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Review Article

METFORMIN – A HYPOGLYCEMIC DRUG, AS AN EFFECTIVE CHEMOTHERAPEUTIC AGENT: A REVIEW

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ABSTRACT

Diabetes mellitus is chronic metabolic disorder affecting millions of people worldwide. The treatment approach involves different mechanisms. Out of which treating diabetes with biguanide derivative viz. metformin is a reliable one for obese patients who having risk of attaining body weight. Clinical evidence suggests that by using metformin which lowers the risk of cancer in diabetic people. This paper reveals about the beneficial role of a anti-diabetic drug as an effective anticancer drug.

Keywords: Diabetes mellitus, metformin, cancer, anti-diabetic drug.

1.0. INTRODUCTION

Metformin (N,N-dimethyl biguanide) is an oral anti-diabetic drug regularly used for the treatment of Type 2 diabetes mellitus, mainly in obese patients. They reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle.Although it must be used with caution in patients with impaired liver or kidney function, by the stimulation of intracellular enzyme AMP activated protein kinase leading to inhibition of gluconeogenesis in liver and increase in glucose uptake in muscles. In addition to its antidiabetic properties, metformin have also been shown to exert effects anticancer therapy.[1]

2.0. **Metformin in cancer chemotherapy**

Healthy, normal people develop incipient cancer cells in their bodies daily; these cells are normally destroyed by a number of natural processes. When those processes break down, the cancer cells are free to proliferate and form a tumor. Even in their earliest stages, aggressive cancer cells are notoriously energy-hungry, burning calories at a stand frenetic rate as they grow out of control. For that reason, targeting cancer cell metabolism now stands at the forefront of cancer prevention research. With its potent ability to shut off the cellular energy pipeline by activating AMPK, metformin is showing its value in preventing or slowing a host of cancer types in laboratory studies. The consequences of AMPK activation by metformin are numerous. Metformin added of cultures of many different cancer cell types, blocks proliferation by “stalling” cells at one of several phases of the cell replication cycle, preventing them from reproducing. Metformin’s stability to starve cancer cells of energy also enhances the rate of cell death by

the process known as apoptosis, one of the body's natural means of cancer control.[2,3]
Perhaps the most detailed picture of metformin's antiproliferate actions comes from a 2011 study in France Researchers there added metformin to melanoma skin cancer cells in culture,and monitored the effects. At 24 hours, metformin had starved the cancer cells to the point that their replicative cell cycle was arrested . By 72 hours, the cells underwent autophagy, a mechanism where bt starving cells literally "eat themselves" in a desperate attempt o survive.And by 96 hours, The cancer cells began dying off enmasse by apoptosis. Several additional antiproliferate mechanisms have recently been demonstrated for metformin in addition to its effects on the AMPK energy-sensing pathway. That ability to act by multiple mechanisms is called pleiotropy. It is powerfully beneficial because it prevents development of resistance to any one pathway. The combined effect of all of main meformin's pleitropic mechanisms is a marked reduction of tumor growth in lab animals implanted with human cancer cells. To date, metformin-induced antiproliferate effects have been demonstrated in cancers of the brain, lung, breast, Ovary, prostate and colon. Human studies are now showing important reductions in various tumor markers when metformin is provided to breast cancer patients prior to tumor surgery .Importantly, in breast cancer cells, metformin is most active against cancer strains that are resistant to standard chemotherapy drugs.[4]

3.0 **Major mechanisms related to anti tumor effects of meformin**:
3.1. Metabolic and signaling effects: More recent experimental evidence indicates that this biguanide can activate AMP-dependent kinase, either by suppressing the tumor suppressor kinase LKB1, or by promoting an increase in AMP: ATP ratios. Activated AMPK can in turn phosphorylate and activate TSC2, a negative regulator of mammalian target of rapamycin [m TOR]. Inhibiting m TOR kinase activity can reduce signaling transduction through the kinase and decrease the efficiency of protein synthesis via decresed phosphorylation of the m TOR targets 4EBP-1 and S6K, which are essential components of the cap-dependent translation machinery.The inhibition of the cap-dependant translation in response to metformin can result in decreased expression of the oncogene Her2 and the cell cycle protein cyclin D1, Illustrating a potential avenue via which metformin can modulate signaling and cell cycle effects. (Figure-1)[5-16]

3.2 .**Direct Mitochondrial effects**
The inhibition of hepatic gluconeogenesis in response to metformin is an AMPK-independent consequence of decreased intracellular ATP levels. This notion suggests that the pleiotropic effects of metformin could be the result of a targeted effect on electron transport in the mitochondria. In light of electron transport in cancer cells is a lethal insult, not because of an ensuing energetic catastrophe-cancer cells derive most of their ATP from glycolysis – but because the accumulation of NADH in the mitochondrial matrix can inhibit the krebs cycle and tha associated amphibolic reactions that support the generation of biomass.[5-16]

3.3.**Immune and hypothalamic effects**
A recent thought- provoking report has shown that metformin can increase the number memory CD8 T cells in wild type mice, and in consequence significantly improve the efficacy of an experimental anticancer vaccine.This report suggested the mechanism that increased fatty acid oxidation in response to metformin can mediate the generation of CD8 T cells.Lastly , Ropelle et al have shown that hypothalamic AMPK activation in response to metformin reverses cancer anorexia in tumor-beraing rats through inhibiting the production of proinflammatory thalamus.[5-16]

4.0.**Clinical evidence for the antitumor and chemopreventive effects of metformin**

4.1.**Metformin on Serum Testosterone and insulin in non-diabetic women with Breast Cancer**

We know that metformin may theoretically reduce cancer risk,through 2 main mechanisms,by activating AMPK,thus mimicking the effect of calorie-energy restriction,which activtes catabolic processes and reduces all energy-consuming processes in the cells,includibg cell proliferation, and by reducing insulin resistance and therefore insulin concentration in blood.We designed our trial to test the effect of different doses of metformin in patients with BC who were not diabetic,with the aim of modifying the hormonal and metabolic parameters linked to the risk of BC recurrences while minimizing drug adverse effects.Our results showed that the dose of 1500 mg/d of metformin causes a significant reduction of insulin and testosterone serum levels.Because the metabolic and hormonal pattern affect BC risk and prognosis,both these changes might have a prognostic importance and open a novel approach to the management of BC.[17,18]

4.2.**Metformin Therapy in patients with type 2 diabetes: Reduces risk of colorectal cancer:**

The results indicate that metformin therapy was associated with an estimated reductionof 37% in the risk of colorectal cancer among patients with type 2 diabetes.In vitro studies have shown that metformin inhibits the proliferation of colorectal cancer cells.In vivo studies have demonstrated that metformin delays tumor onset in mouse models for p53 mutant colon cancer.Another animal model of colon cancer has shown that metformin inhibits colon carcinoma growth stimulated by a high energy diet.Two animal models of colorectal aberrant crypt foci showed that metformin significantly suppresses colonic epithelial proliferation by inhibiting the mammalian target of rapamycin pathway.A randomized clinical trial among nondiabetic patients with a follow up of one month demonstrated that the number of aberrant crypt foci decreased significantly.These findings are encouraging as metformin, in addition to its apparent anticancer properties,has the advantage of high tolerance,affordability,and good compatability with other hypoglycemic agents.[19-22]

4.3.**Metformin impairs the growth of liver kinase B1-Intact cervical cancer cells:**

Metformin is a potential drug for the treatment of cervical cancers, in particular to those with intact LKB1 expression .Administration of cell metabolism agonists may enhance LKB1 tumor suppression,inhibit cell growth, and reduce tumor cell viability via the activation of LKB1 –AMPK signaling.[23]

4.4.**Metformin reduces cisplastin-mediated apoptotic death of cancer cells through AMPK-independent activation of Akt**; The antidiabetic drug metformin reduces cisplastin in vitro anticancer activity through AMPK-independent upregulation of Akt survival pathway.[24]

4.5.**Metformin is a potent inhibitor of cell proliferation in endometrial cancer cell lines**.

This effect is partially mediated through AMPK activation and subsequent inhibition of the m TOR pathway.[25]

4.6. Oral administration of metformin led to a significant reduction in tumor size in a B16 melanoma model.

These data suggest that anti-melanoma effects of metformin are mediated through p21 and AMPK-independent cell cycle arrest ,apoptosis and autophagy associated with p53,mitochondrial damage and oxidative stress.[26]

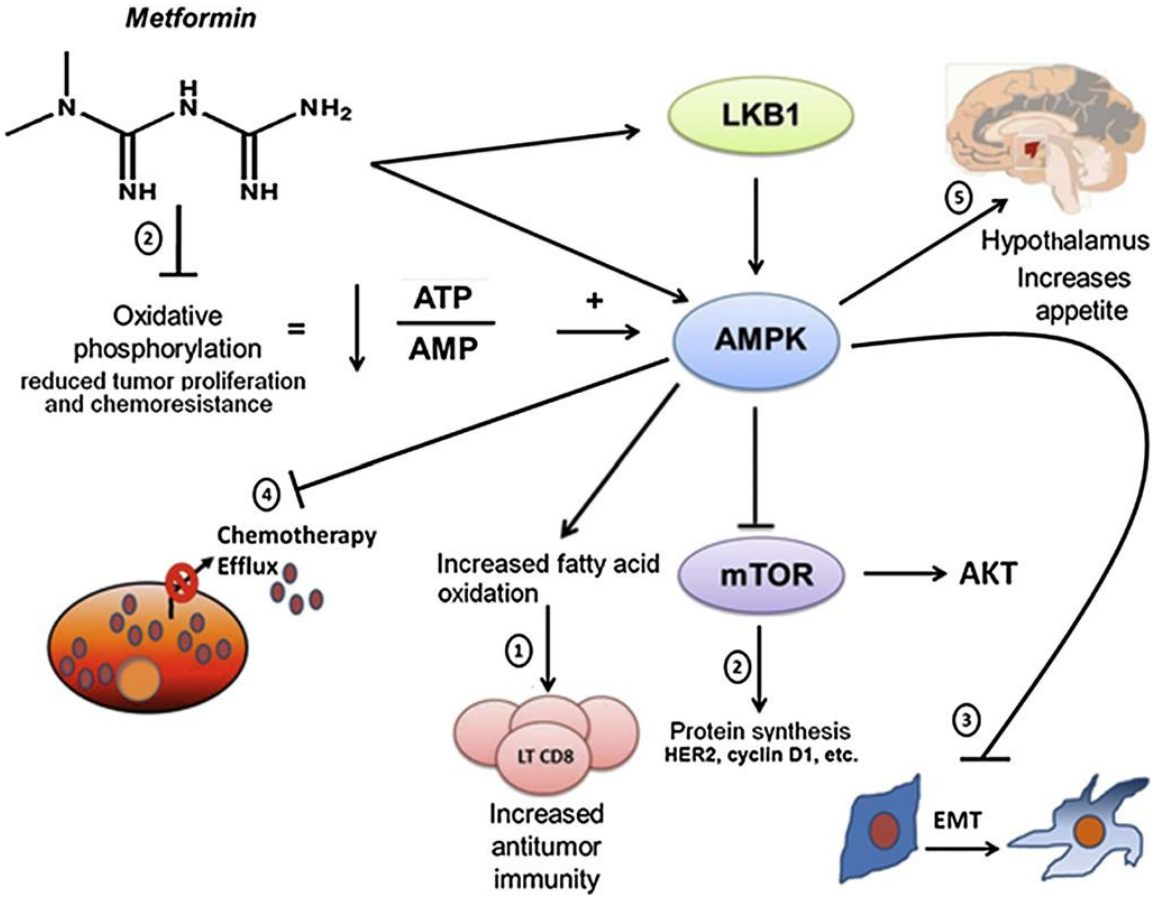

Fig.1

5.0. CONCLUSIONS

Now days Diabetes is a common disorder in elderly people.And on the otherhand the risk of cancer increases with age.Metformin a potent anti-diabetic drug have found its pronounced use in cancers of brain, breast,ovary,lung, prostate.Hence by review of numerous clinical evidences suggests that use of Metformin as anti-diabetic agent lowers the risk of cancer.

6.0. ACKNOWLEDGEMENT

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