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Mini Review

Exploring the Potential of Metformin as an Anti-Cancer Drug in Diabetic Patients: A Review of Current Evidence

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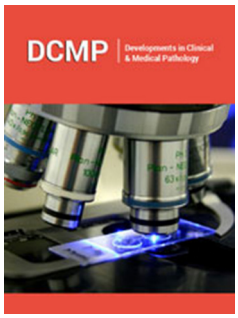

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Introduction

Metformin is the first line antihyperglycemic drug for Type 2 Diabetes Mellitus (T2DM) among the wide array of available drugs due to its minimal side effects and cost-effectiveness. Its mechanism of action includes declining the rate of glycogenesis via Adenosine Monophosphate-Activated Kinase (AMPK) signaling thus increasing glucose influx in myocytes and reducing insulin and blood sugar levels [1-14]. Metformin, a biguanide, apart from its antidiabetic properties was also shown to exhibit anti-cancer effects by blocking intracellular pathways and by stimulating the immune system's T cell-mediated defense against cancer cells [1]. It has drawn attention on a global scale because of its potential to be used to cure or prevent various malignancies. Drug repurposing is an applied treatment strategy that, rather than looking for entirely novel therapeutic agents, explores the additional therapeutic benefits of commercially available medications. Since most currently available oncology drugs have significant negative consequences, poor efficacy, and high expenses, this approach has become of the utmost importance to developing anticancer therapeutics. Metformin is linked to a large decline in neo plasias in general (and breast and prostate cancer in particular), according to epidemiological studies. These findings supported by in vivo and in vitro studies showing metformin's antiproliferative effect on cancer cells, indicate the need for additional study.

The antiproliferative effect of metformin on cancer cells has also been demonstrated in multiple articles, even though the drug's cancer-fighting mechanisms remain to be fully comprehended. According to the research, the following mechanisms frequently contribute to metformin's anti-carcinoma effects. Metformin lowers blood insulin levels, inhibits transcription factors synthesis and thus Unfolded Protein Response (UPR), suppresses protein synthesis and proliferation of cells by activating Ataxia Telangiectasia Mutated (ATM), Liver Kinase B1 (LKB1), and Adenosine Monophosphate-Activated Kinase (AMPK) which reduces mTOR action. It arrests the cell cycle by turning on AMPK and p53 activation, destroys malignant stem cells, prevents angiogenesis and activates the immune system [14-17]. The extracellular glucose concentration significantly influences the anti-cancerous activity of metformin by stimulating AMPK [18]. At low glucose concentrations, metformin exerts its antiproliferative action through major regulators of apoptosis, the ROS/ASK1/JNK or Bcl2 signaling, as endoplasmic reticulum stress is triggered. The glucose withdrawal and metformin inhibit activation of UPR and induce apoptosis contributing further to metformin's antitumor activity [13]. Additionally, the apoptotic effect of metformin has been thoroughly investigated in cancer cell lines of the head and neck [8], liver [19], and ovary Tomic et al. [17] among others.

Numerous investigations on various cancer subtypes have been carried out globally due to metformin's strong anticancer effects. In bladder cancer T2DM patients, metformin intake reduced relapse ($P<0.05$) and advancement ($P<0.05$), as well as improved disease-specific survival ($P=0.002$). Although, metformin failed to prevent cancer occurrence ($P>0.05$) in this 1,270,179 cases cohort from nine studies [7]. Metformin significantly decreased the risk of colorectal benign tumor, advanced adenoma, as well as colorectal cancer ($P<<0.05$), with a greater overall survival rate among metformin users, according to a Singaporean study that analyzed data from 58 studies [12]. Lung cancer occurrence was less likely in T2DM patients on metformin therapy in a cumulative observational study of 13 trials ($P<<0.05$) [20]. Meta-analysis on T2DM cases with breast cancer reported a reduction in chances of breast carcinoma ($OR<1$), a risk reduction of 45 percent, and increased overall survival [3,16]. The impact of metformin administration on biomarkers in patients of breast carcinoma includes low levels of insulin, glycemia, caspase-3, p-Akt, C - reactive protein, and overall lipid profile [15-21].

Atypical endometrial hyperplasia reversal was found in metformin users giving a 51.94% to 34.47% reduction in cell proliferation [10]. Furthermore, a comprehensive evaluation of seven studies found that metformin users had a decreased risk of endometrial cancer recurrence and higher overall survival ($P=0.05$) [2]. Also, a significant reduction in the incidence of ovarian cancer and an improved prognosis was reported in metformin users by a review that included thirteen research studies [15]. Additionally, pancreatic cancer overall survival increased in metformin users as found by two independent studies ($P=0.001$) [6]. Furthermore, in 1,660,795 individuals with carcinoma of the prostate, metformin significantly raised overall and cancer-specific survival along with reduced recurrence ($P<<0.05$), as reported by a systematic review of thirty study cohorts [4].

Therefore, we may state that metformin might be a prospective medicine used in conjunction with other cancer treatments. Metformin is a top competitor for cancer prevention, cancer therapeutic advancements, and tumor non-malignancy, according to several published research stated above. Due to its potential in the treatment of cancer, metformin can be used in radiotherapy and chemotherapy as a complementary drug for cancer treatment and prevention. Notably, synergisms between metformin and several anticancer medications and treatment modalities, including radiation, targeted therapies, and chemotherapy, have been described. Several biological processes may be in charge of the efficacy of metformin's combinatorial effects considering various studies conducted on metformin as a monotherapy and as an adjuvant therapy for cancer treatment and management [5,9,11].

Accordingly, metformin could be used in cancer treatment considering fewer or no side effects, little to no interference with other treatments, cost-effectiveness and accessibility. Future in-depth research and cutting-edge cancer detection and treatment approaches based on cell genomics might aid in understanding the tumor response to the treatment. It is unclear why metformin improved treatment outcomes in some patients while having little impact on others. The reaction to metformin therapy is unambiguous in the context of different cancers studied in different ethnicities. As a result, we require additional knowledge in the domain of genetic polymorphisms, which will be the future focus of in-depth research. Additionally, metformin may be a potential drug for repurposing based on new lines of research in particular populations, including the evaluation of immunotherapy in combination, the efficacy and adverse effects, the method of administration and the record of consumption of this biguanide. In vitro and in vivo evidence of the antiproliferative activity of metformin and several ongoing clinical studies to evaluate its potential as an adjuvant therapy indicate its potential benefits and explain the need to elucidate the precise mechanism of metformin as an anticancer drug.

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