

# Diabetes Mellitus: An Emerging Risk Factor for Oral Cancer?

Ajit Auluck, MDS

## Contact Author

Dr. Auluck  
Email: [drajitauluck@gmail.com](mailto:drajitauluck@gmail.com)



For citation purposes, the electronic version is the definitive version of this article: [www.cda-adc.ca/jcda/vol-73/issue-6/501.html](http://www.cda-adc.ca/jcda/vol-73/issue-6/501.html)

Diabetes mellitus is rapidly becoming a common metabolic problem in urban populations. At the same time, the incidence of oral cancer has not decreased over the years despite exhaustive research. Is the research not well targeted? Not well applied? Or are there new risk factors that predispose patients to oral cancer? Recent studies conducted in India<sup>1</sup> and Hungary<sup>2</sup> show an increased prevalence of premalignant lesions among diabetic patients. Is diabetes mellitus an emerging risk factor for oral cancer? Before we accept such a hypothesis, let us examine this issue.

The oral epithelium provides a normal protective barrier against carcinogens. In diabetic patients, progressive atrophy of oral mucosa occurs due to a decreased rate of salivary secretion and low salivary pH,<sup>3</sup> increasing the possibility of lesions, such as glossitis and cheilitis.<sup>2,4</sup> In theory, loss of the normal protective barrier can increase the permeability of the oral mucosa to carcinogens. However, this hypothesis must be correlated with epidemiologic studies. Many studies (Table 1) suggest a trend in increased prevalence of premalignant lesions, such as leukoplakia, in diabetic patients.

In normal populations, oral cancer mainly involves the tongue, oropharynx and floor of the mouth. The lips, gingiva, dorsum of the tongue and palate are usually not affected.<sup>7</sup> But in people with diabetes, tumours most commonly involve the gums and labial mucosa. Also in contrast to the normal population, in which males are more commonly

affected by oral cancer than females, among those with diabetes, tumours are more frequent in females.<sup>1,2</sup> It has been suggested that women might have poorer metabolic control, leading to greater use of insulin and, probably, more oxidative damage to DNA.<sup>1</sup> Although the gender discrepancy in these results cannot be readily explained, it emphasizes the need for increased surveillance. These findings may also suggest a change in the traditional pattern of oral cancer.

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.<sup>5</sup> But recent studies have shown that precancerous and tumorous oral lesions are more frequent in type 2 diabetes.<sup>2</sup> 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 these studies mentions definitive inclusion criteria for oral leukoplakia, which itself is a controversial issue<sup>8</sup> and none has excluded other possible causes for white lesions in these patients, such as lichenoid lesions due

**Table 1** Epidemiologic studies that suggest an increased prevalence of oral premalignant lesions in diabetic patients

Authors	Inferences and conclusions
Dikshit and others <sup>1</sup>	Diabetic women are at increased risk of developing leukoplakia and erythroplakia.
Ujpal and others <sup>2</sup>	Among people with diabetes, the prevalence of benign tumours (14.5%) and precancerous lesions (8%) was higher than in the control group (6.4% and 3.2%, respectively).
Albrecht and others <sup>5</sup>	The prevalence of oral leukoplakia was higher among diabetic patients (6.2%) compared with control group (2.2%).
Dietrich and others <sup>6</sup>	Those with a positive history of diabetes had more than 2-fold increase in risk of oral leukoplakia.

to oral hypoglycemic drugs.<sup>9,10</sup> The studies also lack information about the onset of diabetes. Did the premalignant lesions develop before or after diagnosis of diabetes mellitus? How many years after diagnosis of diabetes did the patients develop premalignant lesions? Although Albrecht and others<sup>5</sup> found that both leukoplakia and lichen planus occurred most often in the second year of established diabetes, these questions must be investigated in greater detail before we can draw any conclusions.

In diabetic patients, alterations occur in the oxidative equilibrium of free radicals.<sup>2</sup> 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.<sup>11,12</sup>

It has been suggested that poor diabetic control is associated with an increased cancer risk due to enhanced oxidative damage to DNA.<sup>13</sup> Production of reactive oxygen species and lipid peroxidation are increased in diabetic patients, especially in those with poor diabetic control and hypertriglyceridemia. Increased oxidative damage can be due to superoxide radical generation by monocytes through 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<sup>++</sup> and Cu<sup>++</sup>, both these substances contribute to the generation of highly reactive hydroxyl radicals causing damage to cells.<sup>13</sup> 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 tumoro-

genic effects of insulin could be directly mediated by insulin receptors in the pre-neoplastic 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.<sup>14</sup> There is evidence that the effect of IGF-1 might be related to p53 mutations, which are quite common in head and neck tumours.<sup>1</sup> 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.<sup>15</sup> In diabetic patients, T-cell function as well as the cellular immune response is impaired.<sup>4</sup> Thus,

diminished immunity in diabetic patients may facilitate the action of carcinogens. In addition, there can be microangiopathy<sup>16</sup> 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 fibre.<sup>1</sup> 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.<sup>17</sup> More elaborate studies are required to show a significant association 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 leukoplakia, but further research is needed to obtain epidemiologic data and establish the mechanisms involved in this process. Until this information 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. ♦

## THE AUTHOR

*Dr. Auluck is assistant professor in the department of oral medicine and radiology, Manipal College of Dental Sciences, Mangalore.*

**Correspondence to:** Dr. Ajit Auluck, Department of Oral Medicine and Radiology, Manipal College of Dental Sciences, Light House Hill Road, Mangalore-575001, India.

*The views expressed are those of the author and do not necessarily reflect the opinions or official policies of the Canadian Dental Association.*

*This article has been peer reviewed.*

## References

1. Dikshit RP, Ramdas K, Hashibe M, Thomas G, Somanathan T, Sankaranarayanan R. Association between diabetes mellitus and premalignant oral diseases: a cross sectional study in Kerala, India. *Int J Cancer* 2006; 118(2):453–7.
2. Ujpal M, Matos O, Bibok G, Somogyi A, Szabo G, Suba Z. Diabetes and oral tumors in Hungary: epidemiological correlations. *Diabetes Care* 2004; 27(3):770–4.
3. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, and other. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol* 1996; 67(10 Suppl):1085–93.
4. Soskolne WA. Epidemiological and clinical aspects of periodontal diseases in diabetics. *Ann Periodontol* 1998; 3(1):3–12.
5. Albrecht M, Banoczy J, Dinya E, Tamas G Jr. Occurrence of oral leukoplakia and lichen planus in diabetes mellitus. *J Oral Pathol Med* 1992; 21(8):364–6.
6. Dietrich T, Reichart PA, Scheifele C. Clinical risk factors of oral leukoplakia in a representative sample of the US population. *Oral Oncol* 2004; 40(2):158–63.
7. Landis SH, Murray T, Bolden S, Wingo PA. *CA Cancer J Clin* 1999; 49(1):8–31.
8. Auluck A, Pai KM. (Mis)Interpretations of leukoplakia. *J Can Dent Assoc* 2005; 71(4):237–8.
9. Auluck A, Pai KM. Oral cancer risk in diabetic patients. *Dent Update* 2005; 32(2):114–5.
10. Scully C, el-Kom M. Lichen planus: review and update on pathogenesis. *J Oral Pathol* 1985; 14(6):431–58.
11. Tsuji S, Kawai N, Tsujii M, Kawano S, Hori M. Review article: inflammation-related promotion of gastrointestinal carcinogenesis — a perigenetic pathway. *Ailment Pharmacol Ther* 2003; 18(Suppl 1):82–9.
12. Seril DN, Liao J, Yang GY, Yang CS. Oxidative stress and ulcerative colitis-associated carcinogenesis: studies in humans and animal models. *Carcinogenesis* 2003; 24(3):353–62.
13. Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, and other. Oxidative damage to DNA in diabetes mellitus. *Lancet* 1996; 347(8999):444–5.
14. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; 4(8):579–91.
15. Chang MC, Chiang CP, Lin CL, Lee JJ, Hahn LJ, Jeng JH. Cell-mediated immunity and head and neck cancer: with special emphasis on betel quid chewing habit. *Oral Oncol* 2005; 41(8):757–75. Epub 2005; Apr 14.
16. Seppala B, Sorsa T, Ainamo J. Morphometric analysis of cellular and vascular changes in gingival connective tissue in long-term insulin-dependent diabetes. *J Periodontol* 1997; 68(12):1237–45.
17. Franceschi S, Levi F, Conti E, Talamini R, Negri E, Dal Maso L, and others. Energy intake and dietary pattern in cancer of the oral cavity and pharynx. *Cancer Causes Control* 1999; 10(5):439–44.