



A REVIEW ON THE ANTI-TUMOR EFFECT OF METFORMIN IN CANCER

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Article Received on 01/10/2016

Article Revised on 21/10/2016

Article Accepted on 10/11/2016

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ABSTRACT

Metformin (1, 1-dimethylbiguanide hydrochloride), an oral biguanide agent, derived from the herb *Galega officinalis* (French lilac), has been widely used for the treatment of type 2 diabetes. Metformin also displays significant growth inhibitory effects in several cancer cell and mouse tumor models. According to a study conducted by the Indian

council of medical research in 2013, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes. In India, gastric cancer is the fifth most common cancer among males and seventh most common cancer among females. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease. A study by an international team of doctors, reported that only 4% of liver cancer patients survive for five years in India compared to 10% to 20% elsewhere. Observational data including registries of patients with type II diabetes have suggested that use of metformin may be associated with a decreased cancer incidence. The knowledge gained from the molecular mechanisms of metformin action could lead to the development of novel therapies. Therefore, metformin has become an attractive stand-all agent for molecular chemoprevention with an extra significant benefit when combined with common chemo or radiation therapy.

KEYWORDS: Metformin, cancer, molecular action, chemoprevention.

1. INTRODUCTION

Metformin (1, 1-dimethylbiguanide hydrochloride), an oral biguanide agent, derived from the herb *Galega officinalis* (French lilac), has been widely used for the treatment of type 2

diabetes. It remains one of the most commonly prescribed drugs, with nearly 120 million prescriptions filled yearly worldwide (Ben *et al.*, 2010).

Metformin also displays significant growth inhibitory effects in several cancer cell and mouse tumor models. In cell culture, metformin inhibits the proliferation of a range of cancer cells including breast, prostate, colon, endometrial, ovarian, and glioma (Dowling *et al.*, 2011). Metformin has been found to induce apoptosis in certain cell lines derived from endometrial cancers, glioma, and triple negative breast tumors (Cantrell *et al.*, 2010; Isakovic *et al.*, 2007; Liu *et al.*, 2009).

The retrospective epidemiological studies that first identified the potential anticancer effects of metformin are difficult to confirm and contain only diabetic patient populations. While cell culture and mouse models have been integral to the characterization of the mechanism of action of metformin in the inhibition of cancer, they are artificial and rely on non-physiological doses of metformin in the presence of excess insulin and growth factors. New, more physiologically relevant *in vitro* models will be required to fully elucidate the mechanism of action of metformin (Dowling *et al.*, 2007).

Additional studies examining all forms of cancer have reported reduced cancer risk in diabetics on metformin (vs no metformin treatment (Libby *et al.*, 2009 and Monami *et al.*, 2009) and lower cancer-related mortality in patients receiving metformin compared to those receiving other standard diabetic therapies (Bowker *et al.*, 2006).

2. METFORMIN AND CANCER STATUS IN INDIA

2.1. Lung cancer

Lung cancer is the leading cause of cancer-related death worldwide, and no effective chemopreventive agents currently exist. Because a majority of lung cancers are associated with tobacco use (85%–90%), the development of chemopreventive agents is a priority for current or former smokers at high risk for this disease (Quinn *et al.*, 2013).

According to a study conducted by the Indian council of medical research in 2013, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes; it is the commonest cancer and cause of cancer related mortality in men (Malik and Raina, 2015).

2.2. Gastric cancer

Gastric cancer (GC) is still the second most common cause of cancer death worldwide, although the incidence and mortality have fallen dramatically over the last 50 years. The development of gastric cancer is a complex, multistep process involving multiple genetic and epigenetic alterations of oncogenes, tumor suppressor genes, DNA repair genes, cell cycle regulators, and signaling molecules. Despite advances in diagnosis and treatment, the 5-year survival rate of stomach cancer is only 20 per cent. Furthermore, surgery and chemotherapy have limited value in advanced disease and there is a paucity of molecular markers for targeted therapy. Since gastric cancer has a very poor prognosis and the 5-year survival rate is very low, a new look at the development of multi-targeted preventive and therapeutic strategies is important to establish methods for primary prevention (Nagini, 2012).

In India, gastric cancer is the fifth most common cancer among males and seventh most common cancer among females (Sharma and Radhakrishnan, 2011). The age range is 35-55 years in the South and 45-55 years in the North. The disease shows a male preponderance in almost all countries, with rates two to four times higher among males than females (Jemal *et al.*, 2011; Yeole, 2008).

2.3. Cervical cancer

Cervical cancer is the commonest cancer cause of death among women in developing countries. Mortality due to cervical cancer is also an indicator of health inequities, as 86% of all deaths due to cervical cancer are in developing, low- and middle-income countries. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease. India has a population of 432.2 million women aged 15 years and older who are at risk of developing cancer. It is the second most common cancer in women aged 15–44 years (Sreedevi *et al.*, 2015).

2.4. Liver cancer

The most common type of liver cancer, hepatocellular carcinoma (HCC), originates from the main liver cell, the hepatocyte. This is different from metastatic liver cancer, which occurs in a different part of the body and spreads (metastasizes) to the liver. The biggest risk factors for HCC are hepatitis C infection, chronic heavy alcohol consumption, and nonalcoholic fatty liver disease related to diabetes and obesity. These factors produce scarring of the liver (cirrhosis), which increases the risk of HCC (Mokdad *et al.*, 2015).

A study by an international team of doctors, published recently in the medical journal Lancet, tracked the cancer patients from 67 countries, including India reported that only 4% of liver cancer patients survive for five years in India compared to 10% to 20% elsewhere.

3. METFORMIN: MECHANISM OF ACTION

The mechanism of metformin action in the treatment of diabetes involves the inhibition of hepatic gluconeogenesis and the stimulation of glucose uptake in muscle (Hundal *et al.*, 2000). These effects are achieved by AMP-activated protein kinase (AMPK) -mediated transcriptional regulation of genes involved in gluconeogenesis in the liver and those encoding glucose transporters in the muscle. The anticancer effects of metformin are associated with both direct (insulin- independent) and indirect (insulindependent) actions of the drug (Dowling *et al.*, 2007).

The anticancer effects of metformin are associated with both direct (insulin- independent) and indirect (insulindependent) actions of the drug (Figure 1). The direct, insulin-independent effects of metformin originate from Liver kinase B1 (LKB1) -mediated activation of AMPK and a reduction in mammalian target of rapamycin (mTOR) signaling and protein synthesis in cancer cells (Dowling *et al.*, 2007). mTOR is a key integrator of growth factor and nutrient signals and is one of the most frequently deregulated molecular networks in human cancer (Markman *et al.*, 2010).

Metformin-mediated AMPK activation leads to an inhibition of mTOR signaling, a reduction in phosphorylation of its major downstream effectors and an inhibition of global protein synthesis and proliferation in a number of different cancer cell lines (Alimova *et al.*, 2009).

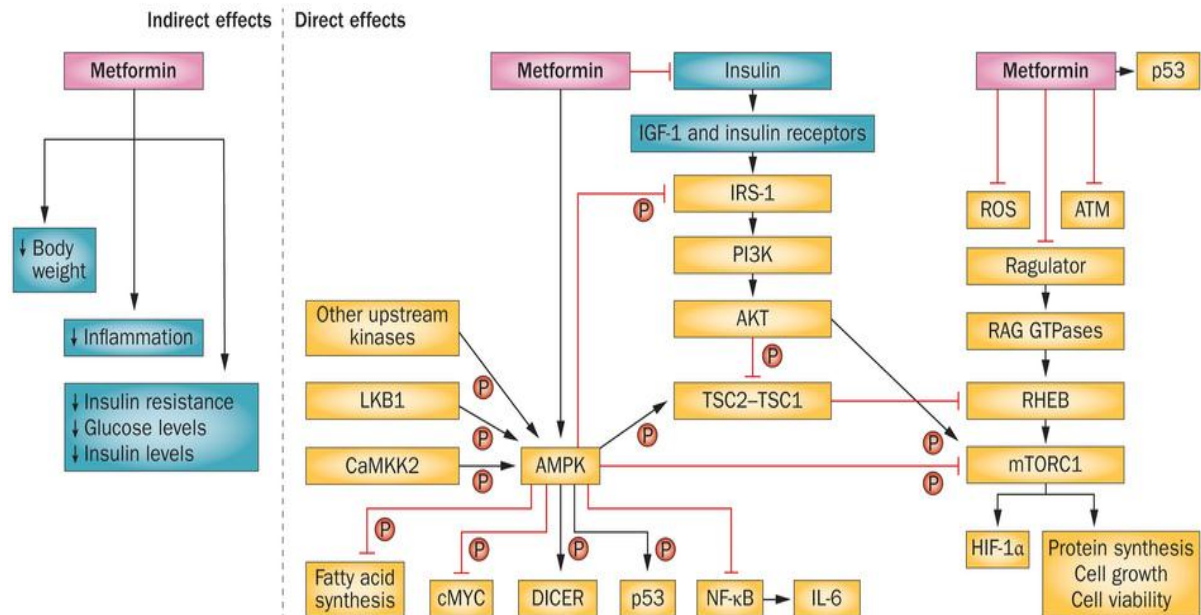


Figure 1: Proposed actions of metformin in cancer. CaMKK2, Calcium/calmodulin-dependent protein kinase kinase 2; IGF-1, insulin-like growth factor 1; IRS-1, insulin receptor substrate 1; IL-6, interleukin 6; LKB1, liver kinase B1; mTORC1, mammalian target of rapamycin complex 1; ROS, reactive oxidative species. (Pernicova and Korbonits, 2014).

The indirect, insulin-dependent effects of metformin are mediated by the ability of AMPK to inhibit the transcription of key gluconeogenesis genes in the liver and stimulate glucose uptake in muscle, thus reducing fasting blood glucose and insulin (Witters *et al.*, 2001). The insulin-lowering effects of metformin may play a major role in its anticancer activity since insulin has mitogenic and prosurvival effects and tumor cells often express high levels of the insulin receptor, indicating a potential sensitivity to the growth promoting effects of the hormone (Belfiore *et al.*, 2008; Frasca *et al.*, 2009).

The effects of metformin on cancer cell proliferation were associated with AMPK activation, reduced mammalian target of rapamycin (mTOR) signaling and protein synthesis, as well as a variety of other responses including decreased epidermal growth factor receptor (EGFR), Src, and mitogen- activated protein kinase (MAPK) activation, decreased expression of cyclins, and increased expression of p27 (Dowling *et al.*, 2011).

4. ANTI TUMOR EFFECT OF METFORMIN

Interim analyses of ongoing studies involving neoadjuvant metformin treatment of newly diagnosed breast cancer patients have demonstrated that metformin is safe and well tolerated,

and exhibits favorable effects on insulin metabolism and tumor cell proliferation and apoptosis (Niraula *et al.*, 2010 and Hadad *et al.*, 2010).

The potential for application of metformin in oncology was first recognized in retrospective epidemiological studies of diabetic patients with cancer. Numerous observational studies reported decreased cancer incidence and cancer-related mortality in diabetics receiving standard doses of metformin (1500 to 2250 mg/day in adults). While the majority of evidence supporting a role for metformin in the treatment of cancer has been derived from retrospective studies involving diabetics, some prospective clinical trials have been completed in nondiabetic patients. In a recent study, low doses of metformin (250 mg/day) reduced the number of rectal aberrant crypt foci (a surrogate marker for colorectal cancer) and decreased the proliferative activity of colonic epithelium (Dowling *et al.*, 2007).

Observational data including registries of patients with type II diabetes have suggested that use of metformin may be associated with a decreased cancer incidence. Therefore, metformin has become an attractive stand-all agent for molecular chemoprevention with an extra significant benefit when combined with common chemo or radiation therapy (Pulito *et al.*, 2013).

An additional benefit for metformin use in oncology is that it's known to modulate energy metabolism, which is a topic that is re-emerging in the cancer field. For instance, cancer cells are often more metabolically active than surrounding non-malignant tissue. As a consequence of this phenotype, any opposition to glucose utilization by low-energy mimetics such as metformin may inhibit tumor proliferation. In fact, recent studies have indicated that tumors carrying mutations in metabolic stress regulators such as LKB1 and p53 undergo substantial apoptosis when treated with biguanides (Shackelford *et al.*, 2013 and Algire *et al.*, 2011).

The clinical safety, well characterized pharmacodynamic profile, and low cost of metformin make it an ideal candidate for development as an anticancer agent. The recent convergence of epidemiologic, clinical and preclinical evidence supporting a potential anticancer effect of metformin has led to an explosion of interest in evaluating this agent in human cancer. Therefore, metformin may become a novel and effective therapy for the treatment and long-term management of gastric cancer, providing additional benefits at low cost (Dowling *et al.*, 2007).

As a stable, inexpensive and highly effective oral drug, metformin has been used for the treatment of type 2 diabetes for several decades. However, the specific mechanisms underlying the effect of metformin on the development and progression of several cancers including gastric cancer remain unclear (Kato *et al.*, 2012).

Interaction of various pathways and drugs and their contribution to the pleiotropic effects attributed to metformin will probably remain a topic of debate in the future. The knowledge gained from the molecular mechanisms of metformin action could lead to the development of novel therapies across multiple fields in medicine with more suitable pharmacokinetic and pharmacodynamic properties (Pernicova and Korbonits, 2014).

5. CONCLUSION

After over 50 years of using metformin for the treatment of type 2 diabetes we continue to learn about how this safe and effective treatment works. The most widely accepted model of the antihyperglycaemic action of metformin is that suppression of hepatic gluconeogenesis occurs principally as a consequence of mitochondrial inhibition. AMPK, which is activated in response to mitochondrial inhibitors, including metformin, has been proposed to be an important effector of metformin. Understanding the molecular mechanism can lead to a more targeted approach to therapy using existing drugs, allowing the development of novel diabetes therapies (Rena *et al.*, 2013).

6. ACKNOWLEDGEMENT

We would like to acknowledge the financial support of Department of Science & Technology (DST) through the INSPIRE fellowship scheme.

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