BAOJ Cancer Research & Therapy

Unmesh Vidyadhar Takalkar, et al., BAOJ Cancer Res Ther 2018, 4: 1
4: 048

Short Communication

Metformin: Promising Anti-Neoplastic Agent in Breast Cancer

Unmesh Vidyadhar Takalkar[1*] and Suresh Advani[2]

[1]UnemshVidyadharTakalkar, Chief Medical Director, United CIIGMA Hospital, Department of Oncology, United CIIGMA Hospital, ShahanoorwadiDarga Road Aurangabad, Maharashtra, India

[2]Suresh Advani, United CIIGMA Hospital, Department of Medical Oncology, Aurangabad, Maharashtra India

Abstract

Role of metformin as an anti-neoplastic agent in the prevention and management of breast cancer has been advocated in past few decades. Several endocrinal mechanisms are involved in the etiopathogenesis of breast cancer. Insulin promotes growth and in vitro survival of malignant mammary cells. High risk for breast cancer among diabetics is attributed to activation of the insulin- and insulin-like growth factor (IGF) signalling pathways and increased signalling through the oestrogen receptors. Metformin, an insulin-lowering drug as an anti-cancer agent in the management of breast cancer in the neoadjuvant and adjuvant settings is under evaluation. It might reduce growth and proliferation of malignant cells either through modulation of various molecular pathways directly or down streaming the targets. But its exact mechanism of action remains unclear.

Several cohort longitudinal studies assessed the influence of metformin on breast cancer. Metformin use has been observed to be associated with increased complete pathological tumor response rate, when it is administered as neoadjuvant therapy for breast cancer. Preclinical research study findings need to be translated to clinical settings to study influence of metformin on tumor incidence and progression. Control of insulin resistance and associated hyperinsulinemia will have important implications in the prevention of breast cancer.

Background

Metformin is the most frequently prescribed first-line therapy for the management of Type 2 Diabetes Mellitus (T2DM). It is an oral hypoglycemic agent that belongs to biguanide class. It reduces insulin resistance and diabetes related complications. Generally it is very safe, well-tolerated drug associated with cardiovascular protection due to its favorable action on lipid metabolism. Few adverse effects of metformin reported like gastrointestinal symptoms and lactic acidosis among patients with poor renal function. In past few decades, researchers attracted towards metformin as anti-neoplastic agent for breast, lung, colon, prostate, and ovarian cancers. Various epidemiological and biological studies examined the possible mechanisms by which metformin exerts not only anti-neoplastic but also chemopreventive activities [1]. Administration of metformin in in cancer therapy, especially breast cancer has been extensively debated. Present review discusses the current and future prospectus of metformin as a potential anti-cancer agent.

Breast Cancer and Insulin

Insulin resistance, obesity and T2DM have been linked with increased risk for development of different cancers due to hyperinsulinemia, hyperglycemia and associated state of chronic low-grade inflammation. T2DM has been proposed as a risk factor as well as prognostic predictor for some cancers including breast cancer. High risk for breast cancer among diabetics is attributed to activation of the insulin- and insulin-like growth factor (IGF) signalling pathways and increased signalling through the oestrogen receptor [2,3]. Insulin plays key role in the regulation of blood glucose levels by action on various metabolic pathways, in fatty acid metabolism, protein synthesis, cell growth and proliferation. Some researchers commented that one trait of cancer cells can adept at absobing glucose from blood without need of insulin [4]. Hyperinsulinemia also decreases hepatic secretion of sex hormone-binding globulin (SHBG) resulting in increased circulating estrogen which can be mitogenic

***Corresponding Author:** Unemsh Vidyadhar Takalkar, United CIIGMA Hospital, Department of Oncology, United CIIGMA Hospital, ShahanoorwadiDarga Road Aurangabad, Maharashtra, India, Tel: 9822042425; E-mail: drunmesh.aurangabad@gmail.com

Sub Date: January 18th, 2018, **Acc Date**: January 27th, 2018, **Pub Date**: January 29th , 2018,

Citation: Unmesh Vidyadhar Takalkar and Suresh Advani (2018) Metformin: Promising Anti-Neoplastic Agent in Breast Cancer . BAOJ Cancer Res Ther 4: 048.

for estrogen-dependent breast cancer [5]. But some researchers have documented reduced incidence of cancers among patients of T2DM receiving metformin for glycemic control. This arose interest among researchers about the role of metformin as anti-neoplastic agent for breast cancer. Metformin use has been observed to be associated with increased complete pathological tumor response rate, when it is administered as neoadjuvant therapy for breast cancer. Several endocrinal mechanisms are involved in the etiopathogenesis of breast cancer. Insulin promotes growth and in vitro survival of malignant mammary cells. Hyperinsulinemia has been proposed as adverse prognostic factor.

Metformin as Therapeutic and Chemopreventive Agent In Breast Cancer

Role of metformin in the prevention and management of breast cancer has been studied widely. In preclinical models, metformin has been studied extensively for its anti-neoplastic properties. It might reduce growth and proliferation of malignant cells either through modulation of various molecular pathways directly or down streaming the targets [6]. But its exact mechanism of action remains unclear. Metformin activates AMP-activated protein kinase (AMPK), which inhibits protein synthesis and gluconeogenesis during cellular stress. Activated AMPK inhibits mammalian target of rapamycin (mTOR), a downstream effector of growth factor signaling. In malignant cells, mTOR pathways are frequently activated and associated with resistance to anti-cancer drugs. The inhibition of mTOR in malignant cells is the key mechanism, which facilitates anti-neoplastic activity of metformin. Metformin can induce arrest in cell cycle and apoptosis and reduce growth factor signaling [7]. Dowling RJ et al investigated the molecular mechanisms to study the effect of metformin treatment on mTOR signaling and translation in MCF-7 breast cancer cells. They observed decreased translation initiation associated with mTOR inhibition through AMPK activation. These effects also associated with decreased phosphorylation of S6 kinase, ribosomal protein S6 and eIF4E binding protein 1 [8]. Metformin has been reported to reduce HER2 expression in human breast cancer cells by direct inhibition of p70S6K1, a downstream effector of mTOR [9]. One more proposed mechanism-linking insulin and breast cancer is the deregulation of some components of IGF axis. There is over expression of IGF-I receptors by epithelial breast cancer cells and IGF-II by tumor stroma. Insulin receptor (IR) isoform A (IR-A) is high affinity receptor for insulin and IGF-II in breast cancer cells and on binding they activate unique signaling pattern. This mediates proliferative effects [3].

Metformin has been evaluated as a potential anti-cancer agent in the management of breast cancer. Several cohort longitudinal studies assessed the influence of metformin on breast cancer. Clinical studies in the neoadjuvant and adjuvant settings are ongoing. Dowling et al conducted a neoadjuvant, single arm, "window of opportunity" trial among 39 newly diagnosed operable, non-diabetic early-stage breast cancer women. To study clinical and biological effects, they administered 500 mg metformin three times daily for median of 18 days (range 13-40), period between diagnosis of the disease by biopsy till surgery. Study findings reported significantly decreased levels of insulin and expression of insulin receptors along with reduced phsphorylation of protein kinase B, extracellular signal-regulated kinase1/2 and AMP activated protein kinase. These results demonstrate significant, indirect anti-cancer properties of metformin [10] . Bayraktar Set al explored association between use of metformin and survival outcomes in triple negative breast cancer patients receiving adjuvant chemotherapy with follow up for 62 months. Their study cohort was comprised of 63 cases receiving metformin, 67 diabetics without metformin and 1318 were non-diabetic patients. They observed no significant difference in distant metastasis-free survival, recurrence free survival and overall survival among three groups. Their analysis of data suggest no impact of metformin on overall survival among diabetics using metformin. But patients not receiving metformin had been found to have trend of high risk for distant metastasis [11]. In a randomized presurgical trial, Bonanni B and colleagues studied effect of metformin 850 mg twice a day per week to 200 nondiabetic women with operable breast cancer on the changes in Ki-67 between pretreatment biopsy and post-treatment surgical specimen. On analysis of data, findings showed statistically non-significant effect on Ki-67, but showed statistically significant differences according to insulin resistance, particularly in luminal B tumours [12]. In cohort of study by Jiralerspong et al, diabetic patients with triple negative breast cancer had 24% rate of pathologic complete response among metformin users versus that of 8% among non-metformin users ($p<0.001$). Triple negative breast cancers have been found to be ultra-sensitive to metformin [13].

Metformin exerts multiple actions like inhibition of hepatic gluconeogenesis, improved insulin sensitivity, improved glycemic control; decrease hyperinsulinemia with anti-inflammatory and immuno-modulatory activity. Its anti-tumor activities include inhibition of proliferation of malignant cells, colony formation, arrest of cell cycle, apoptosis and suppression of xenograft tumor growth in mouse models. Hence it helps in improved prognosis and responsiveness to anti-cancer therapy [14]. Numerous preclinical and epidemiological studies have put forth evidences that suggest utility of metformin,an insulin-lowering drug as an anti-cancer agent. Metformin is under evaluation by researchers as chemopreventive agent for breast cancer.Metformin may be effective in breast cancer prevention and treatment [15] . Leone A et al reviewed epidemiologic, clinical, and preclinical evidences reported in literature and suggested 30% reduction in cancer risk in diabetics using metformin and improve outcomes of many common cancers [16]. Martinez JA et al activated a phase II randomized controlled trial to explore effects of metformin among overweight/obese premenopausal women with metabolic syndrome. The study is going to evaluate changes in biomarkers of breast cancer risk like breast density and multiple metabolic disturbances and anthropometric measures [17].

Conclusion

In the present scenario of ever escalating prevalence of breast cancer, there is an urgent need for a focused, direct preventive and therapeutic strategies in the management of breast cancer. Control of insulin resistance and associated hyperinsulinemia will have important implications in the prevention of breast cancer. Data from experimental and epidemiological studies support the use of metformin in the treatment of breast cancer as an anti-neoplastic agent. Preclinical research study findings need to be translated to clinical settings to study influence of metformin on tumor incidence and progression. In future laboratory investigations and large, prospective population clinical trials are necessary to elucidate anti-neoplastic and chemo-preventive actions of metformin in breast cancer.

References:

1. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF , Bost F (2010) Metformin in Cancer Therapy: A New Perspective for an Old Antidiabetic Drug? Mol Cancer Ther 9(5): 1092-1099.
2. Jalving M, Gietema JA, Lefrandt JD, de Jong S, Reyners AK, et al. (2010) Metformin: Taking away the candy for cancer? European Journal of Cancer 46(13): 2369 – 2380.
3. Belfiore A, Frasca F (2008) IGF and insulin receptor signaling in breast cancer. J Mammary Gland Biol Neoplasia 13(4): 381–406.
4. Balasubramanyam M (2014) Diabetic oncopathy - One more yet another deadly diabetic complication! The Indian Journal of Medical Research 140(1): 15-18.
5. Pike MC, Pearce CL, Wu AH (2004) Prevention of cancers of the breast, endometrium and ovary. Oncogene 23: 6379– 6391.
6. Chae YK, Arya A, Malecek M-K, Shin DS, Carneiro B, et al. (2016) Repurposing metformin for cancer treatment: current clinical studies. Oncotarget 7(26): 40767-40780.
7. Alijada A, Mousa SA (2012) Metformin and neoplasia: Implications and indications Pharmacology and therapeutics 133(1): 108-115.
8. Dowling RJ, Zakikhani M, Fantus IG, Pollak M, Sonenberg N (2007) Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells. Cancer Res 67(22): 10804–10812.
9. Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA (2009) The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells. Cell Cycle 8(1): 88–96.
10. Dowling RJ, Niraula S, Chang MC, Done SJ, Ennis M, et al. (2015) Changes in insulin receptor signaling underlie neoadjuvant metformin administration in breast cancer: a prospective window of opportunity neoadjuvant study. Breast Cancer Res 17: 32.
11. Bayraktar S, Hernadez-Aya LF, Lei X, Meric-Bernstam F, Litton JK ,et al. (2012) Effect of Metformin on Survival Outcomes in Diabetic Patients with Triple Receptor–Negative Breast Cancer. Cancer 118(5): 1202-1211.
12. Bonanni B, Puntoni M, Cazzaniga M, Pruneri G, Serrano D, et al. (2012) Dual effect of metformin on breast cancer proliferation in a randomized presurgical trial. J Clin Oncol 30(21): 2593–2600.
13. Jiralerspong S, Angulo AM, Hung MC (2009) Expanding the arsenal: metformin for the treatment of triple-negative breast cancer? Cell Cycle 8(17): 2681.
14. Camacho L, Dasgupta A, Jiralerspong S (2015) Metformin in breast cancer- an evolving mystery. Breast Cancer Research 17(1): 88.
15. Goodwin, Pamela J (2011) Obesity and insulin resistance in breast cancer – Chemoprevention strategies with a focus on metformin The Breast 20: S31 - S35.
16. Leone A, Di Gennaro E, Bruzzese F, Avallone A, Budillon A (2014) New Perspective for an Old Antidiabetic Drug: Metformin as Anticancer Agent. Cancer Treatment and Research 159: 355-376.
17. Martinez JA, Chalasani P, Thomson CA, Roe D, Altbach M, et al. (2016) Phase II study of metformin for reduction of obesity-associated breast cancer risk: a randomized controlled trial protocol. BMC Cancer 16: 500.