Review paper

Metformin in the treatment of colorectal cancer and neuroendocrine tumours

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Colorectal cancer is being detected in increasingly younger age groups, and its incidence has been on the rise in recent years. Neuroendocrine tumors have also shown an increase in occurrence despite their rarity. Neuroendocrine tumors most commonly occur in the gastrointestinal tract and lungs. Therefore, new, better, and more effective treatment methods are being sought. Metformin, a drug commonly used in the treatment of type 2 diabetes, has demonstrated its ability to reduce the incidence and increase the efficacy of chemotherapy in colorectal cancer and neuroendocrine tumors. The biguanide works by inhibiting the mammalian target of rapamycin pathway, activating 5'AMP activated protein kinase, and reducing insulin-like growth factor 1. In studies conducted on human cells and xenografts, the drug has shown its positive effects in combating these tumors by reducing proliferation, slowing the growth of cancer cells, and inhibiting metastasis. The main goal of this review is to comprehensively summarize the current state of knowledge regarding metformin in the treatment of colorectal cancer and neuroendocrine tumors.

Key words: colorectal cancer, neuroendocrine tumours, metformin, metformin in the treatment of colorectal cancer, metformin in the treatment of neuroendocrine tumours.

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Introduction

Colorectal cancer is increasingly detected in the population worldwide, including the younger population of patients under 50 years [1, 2]. Neuroendocrine cancers are rare, but recent data have shown a significant increase in their incidence. The age-adjusted incidence increased 6.4-fold over 40 years (data from 2012: 6.98 cases *per* 100,000 people in the United States) [3]. Typical sites of neuroendocrine tumours (NET) are the gastrointestinal tract (60–70%) and the lungs (20–30%) [4]. The most common therapeutic procedure is surgical resection of the tumour. However, about 50% of patients have metastases at the time of detection, and in this case surgery is not the solution [5]. Systemic treatment is indicated. Currently, somatostatin analogues, the mammalian target of rapamycin (mTOR) inhibitor, sunitinib tyrosine kinase therapy, and peptide receptor radionuclide therapy are used alone or in combination with cytoreductive procedures. Unfortunately, the results are not satisfactory, and it is necessary to look for other solutions [6]. Metformin, commonly prescribed in the treatment of type 2 diabetes, has shown effectiveness in reducing the incidence of colorectal cancer [7]. Metformin may play a promising role in the treatment of neuroendocrine cancers. It was associated with a lower risk of developing cancer and mortality. Metformin demonstrated anticancer activity in preclinical studies by inhibiting the mTOR pathway [8]. The mechanism of action of this biguanide involves activation of the 5'AMP activated protein kinase (AMPK), mTOR receptors, and lowering insulin-like growth factor 1 (IGF-1) [9]. It also influences pathways both dependent and independent of AMPK, slowing down the mammalian target of rapamycin complex 1 (mTORC1) signalling, which contributes to reduction in carcinogenesis [10]. Metformin has been shown to exhibit anticancer activity in both *in vitro* and *in vivo* assays. It has anti-insulin and IGF-1 secretion properties and has an anti-tumour effect associated with AMPK activation and inhibits the tumour suppressor complex (TSC1-2/mTOR), which mediates the expression of liver kinase B1 (LKB1) oncogene [11]. Retrospective investigator experience in patients with advanced pancreatic well-differentiated NET underlines the role of metformin in improving clinical benefit in diabetic patients receiving everolimus and octreotide [12]. Cancer cells exhibit a distinct metabolism compared to normal cells, with a high metabolic diversity within the tumour. Tumours derive energy from aerobic glycolysis and display aberrant activity in the Hippo, Myc, phosphoinositide 3-kinase (PI3K/AKT), p53, and AMPK/LKB1 metabolic pathways [13]. Cancer therapy includes treatments that directly impact the metabolism of tumours. Mitochondria have a significant impact on carcinogenesis due to various metabolic and respiratory processes occurring there. The use of metformin and phenformin has shown substantial anticancer efficacy by targeting mitochondrial complex I;

although, these drugs often lead to lactic acidosis [14]. Reducing insulin and IGF-1 levels results in an anti-cancer effect. It has anti-inflammatory properties by inhibiting cytokine secretion through nuclear factor κB transcriptional blockade [15]. Metformin also stimulates the immune system to combat tumours, and it activates the AMPK pathway, inhibiting cancer cell proliferation and growth. It exerts an anticancer effect independently of AMPK by activating mTORC1, inhibiting cyclin D1, and inactivating the STAT3 pathway. Additionally, metformin reduces glucose uptake by cancer-altered cells [16].

Colorectal cancer

Human cells

Nangia-Makker *et al.* conducted a study on chemotherapy-resistant colorectal cancer cells, examining the synergistic effect of metformin with fluorouracil and oxaliplatin (OXA). The combination of 10 mM metformin with 200 μM fluorouracil and 5 μM OXA resulted in a 70–80% inhibition of growth in the chemoresistant cells after 72 hours [17]. In comparison, these substances alone caused a decrease in growth of chemoresistant cells by 40–60%. It was also demonstrated that the combined therapy inhibited chemoresistant cells at all concentrations used more effectively than metformin alone [17]. In a limiting dilution assay treating cells (seeded in culture with stem cells) with metformin in combination with fluorouracil and OXA for 72 hours led to a reduction in colonospheres by 7–8 fold, compared to metformin alone which reduced colonospheres by 1.5–2 fold. Metformin (10 mM) in combination with fluorouracil and OXA caused a 6-fold decrease in migration of colorectal cancer cells [17] (Table 1).

Huang *et al.* demonstrated that OXA used in the treatment of colorectal cancer acts synergistically with metformin, leading to a reduction in the levels of high-mobility group box 1 protein (HMGB1). High-mobility group box 1 protein has a pro-tumourigenic effect as it contributes to the progression and metastasis of tumours [18]. The study revealed that cells treated with only OXA stimulate the mRNA expression of HMGB1 by activating the colon cancer DLD-1 cells. According to the scheme created by the research team, the expression of HMGB1 was 2 times lower when treating DLD-1 cells first with metformin and then with OXA, compared to the group treated with only OXA [18].

Metformin inhibits HMGB1 expression in DLD-1 cells through extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) signalling pathways. The combination of these 2 drugs resulted in a reduction in the growth of cancer cells and a synergistic cytotoxic effect on DLD-1 cells, without an increase in HMGB1 expression [18].

Cisplatin used in conjunction with metformin has demonstrated greater efficacy in the treatment of colorectal cancer through the PI3K/AKT pathway, whose activity is elevated in tumours. The combination of cisplatin with metformin reduced the expression of p-PI3K and p-Akt while having no impact on the expression of PI3K and Akt themselves [19]. The effect of metformin alone on SW480 and SW620 colorectal cancer cells resulted in relative protein levels in the range 0.6–0.9 for p-PI3K and 0.6–0.9 for SW480 cells, and above 0.9 for SW620 cells for p-Akt. The effect of cisplatin alone on SW480 and SW620 cells resulted in relative protein levels of approximately 0.6 for p-PI3K [19]. However, the effect of cisplatin alone on p-Akt was relative protein levels above 0.6 for SW480 cells, while for SW620 cells, the range was between 0.6–0.9. The combination of metformin with cisplatin led to a decrease in the relative protein levels to values ranging 0.3–0.6 for the expression of p-PI3K and p-Akt for SW480 and SW620 cells [19]. The combination of cisplatin with metformin led to an increase in the generation of reactive oxygen species (ROS), which deactivated the PI3K/Akt pathway. Treating SW480 and SW620 colorectal cancer cells with a combination of metformin and cisplatin resulted in an increase in the relative ROS levels to around 4 units for SW480 cells, while for SW620 cells, the relative ROS level was 2–3 units [19]. Treating both types of cells with metformin alone led to a decrease in the relative ROS levels to the range 1–2 units. Cisplatin used alone on both types of cells caused a decrease in the relative ROS levels to around 2. The combined treatment resulted in increased apoptosis of the studied cells and a more significant reduction in mitochondrial membrane potential compared to metformin or cisplatin alone [19].

Zhang *et al.* also showed that the combination of both substances significantly lowered the levels of Bcl-2 and Mcl-1 proteins, which are responsible for anti-apoptotic effects, while increasing the levels of Bak and Bax proteins, which exhibit pro-apoptotic effects [19] (Table 2).

Metformin has demonstrated anticancer activity when combined with sirolimus. Mussin *et al.* have shown that the combination of metformin with sirolimus in *in vitro* studies resulted in a significant decrease in the proliferation of colorectal cancer cells. The combination of both substances affected the inhibition of proteins associated with the epithelial-mesenchymal transition (EMT), proteins responsible for apoptosis, and a significant decrease in the expression of TGF-β and p-Smad3 (in one of the 3 cell lines examined). Metformin alone exhibited anti-metastatic effects in *in vitro* studies [20].

Metformin has shown synergistic effects with 5-fluorouracil (5-FU) in limiting invasion and proliferation of col-

Table 1. Effects of metformin, fluorouracil and oxaliplatin therapy, and metformin monotherapy on colorectal cancer cells [17]

Parameters	Inhibition of growth in the chemoresistant cells after 72 hours (%)	Reduction in colonospheres after 72 hours	Decrease in migration of colorectal cancer cells
10 mM metformin with 200 μM fluorouracil and 5 μM oxaliplatin	70–80	7–8 fold	6 fold
10 mM metformin	40–60	1.5–2 fold	–

Table 2. Effects of metformin and cisplatin therapy, and monotherapy of metformin and cisplatin, on 2 lines of colorectal cancer cells [19]

Parameters	Lines of colorectal cancer cells	
	SW480 cells	SW620 cells
Metformin alone	0.6–0.9 relative protein levels for p-Akt 0.6–0.9 relative protein levels for p-PI3K Decrease in the relative ROS levels to a range of 1–2	0.9 relative protein levels for p-Akt 0.6–0.9 relative protein levels for p-PI3K Decrease in the relative ROS levels to a range of 1–2
Cisplatin alone	0.6 relative protein levels for p-Akt 0.6–0.9 relative protein levels for p-PI3K Decrease in the relative ROS levels to around 2	0.6–0.9 relative protein levels for p-Akt 0.6–0.9 relative protein levels for p-PI3K Decrease in the relative ROS levels to around 2
Metformin with cisplatin	0.3–0.6 relative protein levels for p-Akt 0.3–0.6 relative protein levels for p-PI3K Increase in the relative ROS levels to around 4	0.3–0.6 relative protein levels for p-Akt 0.3–0.6 relative protein levels for p-PI3K Increase in the relative ROS levels between 2–3

Akt – protein kinase B, ROS – reactive oxygen species

orectal cancer in both *in vivo* and *in vitro* studies. *In vitro* studies revealed the impact of metformin alone on reducing the proliferation and invasion of cancer cells. Metformin in combination with 5-FU, as well as metformin alone, significantly affected the reduction in the number of cells in a human colorectal cancer cell line [21].

Patients

Patients with refractory colorectal cancer undergoing treatment with metformin in combination with 5-FU achieved disease control after 8 weeks, with 22% of patients experiencing tumour stabilisation [22]. These factors resulted in an extension of progression-free survival (PFS) by 2 months and overall survival (OS) by 7.9 months. Miranda *et al.* demonstrated that PFS and OS are prolonged when tumour stabilisation occurs after 8 weeks of treatment in patients [22].

Patients with colorectal cancer who also have diabetes and are taking metformin, compared to patients with colorectal cancer without diabetes, with *KRAS/BRAF* mutations and mismatch repair (MMR) status, do not show a difference in time to recurrence (TTR). The difference is observed in *KRAS*-wild-type (WT) and *BRAF*-WT tumours (double WT), where tumours are twice the size, and non-diabetic patients in the WT subtype have a longer TTR than diabetic patients taking metformin. Patients with double WT mutation, *KRAS* mutation, and proficient mismatch repair (pMMR) with diabetes using metformin did not exhibit a significantly different OS compared to non-diabetic patients. However, researchers Christou *et al.* identified a shorter OS in diabetic patients not taking metformin [23].

Christou *et al.* have indicated that diabetic patients with wild-type *KRAS* and wild-type *BRAF* tumours, *KRAS*-mutant tumours, and tumours with pMMR exhibit lower chances of survival and higher likelihood of disease relapse. In contrast, diabetic patients without metformin with *BRAF*-mutant and/or mismatch repair-deficient tumours experience more adverse outcomes compared to non-diabetic individuals or those with diabetes who are on metformin [23].

The NIHIS-HEALS cohort study in Korea conducted by researchers Lee *et al.* demonstrated that the use of metformin in patients with diabetes resulted in a reduced incidence of colorectal cancer by activating AMPK and inhibiting mTOR. The study also highlights the fact that the decrease in colorectal cancer incidence among diabetic individuals regularly taking metformin could be influenced by their more frequent adoption of a healthy lifestyle and more regular medical screenings compared to the group of diabetic individuals not taking metformin [24].

The meta-analysis conducted by Zhang *et al.* showed that metformin therapy in patients with type 2 diabetes reduced the risk of colorectal cancer by 37%, which was confirmed by multiple sensitivity analyses, and the consistency of the results was estimated in studies with different protocols. In patients without diabetes receiving metformin, a reduction in the number of abnormal crypt foci was observed. Conversely, this phenomenon was not observed in the group not receiving metformin [25].

Regular consumption of metformin led to a 6% decrease in mortality among patients suffering from colorectal cancer who took the medication consistently for one year, along with a 10% increase in adherence to recommendations. A study conducted by Feng *et al.* has shown that the increase in patient survival is dependent on adherence to medication guidelines [26].

Patients with type 2 diabetes who develop colorectal cancer and use metformin show prolonged OS and specific survival compared to patients not taking metformin, as well as compared to type 2 diabetes patients not taking metformin. Individuals with colorectal cancer and type 2 diabetes who use metformin demonstrate an extended survival of 20 months compared to patients not using metformin. This medication also showed a 15% reduction in overall mortality compared to individuals using insulin [27, 28].

The increased survival effect was also observed in a study conducted in the USA, where patients with colorectal cancer and diabetes showed a 13% increase in survival compared to those treated with other antidiabetic medications. Additionally, an increase in OS and PFS was noted in patients taking metformin compared to those taking other hypoglycaemic agents [28].

Xenografts

Metformin in *in vivo* studies showed tumour-suppressive effects in delaying tumour onset in mice with p53 mutation. In other animal studies, it led to a reduction in the development of diet-induced colorectal cancer and in-

hibited the proliferation of colonic epithelium by inhibiting mTOR [25].

In vivo studies showed that the combination of metformin and sirolimus inhibited tumour growth and caused inhibition of proteins associated with mTOR, apoptosis, and EMT [16]. In another *in vivo* study, the combination of 5-FU with metformin inhibited metastasis and proliferation of colorectal cancer. Meanwhile, mice with colorectal cancer xenografts treated with metformin alone also showed a reduction in tumour proliferation and metastasis [21].

Neuroendocrine tumours

Human cells

Herrera-Martínez *et al.* in *in vitro* studies evaluated the effect of metformin on human NET cells of the 2 BON-1 and QGP-1 lines. Both lines showed reduced survival and significantly reduced mRNA of INSR, a key gene in the pathophysiology of NET tumours. In addition, in BON-1 cells, metformin reduced the phosphorylation of the AKT and ERK signalling pathways and significantly reduced their ability to migrate. Also, it was found that metformin reduced serotonin in BON-1 [29]. Inhibition of the AKT, ERK, and mTOR pathways suggests that the antiproliferative effect of metformin may involve both AMPK-dependent and independent pathways [30].

Similar results and conclusions were obtained in another *in vitro* study conducted by Yamana *et al.* Two human NET cell lines, QGP-1 and NCI-H727, were treated with different concentrations of metformin (0, 1, 3, or 5 mM). These results showed that metformin inhibited the NET cell proliferation in a dose-dependent manner. Growth of the neuroendocrine cells in pancreatic tumour QGP-1 was suppressed after metformin treatment by inhibiting cell cycle progression. Metformin induces QGP-1 cell apoptosis by altering the expression of an apoptosis-associated protein [31].

In a study conducted by Vitali *et al.*, cultured cells obtained from surgically removed pancreatic NET were exposed to metformin. The drug has been shown to reduce cell proliferation [32]. The study was expanded using QGP-1 cells and employing different concentrations of metformin. Decreased levels of cyclin D1, a cell cycle-regulating protein, and accelerated apoptosis in QGP-1 cells have been demonstrated. Regardless of the concentration, metformin significantly reduced the number of cells [32]. Another part of the study involved assessing cancer cells after simultaneous administration of metformin and octreotide. Both drugs separately have anti-proliferative and apoptosis-inducing effects, but there were no synergistic effects when they were used together [32].

One of the mTOR inhibitors used is everolimus. However, its use in the treatment of neuroendocrine cancers is limited due to the development of resistance in cancer cells [33]. A potential solution to this problem could be metformin. The study utilised cultured cells obtained from surgically removed human neuroendocrine tumours. Everolimus and metformin monotherapy reduced the proliferation of neuroendocrine tumour cells. When combined, they were more effective in inhibiting the proliferation of neuroendocrine cancer cells from the pancreas than when used alone. Unfortunately, the synergistic effect has not been confirmed for neuroendocrine cancer cells located in the lungs [6]. Vitali *et al.* conducted further *in vitro* studies on cells from the QGP-1 and H727 cell lines as models for neuroendocrine cancers of the pancreas and lungs. Similar conclusions were drawn as for *in vivo* studies. The combination of metformin and everolimus was more effective than monotherapy at inhibiting QGP-1 cell proliferation. Both metformin and everolimus alone reduced H727 cell proliferation. The incubation time in the first part of the study was 24 hours, but after modifying conditions, extending the incubation time by 7 days, and reducing metformin concentrations, different results were obtained. In monotherapy, both everolimus and metformin reduced cell viability in both lines and reduced cell colonies. What differentiated the results from previous parts of the experiment was that the combination of drugs brought a significantly more beneficial effect, not only limiting cell survival and reducing colonies in QGP-1 cells, but also in H727 cells [6]. Overall, the study concludes that the combination of metformin and everolimus in the treatment of NET provides more benefit than monotherapy with either of these drugs. Additionally, metformin has been shown to be effective in the treatment of everolimus-resistant neuroendocrine cancer cells [6].

Patients

Research conducted by Herrera-Martínez *et al.*, in 2 cohorts of patients with NETs – those with lung carcinoids NET and those with gastroenteropancreatic NET – showed that metformin inhibited cell proliferation in NET cell lines in a dose-dependent manner. The anticancer effects were caused by inhibition of the mTORC1 signalling [29].

The positive effect of metformin on the treatment of neuroendocrine cancers is probably based on the following aspects. Metformin reduces blood glucose, insulin, and IGF-1. In addition, it inhibits mitochondrial oxidation, activates AMPK, and limits antibacterial cell autonomy by inhibiting mTOR. In addition, references have been found in the literature suggesting an oncoprotective effect of metformin. A limited study of 7 patients demonstrated that metformin may interact synergistically with everolimus by inhibiting mTOR and preventing IGF-1 oncogenic axis activation. This evidence suggests that metformin may be used as an anticancer medicine in patients with diabetes [34].

Herrera-Martínez *et al.* come to the conclusion that, in particular, patients with type 2 diabetes treated with metformin had even minor increases in somatostatin receptor (SST), cortisol, and SSTR1, SSTR2, and SSTR3 mRNA levels compared to patients with type 2 diabetes not treated with metformin. Similarly, increases in growth hormone, In1-ghrelin, and ghrelin receptor mRNA levels were observed in metformin-treated patients compared to T2DM patients not taking metformin [29].

While promising in *in vitro* studies, the combination of metformin and everolimus was not confirmed in studies with patients. Hue-Fontaine *et al.* compared the median PFS

of patients with neuroendocrine cancer treated with everolimus. Patients were divided into 3 groups: non-diabetic (n = 165), diabetic patients treated with metformin (n = 19), and diabetic patients treated with other medicines (n = 29). There was no significant difference in median PFS in patients treated with metformin in comparison to others [35].

Conclusions

The contemporary challenge in medicine, which clinicians worldwide strive to address, is improving the quality of life and survival rates of oncological patients. Cancers constitute the leading cause of death globally. According to World Health Organization data for the year 2020, colorectal cancers ranked third in terms of the most frequently diagnosed cancers and second in terms of cancer-related deaths [36]. It should be noted that some colorectal cancers exhibit resistance to conventional 5-FU treatment, whereas the use of metformin in combination with 5-FU significantly reduced proliferation and growth of cancer cells in studies [17]. By inhibiting the mTOR pathway due to AMPK activation and modulating miRNA 21 and 145, metformin possesses potential anti-tumour activity, particularly in treatment-resistant cancers [37].

In vivo studies in animals have also shown a positive impact of metformin on colorectal cancer cells. Metformin exhibited inhibitory effects on tumour development by delaying tumour growth, reducing diet-induced colorectal cancer development, and inhibiting colon epithelial proliferation through mTOR inhibition [26]. The combination of metformin and sirolimus inhibited tumour growth and led to the inhibition of mTOR-associated proteins, apoptosis, and EMT [21]. Additionally, the combination of 5-FU and metformin inhibited metastases and proliferation of colorectal cancer [22].

It is worth noting that, typically, cancer patients receiving metformin were previously using it for diabetes. Most cancer patients without diabetes did not take metformin [38]. Among diabetes patients not taking metformin, the OS was shorter than in diabetes patients taking metformin. However, comparing 2 groups of patients with KRAS-wild and BRAF-wild tumours (double WT subtype), non-diabetic patients in the WT subtype had a longer TTR than diabetic patients taking metformin [24]. Other studies have shown that patients with type 2 diabetes and colorectal cancer who use metformin exhibit extended survival by 20 months compared to those not using metformin [29]. Furthermore, metformin may not only be part of cancer treatment but also a preventive factor [25].

As for neuroendocrine tumours, they occur in the gastrointestinal tract and lungs, treated with surgical intervention, targeted therapy, and chemotherapy [39]. Studies have demonstrated the effectiveness of metformin in these tumours, but researchers disagree on whether the drug concentration is significant. Besides classical everolimus therapy, metformin has also found application in NETs [40]. The combination of everolimus and metformin provided greater benefit than each in monotherapy. The synergistic effect may be based on mTOR inhibition and prevention of IGF-1 oncogenic axis activation [41]. Treatment outcomes have been demonstrated in NET located in the pancreas, in both *in vitro* and *in vivo* studies conducted by Herrera-Martínez *et al.* [42].

Taking into account all the above considerations, based on the presented research, metformin emerges as a promising drug in the treatment of colorectal and neuroendocrine cancers, significantly limiting their proliferation and viability. Its use in conjunction with commonly used anticancer treatment may contribute to improving the quality and length of life of oncological patients; however, this requires further research, including a larger group of patients and a detailed medical history.

Disclosures

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