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LETTER TO THE EDITOR

Impact of poorly controlled type II diabetes mellitus on chemoresistance in colorectal cancer

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Abstract

Type 2 diabetes mellitus (T2DM) significantly elevates the risk of colorectal cancer (CRC) and complicates its treatment by promoting chemoresistance. Poor glycemic control has been linked to exacerbated CRC progression and diminished chemotherapy efficacy, impacting patient outcomes through various mechanisms such as oxidative stress, activation of metabolic pathways, and altered protein modifications that hinder apoptosis and enhance tumor survival. Clinical evidence shows that T2DM patients experience higher rates of chemoresistance and reduced disease-free survival and overall survival compared to non-diabetic patients. Specifically, those with poor glycemic control exhibit increased chemoresistance and poorer survival metrics. Antidiabetic treatments, including metformin, acarbose, and gliclazide, show promise in improving chemotherapy response and glycemic management, potentially enhancing patient outcomes.

Addressing this challenge requires a comprehensive, multidisciplinary approach involving oncologists, endocrinologists, and surgeons to optimize patient care. Integrated strategies that prioritize glycemic control are essential for reducing chemoresistance and improving survival in CRC patients with T2DM.

Key Words: Type 2 diabetes mellitus; Colorectal cancer; Cancer; Chemoresistance; Diabetes mellitus; Hyperglycemia; Chemotherapy

Core Tip: Type 2 diabetes mellitus exacerbates colorectal cancer (CRC) progression by inducing chemoresistance through mechanisms such as oxidative stress, altered metabolic pathways, and disrupted apoptotic signalling. Poor glycemic control worsens patient outcomes, reducing disease-free survival and overall survival. Antidiabetic treatments, notably metformin, show potential in enhancing chemotherapy efficacy while improving glycemic management. A multidisciplinary care model involving oncologists, endocrinologists, and surgeons is essential to mitigate chemoresistance and optimize survival outcomes in CRC patients with type 2 diabetes mellitus. Prioritizing glycemic control through integrated therapeutic strategies offers a promising avenue for improving CRC treatment success in this high-risk patient population.

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TO THE EDITOR

Type 2 diabetes mellitus (T2DM), a common metabolic disorder characterized by hyperglycemia, is brought on by a combination of two main factors: The pancreatic β-cells' impaired ability to secrete insulin and the innate resistance of body cells to insulin action[1]. Its prevalence has increased significantly since the late 20th century due to a combination of global rise in obesity, sedentary lifestyles, high caloric diets, and population aging[1]. The prevalence of diabetes is projected to increase across most countries, though the pattern of growth may vary by region. By 2050, low-income regions are expected to experience an 82.7% rise in age-standardized T2DM prevalence, compared to a relatively lower increase of 30.3% in high-income regions[2].

T2DM has been identified as an independent risk factor for colorectal cancer (CRC), with evidence linking diabetes to CRC carcinogenesis and poorer clinical outcomes[3]. CRC is the third most common cancer and the second leading cause of cancer death globally[4]. The prognosis varies depending upon the tumor site and extent of metastasis, with an average 5-year survival probability of 90.9% and 8.1% in localized and distant CRC, respectively[5]. While surgical resection offers the best prognosis for both obstructing and non-obstructing colon malignancies, chemotherapeutic drugs such as oxaliplatin and 5-fluorouracil (5-FU) are required for non-resectable tumors[6]. Studies have shown a 30%-40% higher mortality rate from postoperative complications in diabetic patients, alongside worse cancer-related survival outcomes[3,7]. Among CRC patients, T2DM is associated with a 13.3% major postoperative complication rate compared to 3.3% in non-T2DM patients, along with significantly higher Clavien-Dindo scores (grade III or higher) and prolonged hospitalization[8]. Additionally, postoperative complications in diabetic CRC patients can delay or hinder the initiation of adjuvant chemotherapy, adversely affecting prognosis[9]. However, optimal perioperative diabetes management, particularly maintaining glycemic control, has been shown to improve postoperative outcomes and facilitate chemotherapy initiation.

Hyperglycemia has also been linked to chemoresistance and metastasis of CRC cells, with elevated glucose levels reducing the efficacy of 5-FU[10,11]. Encouragingly, evidence suggests that chemoresistance can be mitigated through glucose-lowering interventions, such as the administration of metformin, which has demonstrated efficacy in reversing hyperglycemia-induced resistance to 5-FU[12]. These findings underscore the critical importance of integrated T2DM and CRC management to improve postoperative outcomes and survival in CRC patients.

MECHANISMS LINKING T2DM TO CHEMORESISTANCE

In addition to being a risk factor for CRC, hyperglycemia or T2DM contributes to CRC progression through several mechanisms[13]. Poor glycemic control activates polyol and hexosamine metabolic pathways, with evidence indicating that fructose, a byproduct of the polyol pathway, may expedite cancer growth[13,14]. Overexpression of polyol pathway enzymes, such as sorbitol dehydrogenase and aldose reductase, has been observed in 46% of colorectal adenomas and colon cancer cells[15,16]. Similarly, UDP-β-D-N-acetylglucosamine, a byproduct of the hexosamine pathway, plays a critical role in cancer progression by inducing O-GlcNAcylation - a post-translational modification affecting gene

expression and cell adhesion[13,17]. Increased O-GlcNAcylation has been identified in colon cancer cells, particularly in those with higher metastatic potential[18]. Furthermore, hyperglycemia persistently elevates diacylglycerol levels, stimulating the classic protein kinase C (PKC) isoforms α, β, and δ. Evidence links the activation of PKC α and β isoforms with carcinogen-induced malignant transformation, underscoring the role of PKC in CRC development and progression [19,20]. The buildup of advanced glycation end products in a hyperglycemic condition may lead to increased production of inflammatory factors, including interleukin-6 and tumor necrosis factor-α, which in turn trigger the protein kinase B and Wnt signaling pathways responsible for CRC carcinogenesis. Additionally, hyperglycemia influences immune regulation by causing aberrant immune cell activity, including decreased T lymphocyte and macrophage activity and compromised natural killer cell function. Such changes could raise the likelihood of tumor growth by impairing the body's immune surveillance and tumor-clearing capacities. Hyperglycemia can also cause epigenetic modifications resulting in "glucose memory", which is the permanent activation of cancer pathways in tumor cells. This occurs *via* hyperglycemia-induced DNA methylation in CD34+ stem cells, which reduces *CXCR4* gene expression and causes immune suppression in CRC[21].

Cancer cells can become resistant to one or more anticancer drugs through a variety of mechanisms, including decreased drug uptake, increased drug efflux, improved DNA damage repair, suppression of apoptosis, altered drug metabolism, epigenetic modifications, and target gene amplification[22]. Hyperglycemia reduces the efficacy of fluorouracil and oxaliplatin due to decreased sensitivity and rapid clearance from the body[23]. At the same time, high glucose levels inhibit p53 phosphorylation, diminishing its apoptotic activity in colon cancer cells[24]. Additionally, hyperglycemia attenuates docetaxel-induced apoptosis by increasing insulin-like growth factor binding protein 2 production through glucose-induced acetylation of histones at the insulin-like growth factor binding protein 2 promoter [25]. Antidiabetic treatments have also been linked to reduced antiproliferative effects of 5-FU by decreasing cell death and enhancing DNA replication in cancer cells[11]. Reactive oxygen species (ROS) play a dual role in chemoresistance; mild ROS levels promote tumor progression by enhancing proliferation, survival, invasion, and metastasis, while excessive ROS induce oxidative damage and cancer cell death[26]. Hyperglycemia further elevates ROS levels through activation of p38 mitogen-activated protein kinases and extracellular signal-regulated kinase pathways[27]. In addition, high glucose concentrations in CRC patients increase SMAD3 phosphorylation, which subsequently amplifies MYC and euchromatic histone-lysine N-methyltransferase 2 expression, contributing to oxaliplatin resistance[12]. These insights highlight the complex metabolic and molecular alterations by which T2DM fosters chemoresistance in CRC, posing challenges for effective therapeutic interventions. The interplay between T2DM and CRC chemoresistance involves several mechanisms, affecting both chemotherapy sensitivity and tumor progression pathways, as mentioned in Table 1.

Evidence suggests that chemotherapy is less effective in patients with T2DM compared to non-diabetic individuals, with a significantly higher chemoresistance rate in the diabetic group (14.41%) *vs* the non-diabetic group (7.5%)[28]. Long-term outcomes also indicate poorer prognosis for T2DM patients with CRC, as they exhibit lower disease-free survival (DFS) rates compared to their non-diabetic counterparts; however, the difference was not significant [hazard ratio (HR) = 1.388, 95% confidence interval (CI): 0.853-2.258, *P* value = 0.178]. Specifically, the 1-, 3-, and 5-year recurrence-free survival rates for non-diabetic CRC patients are 92.50%, 79.37%, and 78.75%, respectively, while for diabetic CRC patients, these rates are 85.59%, 73.73%, and 72.03%[28]. This highlights the reduced efficacy of standard-dose chemotherapy in T2DM patients with colon cancer. Additionally, poor glycemic control is linked to an even greater rate of chemoresistance, reaching 24.4% among patients with suboptimal management. Interestingly, the administration of antidiabetic medication prior to or during hospitalization does not appear to affect chemoresistance rates, indicating that the presence of T2DM and its long-term control play a more significant role in influencing chemotherapy outcomes[28].

CLINICAL IMPLICATIONS OF GLYCEMIC CONTROL

Glycemic control in patients with T2DM undergoing treatment for CRC is vital, as it significantly affects prognosis, influencing both DFS and overall survival (OS). Evidence has demonstrated that poor glycemic control is associated with poorer outcomes, with HRs indicating that it can increase the risk of adverse survival outcomes (DFS: HR = 2.189, 95%CI: 1.508-4.530, *P* value = 0.011; OS: HR = 2.856, 95%CI: 1.179-6.918, *P* value = 0.011) compared to well-controlled T2DM patients[28]. Specifically, the 1-, 3-, and 5-year DFS rates were 91.78%, 78.67%, and 78.67% for well-controlled patients, whereas those with poor glycemic control had lower rates of 75.56%, 66.6%, and 62.22%, respectively[28]. Likewise, the OS rates were 98.63%, 89.33%, and 87.67% in the well-controlled group, compared to 97.78%, 73.33%, and 71.11% in the poorly controlled group[28]. These disparities emphasize the diminished efficacy of standard-dose chemotherapy in T2DM patients with CRC. Chemoresistance rates also varied based on glycemic control, with a significant difference between well-controlled patients (8.22%) and those with poor control (24.4%, *P* value = 0.015), indicating that optimal glycemic management could enhance chemotherapy response[28].

Understanding effective therapeutic strategies is essential given the critical impact of glycaemic control. Metformin is the most commonly used antidiabetic medication, employed either alone or in combination with other drugs, and has been shown to contribute to good glycemic control in 79% of patients[28]. This medication not only aids in maintaining glycaemic levels but also demonstrates potential anticancer properties, enhancing chemotherapy efficacy in several types of cancer, including ovarian, lung, and acute myeloid leukaemia[29]. This potential is further supported by findings that metformin alone significantly reduced colon cell proliferation[12]. Metformin affects the metabolism of cancer cells by blocking respiratory complex I of the electron transport chain. This stops the production of ROS and stops mutagenesis [29]. Additionally, complex I inhibition causes decreased ATP production and an increase in the ratio of adenosine monophosphate to ATP, consequently activating adenosine monophosphate-activated protein kinase, which causes cell

Table 1 Mechanisms of chemoresistance in hyperglycaemia

Ref.	Mechanism of chemoresistance
Ikemura and Hashida [23]	Decreased sensitivity and faster total body clearance of 5-FU and oxaliplatin
Biernacka *et al*[25]	Lower apoptosis-inducing effects of docetaxel because of higher IGFBP2 production
Ma *et al*[11]	Decrease the effects of 5-FU by increasing DNA replication and attenuating 5-FU-induced cell death
Yang *et al*[12]	Increased phosphorylation of SMAD3 and MYC proteins, subsequently resulting in enhanced expression of EHMT2, which exacerbates oxaliplatin resistance

5-FU: 5-fluorouracil; IGFB2: Insulin-like growth factor binding protein 2; EHMT2: Euchromatic histone-lysine N-methyltransferase 2.

cycle arrest by inducing the tumor suppressor protein p53[29]. Metformin suppresses c-MYC, a proto-oncogene that is essential for growth regulation, differentiation, and apoptosis and is known to be overexpressed in many malignancies [30,31].

Other hypoglycemic agents like acarbose and gliclazide have been found to reduce the risk of CRC[32,33]. Acarbose prolongs bowel transit time, which leads to an increased production of butyrate, a compound that has anti-neoplastic properties and promotes normal colonic mucosal growth. Delayed bowel emptying also confers a protective role by altering the concentration of bile acids that damage DNA[32]. Gliclazide is postulated to possess antioxidant properties that prevent DNA damage[33]. Despite these promising results, there is a need for more research into the effects of other antidiabetic medications that target different metabolic pathways, as they could modulate cancer metabolism and improve treatment response, offering a broader therapeutic perspective by influencing DFS, OS, and chemoresistance in T2DM patients with CRC. Diabetes and cancer have a high likelihood of occurring in the same patient due to their shared risk factors. There is growing evidence that diabetes and cancer can cause each other *via* unique mechanisms[34]. Thus, the substantial impact of glycemic control on CRC management and prognosis underscores the importance of a comprehensive, multidisciplinary approach involving oncologists, surgeons, and endocrinologists. In fact, the coexistence of the two diseases presents significant challenges for both patients and healthcare providers, necessitating a growing need for multidisciplinary collaboration between oncologists and endocrinologists to more effectively manage patients with both diabetes and cancer[35]. Such a strategy is essential to optimize patient care, treatment outcomes, and survival rates.

CONCLUSION

The interplay between T2DM and CRC has significant implications for patient outcomes, particularly in the context of chemoresistance. Hyperglycemia, a hallmark of T2DM, exacerbates CRC progression and compromises the efficacy of chemotherapy through several complex mechanisms, including alterations in metabolic pathways, protein modifications, and oxidative stress. The reduced response to standard chemotherapeutic agents such as 5-FU and oxaliplatin, coupled with increased rates of chemoresistance in patients with poor glycemic control, underscores a pressing need for integrated management strategies. Optimizing blood glucose levels emerges as a critical factor in improving chemotherapy sensitivity and OS. Metformin's potential dual role in glycemic control and cancer treatment further supports the incorporation of antidiabetic therapies into CRC care plans. However, to better tackle chemoresistance and enhance therapeutic effectiveness, future research must explore the broader implications of various antidiabetic treatments and the underlying mechanisms at play. Ultimately, a multidisciplinary, comprehensive approach involving oncologists, endocrinologists, and surgeons is essential for addressing the multifaceted challenges posed by T2DM in CRC patients, fostering improved outcomes and survival.

FOOTNOTES

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