Diabetes: Risk Factor for Oral Cancer? - A Review

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ABSTRACT

Globally, diseases such as diabetes and cancer have a severe impact on the health of people. Recent research has shown that diabetes is one of the contributing factors in the initiation and progression of certain cancers. In addition, certain drugs used for the treatment of diabetic patients may also have a role in cancer initiation, progression and mortality. Epidemiological studies have shown that diabetic patients are at a higher risk in case of common cancers such as pancreatic, liver, breast, colorectal, urinary tract, etc. This article will explore the relationship between diabetes and oral cancer, with its possible mechanisms of carcinogenesis.

Keywords: Diabetes, Insulin, Oral cancer, Periodontitis, Precancerous lesions

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INTRODUCTION

Diabetes mellitus includes a group of metabolic disorders that are characterized by hyperglycemia, caused due to complete or an incomplete lack of insulin secretion, insulin resistance or both. Though diabetes is seen in all age groups, it is much more common in adults.[1] Almost 150 million people worldwide are affected by diabetes.[2] Diabetes is broadly classified into Type I and Type II. Type I is caused by reduced insulin secretion, and Type II by insulin resistance and impaired response to insulin.[3] Both the types cause hyperglycemia, increased water intake, excessive urine output, lethargy, blurring of vision, weight loss, and changes in energy metabolism.[2] Diabetes of long duration leads to various multi-organ dysfunctions such as atherosclerosis, neuropathy, nephropathy and heart disease.[3]

One of the most common causes of death is cancer.[4] Oral cancer accounts for approximately 4-5% of all cancers in the world. Adult males are most commonly affected, with an increased incidence among alcoholics and smokers of sixth and eighth decades of life. The commonly affected sites are buccal mucosa, hard palate, gingiva, floor of the mouth, lips, oropharynx and tongue. The most common risk factor for oral cancer is tobacco. The other risk factors include alcohol, immune defects, genetic factors and viruses such as human papilloma virus, Epstein–Barr virus, hepatitis virus, etc.[5]

Recent epidemiological studies have shown a strong link between diabetes and cancer. These studies report that cancer patients with diabetes have a worse prognosis than patients without diabetes after treatment. Though diabetes and cancer has many common risk factors such as obesity, male sex and ageing, both Type I and Type II diabetes are associated with more incidence of cancer.[3] There are differences in carcinogenesis between diabetes I and diabetes II. Studies have shown that the risk of cancers in breast, colorectum, pancreas, etc. in diabetes II is more compared to diabetes I patients.[2]

Diabetes mellitus causes many immunologic and metabolic changes in the oral mucosa. Many studies have shown the relationship of diabetes with periodontal disease and inflammatory diseases of the oral mucosa. Emerging evidences suggests that diabetic patients show more precancerous lesions like erythroplakia and leukoplakia that leads to oral cancer. The association between diabetes and oral cancer is unclear till date. This review discusses the possible association between diabetes and oral cancer with the available data. Recent discoveries like anti-tumor

effect of metformin can help the diabetologists and oncologists in discovering newer drugs for preventing diabetic complications.

ORAL MANIFESTATIONS OF DIABETES MELLITUS

About 90% of systemic disorders exhibit oral manifestations. Diabetes mellitus is one of the chronic systemic disorders that have a major influence on the microenvironment of the oral cavity.[6] Oral complications of diabetes are:

- Gingivitis and periodontitis
- Periradicular inflammatory osteolytic lesions and their various forms that include acute and chronic periapical osteolytic lesions, odontogenic abscess, granulomas, etc.
- Loss of teeth
- Xerostomia and change in saliva composition
- Lesions of the oral mucosa and tongue.[7]

Oral Lesions in Diabetic Patients

A prevalence study of oral mucosal lesions in diabetic patients by Belmiro *et al*. revealed various lesions like:

- Mucocele
- Fissured tongue
- Lingual varicosity
- Erythematous candidiasis
- Gingival hyperplasia
- Angular cheilitis
- Traumatic ulcer
- Xerostomia
- Atrophy of lingual papillae
- Petechiae
- Hyperkeratosis

Of all these lesions lingual varicosity and erythematous candidiasis were most common.[8]

Histological Changes of Gingiva

The coronal part of the gingival connective tissue underneath the junctional epithelium shows decreased collagen density. Reduction in collagen synthesis and replication of DNA in dermal fibroblasts are seen more in diabetic patients as compared with non-diabetic patients. It is observed that there is an increase in the collagenase activity and abnormalities in neutrophil degranulation due to gingival crevicular fluid collagenase or other metabolic abnormalities in periodontal ligament fibroblasts. The histological sections in diabetic patients showed thickened basement membrane, swollen and proliferated endothelial cells and obliteration of capillaries with narrow capillary lumen.[9]

Diabetes and Cancer

The first association between cancer and diabetes was studied in 1885.[10]

According to few meta-analysis studies diabetic patients have an increased risk of cancers in endometrium, pancreas, colorectum, etc.[11-17]

Mechanisms

Hyperinsulinemia is the characteristic feature of diabetes Type II patients.
1. Insulin activates the structurally similar insulin-like receptor that increases the risk of cancer.
2. Hyperinsulinemia causes unregulated insulin receptor signaling that increases cancer risk by its proliferative and antiapoptotic effects.
3. Increased mitogenic activity of insulin post-receptor molecular mechanisms like intracellular up-regulation of the insulin mitogenic pathway and insulin residence time on the receptor.

The factors supporting the hyperinsulinemia hypothesis are:
1. Pancreatic cancer is reported more frequently with carcinogen or by implantation of cancer cells, when experimental insulin-deficient animals were given supplemental insulin.
2. Type II diabetes patients have a higher risk of cancer than Type I diabetes patients who are insulin deficient.

Hyperglycemia

Hyperglycemia plays a major role in carcinogenesis. Hyperglycemia generates oxidative stress that damages the DNA and induces carcinogenesis.[18]

DNA Damage Due to Oxidative Stress in Diabetes

Increased oxidative stress is seen in diabetes mellitus that may lead to lipid, protein, and DNA modifications. Hyperglycemia causes glycation of proteins, auto-oxidation of glucose, and activation of polyol metabolism that contributes to the formation of reactive oxygen species. This reactive oxygen species causes damage to cellular macromolecules that may lead to protein and DNA modification. The elevated reactive oxygen species in diabetes leads to DNA strand breaks and base modifications. Hyperglycemia also contributes to the increased production of free radicals in the mitochondria and this may lead to a greater DNA damage.[19,20]

Further molecular studies on animal models indicate that diabetes may cause the activation of Ras signal transduction pathway by inducing receptors erbB2 and erbB3, and this may also lead to increased cell

proliferation. In addition, the Bcl-2/Bax ratio was found to be relatively stable in diabetic animals during the oncogenesis process, indicating that diabetes has no effect on apoptosis levels (Figure 1).[21]

Anticancer Drugs and Cancer Risk

Insulin analogues used in the treatment of cancer have a role in cancer. Insulin is a mitogen that stimulates mitogen-activated protein kinase (AMPK) pathway, which in turn causes cancer. Many in vitro studies have revealed that, increased insulin levels affect angiogenesis and promote tumor progression by stimulating the mitogen pathway through insulin and insulin-like growth factor receptors. Studies have reported that there is less cancer risk in case of metformin as compared to other antidiabetic drugs. This is because of certain anti-tumor characteristics of metformin like cell proliferation inhibition. It could also be due to decreased cancer proliferation with the activation of activated protein kinase (AMP), AMP kinase, which is a mediator of tumor suppressor LKB1.[10]

Precancerous Changes in Diabetes

Mihaela *et al*. reported a case having an eleven-year history of Type II diabetic mellitus with a hyperplastic lesion in the inferior vestibule. The biopsy showed moderate elongation of the rete ridges, epithelial hyperplasia due to a moderate acanthosis, mild orthokeratosis with focal parakeratosis and basal cell hyperplasia of basal cell layer.[6] In the study done by Thomas et al. analyzing the risk factors of leukoplakia, he found that diabetic patients are three times more associated with leukoplakia than non-diabetic patients. This increased incidence might be due to the metabolic and immunologic changes in the oral mucosa.[22] Dikshit *et al*. also found that the incidence of leukoplakia and lichen planus in diabetic patients is more in comparison with non-diabetic patients.[23] A study was done by Ujpál *et al*. reveals 25.6% of Type I

and 31.3% of Type II diabetic patients had glossitis and chronic cheilitis that are considered to be precursors of malignant transformations. 10.9% of Type I and 16.9% of Type II had benign tumors. 3.2% of Type I and 11% of Type II had leukoplakia or erythroplakia. There was more incidences of gingival cancer (29%) and lip cancer (24%) as compared to the non-diabetic group.[24] A study by Mohsin *et al*. revealed more oral mucosal lesions such as geographic tongue, fissured tongue, coated tongue in diabetic than non-diabetic patients. An association between premalignant lesions and diabetic patients was not significant according to their study.[25]

Muralidara *et al*. also did not find any association between precancerous lesions and diabetes. They have found only lichen planus in diabetes patients.[26] However, according to the study done by Yadiyal *et al*. there is no correlation between lichen planus and diabetes.[27] The occurrence of lichen planus in diabetes patients might also be due to the lichenoid reaction of the drugs.[28]

There are studies on other site-specific cancers which strongly support an increase in cancer risk and mortality in diabetic patients. The molecular mechanisms associated with diabetes and cancer development are still not clear. However, only few research studies have been done on diabetes and oral cancer. The association between diabetes and oral cancers may be due to shared risk factors between the two diseases, such as diet, aging, obesity and physical inactivity. However, the etiologic factors of oral cancer such as tobacco, alcohol can also contribute to oral cancer in diabetic patients. A few studies on oral cancer and diabetes have shown an association between them while a few studies have indicated the opposite.

CONCLUSION

More advanced studies are necessary to show a definitive relationship between diabetes and oral cancer. Proper blood glucose control is mandatory to avoid diabetes-related complications. For this reason, clinicians and patients should be aware of possible cancer risks in diabetic patients. This awareness will go a long way in reducing the incidence of oncological complications among diabetic patients.

Figure 1: Diabetes and cancer

REFERENCES

1. Al-Maskari AY, Al-Maskari MY, Al-Sudairy S. Oral manifestations and complications of diabetes mellitus. A review. Sultan Qaboos Univ Med J 2011;11:179-86.
2. Lin Y, Sun Z. Current views on type 2 diabetes. J Endocrinol 2010;204:1-11.
3. Sen S, He Y, Koya D, Kanasaki K. Cancer biology in diabetes. J Diabetes Investig 2014;5:251-64.
4. Petersen PE. Oral cancer prevention and control – the approach of the World Health Organization. Oral Oncol 2009;45:454-60.
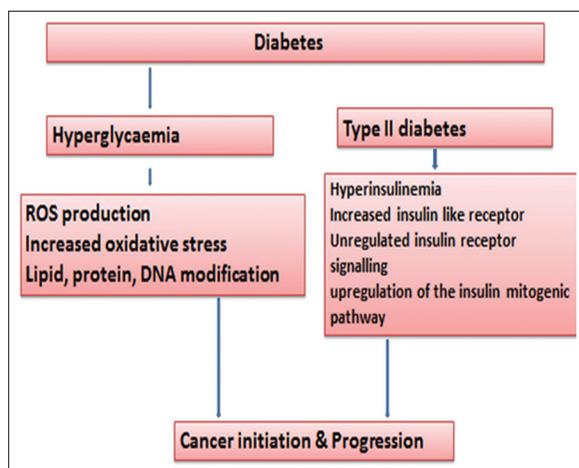
5. Markopoulos AK. Current aspects on oral squamous cell carcinoma. Open Dent J 2012;6:126-30.

6. Girtan M, Zurac S, Staniceanu F, Bastian A, Popp C, Nichita L, *et al.* Oral epithelial hyperplasia in diabetes mellitus. Rom J Intern Med 2009;47:201-3.

7. Straka M. Oral manifestations of diabetes mellitus and influences of periodontological treatment on diabetes mellitus. Bratisl Lek Listy 2011;112:416-20.

8. Vasconcelos BC, Novaes M, Sandrini FA, Maranhão Filho AW, Coimbra LS. Prevalence of oral mucosa lesions in diabetic patients: A preliminary study. Braz J Otorhinolaryngol 2008;74:423-8.

9. Seppälä 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;68:1237-45.

10. Sun G, Kashyap SR. Cancer risk in type 2 diabetes mellitus: Metabolic links and therapeutic considerations. J Nutr Metab 2011;2011:708183.

11. Yoon JM, Son KY, Eom CS, Durrance D, Park SM. Pre-existing diabetes mellitus increases the risk of gastric cancer: A meta-analysis. World J Gastroenterol 2013;19:936-45.

12. Parazzini F, La Vecchia C, Negri E, Riboldi GL, Surace M, Benzi G, *et al.* Diabetes and endometrial cancer: An Italian case-control study. Int J Cancer 1999;81:539-42.

13. Li J, Cao G, Ma Q, Liu H, Li W, Han L. The bidirectional interation between pancreatic cancer and diabetes. World J Surg Oncol 2012;10:171.

14. Huang CW, Sun LC, Shih YL, Tsai HL, Chen CW, Yeh YS, *et al.* The impact on clinical outcome of high prevalence of diabetes mellitus in Taiwanese patients with colorectal cancer. World J Surg Oncol 2012;10:76.

15. Zhu Z, Zhang X, Shen Z, Zhong S, Wang X, Lu Y, *et al.* Diabetes mellitus and risk of bladder cancer: A meta-analysis of cohort studies. PLoS One 2013;8:e56662.

16. Bordeleau L, Lipscombe L, Lubinski J, Ghadirian P, Foulkes WD, Neuhausen S, *et al.* Diabetes and breast cancer among women with BRCA1 and BRCA2 mutations. Cancer 2011;117:1812-8.

17. Yang X, Zhao H, Sui Y, Ma RC, So WY, Ko GT, *et al.* Additive interaction between the renin-angiotensin system and lipid metabolism for cancer in type 2 diabetes. Diabetes 2009;58:1518-25.

18. Noto H, Goto A, Tsujimoto T, Osame K, Noda M. Latest insights into the risk of cancer in diabetes. J Diabetes Investig 2013;4:225-32.

19. Pan HZ, Chang D, Feng LG, Xu FJ, Kuang HY, Lu MJ. Oxidative damage to DNA and its relationship with diabetic complications. Biomed Environ Sci 2007;20:160-3.

20. El-Wassef M, El-Saeed GS, El-Tokhy SE, Raslan HM, Tawfeek S, Siam I, *et al.* Oxidative DNA damage in patients with type 2 diabetes mellitus. Diabetol Croat 2012;41:121-7.

21. Vairaktaris E, Spyridonidou S, Goutzanis L, Vylliotis A, Lazaris A, Donta I, *et al.* Diabetes and oral oncogenesis. Anticancer Res 2007;27:4185-93.

22. Dietrich T, Reichart PA, Scheifele C. Clinical risk factors of oral leukoplakia in a representative sample of the US population. Oral Oncol 2004;40:158-63.

23. Dikshit RP, Ramadas K, Hashibe M, Thomas G, Somanathan T, Sankaranarayanan R. Association between diabetes mellitus and pre-malignant oral diseases: A cross sectional study in Kerala, India. Int J Cancer 2006;118:453-7.

24. Ujpál M, Matos O, Bíbok G, Somogyi A, Szabó G, Suba Z. Diabetes and oral tumors in Hungary: Epidemiological correlations. Diabetes Care 2004;27:770-4.

25. Mohsin SF, Ahmed SA, Fawwad A, Basit A. Prevalence of oral mucosal alterations in type 2 diabetes mellitus patients attending a diabetic center. Pak J Med Sci 2014;30:716-9.

26. Yadiyal M, Shenoy N, Shenoy A, Ahmed J. Are diabetics victims of oral cancer? Int J Bioassays 2013;2:904-6.

27. Borghelli RF, Pettinari IL, Chuchurru JA, Stirparo MA. Oral lichen planus in patients with diabetes. An epidemiologic study. Oral Surg Oral Med Oral Pathol 1993;75:498-500.

28. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, *et al.* Oral lichen planus and oral lichenoid lesions: Diagnostic and therapeutic considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103 Suppl: S25.e1-12.