

Is Metformin a Treatment Opportunity for Colorectal Cancer?

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ABSTRACT

BACKGROUND

Colorectal cancer (CRC) is one of the common deadly cancers worldwide. The incidence of CRC has been increasing nowadays and new therapy agents are still being investigated for the treatment. Metformin (1, 1-dimethyl biguanide), an oral antidiabetic drug from *Galega officinalis* mostly used in the treatment of type 2 diabetes, has gained considerable research interest in cancer prevention and therapy for many types of cancer including CRC. By targeting the specific pathways involved in cell differentiation, metabolism and metastasis, different mechanisms of action of metformin are tried to be elucidated using CRCs in studies.

METHODS

We searched 3 electronic bibliographic databases (Web of Science, PubMed, and Google Scholar) and research in progress using ClinicalTrials.gov from inception to September 20, 2019. Subject headings and key words included 'metformin' and/or 'metformin in colon cancer', and related terms, and various terms related to colon cancer treatment.

RESULTS

Although it seems justified on the basis of the results of a large number of studies, there is much we do not know about the effect of metformin on CRC.

CONCLUSIONS

In this review, we focused on studies showing the potential effects of metformin in CRC, especially its possible mechanisms of action in chemoprevention therapy for colorectal cancers.

KEY WORDS

Metformin, Colorectal Cancer, Anti-Cancer Drugs, Anti-Diabetic Drugs

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Colorectal cancer (CRC) is third most deadly cancer type in the world and the incidence of CRC has been increasing in many countries.⁽¹⁾ Several conventional chemotherapy regimens have been widely used in the treatment of CRC patients.⁽²⁾ Nevertheless, chemotherapy-induced toxicity may limit this treatment in patients. So, it is crucial to identify new therapeutic approaches in combination with traditional therapy to specifically target and eliminate all cancer cells.⁽³⁾

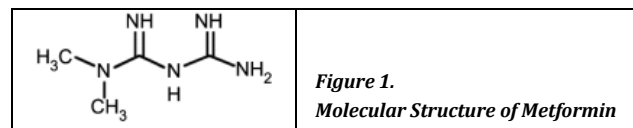
Metformin (1, 1-dimethylbiguanide), a first-line antidiabetic, is being prescribed to over 150 million people in the world at the present time.⁽⁴⁾ It lowers blood glucose concentrations without causing hypoglycaemia and also reduces insulin resistance and plasma fasting insulin level.⁽⁵⁾ Interestingly in addition to its metabolic effects, studies also have shown that metformin may be beneficial for cancer treatment due to anti-cancer properties.⁽⁶⁾ The first study about metformin and cancer by Evans et al showed that the incidence of general cancer was lower in patients metformin-treated patients than other drugs-treated patients.⁽⁷⁾ Since this study a considerable amount of in vivo and in vitro, randomised studies and ongoing clinical trials have indicated that metformin has an antitumour effect in CRCs. Moreover, many studies demonstrated that combined treatment of metformin with other chemotherapeutic and targeted agents synergistically increases the anticancer effect. Taken together, these results propound that metformin may become an alternative adjuvant treatment option for CRC.

A vast number of pre-clinical and clinical studies have suggested that metformin alone or in combination with other chemotherapeutic agents might be useful in the treatment of different forms of CRC. In the current review, we discuss the biology and clinical usage of metformin, the cellular, pre-clinical, and clinical studies that have researched and the possible mechanisms as a potential anti-cancer agent in CRC.

Metformin

Metformin (N-N-dimethylbiguanide hydrochloride, Figure 1) is one of the first preferred oral glucose lowering agents to manage type 2 diabetes.⁽⁸⁾ The herbal line of metformin is based on the use of *Galega officinalis* (also known as French lilac, goat's rue) in Europe.⁽⁹⁾ Metformin was first discovered in 1922 by Emile Werner and James Bell.⁽¹⁰⁾ This compound is effective in reducing the amount of glucose in rabbits and dogs, in contradistinction to other similar compounds, it does not affect heart rate and blood pressure.^(11, 12) In 1957, the doctor Jean Sterne conducted the first clinical trials of metformin and notified the use of metformin to treat diabetes.⁽¹³⁾ Metformin reduces basal glucose output by suppressing glycogenolysis and gluconeogenesis in the liver, and by enhancing glucose uptake in muscles. Moreover, metformin does not directly stimulate insulin secretion.⁽¹⁴⁾ A great number of studies have been expanded to evaluate metformin as an optional treatment potential for polycystic ovary syndrome as well as its antiaging, cardiovascular protective and neuroprotective effects.⁽¹⁵⁻¹⁸⁾ In recent years, several epidemiological, preclinical and clinical studies shed light on the anticancer role of metformin consistently. Studies on various cancer models, including colon, breast, and prostate have indicated the effect of metformin in CSCs by

targeting multiple specific pathways involved in metabolism, cell differentiation, regeneration, and metastasis.⁽¹⁹⁾



Cellular and Pre-Clinical Data

The results of in vivo and in vitro studies in mice and rats confirm that metformin may be an alternative agent in the treatment of colon cancer. Buzzai et al. observed that metformin delayed tumour onset in mice models for p53 mutant colon cancer. It has been found to be selectively toxic in p53 deficient cells (HCT116 p53^{-/-} xenografts) and provides a potential mechanism for decreasing tumour incidence in patients treated with metformin.⁽²⁰⁾ In another study metformin has been demonstrated to have growth inhibitory effects in prostate (PC-3) and colon cancer (HT-29) cell lines.⁽²¹⁾ A study in China showed that the combined use of metformin and vitamin D3 considerably decreases the development of colorectal neoplasia in two colorectal carcinogenesis rodents models and Vitamin D3 increased the chemo preventive effects of metformin in these models. Metformin enhanced also the chemo preventive effects of vitamin D3.⁽²²⁾ A study about anticancer effects of metformin demonstrated that metformin suppressed the azoxymethane (AOM)-induced development of aberrant crypt foci (ACF), a marker of CRC, in BALB/c mice and respectively the polyp growth is suppressed by metformin in ApcMin/+ mice. Inhibition of mTOR phosphorylation was showed in colon cancer models.⁽²³⁾ A study in 2013 showed that metformin might be beneficial in the treatment of IL1 β -induced colon carcinogenesis.⁽²⁴⁾ Nangia-Makker et al. presented that the combined treatment of metformin and other chemotherapeutic agents inhibited cell growth and colonosphere formation in chemo resistant colon cancer cells and it may be an effective treatment regimen for recurrent CRC.⁽²⁵⁾ Zhang Y et al reported the synergistic effect of metformin and 5-Fluorouracil (5-FU) on the proliferation of human colorectal cancer cell line (SW620) and they showed that metformin in combination with 5-FU remarkably inhibited the proliferation of CSCs.⁽²⁶⁾ The anticancer effect of metformin on 1,2-dimethylhydrazine (DMH)-induced colon tumour adenocarcinomas were studied in non-diabetic rats and it was found that metformin decreased the invasiveness of colon carcinomas.⁽²⁷⁾ The effects of metformin on colon cancer were researched in diabetic and non-diabetic mice and it markedly decreased histopathological scores in diabetic mice colons.⁽²⁸⁾ The proliferation of precancerous lesions in colonic tissues was significantly reduced following metformin treatment in diabetic rats. Moreover, metformin also reduced the imbalance between glycolysis and oxidative phosphorylation and reverse the Warburg effect.⁽²⁹⁾ Geagea et al. showed the synergistic effects of metformin and rapamycin in association with the probiotics caused to decreased expression of early lesions in CRC such as ACF in mice with xenografts.⁽³⁰⁾

Clinical Data and Trials

Randomized controlled studies and clinical trials conclude that successful conversion of metformin into clinical practice can be crucial. The first large cohort study was conducted in Tayside, Scotland and this study showed that in diabetic patients receiving metformin, the overall risk of cancer was reduced compared to those receiving other diabetes treatments. This study significantly increased scientific concern in this area, and numerous studies have confirmed its effectiveness in CRC chemoprevention.⁽⁷⁾ Since then, several epidemiologic studies showed that lower colon cancer risk in diabetic patients treated with metformin than in non-metformin users. A pilot study was conducted in Japan to assess the anticancer effect of metformin on ACF and the results of this study showed that the metformin group had a significant reduce in the mean number of ACF, whereas the mean ACF number did not change remarkably in the non-treatment group.⁽³¹⁾ In another study Lee et al conducted a prospective cohort study in diabetic patients from Taiwan treated with or without metformin and this study showed that metformin was able to reduce incidence rates of CRC and hepatocellular carcinoma (HCC) approximate the levels of non-diabetic patients. However, there was a considerable gender difference with metformin in CRC which advantaged women.⁽³²⁾ Additionally, in a large case-control study of US patients with diabetes, they found remarkable reduced risk of developing CRC with any previous or current metformin use.⁽³³⁾ A retrospective cohort study conducted by Currie et al. in diabetic patients treated metformin, sulfonylurea or insulin, metformin taking patients had the lowest risk of developing colorectal or pancreatic cancer. Adding metformin to insulin treatment reduced cancer progression, whereas insulin alone therapy enhanced the risk of colorectal cancer.⁽³⁴⁾ In a retrospective study of Korean patients with CRC and type 2 diabetes, metformin therapy had a lower risk of CRC and all-cause mortality.⁽³⁵⁾ A retrospective study demonstrated that US patients having type 2 diabetes and CRC had higher survival of 76.9 months treated with metformin as compared with 56.9 months in not-treated with metformin.⁽³⁶⁾ A total of 30,493 Danish patients of which 3391 diagnosed with diabetes and 1962 were treated with metformin and it was found that metformin is related with significant reduce in all-cause mortality compared with patients with diabetes not treated with metformin.⁽³⁷⁾ A case-control study of incident CRCs was conducted in Danish people with type 2 diabetes and they observed that an indication of a chemo protective effect of long-term metformin use for CRC in only diabetics women.⁽³⁸⁾ A cohort study was examined variable levels of metformin exposure and connections with colorectal cancer-specific mortality and it was found that significant associations were determined only for metformin use in the diabetic cohort.⁽³⁹⁾ There are currently 7 ongoing or upcoming clinical studies evaluating the place of metformin in the colorectal cancer (table 1). The results obtained from these clinical studies will evaluate the importance of metformin in the prevention and therapy of CRC and allow the determination of future targets.

Potential Mechanisms of Metformin in CRC

The mechanisms underlying the antineoplastic potential of metformin for colorectal cancer have not yet been fully understood. Metformin can inhibit tumourigenesis in various cancers and tumours by different signalling pathways.

Study	Clinical Trials.gov Identifier	Conditions	Interventions
Metformin Plus Irinotecan for Refractory Colorectal Cancer	NCT01930864	Colorectal Neoplasms; Adenocarcinoma	Drug: metformin Drug: irinotecan
A Randomized, 2 x 2 Factorial Design Biomarker Prevention Trial of Low-dose Aspirin and Metformin in Stage I-III Colorectal Cancer Patients.	NCT03047837	Tertiary Prevention in Colon Cancer	Drug: Aspirin (ASA)+Metformin (MET) Drug: ASA Drug: MET Drug: Placebos
Effect of Adjunctive Metformin on Recurrence of Non-DM Stage III Colorectal Cancer: Open Label Randomized Controlled Study	NCT02614339	Non-DM Stage III Colorectal Cancer	Drug: metformin Drug: control
Metformin Treatment for Colon Cancer	NCT03359681	Colon Cancer	Drug: Metformin Hydrochloride Drug: Placebo oral capsule
Nivolumab and Metformin in Patients with Treatment Refractory MSS Colorectal Cancer	NCT03800602	Colorectal Adenocarcinoma; Metastatic Microsatellite Stable Colorectal Carcinoma; Refractory Colorectal Carcinoma; Stage IV, IVA, IVB, IVC Colorectal Cancer; Colorectal Cancer Metastatic	Drug: Metformin Biological: Nivolumab
Metformin with Neoadjuvant Chemo radiation to Improve Pathologic Responses in Rectal Cancer	NCT03053544	Rectal Neoplasm Carcinoma in Situ Adenocarcinoma	Drug: Metformin
The Chemo preventive Effect of Metformin in Patients with Familial Adenomatous Polyposis: Double Blinded Randomized Controlled Study	NCT01725490	Familial Adenomatous Polyposis	Drug: Metformin Drug: Placebo

Table 1. The Ongoing and Upcoming Clinical Trials with Metformin in Colorectal Cancer Prevention and Therapy

*A registry and results database of privately and publicly supported clinical studies of human participants conducted around the world. Available online: www.ClinicalTrials.gov

The Insulin Growth Factor (IGF) Pathway

Several studies have shown that anticancer action of metformin is related to the disruption of insulin signalling. Insulin-like growth factor (IGF) is a growth hormone playing a key role in normal growth and development. IGF signalling pathway is consist of three ligands (IGF-1, IGF-2, and insulin), three receptors [IGF-1 receptor (IGF-1R), IGF-2R, and insulin receptor (IR)].⁽⁴⁰⁾ IGF-1 not only affects cell proliferation, survival and differentiation, but also genetic damage in healthy cells, therefore IGF-1 plays a critical role in the development of cancer.⁽⁴¹⁾ Epidemiologic studies have shown a possible association between IGF level and the development of solid tumours such as colon, prostate and breast cancer.⁽⁴²⁾ Furthermore, metformin is known to inhibit IGF-1R activation through the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (Akt) pathway.⁽⁴³⁾ Metformin has been presented to reduce the risk of colon cancer by targeting the IGF pathway ⁽⁴⁴⁾ and previous studies have demonstrated that metformin down regulated intratumoural IGFR-I in CRC ⁽²⁸⁾

AMPK Pathway

The adenosine monophosphate-activated protein kinase (AMPK) is a excessively conserved heterotrimeric kinase, which is considered to be one of the main regulators of cellular energy status and key cellular processes and liver kinase B1 (LKB1) is a well-conserved kinase, required for AMPK activation.⁽⁴⁵⁾ One of the potential anti-cancer mechanisms of metformin is the activation of AMPK inhibits energy consuming pathways and protein synthesis, metformin has been proposed to inhibit cell proliferation through AMPK.⁽⁴⁶⁾ Metformin activates the AMPK pathway in normal and cancer cells. Studies in animal models show that metformin induces AMPK signalling cascade and inhibits tumour growth and colon tumour formation,^(21,23,47) and also studies in cell lines have reported that metformin reduces cell proliferation in colon cancer by AMPK activation.⁽⁴⁸⁾ Metformin treatment also activated AMPK regulates β -catenin to decrease cell proliferation in human colon carcinoma RKO cells.⁽⁴⁹⁾ It is known that activated AMPK inhibits the synthesis of important proteins mediated by mTOR. The phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR pathway is activated for proliferation of CSCs; thus, the mechanism of action of metformin-induced CSC suppression involves the activation of AMPK and the sequential inactivation of mTOR.⁽⁵⁰⁾ In a study, metformin prevented inflamed colorectal epithelial cells and cancer cells by activating the LKB1/AMPK pathway.⁽⁵¹⁾ On the other hand, metformin can inhibits the mTOR pathway in an AMPK-independent pathway by inactivating Rag GTPases.⁽⁵²⁾

Other Mechanisms

The data from several studies have shown that the antitumour activity of metformin might be as an anti-inflammatory agent in some cancer types via inhibition of the nuclear factor-kappa B (NF- κ B) signalling pathway. In a study metformin inhibited initial cellular transformation and suppresses colon cancer stem cells via inhibition of NF- κ B function by blocking a specific signal transduction pathway.⁽⁵³⁾ Sena et al. also demonstrated that metformin has an antiproliferative effect relevant to changes in the expression of Nuclear factor E2-related factor 2 (NRF-2)/NF- κ B pathways, additionally an apoptotic effect on human colon cancer cells.⁽⁵⁴⁾ Numerous studies have indicated that the antitumour effect of metformin may be due to a relationship between metformin and immune cells. In another study metformin inhibited IL-6-induced epithelial-mesenchymal transition signalling by inhibiting STAT3 phosphorylation in colon cancer lines.⁽⁵⁵⁾

CONCLUSIONS

The current review describes the potential use and mechanisms of action of metformin as a chemotherapeutic agent for CRC based on pre-clinical and clinical studies. Evidences in these studies suggest beneficial effects of metformin in reducing the risk of CRC. On the other hand, more long-term randomized trials with different target population are needed to investigate the role of metformin in CRC treatment and its possible use as an anticancer agent in clinical practice. A better understanding of metformin as a

potential chemotherapeutic drug in colon cancer will provide better information for its use as an effective anticancer agent for CRC treatment.

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