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Review Article

Role of Anti-Diabetic Medications in Modulating Oral Cancer Risk: A Narrative Review of Current Evidence

Chetan Vinay Deshmukh[1], Arun Suresh Dodamani[2], Vibhuti Dilip Mistry[3]*, Shivani Sanjay Ahirrao[4], Dr. Mayuri Bhikaji Nepale[5] and Snehal Sakharam Patil[6]

[1]Assistant Professor, Department of Public Health Dentistry, Nair Hospital Dental College, Mumbai and Ph.D. Scholar, Public Health Dentistry, ACPM Dental College, Maharashtra University of Health Sciences, Nashik, Maharashtra, India

[2]Principal, Professor and Head and Ph.D. Guide, Department of Public Health Dentistry, JMF's ACPM Dental College, Dhule, India

[3]Assistant Professor, Department of Periodontology, JMF's ACPM Dental college, Dhule, Maharashtra, India

[4]Postgraduate Student, Department of Public Health Dentistry, JMF's ACPM Dental College, Dhule, India

[5]Independent Researcher, Public Health Dentistry, India

[6]Assistant Professor, Department of Public Health Dentistry, Rural Dental College, Pravara Insitute of Medical Sciences (Deemed to be University), Loni, India

***Corresponding Author:** Vibhuti Dilip Mistry, Assistant Professor, Department of Periodontology, JMF's ACPM Dental college, Dhule, Maharashtra, India.

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Abstract

Oral cancer and diabetes mellitus are major global health concerns, with emerging evidence suggesting that anti-diabetic therapies may influence carcinogenesis. This review synthesises current evidence on the role of anti-diabetic drugs in modulating oral cancer risk. Metformin demonstrates consistent protective effects through activation of AMP-activated protein kinase (AMPK) and inhibition of mammalian target of rapamycin (mTOR). In contrast, sulfonylureas and insulin may increase cancer risk via hyperinsulinemia and insulin-like growth factor (IGF)-1 signalling. Thiazolidinediones (TZDs) and incretin-based therapies show mixed or inconclusive results. Although meta-analyses support drug-specific variability in cancer risk, oral cancer-specific data remain limited. Understanding these associations is critical for tailoring therapy in diabetic patients with elevated oral cancer risk.

Keywords: Oral Cancer; Diabetes Mellitus; Metformin; Anti-Diabetic Drugs; Carcinogenesis

Introduction

Diabetes mellitus (DM) and oral squamous cell carcinoma (OSCC) represent two global public health challenges with overlapping risk factors and biological pathways. OSCC accounts for more than 90% of oral cancers, particularly prevalent in South and Southeast Asia due to high tobacco and alcohol use [1]. Epidemiological evidence indicates that diabetes is more frequent among patients with oral cancer, with mechanisms such as hyperglycaemia, chronic inflammation, and oxidative stress potentially contributing to oral carcinogenesis [2].

In recent years, attention has shifted to the possible cancer-modulating effects of anti-diabetic medications. Beyond their

primary role in glycemic control, these drugs influence cellular metabolism, proliferation, and apoptosis, thereby intersecting with carcinogenic pathways [3]. This narrative review explores current evidence on the effects of major classes of anti-diabetic medications on oral cancer risk, with a focus on mechanistic insights, clinical studies, and future directions.

A summary of the mechanisms, evidence, and oral cancer risk associated with major anti-diabetic medications is presented in table 1.

Drug Class	Mechanism Relevant to Cancer	Key Evidence	Effect on Oral Cancer Risk	References
Metformin	Activates AMPK → inhibits mTOR, reduces proliferation, induces apoptosis	Preclinical: tumor suppression in OSCC cell lines and xenografts; Epidemiological: lower incidence and improved survival	Protective (dose–response effect observed)	3, 4, 6, 7
Sulfonylureas	↑ Endogenous insulin → IGF-1 signaling, pro-proliferative	Observational studies with conflicting outcomes	Potentially increased risk, inconclusive	2, 8
Insulin therapy	↑ Exogenous insulin → mitogenic signaling, hyperinsulinemia	Cohort studies suggest elevated overall cancer risk	Likely increased risk	2, 8
Thiazolidinediones (TZDs)	PPAR-γ activation → differentiation, apoptosis, anti-inflammatory	Mixed evidence; bladder cancer risk concerns; sparse OSCC data	Neutral to modestly protective, uncertain	9, 10
GLP-1 receptor agonists	Incretin effect; modulate proliferation, immune pathways	Limited preclinical and epidemiological studies	Inconclusive	11
DPP-4 inhibitors	Affect incretin degradation; immune modulation	Meta-analyses show no significant increase in cancer	Neutral	12
Overall evidence	Drug-specific, cancer-type-specific variability	Meta-analyses support protective effect of metformin; limited OSCC-specific trials	Metformin strongest candidate for chemoprevention	3, 7, 12

Table 1: Summary of Evidence Linking Anti-diabetic Medications with Oral Cancer Risk.

(Evidence summarised from preclinical, epidemiological, and meta-analytic studies. References correspond to the main reference list.).

Metformin and Cancer Prevention

Metformin is the most widely prescribed first-line drug for type 2 diabetes. Its potential anticancer role has been extensively studied. Metformin activates AMPK, which down-regulates mTOR signaling, leading to reduced cellular proliferation and enhanced apoptosis [4].

Preclinical evidence shows that metformin suppresses tumourgenesis in oral cancer cell lines and xenograft models [5]. Epidemiological studies report reduced cancer incidence and improved survival among diabetic patients on metformin therapy [6]. Tseng [7] demonstrated that Taiwanese patients with diabetes receiving metformin had a significantly reduced risk of OSCC, with evidence of a dose-response effect.

Meta-analyses consistently associate metformin with decreased cancer incidence and mortality across multiple malignancies [4]. These findings suggest metformin may confer dual benefits of glycemic control and cancer risk reduction, making it particularly relevant in populations at high risk of OSCC.

Sulfonylureas and insulin therapy

Sulfonylureas stimulate pancreatic insulin secretion, while exogenous insulin therapy directly elevates systemic insulin levels. Both therapies increase circulating insulin and IGF-1 activity, pathways implicated in tumourgenesis [8].

Observational studies provide conflicting evidence. Currie., *et al*. [2] reported increased cancer risk in patients treated with insulin or sulfonylureas, while other cohorts suggested neutral effects. These discrepancies likely arise from differences in study populations, drug exposure duration, and cancer endpoints.

Although direct evidence linking sulfonylurea or insulin use to OSCC remains scarce, the mechanistic plausibility of hyperinsulinemia-driven carcinogenesis underscores the need for caution, particularly in patients with premalignant oral lesions.

Thiazolidinediones (TZDs)

TZDs, such as pioglitazone, act as peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists, promoting differentiation, apoptosis, and modulation of inflammation [9]. Experimental studies suggest possible anticancer properties, but clinical findings are inconsistent. Concerns have been raised regarding an increased risk of bladder cancer with prolonged pioglitazone use, highlighted by regulatory warnings [10].

For oral cancer, direct clinical data are sparse. Available evidence suggests neutral to mildly protective effects, though small sample sizes and limited follow-up weaken these conclusions. Further dedicated studies are necessary to clarify the role of TZDs in oral carcinogenesis.

Incretin-based therapies (GLP-1 Receptor Agonists and DPP-4 Inhibitors)

Incretin-based therapies, including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, modulate insulin secretion and immune function. Early preclinical studies suggest they may influence tumour proliferation and immune surveillance [11].

Clinical data remain inconclusive. A meta-analysis by Monami., *et al.* [12] reported no significant increase in overall cancer risk with DPP-4 inhibitors. However, evidence specific to OSCC is lacking, and animal studies provide only preliminary insights. Long-term follow-up studies are needed to establish their oncological safety profile.

Comparative evidence from meta-analyses

Systematic reviews and meta-analyses underscore the variability of cancer risk associated with different anti-diabetic drugs. Metformin consistently shows a protective association with reduced cancer incidence [4], while sulfonylureas and insulin demonstrate signals toward increased risk [2]. Evidence for TZDs and incretin-based agents remains equivocal.

Importantly, oral cancer-specific data are scarce. Subgroup analyses occasionally identify reduced risks of head and neck cancers with metformin use, but few trials have examined OSCC as a primary outcome [7]. This highlights a major research gap.

Clinical implications

The choice of anti-diabetic therapy in patients at risk of or diagnosed with OSCC requires consideration of both metabolic and oncological outcomes. Metformin appears to be the most favourable option, particularly in patients with premalignant lesions or a history of head and neck cancer. By contrast, insulin and sulfonylureas may warrant more cautious use in high-risk populations.

Optimal management requires a multidisciplinary approach involving diabetologists, oncologists, and dental specialists to balance glycemic control with long-term cancer risk mitigation.

Limitations and Future Directions

Safety evaluations of anti-diabetic drugs remain ongoing, with regulatory agencies such as the FDA and WHO highlighting the need for continuous monitoring of potential oncological risks [10,13].

Current evidence is limited by the predominance of retrospective studies, secondary analyses, and heterogeneous cancer endpoints. There is a lack of randomised controlled trials specifically addressing the relationship between anti-diabetic therapy and OSCC.

Future research priorities include

- Prospective longitudinal studies with oral cancer as a predefined endpoint.
- Mechanistic studies on drug-specific effects on oral epithelial cells.
- Clinical trials assessing cancer incidence and survival outcomes in patients on different anti-diabetic regimens.

Conclusion

Anti-diabetic medications exert variable effects on oral cancer risk. Metformin demonstrates the most consistent protective associations, mediated through metabolic and anti-proliferative pathways. Sulfonylureas and insulin may increase risk due to hyper-insulinemia, while evidence for TZDs and incretin-based therapies remains inconclusive. Given the growing burden of both diabetes and oral cancer, integrating oncological risk assessment into anti-diabetic drug selection represents an important step toward personalized care.

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