The Impact of Hyperglycemia on Lung Cancer

Chen Xi

Affiliated Beijing Chaoyang Hospital of Capital Medical University, Beijing, 100024, China

Abstract: Within the last years, hyperglycemia, a major characteristic of the metabolic syndrome, and metabolic syndrome themselves, have been shown to influence the initiation, progression, and metastasis of lung cancer, and the response to treatment of lung cancer. In this article, the authors aim to explore the epidemiological relationship between hyperglycemia and lung cancer from both directions. The authors systematically review the possible mechanisms of this relationship, including metabolic reprogramming, activation of oncogenes, the glycemic influence of hyperglycemia, the tumor (and cancer) microenvironment, and oxidative stress. Clinically, hyperglycemia seems to have a predictive role in the prognosis and treatment response in lung cancer, and complications from the disease. Targeted therapies and immune checkpoint inhibitors may induce hyperglycemia, making the treatment of lung cancer even more challenging. Some studies in the lung cancer and diabetes literature demonstrate that controlling hyperglycemia may control tumor growth, while \antitumor treatments,\ including metformin, show that controlling hyperglycemia may control tumor growth. Additionally, the use of antioxidants may control the hyperglycemia that is contributing to the lung cancer progression. To develop more individualized care, the integration of diabetes and lung cancer care is critical, from direct patient care to research.

Keywords: Hyperglycemia; Lung cancer; Metabolic reprogramming; Oxidative stress; Tumor microenvironment; Metformin; Immune checkpoint Inhibitors; Glycemic control

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1. Introduction

Hyperglycemia, as one of the typical signs of the metabolic syndrome, is an important factor that can shape the outcome of different chronic conditions, cancer being one of them. Lung cancer is one of the most common and fatal malignancies in the world, and it presents a significant therapeutic challenge [1].

Hyperglycemia being common in patients with lung cancer is a condition that is not considered much in clinical practice. A growing body of clinical trials and fundamental research evidence has demonstrated a close association between hyperglycemia and the occurrence, progression and response to treatment of lung cancer [2].

The unfavorable prognosis, decreased treatment efficacy, and increased number of complications during treatment are linked to poor glycemic control in lung cancer patients [1]. This association goes beyond similar epidemiological risk factors, such as obesity and smoking, to complex molecular pathways consisting of metabolic reprogramming, oxidative stress, and immune microenvironment remodeling [3–5].

It is of immense theoretical and clinical significance to have a multi-faceted insight into the effects of hyperglycemia on lung cancer. It can help in a better risk stratification, better treatment plans, and a better clinical outcome of patients with lung cancer.

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About the Author

Chen Xi (2004-), female, Han nationality, Hebei Province, no specific position/title, high school degree, Affiliated Beijing Chaoyang Hospital of Capital Medical University, specializing in clinical medicine.

2. Bidirectionality in Epidemiology

Hyperglycemia is linked to lung cancer, and vice versa. Hyperglycemia is also an epidemiologically recognized lung cancer risk factor [6], a prospective cohort study identified a nonlinear positive correlation between metabolic syndrome components (HDL-C, waist circumference, glycated hemoglobin) and lung cancer risk which was observed to increase with female patient and smoking status, suggesting the necessity to include metabolic status in primary prevention and high-risk population screening [7] On the other hand, hyperglycemia may be caused by lung cancer and its syndromes, thoracic tumours, in particular bronchial carcinoid and small cell lung cancer, are the most frequent cause of ectopic ACTH syndrome (EAS), with 77 percent of patients with ectopic ACTH syndrome developing new-onset or progressive hyperglycemia during active disease [8]. The problem of glucose metabolism among patients with cancer is both hyperglycemia and hypoglycemia, although the former is more common; the clinical presentation depends on the cancer type and age [6]. PET research also shows tumor-specific variations in glucose dependence: hyperglycemia has a greater effect on glucose uptake in breast cancer than in lung cancer, showing different levels of metabolic dependence on different types of tumors [9]. These complications demand an in-depth analysis of the glucose metabolism among lung cancer patients to maximize personalized therapy and enhance clinical outcomes.

3. Molecular Mechanisms of Hyperglycemia in Lung Cancer

(1) Metabolic reprogramming (warburg effect)

The increased aerobic glycolysis, also known as the Warburg effect, is one of the typical features of malignant tumor cell energy metabolism. Cancer cells are selective in their use of glycolysis to quickly produce energy and biosynthetic precursors even in normoxic conditions, thus promoting their uncontrolled growth [10, 11].

When subjected to the conditions of high glucose, the expression of succinate dehydrogenase 5 (SDH5) is suppressed in lung cancer cells, which causes mitochondrial dysfunction and consequential reactive oxygen species (ROS) build-up. This then stabilizes the hypoxia-inducible factor-1alpha (HIF-1A) [12]. The HIF-1α activation increases the expression of genes associated with glycolysis, promoting aerobic glycolysis and strengthening the Warburg effect. This metabolic rearrangement triggers reorganization of cancer cell metabolism: increased glucose concentrations deactivate mitochondrial oxidative phosphorylation and boost glycolytic flux, which furnishes enough energy to sustain cancer cell proliferation and possibly to cause a more invasive phenotype [3].

(2) Hyperglycemia activates oncogenic signaling pathways

PD-L1 expression has been demonstrated to be enhanced by tobacco-induced hyperglycemia in cancer cells in a paracrine pathway that involves tumor-associated macrophages (TAMs) and the IGF2/IR/NPM1 pathway to facilitate immune evasion and tumor progression [4]. Hyperglycemic environment, in particular, increases the glucose uptake in TAMs through upregulation of GLUT1 and GLUT3 transporters, which results in transcriptional upregulation of insulin-like growth factor 2 (IGF2). Secreted IGF2 binds to insulin receptors (IR) on lung cancer cells in a paracrine fashion, which facilitates their nuclear translocation. In the nucleus, IR co-activates the promoter of CD274 in association with nucleolar phosphoprotein NPM1, which causes the expression of PD-L1 to increase and may help the cell to evade the immune system [4].

Moreover, hyperglycemia also has the potential to promote malignant progression by stimulating important oncogenic signaling pathways. As an example, hyperglycemia enhances the tumor progression caused by oncogenic K-Ras through the upregulation of the glucose transporter Glut1 (Slc2a1) to enrich bronchial alveolar stem cells (BASCs) at the bronchioalveolar junction- a population that is suggested to be the tumor-initiating cells [13].

The RCS formed during hyperglycemia are subjected to non-enzymatic reactions with cellular macromolecules

like proteins and lipids, giving rise to the evolution of advanced glycation endpoint products (AGEs). AGEs interaction with their receptor (RAGE) triggers pro-inflammatory and pro-survival downstream signaling cascades, such as nuclear factor κB (NF-kB) and consequently stimulates tumor growth, invasion, and metastasis [14].

Moreover, hyperglycemia has also been suggested to facilitate the progression and migration of gastric cancer through activation of Pin1/BRD4 axis [15]. This observation indicates that Pin1/BRD4 pathway can also significantly contribute to hyperglycemia-enhanced lung cancer progression, but additional research in lung cancer models is justified.

(3) Hyperglycemia promotes lung cancer metastasis

1) Hyperglycemia directly stimulates EMT

Hyperglycemia promotes epithelial-mesenchymal transition (EMT) in lung cancer cells, a process that increases tumor cell migration and ability to invade other tissues. A549 and H1299 lung cancer cell lines exposed to high-glucose concentrations showed increased invasion and migration capacity. This was also correlated with decreased levels of the epithelial marker E-cadherin, and increased levels of the mesenchymal markers N-cadherin, vimentin and Snail. Hyperglycemia activates members of the Rho-GTPase family (specifically RhoA, Rac1 and Cdc42) and their downstream effector p-PAK1, leading to actin Cytoskeletal remodeling and the formation of stress fibers, which enhances cell migration [16].

2) Hyperglycemia affects the tumor microenvironment

Hyperglycemia modulates the tumor microenvironment by enhancing endothelial cell (EC) adhesiveness, facilitating tumor cell adhesion and transendothelial migration. von Willebrand factor (vWF) is a key mediator in this process, as hyperglycemia-induced oxidative stress in ECs upregulates vWF expression via increased GATA1 activity [5]. Short-term hyperglycemia increases P-selectin expression and transiently elongates the endothelial glycocalyx, enhancing lung cancer cell adhesion [17]. In contrast, chronic hyperglycemia shortens the glycocalyx and upregulates E-selectin and ICAM-1, further promoting abnormal tumor-endothelial adhesion [17, 18].

At the molecular level, hyperglycemia enhances VEGF signaling, increasing ROS production and activating transglutaminase 2 (TGase2) in pulmonary microvascular ECs [19]. This promotes disassembly of the VE-cadherin complex, leading to vascular leakage and creating pathways for tumor cell extravasation [20, 21]. Notably, both midazolam (via GABA_A receptor activation) and insulin (via ROS-independent pathways) prevent vascular leakage by inhibiting VEGF-induced TGase2 activation, effectively suppressing tumor lung metastasis in hyperglycemic mouse models [20, 21].

(4) The core role of oxidative stress

Acute hyperglycemia has been shown to increase markedly levels of γ-H2AX, a marker of DNA double-strand breaks, in lung tissue (in obese animal models), suggesting that hyperglycemia itself contributes directly to genomic instability [22].

Systemic and local oxidative stress caused by hyperglycemia represents a key mechanistic factor linking diabetes to the metastasis of malignancies [5]. In diabetic mouse models, plasma lipid peroxide levels increase and directly promote tumor cell proliferation. Importantly, PEG-catalase treatment that specifically scavenges hydrogen peroxide abolishes tumor growth and metastasis in diabetic mouse models [23].

Hyperglycemia and lung cancer have common oncogenic signaling pathways triggered by oxidative stress. Application of such approaches also aided differentiation of the relative features of hyperglycemia and oxidative stress in pathogenesis, as they were shown to activate overlapping pathways (e.g., PI3K/Akt/mTOR and insulin-like growth factor-1 receptor (IGF-1R)), resulting in tumor cell survival [2, 24]. Moreover, the nuclear factor E2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1) oxidative stress response pathway—a key regulator

of cellular antioxidant defense—is often deregulated under hyperglycemic and oxidative conditions, which may represent an attractive therapeutic intervention point [24].

4. Impact of Hyperglycemia on Lung Cancer Treatment Outcomes

(1) Poor prognosis

Hyperglycemia has also been found to be an independent predictor of poor outcome in lung cancer patients, where persistent hyperglycemia has always been linked to poor clinical outcomes. An analysis of patients with non-small cell lung cancer (NSCLC) showed that fasting blood glucose levels ≥126 mg/dl is an independent adverse prognostic factor of overall survival that increases all-cause mortality risk by 69% [25]. In a second study, which concentrated on patients with stage III NSCLC, any blood glucose level 130mg/dL and above during treatment was connected to a trend of worse loco-regional control (LRC) [26]. Further study of 59 patients with limited-stage small cell lung cancer (SCLC) receiving curative radiotherapy in a retrospective study also indicated that chronic hyperglycemia, indicated by increased HbA1c levels, is a major and independent risk factor of high local recurrence and low local recurrence-free survival in both limited-stage patients of SCLC and NSCLC receiving curative radiotherapy [27].

Randomized trials that have been carried out historically into the use of intravenous hyperalimentation (IVH) as an adjunct to SCLC treatment have also determined that IVH has no survival advantage. Rather, it predisposes risks associated with the treatment causing complications like hyperglycemia and infections [28]. These results highlight that good glycemic control is one of the factors that can enhance the prognosis of patients with lung cancer.

However, the existing findings on the association of hyperglycemia with the prognosis of lung cancer are inconclusive. These differences may be related to several factors, among them heterogeneity of the study population (e.g., diabetic status, cancer stage), the measurement of glucose (fasting glucose, random glucose, or glycated hemoglobin), the extent of adjustment of confounding variables such as obesity, smoking and other comorbidities [25, 26, 29].

(2) Poorer treatment efficacy and higher rates of complications

Retrospective studies have shown that patients with lung cancer and poor glycemic control have decreased treatment efficacy and increased rates of complications [1]. Hyperglycemia in a univariate analysis of 242 consecutive patients undergoing pneumonectomy due to lung cancer was significantly related to increasing the risk of bronchopleural fistula (BPF) ($p = 0.003$) [30].

Type 2 diabetes mellitus (T2DM) in patients may be characterized by significant changes in blood glucose levels, dysfunction of the metabolism, and impaired immunity, which not only predisposes to malignancy but also leads to poor response to chemotherapy. Hyperglycemia may cause systemic inflammation that can lead to this process. Among the patients with T2DM and lung cancer, higher blood glucose variability during chemotherapy has been associated with higher blood concentrations of the inflammatory cytokines TNF-A and IL-6, which may reduce chemotherapy effects and cause more adverse reactions [31]. Further evidence indicates that impaired glucose tolerance (e.g., HbA1c ≥ 5.8%) is independent risk factor of cytotoxic chemotherapy-induced lung injury in lung cancer patients with comorbid interstitial lung disease (ILD), a mechanism that may be due to increased advanced glycation end products (AGEs) due to hyperglycemia [32].

A retrospective study has demonstrated in the immunotherapy setting that patients who were already advanced in cancer and diabetic-indicating chronic hyperglycemia-experienced considerably shorter overall and progression-free survival with immune checkpoint inhibitors, indicating that hyperglycemia can possibly counteract the effect of immunotherapeutic agents [33].

The findings underscore the essential role of glycemic control in maximizing treatment outcomes of lung cancer in all treatment modalities.

5. Drugs May Cause Hyperglycemia

(1) Targeted therapies

Ceritinib and lorlatinib are examples of anaplastic lymphoma kinase (ALK) inhibitors used in the treatment of non-small cell lung cancer (NSCLC) that is ALK-positive. In the year 2019, an instance of potential hyperglycemia caused by ceritinib was reported and this necessitates close observation of glucose especially in the initial two weeks of therapy [34]. This was followed by a disproportionality analysis of the Japanese Adverse Drug Event Report database which found that ceritinib was linked to a much greater incidence of hyperglycemia in comparison to crizotinib and alectinib [35]. A recent case report of diabetic ketoacidosis (DKA) was described in a 65-year-old male patient who had ALK-positive lung cancer and pre-existing type 2 diabetes mellitus during the change in therapy to lorlatinib treatment [36].

EGFR tyrosine kinase inhibitors (TKIs) are also first-line agents of NSCLC. Third-generation EGFR TKIs like osimertinib (AZD9291) and rociletinib are effective drugs to overcome resistance mediated by the T790M mutation, but have different adverse effect profiles [37]. Covalent inhibitors such as osimertinib have been reported to cause hyperglycemia, probably as a result of off target action [38]. Likewise, hyperglycemia that can be induced by rosulatinib usually appears during the first three weeks of therapy and can be treated either by reducing the dose or by oral hypoglycemic agents or a combination of both [39].

(2) Immune checkpoint inhibitors

Development of autoimmune type 1 diabetes mellitus (T1DM) has been reported with immune checkpoint inhibitors (ICIs), including pembrolizumab [40], atezolizumab [41], and serplulimab [42]. This class of immune-related adverse event results in absolute deficiency of insulin and can quickly advance to diabetic ketoacidosis (DKA). These cases highlight the importance of frequent monitoring blood glucose during ICI therapy even in a patient without history of diabetes to allow for early recognition and intervention.

(3) Other agents

Anamorelin, a novel ghrelin receptor agonist used to manage cancer cachexia [43, 44], has also been reported to cause hyperglycemic adverse events. This further emphasizes the need for clinicians to continuously monitor and assess blood glucose levels in lung cancer patients receiving these agents and to be prepared to intervene when necessary.

6. Conclusion

Overall, there exists a multifaceted, bi-directional interplay between hyperglycemia and lung cancer at molecular, cellular and clinical levels. Hyperglycemia mechanistically promotes lung cancer progression by rewiring tumor metabolism, activating oncogenic signaling pathways, prompting oxidative stress and remodeling the tumor microenvironment. In clinical practice, hyperglycemia has consistently been linked with poor responses to treatment, increased complication rates, and worse survival. Compounding the problem, several effective anticancer therapies can themselves cause severe hyperglycemia, leading to an intricate therapeutic dilemma requiring careful clinical management.

This data provides compelling evidence to consider glycemic control in the total care of people with lung cancer. Increased mechanistic knowledge concerning the biochemical pathways impinging on these commonalities

between hyperglycemia and lung cancer will be essential moving forward, along with prospective clinical studies regarding adjunctive glucose-lowering agents in the oncology setting. The management of this clinical challenge, therefore, depends on strong cross-disciplinary collaboration between oncology and endocrinology-–a collaboration that is likely to be in the best interest of patients with lung cancer and simultaneous abnormalities of glucose metabolism.

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