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# Effects of Metformin on Colorectal Carcinogenesis

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ABSTRACT

Metformin is widely used as an antidiabetic drug in patients with type II diabetes mellitus. In the last years several studies have tested the role of this substance in cancer treatment and prevention, relying on some interesting biological and functional properties of the molecule. Particular attention has been paid to colorectal carcinogenesis. In vitro studies, and intervention studies in animal models, have shown positive effects on biological and surrogate markers of colorectal cancer. In humans, results are still conflicting and inconsistent, however evidence from epidemiological and intervention studies suggests that metformin may reduce the risk of colorectal adenomas, thus exerting a possible chemopreventive effect on colorectal cancer development.

**Abbreviations:** DMII: Diabetes Mellitus Type II; AMPK: AMP-Activated Protein Kinase; MTOR : Mechanistic Target of Rapamycin; ACF: Aberrant Crypt Foci

## Introduction

Metformin (N,N-Dimethylimido-di-carbonimidic diamide) is a biguanidinic derivative used for the cure of diabetes mellitus type II (DMII). It was described by Werner and Bell in 1922. Its hypoglicemic effect was discovered in 1950, but only in 1957 J. Sterne tested it in diabetic patients. Metformin was introduced in clinical practice in Canada in 1970. In recent years, evidence has emerged that, besides the well-known properties of metformin suitable for its use as first-line therapy of DMII, it has some positive effects on key pathways related to cancer, and even to aging. In this review we will discuss in brief the evidence, coming from laboratory, experimental, epidemiological, and a few clinical studies, which suggests a possible use of metformin as chemopreventive drug in colorectal carcinogenesis, at least in selected groups of subjects at increased risk of large bowel malignancy, as those with colorectal adenomas.

### Effects of Metformin on Carbohydrate Metabolism

The effects of metformin on glucose metabolism are mediated by the activation of the AMP-activated protein kinase (AMPK) in response to metabolic stress, which alters the ratio AMP/ATP, through increased consumption or reduced production of ATP, as following hypoxia, glucose deprivation, or inhibition of mitochondrial oxidative phsphorylation. AMPK drives cells from an anabolic to a catabolic state [1]. Metformin in type II diabetic patients inhibits hepatic gluconeogenesis and glycogenolysis, reduces insulin resistance in target tissues, and increases the uptake of glucose in peripheral tissues, especially in the skeletal muscles [2]. The main side effects of metformin are: nausea and vomiting, diarrhoea or constipation, abdominal discomfort, loss of appetite, usually not severe and revertible.

### Effects of Metformin on Cellular Functions and Metabolism

In order to find possible explanations for the potential anticancer action of metformin, we should evaluate the effects of metformin on cell functions linked to cancer cell growth and survival advantage. The mechanistic target of rapamycin (mTOR), a serine/threonine kinase, and the phosphatidilinositol-3-kinase (PI3K)/Akt signalling pathways are strictly connected and involved in the control of cell growth and survival [3]. They integrate growth factor signals with cellular nutrient and energy balance. In this regard,

the introduction of inhibitors and modulators (sirolimus, temsirolimus, everolimus, and second generation mTORC1/mTORC2 dual inhibitors) of the mTOR pathway is attractive and challenging, and they are actively studied also in colorectal cancer [4-7]. It has been hypothesized that metformin may inhibit the mTOR signalling via activation of the AMP-activated protein kinase (AMPK)-dependent and independent pathways [8]. Metformin has pro-apoptotic effects. It has been demonstrated on cell cultures at concentrations similar to doses used for diabetic patients [9,10]. This effect seems mediated by upregulation of bcl2-associated X protein [11]. Autophagy, a process triggered in cells in conditions of energy deprivation, is enhanced in cancer cells by metformin [12]. Furthermore, metformin can inhibit epithelial-mesenchimal transition, cell migration and metastasis in colon cancer cell cultures [13].

Metformin has also anti-inflammatory effects, through inhibition of NF-κB signalling in atherosclerosis animal models and in cell cultures [14,15]. Moreover, growing evidence suggests that metabolic syndrome, or overweight and obesity, are risk factor for several cancers including colorectal [16,17] probably through increased production of inflammatory-related cytokines by the visceral adipose tissue. Interestingly, metformin seems to induce weight loss in obese people without diabetes [18].

### Effects of Metformin on Surrogate Biomarkers of Colorectal Cancer

All the effects of metformin on various cellular functions, pathways, and metabolism may be extremely useful for colorectal cancer prevention, besides for cancer treatment. When considering colorectal cancer prevention, it is mandatory to evaluate the effects of lifestyle or chemopreventive strategies on precursor lesions of colorectal cancer. Indeed, metformin has been tested on earlier and surrogate markers of colorectal cancer risk, i.e., colorectal epithelial cell proliferation, aberrant crypt foci (ACF) and adenomas. ACF are microscopic lesions that develop on the surface of colorectal mucosa after carcinogen treatment in animal models [19] and in humans after exposure to environmental carcinogens, mainly of dietary origin [20]. Metformin has been shown to reduce colorectal epithelial cell proliferation, the number of ACF in Azoxymethane (AOM)-initiated mice [21] activating the AMPK pathway, and the number of intestinal polyps in APC Min/+ mice [22]. Metformin was also effective in reducing the inflammatory environment of the intestine, and oxidative stress parameters [23]. In humans, evidence is weaker, and results controversial, but the effects on epithelial cell proliferation and ACF seem similar [24]. Different doses of metformin (250, 500, and 1500mg/die) were tested in patients with impaired glucose tolerance, undergoing colonoscopy. The mean number of ACF per patients decreased, at 3 and 6 months of treatment, only in the 500 and 1500 mg groups [25]. So far, only one randomized, placebo-controlled trial tested low dose metformin as chemopreventive agent in non-diabetic subjects after polypectomy at index colonoscopy [26]. The administration of metformin was safe, and after 1 year of treatment, patients taking metformin had a reduced prevalence and number of adenomas. Recent metanalyses and retrospective studies showed not conclusive results: as a whole, they seem to suggest that patients taking metformin have a reduced risk of colorectal adenomas [27-30] and one study found that metformin use was associated with reduced risk only for advanced adenomas [31].

## Conclusion

In conclusion, recent evidence, based on pharmacological, biological and functional studies, along with a few epidemiological and clinical studies, though not conclusive, seems to suggest that metformin may have a beneficial effect on colorectal carcinogenesis. However, further clinical trials are needed in order to validate these preliminary results. Metformin may be considered as a promising chemopreventive agent in patients a high risk of developing colorectal cancer.

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