

Diabetes Mellitus as A Risk Factor for Oral Malignancy

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Abstract: Diabetes mellitus and oral cancer are commonly coexisting illness, and the global incidence and prevalence of both are rising. Cancer patients with diabetes face unique challenges. This review highlights the relationship between diabetes and oral cancer and various aspects related to it. Evidence suggests that cancer patients with diabetes have higher chances for mortality hence a multidisciplinary approach is important in the management of patients with oral cancer for better outcome. Conclusion Furthermore studies are required to better understand the underlying mechanism between the risk of oral cancer and diabetes.

Keywords: Diabetes mellitus; Diabetes; Oral cancer; Hyperglycemia; Hypoglycemia; ILGF (Insulin like growth factor)

Introduction: Diabetes Mellitus comprises a group of metabolic disorder that shares common feature of Hyperglycemia. (1) Prevalence of diabetes mellitus in India is approximated to be about 77 million in 2019 which is expected to rise to 134 million by 2045. Approximately 57% cases remain undiagnosed. (2)

Any uncontrolled growth of cells that invade and cause the impairment of adjacent tissue impairment is known as cancer. Oral cancer ensues with a small, unfamiliar, unexplained growth or sore in the mouthparts that include lips, cheeks, sinuses, tongue, hard and soft palate, the base of the mouth extended to the oropharynx. Globally, oral cancer ranks sixth among all types of cancer. India has the largest number of oral cancer cases and one-third of the total burden of oral cancer globally. (3)

In India, around 77,000 new cases and 52,000 deaths are reported annually, which is approximately one-fourth of global incidences. The increasing cases of oral cancer are the most important concern for community health as it is one of the common types of cancers in India. As compared to the west, the concern of oral cancer is significantly higher in India as about 70% of the cases are reported in the advanced stages (American Joint Committee on Cancer, Stage III-IV). (4)

Diabetes and Oral Cancer Co Relation Study

Diabetes mellitus is classified as type 1 (insulin dependent) or type 2 (non-insulin dependent). Earlier studies have shown an increased prevalence of leukoplakia and lichen planus among insulin-dependent (type 1) diabetes patients. (5) But recent studies have shown that precancerous and tumorous oral lesions are more frequent in type 2 diabetes. (6) Although many epidemiologic studies have suggested an association between type 2 diabetes and oral leukoplakia, none is supported by a definitive histopathologic diagnosis. In view of the lack of information about the dysplastic features of these lesions, it cannot be assumed that they will progress to oral cancer. Also, a possible association between diabetes and oral leukoplakia does not necessarily indicate a similar association between diabetes and any other oral precancerous condition or between diabetes and oral cancer.

None of the studies mentions definitive inclusion criteria for Oral leukoplakia which itself is controversial issue (7) and none has excluded other possible causes for white lesions due to oral hypoglycemic drug (8,9). In diabetic patients, alterations occur in the oxidative equilibrium of free radicals (6). Elevated blood glucose levels can lead to excessive formation of free radicals. Also due to protein breakdown, the activity of antioxidant scavengers and enzymes is reduced. Both the increase in free radicals and oxidative stress promote carcinogenesis. (10,11)

It has been suggested that poor diabetic control is associated with an increased cancer risk due to enhanced oxidative damage to DNA (12).

Production of reactive oxygen species and lipid peroxidation are increased in diabetic patients, especially in those with poor diabetic control and hyperglycemia.

Increased oxidative damage can be due to superoxide radical generation by monocytes through nicotinamide adenine dinucleotide nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Superoxide can undergo either enzymatic or nonenzymatic dismutation to generate hydrogen peroxide. In the presence of transition metals, such as Fe⁺⁺ and Cu⁺⁺, both these substances contribute to the generation of highly reactive hydroxyl radicals causing damage to cells. (12)

Therefore, those with uncontrolled diabetes are at even greater risk of developing oral cancer.

Type 2 diabetes is usually associated with insulin resistance and increased pancreatic secretion. Chronically increased levels of insulin result in hyperinsulinemia and have been associated with cancer of the colon, breast, pancreas and endometrium. These

tumorogenic effects of insulin could be directly mediated by insulin receptors in the preneoplastic target cells or might be due to related changes in endogenous hormone metabolism. Insulin promotes the synthesis and biologic activity of insulin-like growth factor (IGF) 1. Insulin and IGF-1 promote cell proliferation and inhibit apoptosis (13).

There is evidence that the effect of IGF-1 might be related to p53 mutations, which are quite common in head and neck tumors. (14)

Therefore, there is a need to study the molecular mechanisms involved in the etiology of leukoplakia among diabetic patients. Components of betel quid can affect cell-mediated immunity. (13)

In diabetic patients, T-cell function as well as the cellular immune response is impaired.(15)

Thus, diminished immunity in diabetic patients may facilitate the action of carcinogens. In addition, there can be microangiopathy (16) in the gingival tissues causing tissue hypoxia and a reduced blood supply, which together with the impaired cellular immune response may play a role in the development of oral cancer.

It is also possible that a positive association between diabetes mellitus and premalignant lesions might occur due to shared risk factors. Both are associated with late onset, as well as a diet high in fat and energy and low in fiber. (14)

Increased consumption of saturated fats increases the risk of diabetes mellitus, but recently it has been suggested that it also increases the risk of oral cancer. (17).

It is also possible that a positive association between diabetes mellitus and premalignant lesions might occur due to associated risk factor.

Some of the epidemiologic studies related are hereby inferred in the table 1.1

Authors	Inference and Conclusions
Mounika Reddy Mekala and Others (21)	On comparison between oral cancer, diabetes and habits in study group and control group, decreased risk was observed with smokers (OR: 1.131 and 95% CI: 0.68 - 1.86) and non-chewers (OR: 2.43 and 95% CI: 1.31 - 4.49) and non-alcoholics (OR: 1.78 and 95% C.I.: 1.18 - 2.68). Metformin use among diabetic participants was associated with a decreased risk of oral cancer (OR: 0.51 and 95% C.I.: 0.33 - 0.77). A negative association was observed in smokers (OR: 0.19 and 95% C.I.: 0.078 - 0.459), non-chewers (OR: 0.24 and 95% C.I.: 0.11 - 0.53) and non-alcoholics (OR: 0.46 and 95% C.I.: 0.29 - 0.727).
Shrdha S Vyas (23)	In Indian population, the findings appeared to show a higher hazards of all cancer incidence, lip/oral/pharyngeal and respiratory tract cancer among people with diabetes compared to people without diabetes
Albercht and others (5)	The prevalence of oral leukoplakia was higher among diabetic patients (6.2%) compared with controlled group (2.2%)
Dietrich and Others (18)	Those with positive history of diabetes had more than 2-fold increase in risk of oral leukoplakia
Rajendra Prabhu and Others (20)	Diabetes Mellitus Type 2 patients have lowered immunity and cofactor for premalignant changes
Dikshit and others (14)	Diabetic women are at risk of developing leukoplakia
Mannu Prasad and Others (22)	The following conclusions were drawn, hyperglycemia (which includes impaired fasting glucose, IGT and diabetes) increase the risk of oral cancer two-folds, and however IGT alone as defined by ADA does not appear to play a role. Several potential confounders of the association between DM and cancer incidence were accounted for in the analysis, although the possibility of residual confounding factors cannot be denied.
Ujpal and Others (6)	Among people with diabetes, the prevalence of benign tumors (14.5%) and precancerous lesions (8%) was

	higher than in control group (6.4% and 3.2% respectively)
Rabia K. Shahid and Others (24)	Diabetes and hyperglycemia are associated with an elevated risk of developing of many cancers. Hyperglycemic and diabetic patients experience higher mortality and recurrence rates after diagnosis with, and treatment for, cancer.
Marni Stott – Miller and others (25)	We observed a weak association between diabetes and the incidence of HNC overall (OR, 1.09; 95% CI: 0.95–1.24). However, we observed a modest association among never smokers (OR, 1.59; 95% CI: 1.22–2.07), and no association among ever smokers (OR, 0.96; 95% CI: 0.83–1.11); likelihood ratio test for interaction $P = 0.001$

Table 1.1 Researches and Conclusion And Inference to related studies

Conclusion

The subject requires more elaborate studies to show an association that is significant relation between diabetes mellitus and oral cancer, as these initial findings may be coincidental. In conclusion, diabetic patients who smoke and consume alcohol may constitute a relatively high-risk group for developing oral premalignant lesions, but further research is needed to obtain epidemiologic as well histopathology data so as to establish the mechanisms involved in this process. Until the circumstantial data is available, dentists must screen all adult patients and pay more attention to the gum and labial mucosa of diabetic patients. Increased surveillance and screening by dentists will certainly facilitate research in this area.

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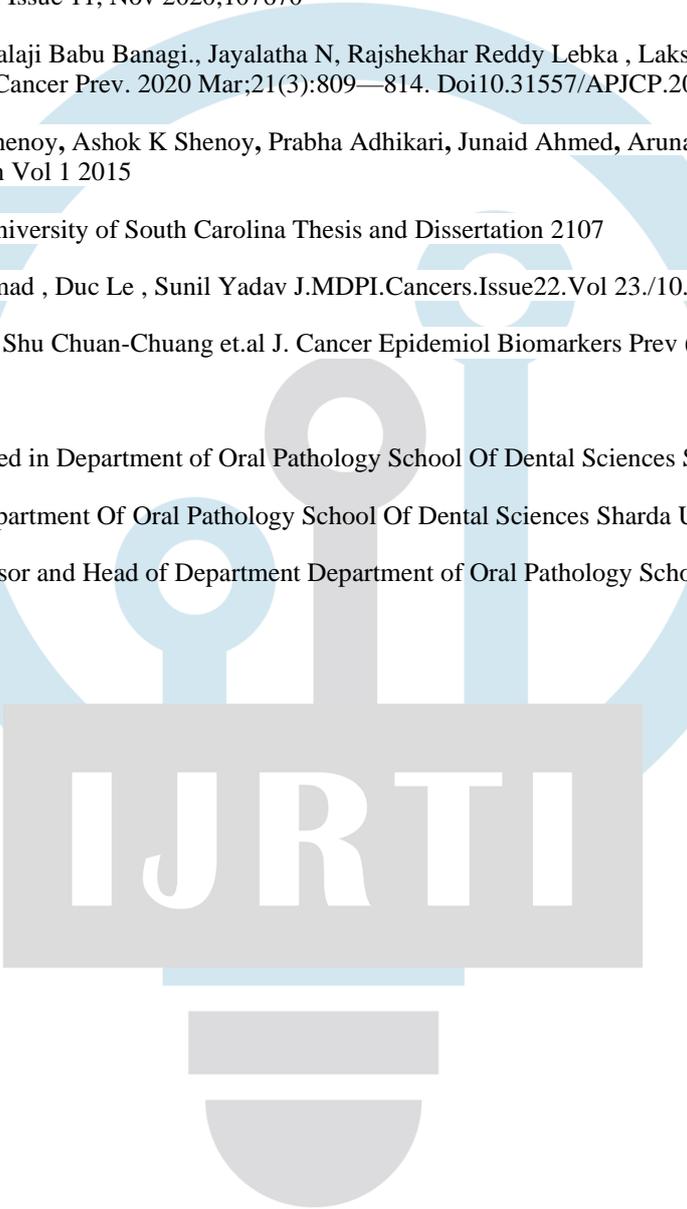
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