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Using Metformin for Cancer Prevention/Treatment

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Review Article

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ABSTRACT

Metformin belongs to the class *biguanides*. Unlike metformin, phenformin and buformin also belong to biguanides which are developed for type-2 diabetes. These biguanides are derived from the herb *Galega officinalis* (French lilac, also known as Goat's Rue or Italian Fitch). Among these Metformin is used widely and taken orally as it is used as anticancer agent. The trade name of Metformin in the market is Glucophage. Metformin helps to control sugar levels in the blood by decreasing the production of glucose in the liver. It also decreases the amount of glucose that is absorbed from the food and increases body's response to insulin, which naturally controls glucose levels in blood. Hence it can be used in the treatment of cancers which are associated with hyperinsulinemia, such as those of the breast and colon. Metformin was discovered in 1922 and it was introduced in 1950s along with phenformin in to the market. Unlike metformin, the other biguanides (phenformin, buformin) were toxic and often caused fatal condition, hence removed from the U.S. market in 1977. This affected the use of metformin in the market. It is also used to treat people with polycystic ovary syndrome in females but cannot be used to treat people with liver diseases or kidney disorders. It has common side effects like nausea, vomitings, diarrhoea, weakness, breathlessness, abdominal pain. Hence, the U.S. Food and Drug Administration (FDA) required large safety studies of metformin.

The review would cover the topics like How the drug has come into the society? How far the drug was useful to the society and pharmaceutical industries? What advantages and disadvantages the drug has? How it can be used as an anticancer agent? How it improves the survival of some breast cancer patients?

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DESCRIPTION

WHAT METFORMIN DOES?

At the cell level, metformin initiates AMP-activated protein kinase (AMPK), a vitality sensor required in directing cell digestion system that is enacted by expansions in the intracellular levels of AMP [1-4]. Metformin by implication enacts AMPK by disturbing complex I of the mitochondrial respiratory chain, which prompts diminished ATP combination and an ascent in the cell AMP: ATP proportion [5-7]. Expanded relationship of AMPK with AMP under such conditions prompts incitement of AMPK action by three components. AMP allosterically enacts AMPK and encourages phosphorylation of its synergist subunit on buildup Thr172 by the upstream kinase liver kinase B1 (LKB1, otherwise called STK11), the protein result of the tumor silencer quality transformed in the Peutz-Jeghers malignancy inclination disorder [8-10]. Official of AMP to AMPK likewise forestalls dephosphorylation of AMPK Thr172 by protein phosphatases. Enacted AMPK phosphorylates various downstream targets prompting incitement of catabolic procedures that produce ATP, for example, unsaturated fat β-oxidation and glycolysis, and concealment of a number of the procedures subject to adequate cell ATP supply, including gluconeogenesis, protein and unsaturated fat amalgamation and cholesterol biosynthesis [11-13].

The system of metformin activity in the treatment of diabetes includes the restraint of hepatic gluconeogenesis and the incitement of glucose uptake in muscle [14,15]. These impacts are accomplished by AMPK-

interceded transcriptional control of qualities required in gluconeogenesis in the liver and those encoding glucose transporters in the muscle, for example, peroxisome proliferator-initiated receptor-γ coactivator 1α (PGC-1α) and glucose transporter sort 4 (GLUT4), separately [16,17]. Thus, metformin improves insulin affectability and brings down fasting blood glucose and insulin in diabetics.

METFORMIN IN CANCER PATIENTS

The potential for utilization of metformin in oncology was recognised in epidemiological investigations of diabetic patients with cancer. Through many studies it is observed that tumor rate and its malignancy is decreased with the use of standard doses of metformin [18-23]. For instance, Evans and colleagues reported decreased danger effects with the subsequent use of metformin in diabetic patients with cancer (vs those who do not take metformin), and also defensive impact increases with greater exposure to the drug. Additional studies analysing all types of malignancy have reported decreased disease hazard in diabetics on metformin (vs no metformin treatment) tumor related mortality in patients getting metformin contrasted with those accepting other standard diabetic treatments. Besides, a late epidemiological investigation of 2,529 ladies with breast cancer reported higher pathologic complete reaction rates (pCRs; considered a surrogate for general survival in this setting) to neoadjuvant systemic treatment in diabetic patients accepting metformin (pCR 24%) contrasted with diabetic patients not getting metformin (pCR 8%) and non-diabetic patients not accepting metformin (pCR 16%) [24]. However, inspite of expansion in pCR, metformin did not altogether enhance the evaluated 3-year backslide free survival rate in this study. Moreover, a comparative investigation in diabetics with prostate cancer with the use of drug did not show much benefits [25]. Thus, further clinical exploration is expected for tumor recurrence and survival with the impact of metformin.

While the restrospective studies involving diabetics have shown the major result of use of metformin in cancer treatment. In a recent study, less amount of metformin decreased the number of rectal aberrant crypt foci (a surrogate marker for colorectal cancer) and proliferative activity of colonic epithelium in non-diabetic patients [26]. Moreover, between times investigations of continuous studies including neoadjuvant metformin treatment of breast cancer patients have shown that metformin is safe and tolerated. It also showed good effects on insulin metabolism and malignancy and apoptosis [27-29].

In a cell culture, metformin also shows inhibitory effects on proliferation of mouse tumor models and cancer cells including breast, prostate, colon, endometrial, ovarian, and glioma [30-35]. The impact of metformin on tumor cells were associated with AMPK activation, lessened mammalian focus of rapamycin and protein synthesis, also from other responses including increased expression of p27 [36]. While not generally seen in all cells, drug has been found o induce apoptosis in certain cell lines derived from endometrial cancers, glioma, and triple negative breast tumors [37].

Further studies, showed that the use of metformin also targeted the cancer-initiating cells. For instance, the ability to form tumors in mice was decreased with the use of metformin because of its inhibitory effects on breast cancer cells [38-41]. Metformin when combined with trastuzumab, it decreases the cancer-initiating cells in Her2-amplified breast cancer cells [42,43]. Likewise, it may also control the cancer-initiating cells by transcriptionally repressing the procedure of epithelial to mesenchymal [44-47]. Metformin also supresses the development of breast, colon and other tumors in transgenic mice and decreases tumor xenografts those established form breast and prostate cancer cells [48,49].

MECHANISM OF METFORMIN

The action of the drug can be both direct (insulin- independent) and indirect (insulin-dependent). The impact of metformin in indirect, insulin-dependent action can be noticed by AMPK ability to inhibit transcription of gluconeogenesis genes in liver and stimulate the uptake of glucose by muscles, further decreasing blood glucose and insulin [50-52]. The insulin-lowering impact of metformin plays a major role in its anticancer action since insulin has mitogenic and prosurvival impacts. The cancer cells rarely express high amounts of insulin receptors, indicating potential impacts to the growth promoting hormones [53]. Hence, obesity and high insulin levels are predictable factors for a variety of cancers particularly seen in those with breast, prostate and colon cancers [54-57]. Thus, metform may reduce the negative impacts of insulin on cancer development. Also it supresses the stimulatory impact of obesity and hyperinsulinemia on lung tumor growth in mice by increasing insulin sensitivity, lowering circulating insulin, and activating AMPK signaling [58]. Likewise, metformin decreased flowing insulin levels by 22% and enhanced insulin affectability by 25% in non-diabetic women with breast cancer, highlighting the insulin-lowering impacts of metformin as a potential system of activity in the treatment of breast cancer [59,60].

The impact of metformin in direct, insulin-independent start from LKB1-mediated activation of AMPK and decrease in mTOR signaling and protein synthesis in cancer cells. AMPK impacts mTOR through phosphorylation and initiation of the tumor silencer tuberous sclerosis complex 2 (TSC2, tuberin), which negatively regulates mTOR action [61-63]. mTOR is an important mediator of the phosphatidylinositol-3-kinase/protein kinase B/Akt (PI3K/PKB/Akt) signaling pathway, which is a standout amongst the most frequently deregulated molecular networks in human cancer [64,65]. Metformin-mediated AMPK acivation leads to hindrance of mTOR signaling, a

lessening in phosphorylation of its major downstream effectors, the eukaryotic start variable 4E-restricting proteins (4E-BPs) and ribosomal protein S6 kinases (S6Ks), and a restraint of worldwide protein union and expansion in various diverse growth cell lines [66-70].

Few recent studies raise the possibility that metformin may intervene additional anticancer impacts independent of AMPK, LKB1 and TSC2 [71,72]. Which means it inhibits Rag GTPase-mediated activation of mTOR by decreasing the mTOR signalling. Incomprehensibly, at least in one cell model framework, loss of capacity of LKB1 sensitized cells to the inhibitory impacts of metformin under states of low glucose [73-75]. Also, metformin lessened hepatic gluconeogenesis by lowering hepatic energy levels without AMPK and LKB1 [76-80]. While these extra impacts are captivating, LKB1-dependent suppression of mTOR signalling remains the key hopeful instrument of antitumor activity of metformin [81-83].

CONCLUSION

In accordance with the recent convergence of clinical, preclinical and epidemiologic evidences, we can safely assume that it is in race for becoming the best anticancer agent due to its low cost, tested and tried pharmacodynamics profile. But there are still many gaps for this drug to become the silver bullet for cancer among human race. For instance, lack of confirmation for of potential anticancer effects of metformin which were tried only diabetic patients initially. The actions of mechanism of this drug depicted by cell structure and mouse models were artificial and totally relying on non-physiological doses when insulin is in excess in the patient [84,85]. Now to have a better understanding of action of mechanism, more physiological 'in-vitro' models are needed that are more relevant in giving enough reason (in both insulin dependent and independent cases) to the clinical community. Even further, more research is required in figuring out of key patient and tumour factors which define metformin's sensitivity. And this is very much critical in identification of patients which may be best suited to be treated with this drug.

However there are many clinical trials examining the use of metformin as an anticancer agent are underway covering different lines of studies in breast, pancreatic, endometrial and prostate cancer patients. When we have right preclinical models being applied to this data, rest assured metformin could be that one good anticancer drug in the coming years.

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