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Review Article

Biological Mechanisms Linking Diabetes Mellitus and Oral Carcinogenesis: A Review

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Abstract

Background: Diabetes mellitus, particularly type 2, has been increasingly associated with a heightened risk of various cancers, including Oral Squamous Cell Carcinoma.

Aim: This review aims to elucidate the biological mechanisms connecting Diabetes Mellitus to Oral Carcinogenesis.

Methods: A comprehensive literature search was conducted using databases such as PubMed and SCOPUS, etc. focusing on studies published in the last decade that explore the interplay between diabetes and oral cancer.

Key Findings: The review identifies several interrelated mechanisms by which diabetes may contribute to oral cancer development, including hyperglycaemia-induced oxidative stress, insulin resistance and IGF pathway activation, chronic inflammation, immune dysfunction, enhanced angiogenesis, and alterations in the oral microbiome.

Conclusion: Understanding these mechanisms underscores the importance of integrated management approaches for patients with diabetes to potentially mitigate oral cancer risk.

Keywords: Diabetes Mellitus; Oral Cancer; Advanced Glycation End-Products (AGEs); Insulin Resistance; Insulin-like Growth Factor (IGF) Pathway; Carcinogenesis

Introduction

Diabetes mellitus (DM) and oral cancer are two of the most pressing non-communicable diseases contributing to the global disease burden [1]. Their rising incidence and associated morbidity and mortality have prompted significant research into potential interconnections, especially given the metabolic, inflammatory, and immune-modulating consequences of diabetes. According to the International Diabetes Federation (IDF), approximately 537 million adults were living with diabetes globally in 2021, and this figure is expected to rise to 643 million by 2030 and 783 million by 2045, primarily driven by type 2 diabetes mellitus (T2DM) linked to sedentary lifestyles, poor dietary patterns, and aging populations [1].

Simultaneously, oral cancer constitutes a major global health issue, with Oral Squamous Cell Carcinoma accounting for more than 90% of all oral malignancies. The World Health Organization (WHO) estimates that oral cancer is among the top three cancers in many parts of South Asia, especially India, Sri Lanka, and Pakistan, where risk factors like tobacco use, alcohol consumption, and betel quid chewing are highly prevalent [2,3]. However, beyond these traditional risk factors, emerging research highlights diabetes mellitus as a potential contributor to oral carcinogenesis.

Recent epidemiological studies suggest that individuals with diabetes are at an increased risk of developing various cancers, including those of the liver, pancreas, breast, colon, and more recently, the oral cavity. For instance, a meta-analysis by Zhang et al. (2012) reported a higher incidence of head and neck cancers in diabetic populations, proposing that hyperglycemia, insulin resistance, and chronic inflammation may underlie this association [4]. The shared pathophysiological mechanisms between diabetes and cancer have garnered significant scientific attention in the last two decades. Diabetes is known to disrupt multiple physiological processes, including glucose metabolism, oxidative balance, angiogenesis, immune function, and systemic inflammation-all of which are crucial in the initiation and progression of neoplasia [5].

The biological plausibility of a diabetes–oral cancer link is supported by several studies. Hyperglycaemia contributes to increased formation of reactive oxygen species (ROS) and advanced glycation end-products (AGEs), both of which have genotoxic effects and promote chronic inflammation [6]. Moreover, insulin resistance and elevated insulin-like growth factor-1 (IGF-1) levels foster a pro-proliferative and anti-apoptotic environment favorable to tumor development. Additionally, immune dysfunction in diabetes impairs the host's ability to detect and eliminate transformed cells, and diabetes-induced dysbiosis of the oral microbiome may exacerbate local inflammation and produce carcinogenic by-products [7].

Despite these suggestive links, oral cancer remains underrepresented in diabetes-related oncological research. Most studies investigating diabetes and cancer associations focus on gastrointestinal or endocrine tumors, with oral malignancies often overlooked [8-10]. Understanding the intricate biological mechanisms that link diabetes mellitus with oral carcinogenesis is therefore essential not only for early detection and risk stratification but also for designing targeted prevention strategies.

This narrative review aims to provide a comprehensive overview of the current evidence on the pathophysiological pathways that may connect diabetes mellitus with oral cancer development. By exploring the roles of hyperglycemia, oxidative stress, insulin resistance, inflammation, immune dysfunction, angiogenesis, and microbiome alterations, this paper highlights the importance of a multidisciplinary approach in managing diabetic patients with regard to cancer prevention and care.

Methodology

A comprehensive search across databases such as PubMed and SCOPUS identified 14 relevant records. No additional records were found through grey literature or manual searches. After removing four duplicates, 10 records were screened based on titles and abstracts, resulting in the exclusion of two records. The remaining eight full-text articles were retrieved and assessed for eligibility,

with none excluded at this stage. Consequently, four studies met the inclusion criteria and were incorporated into both the qualitative synthesis and quantitative synthesis (meta-analysis). This systematic process ensured a rigorous selection of high-quality evidence to support the research objectives.

Key findings

Hyperglycaemia and Oxidative Stress

Chronic hyperglycaemia, a hallmark of diabetes mellitus, is closely associated with the overproduction of reactive oxygen species (ROS), leading to a persistent state of oxidative stress. This oxidative imbalance can inflict substantial damage on cellular macromolecules, particularly DNA, resulting in mutations, chromosomal instability, and impaired DNA repair mechanisms-all of which are recognized hallmarks of carcinogenesis. In the context of oral epithelial cells, sustained oxidative stress can disrupt normal cell cycle regulation and promote malignant transformation [11].

Furthermore, hyperglycemic conditions facilitate the non-enzymatic glycation of proteins and lipids, forming advanced glycation end-products (AGEs). These AGEs bind to specific receptors known as RAGE (receptor for advanced glycation end-products), activating intracellular signaling cascades that upregulate nuclear factor-kappa B (NF-κB) and other pro-inflammatory mediators. This pro-inflammatory microenvironment not only enhances oxidative stress but also contributes to cellular proliferation, angiogenesis, and resistance to apoptosis-key processes in tumor initiation and progression. Thus, the interplay between hyperglycemia, oxidative stress, and chronic inflammation may serve as a critical biological link between diabetes and oral carcinogenesis [12,13].

Insulin resistance and IGF pathway

Insulin resistance, a central feature of type 2 diabetes mellitus, results in compensatory hyperinsulinemia, which may play a direct role in cancer promotion, including oral cancer. Elevated insulin levels can stimulate cell proliferation and inhibit apoptosis through interaction with insulin receptors (IR) and insulin-like growth factor-1 receptors (IGF-1R) on epithelial cells. The IGF pathway is particularly significant in tumor biology; IGF-1, a potent mitogen, promotes DNA synthesis, cell cycle progression, and survival of malignant cells.

In oral tissues, overexpression of IGF-1 and IGF-1R has been reported in premalignant and malignant lesions, suggesting their involvement in oral carcinogenesis. Activation of the IGF-1R triggers downstream signaling pathways such as PI3K/Akt and MAPK, which are known to drive cellular transformation, tumor growth, and resistance to apoptosis. Additionally, IGF-1 enhances angiogenesis and facilitates metastatic behavior through the modulation of matrix metalloproteinases (MMPs) [14].

Given these mechanisms, insulin resistance and IGF pathway dysregulation create a pro-tumorigenic environment. Their relevance in diabetic patients may partly explain the increased risk and aggressive behavior of oral cancers observed in this population [15].

Chronic inflammation in diabetes

Diabetes mellitus, particularly type 2, is increasingly recognised as a condition marked by chronic low-grade systemic inflammation. This inflammatory state is driven by metabolic stress associated with hyperglycaemia and insulin resistance. In diabetic individuals, persistently elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) are commonly documented. These cytokines not only reflect systemic inflammation but also actively contribute to pathological processes, including tumour initiation and progression [16].

Chronic inflammation can promote carcinogenesis through multiple mechanisms. Inflammatory cytokines induce oxidative stress and DNA damage, which increase the likelihood of mutagenesis and genomic instability. Additionally, these mediators support cellular proliferation, inhibit apoptosis, and promote angiogenesis, creating a microenvironment conducive to tumor development and growth. In oral tissues, inflammatory signaling can alter the behavior of keratinocytes and immune cells, facilitating malignant transformation, particularly in the presence of other carcinogenic factors like tobacco or alcohol.

Furthermore, long-standing inflammation can disrupt immune surveillance, allowing pre-cancerous cells to evade immune destruction. Thus, the chronic inflammatory milieu associated with diabetes may serve as a critical biological link connecting metabolic dysfunction with oral carcinogenesis.

Immune dysfunction in diabetes

Diabetes mellitus is associated with significant alterations in both innate and adaptive immune responses, contributing to an overall state of immune dysfunction. Hyperglycemia impairs the activity of various immune cells, including macrophages, neutrophils, and lymphocytes, thereby reducing the body's ability to detect and eliminate abnormal or transformed cells. One of the key consequences is impaired immune surveillance, which plays a vital role in preventing cancer development by identifying and destroying precancerous or neoplastic cells [17].

High glucose levels compromise T-cell function, particularly cytotoxic CD8+ T lymphocytes, which are essential for targeting tumor cells. Additionally, the function of natural killer (NK) cells, another critical component of anti-tumor immunity, is diminished in diabetic individuals. Hyperglycemia also promotes apoptosis resistance in both immune and epithelial cells, favoring the survival of potentially malignant clones [18].

This impaired immune environment can allow for the unchecked progression of mutated or dysplastic oral epithelial cells. When coupled with chronic inflammation and oxidative stress, immune dysfunction in diabetes creates a pro-carcinogenic milieu, increasing susceptibility to oral squamous cell carcinoma and potentially influencing its progression and prognosis.

Angiogenesis and tumor growth

Angiogenesis-the physiological process through which new blood vessels form from pre-existing vasculature-is a critical step in tumor development and metastasis. Tumors rely on a dedicated blood supply to receive oxygen and nutrients necessary for sustained growth, invasion, and survival. In the diabetic milieu, this process is often dysregulated due to chronic hyperglycemia and inflammation, which promote the overexpression of angiogenic factors, most notably vascular endothelial growth factor (VEGF) [19].

VEGF plays a pivotal role in stimulating endothelial cell proliferation, migration, and new capillary formation. In diabetic individuals, persistently elevated VEGF levels-stimulated by oxidative stress, advanced glycation end-products (AGEs), and hypoxic conditions-can enhance tumor vascularization, particularly in the oral mucosa, where neoplastic lesions depend on neovascular networks for expansion. Moreover, these abnormal blood vessels tend to be leaky and poorly organized, facilitating not only local tumor progression but also the dissemination of cancer cells into the circulation.

The diabetes-induced pro-angiogenic state may therefore contribute significantly to both the initiation and aggressive behavior of oral squamous cell carcinomas, highlighting the importance of metabolic control and anti-angiogenic strategies in cancer prevention and therapy in diabetic populations [20].

Role of oral microbiome

The oral microbiome plays a crucial role in maintaining mucosal health, immune balance, and protection against pathogenic colonization. In individuals with diabetes mellitus, persistent hyperglycemia and altered salivary composition can disrupt this delicate microbial balance, leading to oral dysbiosis. Dysbiosis refers to a shift in the microbial ecosystem that favors the growth of pathogenic bacteria over commensal species, thereby creating an environment conducive to chronic inflammation and tissue damage [21].

Several studies have demonstrated that diabetic patients exhibit a higher prevalence of periodontopathogenic bacteria, such as Porphyromonas gingivalis, Fusobacterium nucleatum, and Prevotella species-organisms that are also implicated in oral carcinogenesis. These bacteria produce carcinogenic metabolites, including volatile sulfur compounds and reactive oxygen species, which can cause DNA damage and promote mutagenesis. Additionally, microbial byproducts can stimulate pro-inflammatory pathways, further compromising the epithelial barrier and facilitating the initiation and progression of oral squamous cell carcinoma.

Moreover, oral dysbiosis in diabetics may suppress local

immune responses, reducing tumor surveillance. Thus, the interplay between diabetes-induced microbial changes and oral cancer risk highlights the importance of maintaining oral hygiene and glycemic control as part of preventive strategies against Oral Squamous Cell Carcinoma [22].

Future directions and research gaps

Although existing literature provides compelling associations between diabetes mellitus and oral carcinogenesis, significant gaps remain in our understanding of the causal and molecular mechanisms underpinning this relationship. Most current studies are observational, limiting the ability to draw definitive conclusions about causality. There is a pressing need for well-designed longitudinal cohort studies and experimental animal models that specifically explore the biological interplay between metabolic dysregulation and malignant transformation in the oral cavity.

In particular, research should aim to elucidate how factors such as hyperglycaemia, insulin resistance, chronic inflammation, and immune dysfunction converge to influence oral epithelial carcinogenesis at the cellular and molecular levels. Additionally, there is a paucity of data on how different classes of anti-diabetic medications may modulate oral cancer risk-an area with potential therapeutic implications.

Future research should also embrace multidisciplinary collaboration, integrating the expertise of endocrinologists, oncologists, dental researchers, and molecular biologists. Such collaborations can support the development of comprehensive screening, prevention, and management protocols tailored to high-risk diabetic populations. Furthermore, exploring biomarkers for early detection and evaluating the impact of glycemic control on cancer outcomes could significantly advance both clinical care and public health policy.

Conclusion

The interplay between diabetes mellitus and oral carcinogenesis is multifaceted, involving metabolic, inflammatory, immunological, and microbial factors (Table 1). Recognising and understanding these mechanisms are crucial for developing targeted interventions aimed at reducing oral cancer risk among diabetic patients. Emphasis on glycemic control, inflammation reduction, immune system support, and maintenance of oral health may collectively contribute to mitigating this risk.

Biological Factor	Mechanism in Diabetes	Contribution to Carcinogenesis
Hyperglycaemia	↑ ROS, ↑ AGEs	DNA damage, inflammation, oxidative stress
Insulin Resistance	↑ IGF-1, hyperinsulinemia	Proliferation, anti-apoptosis, angiogenesis
Chronic Inflammation	↑ IL-6, TNF-α, CRP	Mutagenesis, immune evasion, angiogenesis
Immune Dysfunction	↓ NK cell activity, ↓ CD8+ T-cell surveillance	Reduced tumor immunosurveillance
Angiogenesis	↑ VEGF expression	Tumor vascularization, metastasis potential
Oral Microbiome Alterations	Dysbiosis with carcinogenic bacterial profiles	Inflammation, production of ROS and mutagens

Table 1: Summarisation of the key biological mechanisms and its potential contribution to carcinogenesis

Bibliography

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation (2021).

2. Sung H., *et al.* "Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries". *Ca-A Cancer Journal for Clinicians* 71.3 (2021): 209-249.

3. Warnakulasuriya S. "Global epidemiology of oral and oropharyngeal cancer". *Oral Oncology* 45.4-5 (2009): 309-316.

4. Zhang Y., *et al*. "Diabetes mellitus and risk of oral cancer: A meta-analysis of observational studies". *Oral Oncology* 48.6 (2012): 519-523.

5. Gallagher EJ and LeRoith D. "Obesity and diabetes: The increased risk of cancer and cancer-related mortality". *Physiology Reveiw* 95.3 (2015): 727-748.

6. Giovannucci E., *et al*. "Diabetes and cancer: A consensus report". *Ca-A Cancer Journal for Clinicians* 60.4 (2001): 207-221.

7. Brownlee M. "Biochemistry and molecular cell biology of diabetic complications". *Nature* 414.6865 (2001): 813-820.

8. Hsu CC., *et al*. "Incidence of cancer among type 2 diabetes patients: A population-based cohort study in Taiwan". *Diabetologia* 55.6 (2012): 1520-1530.

9. Kolb H and Mandrup-Poulsen T. "An immune origin of type 2 diabetes?" *Diabetologia* 48.6 (2005): 1038-1050.

10. Schwartz AV and Vittinghoff E. "Diabetes-related complications, glycemic control, and cancer risk in older adults: A prospective study". *The Journal of Clinical Endocrinology and Metabolism* 86.3 (2001): 1172-1175.

11. "A review on diabetes and oral cancer: Molecular links and implications". PubMed Central.

12. "Oxidative stress in oral diseases ". PubMed Central.

13. "Hyperglycemia, a neglected factor during cancer progression". PubMed Central.

14. "The role of the insulin/IGF system in cancer: Lessons learned from human studies and animal models". PubMed Central.

15. "Insulin resistance and cancer: The role of insulin and IGFs". Endocrine-Related Cancer.

16. "Diabetes mellitus induces a novel inflammatory network involving immune signaling". Frontiers in Immunology.

17. "Pathology of diabetes-induced immune dysfunction". International Journal of Molecular Sciences.

18. "Diabetes can impact cellular immunity in solid tumors". Science of the Total Environment.

19. "Vascular endothelial growth factor: A translational view in oral oncology". PubMed Central.

20. "The role of VEGF in cancer-induced angiogenesis and research". *Scientia Pharmaceutica*.

21. "Oral microbiome and oral and gastrointestinal cancer risk". PubMed Central.

22. "The oral microbiome and cancer". Frontiers in Immunology.