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Review Article

Effects of metformin on endometrial cancer: Systematic review and meta-analysis

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HIGHLIGHTS

- Metformin use seems to be associated with positive outcomes in atypical endometrial hyperplasia and endometrial cancer.
- Metformin treatment may assist in the reversal of atypical hyperplasia to a normal endometrial histology.
- Metformin treatment may assist in the decrease of tumor biomarkers and in improving overall survival in endometrial cancer.

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ABSTRACT

Background. Endometrial cancer is one of the most common gynecological cancers, which is frequently preceded by atypical endometrial hyperplasia, a premalignant lesion. Metformin, an antidiabetic drug, has emerged as a new adjunctive strategy for different cancer types, including endometrial cancer. This systematic review and meta-analysis aimed to evaluate the effects of metformin in atypical endometrial hyperplasia and endometrial cancer patients.

Methods. The search was conducted on January 2017 and the articles were collected in Cochrane, LILACS, PubMed, Scopus and Web of Science. A grey literature search was undertaken using Google SCHOLAR, ProQuest and Open Grey. Nineteen studies were included, which contained information about the following outcomes: reversal of atypical endometrial hyperplasia, cellular proliferation biomarkers expression and overall survival in metformin-users compared to non-users.

Results. Metformin was associated with reversion of atypical endometrial hyperplasia to a normal endometrial, and with decreased cell proliferation biomarkers staining, from 51.94% (CI = 36.23% to 67.46%) to 34.47% (CI = 18.55% to 52.43%). However, there is a high heterogeneity among studies. Metformin-users endometrial cancer patients had a higher overall survival compared to non-metformin users and non-diabetic patients (HR = 0.82; CI: 0.70–0.95; $p = 0.09$, $I^2 = 40\%$).

Conclusion. Regardless the high heterogeneity of the analyzed studies, the present review suggests that adjunct metformin treatment may assist in the reversal of atypical endometrial hyperplasia to normal endometrial histology, in the reduction of cell proliferation biomarkers implicated in tumor progression, and in the improvement of overall survival in endometrial cancer. Further work on prospective controlled trials designed to address the effects of adjunct metformin on clinical outcomes is necessary for definite conclusions.

Contents

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1. Introduction

Endometrial cancer (EC) is one of the most common gynecological cancers. In 2012, 320,000 new cases and 72,000 deaths related to EC were reported worldwide [1]. The American Cancer Society estimates that approximately 60,050 new EC cases will be diagnosed in the USA in 2016 [2]. The main symptoms of EC are hypermenorrhea, dysfunctional uterine bleeding, and infertility [3]. Tumor classification is based on histological characteristics, grade, and hormone receptor expression (4). Briefly, there are two major histological types of EC: type I, also known as endometrioid or estrogen-dependent, and type 2, non-endometrioid or estrogen-independent. Type I EC comprises 75% to 85% of all cases. It commonly occurs in postmenopausal women, and is associated with a history of polycystic ovary syndrome (PCOS), insulin resistance, obesity and type 2 diabetes mellitus (T2DM). It is usually a low-grade neoplasm, with good prognosis [4,5,6,7]. Conversely, type II EC is a high-grade malignancy, which frequently presents a more aggressive course, often associated with metastasis [4,5,7]. The two subtypes of EC have been shown to have a distinct genetic background, with otherwise diverse etiologies [4].

Endometrial cancer may be preceded by atypical endometrial hyperplasia (AEH), a pre-malignant condition, which may progress to overt malignancy in approximately 20–30% of cases [8]. Some factors that might contribute to cancer progression are menopause hormone replacement therapy, a high body mass index, a family history of colorectal and endometrial cancer, diabetes, parity, and smoking [9]. The first-line approach in all women with endometrial cancer is surgical staging, while definition of the treatment is based on final histopathology, tumor type, grade and staging. Total hysterectomy and bilateral salpingo-oophorectomy with or without regional lymphadenectomy is the standard surgical procedure for EC, but young women with low-risk endometrial carcinoma who wish to preserve fertility may be candidates for treatment with oral progestin therapy, mainly medroxyprogesterone acetate (MPA) or megestrol acetate. However, despite timely and evidence-based treatment, EC sometimes progresses, thus raising the need for the development of new therapeutic strategies especially with the potential of fertility preservation [10].

Metformin is a biguanide widely used in the treatment of T2DM, which has been available in Europe since 1950's [11]. In the last years, evidences from epidemiological studies and clinical trials, as well as experimental studies involving several cancer cell lines, such as thyroid [12], head and neck [13], liver [14], colorectal [15], breast [16], pancreatic [17], among others [18] have raised the interest on the anti-carcinogenic properties of metformin. Furthermore, there has been an effort to understand the mechanisms that underlie the anti-carcinogenic effects of metformin, as an adjunct drug in the long-term management of some types of cancer. It has been proposed that this effect may be indirect or direct [18]. The first is related to the reduction of insulin levels and resistance. The direct effect is associated with the negative modulation of several cellular growth and proliferation signaling pathways. The foremost effect involves alterations in the Adenosine monophosphate/Adenosine diphosphate/Adenosine triphosphate (AMP/ADP/ATP) ratio, which generates a state of cellular energetic stress, and culminates with Adenosine Monophosphate-Activated Protein Kinase (AMPK) activation. AMPK is one of the major mediators of energy homeostasis in the cells. Once AMPK is activated, the subsequent induction of a myriad of tumor suppressor genes, such as Phosphatase and Tensin Homolog/Protein kinase B (PTEN/AKT) and Tuberous Sclerosis Complex 2/Tuberous Sclerosis Complex 1 (TSC2/TSC1), leads to downregulation of growth pathways, specifically Mammalian target of rapamycin (mTOR) signaling [18]. Metformin also affects AMPK-independent pathways responsible for tumor growth and cell proliferation, for instance, decreasing Antigen Ki-67 (Ki-67) and Paired box 2 (PAX2) expression (18, 19). However, diverse pathogenic mechanisms may be involved in different types of cancer and could influence the potential anti-carcinogenic response to metformin.

Considering that some factors associated with AEH or EC development may benefit from metformin therapy, especially insulin resistance and T2DM, the biologic rationale for the use of metformin in these conditions appears to be strong. However, data regarding the effects of metformin in endometrial neoplasms have not been formally summarized. Therefore, we performed a systematic review and meta-analysis to investigate the effects of metformin treatment on the outcomes of AEH and EC.

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