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OPINION REVIEW

How far along are we in revealing the connection between metformin and colorectal cancer?

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Abstract

Colorectal cancer (CRC) is among the most prevalent cancers worldwide, and its prevention and reduction of incidence is imperative. The presence of diabetes has been associated with a 30% increased risk of CRC, likely through the mechanism of hyperinsulinemia, which promotes tumorigenesis *via* the insulin receptor in the epithelium or by insulin-like growth factor pathways, inflammation, or adipokines, inducing cancer cell proliferation and cancer spread. Metformin, the first-line agent in treating type 2 diabetes, has a chemopreventive role in CRC development. Additionally, preclinical studies suggest synergistic effects of metformin with oxaliplatin in inhibiting *in vitro* models of colon cancer. Although preclinical studies on the post diagnostic use of metformin were promising and suggested its synergistic effects with chemotherapy, the data on the possible effects of metformin after surgery and other CRC treatment in the clinical setting are less conclusive, and randomized controlled trials are still lacking.

Key Words: Metformin; Type 2 diabetes mellitus; Colorectal cancer; Chemoprevention; Recurrence-free survival; Surgery

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Core Tip: Metformin is one of the oldest oral antidiabetic agents used to treat type 2 diabetes mellitus. While there is substantial evidence that metformin may have a chemopreventive role in colorectal cancer (CRC) development, the data on the possible effects of metformin after surgery and other CRC treatment is much less conclusive.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide, irrespective of gender. Factors contributing to the risk of development of CRC include lifestyle, genetics, and chronic diseases such as diabetes mellitus and obesity[1-3]. Although patient survival has increased over the years due to more effective treatments, there is still a problem with adverse effects and therapy costs. The prevention and reduction of CRC incidence is imperative. Several agents with chemopreventive effects have emerged. Cyclooxygenase-2 inhibitors offered the most promising results in CRC prevention, but their use was associated with elevated cardiovascular risk. Considering that CRC patients often have diabetes mellitus and obesity, which also confers cardiovascular risk, novel targets for CRC chemoprevention are needed. Accumulating data indicates that metformin, the first-line treatment for type 2 diabetes mellitus, may be a candidate chemoprevention agent for cancer, including CRC.

METFORMIN-CLINICAL USE AND MODE OF ACTION

Metformin is one of the oldest oral antidiabetic agents used to treat type 2 diabetes mellitus alone or in combination with other oral or injectable agents. It lowers blood glucose levels by reducing hepatic glucose production, stimulating glucose uptake by peripheral tissues (muscle and fat), and lowering intestinal glucose absorption[4]. The presence of diabetes has been associated with a 30% increased risk of CRC. This potentially occurs through the mechanism of hyperinsulinemia accompanying insulin resistance, which promotes tumorigenesis *via* action on the insulin receptor in the epithelium or by influencing insulin-like growth factor pathways, inflammation, or adipokines inducing cancer cell proliferation and metastasis[5-7]. Therefore, metformin might provide preventive effects by reducing insulin resistance and lowering hyperinsulinemia[8] (Figure 1). Additionally, the use of metformin in various cancer models provided anticarcinogenic action by inhibiting angiogenesis or through antimetabolic and radio-chemosensitizer effects[9]. This is mediated by the synergistic regulation of metformin on adenosine monophosphate-activated protein kinase (AMPK), glycogen synthase kinase-3β, and proliferator-activated receptor-γ as observed in the case of pancreatic cancer[10].

The mechanistic target of rapamycin (mTOR) pathway, with complex multiple feedback loops, plays a central role in coordinating cell growth and proliferation in CRC carcinogenesis. Different mTOR inhibitors have been extensively studied for preventing and/or treating CRC, but no single agent has shown a significant therapeutic efficacy towards CRC potentially because many of the genetic pathways involved in CRC development lie upstream of mTOR and elicit the oncogenic effect through the mTOR signaling pathway[11]. According to the contemporary understanding, the mTOR pathway is continuously activated by various hormones, inflammation, and energy-related factors such as glucose, insulin, and insulin-like growth factor 1. The hypothesis to combine inhibition of these pathways seems promising in providing more effective tumor suppression[12]. Metformin inhibits mitochondrial mammalian respiratory chain complex I followed by activation of liver kinase B1 and downstream target AMPK that results in an inhibition of mTOR activity[13,14]. Metformin also exerts its metabolic effects by improving insulin resistance, hyperinsulinemia, and glycemia. Metformin has apoptotic effects on cancer

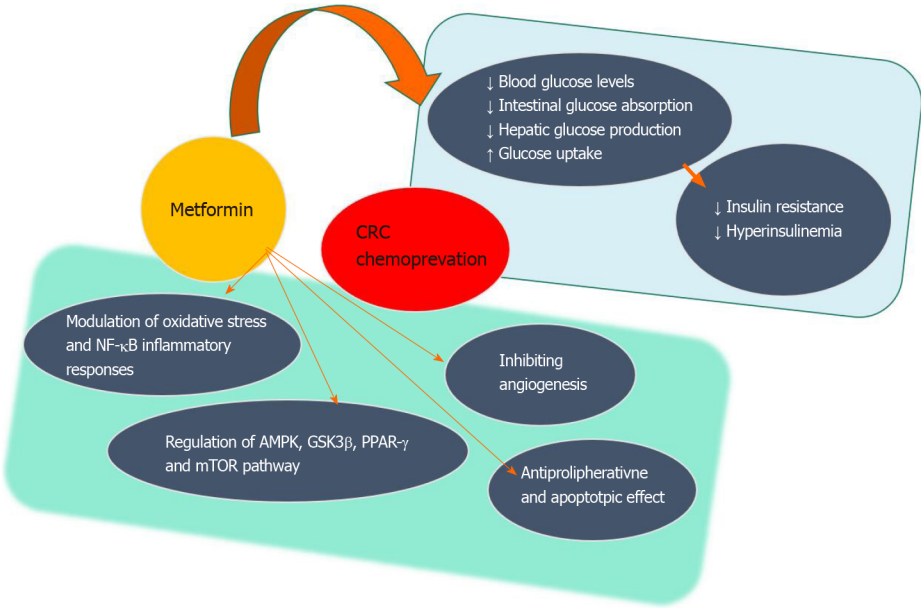

Figure 1 Metformin mode of action including chemopreventive potential in colorectal cancer development. CRC: Colorectal cancer; NF-kB: Nuclear factor kB; AMPK: Adenosine monophosphate-activated protein kinase; GSK3β: Glycogen synthase kinase-3β; PPAR-γ: Proliferator-activated receptor-γ; mTOR: Mechanistic target of rapamycin.

stem cells and potentially has a synergistic effect with other chemotherapeutics[15,16].

Animal and *in vitro* studies indicate that the role of metformin as an antiproliferative agent on CRC cells is through the activation of AMPK[17,18]. One of the first reports on anticancer effect of metformin in a CRC cell model showed the concentration and time-dependent effects on AMPK activation and the reduction of cancer cell proliferation[19]. Other research provided further evidence of the apoptotic effects of metformin by modulating oxidative stress and nuclear factor-κB inflammatory responses[20-22]. In the *in vitro* models, metformin was used either alone or in combination with other agents, primarily fluorouracil (commonly referred to as 5-FU)[20,23-25], which is similar to its use in clinics.

CHEMOPREVENTIVE EFFECTS OF METFORMIN IN CRC TREATMENT

Previous studies have indicated that metformin may decrease the risk of development of colorectal carcinoma[26,27]. Observational data indicates lower tumor incidence in diabetic patients taking metformin, and results from interventional studies show a reduction in the incidence of colorectal adenomas in patients without diabetes taking low-dose metformin[28-30]. Specifically, in a phase 3 randomized trial, a 1-year treatment with low-dose metformin reduced the number and prevalence of premalignant colorectal lesions, such as polyps and adenomas, in patients without diabetes post polypectomy[30]. A recently published retrospective cohort study including 47351 people found an inverse association between long-term (> 5 years) exposure to metformin in diabetic patients and the risk of CRC[31], suggesting its chemopreventive potential. This finding was substantiated with the meta-analysis results of 58 studies showing that metformin usage significantly reduced the incidence of colorectal adenoma and CRC, improving overall and CRC-specific survival rates[32].

On the other hand, data on the role metformin plays in CRC carcinogenesis in nondiabetic patients are not extensive. According to the randomized placebo-controlled trial results, metformin has the chemopreventive potential in nondiabetic patients with a high risk for CRC development[33]. Although metformin therapy was usually well tolerated by patients with different cancers and side effects did not differ from those seen in diabetic patients (dose-related gastrointestinal adverse effects, rarely lactic acidosis, and vitamin B12 deficiency), more data are needed on the optimal dose, schedule, route of administration, treatment duration, and combinations with other chemotherapeutic agents for CRC patients (especially nondiabetic patients) to be able to minimize the potential side effects[34-36].

METFORMIN AND SURVIVAL OF PATIENTS UNDERGOING TREATMENT FOR CRC

While there is substantial evidence that metformin may have a chemopreventive role in CRC development, the data on the possible effects of metformin after surgery and other CRC treatments are much less conclusive.

Lee *et al*[37] first observed a protective effect of metformin after CRC diagnosis in a single institution cohort of 595 patients. Metformin use showed a lower risk of overall mortality [hazard ratio (HR) = 0.66; 95% confidence interval (CI): 0.476-0.923] and CRC-specific mortality (HR = 0.66; 95%CI: 0.45-0.975) in patients with diabetes. However, this analysis suffered from immortal time bias, which may have influenced the results[38]. Fransgaard *et al*[39] examined the association between metformin and overall survival after resection for CRC in patients from the national Danish CRC database. They found better overall survival of patients treated with metformin compared to patients treated with insulin. However, cancer-specific mortality was not differentiated from diabetes-specific mortality, and it is not clear what their respective roles were in all-cause mortality. Therefore, it is impossible to ascertain whether better overall survival in the metformin-treated group can be attributed to metformin or the antitumor effects of other factors. Interestingly, in a recent paper, the same group found no association between metformin use and recurrence-free survival or disease-free survival in patients with surgically treated CRC[40]. The findings of a large population-based analysis from the United Kingdom also do not support a protective association between post-diagnostic metformin use and survival in a cohort of CRC patients with type 2 diabetes mellitus[41].

Several meta-analyses have been published on the topic, and most of them have reported a reduction in CRC-specific mortality with metformin use compared with nonuse in CRC patients[42-45]. However, the studies included in these meta-analyses are very heterogeneous regarding their design and inclusion criteria (*e.g.*, analyzing patients with different CRC stages). Also, information is often not available on the types of surgeries and administered chemotherapy in the included studies.

Evidence exists that metformin in combination with adjuvant therapy may be associated with a better prognosis in CRC patients treated with metformin post-surgery. In preclinical studies, metformin has shown synergistic effects with oxaliplatin in inhibiting *in vitro* models of colon cancer[46]. Based on such evidence, it was hypothesized that metformin combined with adjuvant chemotherapy might be associated with a better prognosis in patients with resected CRC. This was not confirmed in the setting of a randomized study in patients with resected high-risk stage II or stage III CRC who received FOLFOX-4/XELOX adjuvant therapy[47]. Another study exploring the impact of metformin on overall survival and recurrence-free survival in a homogenous group of stage III CRC patients receiving FOLFOX adjuvant therapy failed to find a significant association[48].

These findings stand in contrast to the findings of studies that found an association between metformin use and improved outcomes. However, these were the studies that considered patients with stages I-IV treated with different chemotherapy regimens, including both patients with low stages without adjuvant chemotherapy and patients with advanced stages who received multiple chemotherapeutics[37,49,50]. Therefore, the effect of metformin on overall survival and recurrence-free survival in patients with CRC receiving chemotherapy after resection remains uncertain. Extensive prospective studies that include homogenous patient populations, ideally within randomized trials, with longer follow-up would provide more evidence on the possible association of metformin use and improved survival of patients after CRC treatment.

CONCLUSION

Mounting evidence suggests a chemopreventive role of metformin on CRC development, but the data on its role in diagnosed CRC in adjunct to surgery and chemotherapy are still inconclusive. Additional evidence from prospective, randomized controlled trials are required.

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