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The Impact of Hyperinsulinemia and Hyperglycemia on Cancer Risk and Progression in Obese Diabetics

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ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) are metabolic disorders that are increasingly prevalent worldwide and frequently co-exist, forming a syndemic with cancer. Central to the pathological link between these conditions are persistent hyperinsulinemia and hyperglycemia hallmarks of insulin resistance. Chronic hyperinsulinemia stimulates mitogenic signaling pathways, reduces apoptosis, and increases bioavailability of insulin-like growth factors (IGFs), all of which contribute to tumor initiation and progression. Concurrently, hyperglycemia fosters a pro-tumorigenic environment through oxidative stress, inflammation, and enhanced glucose availability to cancer cells, which depend heavily on glycolysis. Together, these metabolic disturbances synergistically promote oncogenesis, particularly in tissues sensitive to insulin and glucose, including the breast, colon, pancreas, and liver. This review explores the mechanistic underpinnings and epidemiological evidence linking hyperinsulinemia and hyperglycemia to cancer risk and progression in obese diabetic individuals. It also highlights emerging therapeutic interventions aimed at modulating insulin and glucose levels as a strategy to mitigate cancer burden in this high-risk population.

Keywords: Hyperinsulinemia, Hyperglycemia, Obesity, Type 2 Diabetes Mellitus, Cancer Risk, Tumor Progression, Insulin Resistance, IGF-1, Metabolic Reprogramming, Inflammation

INTRODUCTION

The escalating prevalence of obesity and type 2 diabetes mellitus (T2DM) has emerged as a major public health crisis worldwide. Both conditions are intricately linked and are collectively referred to as components of the metabolic syndrome, a cluster of metabolic abnormalities that include central obesity, hyperglycemia, hypertension, and dyslipidemia[1–4]. While these disorders are well recognized for their roles in increasing the risk of cardiovascular diseases, accumulating evidence has demonstrated their significant contribution to cancer risk, progression, and overall mortality[5–7]. Numerous epidemiological studies have identified a higher incidence of several cancer types, such as colorectal, breast, endometrial, pancreatic, liver, and kidney cancers, in individuals with obesity and/or T2DM[8–10]. This correlation is not merely coincidental but is grounded in shared biological mechanisms that promote tumorigenesis.

Two key metabolic abnormalities seen in both obesity and T2DM, hyperinsulinemia and hyperglycemia, play central roles in creating a systemic environment conducive to cancer development[11, 12]. Hyperinsulinemia, often an early feature of insulin resistance, results from the pancreas compensating for the reduced insulin sensitivity of peripheral tissues. Over time, this compensatory mechanism leads to elevated circulating insulin levels, which have profound mitogenic and anti-apoptotic effects through activation of insulin and insulin-like growth factor (IGF) pathways[13–16]. Hyperglycemia, a hallmark of T2DM, exacerbates this scenario by providing an abundant energy source for rapidly dividing tumor cells, while also generating reactive oxygen species (ROS) and advanced glycation end-products (AGEs) that contribute to DNA damage, chronic inflammation, and immune evasion [17].

The adipose tissue in obese individuals functions not just as a fat storage depot but as an active endocrine organ. It secretes a variety of adipokines and cytokines, many of which have pro-inflammatory or tumor-promoting properties[6, 18–20]. Alterations in adipokine secretion, such as increased leptin and reduced adiponectin levels,

further enhance cancer risk. Chronic low-grade inflammation, another common feature of both obesity and T2DM, creates a permissive microenvironment for malignant transformation and progression. Understanding the interplay between these metabolic disorders and cancer is critical for designing preventive and therapeutic interventions[21–23]. While lifestyle modifications such as weight loss, increased physical activity, and dietary regulation remain cornerstone strategies, there is growing interest in pharmacological agents that can modulate insulin sensitivity and glucose metabolism to reduce cancer risk. Furthermore, novel biomarkers related to hyperinsulinemia and hyperglycemia are being investigated for their potential in early cancer detection and prognosis in obese diabetic individuals.

In sum, the convergence of obesity, T2DM, and cancer represents a complex yet increasingly recognized public health concern. The mechanistic links involving hyperinsulinemia and hyperglycemia offer compelling targets for intervention. Future research focused on dissecting these pathways will be crucial for mitigating cancer risk and improving clinical outcomes in populations affected by metabolic disorders.

2. Hyperinsulinemia and Cancer Risk

Hyperinsulinemia, defined as an abnormally high level of insulin in the blood, is a hallmark of early type 2 diabetes and insulin resistance, particularly in obese individuals[4, 24]. This compensatory response by pancreatic β-cells aims to overcome decreased insulin sensitivity in peripheral tissues, particularly muscle and adipose tissue. However, prolonged hyperinsulinemia is not a benign physiological adaptation; it plays a direct and indirect role in promoting oncogenesis[25, 26]. One of the primary ways hyperinsulinemia contributes to cancer risk is through persistent activation of the insulin receptor (IR) and its downstream signaling pathways. When insulin binds to IR on the surface of cells, it activates intracellular cascades such as the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway and the mitogen-activated protein kinase (MAPK) pathway. These pathways regulate cellular processes such as growth, proliferation, survival, and metabolism—key components of cancer biology[27, 28]. Chronic stimulation of these pathways can lead to uncontrolled cell division, inhibition of apoptosis (programmed cell death), and enhanced cellular transformation.

Furthermore, insulin exerts its mitogenic effects through interaction with the insulin-like growth factor (IGF) system. Hyperinsulinemia suppresses the hepatic production of IGF-binding proteins, particularly IGFBP-1 and IGFBP-2, which normally regulate the availability of IGF-1. Reduced levels of these binding proteins result in increased circulating free IGF-1, a potent mitogen with strong anti-apoptotic and pro-angiogenic properties[28, 29]. IGF-1 activates the IGF-1 receptor (IGF-1R), which further amplifies the PI3K/Akt and MAPK signaling cascades. This dual activation via insulin and IGF-1 represents a powerful oncogenic stimulus, particularly in insulin-sensitive tissues.

Epidemiological studies have consistently shown that individuals with elevated fasting insulin levels are at increased risk for several types of cancer, including colorectal, pancreatic, breast, and endometrial cancers[30]. For example, hyperinsulinemia has been associated with a two- to threefold increase in colorectal cancer risk, likely due to insulin and IGF-1 promoting the proliferation of colonic epithelial cells. In postmenopausal women, high insulin levels have been linked to an increased risk of estrogen receptor-positive breast cancer, possibly due to crosstalk between insulin signaling and estrogen pathways[31–34]. Experimental models support these observations. In vitro studies demonstrate that insulin and IGF-1 promote the growth of cancer cell lines, while in vivo models show that hyperinsulinemia enhances tumor growth and metastasis[35, 36]. Moreover, pharmacological or genetic attenuation of insulin signaling in animal models leads to reduced tumor incidence and growth, highlighting the therapeutic potential of targeting this axis.

Hyperinsulinemia acts as a key metabolic driver of cancer risk through its ability to stimulate mitogenic and survival pathways, reduce the availability of IGF-binding proteins, and enhance the activity of IGF-1. These effects collectively create a tumor-promoting environment, particularly in individuals with obesity and insulin resistance. Addressing hyperinsulinemia through lifestyle changes or pharmacological interventions, such as insulin sensitizers (e.g., metformin), may reduce cancer risk and improve outcomes in this high-risk population.

3. Hyperglycemia and Tumor Metabolism

Hyperglycemia, defined as elevated blood glucose levels, is a central feature of uncontrolled T2DM and has profound implications for cancer biology. Malignant cells are known to exhibit altered metabolic preferences a phenomenon described as the "Warburg effect" whereby they rely on glycolysis for ATP production, even in the presence of oxygen[37]. This metabolic shift allows for rapid energy production and accumulation of biosynthetic intermediates necessary for cell growth and proliferation. In the context of hyperglycemia, the abundance of glucose serves as a rich energy source that cancer cells can exploit to fuel their growth[37]. The facilitation of glucose uptake is achieved by the overexpression of glucose transporters (GLUTs), particularly GLUT1, on the surface of cancer cells[38]. Once inside the cell, glucose is rapidly metabolized through glycolysis, with the resulting pyruvate often being converted into lactate rather than entering the mitochondrial oxidative phosphorylation pathway. This shift not only supports ATP production but also contributes to acidification of the tumor microenvironment, which favors invasion and metastasis[38].

Hyperglycemia also increases the production of reactive oxygen species (ROS), which can damage DNA, proteins, and lipids[39, 40]. This oxidative stress promotes genomic instability, a hallmark of cancer. Moreover, ROS can activate pro-survival signaling pathways such as NF-κB and HIF-1α, which support tumor cell survival under adverse conditions. Chronic oxidative stress in hyperglycemic states thereby enhances both the initiation and progression of cancer[38].

Another significant contributor to cancer pathophysiology in hyperglycemia is the formation of advanced glycation end-products (AGEs)[41]. These are formed when glucose reacts non-enzymatically with proteins and lipids, leading to their structural modification and functional impairment [42]. AGEs bind to their receptor, RAGE, present on various cell types including endothelial and immune cells[43]. RAGE activation triggers downstream signaling cascades that promote inflammation, fibrosis, and cellular proliferation.[43] The AGE-RAGE axis has been implicated in creating a pro-tumorigenic environment by enhancing angiogenesis, impairing immune surveillance, and promoting epithelial-mesenchymal transition (EMT), a key step in metastasis.

Inflammation further amplifies these effects. Hyperglycemia is associated with elevated levels of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)[44]. These cytokines promote tumor progression by activating oncogenic pathways and altering the tumor microenvironment. For instance, IL-6 activates STAT3 signaling, which enhances tumor cell proliferation, survival, and angiogenesis. TNF-α can induce EMT and facilitate tumor cell migration and invasion[44]. Additionally, hyperglycemia impairs immune function, thereby compromising the body's ability to detect and eliminate malignant cells. Chronic high glucose levels can inhibit cytotoxic T-cell activity and promote the expansion of immunosuppressive cell populations such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)[45]. This immunosuppressive environment further enables tumor growth and progression.

Hyperglycemia promotes tumor development through multiple interconnected mechanisms: providing metabolic fuel, inducing oxidative stress and DNA damage, activating the AGE-RAGE axis, and fostering chronic inflammation and immune dysfunction[46]. These effects are particularly pronounced in individuals with poorly controlled diabetes, underscoring the importance of glycemic control not only for metabolic health but also as a potential strategy for cancer prevention and management[46]. Therapeutic interventions aimed at normalizing glucose levels may thus represent a viable approach to reducing cancer risk in diabetic patients.

4. Synergistic Effects of Hyperinsulinemia and Hyperglycemia

The simultaneous presence of hyperinsulinemia and hyperglycemia in obese individuals with type 2 diabetes mellitus (T2DM) creates a biologically aggressive environment that promotes carcinogenesis more significantly than either abnormality alone[47]. Hyperinsulinemia, which results from insulin resistance, leads to elevated circulating insulin levels that exert mitogenic and anti-apoptotic effects through activation of the insulin and insulin-like growth factor (IGF) signaling pathways[48]. These pathways stimulate downstream effectors such as PI3K/Akt and MAPK, which promote tumor cell survival, proliferation, and angiogenesis. At the same time, hyperinsulinemia increases the expression of glucose transporters (especially GLUT1 and GLUT3) on the surface of tumor cells, facilitating enhanced glucose uptake[48].

Hyperglycemia, a hallmark of diabetes, provides the necessary substrate for the increased metabolic demands of rapidly proliferating tumor cells[49–51]. Through the Warburg effect a metabolic reprogramming where cancer cells rely heavily on aerobic glycolysis even in the presence of oxygen tumor cells utilize excess glucose to generate ATP and biosynthetic intermediates required for nucleic acid, protein, and lipid synthesis. The chronic availability of glucose thus fuels unrestrained cell division and tumor expansion.

Moreover, both hyperinsulinemia and hyperglycemia exacerbate systemic inflammation. Chronic low-grade inflammation is a common feature in obesity and T2DM, characterized by elevated levels of cytokines such as TNF-α, IL-6, and CRP[52, 53]. These inflammatory mediators activate signaling cascades like NF-κB and STAT3, which are known to induce tumor-promoting genes and inhibit apoptosis. Obesity further amplifies this inflammatory state through the dysregulated secretion of adipokines. Leptin, a pro-inflammatory adipokine upregulated in obesity, promotes angiogenesis, cell proliferation, and immune evasion in tumors[54]. Conversely, adiponectin, which possesses anti-inflammatory and anti-proliferative properties, is typically reduced in obese diabetics, removing a protective barrier against cancer development.

The metabolic triad of hyperinsulinemia, hyperglycemia, and obesity-induced inflammation works synergistically to create a pro-tumorigenic environment. These factors reinforce each other in a vicious cycle. For example, inflammation worsens insulin resistance, leading to further increases in insulin and glucose levels[52, 55, 56]. Tumors, in turn, create a microenvironment that sustains inflammatory and angiogenic signaling, further complicating disease control. The presence of these concurrent metabolic insults in obese diabetics not only increases the risk of cancer initiation but also drives more aggressive tumor growth and metastasis.

This synergy also presents significant challenges for clinical management. Cancer therapies may be less effective in patients with poorly controlled diabetes due to altered drug metabolism, increased toxicity, and reduced

immune response[57–59]. Additionally, standard chemotherapeutic agents may further disrupt glucose metabolism, complicating glycemic control. These insights underscore the importance of comprehensive metabolic monitoring and intervention in cancer patients with coexisting T2DM and obesity[60]. Addressing the synergistic effects of hyperinsulinemia and hyperglycemia is not just a metabolic concern—it is critical for effective oncologic treatment and improved patient survival.

5. Clinical and Epidemiological Evidence

An expanding body of clinical and epidemiological evidence strongly supports the association between metabolic dysregulation, particularly hyperinsulinemia, hyperglycemia, and insulin resistance, and increased cancer risk and progression[61]. Numerous large-scale cohort studies, case-control analyses, and meta-analyses have demonstrated a higher incidence of several cancer types in individuals with type 2 diabetes mellitus (T2DM). These include cancers of the liver, pancreas, colon, breast, and endometrium[61]. The correlation is especially pronounced in patients with long-standing diabetes and poor glycemic control.

Hyperinsulinemia, a key feature of early T2DM, has emerged as a critical driver of carcinogenesis. Elevated insulin levels lead to a reduction in insulin-like growth factor-binding proteins (IGFBPs), resulting in increased bioavailability of IGF-1, a potent mitogen[62]. Epidemiological data suggest that individuals with hyperinsulinemia have nearly a twofold higher risk of colorectal and endometrial cancers[63]. Similarly, hyperglycemia, independent of insulin levels, is associated with a higher incidence of hepatocellular carcinoma and breast cancer. Chronic exposure to elevated glucose may contribute to DNA damage, oxidative stress, and inflammatory responses, all of which are conducive to malignant transformation[63]. Furthermore, the duration of diabetes and the degree of metabolic control are predictive of cancer-related outcomes. Patients with longstanding diabetes or poorly managed glycemic indices exhibit worse cancer prognoses and higher mortality rates[63]. This is attributed in part to the metabolic environment that favors tumor growth and resistance to therapy. For example, breast cancer patients with T2DM often present with larger tumors and higher-grade malignancies at diagnosis. In pancreatic cancer, diabetes has been linked to both increased risk and worse survival outcomes.

From a clinical perspective, T2DM also negatively impacts cancer treatment outcomes. Studies show that diabetic patients with cancer often experience reduced chemotherapy efficacy, increased drug toxicity, and a greater risk of complications. Hyperglycemia can impair immune function, which is critical for tumor surveillance and response to immunotherapy. Moreover, insulin resistance may interfere with the cellular uptake and metabolism of anticancer drugs, limiting their effectiveness.

Population-based studies further support the call for integrated care models that address both metabolic and oncologic health. Data from the UK Biobank, Nurses' Health Study, and other registries confirm the need for routine cancer screening in diabetic patients, especially those with high BMI and poorly controlled glucose levels[64]. In addition, ethnic and geographic disparities in metabolic disease prevalence correlate with cancer incidence, highlighting the importance of tailored public health interventions.

6. Therapeutic Implications and Future Directions

The dual burden of type 2 diabetes mellitus (T2DM) and cancer demands a strategic, integrated therapeutic approach. As evidence mounts regarding the interplay between metabolic dysregulation and tumor progression, attention has turned to therapies that address both conditions simultaneously. Among antidiabetic agents, metformin stands out as a promising dual-purpose drug. Beyond its glucose-lowering effects via inhibition of hepatic gluconeogenesis, metformin reduces circulating insulin levels and activates AMP-activated protein kinase (AMPK), a key energy sensor[65–68]. This activation downregulates the mTOR pathway, which is central to cell proliferation and survival in many cancers. Preclinical and epidemiological studies suggest that metformin use is associated with reduced incidence and improved prognosis in cancers such as breast, colorectal, and liver.

Thiazolidinediones (TZDs), such as pioglitazone, are PPAR-γ agonists that improve insulin sensitivity in peripheral tissues[64]. While their use in cancer therapy is still under investigation, they have shown potential in inhibiting tumor cell growth and inducing apoptosis in certain contexts. Similarly, GLP-1 receptor agonists and DPP-4 inhibitors, which modulate the incretin system to regulate insulin secretion, may hold promise in reducing inflammation and insulin resistance while exhibiting modest anticancer properties[69]. Lifestyle modification remains a cornerstone of prevention and therapeutic intervention. Dietary interventions, such as low-glycemic diets and Mediterranean-style nutrition, have demonstrated benefits in improving insulin sensitivity and reducing cancer risk markers. Regular physical activity not only improves glycemic control but also modulates immune response, reduces systemic inflammation, and may directly inhibit tumor growth[69]. Weight loss in obese patients has been shown to improve metabolic parameters and reduce cancer incidence, particularly in hormone-sensitive malignancies.

Looking ahead, the future of managing patients with comorbid diabetes and cancer lies in precision medicine. Advances in genomics, metabolomics, and systems biology are paving the way for individualized risk assessment and therapy. For example, profiling tumor metabolism in diabetic patients could guide the selection of metabolic adjuvants that enhance the efficacy of standard cancer therapies. Furthermore, combination therapies targeting

insulin/IGF signaling alongside oncogenic pathways such as PI3K/Akt or mTOR could provide synergistic anticancer effects. There is also a need for integrated care models that unite oncology and endocrinology. Such collaboration would facilitate more effective monitoring of metabolic health during cancer treatment, enabling timely adjustments to therapy that optimize both glycemic control and tumor response. Clinical trials specifically designed to evaluate antidiabetic drugs in cancer patients, as well as cancer therapies in diabetic cohorts, are essential to fill current knowledge gaps.

CONCLUSION

Hyperinsulinemia and hyperglycemia are critical drivers of cancer risk and progression in obese diabetic individuals. Their combined effects foster an environment characterized by unregulated cell growth, resistance to apoptosis, and enhanced metastatic potential. As the incidence of obesity and T2DM continues to rise globally, addressing these metabolic disturbances becomes increasingly urgent. Integrating cancer prevention strategies into diabetes care and exploring metabolic therapies with anticancer potential may offer significant benefits. A multidisciplinary approach that bridges metabolic disease management with oncologic vigilance is essential to curb the rising tide of obesity-associated cancers.

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