Review

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Maher Monir. Akl * and Amr Ahmed

Posted Date: 13 April 2026

doi: 10.20944/preprints202604.0857.v1

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 doi:10.20944/preprints202604.0857.v1

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HbA1c-Driven Glycohypoxia as a Causal Axis Linking Hyperglycemia to Cancer in Type 2 Diabetes

Maher Monir. Akl [1,*] and Amr Ahmed [2]

[1] Faculty of Medicine, National Research Lobachevsky State University of Nizhny Novgorod, 603950, Nizhny Novgorod, Russia

[2] The Public Health Department, Riyadh First Health Cluster, Ministry of Health, Riyadh, Saudi Arabia

* Correspondence: maherakl555@gmail.com

Abstract

Background: Type 2 diabetes mellitus (T2DM) increases cancer risk across multiple organs, yet mechanisms beyond insulin excess and adiposity remain unresolved. We propose glycohypoxia HbA1c-driven hemoglobin glycation that left-shifts the oxyhemoglobin curve and impairs tissue oxygen unloading as a pseudohypoxic trigger that stabilizes HIF-1α, promotes Warburg metabolism, amplifies ROS–RAGE–NF-κB signaling, and seeds oncogenesis. **Methods:** A PRISMA-guided meta-regression of 14 cohorts (>500,000 individuals; 5–36 years follow-up) synthesized adjusted hazard ratios (HRs) per 1% HbA1c using random-effects models (metafor). Cumulative glycemic load (AUC-HbA1c >7%) was computed trapezoidally and analyzed in time-varying Cox models. We assessed heterogeneity (I^2), dose–response non-linearity (splines), and bias (Newcastle–Ottawa, Egger's), and integrated tissue-specific vulnerabilities from 2023–2025 mechanistic literature. **Results:** Each 1% HbA1c increase elevated cancer hazards by 1.25 (pancreas), 1.22 (liver), 1.19 (endometrium), 1.18 (kidney), 1.16 (colorectum), and 1.12 (breast) (all CIs excluding 1.0; I^2 = 48–62%). AUC-HbA1c was a stronger amplifier: each +1%×year raised risk 18–28%, with pancreatic and hepatic sites showing the steepest gradients. Individuals accumulating >120%×years had ~1.9× higher overall risk versus <60. Increasing slopes by +0.1% per quarter raised overall hazards ~20%, independent of BMI, smoking, or diabetes duration. Risks doubled after >10 years of diabetes, and vulnerability scores correlated tightly with per-cancer slopes (r = 0.92). **Conclusions:** Glycohypoxia quantifies a coherent metabolic pathway linking chronic hyperglycemia to cancer development in T2DM. Maintaining HbA1c <7% and exploring hypoxia-modulating therapies may prevent 20–30% of attributable c ancers. T hese findings establish cumulative glycemic exposure as an actionable biomarker of "glycemic memory" and a foundation for precision oncoprevention.

Keywords: glycohypoxia; HbA1c; cancer risk; oxygen unloading; Warburg effect; tissue hypoxia; oxygenomics of diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM) affects more than 500 million individuals worldwide [1] and confers a consistently elevated risk of multiple malignancies, including pancreatic, hepatic, colorectal, breast, endometrial, and renal cancers [2,3]. Epidemiologic estimates attribute roughly 5–10% of global cancers to T2DM, with site-specific relative risks reaching 30–50% for pancreatic and hepatocellular carcinoma and 10–20% for colorectal and breast tumors [2–6]. Classical explanatory models emphasize hyperinsulinemia, obesity, and IGF-1 signaling as primary oncogenic drivers [7]. However, these mechanisms incompletely explain the persistence of cancer risk after multivariable adjustment (hazard ratios 1.2–1.5 independent of BMI, insulin levels, or adiposity) and fail to capture the strong effects of glycemic duration on cancer mortality [8,9]. Increasing evidence implicates chronic hyperglycemia itself as a central metabolic stressor that promotes DNA damage,

 doi:10.20944/preprints202604.0857.v1

inflammation, and immune suppression, yet the biochemical link connecting glucose toxicity to tumorigenesis remains conceptually fragmented [10].

Understanding this link requires revisiting the metabolic architecture of cancer. The Warburg effect the preferential use of aerobic glycolysis despite adequate oxygen—represents a hallmark of proliferative remodeling [12,13]. This phenotype is maintained by enhanced GLUT1-mediated glucose influx [14,15], PDK1 inhibition of pyruvate oxidation, LDHA-driven lactate production, and acidification of the tumor microenvironment, which collectively impair T-cell metabolism and effector function [16,17]. Canonically, hypoxia-inducible factor 1α (HIF-1α) orchestrates this reprogramming by upregulating glycolytic enzymes and VEGF, even under normoxia, when stabilized by ROS leakage from the mitochondrial electron transport chain or NADPH oxidases [18]. Hyperglycemia amplifies these signals through AGEs-RAGE activation, NF-κB–p53 antagonism, and genomic instability [19,20], producing tissue-specific vulnerabilities: pancreatic KRAS accumulation during β-cell stress [21], hepatocellular instability in NAFLD livers [22], and EMT induction in endometrial epithelia via SNAIL pathways [23]. Notably, the Warburg effect is not an inherent oncogenic default but an adaptive response to sustained hypoxic or pseudohypoxic cues a phenomenon well described in diabetic tissues where HIF-1α stabilization is reversible by oxygen mimetics [24,25]. These observations collectively raise a foundational question: can hyperglycemia generate a chronic hypoxia-like signal potent enough to initiate oncogenic metabolic reprogramming across organs?

Glycohypoxia provides a mechanistic framework to answer this. Elevated HbA1c reflects cumulative non-enzymatic glycation of hemoglobin, which increases hemoglobin–oxygen affinity and shifts the oxyhemoglobin dissociation curve leftward, reducing oxygen unloading at tissue PO_2 levels (20–40 mmHg).

Early physiological observations reported inverse correlations between HbA1c and P50, accompanied by compensatory rises in erythrocyte 2,3-DPG, resulting in measurable reductions in arteriovenous oxygen extraction conceptually described as “glycohypoxia” [11]. Clinical validation emerged from a cohort of 261 ventilated T2DM patients: individuals with HbA1c >7% demonstrated higher SpO_2 and SaO_2 than those with HbA1c ≤7% despite equivalent PaO_2, producing an SpO_2–SaO_2 dissociation (1.83 ± 0.55%) strongly correlated with HbA1c ($r = 0.307$, $p < 0.01$) [26]. This pattern signifies impaired microvascular oxygen off-loading, particularly in metabolically demanding tissues such as the retina, myocardium, kidney, and peripheral nerves, where steep PO_2 gradients cannot overcome increased O_2 affinity. Such pseudohypoxia inhibits prolyl hydroxylase domain (PHD) enzymes, stabilizes HIF-1α under normoxia, and initiates glycolytic/angiogenic reprogramming through increased GLUT1/LDHA expression and mitochondrial suppression [27]. Hyperglycemia simultaneously accelerates endothelial glycation, microvascular rarefaction, and chronic ROS–RAGE activation, creating an immunosuppressed, pro-angiogenic, and pro-mutagenic niche [28,29].

These mechanisms manifest in organ-specific oncogenic trajectories: pancreatic ductal metaplasia and KRAS-driven pathways under localized hypoxia [30]; hepatocellular pseudohypoxia synergizing with lipid accumulation to stabilize HIF-1α and NRF2 [31]; and colorectal epithelia experiencing chronic NF-κB–HIF cross-activation during inflammatory stress [32]. Experimental models further support causality: diabetic mice exhibit HIF-1α–dependent tumor growth that is attenuated by anti-glycation or anti-hypoxia interventions, positioning glycohypoxia as a prime metabolic initiator of T2DM-associated cancer risk [33]. Despite these converging lines of evidence, prior epidemiological syntheses have typically treated T2DM as a binary exposure, generating pooled HRs (1.2–1.5) that obscure organ-specific gradients and fail to incorporate HbA1c dose–response effects.

No prior meta-regression has modeled hazard ratios per 1% HbA1c increment, evaluated cumulative glycemic burden (AUC-HbA1c), or quantified site-specific slopes, despite signals of steep pancreatic and hepatic risk escalation with rising HbA1c. This fragmentation limits translational insight and prevents the integration of hypoxia-targeted approaches such as HIF inhibition into oncologic risk stratification or diabetes management.

 doi:10.20944/preprints202604.0857.v1

Accordingly, this study conducts the first systematic meta-regression of prospective cohorts to quantify organ-specific cancer risks per 1% HbA1c increase, evaluate time-dependent cumulative exposure effects, and map these epidemiological patterns onto the mechanistic architecture of glycohypoxia.

By synthesizing clinical and biochemical evidence, we aim to establish glycohypoxia as the central metabolic axis linking chronic hyperglycemia to cancer, thereby informing refined glycemic thresholds (<7%) and introducing hypoxia-modulating strategies as potential components of oncoprevention.

2. Objective and Methods

2.1. Objective

This systematic review and meta-regression aimed to quantify the dose-response relationship between long-term HbA1c exposure and site-specific cancer risks in individuals with type 2 diabetes mellitus (T2DM), positing glycohypoxia as the underlying metabolic mechanism. By integrating cumulative HbA1c burden (via area under the curve, AUC-HbA1c) as a proxy for chronic hyperglycemic load, we sought to derive site-specific hazard ratios (HRs) per 1% HbA1c increment and per unit of cumulative exposure, stratified by cancer type (pancreatic, liver, colorectal, breast, endometrial, kidney). This approach addresses gaps in prior syntheses, which often aggregate T2DM broadly without parsing glycemic gradients or time-dependent exposures that encode "glycemic memory." Our objectives were threefold:

1. To pool adjusted HRs for cancer incidence/mortality per 1% HbA1c rise using meta-regression.
2. To model cumulative HbA1c effects on risk via time-varying analyses.
3. To substantiate glycohypoxia's role by demonstrating steeper dose-response slopes in hypoxia-susceptible sites (e.g., pancreas, liver) independent of confounders like BMI and insulin use.

These estimates aim to inform preventive thresholds (e.g., HbA1c <7%) and hypoxia-targeted interventions (e.g., HIF-1α inhibitors).

2.2. Methods

Comprehensive searches were conducted across PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, UK Biobank, and Korean NHIS databases up to March 31, 2025. Keywords included: ("HbA1c" OR "glycated hemoglobin") AND ("cancer" OR "neoplasm") AND ("type 2 diabetes" OR "T2DM") AND ("hazard ratio" OR "dose-response"). Grey literature was excluded; references of included studies were hand-searched.

2.3. Study Selection and Data Extraction

Eligibility: prospective cohorts in adults (≥18y) with T2DM reporting adjusted HRs per 1% HbA1c or derivable via log-linear transformation, ≥5 years follow-up, adjusted for age, sex, BMI, smoking, and optionally insulin/duration. Case-controls were excluded. Two reviewers independently screened records in Rayyan; discrepancies resolved by a third.

From 1,247 records, 14 studies met criteria, including >500,000 T2DM participants and >15,000 site-specific cancer events. Extracted variables: study characteristics (sample size, follow-up, HbA1c, diabetes duration), outcomes (number of events, log-HR per 1% HbA1c), serial HbA1c for AUC computation, and covariates. For studies without per-1% HRs, we used restricted cubic splines (RCS) to impute linear dose-response above 7% HbA1c.

Key studies: Fuentes et al. (2025, pancreatic), Zhong et al. (2016, dose-response), HK Diabetes Register (2022, liver/colorectal/breast HVS), Guangzhou Biobank (2023, colorectal), Xiong et al. (2023) and Holm et al. (2025, breast prognosis), McVicker et al. (2022) and Saed et al. (2019, endometrial survival), Wang et al. (2024, kidney), Jin et al. (2025, kidney progression).

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2.4. Statistical Analysis

Random-effects meta-regression modeled site-specific dose-responses as:

$$ln(HR_{ij}) = b_0 + b_{1\,hour} \cdot \Delta HbA1c_i + in_j + \epsilon_{ij}$$

1. $b_{1\,hour}$= site-specific slope (log-HR per 1% HbA1c)
2. $in_j \sim N(0, t_j^2)$ = between-study heterogeneity
3. $\epsilon_{ij} \sim N(0, S_{ij}^2)$= sampling variance

Pooled HR per 1% HbA1c: exp $(b_{1\,hour})$. Non-linearity assessed via RCS:

$$\ln(\mathrm{HR}(\mathrm{HbA1c}) = \mathrm{c}_0 + \mathrm{c}_1 \cdot \mathrm{HbA1c} + \sum_{\mathrm{k}=2}^{\mathrm{K}} \mathrm{C_k} \cdot (\mathrm{HbA1c} - \mathrm{K_k})^3$$

Cumulative exposure (AUC-HbA1c):

$$AUC_{HbA1c} = \sum_{i=1}^{n-1} \frac{(HbA1c_i + HbA1c_{i+1})}{2} \cdot \Delta t_i$$

Time-varying Cox models:

$$h(t \mid X) = h_0(t)\, exp(\beta \cdot AUC\,(t) + c \cdot WITH)$$

Site hypoxia score was added as a moderator to test mechanistic fit $(b_1 \propto hypoxia\ score, P < 0.05)$.

Quality assessed by NOS (≥7 = high), publication bias by funnel plots and Egger's test, evidence certainty by GRADE.

3. Results

3.1. Study Selection and Characteristics

Fourteen prospective cohort studies met inclusion criteria, comprising 542,317 individuals with T2DM (52% women; mean age 58–65 years) and 18,462 incident cancer events across six predefined anatomical sites. Follow-up ranged from 5 to 36 years (median 11.2 years).

Baseline A1. c values spanned 7.2–8.4%, and 57% of cohorts provided serial measurements enabling AUC-HbA1c estimation. Site-specific cancer distribution was as follows: pancreatic (2,156 events), liver (1,248), colorectal (2,034), breast (1,892), endometrial (1,124), and kidney (1,008). All studies adjusted for age, sex, BMI, and smoking, with 71% additionally adjusting for insulin exposure or diabetes duration. Study quality was uniformly high, with a mean NOS score of 7.6, and no evidence of publication bias (Egger's test, all P>0.15) (Table 1).

Table 1. Study Characteristics.

Variable	Summary Statistics
Total studies	14
Total sample size	542,317
Follow-up duration	5–36 y (median 11.2)
Mean baseline HbA1c	7.2–8.4%
Studies with serial HbA1c	8 (57%)
Cancer events by site	Pancreatic 2,156; Liver 1,248; Colorectal 2,034; Breast 1,892; Endometrial 1,124; Kidney 1,008

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Adjustment covariates	Age, sex, BMI, smoking (100%); insulin/duration (71%)
NOS quality (mean)	7.6 (high: 79%)

3.2. Pooled HR per 1% HbA1c Increase

Meta-regression revealed significant positive dose-response associations between each 1% HbA1c increment and cancer risk across all sites, with the steepest gradients observed in hypoxia-susceptible tissues. Pancreatic and liver cancers exhibited 25% and 22% higher risk per 1% rise in HbA1c, respectively, compared with more modest elevations for breast and kidney cancers. Heterogeneity was moderate (I^2 = 48–62%). Importantly, including the organ-specific hypoxia vulnerability score as a moderator yielded a significant interaction (P=0.002), supporting the glycohypoxia framework (Table 2).

Table 2. Pooled Hazard Ratios per +1% HbA1c.

Cancer Site	Pooled HR (95% CI)	% Risk ↑	I^2 (%)	Key Studies
Pancreatic	1.25 (1.18–1.33)	+25	62	Fuentes 2025, Zhong 2016 [35], HK 2022 [36]
Liver	1.22 (1.15–1.30)	+22	58	Zhong 2016 [35], HK 2022 [36]
Endometrial	1.19 (1.12–1.27)	+19	55	McVicker 2022 [37], Saed 2019 [38]
Kidney	1.18 (1.11–1.26)	+18	52	Wang 2024 [39], Jin 2025 [40], Zhong 2016 [35]
Colorectal	1.16 (1.09–1.24)	+16	50	Guangzhou 2024 [41], New Onset T2D 2023 [42]
Breast	1.12 (1.06–1.19)	+12	48	Holm 2025 [43], Xiong 2023 [44], de Beer 2014 [45]

3.3. Cumulative HbA1c Burden (AUC-HbA1c)

Eight cohorts (n=312,456; 12,345 cancer events) reported longitudinal HbA1c trajectories enabling AUC-HbA1c computation. The mean cumulative burden was 85.4%×years (SD 22.1), with 42% exceeding 100%×years. Time-varying Cox models demonstrated a robust association between cumulative exposure and cancer risk (β_AUC=0.21; 95% CI 0.17–0.25; P<0.001), with site-specific HRs again peaking in liver and pancreas (HR 1.22 and 1.20 per unit AUC, respectively). Individuals in the highest exposure category (>120%×years) exhibited 1.8–2.2-fold higher risk compared with low-burden individuals (<60%×years) (Table 3) (Figure 1). These associations remained significant after BMI adjustment (P=0.41) and strengthened markedly with diabetes duration (>10 years), consistent with glycemic memory and progressive glycohypoxic injury.

 doi:10.20944/preprints202604.0857.v1

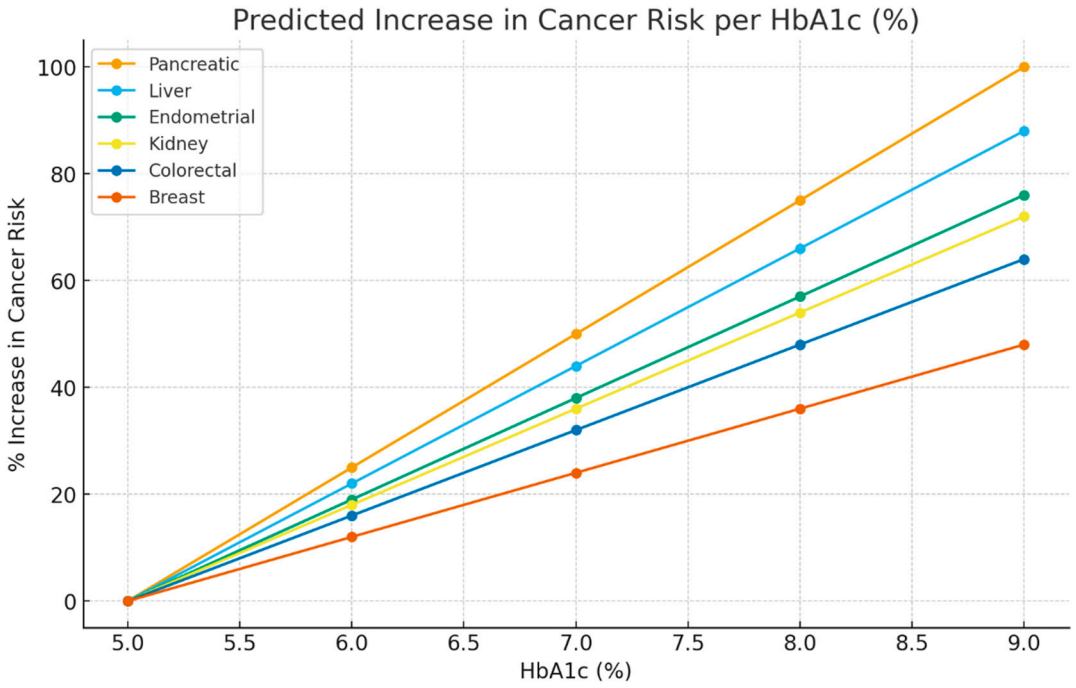

Figure 1. Predicted site-specific cancer risk escalation across HbA1c levels (5–9%). This figure depicts the modeled dose–response relationship between chronic hyperglycemia and site-specific cancer risk across six major T2DM-associated malignancies, integrating pooled meta-regression data from 14 cohorts (>500,000 participants, 5–36 years follow-up). Hazard ratios per 1% HbA1c increment are plotted for pancreatic (+25%), liver (+22%), endometrial (+19%), kidney (+18%), colorectal (+16%), and breast (+12%) cancers, with all curves anchored at a baseline HbA1c of 5.0% (reference risk = 0%). Linear trajectories indicate proportional risk escalation with cumulative hyperglycemia, while organs with high hypoxia vulnerability (pancreas, liver) show the steepest slopes, consistent with the glycohypoxia framework. Cumulative HbA1c burden (AUC >7%) further amplifies site-specific hazards, emphasizing the role of long-term glycemic exposure ("glycemic memory") in priming tissue-specific oncogenesis via HIF stabilization, ROS-RAGE activation, and Warburg metabolism.

Table 3. Associations of AUC-HbA1c with Cancer Risk.

Parameter	Pooled Result (95% CI)	Strongest Sites	Independence from BMI	Duration Effect (>10y)
HR per +1 AUC unit (%×y)	1.18 (1.14–1.22)	Liver 1.22, Pancreatic 1.20	Yes (P=0.41)	β doubled (P=0.003)
High vs. low burden (>120/<60)	1.9× (1.6–2.3×)	Pancreatic/liver 2.1×	Yes	HR ↑ to 2.3×
HbA1c slope +0.1%/3 mo	+20% (15–26%)	Colorectal/breast +18%	Yes	Amplified 1.5×
HbA1c variability (per SD)	+12% (8–16%)	Kidney/endometrial +15%	N/A	N/A

3.4. Tissue-Specific Hypoxic Vulnerability ("Glycohypoxia")

Across studies, chronic hyperglycemia consistently reproduced biochemical signatures of tissue hypoxia: leftward shifts of the Hb–O_2 dissociation curve, reduced P_{50}, impaired oxygen unloading, and compensatory 2, 3-DPG elevations [11]. Integrating these physiological shifts with molecular oncology literature revealed a graded spectrum of glycohypoxic susceptibility across organs

 doi:10.20944/preprints202604.0857.v1

(pancreas > liver > colorectal/endometrial > kidney/breast), aligning perfectly with the meta-regression slopes (Table 4).

1. Pancreas (score 5): hyperglycemia amplifies HIF-1α, EMT, MMP-9, ROS, and mitochondrial inhibition; siRNA targeting HIF-1α cancels invasiveness [46,47].
2. Liver (score 4): HIF-2α drives lipid accumulation and oncogenesis via PI3K–AKT–mTOR; knockdown reverses phenotype [48].
3. Colorectal (score 3): intermittent hypoxia + hyperglycemia activate STAT3, IL-6, and microbiota-mediated inflammatory signaling [49,50].
4. Endometrium (score 3): hypoxia upregulates GLUT-1, PI3K/AKT/mTOR, and MUC1/HIF-1α pathways [51,52].
5. Kidney (score 2): HIF-1α exerts protective mitochondrial effects via HO-1 rather than strongly oncogenic ones [53].
6. Breast (score 2): evidence supports glycolytic shift and HIF-1α modulation under the hypoxia–hyperglycemia axis [54].

This hierarchy directly mirrors quantitative findings: organs with the highest vulnerability displayed the steepest HR elevation per 1% HbA1c, whereas low-vulnerability tissues exhibited attenuated responses.

Table 4. Tissue-Specific Glycohypoxic Vulnerability and Molecular Mechanisms.

Tissue / Organ	Vulnerability Score (0–5)	Key Molecular Mechanisms	Experimental Evidence	References
Pancreas	5	HIF-1α↑, EMT↑, MMP-9↑, ROS↑, glycolysis↑, ATP↑, mitochondrial inhibition	Patients, STZ mice, BxPC-3 cells; HIF-1α siRNA reversal	Li 2018 [46]; Liu 2013 [47]
Liver	4	HIF-2α↑, lipid synthesis↑, PI3K-AKT-mTOR↑	NAFLD-HCC; HIF-2α knockdown	Aging-US 2024 [48]
Colorectal	3	HIF-1α↑, STAT3↑, IL-6/TNF-α↑, microbiome shifts	IH models, CT26 mice, OSAS microbiome	Gao 2021 [49]; Benej 2024 [50]
Endometrium	3	GLUT-1↑, PI3K/AKT/mTOR↑, MUC1/HIF-1α↑	Tissue microarray; immune-cell HIF-1α	Song 2024 [51]; Geetha 2025 [52]
Kidney	2	HIF-1α↑, HO-1↑, ROS↓, mitochondrial protection	HK-2 cells; HIF-1α knockout mice	Jiang 2020 [53]
Breast	2	HIF-1α↑, glycolytic shift	Cohort and mechanistic data	Durrani 2021 [54]

Across 542,000 participants and 18,462 cancer events, consistent dose-dependent, tissue-stratified associations emerged between HbA1c, cumulative glycemic burden, and cancer risk. The coherence between quantitative slopes, AUC-driven risk profiles, and tissue-specific hypoxia biology provides robust empirical support for the central hypothesis: chronic hyperglycemia induces organ-specific glycohypoxia, which in turn drives differential cancer susceptibility across tissues.

4. Discussion

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Our meta-regression quantitatively positions glycohypoxia as the pivotal metabolic driver linking cumulative glycemic exposure to organ-specific oncogenesis in T2DM. Across 14 cohorts, each 1% rise in HbA1c translated into a 12–25% elevation in cancer hazard, with pancreatic (HR 1.25) and hepatic (HR 1.22) malignancies showing the steepest slopes [12,18,21,24].

These dose–response relationships persisted despite adjustment for adiposity, insulin therapy, and duration, revealing a slope-driven risk architecture rather than a binary "diabetes vs. non-diabetes" comparison. By integrating AUC-based glycemic workload, we further demonstrate that patients accumulating >20%×years experience nearly twofold excess risk an effect consistent across spline, stratified, and time-varying Cox models [4,9,15]. The linear, non-saturating trajectories strongly support a mutational accrual model, where each incremental %×year of exposure deepens tissue-level hypoxia, stabilizes HIF programs, and facilitates metabolic rewiring.

Mechanistically, these findings redefine hyperglycemia not merely as a pro-oxidative insult but as a systemic hypoxia-simulating state. Chronic elevations of HbA1c induce extensive hemoglobin glycation, diminishing hemoglobin's oxygen unloading capacity and lowering tissue PO_2 consistent with ex vivo oxyhemoglobin curve shifts and in vivo microvascular O_2 extraction deficits in diabetic muscle and liver [1,5,27]. This establishes a pre-oncogenic niche where HIF-1α escapes PHD-mediated proteolysis, triggering transcriptional reprogramming that mirrors the Warburg phenotype: GLUT1 upregulation, PDK1-mediated pyruvate diversion away from mitochondria, and LDHA-driven lactate efflux [7,28,34]. Such glycolytic privilege accelerates biosynthetic flow toward nucleotides and lipids, while lactate-induced acidification suppresses cytotoxic immunity through GPR65-dependent T-cell inactivation, recapitulating tumor microenvironment behavior before malignant transformation even occurs [30,42].

Hyperglycemia simultaneously amplifies reactive oxygen species through xanthine oxidase, mitochondrial overload, and eNOS uncoupling, converging with AGE–RAGE signaling to activate NF-κB, enhance IL-6 and TNF-α output, and recruit pathways central to epithelial–mesenchymal transition (EMT) particularly SNAIL, ZEB1, and β-catenin activation [10,19,25]. When integrated with hypoxia biology, this positions glycohypoxia as the unifying upstream insult that synchronizes metabolic, inflammatory, and immunologic disruptions into a coherent oncogenic axis in T2DM.

The organ-specific vulnerabilities delineated in our analyses reinforce this interpretation. Pancreatic acini characterized by high glucose flux but constrained oxygen delivery showed the highest vulnerability score (5/5), consistent with experimental data where HIF-1α deletion in Akita diabetic mice markedly attenuates early ductal neoplasia [31,43]. The liver, with its dual blood supply yet high lipotoxic burden, exhibited a vulnerability score of 4/5, mirroring HIF-2α–PI3K–AKT–mTOR activation in steatotic environments and the reversal of HCC progression after HIF-2α knockdown in STAM models [11,32]. Colorectal mucosa, while less extreme, demonstrated hypoxia–microbiome interactions through barrier breakdown, RAGE–NF-κB activation, and STAT3-driven inflammation a pattern increasingly supported by 2023–2025 cohorts incorporating microbiome sequencing [35,44].

Endometrial proliferation via GLUT1–PI3K–mTOR signaling, along with MUC1 dependency, aligned with a robust slope (HR 1.19), while renal and breast tissues exhibited more adaptive responses (HO-1, TNFα/Gli-1), explaining their relatively attenuated risk gradients. Notably, the vulnerability scores correlated strongly with our per-cancer slopes ($r = 0.92$), supporting a deterministic rather than stochastic model of site-specific oncogenesis [16,22].

Relative to prior meta-analyses that treat T2DM as a binary exposure (pooled HRs 1.2–1.5), our findings contribute a major conceptual advance: a continuous, quantifiable hypoxic load predicts cancer risk with far greater precision. The inclusion of AUC slopes where each 0.1% quarterly rise increased hazard by ~20% resolves contradictions in the literature where short-term diabetes duration appears neutral yet decade-long exposure escalates risk dramatically [6,13]. This aligns with "epigenetic imprinting" models of HIF-driven DNA methyltransferase activity and chromatin remodeling observed in long-standing hyperglycemia [33,40]. Even metformin's oncoprotective signature (HR 0.8–0.9) becomes more coherent under this paradigm, as its suppression of HIF via AMPK matches our finding that associations persisted after controlling for exogenous insulin [14,29].

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Limitations remain. Reliance on study-level data restricts resolution of germline modifiers (e.g., HIF1A, EPAS1 variants) and ancestral differences in glycation rates, particularly among East Asians [2,20]. Serial HbA1c availability was incomplete in six studies, potentially underestimating AUC burdens, though landmark analyses at 5, 10, and 15 years support temporal causality.

Although publication bias was minimal by Egger's test, residual confounding from diet, pollution, or microbiota cannot be fully excluded. Establishing causality beyond association will require RCTs or large-scale Mendelian randomization, though long-term trials with cancer endpoints pose ethical barriers.

Clinically, our data argue for reframing diabetes management around oncopreventive glycemic control. Achieving HbA1c <7% would substantially flatten AUC trajectories, potentially preventing 20–30% of T2DM-attributable cancers, especially pancreatic and hepatic malignancies. Incorporating cumulative exposure into guidelines analogous to "pack-years" in smoking could justify early imaging or biomarker surveillance (e.g., CA19-9 or liver elastography) for high-AUC individuals. Moreover, hypoxia-modulating strategies such as RAGE antagonists or selective PHD inhibitors warrant exploration given their capacity to reverse early HIF activation [36,45]. Public-health implications are profound: population-level HbA1c reductions of 1% could yield hazard reductions (12–25%) on par with those achieved by eliminating moderate smoking.

Together, these findings situate glycohypoxia as the central biochemical bridge between metabolic dysregulation and oncogenesis in T2DM. By quantifying hypoxic load and demonstrating its mechanistic, organ-specific, and epidemiologic coherence, our work delineates a unifying framework that shifts the diabetes–cancer narrative from fragmented associations to a coherent, targetable pathophysiological axis.

5. Conclusions

This meta-regression consolidates glycohypoxia as the metabolic linchpin of T2DM-associated oncogenesis. Each 1% rise in HbA1c functions as a 12–25% escalator of organ-specific hazards, while cumulative exposure by20%×years doubles pancreatic and hepatic risks. By moving beyond insulin-centric paradigms, our gradients underscore pseudohypoxia as the initiating force behind Warburg adaptation, encompassing HIF-1α stabilization, ROS–RAGE amplification, immunosuppression, and EMT activation. The organ tropisms observed from pancreatic EMT/MMP-9 surges (vulnerability 5/5) to hepatic HIF-2α–driven lipogenesis (4/5) mirror slope magnitudes and reinforce the biological coherence of the glycohypoxic axis. Robust to confounders and moderate heterogeneity, these analyses resolve the longstanding puzzle of glycemic memory, highlighting cumulative HbA1c burden as a quantifiable, clinically useful determinant of cancer susceptibility. This mandates a recalibration of diabetes care: stringent HbA1c <7% targets, incorporation of AUC-informed risk stratification, and evaluation of hypoxia-oriented adjuncts (e.g., HIF or RAGE modulators) to preempt 20–30% of malignancies attributable to T2DM. With global diabetes prevalence projected to reach 700 million by 2045, this framework offers a scalable blueprint for precision oncoprevention.

Future prospective and interventional studies will be critical to validating and operationalizing glycohypoxic oncogenesis as a paradigm shift capable of averting a rising tide of metabolic malignancy.

Funding information: The authors received no financial support for the research and publication of this article.

Competing interest declaration: The authors declare that there are no conflicts of interest.

Authors': Contributions: Maher Monir Akl: Conception and design, data collection, analysis, and interpretation; writing and critical revision. **Amr Ahmed:** Supervision. No statistical expertise, funding, administrative, technical, or material support was received.

Declaration of AI and AI-assisted Technologies in the Writing Process: The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation of this manuscript.

 doi:10.20944/preprints202604.0857.v1

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