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Anticancer and anti-metastatic effects of metformin in cervical cancer: A narrative review

Chandni Patel[1,2*], Rebecca Murerwa[1,2], Thomas Amuti[1,2], Innocent Ouko[1,2]

[1] School of Medicine, University of Nairobi, Nairobi, Kenya.
[2] Research in Medicine (ReMed), Kenya.

***Correspondence**: halaichandni@gmail.com

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Abstract

Background: Cervical cancer is a significant cause of maternal morbidity and mortality despite concerted efforts towards its prevention. The high disease burden is attributed to the high prevalence of HIV, high treatment costs, and inaccessibility to treatment, particularly in developing countries. Multiple interventions, including metformin therapy, have been proposed for cervical cancer management. Metformin is a standard antidiabetic drug. In vitro studies have demonstrated mechanisms through which it can disrupt cervical cancer pathogenesis.

Objective: To review the literature on metformin's anticancer and anti-metastatic effects in cervical cancer.

Methods: Literature searches were performed in the Google Scholar, PubMed, and ScienceDirect databases using keywords 'metformin', 'cervical cancer', and 'direct drug delivery'.

Results: Forty-four studies were included in this review. Metformin acts directly or indirectly on the molecular pathways involved in cervical cancer pathogenesis. Direct inhibition targets protein synthesis and angiogenesis, whereas indirect effects occur through increased insulin levels and the resultant decrease in glucose levels leading to glucose deprivation in cancer cells. The anti-metastatic effects of metformin are dose-dependent; therefore, high concentrations are required to achieve maximum effect. Direct drug delivery of metformin to tumor cells is viable to increase the bioavailability and minimize the systemic effects of metformin.

Conclusion: Metformin is affordable and readily available, with the potential to manage cervical cancer. High doses are needed to achieve anti-metastatic effects. Direct delivery of metformin may mitigate the adverse effects of the required high doses.

Keywords: anticancer, anti-metastatic, cervical cancer, diabetes, nanoparticulate, metformin

Introduction

Cervical cancer ranks fourth among the most common cancers and the third leading cause of cancer-related deaths globally. Africa has the highest age-standardized mortality rate (1). This is due mainly to late detection, which usually occurs when apparent symptoms, including vaginal bleeding, arise (2,3). The high incidence and uncurbed progression of cervical cancer in low-resource settings, especially sub-Saharan Africa, is attributed to the region's high burden of HIV and AIDS (4). The five-year survival rate for stage III-IV cervical cancer is 20% in sub-Saharan Africa (5). However, it is treatable when detected early in stages I-III. In the early stages, interventions to prevent the invasion and migration of cancer cells and their progression to stage IV (metastatic disease) have been explored.

Interventions for the management of cervical cancer include metformin therapy (6). Metformin is a standard antidiabetic drug that is widely available, safe, and affordable. Metformin has been associated with a reduced incidence of cervical cancer in patients with diabetes (7). Various anti-neoplastic properties of metformin have been explored. The activation of adenosine monophosphate protein kinase (AMPK) and its downstream phosphatidylinositol-3-kinase (PI3K) through protein kinase B (AKT) and mechanistic target of rapamycin (mTOR) (PI3K/AKT/mTOR) pathway, which inhibit cellular proliferation, are thought to be critical for its potent effect (8,9). In vitro studies on HeLa cells, used to study cancer medication, demonstrated reduced invasion and migration of cervical cancer cells when exposed to high metformin concentrations (9). This effect could limit the progression of locally advanced diseases. Besides, metformin is safer than existing chemotherapy options that trigger adverse effects such as vomiting, nausea, nephrotoxicity, and myelosuppression (10).

High treatment costs and limited access to care in low and middle-income countries (LMICs) significantly contribute to cervical cancer's increased severity and persistence (11). Metformin is inexpensive and can be self-administered. The translation of the anti-metastatic effects of metformin in vivo may aid in preventing metastasis of cervical cancer cells (7). Although recent literature on its use has shown its potential benefits in the management of cervical cancer, large-scale applicability remains a challenge (12). Additionally, there remains a paucity of data on the anti-metastatic mechanism of action. Therefore, this study aimed to review metformin's anticancer and anti-metastatic effects in cervical cancer.

Methods

Systematic literature searches were performed in the Google Scholar, ScienceDirect, and PubMed databases. The search keywords were: 'direct drug delivery', 'metformin', 'metformin mechanism of action', 'cervical cancer', 'pathophysiology', and 'cancer'. The search period was 1995 to 2020. Studies were considered eligible if they reported on cervical cancer pathophysiology, metformin's anti-metastatic effect in cervical cancer, and direct drug delivery of metformin in cancer management. A backward snowballing method was employed to identify relevant references in selected articles. Non-English articles, duplicates, conference abstracts, case reports, and letters to the editor were excluded. The review was conducted following the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines (13). Forty-eight articles were included in this review.

Results

Invasion and migration of cancer cells

Various molecular and biochemical pathways are involved in cervical cancer cell invasion and migration. Angiogenesis is a critical step in tumorigenesis. A robust blood supply is essential for maintaining tumor growth and facilitating tumor metastasis. Hypoxic conditions in the tumor environment recruit macrophages which synthesize and release angiogenic proteins and mobilize angiogenic proteins from the extracellular matrix (14). Factors commonly expressed in tumor cells include angiogenic proteins such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) (15). The high density of microvessels in tumors is a predictor of metastatic risk and a poor prognosis in cervical cancer (16). The invasion and migration of cancer cells are facilitated by various cellular pathways, including:

- Pro-tumor (M2) macrophages secrete transforming growth factor-beta (TGF-β), matrix metalloproteinases (MMPs), and VEGF, which are involved in tumor metastasis (17).
- Vascular endothelial growth factor increases the motility of cervical cancer cells through VEGF-C-mediated phosphorylation and activation of focal adhesion kinase (FAK) (18). The VEGF-C/Flt-4 axis increases tumor cells' motility and proliferation of lymphatic and vascular endothelial cells (19).
- Cervical cancer's invasive and metastatic potential correlates with FAK expression (20). Downstream effectors, Rac and RhoA,

are activated by FAK, which then activates the development of cell membrane filopodia and lamellipodia required for cancer migration and metastasis (21).

- The activity of matrix metalloproteinases (MMPs) is promoted by oncoproteins E6 and E7 of high-risk human papillomavirus (HPV). Degradation of the extracellular matrix (ECM) facilitated by MMPs facilitates migration and metastasis of cancer cells. Poor prognosis is mainly associated with MMP-2 and MMP-9 (22).

- M2 macrophages express transforming growth factor-beta (TGF-β), which induces epithelial to mesenchymal transition (EMT) through Twist upregulation, thereby enhancing the malignant progression of cervical cancer (23). Changes in gene expression of pro-proliferative and anti-apoptotic molecules, including mitogen-activated protein kinase (MAPK), Wingless type (WNT), and tumor necrosis factor-alpha (TNF-α), are also induced by TGF-β (24).

- Non-coding RNA, metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) promotes tumor growth and metastasis in HPV-positive cervical cells (25). The interactions of molecular mechanisms of MALAT-1, including the advancement of epithelial to mesenchymal transition and MALAT1-miR-124-RBG2 axis, facilitate regulation of gene expression and promote tumor growth and invasion (26).

- Cadherin switch is associated with HPV E6/E7 expression, which results in reduced epithelial-cadherin expression, promoting cell growth and migration and consequently the invasion of cervical cancer cells (27). This is due to the loss of cadherin function, including the maintenance of tissue architecture (28).

- Adenosine monophosphate protein kinase (AMPK) regulates cellular metabolism and energy homeostasis. The dual role of AMPK is implicated in cervical carcinogenesis. Loss of AMPK may result in uncontrolled cell growth in the tumor microenvironment (29). Recent studies have shown that AMPK activation may promote metastasis by promoting epithelial to mesenchymal transformation in cancer cells (30). The cellular environment, isoform activation, and degree of activation determine whether AMPK functions as a tumor suppressor or oncogene (31).

- Cell proliferation, differentiation, metabolism, angiogenesis, and migration are regulated by phosphatidylinositol-3-kinase (PI3K) through protein kinase B (AKT) and mechanistic target of rapamycin (mTOR). Cell membrane phospholipids are phosphorylated by PI3K, allowing AKT recruitment through mTORC1 to promote cell growth and proliferation (20).

Anticancer effect of metformin

Retrospective observational studies have demonstrated that metformin has an anticancer effect in cervical cancer. Han et al. (32) reported a significant decrease in cervical cancer-specific mortality and overall mortality of women diagnosed with diabetes and cervical cancer managed with metformin. An improved disease-free survival without improvement in overall survival among cervical cancer patients managed with metformin was also observed elsewhere (33). The majority of the literature addresses the association between metformin and cervical cancer risk or mortality among people with diabetes (34). There is limited literature on metformin use in cervical cancer management among non-diabetic individuals.

Anti-metastatic effect of metformin

Multiple mechanisms of action through which metformin may exert an anti-metastatic effect in cervical cancer have been described, including:

- Metformin suppresses macrophage polarization towards the M2-type that promotes angiogenesis, migration, and invasion of tumor cells (35). Metformin-directed adenosine monophosphate-activated protein kinase-nuclear factor kappa light chain enhancer of B cells (AMPK-NF-kB) signaling cascade activation polarizes macrophages towards the M1-type (36). Additionally, these macrophages inhibit the anti-tumor immune response.

- Metformin suppresses angiogenesis by two main mechanisms; macrophage polarization to the M1-type and the HER2/HIF-1α/VEGF axis inhibition. M1-type macrophages are associated with reduced levels of VEGF. Lower levels of HER2 expression are associated with lower levels of hypoxia-inducible factor-1α (HIF-1α). Low levels of HIF-1α are associated with a reduction in VEGF expression (37).

- Metformin inhibits matrix metalloproteinases 6 and 9 (MMP-6 and MMP-9), thereby inhibiting migration and invasion of cancer cells. This is accomplished by activating the AMPK/mTOR/autophagy-related pathway and a calcium and protein kinase c-alpha dependent pathway (38,39).

- Metformin suppresses the expression of MALAT-1 and induces expression of a tumor suppressor microRNA (miR-142-3p). The binding of this tumor suppressor to a transcription factor involved in tumorigenesis, high-mobility group AT-hook 2 (HMGA2), inhibits HMGA2 activity impairs the invasion and migration of cervical cancer cells in vivo and in vitro (40).

- Metformin inhibits cervical cancer growth by activating AMPK, which interrupts the AKT/FOXO3a/FOXM1 pathway and the WNT/beta-catenin pathway. Through its action on these pathways, metformin impairs cancer cell proliferation by inhibiting FOXM1, a transcription factor in cervical cancer development and progression (41).

- A study on HeLa cells indicated that DVL3 is inhibited by AMPK, a molecule that positively regulates the WNT/β-catenin pathway. By inhibiting AMPK, metformin suppresses the expression of β-catenin, causing reduced cervical cancer proliferation (42).

- Metformin suppresses TGF-β1, consequently inhibiting the mTOR/p70s6k/PKM2 signaling pathway and epithelial to mesenchymal transition. There is downregulation of pyruvate kinase isoenzyme type M2 by inhibiting mTOR activity, which promotes tumor growth and facilitates aerobic glycolysis (43).

- Metformin suppresses the PI3K/AKT/mTOR pathway by inhibiting PI3K and reducing downstream expression of AKT and mTOR. Inhibition of this pathway results in an anti-tumor immunity glycoprotein, MHC Class I chain-related protein A (MICA), a protein in the major histocompatibility class I (MHC-I) family. MICA binds to natural killer (NK) cells and facilitates the NK cells' killing effect on tumors. The overall effect of metformin on this pathway is decreased cancer cell proliferation and increased cellular apoptosis (9).

- Lamellipodia and filopodia in the HeLa cell line are reduced by metformin. This is thought to occur due to attenuation of FAK and AKT signaling pathways and the resultant Rac1 and RhoA-GTP migratory protein controls reduction. In this way, migration and invasion of cervical cancer cells are inhibited by metformin (44).

Challenges in the clinical utilization of metformin

As an anti-tumor drug, metformin has a bi-modal mechanism of action, first by the direct action on the metabolism of the tumor through inhibiting the protein synthesis pathways, including the AMPK and mTOR pathways and second, indirect action on cancer by reducing the levels of insulin (7). Previous works show that metformin inhibits the transcription of key gluconeogenesis genes in the liver, consequently enhancing glucose uptake by muscle cells. Through these processes, insulin levels tend to reduce (45). In contrast, tumorigenesis is attributed to high levels of insulin that can potentially lead to the fetal isoforms of insulin receptor (IR-A) being activated (46). Metformin as an anti-tumorigenic drug might require doses higher than those recommended for antidiabetic effects. High doses of metformin in systemic route administration may increase systemic adverse effects such as lactic acidosis and possible hypoglycemia (47). More research is required to identify alternative methods of administration that ensure the maintenance of the drug's anticancer effects with minimal adverse effects.

Direct delivery of metformin

Since the anticancer effect of metformin is dose-dependent, direct drug delivery of metformin may achieve targeted delivery, reducing the doses required for the anticancer effect and increasing the bioavailability of the drug. Consequently, the systemic adverse effects are reduced. Direct drug delivery in cervical cancer is possible through microparticulate or nanoparticulate delivery modes. Nanoparticulate delivery systems have been tested in animal models. Nano particulates directly deliver high concentrations at the site of action, reducing the doses required of the drug and thereby reducing systemic adverse effects. This mode of delivery can also be fine-tuned to allow for the slow release of the drug. The tumor's acidic (anaerobic) environment facilitates the nanoparticulate release of the metformin. High metformin concentrations within the tumor cells are therefore attainable (48). Unlike the oral formulations, this direct delivery mode allows for the slow reduction of blood glucose while simultaneously increasing drug bioavailability. Nanoparticulate delivery of metformin is a viable option and potential solution to slow down cervical cancer progression.

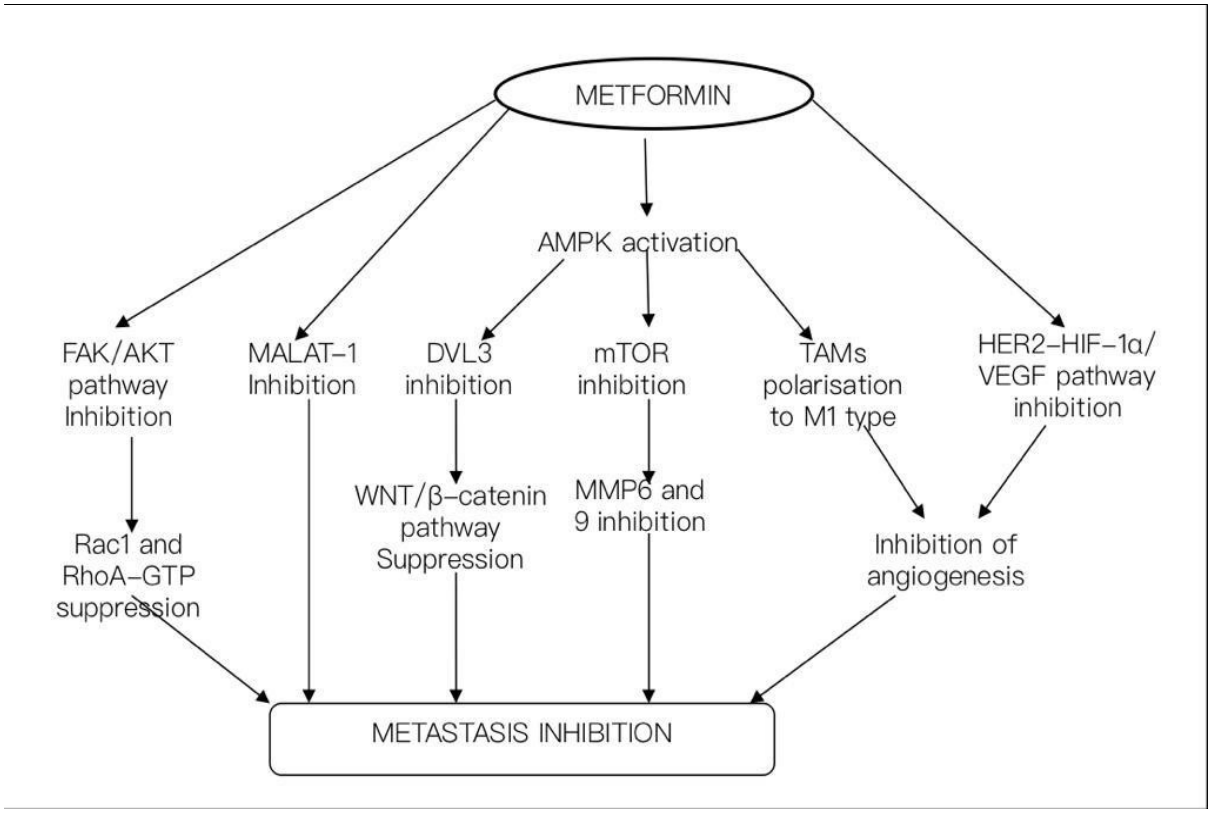

Figure 1: The mechanisms through which metformin inhibits angiogenesis and invasion of cancer cells and eventual inhibition of cervical cancer metastasis.

Limitations

This review did not identify human trials on the management of cervical cancer using metformin. The studies included in this review were in vitro studies that may not yield similar results in vivo. Additionally, studies on metformin in patients without diabetes were not found. The safety profile of metformin in these patients for the management of cervical cancer requires further research.

Conclusion

Metformin is affordable and readily available, with the potential to manage cervical cancer. High doses are needed to achieve anti-metastatic effects. Direct delivery of metformin may mitigate the adverse effects of the required high doses.

Recommendations

Clinical trials are recommended to substantiate the in vitro studies. There is also the need to consider the nanoparticulate mode of delivery in these trials through novel administration methods such as bioadhesive patches, vaginal rings, and vaginal tablets.

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Conflict of interests

The authors declare no conflicts of interest.

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