Importance Of Glycemic Controlin Individuals With Type 2 Diabetes and Oral Cancer

Research Article

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Abstract

Globally, the prevalence/incidence of type 2 diabetes and oral cancer has increased dramatically in the past few decades. Studies have shown that type 2 diabeteshas an elevated risk of oral cancer, mediated by promoting DNA damage through oxidative stress caused by an increased mitochondrial glucose oxidation.Few studies have shown that higherglycated hemoglobin (HbA1c) levels increase the risk of certain cancers including cancers of oral cavity. Glycemic control, believed to be one of the causes of the outcome differences between cancer patients with and without diabetes, plays an important role in health related quality of life, recurrence of cancer, severity of symptomand pain,risk for infections, increased hospitalization and stay and lead to stoppage or reduction in dose of chemotherapy, which can lead to poor outcomes and reduce the lifespan. Very few studies have evaluated the link between oral cancer and HbA1c and the findings are equivocal. Thus, to increase the survival and improve the health outcomesinindividuals with oral cancer and diabetes, the role of glycemic control must be further elucidated and studies are urgently needed on this topic.

Diabetes and cancer are non-communicable diseases with huge impact on health worldwide [1]. According to the recent GLOBOCAN report, globally, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths have occurred in 2020 [2]. While the International Diabetes Federation (IDF) has reported that in 2019, 463 million had diabetes and mortality attributable to diabetes and associated complications in adults was 4.2 million [3]. In 2020, oral cancer which include cancers of the mucosal lip, tongue, gum, floor of the mouth, palate and mouth was reported as the sixteenth most common form of cancer in the world with 377,713 new cases and 177,757 deaths [2]. There are evidences to substantiate the link between diabetes and the increased prevalence and progression of various cancers including cancers of the breast,colon, lung, prostate, pancreasand oral cavity [4, 5]. The prevalence of co-existing diabetes among newly diagnosedcancer patients varies from 8 to 18% [6].

The common diabetes associated complications include microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular complications (cardiovascular disease, peripheral vascular disease and cerebrovascular disease) [7]. However, recently'diabetic oncopathy' has been implicated as one of the complications of diabetes [8].The biological mechanisms underlying the association between cancer and diabetes have been debated and are not clear. It has been suggested that hyperglycemia could be one of the underlying mechanisms for the association between diabetes and cancer risk by promoting DNA damage through oxidative stress caused by an increased mitochondrial glucose oxidation [9, 10]. It is also a known promoter of oncogenesis and metastasis [10]. Other possible mechanisms for a direct link between these two conditions include hyperinsulinemia and inflammation [4, 5].

Some studies link higherglycated hemoglobin (HbA1c) levels, one of the key biomarkers in identifying patients with diabetes and a reflective measure of blood glucose values over a period of about 3 months, and other measures of hyperglycemia to increased risk of certain cancers [11-13]. Glycemic control is also hypothesized as one of the causes of the outcome differences between cancer patients with and without diabetes. Glycemic control was found

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to play an important role in the level of health-related quality of life experienced, level of symptom, severity experienced, which can influence the survival of the individual with cancerand diabetes [14]. Several studies have assessed the relationship between glycemic control and various cancers including pancreatic cancer, lung cancer, gastroesophagealcancer etcand the results are equivocal [15-18]. It has also been reported that with increasing HbA1c levels, there is increased risk for higher cancer stage and cancer pre-cursor incidence for some cancer types [18]. However, data on glycemic control and oral cancer are very sparse.

Oral cancer is one of the main causes for morbidity worldwide. Oral squamous cell carcinoma (OSCC) is the most prevalent oral malignancy, representing up to 80-90% of all malignant neoplasms of the oral cavity [19]. The most common sites of oral cancer in the European and the American population are the tongue, whileoral cancer in thebuccal mucosa is commonly seen in the Southeast Asian and Indian region. Moist snuff kept between the buccal mucosa and gingival region, is attributed to the development of cancers of the buccal mucosa [20]. The 5-year survival rate is close to 50% after cancer treatment. The best prognosis and 5-year survival rate are seen for cancers of the lip region [21]. Hyperglycaemia has been reported to increase the risk of oral cancer by two-fold [22]. Tay et al [23], investigated the relationship between preoperative HbA1c levels and OSCCon treatment outcomesin 89 patients with OSCC who were diagnosed with diabetes. This study reported that OSCC patients with higher HbA1c levels had longer hospitalizationand intensive care unitstays. In addition, these patients also had significantly worse survival outcomes, which included increased rates of locoregional recurrence, distant metastases and development of second primary tumors.

A US based study which examined the impact of diabetes on survival ofpatients with OSCC and the impact of OSCC on glycemic control, reported that the 5-year overall survival was 61% in patients with diabetes compared to 78% in those without diabetes. Regarding HbA1c, it significantly decreasedover time and OSCC did not affect glycemic control [24].Similarly, the New Zealand population-based linkage study [13], which assessed the association between HbA1c levels and cancer risk in 46 575 participants with a median follow-up of 4.4 years reported that oral and digestive cancersmade up 18% of new cancer cases. However,a non-significant 17% increasewas observed in persons with higher HbA1c levels (≥7%) [HR 1.17, 95% CI: 0.60–2.28) as compared with personshaving normal HbA1c levels.

From the available literature it is observed that not many studies have looked at the role of HbA1c, as a risk factor for development of oral cancers and its outcomes in patients with diabetes. In general, improving the glycemic control in individuals with diabetes and any type of cancer,including oral cancer, may improve the prognosis, reduce complications in those undergoing cancer therapy and decreasemortality. Glycemic control can affect an individual's ability to complete treatment as well as their survival and end-of-life quality [25]. Management of the duo, i.e., diabetes and cancer, is a great challenge for health care providers. Hershey et al [26] has reported that individuals with diabetes and cancer give priority to cancer management over their diabetes care. This could affect their glycemic status and increase their risk for mortality [27]. Individuals with both the disorders have a higher prevalence of non-adherence to oral anti-diabetic agents compared to those only with diabetes, which may lead touncontrolled diabetes/poor glycemic control. Adherence to oral agents is associated with 24% fewer hospitalizations in cancer patients with diabetes [28].

Studies have also shown that chemotherapy and corticosteroids used for cancer therapy can affect glycemic control leading to poor outcomes [26, 29]. Similarly, it has been reported that individuals with type 2 diabetes and cancer with poor glycemic control were more likely to develop infections orrequire hospitalization, or a chemotherapy dose reduction or stoppage [30]. In addition, it also increases symptom and pain severity. Based on the available literature, Figure 1 presents the potential effects of poor glycemic control in individuals with diabetes and oral cancer.

To increase the lifespan and improve the quality of lifeinindividuals with oral cancer and diabetes, the role of glycemic control must be further elucidated.Awareness and management of the glycemic status of individuals with cancer and diabetes should be part of the patients' treatment plan right from the day of diagnosis.Education should be targeted to enhance health outcomes in thosewith diabetes and cancer which addresses the "cause" not just the "source" of the problem. HbA1c appears to be associated with oral cancer incidence and/or mortality, however, further studies areneeded to fully understand the relationship between oral cancerand HbA1c and this is an urgent unmet need in research.

Figure 1. Potential effects of poor glycemic control in individuals with diabetes and oral cancer.
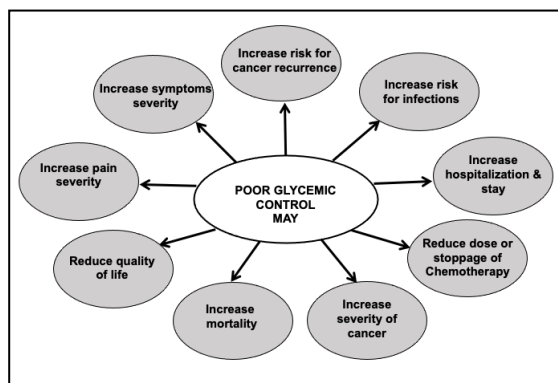
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