

**DIABETES MELLITUS AND ORAL
COMPLICATIONS:
GLYCAEMIC CONTROL AS A DETERMINANT OF
PERI-IMPLANT AND HEAD AND NECK
ONCOLOGICAL OUTCOMES**

Ph.D. Thesis

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**“Truth tends to reveal its highest wisdom in
the guise of simplicity”**

Friedrich Nietzsche

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1. LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AGE	Advanced glycation end-product
AMPK	5' adenosine monophosphate-activated protein kinase
BoP	Bleeding on probing
CBL	Crestal bone loss
CI	Confidence Interval
CVD	Cardiovascular disease
DFS	Disease-free survival
DM	Diabetes mellitus
DMFS	Distant metastasis-free survival
DSS	Disease-specific survival
EBV	Epstein–Barr virus
GLP-1	Glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	Glycated haemoglobin
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HR	Hazard ratio
IGF-1	Insulin-like growth factor-1
IL	Interleukin
IS	Implant survival
LOS	Length of (hospital) stay
MD	Mean difference
mTOR	Mechanistic target of rapamycin
NLM	National Library of Medicine

OPG	Osteoprotegerin
OR	Odds ratio
ORN	Osteoradionecrosis
OS	Overall survival
OSCC	Oral squamous cell carcinoma
OPSCC	Oropharyngeal squamous cell carcinoma
PC	Poorly controlled (type 2 diabetes; HbA1c > 8%)
PD	Prediabetes (HbA1c 5.7–6.4%)
PECOS	Population, exposure, comparison, outcomes, study design
PI	Plaque index
PISF	Peri-implant sulcular fluid
PPD	Probing pocket depth
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QUIPS	Quality In Prognosis Studies
RANKL	Receptor activator of nuclear factor kappa-B ligand
ROS	Reactive oxygen species
SCC	Squamous cell carcinoma
SGLT-2	Sodium-glucose cotransporter-2
SSI	Surgical site infection
TGF-β	Transforming growth factor beta
TNF-α	Tumour necrosis factor alpha
WC	Well-controlled (type 2 diabetes; HbA1c < 8%)

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My academic and clinical career is oriented towards bridging the gap between systemic medicine and oral health, with a particular focus on the impact of metabolic diseases, primarily diabetes mellitus, on oral surgical, implantological, and oncological outcomes. My mission is to generate high-quality, clinically translatable evidence through rigorous systematic reviews and meta-analyses, and to embed this evidence into the everyday practice of prosthodontists, oral surgeons, and multidisciplinary teams managing complex patients.



The specific goals for this doctoral work are threefold: first, to establish a glycaemic-threshold-based framework for the safe provision of implant therapy in patients with type 2 diabetes mellitus; second, to characterise the prognostic role of DM across head and neck squamous cell carcinoma subtypes; and third, to advocate for routine glycaemic screening as a standard component of the pre-treatment assessment of oral surgical and oncological patients. These goals are pursued in alignment with the translational medicine mission of Semmelweis University's Centre for Translational Medicine.

2.2. Scientometrics

The following table (**Table 1.**) summarises the scientometric indicators as recorded in the Hungarian Scientific Bibliography (MTMT; author identifier 10088002).

Table 1. Summary of scientometric indicators (source: MTMT, author ID 10088002).

Number of all publications:	12
Cumulative IF:	33.8
Av IF/publication:	2.81
Ranking (SCImago):	D1:4, Q1:4, Q2:2
Number of publications related to the subject of the thesis:	2
Cumulative IF:	9.3
Av IF/publication:	4.65
Ranking (Sci Mago):	D1:1, Q1:1
Number of citations on Google Scholar:	146
Number of citations on MTMT (independent):	69
H-index:	5

2.3. Future plans

In the short term, I intend to extend the line of inquiry established in this thesis through prospective, protocol-driven clinical studies that incorporate standardised, repeated HbA1c measurement during follow-up. For implant therapy, I plan to test prospectively whether normalisation of glycaemic levels prior to surgery improves peri-implant outcomes in patients who initially present with poor control, and to clarify the interaction between glycaemic status, implant level, and peri-implant tissue phenotype. For head and neck oncology, I aim to build cohorts in which diabetes type, diagnostic method, and glycaemic control are uniformly documented, enabling subgroup analyses that the current literature cannot support.

In the longer term, my objective is to develop and validate a simple, point-of-care glycaemic screening pathway that can be integrated into routine oral surgical and oncological assessment, and to evaluate its impact on clinical outcomes and health-economic endpoints. I intend to pursue these aims within the multidisciplinary, translational framework of the Centre for Translational Medicine, in close collaboration with diabetologists, oncologists, and maxillofacial surgeons, so that the evidence acquired is directly usable at the point of care.

3. SUMMARY OF THE PH.D.

Diabetes mellitus (DM) is among the most prevalent chronic diseases worldwide and causes wide-ranging effects on the oral cavity. This thesis investigates the relationship between DM and two clinically important oral complications through two preregistered systematic reviews with meta-analyses conducted within the framework of the Centre for Translational Medicine of Semmelweis University.

Study I examined whether type 2 DM and prediabetes, and the quality of glycaemic control, are associated with worse peri-implant complications in adults with dental implants. From 2,660 records, 35 studies (1,761 individuals, 3,902 implants) were included. Patients with poorly controlled DM ($\text{HbA1c} > 8\%$) and prediabetes showed significantly greater crestal bone loss (1.8 mm and 1.2 mm, respectively) and worse probing pocket depth, bleeding on probing, and plaque index than controls without diabetes, whereas well-controlled DM ($\text{HbA1c} < 8\%$) was not a risk indicator. Meta-regression showed that each 1% increase in HbA1c elevated crestal bone loss by approximately 0.2 mm, with longer follow-up amplifying the effect; implant survival did not differ between the groups.

Study II examined the prognostic impact of DM in squamous cell carcinoma of the head and neck (HNSCC). From 18,326 records, 63 studies (approximately 138,000 individuals, of whom 22,800 had DM) were included. DM was associated with significantly worse disease-specific (Hazard Ratio (HR) 1.47), overall (HR 1.31), and disease-free survival (HR 1.58), with greater effects in oral and oropharyngeal subsites, whereas laryngeal and nasopharyngeal subtypes were less affected. Posttreatment stroke (HR 2.11) and osteoradionecrosis (HR 2.2) were significantly elevated, and surgical site infection showed a clinically relevant but statistically non-significant increase.

Together, the two studies converge on a single translational message: glycaemic status is a modifiable determinant of oral surgical and oncological risk. For implant therapy, the evidence supports a practicable HbA1c threshold of 8%, below which type 2 DM should not contraindicate surgery. For HNSCC, the absence of glycaemic data prevents threshold-based guidance, but the consistent association of DM with worse survival and complications allows for routine glycaemic screening to detect undiagnosed or poorly controlled disease.

4. GRAPHICAL ABSTRACT

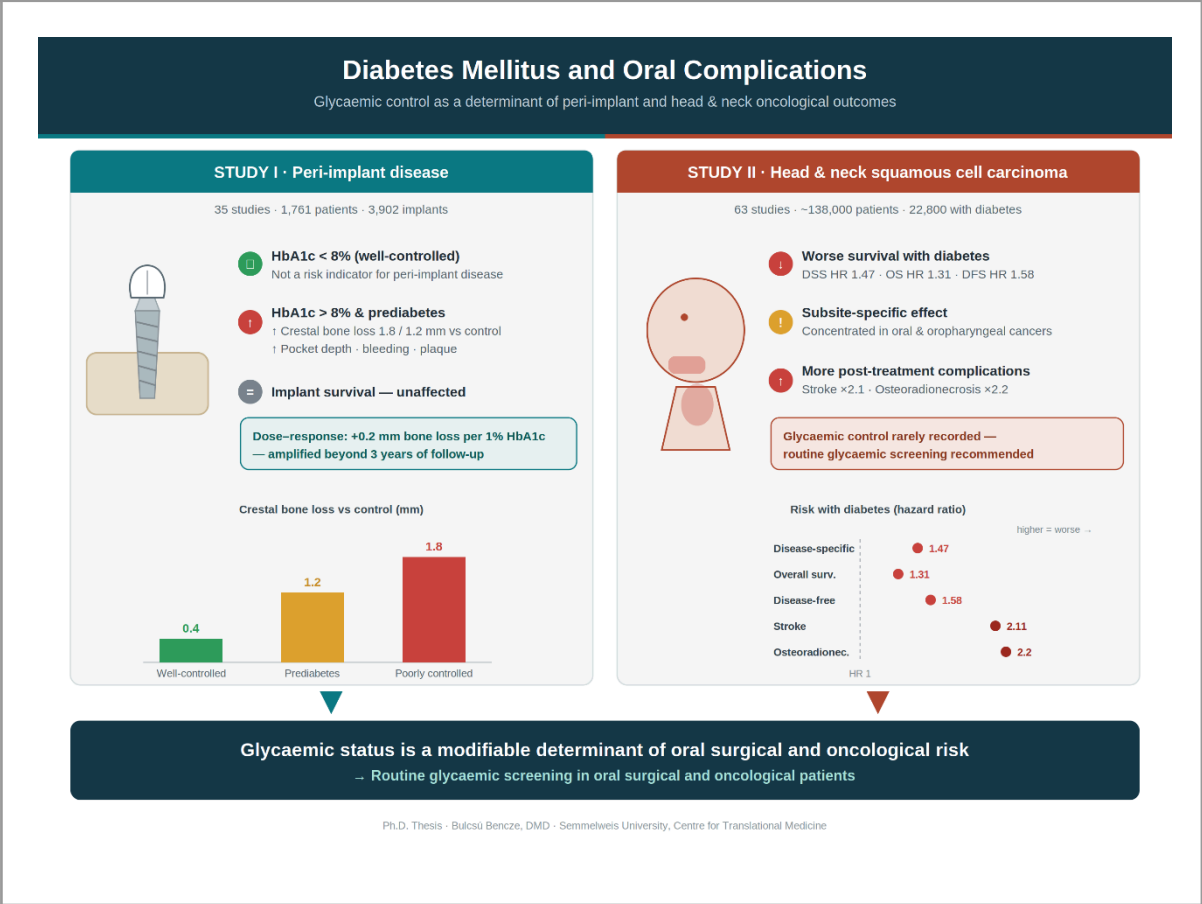


Figure 1. Graphical abstract integrating the principal findings of Study I (peri-implant diseases) and Study II (head and neck squamous cell carcinoma).

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Diabetes mellitus (DM) is a group of chronic metabolic disease characterised by sustained hyperglycaemia resulting from impaired insulin secretion, impaired insulin action, or both, leading to underutilisation of glucose and to its overproduction through inappropriate gluconeogenesis and glycogenolysis (1). Clinically, the diagnosis is based on elevated venous plasma glucose concentrations or on increased glycated haemoglobin (HbA1c) levels, while several categories are recognised, including type 1, type 2, gestational, and other specific types (1). The disease is considered a worldwide epidemic, with an estimated 460 million people living with diabetes by the end of the last decade, with approximately half of those cases remaining undiagnosed (2), also the most recent atlas estimates place the global figure at 540 million, projected to rise to 780 million by 2045 (3). In the United States alone, the prevalence of type 2 DM and prediabetes is estimated at above 11% and 38%, respectively (4).

This thesis follows the intersection between DM and oral complications, a field of growing clinical and public-health relevance. The relationship between diabetes and the oral tissues is bidirectional and well documented for periodontal disease (5), but its consequences extend to two further domains that determine the success of dental and oncological care: the health of tissues surrounding osseointegrated dental implants, and the prognosis of squamous cell carcinoma of the head and neck (HNSCC) region. The thesis is built upon two systematic reviews with meta-analyses, designated Study I and Study II, that addresses these two domains, respectively, and together investigate whether and how glycaemic status changes oral surgical and oncological outcomes.

5.1.2. What is the problem to solve?

The first problem is clinical uncertainty regarding implant therapy in patients with type 2 DM. Although diabetes has been described as a risk indicator for peri-implant disease (6), the association remains controversial, because several of the largest observational studies have failed to confirm it (7, 8). It has remained unclear whether good glycaemic control pose no risk, and the literature has not provided a usable glycaemic threshold to

guide the timing and safety of implant surgery. Previous meta-analyses did not separate prediabetes, well-controlled, and poorly controlled disease, did not account for major confounders, and did not solve the issue of substantial overlap of HbA1c intervals between control categories. Study I was designed to resolve this uncertainty by classifying patients according to objective glycaemic criteria.

The second problem is the unclear prognostic role of DM in HNSCC. Diabetes is biologically an adverse prognostic factor through chronic inflammation, oxidative stress, and metabolic reprogramming that favour tumour growth and therapy resistance, as well as impaired immune response and wound healing (9-11). However, no comprehensive synthesis had separated the anatomical subsites of HNSCC, distinguished univariate from multivariate estimates, or systematically examined posttreatment complications. Moreover, the overwhelming majority of primary studies do not report glycaemic control or even specify the type of diabetes, which constrains the type of clinical recommendation that can be made. Study II was designed to quantify the prognostic impact of DM across HNSCC subsites and to characterise its effect on posttreatment complications.

5.1.3. What is the importance of the topic?

The importance of the topic follows from the convergence of two epidemic trends. Tooth loss remains common, and the use of dental implants is expanding rapidly: the prevalence of dental implants in the United States population, estimated at 5.7%, is projected to reach 23% by 2026 (12). Peri-implantitis is a frequent biological complication of implant therapy and its treatment is of limited efficacy, so current management depends on prevention, early diagnosis, and the control of modifiable risk factors (7, 13, 14). If hyperglycaemia is a modifiable determinant of peri-implant disease, identifying it before surgery becomes an important preventive opportunity.

HNSCC is a major global health concern, with approximately 650,000 new cases and 330,000 deaths annually, ranking as the sixth most common cancer worldwide (15). Its incidence is projected to rise by around 30% by 2030, particularly in lower Human Development Index regions where alcohol, tobacco or betel use, and oncogenic viral infection (HPV-16) are prevalent (16). Because diabetes and HNSCC frequently coexist in the same demographic strata, even a moderate prognostic effect of DM translates into

a substantial population-level burden. Analysing the magnitude and the subsite specificity of that effect is therefore a direct clinical importance.

5.1.4. What would be the impact of our research results?

The intended impact is to translate epidemiological association into actionable clinical recommendation. For implant dentistry, a glycaemic threshold allows clinicians to decide, on an objective basis, when type 2 DM should and should not be regarded as a contraindication, and when preoperative metabolic optimisation is warranted. For head and neck oncology, quantifying the prognostic effect of DM by subsite and complication supports the case for systematic glycaemic screening in this population, even where threshold-based treatment modification is not yet justified by the evidence. In both domains, the results highlight the value of cooperation between dental and medical specialists and provide an opportunity for prospective research, for practice recommendations, and for health-policy measures aimed at preventive screening.

5.2. Diabetes mellitus and the oral cavity

A shared pathophysiology connects the two clinical problems addressed in the thesis. Patients with type 2 DM possess elevated levels of tumour necrosis factor alpha (TNF- α) and interleukin-6 (IL-6), pro-inflammatory cytokines that also accumulate in periodontal and peri-implant tissues (17). These mediators promote soft-tissue inflammation through the elevation of the receptor activator of nuclear factor kappa-B ligand (RANKL) and matrix metalloproteinases, and cause hard-tissue effects through reduced osteoprotegerin (OPG), shifting the RANKL/OPG ratio towards bone resorption (18). Chronic hyperglycaemia promotes the formation of advanced glycation end-products (AGEs), which bind on monocytes and osteoblasts to amplify local cytokine production, to impair collagen production, and to promote bone resorption, while oxidative stress, increased reactive oxygen, and dysregulated neutrophil function contribute to additional tissue damage (19).

The clinical consequence is a well-researched, bidirectional relationship between diabetes and periodontitis: hyperglycaemia worsens periodontal inflammation, raises the risk of tooth loss, whereas periodontal inflammation in turn impairs metabolic control, with the effect most pronounced when glycaemic control is poor (5, 20, 21). Importantly, prediabetes is increasingly recognised as a clinically meaningful state; it

shares dysglycaemia, dyslipidaemia, obesity, hypertension, and cytokine dysregulation with manifest diabetes and therefore carry comparable oral risk despite lower HbA1c values. Diabetes also impairs polymorphonuclear leucocyte chemotaxis and phagocytosis and delays wound healing, which is directly relevant to any oral surgical intervention and provides the need for preoperative metabolic assessment, including the measurement of HbA1c and blood glucose before oral surgery and implant treatment (22).

5.3. Peri-implant health and disease

Osseointegrated dental implants have become a gold-standard solution for tooth replacement, and their use is expanding rapidly: the prevalence of dental implants in the United States population, estimated at 5.7%, is projected to reach as high as 23% by 2026 (12). With this expansion comes a rising burden of biological complications. Peri-implant mucositis is a reversible inflammatory lesion in the peri-implant mucosa, whereas peri-implantitis is a plaque-associated pathological condition characterised by mucosal inflammation and progressive loss of crestal bone (13). Reported prevalences vary widely with case definition, but population-based estimates place peri-implantitis at roughly one in five implants (7, 8).

Peri-implantitis is a plaque-associated, site-specific inflammation, which is modified by local and systemic predisposing factors (23). Because surgical and non-surgical treatment of peri-implantitis is limited and unpredictable, the main management prioritises prevention, early diagnosis, and the control of modifiable risk factors (14). Diabetes has been proposed as a systemic risk indicator (6), yet the association is still debated: several large observational studies have failed to confirm it, and earlier syntheses neither separated patients by glycaemic control nor consistently excluded major confounding factors (7, 8). Crestal bone loss (CBL) is the most informative criterion of implant success, being more sensitive than the dichotomous implant survival. The peri-implant phenotype, and whether an implant is placed at bone or tissue level, or the type of fixation protocol further modifies the severity of CBL. These considerations need to be addressed by Study I: to determine whether, and above what glycaemic threshold, diabetes meaningfully compromises peri-implant health.

5.4. Squamous cell carcinoma of the head and neck

Head and neck squamous cell carcinoma (HNSCC) is a major global health concern, accounting for approximately 650,000 new cases and 330,000 deaths each year and ranking as the sixth most common cancer worldwide (15). Its incidence is projected to rise by around 30% by 2030, particularly in lower Human Development Index regions where alcohol consumption, tobacco or betel use, and oncogenic viral infection, most notably human papillomavirus type 16, are prevalent (16, 24). The disease is anatomically heterogeneous, containing oral, oropharyngeal, hypopharyngeal, laryngeal, and nasopharyngeal subsites that differ in aetiology, biological behaviour, and prognosis, and is managed with combinations of surgery, radiotherapy, and chemoradiotherapy, each carrying its own profile of posttreatment complications such as surgical site infection, free-flap failure, osteoradionecrosis, cerebrovascular events, and prolonged hospital stay.

Diabetes may be an adverse factor in this setting. Epidemiological evidence links type 2 diabetes to an increased risk of developing oral squamous cell carcinoma (25), and studies show that hyperglycaemia and hyperinsulinaemia promote tumour-cell proliferation through up-regulation of insulin-like growth factor-1 and erythroblastic leukaemia viral oncogene homologue receptor signalling, increase glucose uptake and promote a metabolic shift towards aerobic glycolysis, and stimulate matrix metalloproteinase activity and epigenetic modifications that enhance invasion and therapy resistance (9, 10, 26, 27). Also, diabetes elevates systemic cytokine levels, hosts a pro-inflammatory and immunosuppressive environment, and through the same impairment of immune function and wound healing described above, predisposes to higher posttreatment complication rates (11). Despite this strong rationale, no prior synthesis had quantified the prognostic impact of diabetes across the distinct HNSCC subsites or systematically examined its effect on posttreatment complications, the gap addressed by Study II.

5.5. Rationale and translational framework

The two domains, though clinically distinct, are united by the degree of hyperglycaemia, plausibly affecting the severity of oral surgical and oncological complications. Peri-implant tissues are more prone to severe and treatment-resistant inflammation compared to tissues surrounding natural teeth, providing a biological

rationale for an amplified local effect of hyperglycaemia, while in oncology the same metabolic and immune impairments operate at the level of tumour biology and posttreatment recovery. This common pathophysiology motivates the hypothesis of the thesis and the decision to address both domains within a single work.

Both studies were conducted within the translational-medicine framework of the Centre for Translational Medicine of Semmelweis University, whose purpose is to accelerate the cycle from robust evidence synthesis to bedside implementation (28). Accordingly, the studies were designed not only to estimate associations but to yield concrete, actionable evidence: a usable glycaemic threshold for implant therapy, a subsite-specific account of the prognostic role of diabetes in HNSCC, and a clear case for routine glycaemic screening in oral surgical and oncological patients. The thesis sets out the objectives, methods, and results of the two studies, integrates their findings, and translates them into recommendations for practice and research.

6. OBJECTIVES

6.1. Study I - Prediabetes and poorly controlled type-2 diabetes as risk indicators for peri-implant diseases: A systematic review and meta-analysis

Study I was designed to answer the following PECOS question: in human adults with dental implants (P), do subjects suffering from type 2 diabetes or prediabetes (E) have worse peri-implant conditions (O) than subjects without type 2 diabetes or prediabetes (C) across observational designs (S)? The principal objective was to determine whether glycaemic status and the quality of glycaemic control are associated with the severity of peri-implant disease, and to establish whether a clinically usable HbA1c threshold distinguishes patients at elevated risk from those who are not.

The working hypothesis, based on the existing literature, was that patients with type 2 diabetes and prediabetes have significantly worse peri-implant outcomes than patients without these conditions, and that the magnitude of the effect is graded by glycaemic control such that well-controlled diabetes causes little or no risk. The specific aims were: (1) to quantify the difference in crestal bone loss (CBL) as a primary outcome; probing pocket depth (PPD), bleeding on probing (BoP), plaque index (PI), peri-implant sulcular fluids (PISF) and implant survival (IS) as secondary outcomes; between exposed and control patients; (2) to stratify these outcomes by prediabetes, well-controlled ($\text{HbA1c} < 8\%$) and poorly controlled ($\text{HbA1c} > 8\%$) type 2 diabetes as described by the American Diabetes Association; and (3) to model the continuous relationship between HbA1c, follow-up time, disease duration, and peri-implant outcomes by meta-regression.

6.2. Study II - Diabetes is associated with elevated mortality, stroke, and osteoradionecrosis in squamous cell carcinomas of the head and neck: a systematic review and meta-analysis

Study II was designed to answer the following PECOS question: in patients diagnosed with squamous cell carcinoma of the head and neck (P), does the presence of diabetes mellitus, type 1 or type 2 (E), compared with its absence (C), affect survival endpoints and posttreatment complication rates (O), across observational study designs (S)? The principal objective was to quantify the prognostic impact of DM on survival and on

posttreatment complications in HNSCC, and to determine whether this impact differs by anatomical subsite.

The working hypothesis was that DM is associated with significantly worse survival outcomes and increased complication rates in patients with HNSCC. The specific aims were: (1) to estimate the association between DM and disease-specific, overall, disease-free, and distant metastasis-free survival as primary outcomes; (2) to estimate the association between DM and posttreatment complications, namely length of hospital stay, flap complications, surgical site infection, stroke, cardiovascular complications, and osteoradionecrosis as secondary outcomes; (3) to perform subgroup analyses by carcinoma location; and (4) to summarise the available evidence on glycaemic control and on the potential modifying role of antidiabetic medication, particularly metformin.

7. METHODS

Both studies were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline (29), and both protocols were prospectively registered on PROSPERO. Record management and screening were performed with EndNote and the Rayyan web application (30). Risk of bias was assessed in duplicate using the Quality In Prognosis Studies (QUIPS) tool, which appraises six domains, study participation, study attrition, measurement of the prognostic factor, measurement of the outcome, adjustment for confounding, and statistical analysis and reporting, with overall quality determined by the highest-risk domain; a study was rated high risk if any single domain was high risk or if at least three of six domains were moderate risk. The certainty of evidence was evaluated for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, which assess confidence based on risk of bias, inconsistency, indirectness, imprecision, and publication bias. All analyses used random-effects models, with between-study heterogeneity measured by the I^2 statistic (31) and small-study or publication bias assessed by funnel-plot and Egger's test (32), a p-value below 0.10 to indicate possible bias. Statistical analysis was performed in R (33) using the meta (34) and metafor (35) packages.

7.1. Study I

7.1.1 Methodology and Protocol

The systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. The protocol for Study I was registered as CRD42022375263.

7.1.2 Eligibility Criteria

Eligibility was defined within the PECOS framework. The population comprised patients with dental implants and a minimum follow-up or implant function time of one year; the exposure was type 2 diabetes or hyperglycaemia; the comparison was the absence of type 2 diabetes or hyperglycaemia; the outcomes were CBL, BoP, PPD, PI, IS, and peri-implant sulcular fluid (PISF); and eligible designs were observational

case-control, cohort, and cross-sectional studies. To reduce confounding, studies were excluded if patients had other chronic systemic diseases (for example HIV or kidney failure), pregnancy, current smoking, bone metabolic or periodontal disease, cardiovascular disease, bone augmentation, head and neck irradiation, or bisphosphonate therapy in the preceding year, and if implants carried special surface modifications such as hydroxyapatite coating.

7.1.3 Information Sources and Search Strategy

MEDLINE, Embase, and the Cochrane Library were searched with a specific search key without language restrictions or filters on April 2024, complemented by reference-list and citation chasing.

7.1.4 Study Selection and Data Extraction

Two reviewers (BB and VR) independently screened titles and abstracts and then full texts, with disagreements resolved by consensus or by a third reviewer (DV); inter-reviewer agreement was rated using Cohen's kappa. Data extraction was performed independently and in duplicate using a standardised electronic form capturing study and population characteristics, metabolic status at surgery, HbA1c values, the timing and method of HbA1c measurement, and the predefined clinical outcomes; preoperative and primary HbA1c measurements were prioritised where available.

7.1.5 Risk of Bias and Quality of Evidence Assessment

Risk of bias was assessed in duplicate using the Quality In Prognosis Studies (QUIPS) tool and the certainty of evidence was evaluated for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

7.1.6 Data Synthesis and Analysis

For the continuous outcomes the mean difference (MD) was used as the effect measure with 95% confidence intervals, and for the dichotomous implant-survival outcome odds ratios (OR) were calculated. Because several articles contributed multiple data points, a three-level multilevel model with study identity as a random factor was applied to obtain conservative CI estimates. Subgroup analyses were performed according to glycaemic control, distinguishing prediabetes (HbA1c 5.7–6.4%), well-controlled

(HbA1c < 8%) and poorly controlled (HbA1c > 8%) type 2 diabetes in line with the American Diabetes Association recommendations (36), and according to follow-up time (less than versus more than three years). To prevent contamination of the glycaemic subgroups, all studies with more than a 1% HbA1c overlap between control categories were excluded from the glycaemic subgroup analyses. Multivariable random-effects meta-regression was fitted for CBL and PPD with follow-up time, HbA1c, and disease duration as moderators; because disease duration was not a significant predictor, a reduced model excluding it was also applied.

7.2. Study II

7.2.1 Methodology and Protocol

The systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. The protocol for Study II was registered as CRD42025634653.

7.2.2 Eligibility Criteria

Eligibility followed the PECOS framework. The population comprised patients diagnosed with squamous cell carcinoma of the head and neck region; the exposure was diabetes mellitus of either type 1 or type 2; the comparison was the absence of diabetes; the outcomes were survival endpoints together with surgical site infection, flap complications, cardiovascular complications, osteoradionecrosis, and length of hospital stay; and eligible designs were retrospective and prospective observational studies. Patients with other chronic systemic diseases (such as HIV or renal failure), another cancer, recurrent or previously treated cancer, or distant metastasis at diagnosis were excluded, strengthening the comparability and generalisability of the analysis.

7.2.3 Information Sources and Search Strategy

Embase, MEDLINE, and the Cochrane Library were searched with a specific search key in August 2025 without language restriction, reference-list and citation searches.

7.2.4 Study Selection and Data Extraction

Title and abstract screening and full-text selection were performed independently and in duplicate by two reviewers (BB and VR), with disagreements resolved by consensus or a third reviewer (DV) and inter-reviewer agreement quantified by Cohen's kappa. Data were extracted in duplicate on study and population characteristics, disease location, diabetes status and type, the means of diabetes diagnosis, HbA1c values, where reported, disease classification and staging, and the predefined clinical outcomes.

7.2.5 Risk of Bias and Quality of Evidence Assessment

Risk of bias was assessed in duplicate using the Quality In Prognosis Studies (QUIPS) tool and the certainty of evidence was evaluated for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

7.2.6 Data Synthesis and Analysis

Hazard ratios (HRs) with 95% confidence intervals were used as the effect measure for survival endpoints and for osteoradionecrosis, cardiovascular, and stroke outcomes. Where raw data were available, HRs were calculated using the Paule–Mandel method; where only an HR with its confidence interval was reported, these were used directly under a Wald-type assumption with restricted maximum-likelihood estimation, and Q-profile confidence intervals were computed. For length of stay the mean difference was used, and for flap complications and surgical site infection odds ratios were calculated. A three-level multilevel model was applied because multiple articles reported data from the same centre, so that data centre was treated as a random variable in addition to study identity. Subgroup analyses were performed according to carcinoma location (oral, oropharyngeal, hypopharyngeal, laryngeal, nasopharyngeal, and mixed head and neck).

8. RESULTS

8.1. Study I - Prediabetes and poorly controlled type-2 diabetes as risk indicators for peri-implant diseases: A systematic review and meta-analysis

8.1.1 Study Search and Selection

A total of 2,660 records were identified; after duplicate removal 2,081 remained. Title and abstract screening ($\kappa = 0.8$) and full-text assessment ($\kappa = 1.0$) yielded, after reference and citation searches, 35 articles (1,761 individuals, 3,902 implants) for qualitative synthesis and 28 articles (1,469 individuals, 3,434 implants) for quantitative analysis (**Figure 2.**). The included studies were published between 2013 and 2022 and originated from a range of countries, with the largest contribution from Saudi Arabia; nine were retrospective, eleven prospective, and fourteen cross-sectional. Patients ranged in age from 30 to 87 years (mean 53) and were predominantly male (72%), and the mean duration of metabolic disease was 8.2 years. Five studies were judged to be at high risk of bias and were excluded from the quantitative analyses.

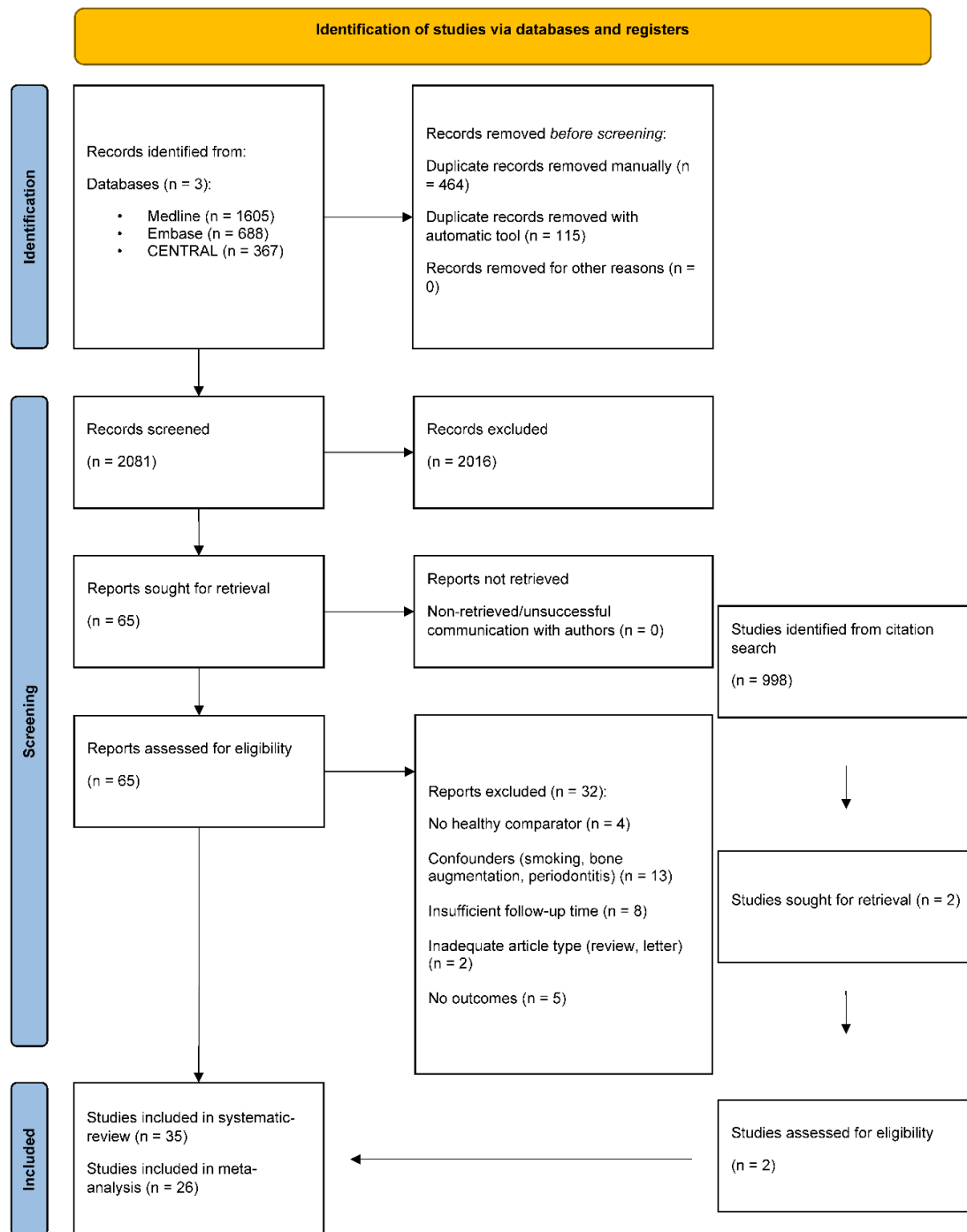


Figure 2. PRISMA 2020 flow diagram for the study-selection process of Study I.

8.1.2 Primary Outcomes

For crestal bone loss, the meta-analysis demonstrated statistically significant differences between patients with and without type 2 diabetes and prediabetes (0.9 mm and 1.0 mm, respectively), with very high heterogeneity ($I^2 = 100\%$). Patients receiving bone-level

implants had lower CBL (0.5 mm) than those with tissue-level implants (1.0 mm). When stratified by glycaemic control, after excluding comparisons with significant HbA1c overlap, CBL was 1.2 mm (95% CI 0.4; 2.1) in prediabetes, 1.8 mm (1.0; 2.7) in poorly controlled diabetes, and 0.4 mm (−0.3; 1.1) in well-controlled diabetes, the last being statistically non-significant. Stratification by follow-up time showed that the long-term results remained significant for the poorly controlled and prediabetes subgroups (2.7 mm and 1.8 mm, respectively).

8.1.3 Secondary Outcomes

Probing pocket depth followed the same pattern, with significant differences for type 2 diabetes and prediabetes versus controls (1.0 mm and 1.1 mm) and glycaemic-control subgroup values of 1.2 mm (prediabetes), 1.8 mm (poorly controlled), and a non-significant 0.4 mm (well-controlled). Bleeding on probing and plaque index were significantly worse in prediabetes and poorly controlled diabetes but not in well-controlled diabetes. Implant survival did not differ significantly between any glycaemic group and the controls.

Patients with elevated glycaemic levels showed significantly higher PISF concentrations of advanced glycation end-products, pro-inflammatory cytokines, and cortisol, together with lower levels of bone-protective mediators. The qualitative synthesis was coherent with the quantitative results across the included studies, and the direction of effect was stable whether studies were retrospective, prospective, or cross-sectional. The main glycaemic-control results are summarised in **Table 2**.

Table 2. Meta-analytic estimates for peri-implant outcomes in Study I, stratified by glycaemic control.

Outcome	Prediabetes	Poorly controlled (>8%)	Well-controlled (<8%)
Crestal bone loss (mm)	1.2 [0.4; 2.1]	1.8 [1.0; 2.7]	0.4 [−0.3; 1.1]
Probing pocket depth (mm)	1.2 [0.2; 2.1]	1.8 [0.9; 2.7]	0.4 [−0.3; 1.2]
Bleeding on probing (%)	0.2 [0.1; 0.2]	0.2 [0.1; 0.3]	0.1 [−0.02; 0.2]
Plaque index (%)	0.1 [0.1; 0.2]	0.2 [0.1; 0.3]	0.04 [−0.1; 0.2]
Implant survival (OR)	1.0 [0.1; 10.3]	1.7 [0.4; 7.7]	1.2 [0.5; 2.7]

Values are pooled mean differences versus controls. Millimetres (mm) for CBL and PPD; index values for BoP and PI) or odds ratios (OR) for implant survival, with 95% confidence intervals. Statistically significant estimates are those whose interval excludes the null.

Meta-regression confirmed a continuous relationship. A 1% increase in HbA1c was associated with a mean increase in CBL of 0.2 mm (95% CI 0.1–0.4 mm), and a follow-up time exceeding three years added a further 1.4 mm (1.0–1.8 mm) (**Figure 3a.**); for PPD the corresponding figures were 0.25 mm per 1% HbA1c (0.1–0.4 mm) and 1.3 mm for follow-up beyond three years (0.8–1.8 mm) (**Figure 3b.**). Disease duration was not a significant moderator of either outcome.

8.1.4 Risk of Bias Assessment and Quality of Evidence

On average, studies participating in the analysis had low risk of bias. Significant publication bias was suggested for the overall CBL and plaque-index analyses. The certainty of evidence was low for CBL and PPD and very low for BoP, PI, implant survival, and PISF content.

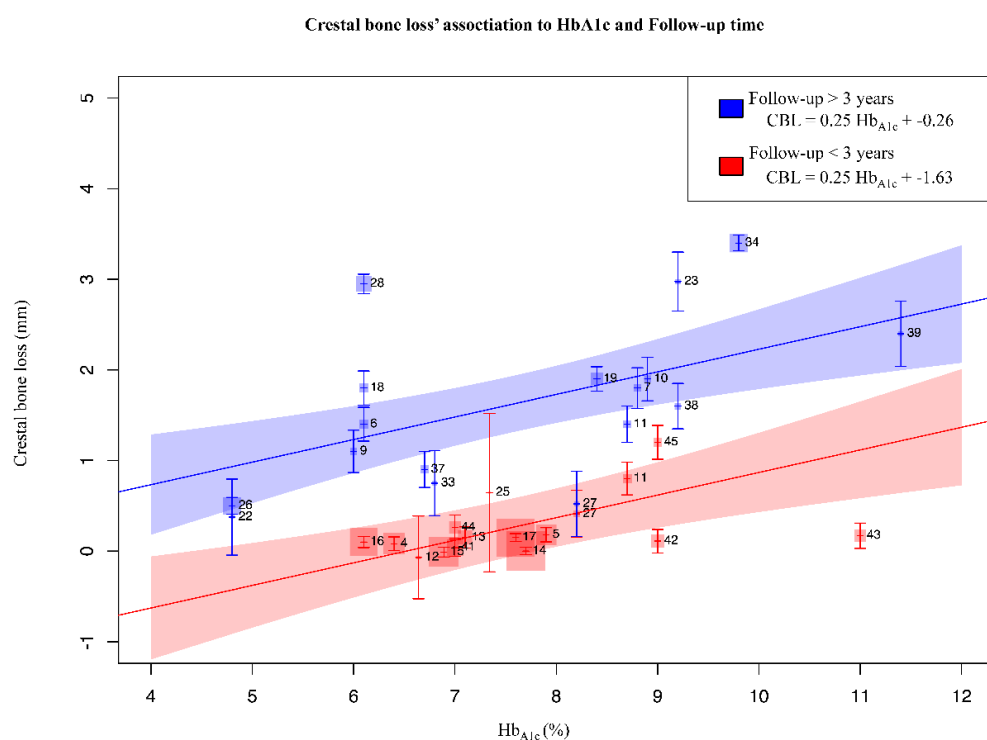


Figure 3a. Meta-regression of crestal bone loss outcomes against HbA1c and follow-up time; CIs of the regression lines are represented by corresponding colour and study level CIs by error bars, while study weights by boxes. CBL, Crestal bone loss.

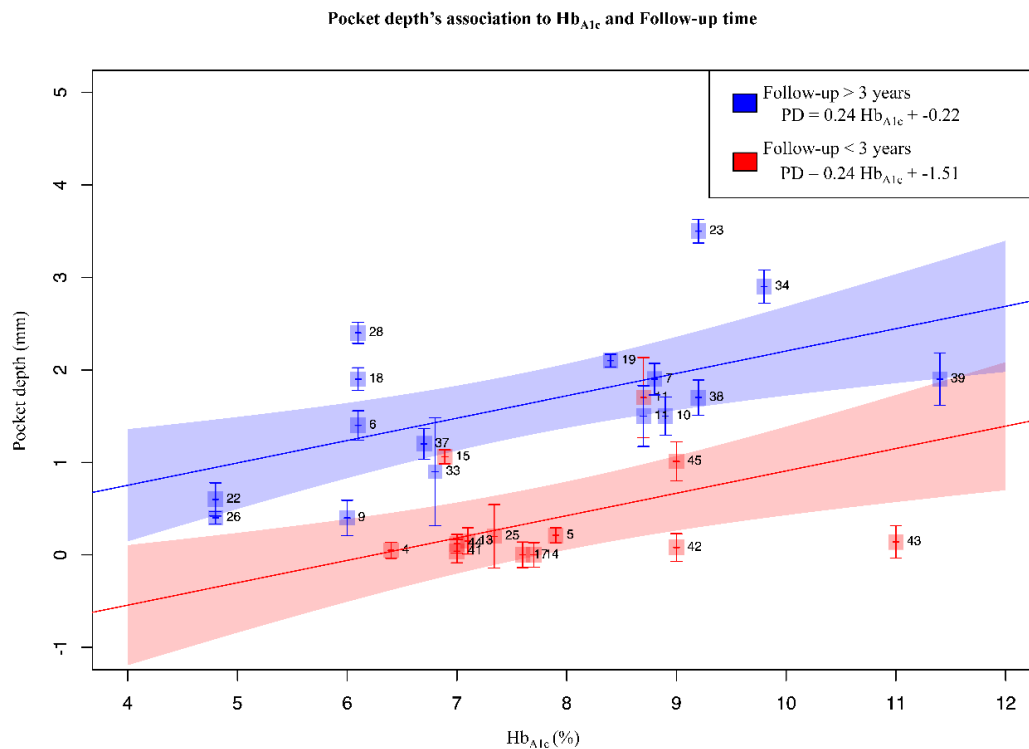


Figure 3b. Meta-regression representing the results of pocked depth in association with HbA1c; The CIs of the regression lines are shown with a field in matching colour and study-level CIs are shown by error bars, while study weights by boxes. PD, probing depth.

8.2. Study II - Diabetes is associated with elevated mortality, stroke, and osteoradionecrosis in squamous cell carcinomas of the head and neck: a systematic review and meta-analysis

8.2.1 Study Search and Selection

Altogether 18,326 records were identified, of which 16,353 remained after duplicate removal. Title and abstract screening ($\kappa = 0.82$) yielded 560 studies for full-text review ($\kappa = 1.0$), and after citation searching 63 articles were included in the final pool (**Figure 4**). These comprised approximately 138,000 individuals, including 22,800 patients with diabetes, and were published between 2006 and 2024, predominantly from Taiwan, the United States, and China. Four studies were prospective and 59 retrospective; the population had a mean age of 58.7 years and was predominantly male (72.7%). Nineteen studies investigated type 2 diabetes, two included both type 1 and type 2, and 42 did not specify the type; HbA1c was used to assess glycaemic control in only six

studies. Only one study was rated at high overall risk of bias, although concerns regarding the definition and measurement of the prognostic factor and the adjustment for confounders were common.

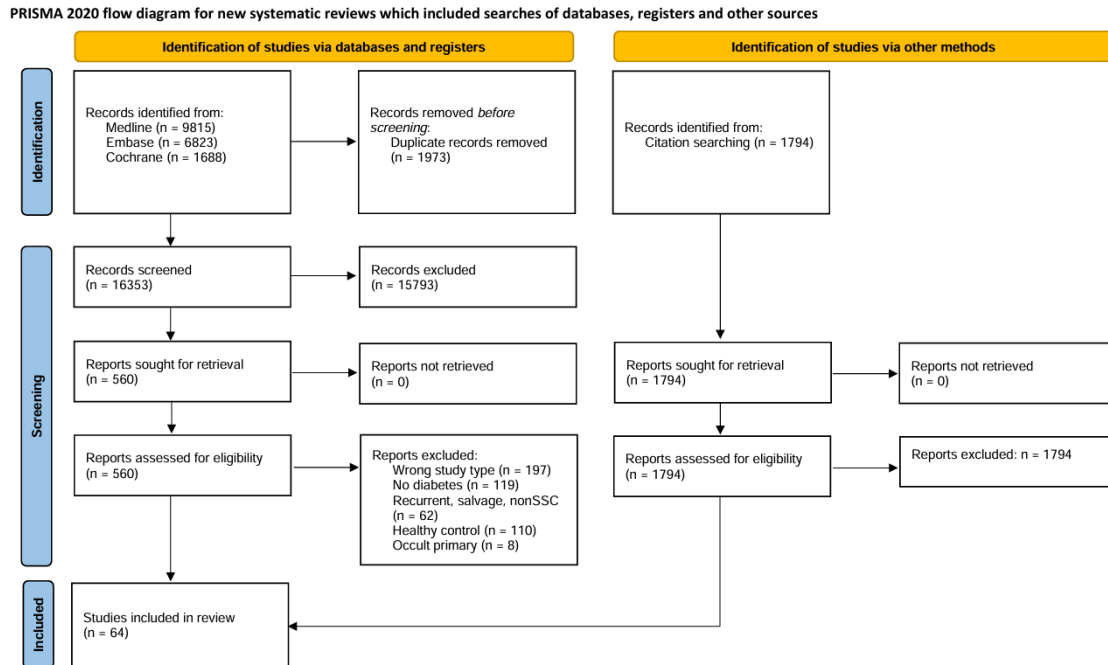


Figure 4. PRISMA 2020 flow diagram for the study-selection process of Study II.

8.2.2 Primary Outcomes

Diabetes was associated with significantly worse disease-specific survival. Ten studies reported disease-specific survival across subtypes, with univariate hazard ratios ranging from 0.71 in mixed head and neck disease to 4.82 in oropharyngeal disease; eight studies were eligible for the quantitative synthesis, yielding a pooled HR of 1.47 (95% CI 1.11–1.96) with substantial heterogeneity ($I^2 = 60\%$) (**Figure 5a.**). The effect was significant in the oral subsite (HR 1.44, 1.18–1.76), and one study that distinguished patients by medication found better survival among those taking metformin (HR 0.71) than among those not taking it (HR 1.62). Overall survival was reported by thirty-one studies and pooled from fifteen, giving an HR of 1.31 (1.23–1.39) with low heterogeneity ($I^2 = 4\%$); subgroup analysis showed significant effects in the oral (HR 1.35), oropharyngeal (HR 1.30), and mixed head and neck (HR 1.38) groups, whereas laryngeal and nasopharyngeal subtypes were not significantly affected, and metformin was again associated with more favourable survival (**Figure 5b.**). Disease-free survival was significantly worse in patients with diabetes (HR 1.58, 1.12–2.24; $I^2 = 58\%$), while

distant metastasis-free survival did not differ significantly overall (HR 1.28, 0.96–1.70), although a single study found that metformin substantially reduced the risk of distant metastasis (HR 0.93 versus 1.78).

8.2.3 Secondary Outcomes

Among posttreatment outcomes, length of hospital stay was longer in patients with diabetes by approximately 3.3 days, but the difference was not statistically significant (MD 3.29 days, –0.08–6.65). Flap complications were more frequent without reaching significance (OR 1.37, 0.74–2.54; head and neck subgroup OR 1.54), and the pooled univariate estimate for surgical site infection was non-significant (OR 1.63, 0.98–2.69) even though every study reporting multivariable estimates found a significant association, with risks between roughly 1.4- and six-fold. Posttreatment stroke (HR 2.11, 1.15–3.87) and osteoradionecrosis (HR 2.2, 1.38–3.53) were both significantly elevated (**Figure 5c. and 5d.**). Among four studies of cardiovascular complications, patients taking antidiabetic medication had a lower risk than those not taking it (HR 1.93 versus 3.52). Across the analyses, metformin use was consistently associated with more favourable survival and complication profiles. The main results are summarised in **Table 3**.

Table 3. Meta-analytic estimates for survival and posttreatment complication outcomes in Study II, comparing patients with diabetes mellitus against those without.

Outcome	Measure	Pooled estimate [95% CI]	I ²
Disease-specific survival	HR	1.47 [1.11; 1.96]	60%
Overall survival	HR	1.31 [1.23; 1.39]	4%
Disease-free survival	HR	1.58 [1.12; 2.24]	58%
Distant metastasis-free survival	HR	1.28 [0.96; 1.70]	n/r
Length of hospital stay (days)	MD	3.29 [–0.08; 6.65]	n/r
Flap complication	OR	1.37 [0.74; 2.54]	n/r
Surgical site infection	OR	1.63 [0.98; 2.69]	n/r
Stroke	HR	2.11 [1.15; 3.87]	70%

Osteoradionecrosis	HR	2.2 [1.38; 3.53]	11%
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HR, hazard ratio; OR, odds ratio; MD, mean difference; CI, confidence interval; I^2 , heterogeneity statistic; n/r, not reported as a pooled value.

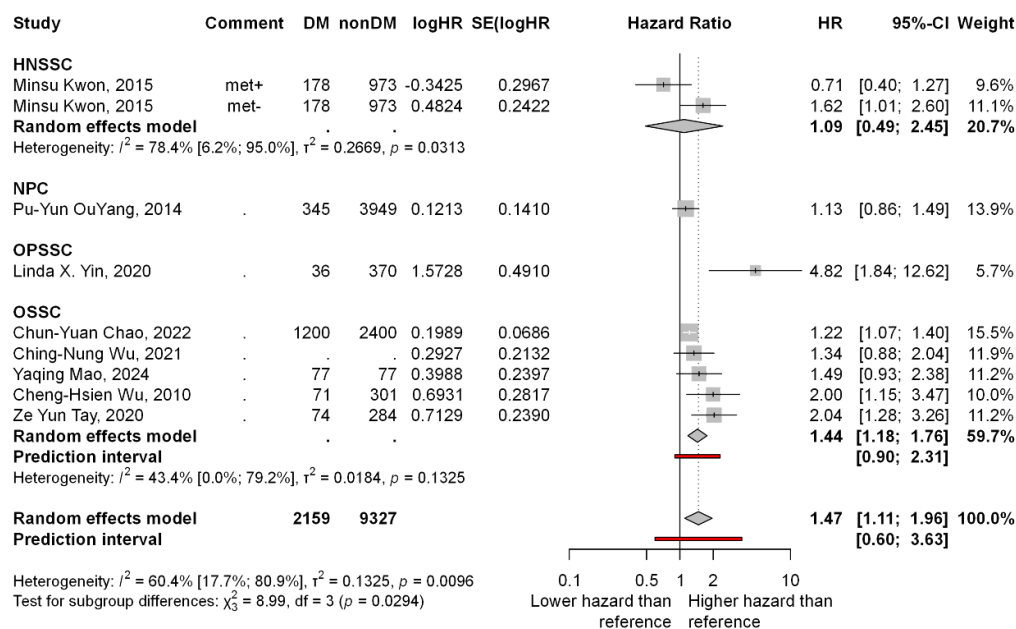


Figure 5a. Forest plot of disease-specific survival results of Study II, stratified by carcinoma location. HNSSC, head and neck squamous cell carcinoma; NPC, nasopharyngeal carcinoma; OPSSC, oropharyngeal squamous cell carcinoma; OSSC oral squamous cell carcinoma; DM diabetes mellitus; HR, hazard ratio.

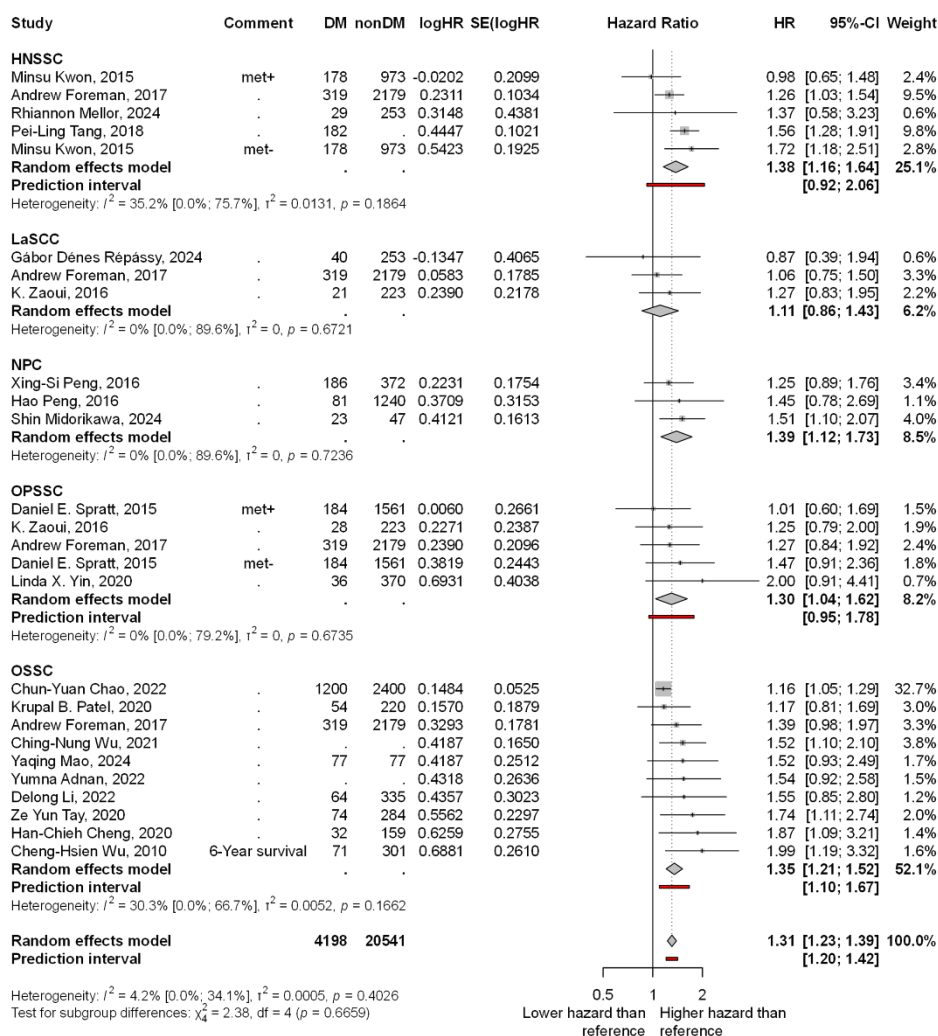


Figure 5b. Forest plot of overall survival results of Study II, stratified by carcinoma location. HNSSC, head and neck squamous cell carcinoma; LaSCC, laryngeal squamous cell carcinoma; NPC, nasopharyngeal carcinoma; OPSSC, oropharyngeal squamous cell carcinoma; OSSC oral squamous cell carcinoma; DM diabetes mellitus; HR, hazard ratio.

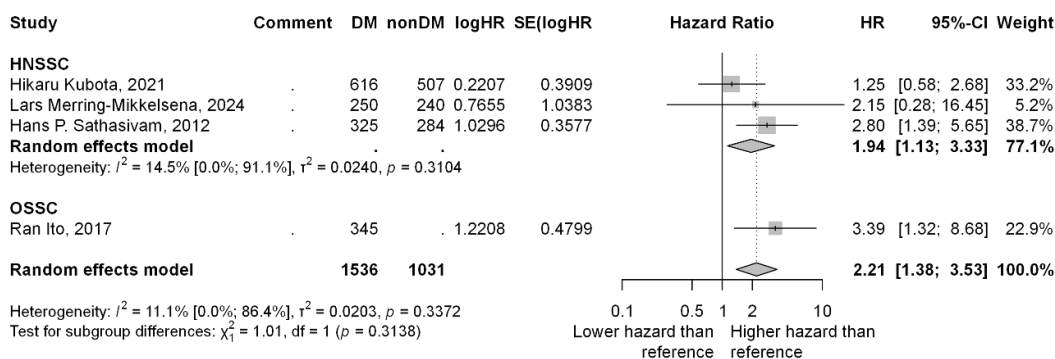


Figure 5c. Forest plot of stroke development results of Study II, stratified by carcinoma location. HN SSC, head and neck squamous cell carcinoma; OSSC oral squamous cell carcinoma; DM diabetes mellitus; HR, hazard ratio.

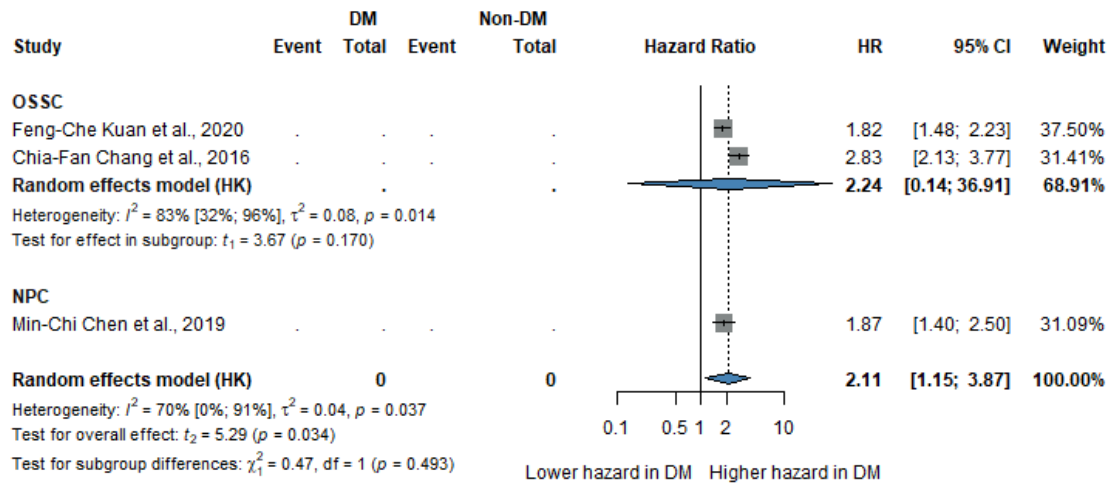


Figure 5d. Forest plot of osteoradionecrosis results of Study II, stratified by carcinoma location. NPC, nasopharyngeal carcinoma; OSSC oral squamous cell carcinoma; DM diabetes mellitus; HR, hazard ratio.

8.2.4 Risk of Bias Assessment and Quality of Evidence

On average, studies participating in the analyses had low risk of bias. Publication bias was assessed for overall survival, where it may be present (Egger $p = 0.037$). The certainty of evidence was moderate for disease-specific survival, distant metastasis-free survival, and osteoradionecrosis; low for overall survival, disease-free survival, flap complications, length of stay, and surgical site infection; and very low for stroke.

9. DISCUSSION

9.1. Summary of findings and international comparisons (including all studies)

The two studies provide evidence that the degree of hyperglycaemia, rather than diabetes alone, affects the severity of oral surgical and oncological complications. In Study I, poorly controlled type 2 diabetes and prediabetes were associated with worse crestal bone loss, probing pocket depth, bleeding on probing, and plaque index, whereas well-controlled diabetes was not, and implant survival was unaffected. Poorly controlled patients and patients with prediabetes had approximately five-fold and three-fold higher crestal bone loss than well-controlled individuals. In Study II, diabetes was associated with significantly worse disease-specific, overall, and disease-free survival in HNSCC and with a roughly two-fold increase in posttreatment stroke and osteoradionecrosis, the survival effects being concentrated in the oral and oropharyngeal subsites.

Taken together, the two studies conclude a single, clinically important principle: glycaemic status, expressed as a continuous variable rather than a binary diagnosis, is a modifiable determinant of oral surgical and oncological risk. Where the data permit a threshold to be defined, as in implant therapy, where HbA1c is routinely available and 8% cut-off cleanly separates patients at elevated risk from those who are not, that threshold can be inserted directly into clinical decision-making. Where the data do not permit it, as in head and neck oncology, where glycaemic control is rarely recorded, the same principle justifies systematic measurement of glycaemic status, both to identify undiagnosed disease and to allow for the threshold-based reasoning that future, better-characterised cohorts may support.

The findings of Study I both extend and clarify the previous literature. Earlier meta-analyses reported only small crestal bone loss differences in poorly controlled patients and were inconsistent regarding the role of glycaemic control; only Tan and colleagues had previously demonstrated a statistically significant difference between well- and poorly controlled patients (37). Other syntheses did not exclude major confounders such as bone augmentation, smoking, or special implant surfaces, did not perform glycaemic subgroup analysis, and none had accounted for the substantial overlap of HbA1c intervals between control categories (38-40). By correcting for this

overlap and separating prediabetes from controlled and uncontrolled diabetes, Study I provides a more robust estimate. Consistent with prior work, implant survival was not associated with diabetes (41, 42), confirming that survival is not a sensitive endpoint to capture the biological effect, which is better reflected by crestal bone loss, the most demanding criterion of implant success, for which annual loss above 0.44 mm means progression (43). The observation that bone-level implants outperformed tissue-level implants in patients with diabetes aligns with a recent synthesis of implant-level differences (44), although peri-implant tissue phenotype is itself an independent determinant of bone loss. The results are coherent with the role of plaque as the main reason of peri-implant inflammation and with the impaired compliance and dysregulated cytokine environment shared by prediabetes and poorly controlled diabetes (23).

The findings of Study II are consistent with, and extend, the existing evidence. A previous synthesis reported an association between type 2 diabetes and the risk of developing oral squamous cell carcinoma, particularly in East Asian populations (45), and a recent meta-analysis found worse overall survival in oral and oropharyngeal cancers but did not separate subtypes or distinguish univariate from multivariate estimates (46). By analysing subsites separately, Study II showed that the prognostic effect of diabetes is concentrated in the oral and oropharyngeal regions, where local exposure to hyperglycaemia and the pro-inflammatory, dysbiotic environment are most pronounced, while nasopharyngeal disease, more strongly driven by Epstein–Barr virus oncogenesis, and laryngeal disease are less affected (47). The recurring signal that metformin is associated with better outcomes is supported by an independent meta-analysis (48) and by preclinical work showing that metformin targets carcinoma-initiating cells through AMPK activation and mTOR inhibition and enhances natural-killer-cell activity through CXCL1 inhibition (49, 50). The single study that examined glycaemic control directly reported substantially worse survival in poorly controlled than in well-controlled patients (51), similarly to the threshold effect demonstrated quantitatively in Study I. For posttreatment complications, the two-fold stroke risk is consistent with radiotherapy-induced carotid and vertebral vasculopathy enhanced by hyperglycaemia-associated inflammation (52, 53), and the two-fold osteoradionecrosis risk connects the detrimental effect of diabetes on irradiated bone

healing (54). The non-significant but clinically relevant increases in surgical site infection and flap complications are similar with larger analyses that included recurrent and salvage cases (55-57), and the consistent significance of multivariable infection estimates suggests a significant association weakened in univariate pooling.

Two further observations have direct therapeutic relevance. First, the benefit of metformin across disease-specific, overall, and distant metastasis-free survival, and across cardiovascular complications, is biologically supported and clinically interesting, but the weak evidence derives from heterogeneous observational data and may be subject to confounding; it should therefore be regarded as a hypothesis-generating observation. Evidence on newer antidiabetic drugs is thin: glucagon-like peptide-1 receptor agonists have shown no clear effect on survival in the limited data available, whereas sodium-glucose cotransporter-2 inhibitors have been associated with reduced all-cause mortality in patients with other cancers, and both need dedicated studies in the head and neck setting. Second, although the increase in length of hospital stay did not reach statistical significance, an additional three days is clinically meaningful against a typical baseline of three to eight days and carries implications for resource use and hospital-acquired infection; the available evidence further suggests that well-controlled patients have a length of stay similar to that of individuals without diabetes, reinforcing the central message that it is glycaemic control, that drives excess risk.

9.2. Strengths (including all studies)

The main methodological strength common to both studies is adherence to a prospectively registered protocol, duplicate screening and extraction, formal risk-of-bias appraisal with the QUIPS tool, conservative three-level multilevel modelling, and GRADE assessment of certainty. Both syntheses were based on large and up-to-date body literature and applied rigorous exclusion criteria to limit confounding.

Study I introduced two specific methodological advances over previous meta-analyses: the separation of prediabetes, well-controlled, and poorly controlled diabetes, and the exclusion of cohorts with substantial HbA1c overlap between glycaemic categories, which together yield a cleaner estimate of the effect of glycaemic control and support an evidence-based clinical threshold. Study II advanced the field by separating the anatomical subsites of HNSCC, by distinguishing univariate from multivariate

estimates, by analysing multiple survival outcomes alongside posttreatment complications, and by excluding recurrent disease, pre-existing distant metastases, salvage surgery, and second primaries, thereby improving the comparability and generalisability of the pooled estimates relative to earlier work.

9.3. Limitations (including all studies)

Several limitations weaken the conclusions. In Study I the definitions of glycaemic control and of type 2 diabetes varied across primary studies, and the timing and method of HbA1c measurement were heterogeneous; the heterogeneity of the pooled estimates was very high, and unmeasured factors such as surgical protocol, implant system, oral hygiene, and peri-implant tissue thickness could not be fully controlled. The limited number of studies disallowed subgroup analyses by fixation and loading protocol, and the certainty of evidence was low. Publication bias was suggested for some outcomes.

In Study II the dominant limitation was the inconsistent characterisation of the prognostic factor: many studies did not specify the type of diabetes or the diagnostic criteria, and only a minority reported HbA1c or any measure of glycaemic control, which disallowed subgroup analysis by metabolic control and contained residual confounding. The covariates used in multivariable models differed considerably between studies, so only univariate estimates could be pooled quantitatively. The mainly retrospective design, variation in disease stage, treatment modality, and population characteristics, and the limited number of studies for some complication outcomes contributed to heterogeneity and to low or very low certainty for several endpoints. These limitations directly recommend that future studies document diabetes type, diagnostic method, and glycaemic control uniformly.

A limitation common to both studies concerns generalisability and the nature of the pooled estimates. Both syntheses drew predominantly on observational data, so the associations reported cannot be interpreted as causal, and the decision to pool univariate rather than adjusted estimates means that the pooled effects may incorporate confounding by shared risk factors such as smoking, alcohol use, age, and socioeconomic status. The geographic concentration of the source literature, particularly the predominance of East Asian cohorts in Study II, may limit applicability to other

populations, and differences in healthcare systems, surgical protocols introduce further heterogeneity.

10. CONCLUSIONS

Within the limitations of the available evidence, this thesis supports two main conclusions. First, in patients with dental implants, poorly controlled type 2 diabetes ($\text{HbA1c} > 8\%$) and prediabetes are associated with a higher risk of peri-implant disease, whereas well-controlled type 2 diabetes ($\text{HbA1c} < 8\%$) is not a risk indicator; HbA1c shows a continuous relationship with crestal bone loss and probing pocket depth that is amplified by longer follow-up, while implant survival is unaffected. An HbA1c value of 8% therefore constitutes a practicable threshold for distinguishing patients in whom diabetes elevates peri-implant inflammation risk.

Second, in patients with head and neck squamous cell carcinoma, diabetes is associated with significantly worse disease-specific and, with weaker evidence, overall survival, predominantly in oral and oropharyngeal subtypes, and with an approximately two-fold increased risk of osteoradionecrosis and, with weaker evidence, of posttreatment stroke; laryngeal and nasopharyngeal subtypes are less affected. Because the primary literature lacks glycaemic control or diabetes type, a threshold-based recommendation cannot be made for this population. Taken together, the two studies identify glycaemic status as a modifiable determinant of oral surgical and oncological risk and provide an evidence-base for preoperative glycaemic assessment and for closer cooperation between dental and medical specialists.

11. IMPLEMENTATION FOR PRACTICE

For implant dentistry, clinicians should consider measuring blood HbA1c, by laboratory or validated point-of-care methods, when planning implant-supported restorations. This enables identification of patients with undiagnosed or poorly controlled type 2 diabetes and allows glycaemic optimisation before surgery. On the basis of the present evidence, well-controlled type 2 diabetes (HbA1c < 8%) should not by itself be regarded as a contraindication to implant therapy, whereas an HbA1c above 8% or a prediabetic state prove as a risk. Preoperative metabolic management in cooperation with a diabetologist specialists, and stricter primary-preventive measures such as tighter maintenance intervals after rehabilitation are suggested.

For head and neck oncology, diabetes should be treated as an adverse prognostic and complication-associated comorbidity that justifies careful metabolic assessment and multidisciplinary management. Although a glycaemic threshold cannot yet be specified, systemic glycaemic measurement is recommended to identify underlying or poorly controlled diabetes and to create the opportunity for metabolic intervention, with particular attention to the elevated risks of osteoradionecrosis and posttreatment stroke. Regular screening of patients with hyperglycaemia for potentially malignant or malignant oral lesions is also advisable given the association between diabetes and the development of oral squamous cell carcinoma.

12. IMPLEMENTATION FOR RESEARCH

12.1. Methodology and Study Design

Future research on HNSCC should prioritise the uniform documentation of diabetes type, diagnostic method, and glycaemic control, with rigorous and repeated HbA1c measurement during follow-up, so that subgroup analyses by metabolic control become possible. Standardised reporting of carcinoma location, stage, and treatment, and cohorts matched for HbA1c and antidiabetic medication, would yield more accurate estimates of the true prognostic effect of diabetes.

In design terms, the questions raised by this thesis are best addressed through prospective, protocol-driven cohorts with standardised glycaemic measurement, because they would remove the main limitation of the existing literature. For implant therapy, whether preoperative normalisation of HbA1c in poorly controlled patients improves peri-implant outcomes can be tested in an interventional design, comparing immediate placement and with placement after metabolic optimisation, with crestal bone loss as the primary endpoint and follow-up beyond three years. For oncology, well-characterised registries with comparable data offer the most realistic route to subsite- and control-stratified estimates. Across both domains, the data collection of patient-reported outcomes and health-economic endpoints would broaden the evidence base beyond clinical outcomes.

12.2. New Areas

Future research on peri-implant disease should be prospective and should investigate the effect of other systemic factors, hyperlipidaemia, obesity, and lifestyle, in conjunction with elevated glycaemic levels. There is currently no evidence on whether normalising glycaemic levels in poorly controlled patients improves clinical and radiographic peri-implant outcomes, and this question should be addressed directly with longer follow-up, frequent HbA1c measurement, strict definitions of prognostic factors, and reporting of implant system, fixation, and loading protocols. Cohorts matched for oral hygiene would further reduce confounding.

The modifying role of antidiabetic medication deserves dedicated study: the apparent benefit of metformin should be confirmed prospectively, and the impact of newer agents

such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, on which evidence is currently scarce, should be evaluated.

13. IMPLEMENTATION FOR POLICYMAKERS

The evidence assembled in this thesis supports the integration of glycaemic screening into routine pre-treatment assessment for oral surgical and oncological care. Because a substantial proportion of diabetes is undiagnosed, embedding a simple HbA1c or blood-glucose check into the implant and head-and-neck-cancer care pathways would identify at-risk patients at a point where intervention is feasible and inexpensive relative to the cost of managing peri-implant inflammation, prolonged hospital stays, osteoradionecrosis, or stroke.

Policymakers are therefore encouraged to consider formal recommendations for preoperative glycaemic assessment, to support structured referral pathways between dental and diabetology care, and to fund the prospective, well-characterised studies needed to refine glycaemic thresholds, especially in oncology, where the current evidence base is insufficient to specify them. Such measures align preventive screening with the translational-medicine objective of converting robust evidence into measurable improvements in patient outcomes at the population level.

14. FUTURE PERSPECTIVES

The work presented here defines glycaemic status as a shared, modifiable axis of risk across two distinct domains of oral medicine and creates a template for translating systematic-review evidence into clinical recommendations. The progression is from association to intervention: prospective trials testing whether preoperative glycaemic optimisation improves peri-implant and oncological outcomes would convert the present prognostic findings into causal, actionable evidence.

A second perspective concerns measurement and integration. The development and validation of a standardised, point-of-care glycaemic screening pathway, coupled with structured data capture of diabetes type and control, would simultaneously improve patient care and remove the main limitation in Study II. Finally, the convergence of metabolic medicine, implant dentistry, and head and neck oncology argue for genuinely multidisciplinary models of care, in which dentists, diabetologists, oncologists, and surgeons cooperate around the shared goal of mitigating the oral and surgical consequences of dysglycaemia. Pursuing these directions within a translational framework offers a realistic path towards measurable reductions in peri-implant disease, treatment complications, and cancer mortality in patients with diabetes.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis

Study I:

- I. Bencze B, Golzio Navarro Cavalcante B, Romandini M, Róna V, Váncsa S, Varga G, Kivovics M, Szabó B, Agócs G, Géczi Z, Hermann P, Hegyi P, Végh D. Prediabetes and poorly controlled type-2 diabetes as risk indicators for peri-implant diseases: a systematic review and meta-analysis. *J Dent.* 2024;146:105094. Impact factor: 5.5

Study II:

- II. Bencze B, Golzio Navarro Cavalcante B, Róna V, Szabó B, Schulze Wenning A, Hermann P, Varga G, Németh O, Hegyi P, Végh D. Diabetes is associated with elevated mortality, stroke, and osteoradionecrosis in squamous cell carcinomas of the head and neck: a systematic review and meta-analysis. *BMC Oral Health*; 2026. Impact factor: 3.1

16.2. Publications not related to the thesis

Haba, K. S., Bencze, B., Kammerhofer, G., Ujpal, M., Banyai, D., Hermann, P., ... Alghamdi, H. (2025). Locally delivered 1% metformin gel improves periodontal parameters: A systematic review and meta-analysis. *SAUDI DENTAL JOURNAL*, 37(7–9). <http://doi.org/10.1007/s44445-025-00045-8>

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Hegedüs, T., Al-Hassiny, A., Dickie, J., Bencze, B., Samaranayake, L., Géczi, Z., ... Végh, D. (2025). User experience of 3D printing in dentistry. *JOURNAL OF DENTISTRY*, 163. <http://doi.org/10.1016/j.jdent.2025.106200>

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18. PUBLICATIONS

The full texts of the two publications forming the basis of this thesis are attached as appendices.