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Metformin in Cancer Prevention and Therapy: New Application of an Old Drug

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Abstract
Metformin, one of most widely prescribed oral anti-diabetic drug has emerged as a potential anti-cancer drug because of its potential anti-tumorigenic effects that are thought to be independent of its hypoglycaemic effects. Over the last few years, a mass of epidemiologic, outcomes and preclinical data has emerged that demonstrate the potential clinical relevance and the mechanistic basis of the anti-cancer activity of this well tolerated drug.
Several potential mechanisms have been suggested for the ability of metformin to suppress cancer growth in vitro and vivo: activation of LKB1/AMPK pathway, induction of cell cycle arrest and/or apoptosis, inhibition of protein synthesis, reduction in circulating insulin levels, inhibition of the unfolded protein response (UPR), activation of the immune system, and eradication of cancer stem cells.
There is also a growing number of evidence, mostly in the form of retrospective clinical studies that suggest that metformin may be associated with a decreased risk of developing cancer and with a better response to chemotherapy. There are currently several ongoing randomized clinical trials that incorporate metformin as an adjuvant to classic chemotherapy and aim to evaluate its potential benefits in this setting.
This review highlights basic aspects of the molecular biology of metformin and summarizes new advances in basic science as well as intriguing results from recent clinical studies.
Keywords: *Metformin, cancer, molecular action, clinical evidence.*

Introduction

Conventional therapeutic approaches for carcinoma are associated with many adverse effects that reduce quality of life. Therefore, identification of new less cytotoxic treatments is highly important. Metformin, which is commonly used for type 2 diabetes, may reduce cancer risk. A few clinical studies have examined the association between cancer and metformin.

Therefore, the aim of this systematic review was to synthesize the available literature of the potential effect of prevention and treatment of cancer.

Metformin (N0,N0-dimethylbiguanide) is the most widely prescribed oral hypoglycemic agent. It is believed to exert its effect by reducing hepatic glucose production and by increasing insulin sensitivity as well as glucose use by peripheral tissues. [1] Guanidine was the active ingredient of Galega officinalis (goat's-rue or French lilac), which was used to alleviate polyuria in medieval Europe. In the 1920s, diabetes pathophysiology was traced to the pancreas, and in the 1950s metformin and phenformin, the two main biguanides, were introduced.[1,2]

Metformin for the treatment of diabetes was approved in the 1970s in Europe and in 1995 in the United States. Since then, metformin use has been gradually increasing with 25 million prescriptions filled in 2000 and more than 40 million in 2008 in the United States. Its use in diabetes has shown to increase overall survival and prevent macrovascular complications better than other oral hypoglycemic drugs [1]

Metformin now has a wide variety of indications. It has successfully been used in polycystic ovarian syndrome (PCOS), where insulin resistance is a key factor for the development of the metabolic disturbances. In this setting, it has a favorable effect not only on subfertility but also on cardiometabolic aberrations observed in this syndrome, such as hyperlipidemia and hyperten-sion [2]. It is also used in the management of the metabolic syndrome [3] and diabetes prevention [4] in high-risk populations.

Metformin has recently received increased attention for its potential antitumorigenic effects that are thought to be independent of its hypoglycemic effects. This has been evaluated in multiple in vitro and in vivo studies and is now being tested in clinical trials as an adjuvant to classic chemotherapeutic regimens.

Material and Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Studies were gathered by searching PubMed, MEDLINE, EMBASE, LILACS, and the Cochrane database with no time or language restrictions. Studies that evaluated individuals of any age that underwent metformin and had cancer and compared with patients without treatment or patients that use other kind of treatment for HNSCC (drugs or radiotherapy) were considered.

Selected articles were evaluated according to the Critical Appraisal Skills Programs. Of 107 identified citations, 3 studies met the inclusion criteria and were used for qualitative analysis.

Discussion

The current proposed anticancer molecular action of metformin is mainly associated with the inhibition of the mammalian target of rapamycin complex 1 (mTORC1).The mTOR pathway plays a pivotal role in metabolism, growth and proliferation of cancer cell [5]. Metformin is thought to inhibit mTORC1 pathway . It is believed that systemic effect of metformin manifested by the reduction of circulating level of insulin and insulin like growth factor 1 (IGF-1) might be associated with anticancer action [6]. Insulin/IGF-1 is involved not only in regulation of glucose uptake but also in carcinogenesis through upregulation of insulin/IGF receptor signalling pathway [6]. The excessive food consumption (insulin) leads to increased liver production of IGF-1 that binds to IGF-1 receptor and insulin receptor. Then, through insulin receptor substrate (IRS) the signal is transmitted to phosphoinositide 3-kinase (PI3K), and Akt/protein kinase B (PKB) that indirectly activates (not phosphorylates) mTORC1.

Additionally, insulin receptor through growth factor receptor-bound protein 2 (GRB2) propagates signal to Ras/Raf/ERK pathway that drives cell growth. Evidences indicate that these pathways play important role in changes of cellular metabolism that are typical feature of

tumor cells [7]. Increased levels of circulating insulin/IGF1 and upregulation of insulin/IGF receptor signaling pathways were demonstrated to be involved in the formation of many types of cancer. Metformin was found to reduce insulin level, inhibit insulin/IGF signaling pathways, and modify cellular metabolism in normal and cancer cells [8].

Evidences suggest that the inhibition of mTOR pathway by metformin proceeds dependent and independent on AMP-activated protein kinase (AMPK) activation. AMPK phosphorylates tuberous sclerosis complex protein 2 (TSC2) that inhibits mTORC1 leading to decrease in protein synthesis and cell growth [9]. Among the first studies that showed the participation of AMPK activation in antitumor action of metformin were researches performed on breast cancer cells [10,11]. Dowling *et al*. showed that compound C, an inhibitor of AMPK, reversed inhibition of initiation of translation evoked by metformin [10].

Several studies identified that liver kinase B1 (LKB1), a major upstream kinase of AMPK, may be involved in anticancer action of metfromin associated with inhibition of mTOR. *In vitro* and *in vivo* studies revealed that deletion of LKB1 function accelerated proliferation of tumor cell and sensitized them to activators of AMPK such as biguanide [12,13].

Growing evidences from *in vivo* and *in vitro* studies of various cancers revealed that metformin blocked cell cycle in G0/G1 phase with a significant decrease expression of G1 cyclins (including cyclin D1) without changes in p53 status [14,15]. However, others researches indicated that inhibitory effect on cancer cell growth of metformin was associated with p53 activity [16,17]. Taking together the results of preclinical studies are inconclusive whether antitumor action of metformin is associated with p53.

There are currently several clinical trials under way that aim to test the efficacy of metformin as an adjuvant to conventional chemotherapy as well as in combination with new, targeted agents in various settings such as breast, prostate cancer, and other solid malignancies. First, in some of these studies, metformin was tested for the first time in nondiabetic patients. Diabetes and higher serum insulin levels are a well-recognized risk factor for numerous malignancies including pancreatic [18], prostate [19], as well as breast cancer [20].

If insulin is in fact directly involved in the pathogenesis of these cancers, it is reasonable to expect a greater effect size if metformin was tested in diabetic patients and a smaller one in nondiabetics. Significant differences in nondiabetic patients will be very encouraging and will prompt further research in diabetic patients at least for the subset of malignancies where diabetes is a risk factor. In addition, not involving diabetic patients will put the emphasis on the inherent, direct antitumorigenic effects of metformin and not on its indirect ones.

Summary and Conclusion

Review of existing literature revealed that individuals taking metformin had decreased rates of locoregional recurrence and metastasis and improved overall survival and disease-free survival rates. Individuals taking metformin had a lower incidence of cancer than those not taking metformin. Though there are only a few studies on the topic, currently available evidence suggests an inverse association between cancer recurrence and metformin use.

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