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Metformin in selected malignancies in women

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ABSTRACT

The results of preclinical, epidemiological and clinical studies have shown that metformin, the main drug used in the treatment of type 2 diabetes, has antitumor activity.

Metformin reduces the incidence of malignant neoplasms in various locations, including gynaecological tumours. It lowers morbidity, has a positive effect on the course of the disease and reduces mortality. The mechanism of the antitumor action of metformin is pleiotropic and involves several signalling pathways, including AMPK/mTOR (mitogen activated protein kinase/mammalian target rapamycin), STAT3 (signal transducer and activator of transcription) and numerous factors: NF-KB (nuclear factor kappa), HIF-1 alpha (hypoxia inducible factor 1), IGF-1 (insulin-like growth factor-1), which affect cell proliferation and apoptosis. In addition, metformin eliminates CSCs (cancer stem cells) that are associated with cancer progression, metastasis and resistance to treatment.

The effect of metformin in breast and endometrial cancer is favourable in the vast majority of studies. The results of studies on ovarian and cervical cancer promote metformin as a candidate in the combination treatment of these cancers. More results from meta-analyzes and clinical trials are awaited. It is clearly recognized that metformin as an antidiabetic in women with type 2 diabetes has an advantage over other antidiabetics due to its anticancer activity.

Key words: metformin; breast cancer; endometrial cancer; ovarian cancer; cervical cancer

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INTRODUCTION

Obesity is the main factor in the development of type 2 diabetes (DMT2). Epidemiological studies show that both obesity and diabetes increase the incidence of malignant neoplasms in various locations and increase the mortality rate in some types of cancer. The global trend is towards higher prevalence of obesity and diabetes due to which the rising number of malignant neoplasms may become an increasingly significant issue [1, 2].

It has been shown that throughout obesity and diabetes, hyperinsulinemia, chronic inflammation, and increased levels of adipokines play a main role in the formation of neoplasms. Another pathomechanism is the activation of numerous signalling pathways including canonical Wnt/β catenin, MAPK (mitogen-activated protein kinase), PI3K (phosphoinositide inositol 3 kinase), AMPK (adenosine monophosphate-activated protein kinase), STAT3 (signal transducer and activator of transcription 3) and mTOR (mammalian target of rapamycin), which regulate growth, proliferation, apoptosis, autophagy, angiogenesis and protein synthesis [1, 2]. Metformin has been used as a standard for the treatment of DMT2, especially in overweight and obese people. The drug belongs to the group of biguanides; it is derived from the herb *Galaga officinalis.*

Metformin used in the treatment of people with diabetes has anti-cancer properties. It reduces incidence and mortality of malignant neoplasms compared to other antidiabetic drugs, e.g., sulfonylureas or insulin [3, 4].

A meta-analysis of electronic databases involving 65 540 patients with cancer and diabetes treated with metformin showed a 31% reduction in cancer incidence and a 34% reduction in mortality (RR 0.69 and RR 0.66, respectively) compared with other anti-diabetic compounds [5]

The mechanism of the antitumor activity of metformin is pleiotropic and involves many routes of action, including the following [4, 6, 7]:

- activation of the AMPK/LKB1 kinase pathway (liver kinase B1). AMPK plays a key role in cells: including

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glucose, lipid and energy homeostasis metabolism; metformin increases the of AMPK through LKB1. Activation of AMPK leads to phosphorylation of TSC2 (tuberous sclerosis complex 2), which inhibits mTOR signalling. This results in inhibition of cell proliferation, protein synthesis and angiogenesis, and cell apoptosis. The inhibitory effect of AMPK on mTOR leads to inhibition of the PI3K/Akt pathway, resulting in the suppression of various proteins involved in basic cellular processes such as proliferation and apoptosis;

- direct impact on the mTOR pathway with the result described above, independent of AMPK, LKB1 and TSC2, due to interaction with RagGTPase;
- lowering the concentration of circulating insulin and IGF1, which decreases cell proliferation and supports the reduction of cancer recurrence;
- inhibition of STAT3 phosphorylation of activator of gene expression related to cell survival, resulting in apoptosis;
- inhibition of cyclin D1 activity by the arrest of the cell cycle in the G1 phase resulting in suppression of cell proliferation;
- inactivation of the nuclear kappa factor (NFkB) and hypoxia factor (HIF-1α), which reduces the production of TNFα and IL-6 cytokines, enhancing the anti-inflammatory and anti-angiogenic effect;
- elimination of stem cells;
- elimination of CSCs (cancer stem cells), which are associated with cancer initiation, development of resistance to chemotherapy and radiotherapy, as well as cancer recurrence and metastasis.

The activity of metformin is discussed below in gynaecological malignancies including breast, ovarian, endometrial and cervical cancer.

BREAST CANCER

In 2020, 2 261 419 cases of breast cancer were diagnosed in women worldwide, which accounts for 11.7% of all cancers of both sexes. It is the first cancer in terms of prevalence in the world, the risk factor is 5.20. In 2020, 684 996 women died of breast cancer, which is the fourth neoplasm in terms of deaths among all cancers (risk 1.49) [8]. In epidemiological studies, the administration of metformin in diabetic patients was associated with a reduction in the incidence and mortality of neoplasms, including breast cancer [9]. Metformin has been reported to have anti-inflammatory, antitumor, hepatoprotective, cardioprotective, otoprotective, renoprotective, radioprotective activity, as well as being radiotherapy sensitizing and possessing antioxidant properties. Metformin has been shown to have a synergistic effect with chemotherapeutic agents, especially by acting on breast cancer stem cells both in an *in vitro* and *in vivo* model [10]. It has been noted that the administration of metformin in patients with diabetes and during neoadjuvant treatment for breast cancer increases the pCR (pathological complete response) compared to diabetic patients not receiving metformin and patients without diabetes (pCR 24% vs 8% vs 26%). Moreover, metformin reduces the risk of cancer progression by 23% [11]. In the METTEN — Phase II trial in which metformin was administered as a neoadjuvant treatment in combination with trastuzumab and chemotherapy in women with early-stage HER2 positive breast cancer; pCR was also higher for the metformin group (pCR 65.5 vs 58.6%; p = 0.589). In the metformin group, there was also a higher percentage of breast-conserving procedures (79.3% vs 58.9%; p = 0.089) — however, due to the small group, these data should be treated with caution [12]. A similar group was studied in patients with TNBC (triple negative breast cancer) and no association between the administration of metformin during adjuvant therapy and longer survival of patients with breast cancer was noticed. However, it was observed that breast cancer patients who were not treated with metformin or patients without a diagnosis of diabetes tended to have more distant metastases [13]. In the study by Berstein et al. [14], the status of receptors was determined in patients with breast cancer who, for at least 12 months before the procedure, had been treated for diabetes with metformin or other methods, such as diet, insulin, or sulfonylurea derivatives — in monotherapy or in combination with metformin. The presence of positive estrogen receptors did not differ significantly in the studied groups. However, the frequency of progesterone receptors in women treated with metformin was significantly higher compared to groups using other treatments, which may prove important in the treatment of breast cancer. There is some evidence that the use of metformin on breast cancer cell lines may lead to a reduction in the human epithelial growth factor receptor (HER2) and HER3 levels with possible cell cycle arrest. The Sonnenblick et al. study [9] presents the thesis that the administration of metformin may improve the worse prognosis in diabetic patients treated with insulin, especially in diabetics with HER2-positive and receptor-positive breast cancer. An *in vitro* study on breast cancer cell lines indicated that metformin alone or in combination with cytostatics and/or an inhibitor of the mTOR RA D001 pathway may be a promising option in the treatment of breast cancer [15]. The combination of metformin with everolimus may have a synergistic anti-proliferative effect on breast cancer cells, but these conclusions require further studies before a possible change in treatment standards [16]. It has also been proposed that the combination of metformin with HER2 protein kinase inhibitors in the treatment of breast cancer may be of clinical benefit. Moreover, it has been shown that metformin can suppress molecular resistance to lapatinib and trastuzumab [9]. The study by Yam

et al. [17] investigated the effect of metformin, everolimus and exemestane in overweight and obese postmenopausal women with diagnosed metastatic hormone positive HER2 negative breast cancer. In this phase II study, it was noted that the combination of the above drugs was safe but had moderate clinical benefit for the patients in the study. The MYME study [18] didn't prove the anti-cancer effect of metformin in combination with chemotherapy in the first-line treatment of patients with metastatic breast cancer. Statistically significant lower PFS (progression free survival) was observed in insulin-resistant patients. Pimentel et al. [19] indicated that the administration of metformin in patients without diabetes had no effect on RR (response rate), PFS and OS (overall survival). This does not support the theory of the use of metformin as a treatment regimen for metastatic breast cancer in nondiabetic patients.

Research is ongoing into the immunomodulatory properties of metformin. Meanwhile, 11 ongoing and 13 completed studies show different ways of combining metformin with other molecules in an attempt to achieve the apoptotic effect of breast cancer cells. Unfortunately, the above data indicate that the use of metformin in the treatment of breast cancer still requires research to prove its effectiveness in the prevention and treatment of breast cancer [10].

ENDOMETRIAL CANCER

Endometrial cancer is the most common cancer of the female reproductive system and is detected in developed countries. The recognized risk factors for the growth of this cancer include obesity, hypertension, diabetes mellitus, and pre-diabetes with hyperinsulinemia [20]. Hyperinsulinemia is associated with the formation of this neoplasm in both pre- and postmenopausal women [21]. Type 2 diabetes is also a recognized risk factor for death in this group of patients [22]. The mechanisms of the increased circulating pool of insulin and IGF-1 interactions, and the role of IR and IGF-1R receptors in endometrial carcinogenesis, are not entirely clear.

The endometrium is a hormone-dependent tissue that is influenced by estrogens and progesterone. In the case of a disturbed balance between these 2 hormones, with the predominance of estrogens, excessive cell proliferation and tumor formation occur.

In healthy endometrial tissue, estrogen, through its ER receptor, acts as a transcription factor promoting the production of IGF-1. Additionally, estrogens increase the expression of IGF-1 receptors, i.e., IGF-1R. Progesterone, however, has the opposite effect: through its receptor, it increases the production of IGFBP-1 (IGF-1 binding protein) which in turn, by combining with IGF-1 inhibits its activity. Active IGF-1 stimulates the PI3K/Akt and MAPK pathways, which are responsible for the regulation of cell proliferation and apoptosis [23]. In endometrial cancer, high levels of IGF-1 may also reduce the expression of PR, which is crucial for the cellular response to gestagen therapy. Excess circulating insulin acts on insulin receptors α (IRα) and IRβ. IR α is responsible for the increased proliferation of cells in the EC and its expression in this tumour tissue is increased [24]. Additionally, excess insulin reduces the concentration of SHBG (sex hormone-binding globulin), which then increases the amount of the circulating levels of free estrogens [25]. Higher serum estrogen levels are also associated with, conditions in which aromatase converts androgens into estrogens in adipose tissue.

Metformin has a positive effect on reducing insulin resistance, thus reducing the level of circulating insulin. Additionally, it helps to reduce body fat, which inhibits local estrogen production. In neoplastic tissue, metformin inhibits cellular proliferation and promotes apoptosis, reduces cell migration, and regulates their invasiveness. By sensitizing the tissues to insulin, metformin reduces circulating levels of insulin and IGF-1 and thus inhibits the stimulation of the Akt-dependent pathway. A dose of 500 mg administered three times a day significantly lowers the concentration of IGF-1 in the serum and reduces its expression in endometrial cancer cells [26, 27]. Additionally, it has been noticed that metformin may increase the pool of PR and lower the ER in neoplastic cells [28]. Despite the theoretical premises of the benefits of metformin in the prevention and treatment of endometrial cancer, the results of clinical trials are contradictory and do not provide grounds for the introduction of this drug into everyday practice. A randomized trial evaluated the efficacy of typical and early-stage endometrial cancer sparing treatment with megestrol acetate and megestrol acetate in combination with metformin. The combination therapy was shown to be more effective in precancerous conditions, but not in EC. In patients treated with combination therapy, a complete response was achieved in 39.6% of cases, compared with 20.4% in a group of women treated with gestagens only (OR 2.56; 95% CI 1.06–6.21; p = 0.04) [29]. Another randomized study investigated the effect of metformin on endometrial cancer tissue in women awaiting surgery [30]. The drug was administered quickly, about 1–5 weeks after diagnosis, preceded by curettage of the uterine cavity, up to the planned hysterectomy. Ki69 was assessed as a marker of cell proliferation. This study did not show any effect of preoperative metformin on the degree of cell proliferation in the neoplastic tissue.

A similar study among non-diabetic women with endometroid cancer was conducted in Thailand. In this study, the Ki67 index in neoplastic tissue decreased on average by 23.3% in a metformin-receiving group compared to 5.1% in the placebo group, (p = 0.001) [31]. Some researchers indicate that metformin prevents the formation of endometrial

cancer. A meta-analysis by Chu et al. [32] including seven retrospective studies showed that metformin did not reduce the risk of EC in the general population and in diabetic women (OR 1.05; 95% CI 0.82–1.35; p = 0.70 and OR 0.99; 95% CI 0.78–1.26; p = 0.95). However, it was found that in the group of patients taking metformin, OS improved statistically (HR 0.61; 95% CI 0.48–0.77 — for the entire patient population and HR 0.47; 95% CI 0.33–0.67; p < 0.05 — for patients with diabetes) and the risk of relapse is lower (OR 0.50; 95% CI 0.28–0.92; p < 0.05).

OVARIAN CANCER

Ovarian is the most unfavourable malignant neoplasm of all gynaecological neoplasms due to its prognosis. Approximately 70% of cases are diagnosed in the advanced stages. Despite a positive response to the primary standard treatment in 70–80% of patients, as well as the use of new drugs such as anti-angiogenic antibodies or ADP-ribose polymerase inhibitors, the 5-year survival rate is less than 35% [8].

Metformin — a repositioned drug — is believed to be active in the prevention and treatment of ovarian cancer. Gadducci et al. [33] showed that metformin together with cisplatin in an in vitro study on OVCAR-3 and OVCAR-4 ovarian cancer cell lines induce apoptosis in these cells by affecting the Bcl2 and Bax proteins associated with apoptosis and potentiating cisplatin-induced cytotoxicity.

In vivo studies showed that metformin, either alone or in combination with cisplatin, decreased tumour cell proliferation, tumour growth, reduced tumour size, and inhibited metastasis [34]. This mechanism was associated with a decrease in the expression of cyclin D1 and a decrease in Ki67 as well as inhibition of angiogenesis by suppressing the mTOR pathway [35].

Epidemiological and observational studies have shown that metformin reduces the incidence of ovarian cancer [36, 37]. According to a meta-analysis of the results of electronic databases, metformin significantly reduced the incidence of ovarian cancer among women with type 2 diabetes treated with metformin (OR 0.57; 95% CI 0.16–1.99) [36]. It has also a beneficial effect on the course of ovarian cancer [37–39].

Among 341 women with ovarian cancer, 5-year PFS was significantly higher in DMT2 patients treated with metformin in comparison to diabetic patients who did not use metformin (51% and 23% respectively) [38].

Numerous studies have shown that the use of metformin in patients with ovarian cancer and DMT2 prolongs OS [37, 39]. According to Kumar et al. [39], in a retrospective case-control study, the use of metformin significantly prolongs OS compared to not using metformin in patients with ovarian cancer and diabetes (73% vs 44%; p = 0.0002). Similar results have been provided by long-term studies involving 797 patients with ovarian cancer. OS was significantly higher in patients receiving metformin for DMT2 treatment compared to those not treated with metformin (p = 0.03). The authors deduced that the activity of metformin concerned mainly the inhibition of the AKT/mTOR pathway [37].

A retrospective study by Wang et al. [40]. showed that among ovarian cancer patients using metformin, both PFS and OS are better than in patients with ovarian cancer and DMT2 not using metformin (p = 0.01). In addition, metformin lowers the risk of relapse (p < 0.01).

Previous laboratory studies have shown that the beneficial effect of metformin in ovarian cancer is associated with an inhibitory effect on CSCs in vitro and in vivo [41]. This was confirmed in the phase II clinical trial. The effect of metformin on CSCs with markers typical of ovarian cancer (CD 133+ and ALDH+) and clinical response to metformin neoadjuvant treatment and chemotherapy as well as adjuvant regimens in patients who underwent surgery for ovarian cancer in stages II C — IV was assessed. The metformin-treated cancers showed a 2-4-fold decrease in CSCs markers as well as a greater sensitivity to cisplatin. The authors are awaiting the results of phase III studies [42].

A somewhat controversial study on the beneficial effects of metformin has also been published. Romero et al. [38] found no effect on OS, and according to Urpilainen et al. [43], there are no well-defined epidemiological studies to verify metformin as an ovarian cancer preventing drug.

CERVICAL CANCER

Cervical cancer is the second most common malignant neoplasm in women in developing countries. There are approximately 530 000 cases of cervical cancer worldwide annually. It is estimated that in 2040 it will be the cause of approximately 460 000 deaths [8]. Studies have shown that the use of metformin significantly reduces the risk of cervical cancer (OR 0.558; 95% CI 0.401–0.778) [44]. Based on the analyzes performed, the beneficial effect of metformin on the course of the disease was proved. Retrospective studies have shown an increase in disease-free survival in patients with cervical cancer treated with metformin for type II diabetes, compared with patients not taking metformin (DFS 81.5% vs 65%). However, in terms of OS, no statistically significant differences were found between the 2 groups (OS 93% vs 86.8%) [45]. In other studies, elderly patients treated with metformin due to type II diabetes mellitus showed a reduction in mortality after cervical cancer treatment (HR 0.79; 95% CI 0.63–0.98) [46].

The mechanism of metformin action in cervical cancer is complex. It reduces the concentration of circulating insulin, which has a strong mitogenic effect through the insulin-like growth factor 1 receptor (IGF-1), and by reducing hyperglycemia, it reduces oxidative stress that intensifies carcinogenesis [47].

In studies on mechanisms of metformin action in cervical cancer, it was found that, compared to the control group, metformin significantly inhibits the migration of cancer cells and induces apoptosis and cell cycle arrest. Increased expression of the p-AMPK-activated protein kinase and the suppressor p53 protein have been observed.

Independently conducted studies also proved the effect of metformin on the induction of apoptosis and cell cycle arrest as a result of PCNA (proliferating cell nuclear antigen) expression inhibition, as well as its inhibitory effect on the PI3K/AKT pathway. It was observed that metformin regulated the expression of mRNA and MICA and HSP70 proteins on the surface of cervical cancer cells, increasing the cytotoxicity of NK cells [48].

Based on the available research results, it can be concluded that metformin has an antitumor effect in cervical cancer in vitro and in vivo and may serve as a chemotherapeutic agent in the treatment of this cancer. It can also be used as an immunopotentiator and therefore, according to Xia et al. [48], metformin should be considered a viable candidate for combination therapy with immunotherapy.

CONCLUSIONS

The majority of the studies presented showed that metformin used to treat women with DMT2 reduces the incidence of gynaecological cancers. This drug also has a beneficial effect on the course of the disease by prolonging PFS, OS and the reduces the risk of relapse. This is mainly due to the sensitizing effect of metformin on cytotoxicity induced by cytotoxicity and the inhibitory effect on CSCs. Metformin is considered a viable candidate for combination therapies commonly used in the treatment of gynecological tumors in women with DMT2. A number of studies have described controversial results concerning the action of metformin regarding the incidence and course of gynaecological neoplasms. Therefore, further clinical and epidemiological studies, especially into metformin's activity in cancer prevention, are necessary.

Conflict of interest

All authors declare no conflict of interest.

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