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Do endometrial cancer patients benefit from metformin intake?

Czy metformina pomaga pacjentkom z rakiem endometrium?

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Abstract

Objectives: *Since metformin was reported to decrease overall cancer incidence and mortality and to have antiproliferative and antiinvasive properties, we investigated the impact of metformin intake on survival in endometrial cancer patients.*

Material and methods: *Medical records and survival data of 126 patients with endometrial cancer were analyzed retrospectively. U Mann-Whitney and chi-square tests were applied to compare clinicopathological features. Kaplan Meier model with log-rank test was used to compare survival in the subgroups. Cox proportional hazard model was applied to analyze the relationships between particular factors and overall survival.*

Results: *107 patients met study criteria and were divided into three groups: 1) patients with type 2 diabetes and metformin users (n=30), 2) patients with type 2 diabetes and metformin non-users (n=38), 3) patients without diabetes mellitus (n=39). No difference in survival between metformin users versus metformin non-users (p=0,86) was observed. Metformin intake, diabetes mellitus co morbidity, plasma glucose level and BMI appeared without influence on survival. When the analysis was restricted to the subgroup of type I endometrial cancer or to endometroid histological type, still neither metformin intake nor diabetes influenced the prognosis.*

Conclusions: *Metformin intake does not alter overall survival in endometrial cancer patients. Diabetes mellitus has no influence on survival in endometrial cancer patients.*

Key words: **metformin** / **endometrial cancer** / **survival** / **metabolic disorders** / / **diabetes** /

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Streszczenie

Cel pracy: *Wobec doniesień o korzystnym działaniu metforminy polegającym na zmniejszaniu zapadalności i umieralności na choroby nowotworowe oraz o jej właściwościach antyproliferacyjnych i hamujących naciekanie, w tej pracy postanowiliśmy zbadać wpływ metforminy na przeżycie pacjentek z rakiem endometrium.*

Materiał i metody: *Retrospektywnej analizie poddane zostały historie chorób 126 pacjentek z rakiem endometrium. Cechy histopatologiczne porównano przy użyciu testów U Mann-Whitney i chi-kwadrat, a przeżycie pacjentek w podgrupach za pomocą estymatora Kaplana Meiera (test log-rank). Model Coxa zastosowano, żeby określić zależności pomiędzy poszczególnymi czynnikami a całkowitym czasem przeżycia.*

Wyniki: *Do badania zakwalifikowano 107 pacjentek, które podzielono na 3 grupy: 1) pacjentki z cukrzycą typu 2 stosujące metforminę (n=30), 2) pacjentki z cukrzycą typu 2 nieleczone metforminą (n=38), 3) pacjentki niechorujące na cukrzycę typu 2. Nie zaobserwowano istotnej statystycznie różnicy w czasie całkowitego przeżycia pomiędzy pacjentkami leczonymi a nieleczonymi metforminą (p=0,86). Podobnie stosowanie metforminy, współistnienie cukrzycy typu 2, poziom glukozy we krwi i indeks masy ciała (BMI) nie miały wpływu na przeżycie chorych. Zawężając analizowaną grupę do raka endometrium typu I lub do histologicznego typu endometrioidalnego uzyskano takie same wyniki.*

Wnioski: *Zażywanie metforminy nie ma wpływu na czas całkowitego przeżycia pacjentek chorych na raka endometrium. Współistnienie cukrzycy również pozostaje bez wpływu na przeżycie w tej grupie pacjentek.*

Słowa kluczowe: **metformina** / **rak endometrium** / **cukrzyca** / **przeżycie całkowite** / / **zaburzenia metaboliczne** /

Introduction

Endometrial cancer (EC) is a common gynecological malignancy It typically affects postmenopausal women. Obesity, type 2 diabetes, insulin resistance, metabolic syndrome and relative excess of estrogens are among its well-recognized risk factors [1]. Rising obesity and infertility problems in western world populations along with an increasing life expectancy, and thus increasing population of women at high risk of developing endometrial malignancy, imply that endometrial cancer will become an even more substantial public health issue in future.

Metformin is a relatively cheap biguanide drug commonly used as a first-line pharmacological treatment in type 2 diabetes which is characterized by insulin resistance and, consequently, hyperinsulinemia. Metformin acts as an insulin sensitizer and thus decreases serum insulin level. High levels of insulin were proven to promote endometrial proliferation and contribute to endometrial cancer development [2] as well as to be associated with a more aggressive course of the disease in some groups of patients [3]. Therefore several studies concluded that combating insulin resistance may be potentially preventive and therapeutic for endometrial cancer. What has to be emphasized is that whereas the majority of drugs used for treatment of type 2 diabetes decrease serum glucose level, only few of them reduce hyperinsulinemia at the same time.

Several meta-analyses investigating the relation between metformin intake and cancer incidence and mortality were published in recent years. All of them report a decreased overall cancer incidence in metformin users versus metformin non-users among patients with type 2 diabetes and two of them additionally report a decrease in overall cancer mortality [4,5]. However, also all of them conclude that these results need to be confirmed in long-term randomized controlled trials.

A meta-analysis performed by Zhang P et al. confirmed the negative association between cancer incidence and metformin intake for breast cancer, colorectal cancer, liver cancer, pancreatic cancer and additionally a reduced mortality for breast cancer and liver cancer [5]. Another meta-analysis reports improved survival in cancer patients with concurrent diabetes for breast, colorectal, ovarian cancer [6].

What is even more striking, a study by Currie et al. concludes that type 2 diabetes patients with solid tumors treated with metformin had better survival not only in comparison to those treated with other antidiabetic drugs (sulfonylureas and insulin) but also to nondiabetic patients, even if type 2 diabetes itself was associated with poorer prognosis [7].

Several in vitro studies on EC cell lines reported antiproliferative and antiinvasive properties of metformin [8-10]. Other proved that it can sensitize cells to chemotherapeutical agents and hormonal drugs [11-14]. However, our research is one of the first that investigates the association between metformin intake and mortality in EC patients.

Based on the cited promising studies, we hypothesized that metformin intake improves overall survival in endometrial cancer patients.

Materials and Methods

A group of 126 patients with EC admitted to the Department of Gynecologic Oncology of Poznan University of Medical Sciences between 2002 and 2010 was analyzed retrospectively. Patients were assigned to one of three groups: 1) individuals with type 2 diabetes mellitus treated with metformin at the time of EC diagnosis, 2) individuals with type 2 diabetes mellitus without metformin therapy, 3) individuals without diabetes mellitus. Patients matching these criteria were recruited consecutively so

as to reach comparable group numbers. Co-existence of another malignancy or ambiguous result of pathological examination constituted exclusion criteria.

Information extracted from medical database included preoperative co-morbidities, metformin use, plasma glucose level, treatment modalities (hysterectomy, radiation therapy, chemotherapy), pathological features of the tumor. Time of first pathological diagnosis was recorded. Time of death or last vital status verification were obtained thanks to the courtesy of Agnieszka Dyzmann-Sroka MD, Ph.D., Greater Poland Cancer Registry. Patients who were not described in the Registry were excluded from the further analysis.

U Mann-Whitney and chi-square tests were applied to compare clinicopathological features. Kaplan-Meier model with log-rank test was used to compare survival in the subgroups. Cox proportional hazard model was applied to analyze the relationships between particular factors and overall survival. A *p* value below 0,05 was considered statistically significant.

Results

107 patients met study criteria. The analysis included EC patients 1) with type 2 diabetes mellitus treated with metformin (n=30), 2) with diabetes mellitus not receiving metformin (n=38) and 3) without diabetes mellitus (n=39). Mean age of the group was 63 years old (range 40-91). The majority of the patients had stage I (n=58, 54%) and grade I tumors (n=56, 52%) and underwent radical hysterectomy (n=96, 90%).

To identify factors that could influence survival we compared clinicopathological features of metformin users and patients without metformin therapy. Although these subgroups did not differ in terms of age and the number of hysterectomies, metformin users had higher body mass index (*p*=0,03) and more often suffered from arterial hypertension (*p*=0,01) as well as more rarely underwent radiation therapy (*p*=0,04) (Table I). The stage, grade and histological type of endometrial carcinoma were unrelated to metfomin therapy (Table II).

Patients under metformin therapy lived as long as those without this treatment according to Kaplan-Meier model with log-rank test (Figure 1). Metformin intake along with diabetes mellitus co-morbidity, plasma glucose level and BMI appeared without influence on survival in Cox proportional hazard model (Table III).

Factors such as age (p=0,006), high grade (p=0,005) and stage (p=0,02), lack of radical hysterectomy (p=0,002) and type II histology (p=0,001), as expected, confirmed their established negative prognostic significance in the cohort. When the analysis was restricted to the subgroup of type I endometrial cancer or to endometroid histological type, both metformin intake and diabetes still did not influence the prognosis.

Discussion

Many studies have investigated metformin's cellular and molecular mechanisms of action in an attempt to explain its beneficial effects in cancer patients. Firstly, metformin acts indirectly by reducing hyperinsulinemia. As insulin inhibits sex hormone binding globulin (SHBG) production, lower serum insulin level results in an increase of SHBG which in turn leads to a decrease of biologically active estrogen and androgen forms in serum [15]. Both hyperinsulinemia itself and excessive estrogen

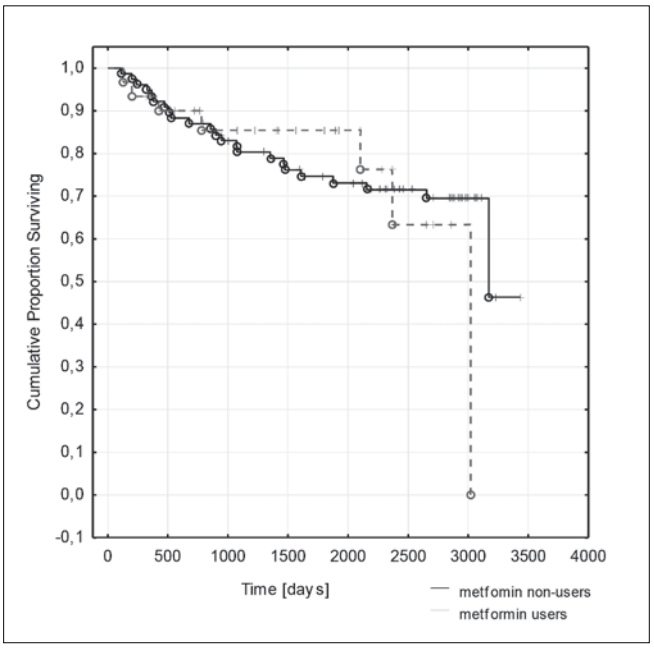

Figure 1. Metformin users do not have improved overall survival compared to metformin non users group (log-rank test, p=0,86).

stimulation promote EC carcinogenesis. Secondly, it activates the AMP-activated protein kinase (AMPK) which suppresses the mammalian target of rapamycin (mTOR) – a signaling pathway that plays a major role in cancer cells proliferation [16]. It is known that loss of PTEN, a negative regulator of the mTOR pathway, is a molecular abnormality that occurs in up to 83% of type I endometrial cancers [17, 18]. Thus, mTOR inhibitors are investigated as potential drugs for endometrial cancer. Acting as a mTOR inhibitor is a possible explanation of the beneficial effect of metformin in EC patients (9). Moreover, the activation of AMP-activated protein kinase induces cell cycle arrest in G(0)/G(1) phase [19].

Taking into account the observed protective effect of metformin against cancer and the strong correlation between glucose metabolism disorders and EC, several in vitro studies were conducted in order to determine the influence of metformin on endometrial cancer cell lines. They reported its antiproliferative, antiinvasive and antimetastatic properties that were dose-dependent and concluded that it could be used as a preventive and/or curative agent for endometrial cancer [8–10, 20]. And although Cantrell et al. admit that the in vitro concentrations used in the study were superior to those obtained in the tissues in vivo, the research conducted by Tan et al. used sera from women with polycystic ovary syndrome treated with metformin (850mg twice a day for 6 months) [9, 10].

Finally, metformin was proven to enhance the cytotoxicity of chemotherapeutic agents such as cisplatin in non-small-cell lung cancer cells and ovarian cancer, cisplatin and paclitaxel in endometrial cancer cells and of hormonal drugs by promoting progesterone receptor expression in endometrial cancer cells [11-14, 21-23]. Therefore, the co-treatment with metformin could allow us to reduce the doses of chemotherapeutical drugs and help to prevent the development of drug resistance.

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Table I. Clinical characteristics of patients with metfomin therapy versus those not receiving metfomin.

	Metformin users (n=30)	Metformin non-users (n=77)
Age (years)	65	64
BMI (kg/m^2)	35*	32*
Radiation therapy	10 (33%)†	42 (54%)†
Histerectomy	26 (96%)	70 (92%)
Arterial hypertention	28 (96%)†	56 (74%)†

Asterix (*) and cross (†) designate values significantly different according to U Mann-Whitney and Chi-square tests, respectively (p<0.05).

Table II. Pathological features of endometrial carcinoma tumors.

	Metformin users (n=30)	Metformin non-users (n=77)
Grade		
1 2 3	**16 (53%)** **7 (23%)** **4 (13%)**	**40 (52%)** **25 (32%)** **5 (6%)**
Stage		
I II III	**14 (60%)** **7 (30%)** **2 (9%)**	**44 (68%)** **15 (23%)** **5 (8%)**
Type		
I II	**23 (77%)** **6 (20%)**	**59 (76%)** **11 (14%)**
Histology		
– squamous – serous – endometrioid – endometrioid with planoepithelial metaplasia – clear cell – undifferentiated – mucinous – adenosquamous	**1 (3%)** **3 (10%)** **17 (57%)** **5 (17%)** **1(3%)** **2 (7%)** **0** **0**	**0** **5 (6%)** **54 (70%)** **2 (3%)** **1(1%)** **1 (1%)** **1 (1%)** **3 (4%)**

Table III. Univariate analysis of clinicopathological factors using Cox proportional hazard model.

	Hazard ratio	Confidence interval
Age	1,05*	1,01-1,09
Metformin use	1,08	0,46-2,56
Diabetes melitus type 2	1,13	0,54-2,39
Arterial hypertension	1,05	0,43-2,60
BMI	1,01	0,96-1,06
Glucose level	1,00	0,99-1,00
Grade	2,29*	1,27-4,15
Stage	1,29*	1,03-1,63
Hysterectomy	0,17*	0,06-0,53
Radiation therapy	0,91	0,44-1,87
Type II endometrial cancer	5,50*	2,54-11,9

Asterix (*) designates values significant according to Cox proportional hazard model (p<0.05, 95% confidence interval).

Additionally, a case report of successful treatment of atypical endometrial hyperplasia using one month therapy with metformin was published [24]. Another small study applied metformin together with hormonal treatment in an attempt to conservatively treat early stage of type I EC (stage Ia/G1) in 5 young women achieving good results [25].

Despite the very promising results of in vitro and observational studies and an obvious pathogenetic link between metabolic syndrome and EC, a recently published large case-control analysis that encompassed 17,878 patients, including 2554 endometrial cancer cases, concluded that there was no association between metformin or other antidiabetic drugs intake and an altered risk of EC [26]. Thus, it undermined the hypothesis that metformin could be useful as a preventive agent against this malignancy. Although the cited study investigated the preventive potential of metformin, as opposed to its curative potential analyzed in our paper, both studies are consistent in that they negate the influence of the drug on endometrial cancer.

Our research showed no influence of metformin intake on survival in EC patients. What is worth noticing, established negative prognostic factors for endometrial cancer, such as high grade, advanced stage, lack of radical hysterectomy and type II histology, did have an impact on survival, which proves that the cohort was representative.

Very recently, the only two studies analyzing survival in EC patients were published. The research by Ko et al. included 196 metformin users among 1495 EC patients and reported improved RFS (recurrence free survival) and OS (overall survival) but not TTR (time to recurrence) among metformin users, most likely due to improving all-cause mortality [27]. The limitation of this study is that the patients were allocated to the group of metformin users based on medication review at the time of diagnosis and it lacks data on how long and in which dose the drug was used. The second research was conducted on 985 patients, 114 of which were diabetics treated with metformin. In this study greater OS among EC patients was observed in diabetics using metformin but only with non-endometrioid histology. What is important, metformin use did not improve OS in metformin users with endometrioid histology [28]. These results are consistent with our findings: after restricting our analysis to the subgroup of endometroid histological type, we observed no influence on prognosis of both metformin intake and diabetes. Both cited studies were limited by retrospective data collection and thus the inability to adequately record the timing, dose and adherence to treatment with metformin.

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Although the evidence we present is of great clinical value, our study has various limitations that could have distorted the results. First of all, we observed differences between the analyzed groups in factors that could have affected the survival: BMI, arterial hypertension comorbidity and the rate of application of radiation therapy were significantly different. Moreover, we lacked data on how long metformin was used by the patients and in which dose. Due to the retrospective nature of the study, we were also unable to determine whether the patients were formerly treated with different antidiabetic drugs and if the control of glycemia was adequate. Nevertheless, our study was one of the first that attempted to determine the impact of metformin therapy on survival in endometrial cancer patients.

Despite promising results of in vitro studies, our research shows that metformin intake does not alter the overall survival in endometrial cancer patients. It also reports no influence of diabetes mellitus on survival in endometrial cancer patients. Further research in vivo is needed in order to determine the impact of metformin on treatment outcomes in oncological patients. Currently, several clinical studies on metformin and endometrial cancer in the United States are ongoing or recruiting patients. We can expect the results soon [29].

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