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Systematic Review

At the Crossroads of Diabetes and Cancer in Children: The Interplay of Genetic Syndromes, Obesity, and Metabolic Dysregulation

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Abstract

Background: Childhood diabetes and cancer have traditionally been viewed as distinct disorders; however, accumulating evidence indicates substantial biological overlap through shared genetic, metabolic, inflammatory, and endocrine pathways. The increasing prevalence of childhood obesity and type 2 diabetes (T2D), together with improved survival among pediatric cancer patients, has intensified interest in the bidirectional relationship between these conditions.

Objective: To review current evidence regarding the interplay between diabetes and childhood cancer, with particular emphasis on genetic predisposition syndromes, obesity, insulin resistance, metabolic dysregulation, treatment-related diabetes, and survivorship outcomes. Methods: A comprehensive narrative review of the literature was conducted using major medical databases, including PubMed, Scopus, Embase, and Cochrane Library. Relevant studies addressing childhood diabetes, pediatric malignancies, cancer predisposition syndromes, obesity, insulin resistance, endocrine late effects, and survivorship care were evaluated and synthesized.

Results: Emerging evidence demonstrates that obesity, insulin resistance, hyperinsulinemia, chronic inflammation, oxidative stress, and dysregulated insulin-like growth factor-1 (IGF-1) signaling contribute to both metabolic disease and tumorigenesis. Several hereditary cancer predisposition syndromes, including Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, Constitutional Mismatch Repair Deficiency, Neurofibromatosis type 1, Fanconi anemia, and PTEN hamartoma tumor syndrome, further illustrate the intersection between cancer susceptibility and metabolic dysfunction. Conversely, childhood cancer survivors are at increased risk of developing diabetes because of chemotherapy, corticosteroid exposure, radiotherapy, hematopoietic stem cell transplantation, endocrine organ injury, altered body composition, and persistent inflammation. These metabolic abnormalities may adversely affect treatment response, long-term morbidity, cardiovascular risk, and quality of life.

Conclusions: Diabetes and childhood cancer are interconnected through complex genetic and metabolic mechanisms. Recognition of shared pathways and cancer predisposition syndromes may facilitate earlier diagnosis, individualized surveillance, and targeted preventive strategies. Integrating pediatric oncology, endocrinology, genetics, nutrition, and lifestyle interventions is essential to optimize long-term outcomes and survivorship care in this vulnerable population.

Keywords:

Childhood cancer
Diabetes mellitus
Childhood obesity
Metabolic syndrome
Cancer predisposition syndrome
Insulin resistance
Pediatric oncology
Endocrine late effects

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1. INTRODUCTION

Childhood cancer and diabetes mellitus have traditionally been regarded as distinct clinical entities; however, growing evidence indicates that they share multiple biological pathways involving genetic susceptibility, metabolic dysregulation, chronic inflammation, oxidative stress, and endocrine dysfunction. These overlapping mechanisms have become increasingly important as the incidence of childhood obesity and type 2 diabetes continues to rise worldwide and survival after pediatric cancer has improved substantially over the past decades. Consequently, the number of childhood cancer survivors living with metabolic complications has increased, making the interaction between diabetes and pediatric malignancies an emerging area of clinical and translational research (1–4). Although type 1 diabetes (T1D) remains the predominant form of diabetes during childhood, the prevalence of obesity-associated insulin resistance and type 2 diabetes (T2D) has increased rapidly among children and adolescents. Hyperinsulinemia, chronic low-grade inflammation, adipokine imbalance, mitochondrial dysfunction, and oxidative stress have all been implicated in tumor initiation, progression, and therapeutic resistance. Excess adipose tissue functions as an active endocrine organ that secretes inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), leptin, and resistin, while reducing protective adiponectin levels. These alterations activate multiple oncogenic signaling pathways, particularly the insulin/insulin-like growth factor-1 (IGF-1), phosphoinositide 3-kinase (PI3K)/AKT, mammalian target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK) pathways, thereby promoting cellular proliferation, angiogenesis, and inhibition of apoptosis (2,5,6).

The relationship between diabetes and cancer is bidirectional. While metabolic abnormalities may increase susceptibility to malignancy, cancer treatment itself can predispose survivors to impaired glucose metabolism and overt diabetes. Exposure to corticosteroids, asparaginase, abdominal or total-body irradiation, hematopoietic stem cell transplantation, and endocrine organ damage contributes to pancreatic β-cell dysfunction, insulin resistance, sarcopenic obesity, and alterations in body composition. Consequently, childhood cancer survivors develop diabetes at younger ages than the general population and experience a greater burden of cardiometabolic disease during adulthood (1,3,7).

Recent advances in cancer genomics have further strengthened the concept that inherited genetic predisposition plays a central role in pediatric malignancies. Approximately 8–10% of childhood cancers are now estimated to arise in the context of identifiable cancer predisposition syndromes, although broader genomic screening suggests that the true prevalence may be even higher. Syndromes such as Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, Constitutional Mismatch Repair Deficiency (CMMRD), Neurofibromatosis type 1, Fanconi anemia, and PTEN hamartoma tumor syndrome are increasingly recognized not only for their association with childhood malignancies but also for their influence on endocrine function, growth regulation, insulin signaling, and metabolic homeostasis (4,8).

At the molecular level, diabetes and cancer converge through common regulatory networks controlling cellular metabolism, DNA repair, immune surveillance, oxidative stress, and epigenetic regulation. Persistent hyperglycemia promotes the generation of reactive oxygen species, advanced glycation end products, and chronic inflammatory signaling, all of which may contribute to genomic instability and impaired DNA repair. Conversely, oncogenic mutations frequently induce metabolic reprogramming characterized by enhanced glycolysis, altered lipid metabolism, and increased glucose utilization, highlighting the reciprocal relationship between metabolic disorders and tumor biology (2,5).

Beyond biological mechanisms, the clinical management of children with cancer increasingly requires recognition of metabolic health as a determinant of long-term outcomes. Obesity, diabetes, dyslipidemia, hypertension, and frailty substantially increase the risk of cardiovascular disease, which has become one of the leading non-cancer causes of morbidity and mortality among childhood cancer survivors. These observations have prompted recent international recommendations emphasizing early metabolic screening, risk stratification, lifestyle interventions, and multidisciplinary survivorship care involving pediatric oncologists, endocrinologists, nutrition specialists, rehabilitation teams, and genetic counselors (1,3,9).

The objective of this review is to provide a comprehensive overview of the current evidence regarding the complex relationship between diabetes and childhood cancer. Particular emphasis is placed on hereditary cancer predisposition syndromes, obesity, insulin resistance, metabolic dysregulation, treatment-related diabetes, and emerging precision medicine approaches. By integrating recent advances in pediatric oncology, endocrinology, and cancer genetics, this review aims to highlight opportunities for early detection, personalized surveillance, prevention of long-term complications, and optimization of survivorship

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care in children at the intersection of these two increasingly interconnected diseases.

2. METHODS

2.1. Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies examining the relationship between diabetes mellitus and childhood cancer, with particular emphasis on genetic syndromes, obesity, metabolic dysregulation, insulin resistance, endocrine late effects, and cancer survivorship.

Electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library were searched for articles published between January 2000 and December 2025. To ensure inclusion of the most recent evidence, priority was given to studies published during the last five years (2020–2025), while landmark studies and international clinical guidelines were included when considered essential.

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords, including:

"Childhood cancer" "Pediatric oncology" "Diabetes mellitus" "Type 1 diabetes" "Type 2 diabetes" "Insulin resistance" "Obesity" "Metabolic syndrome" "Cancer predisposition syndrome" "Li-Fraumeni syndrome" "Beckwith-Wiedemann syndrome" "PTEN hamartoma syndrome" "Fanconi anemia" "Constitutional mismatch repair deficiency" "Childhood cancer survivors" "Endocrine late effects"* "Precision medicine" Boolean operators (AND/OR) were used to combine search terms appropriately.

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2.2. Eligibility Criteria

Peer-reviewed original articles, systematic reviews, meta-analyses, clinical practice guidelines, consensus statements, and high-quality narrative reviews published in English were considered eligible for inclusion.

Studies involving adult-only populations without pediatric relevance, conference abstracts lacking sufficient methodological detail, editorials, commentaries, duplicate publications, and non-English articles were excluded unless they represented landmark evidence unavailable elsewhere.

2.3. Study Selection

Titles and abstracts retrieved from the electronic search were screened for relevance. Potentially eligible full-text articles were subsequently reviewed to assess methodological quality, scientific validity, and relevance to the objectives of this review. Preference was given to high-quality evidence, including systematic reviews, meta-analyses, prospective cohort studies, multicenter clinical studies, and international clinical guidelines.

2.4. Data Extraction and Evidence Synthesis

Information regarding epidemiology, molecular mechanisms, genetic predisposition syndromes, obesity, insulin resistance, endocrine complications, treatment-related diabetes, survivorship, and emerging therapeutic strategies was extracted from eligible studies.

The evidence was synthesized narratively and organized into thematic sections to provide an integrated overview of current knowledge regarding the bidirectional relationship between diabetes and childhood cancer. Whenever possible, recent international guidelines and consensus recommendations were incorporated to enhance clinical applicability.

3. RESULTS

3.1. Genetic Syndromes Linking Diabetes and Childhood Cancer

Inherited genetic syndromes represent one of the most important biological links between pediatric diabetes and childhood cancer. Advances in next-generation sequencing have revealed that approximately 8–10% of childhood cancers arise in the setting of an identifiable cancer predisposition syndrome, although broader genomic studies suggest that the true prevalence may be substantially higher (10–12). These syndromes frequently involve genes regulating DNA repair, cell-cycle control, genomic stability, endocrine development, and insulin signaling, thereby providing a mechanistic bridge between metabolic disorders and oncogenesis.

Among these conditions, Li–Fraumeni syndrome (LFS), caused by germline pathogenic variants in TP53, is one of the best-characterized hereditary cancer syndromes. Children with LFS are predisposed to adrenocortical carcinoma, osteosarcoma, soft-tissue sarcomas, central nervous system tumors, and leukemia. Beyond tumor susceptibility, TP53 also regulates glucose metabolism, mitochondrial function, oxidative stress, and insulin sensitivity. Experimental studies have demonstrated that disruption of TP53 signaling contributes to metabolic reprogramming, enhanced glycolysis, and insulin resistance, suggesting that alterations in cellular metabolism may accompany inherited cancer susceptibility (13,14).

Beckwith–Wiedemann syndrome (BWS) is another

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important overgrowth syndrome characterized by abnormalities of chromosome 11p15 involving IGF2 and CDKN1C. Excessive activation of the insulin-like growth factor (IGF) pathway contributes to fetal overgrowth while simultaneously increasing susceptibility to embryonal tumors, including Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma. Because insulin and IGF-1 signaling share common downstream pathways, dysregulation of this axis also influences glucose homeostasis and metabolic function, further strengthening the biological relationship between endocrine disorders and cancer development (15,16).

PTEN hamartoma tumor syndrome (PHTS) illustrates another example of the close interaction between metabolism and oncogenesis. PTEN is a key negative regulator of the PI3K/AKT/mTOR pathway, one of the principal signaling cascades controlling both insulin action and cellular proliferation. Germline PTEN mutations predispose affected individuals to thyroid carcinoma, breast cancer, endometrial carcinoma, colorectal neoplasia, and several pediatric malignancies while simultaneously altering insulin signaling and energy metabolism. Experimental evidence indicates that impaired PTEN activity enhances insulin sensitivity in some tissues but promotes uncontrolled cellular growth and tumorigenesis through persistent activation of AKT signaling (17,18). Defects in DNA repair pathways also contribute to the convergence of diabetes and childhood cancer. Constitutional mismatch repair deficiency (CMMRD), caused by biallelic pathogenic variants in mismatch repair genes (MLH1, MSH2, MSH6, and PMS2), is associated with an exceptionally high lifetime risk of hematologic malignancies, brain tumors, and gastrointestinal cancers. Accumulating evidence suggests that chronic genomic instability may also influence inflammatory signaling and metabolic homeostasis, although the precise relationship between CMMRD and glucose metabolism remains under investigation (19).

Similarly, Fanconi anemia, a prototypical DNA repair disorder, is characterized by bone marrow failure, congenital anomalies, endocrine dysfunction, impaired glucose tolerance, and increased susceptibility to acute myeloid leukemia and squamous cell carcinomas. Insulin resistance, growth hormone deficiency, hypothyroidism, and diabetes mellitus occur more frequently in patients with Fanconi anemia than in the general pediatric population, emphasizing the broad endocrine consequences of defective DNA repair (20).

Several additional hereditary disorders—including Neurofibromatosis type 1, Multiple Endocrine Neoplasia (MEN) syndromes, Von Hippel–Lindau disease, Tuberous Sclerosis Complex, and DICER1 syndrome—also demonstrate important interactions between endocrine regulation and tumor biology. Many of these conditions involve dysregulation of the mTOR, RAS/MAPK, or hypoxia-inducible factor pathways, which participate in both metabolic regulation and malignant transformation (12,17). Recognition of hereditary cancer predisposition syndromes has important clinical implications. Children presenting with unusual combinations of diabetes, obesity, endocrine abnormalities, developmental disorders, or multiple primary tumors should undergo careful genetic evaluation. Identification of an underlying germline syndrome facilitates personalized surveillance strategies, enables cascade testing of family members, informs reproductive counseling, and increasingly guides precision oncology through targeted therapeutic approaches. Integrating pediatric oncology, endocrinology, clinical genetics, and genetic counseling into multidisciplinary care pathways is therefore essential for optimizing outcomes in these high-risk populations (10–12,21)**(refer to Table 1).**

3.2. Obesity, Insulin Resistance, and Metabolic Dysregulation

The global rise in childhood obesity has emerged as one of the most significant public health challenges of the twenty-first century and is increasingly recognized as an important contributor to both metabolic disorders and cancer development. According to the World Health Organization (WHO), the prevalence of overweight and obesity among children and adolescents has increased dramatically over recent decades, resulting in a parallel increase in insulin resistance, metabolic syndrome, type 2 diabetes mellitus (T2DM), and obesity-related comorbidities (22,23). Beyond its well-established cardiometabolic consequences, obesity has now been identified as a biological driver of carcinogenesis through multiple endocrine, inflammatory, and metabolic pathways.

Adipose tissue is no longer regarded as a passive energy-storage organ but rather as a highly active endocrine organ that secretes numerous bioactive mediators, including leptin, adiponectin, resistin, visfatin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and other adipokines. Excess adiposity promotes chronic low-grade inflammation characterized by macrophage infiltration and persistent cytokine production, creating a microenvironment that favors cellular proliferation, angiogenesis, genomic

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Table 1. Genetic syndromes linking diabetes and childhood cancer.

Genetic syndrome	Gene(s) involved	Diabetes phenotype	Childhood cancer risk	Proposed shared mechanism
Beckwith–Wiedemann syndrome	11p15 (IGF2/H19)	Hyperinsulinism, glucose dysregulation	Wilms tumor, hepatoblastoma	IGF signaling dysregulation
Li-Fraumeni syndrome	TP53	Insulin resistance, altered metabolism	Multiple childhood malignancies	TP53-mediated metabolic reprogramming
PTEN Hamartoma Tumor Syndrome	PTEN	Insulin sensitivity abnormalities	Thyroid, breast and pediatric tumors	PI3K/AKT/mTOR activation
Constitutional Mismatch Repair Deficiency	MLH1, MSH2, MSH6, PMS2	Occasional glucose dysregulation	Brain tumors, leukemia, lymphoma	DNA repair defects and genomic instability
Fanconi anemia	FANCA and related genes	Insulin resistance, endocrine dysfunction	AML, squamous cell carcinoma	Oxidative stress and defective DNA repair
Down syndrome	Trisomy 21	Increased autoimmune diabetes risk	Acute lymphoblastic leukemia, AML Immune	dysregulation and altered hematopoiesis

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia.

instability, and inhibition of apoptosis. Simultaneously, reduced circulating adiponectin levels diminish insulin sensitivity and eliminate an important anti-inflammatory and anti-proliferative mechanism (22,24).
Insulin resistance represents a central mechanism linking obesity with cancer biology. As peripheral tissues become less responsive to insulin, compensatory hyperinsulinemia develops, leading to increased activation of insulin receptors and insulin-like growth factor-1 (IGF-1) receptors. Activation of these receptors stimulates several oncogenic signaling cascades, including the phosphatidylinositol-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway and the RAS/RAF/mitogen-activated protein kinase (MAPK) pathway. These signaling networks regulate cell-cycle progression, protein synthesis, angiogenesis, glucose metabolism, and resistance to apoptosis, thereby promoting tumor initiation and progression (25,26).
The IGF axis plays a particularly important role during childhood because of its physiological involvement in growth and development. Dysregulation of IGF-1 signaling has been implicated in multiple pediatric malignancies, including osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, medulloblastoma, and several hematologic malignancies. Persistent hyperinsulinemia suppresses hepatic production of IGF-binding proteins, increasing circulating free IGF-1 concentrations and enhancing mitogenic signaling within susceptible tissues (25,27).
Chronic obesity also induces profound alterations in immune function. Increased adiposity is associated with impaired natural killer (NK) cell activity, T-cell dysfunction, macrophage polarization toward a pro-inflammatory phenotype, and altered cytokine production. These changes weaken immune surveillance against malignant cells while maintaining a chronic inflammatory environment that promotes tumor growth. Furthermore, obesity-related oxidative stress results in excessive production of reactive oxygen species (ROS), DNA damage, mitochondrial dysfunction, telomere shortening, and epigenetic modifications, all of which contribute to genomic instability and carcinogenesis (24,28).Metabolic dysregulation may also influence cancer treatment outcomes. Obesity has been associated with altered pharmacokinetics of chemotherapeutic agents, increased treatment-related toxicity, reduced physical activity, sarcopenic obesity, and

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inferior health-related quality of life among childhood cancer survivors. Several cohort studies have reported that obesity at diagnosis or excessive weight gain during therapy may adversely affect treatment response and increase the risk of relapse in selected pediatric malignancies, particularly acute lymphoblastic leukemia (ALL), although findings remain inconsistent across disease subtypes (29,30). Conversely, cancer therapy itself frequently contributes to obesity and metabolic syndrome. Corticosteroids, cranial irradiation, hypothalamic injury, reduced physical activity, endocrine dysfunction, and alterations in body composition promote excessive adiposity and insulin resistance during survivorship. Consequently, childhood cancer survivors exhibit substantially higher rates of obesity, dyslipidemia, hypertension, impaired glucose tolerance, and type 2 diabetes compared with age-matched controls, highlighting the bidirectional relationship between metabolic disease and pediatric cancer (31,32).

Emerging evidence also suggests that obesity-induced metabolic reprogramming may reduce the efficacy of novel anticancer therapies, including targeted agents and immunotherapies. Altered glucose metabolism within the tumor microenvironment influences T-cell activation, macrophage polarization, and immune checkpoint signaling, potentially modifying therapeutic responses. Understanding these metabolic interactions has stimulated growing interest in combining lifestyle interventions, nutritional optimization, exercise programs, and pharmacologic metabolic modulation with conventional cancer treatment as part of comprehensive pediatric oncology care (24,33).

Collectively, current evidence indicates that obesity and insulin resistance are not merely comorbid conditions but integral components of the biological network linking diabetes and childhood cancer. Addressing metabolic health from the time of diagnosis through long-term survivorship may therefore improve treatment tolerance, reduce late effects, and enhance overall survival. Future research should focus on identifying metabolic biomarkers that enable early risk stratification and on evaluating interventions capable of simultaneously improving metabolic control and oncologic outcomes (22–33).

3.3. Diabetes as a Consequence of Childhood Cancer and Its Treatment

The relationship between diabetes and childhood cancer is bidirectional. While metabolic abnormalities may contribute to carcinogenesis, cancer treatment itself substantially increases the risk of impaired glucose metabolism, insulin resistance, and both transient and permanent diabetes mellitus. As survival rates of pediatric malignancies continue to improve, endocrine and metabolic late effects have become major determinants of long-term morbidity and mortality among childhood cancer survivors (34–36).

Treatment-related diabetes may develop during active therapy or many years after completion of treatment. The underlying mechanisms are multifactorial and include pancreatic β-cell injury, chronic insulin resistance, hypothalamic-pituitary dysfunction, altered body composition, chronic inflammation, mitochondrial dysfunction, and endocrine organ damage. The relative contribution of each mechanism depends on the patient's age, cancer type, treatment protocol, radiation exposure, genetic susceptibility, and lifestyle factors (34,37).

Glucocorticoids remain one of the principal causes of hyperglycemia during pediatric cancer treatment. Dexamethasone and prednisone, which are essential components of acute lymphoblastic leukemia (ALL) protocols, impair insulin signaling, increase hepatic gluconeogenesis, reduce peripheral glucose uptake, and promote skeletal muscle proteolysis. Steroid-induced hyperglycemia is usually transient but may become persistent in genetically susceptible children or in those with obesity and pre-existing insulin resistance (38).

L-asparaginase, another cornerstone of ALL therapy, contributes to hyperglycemia through mechanisms distinct from corticosteroids. By inhibiting protein synthesis within pancreatic β-cells, asparaginase reduces insulin secretion and may induce acute pancreatitis, further compromising endocrine pancreatic function. The simultaneous administration of corticosteroids and asparaginase markedly increases the incidence of treatment-related hyperglycemia, particularly in adolescents, obese patients, and individuals with Down syndrome or a family history of diabetes (39,40).

Radiation therapy also plays an important role in the development of diabetes among childhood cancer survivors. Total body irradiation (TBI), abdominal irradiation, and cranial irradiation may disrupt glucose homeostasis through several mechanisms. TBI promotes sarcopenia, visceral adiposity, chronic inflammation, and insulin resistance, whereas abdominal irradiation can directly damage pancreatic β-cells, especially when the pancreatic tail is included within the radiation field. Cranial irradiation may impair hypothalamic-pituitary regulation of appetite, growth hormone secretion, and energy balance, thereby increasing the long-term risk of obesity and metabolic syndrome (35,41).

Hematopoietic stem cell transplantation (HSCT) further increases metabolic risk. In addition to prior exposure to

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chemotherapy and irradiation, transplant recipients frequently receive prolonged corticosteroid therapy and calcineurin inhibitors, both of which contribute to insulin resistance and pancreatic dysfunction. Chronic graft-versus-host disease (GVHD), reduced physical activity, systemic inflammation, and endocrine complications further amplify the risk of diabetes following transplantation (42). Several large cohort studies have demonstrated that childhood cancer survivors experience significantly higher rates of diabetes than the general population. Data from the Childhood Cancer Survivor Study (CCSS) indicate that survivors exposed to abdominal radiation or total body irradiation have a substantially increased lifetime risk of diabetes, metabolic syndrome, and premature cardiovascular disease. Importantly, diabetes in this population often develops at younger ages than expected and may occur even in individuals with normal body mass index, suggesting that treatment-related pancreatic injury contributes independently of obesity (35,43).

Metabolic complications rarely occur in isolation. Diabetes frequently coexists with dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), reduced bone mineral density, sarcopenia, and obesity, collectively increasing the long-term burden of cardiovascular disease. Cardiovascular complications have emerged as one of the leading non-cancer causes of mortality among childhood cancer survivors, emphasizing the need for comprehensive metabolic surveillance throughout survivorship (34,36). Recognizing these risks, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) and the Children's Oncology Group (COG) recommend lifelong screening for glucose intolerance and diabetes in survivors exposed to pancreatic irradiation, total body irradiation, prolonged corticosteroid therapy, or hematopoietic stem cell transplantation. Periodic assessment of fasting plasma glucose, glycated hemoglobin (HbA1c), body mass index, blood pressure, lipid profile, and lifestyle factors should be incorporated into survivorship care plans to facilitate early diagnosis and timely intervention (44,45).

Preventive strategies should extend beyond laboratory surveillance. Nutritional counseling, structured exercise programs, weight management, smoking avoidance, and individualized endocrine follow-up are increasingly recognized as integral components of comprehensive survivorship care. Early identification of high-risk individuals may permit implementation of targeted interventions capable of reducing the burden of diabetes, cardiovascular disease, and other metabolic complications later in life (34,44,45).

Overall, treatment-related diabetes represents one of the most important chronic health conditions affecting survivors of childhood cancer. Understanding its multifactorial pathogenesis and implementing evidence-based surveillance programs are essential for improving long-term health outcomes and quality of life in this rapidly growing population **(refer to Table 2).**

3.4. Shared Molecular Mechanisms Linking Diabetes and Childhood Cancer

Recent advances in molecular biology have demonstrated that diabetes and cancer are interconnected through multiple signaling pathways that regulate cellular proliferation, energy metabolism, apoptosis, inflammation, and genomic stability. Rather than representing independent disease processes, both disorders share common molecular mechanisms that contribute to tumor initiation, progression, therapeutic resistance, and metabolic dysfunction (46–49).

3.5. The Insulin–IGF Axis

The insulin/insulin-like growth factor (IGF) signaling pathway represents one of the principal biological links between diabetes and cancer. Hyperinsulinemia, a hallmark of insulin resistance and obesity, increases circulating insulin concentrations and suppresses hepatic synthesis of insulin-like growth factor binding proteins (IGFBPs), thereby increasing the bioavailability of IGF-1. Binding of insulin and IGF-1 to their respective receptors activates intracellular signaling cascades that stimulate cellular proliferation while inhibiting programmed cell death (46,50).

Activation of the insulin receptor (IR) and IGF-1 receptor (IGF-1R) initiates phosphorylation of insulin receptor substrates (IRS-1 and IRS-2), leading to downstream activation of phosphatidylinositol-3 kinase (PI3K), protein kinase B (AKT), and mammalian target of rapamycin (mTOR). These pathways regulate protein synthesis, glucose utilization, angiogenesis, cell-cycle progression, and survival of malignant cells. Persistent activation of PI3K/AKT/mTOR signaling has been documented in numerous pediatric malignancies, including acute lymphoblastic leukemia, neuroblastoma, medulloblastoma, osteosarcoma, rhabdomyosarcoma, and high-grade gliomas (47,51).

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Table 2. Cancer therapies associated with diabetes and metabolic dysfunction in childhood cancer survivors.

Treatment modality	Mechanism	Metabolic consequences	High-risk patients	Long-term monitoring
Corticosteroids	Increased hepatic gluconeogenesis and insulin resistance	Hyperglycemia, diabetes	ALL induction therapy	Fasting glucose, HbA1c
L-Asparaginase	Reduced pancreatic insulin secretion	Transient diabetes, pancreatitis	ALL	Blood glucose monitoring
Cranial irradiation	Hypothalamic-pituitary injury	Obesity, insulin resistance	Brain tumor survivors	BMI, endocrine evaluation
Total body irradiation	Adipose tissue dysfunction and sarcopenia	Metabolic syndrome, diabetes	HSCT recipients	Cardiometabolic screening
Abdominal/Pancreatic irradiation	β-cell injury	Permanent diabetes mellitus	Neuroblastoma, Wilms tumor	OGTT/HbA1c
Hematopoietic stem cell transplantation	Chronic inflammation, prolonged steroid exposure	Metabolic syndrome	Allogeneic HSCT	Lifelong endocrine follow-up
Targeted therapies/Immunotherapy	Variable endocrine and immune effects	Emerging risk of dysglycemia	Selected pediatric cancers	Individualized monitoring

3.6. PI3K/AKT/mTOR Signaling

The PI3K/AKT/mTOR pathway integrates extracellular growth signals with intracellular nutrient sensing. Under physiological conditions, this pathway maintains glucose homeostasis, regulates glycogen synthesis, and coordinates cellular growth according to nutrient availability. However, chronic hyperinsulinemia, obesity, and activating oncogenic mutations result in sustained pathway activation, promoting uncontrolled cellular proliferation and resistance to apoptosis (47,52).

Alterations in genes regulating this pathway—including PIK3CA, PTEN, AKT1, and TSC1/TSC2—have been identified in several childhood malignancies and hereditary cancer predisposition syndromes. These observations further support the concept that metabolic dysregulation and tumorigenesis share common molecular determinants (17,52).

3.7. AMPK and Cellular Energy Homeostasis

AMP-activated protein kinase (AMPK) serves as the master regulator of cellular energy balance. AMPK is activated during conditions of energy depletion and suppresses anabolic pathways while promoting catabolic processes to restore intracellular ATP levels. Importantly, AMPK negatively regulates mTOR signaling and therefore functions as an endogenous tumor suppressor (53).

In obesity and diabetes, chronic nutrient excess suppresses AMPK activity, resulting in persistent mTOR activation, increased lipid synthesis, impaired autophagy, and accelerated cellular proliferation. Experimental studies have suggested that pharmacologic activation of AMPK may exert antitumor effects by inhibiting protein synthesis and enhancing apoptosis, providing a biological rationale for investigating metabolic therapies as adjuncts to conventional cancer treatment (53,54).

3.8. Chronic Inflammation and Cytokine Signalling

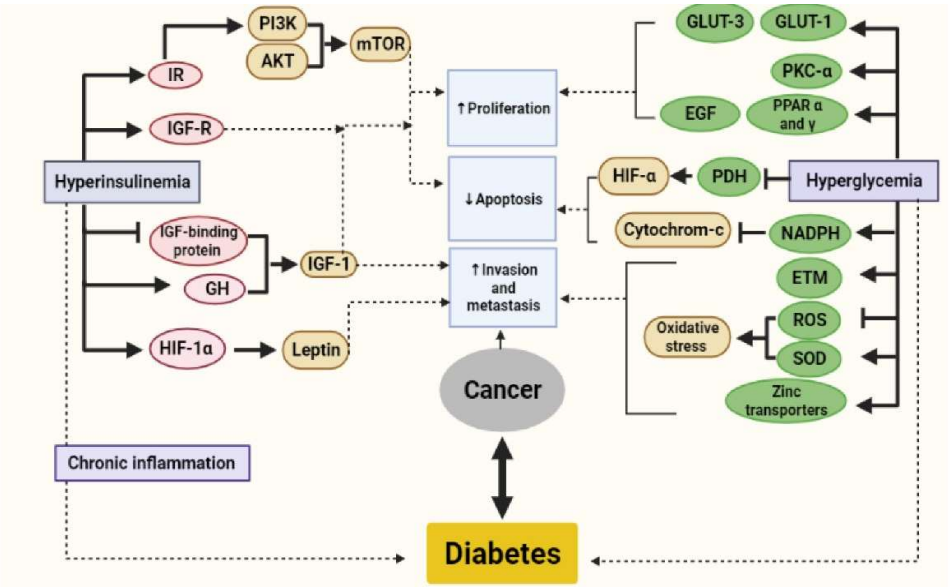
Chronic low-grade inflammation is another fundamental mechanism linking diabetes with malignancy. Obesity-associated macrophage infiltration within adipose tissue leads to sustained secretion of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and C-reactive protein (CRP). These mediators activate nuclear factor-kappa B (NF-κB), Janus kinase/signal transducer and activator of

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Table 3. Shared biological pathways linking diabetes and childhood cancer and potential therapeutic implications.

Biological pathway	Role in diabetes	Role in cancer	Potential therapeutic implication
Insulin/IGF-1 signaling	Hyperinsulinemia	Tumor proliferation	IGF-1 pathway inhibition
PI3K/AKT/mTOR pathway	Insulin signaling	Cell survival and proliferation	PI3K/mTOR inhibitors
AMPK pathway	Energy homeostasis	Suppresses tumor growth	Metformin, AMPK activation
Chronic inflammation	Insulin resistance	Tumor-promoting microenvironment	Anti-inflammatory interventions
Oxidative stress	β-cell dysfunction	DNA damage	Antioxidant strategies
Gut microbiome	Glucose metabolism	Immune modulation	Microbiome-targeted therapies
Mitochondrial dysfunction	Impaired insulin secretion	Metabolic reprogramming	Mitochondrial-targeted therapies
Epigenetic alterations	β-cell dysfunction	Oncogene/tumor suppressor regulation	Precision medicine approaches

Figure 1. Shared Molecular Mechanisms Linking Diabetes and Childhood Cancer: The Roles of Insulin/IGF-1 Signaling, PI3K/AKT/mTOR Pathway, Inflammation, and Metabolic Reprogramming.



transcription (JAK/STAT), and other inflammatory pathways that promote cellular proliferation, angiogenesis, immune evasion, and metastatic potential (24,55).

Persistent inflammatory signalling also interferes with insulin receptor function, thereby aggravating insulin resistance and establishing a self-perpetuating cycle in which inflammation accelerates both metabolic dysfunction and tumor progression.

3.9. Oxidative Stress and Genomic Instability

Hyperglycemia increases intracellular production of reactive oxygen species (ROS) through mitochondrial dysfunction and activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Excessive ROS production induces DNA strand breaks, lipid peroxidation, protein oxidation, and mitochondrial damage while impairing DNA repair mechanisms. These processes contribute to genomic instability, one of the hallmarks of cancer (56).

Cancer cells similarly exhibit increased oxidative stress resulting from rapid proliferation and metabolic reprogramming. Although moderate ROS levels stimulate tumor growth through activation of mitogenic signaling pathways, excessive oxidative stress may also enhance sensitivity to chemotherapy and radiotherapy, illustrating

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the complex role of redox biology in pediatric oncology (56,57).

3.10. Epigenetic Regulation

Epigenetic modifications provide another important connection between diabetes and cancer. Hyperglycemia and obesity alter DNA methylation, histone acetylation, and non-coding RNA expression, leading to persistent changes in gene transcription without alteration of the underlying DNA sequence. These epigenetic alterations influence insulin signaling, inflammatory responses, cellular differentiation, and oncogene activation (58).

MicroRNAs (miRNAs), particularly miR-21, miR-34a, miR-155, and miR-126, have emerged as important regulators of both glucose metabolism and tumor biology. Dysregulated miRNA expression has been associated with insulin resistance, β-cell dysfunction, leukemia progression, glioma invasion, and therapeutic resistance, making these molecules promising biomarkers and potential therapeutic targets (58,59).

3.11. The Gut Microbiome

Accumulating evidence indicates that intestinal microbiota participates in the regulation of metabolism, immunity, and carcinogenesis. Alterations in gut microbial composition have been associated with obesity, diabetes, chronic inflammation, and impaired immune surveillance. Microbial metabolites, including short-chain fatty acids, bile acids, and tryptophan derivatives, influence insulin sensitivity, intestinal barrier integrity, and systemic inflammatory responses (60).

In pediatric oncology, chemotherapy-induced dysbiosis further disrupts microbial homeostasis, potentially contributing to metabolic complications, infection risk, and altered responses to immunotherapy. Although pediatric data remain limited, modulation of the gut microbiome through dietary interventions, probiotics, or microbiota-directed therapies represents an emerging area of translational research (60).

3.12. Clinical Implications

Understanding these shared molecular pathways has important therapeutic implications. Several targeted agents currently used in oncology—including PI3K inhibitors, AKT inhibitors, mTOR inhibitors, and immune checkpoint inhibitors—directly or indirectly influence glucose metabolism. Conversely, medications traditionally used to treat diabetes, particularly metformin, are being investigated for their potential antitumor properties through activation of AMPK, inhibition of mTOR signaling, reduction of hyperinsulinemia, and modulation of the tumor microenvironment (53,61).

Collectively, these observations demonstrate that diabetes and childhood cancer share an intricate molecular network involving insulin signaling, inflammation, oxidative stress, epigenetic regulation, and metabolic reprogramming. A deeper understanding of these mechanisms may facilitate the development of precision medicine strategies that simultaneously target metabolic dysfunction and tumor progression, ultimately improving long-term outcomes for children affected by these complex disorders.

3.13. Clinical Implications and Future Perspectives

The increasing recognition of the complex relationship between diabetes and childhood cancer has important implications for clinical practice. Historically, pediatric oncology and pediatric endocrinology have functioned as separate disciplines. However, accumulating evidence suggests that metabolic health should become an integral component of cancer prevention, treatment, survivorship, and long-term follow-up. A multidisciplinary approach involving pediatric oncologists, endocrinologists, geneticists, nutrition specialists, exercise physiologists, psychologists, and primary care physicians is essential for optimizing outcomes in children affected by these overlapping disorders (62–64).

3.14. Early Identification of High-Risk Children

Early recognition of children at increased risk for metabolic complications is fundamental. Comprehensive assessment at cancer diagnosis should include evaluation of body mass index (BMI), waist circumference, family history of diabetes, baseline fasting glucose, glycated hemoglobin (HbA1c), lipid profile, blood pressure, and lifestyle factors. Children with obesity, Down syndrome, inherited cancer predisposition syndromes, previous pancreatic disease, or a strong family history of diabetes warrant closer metabolic surveillance throughout treatment and survivorship (34,44,62).

Genetic counseling has become increasingly important in pediatric oncology. Identification of germline pathogenic variants not only facilitates individualized cancer surveillance but also enables risk assessment for endocrine complications, reproductive counseling, and cascade testing of at-risk family members. The incorporation of multigene panel testing and next-generation sequencing into routine pediatric oncology practice has substantially improved the detection of hereditary cancer predisposition syndromes

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and supports the implementation of precision medicine strategies (12,21).

3.15. Lifestyle-Based Interventions

Lifestyle modification remains the cornerstone of metabolic risk reduction among childhood cancer survivors. Regular physical activity improves insulin sensitivity, preserves lean body mass, reduces adiposity, enhances cardiovascular fitness, and improves psychological well-being. Nutritional interventions emphasizing balanced caloric intake, reduced consumption of ultra-processed foods and sugar-sweetened beverages, and increased intake of fruits, vegetables, whole grains, and dietary fiber have demonstrated beneficial effects on metabolic health in both healthy children and cancer survivors (65,66).

Structured exercise programs initiated during or shortly after cancer treatment may attenuate treatment-related declines in muscle mass and physical function while reducing the incidence of obesity and metabolic syndrome. Although randomized pediatric trials remain limited, current international survivorship guidelines strongly support individualized exercise prescriptions as part of routine follow-up care (66,67).

3.16. Pharmacologic Prevention and Emerging Therapies

Beyond lifestyle interventions, pharmacologic approaches targeting metabolic pathways have attracted increasing interest. Metformin has been extensively investigated because of its ability to activate AMP-activated protein kinase (AMPK), inhibit mTOR signaling, reduce hepatic gluconeogenesis, improve insulin sensitivity, and decrease circulating insulin concentrations. Observational studies and clinical trials suggest that metformin may possess antineoplastic properties in selected malignancies, although definitive evidence in pediatric oncology remains limited (53,61).

Novel therapies targeting the PI3K/AKT/mTOR pathway, insulin signaling, inflammatory cytokines, and immune checkpoints are also being explored. As precision oncology evolves, integrating metabolic biomarkers into therapeutic decision-making may help identify patients most likely to benefit from targeted metabolic interventions.

3.17. Precision Medicine and Artificial Intelligence

Advances in genomics, transcriptomics, metabolomics, proteomics, and epigenomics are reshaping the understanding of both diabetes and childhood cancer. Multi-omics approaches provide unprecedented opportunities to identify molecular signatures associated with treatment response, late effects, and long-term survivorship. Artificial intelligence (AI) and machine learning algorithms are increasingly capable of integrating complex clinical, imaging, and molecular datasets to predict treatment toxicity, metabolic complications, and individualized cancer risk (68,69).

Digital health technologies—including wearable devices, continuous glucose monitoring systems, remote patient monitoring, and mobile health applications—may further enhance long-term metabolic surveillance while improving patient engagement and adherence to lifestyle recommendations.

3.18. Long-Term Survivorship Care

The rapidly expanding population of childhood cancer survivors necessitates comprehensive survivorship programs extending well beyond completion of therapy. International guidelines recommend lifelong surveillance for obesity, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, endocrine dysfunction, and secondary malignancies. Survivorship clinics integrating pediatric oncology, endocrinology, cardiology, nutrition, rehabilitation medicine, psychology, and primary care have demonstrated improved coordination of care and earlier recognition of late effects (44,45,62).

Transition from pediatric to adult healthcare services represents another vulnerable period during which many survivors become lost to follow-up. Development of structured transition programs with standardized survivorship care plans may improve continuity of care and facilitate long-term monitoring of metabolic health.

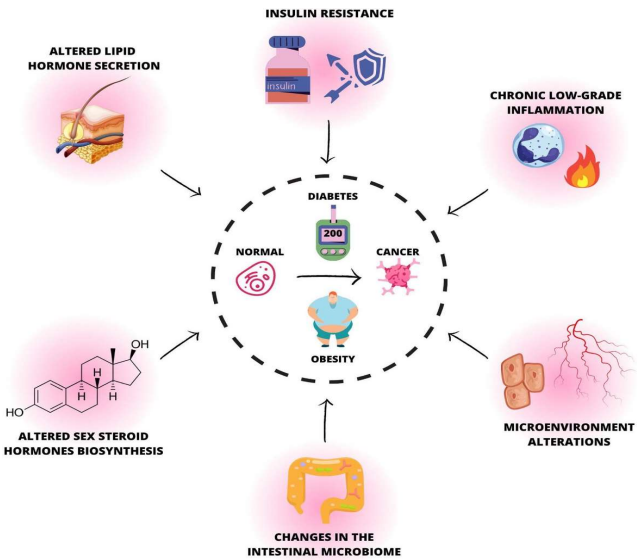


Figure 2. Precision Survivorship Model for Long-Term Metabolic Monitoring in Survivors of Childhood Cancer.

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4. RESEARCH PRIORITIES

Despite substantial progress, several important knowledge gaps remain. Most available evidence originates from retrospective studies conducted in heterogeneous survivor populations, limiting causal inference. Large prospective multicenter cohorts are required to clarify the temporal relationship between metabolic abnormalities and cancer outcomes, identify reliable biomarkers for early risk prediction, and evaluate targeted preventive interventions.

5. FUTURE RESEARCH SHOULD FOCUS ON:

- Defining molecular mechanisms linking diabetes and pediatric malignancies.
- Identifying genomic and epigenomic biomarkers predictive of metabolic complications.
- Evaluating microbiome-directed therapies in childhood cancer survivors.
- Investigating the role of precision nutrition and individualized exercise interventions.
- Assessing the long-term oncologic effects of antidiabetic medications.
- Developing AI-driven prediction models for metabolic late effects.
- Establishing international collaborative registries integrating clinical, metabolic, genetic, and survivorship data.
- Ultimately, integrating pediatric oncology, endocrinology, medical genetics, and precision medicine has the potential to transform survivorship care and improve both longevity and quality of life for children diagnosed with cancer.

6. CONCLUSION

The relationship between diabetes and childhood cancer is increasingly recognized as a complex, bidirectional interaction mediated by shared genetic susceptibility, metabolic dysregulation, endocrine dysfunction, chronic inflammation, and common molecular signaling pathways. While obesity, insulin resistance, and hyperinsulinemia may contribute to tumor initiation and progression through activation of the insulin/IGF-1, PI3K/AKT/mTOR, and inflammatory signaling pathways, cancer therapy itself substantially increases the risk of diabetes and other metabolic complications among childhood cancer survivors. Consequently, metabolic disorders should no longer be considered merely treatment-related comorbidities but rather integral components of pediatric oncology that influence treatment response, survivorship, and long-term

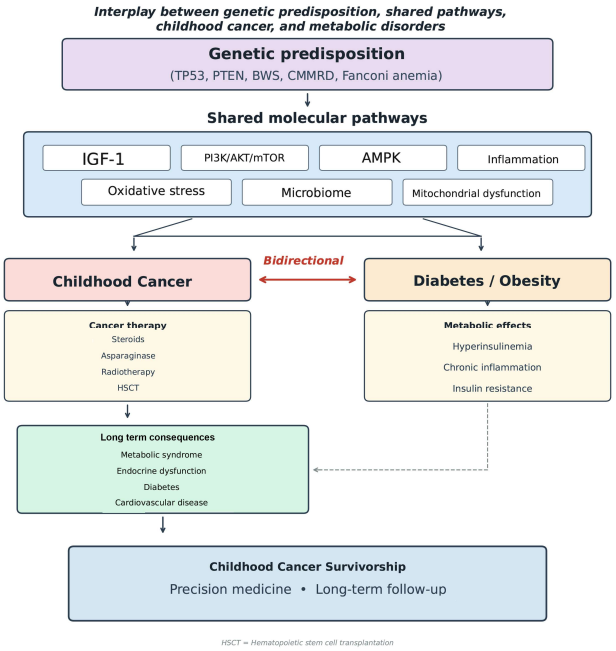


Figure 3. Graphical abstract. Bidirectional interplay between diabetes and childhood cancer in the context of genetic predisposition, metabolic dysregulation and cancer therapy.

quality of life (1–6,22,34). Recent advances in cancer genetics have further expanded our understanding of the biological overlap between endocrine disorders and pediatric malignancies. Identification of hereditary cancer predisposition syndromes has demonstrated that many genes regulating genomic stability also participate in insulin signaling, cellular metabolism, oxidative stress, and endocrine homeostasis. These discoveries support a precision medicine approach in which genomic information may guide individualized cancer surveillance, metabolic screening, targeted therapies, and family counseling (10–21). Equally important is the recognition that metabolic health should become a routine component of pediatric cancer care. Early identification of obesity, insulin resistance, dyslipidemia, hypertension, and impaired glucose tolerance provides an opportunity to implement preventive interventions before irreversible complications develop. Lifestyle modification, nutritional optimization, structured exercise programs, and long-term endocrine follow-up should therefore be incorporated into survivorship programs alongside conventional oncologic surveillance (44,45,62–67).

Emerging technologies—including multi-omics profiling, artificial intelligence, digital health platforms, continuous glucose monitoring, and precision therapeutics—offer unprecedented opportunities to improve individualized risk

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prediction and optimize long-term outcomes. Future multicenter prospective studies integrating genomic, metabolic, immunologic, and clinical data are needed to clarify causal mechanisms, identify novel biomarkers, and develop personalized preventive strategies for children at increased risk of both diabetes and cancer (68,69). Ultimately, strengthening collaboration among pediatric oncologists, endocrinologists, geneticists, nutrition specialists, rehabilitation teams, and primary care physicians will be essential for translating these scientific advances into clinical practice. Such multidisciplinary models have the potential not only to reduce treatment-related morbidity but also to improve survival, functional outcomes, and quality of life for the rapidly growing population of childhood cancer survivors.

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Conflict of interest

The authors declare that they have no conflicts of interest related to this work.

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Ethical statement

This study was a systematic review of previously published literature and did not involve the collection or analysis of individual-level data from human participants. Therefore, ethical approval and informed consent were not required.

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