done by observing loss of attachment with the help of radiographs by a trained examiner blind to the status of the disease. It was concluded that effective periodontal treatments plans reduced the risk of development of oral squamous cell carcinoma. Further studies have shown HPV as a common etiological factor in head and neck malignancies; and HPV related HNSCC is on the rise with HPV16 seen as the most commonly associated subtype with oral cancer. Routine testing in individuals diagnosed with oral cancer has shown that HPV positive malignancies have a better prognosis over HPV negative. This association between chronic



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periodontitis, HPV infection and tongue cancer was seen in a study conducted by Tezal et al. [8], at the Rosewell Park Cancer Institute. A case control study was performed on thirty patients recently diagnosed with tongue Edentulous carcinoma. and immunocompromised patients were excluded. Tumour samples were obtained and tested for HPV 16 and HPV 18 DNA by polymerase chain reaction. Analysis showed that 70% were HPV 16 positive and a 4 times increased risk rate to HPV positive tumours with one-millimetre increase in attachment loss. Therefore, this study concluded the possibility of longstanding periodontal disease playing a major role as a part of HPV infections in patients diagnosed with tongue base tumours.

Summary

Chronic periodontitis is a disease affecting the periodontium, leading to loss of attachment. The oral microbiota involved in causing periodontitis releases a variety of inflammatory cytokines which assist in development of tumours. The periodontal pocket, being a reservoir of HPV is strongly associated with HPV16 positive tongue base carcinoma. Many studies in literature have reported the association between periodontal disease and oral cancer. From these studies, it can be concluded that periodontal disease, along with history of smoking and tobacco consumption is a significant risk factor associated with development of oral cancer.

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