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Original Research

Effect of metformin on clinical-pathological variables in women with endometrial cancer. A multicenter study

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Summary

Objective: Endometrial cancer (EC) is the most common gynecological malignancy in economically developed countries. Documented risk factors include diabetes mellitus and obesity. Metformin, a derivative of biguanide, applied in treatment of type 2 diabetes, also has anti-neoplastic effects. The analysis presented below represents an attempt to determine the effects of metformin on clinical–pathological variables of EC, linked to the morbidity and course of EC. *Material and Methods:* 1,305 patients with EC were included in this retrospective study, the control group consisted of 1,016 EC patients who were diabetes-free, 144 patients with EC and type 2 diabetes treated with metformin, and 145 patients with EC and type 2 diabetes treated with other antidiabetic agents. The analyzed variables included age upon diagnosis of EC, BMI, parity, clinical stage according to FIGO, histological type of cancer (type I or type II EC), grading, type of surgery, adjuvant treatment (radio- or chemotherapy), and comorbidities. *Results:* EC in females with type 2 diabetes treated with metformin or other antidiabetic agents were diagnosed at a more advanced age than those in the control group. Both groups of patients with type 2 diabetes manifested morbid obesity significantly more frequently than the control group. Advanced stages of cancer were detected less frequently among metformin users compared to the control group and among patients with diabetes treated with other antidiabetic agents. Moreover, in the metformin group, total abdominal hysterectomy and adnexectomy were less common than in the remaining groups. Adjuvant radiotherapy was applied more frequently in the metformin-treated group. Both groups of type 2 diabetes patients were also more likely to suffer from hypertension. *Conclusion:* Compared to the control group, women with EC and diabetes mellitus were diagnosed at a more advanced age. A lower percentage of women with EC using metformin were diagnosed at advanced stages of EC according to FIGO in contrast to the control group and the group with diabetes treated with other antidiabetic agents. Patients treated with metformin underwent TAHBSO less frequently, but radiotherapy was applied more often. The present results show that type 2 diabetes patients also suffer from hypertension more frequently regardless of the diabetes treatment applied.

Key words: Endometrial cancer; Type 2 diabetes; Metformin.

Introduction

Endometrial cancer (EC) is one of the most common gynecological tumors; it comprises 6.2% of all incidences of malignant tumors in women. An increase in related morbidity has been observed over the last ten years [1-3]. Numerous studies determined that obesity, insulin resistance, and diabetes represent risk factors of EC development [4-7]. The risk of EC is also related to reproductive factors (early menarche, late menopause, infertility or nulliparity), endogenous or exogenous hyperestrogenism, hypertension, genetic disorders (Lynch syndrome, Cowden's syndrome, mutations of p53, PI3K, K-Ras, β-catenins, BRCA) or long-term tamoxifen use [3, 8, 9]. Factors linked to the prognosis of this heterogenous disease also have been recognized: histological type and histological maturity (G), invasion of myometrium and lymphatic spaces (LVSI), metastases to lymph nodes, diameter of the tumor. and status of hormonal receptors [3, 9, 10].

Observational studies on over 11,000 patients with type 2 diabetes demonstrated a 23% reduction in morbidity involving malignant tumors of various locations in patients treated with metformin, compared to those treated with sulphonylurea derivatives [11-16].

According to population studies in over 10,000 patients with type 2 diabetes, metformin also significantly reduced total mortality due to malignant tumors, in comparison to treatment with sulphonylurea derivatives and insulin (3.5% *vs.* 4.9%, *vs.* 5.8%) [17].

Metformin is a biguanide derivative originating from

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Table 1. — *Characteristics of patients with endometrial cancer included in the study.*

		Control	Metformin	Insulin and other
Number of patients		1,016	144	145
Mean age (in years)		62.2	67.0	68.1
		n/%	n/%	n/%
BMI (kg/m^2)	<30 kg/m2	534 / 52.6%	47 / 32.6%	39 / 26.9%
	30-39 kg/m2	412 / 40.6%	69 / 47.9%	82 / 56.6%
	>40 kg/m2	70 / 6.9%	28 / 19.4%	24 / 16.6%
Parity	Nulliparous	122 / 12.0%	20 / 13.9%	9 / 6.2%
	Multiparous	192 / 18.9%	48 / 33.3%	33 / 22.8%
Clinical stage	IA	292 / 28.7%	46 / 31.9%	43 / 29.7%
	IB	258 / 25.4%	34 / 23.6%	37 / 25.5%
	II	292 / 28.7%	40 / 27.8%	31 / 21.4%
	IIIA	59 / 5.8%	13 / 9%	13 / 9%
	IIIB	47 / 4.6%	7 / 4.9%	9 / 6.2%
	IIIC	54 / 5.3%	3 / 2.1%	9 / 6.2%
	IVA	13 / 1.3%	1 / 0.7%	3 / 2.1%
	IVB	1 / 0.1%	0 / 0.0%	0 / 0.0%
Histopathology	Type I -EC	884 / 87.0%	131 / 91.0%	124 / 85.5%
	Type II -EC	132 / 13.0%	13 / 9.0%	21 / 14.5%
Grading	G1	354 / 34.8%	42 / 29.2%	46 / 31.7%
	G2	521 / 51.3%	84 / 58.3%	77 / 53.1%
	G3	141 / 13.9%	18 / 12.5%	22 / 15.2%
Type of surgery	TAHBSO	961 / 94.6%	126 / 87.5%	136 / 93.8%
	Other	55 / 5.4%	18 / 12.5%	9 / 6.2%
Adjuvant therapy	Chemotherapy	159 / 15.6%	27 / 18.8%	30 / 20.7%
	Radiotherapy	481 / 47.3%	86 / 59.7%	79 / 54.5%
Comorbidities	Hypertension	538 / 53.0%	114 / 79.2%	114 / 78.6%

Gallega officinalis and has been applied in the treatment of type 2 diabetes for over 50 years. Metformin has a pleiotropic anti-neoplastic effect involving several pathways of interaction [14, 16, 18-21].

Metformin plays a key role in the activation of kinase axis LKB1/AMP (liver kinase B1/AMP activated protein kinase), which leads to the inhibition of mTOR (mammalian target of rapamycin) signalling; metformin also manifests a capacity to directly inhibit mTOR. It inhibits the phosphorylation of STAT-3, reduces the concentration of circulating insulin, the concentration of IGF-1 and IGF-1R, and the production of anti-inflammatory and anti-angiogenic cytokines: TNF-α, IL-6 and VEGF-1. It also blocks cell cycle at the G-1 phase and reduces the expression of cyclin D1. According to more recent studies it eliminates cancer stem cells (CSCs) that are responsible for resistance to treatment, cancer progression, and relapse. Such variability of metformin activity inhibits the growth and proliferation of cancer cells, exerts an anti-angiogenic and proapoptotic effect, which results in blocking EC growth, invasion, and metastases [14, 21-23]. The antineoplastic activity of metformin presented above has been illustrated by numerous clinical studies.

Tang *et al.* [24] presented a meta-analysis involving over 766,000 patients with type 2 diabetes identified in an electronic database. Treatment with metformin reduced morbidity involving EC by 18% compared to patients treated with other antidiabetics, which is statistically significant. Also, metformin use was accompanied by longer patient survival (HR=0.63).

A similarly favorable effect of metformin, reducing morbidity and mortality in women with EC and type 2 diabetes was documented in the review by Gadducci *et al.*[14]. Perez-Lopez *et al.* [7] demonstrated that metformin, applied in over 4000 patients with EC and type 2 diabetes, reduced the percentage of overall mortalities. Arima *et al.* [25], in their analysis of EC course in 1,215 patients with type 2 diabetes treated with various antidiabetic agents showed that metformin reduced mortality of women due to comorbidities in the cohort.

According to several reviews demonstrating the favorable effect of metformin in women with EC and type 2 diabetes on progression-free survival (PFS) and overall survival (OS), further studies taking additional clinical/pathological factors linked to EC into account are necessary in order to confirm the results [21-24].

Materials and Methods

The study included 1,305 patients with endometrial cancer, 1,016 of whom were diabetes free and formed the control group, 144 patients with metformin-treated type 2 diabetes, and 145 patients with type 2 diabetes who were treated with insulin and other antidiabetics.

The analyzed parameters in the cohort included age, BMI, par-

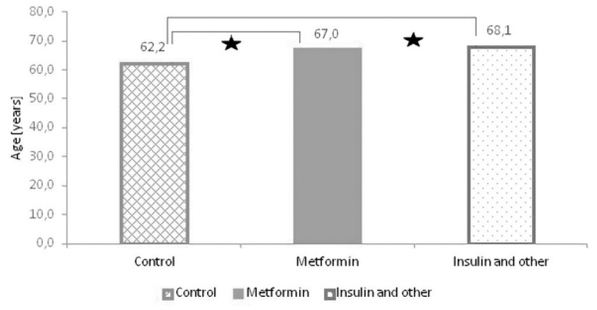

Figure 1. — Comparison of age in the control group, metformin-treated group, and group treated with insulin or other antidiabetic agents ($p < 0.05$)

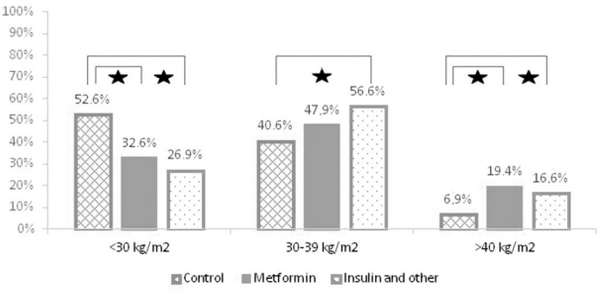

Figure 2. — Comparison of BMI in the control group, metformin-treated group, and group treated with insulin or other antidiabetic agents ($p < 0.05$).

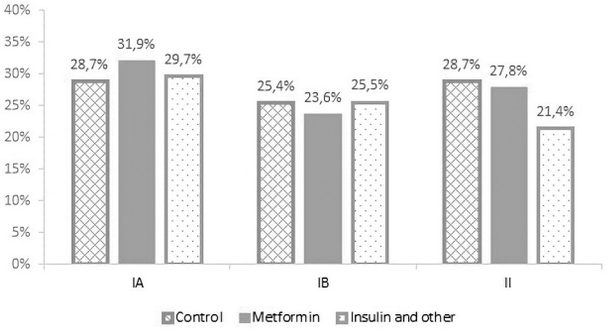

Figure 3. — Comparison of frequency manifested by early FIGO stages in the control group, metformin-treated group, and in the group treated with insulin or other antidiabetic agents.

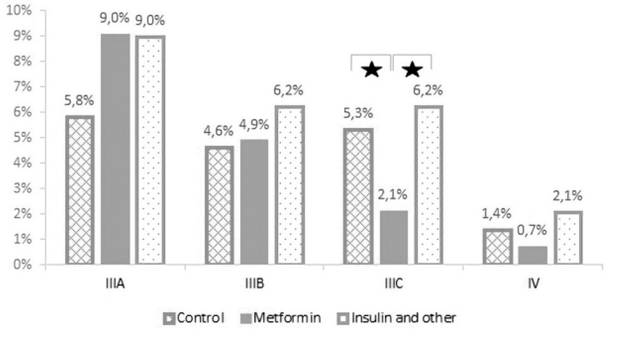

Figure 4. — Comparison of frequency of advanced cancer stages (IIIC and IV according to FIGO) in the control group, group treated with metformin, and group treated with insulin or other antidiabetic agents ($p < 0.05$).

ity, FIGO, histological type of cancer, grading (G), type of operation, need for subsequent radio- or chemotherapy, and comorbidities.

The analyzed patients were between 28 to 98 years of age (a mean of 64 years). In the control group the mean age amounted to 62.2 years, 67.0 in the metformin-treated group, and 68.1 in the group treated with insulin or other antidiabetics. Of the entire cohort, 1,154 women were multipara and 151 nullipara.

Type I EC was diagnosed in 1,139 women and type II EC in 166. The analysis of histopathological differentiation demonstrated G1 in 442 patients, G2 in 682 patients, and G3 in 181 patients. Of the 1,305 analyzed patients, the tumor was diagnosed at FIGO Stage I in 710 women, 363 were in FIGO Stage II, 214 in FIGO Stage III, and 18 patients in FIGO Stage IV.

Of the discussed study cohort, 1,223 patients underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO). Eighty-two patients were subjected to other types of surgery: in 39 cases TAHBSO was accompanied by omentectomy (in a proportion of type II EC cases), in 43 cases, only diagnostic hysteroscopy or curettage of the uterine cavity were conducted due to advancement of cancer or comorbidities linked to the patient's general condition, mainly morbid obesity (BMI > 40) and hypertension; 646 patients were subjected to post-surgical radiotherapy and 216 patients underwent post-surgical chemotherapy. Regarding comorbidities, hypertension was detected in as many as 766 patients (58.7%). Full patient characteristics are presented in Table 1.

Statistical calculations were conducted using Ona-Way ANOVA and Fisher LSD post-hoc for continuous variables and for nominal variables the chi-square test, in subgroups of low numerical force Yates correction was also applied. The level of significance was accepted as 0.05, but this level was adjusted by introducing Bonferroni correction for multiple comparisons. In calculations the authors applied PQStat 1.6.6. software.

Results

Analysis of the accumulated data showed that endometrial cancer was diagnosed at a later age in patients with diabetes, both metformin users and other antidiabetic agents users, when compared to the control group (67.0 and 68.1 *vs.* 62.2; $p < 0.0001$ and $p < 0.0001$, respectively). No differences were revealed between patients treated with metformin and the cohort treated with other antidiabetic agents ($p = 0.41$) (Figure 1).

The presented data showed that patients with EC and diabetes suffered from morbid obesity (BMI > 40 kg/m^2) significantly more frequently than patients with EC but without diabetes. In metformin-treated patients BMI index > 40 kg/m^2 was detected in 19.4%, in the non-metformin users group in 16.6% and in the control group only in 6.9% (metformin *vs.* control, $p < 0.0001$, insulin and other vs

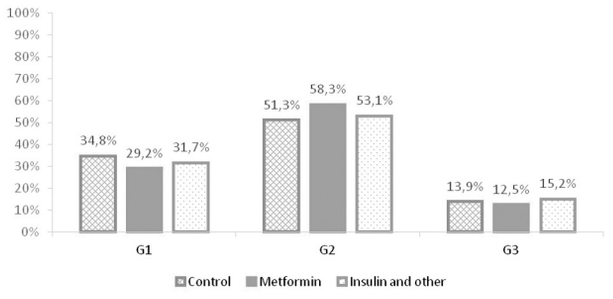

Figure 5. — Patient groups according to Grade.

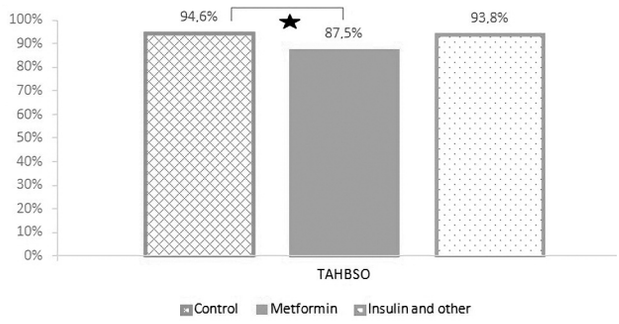

Figure 6. — Comparison of frequency of various types of operations performed in the analyzed patient cohorts ($p < 0.05$).

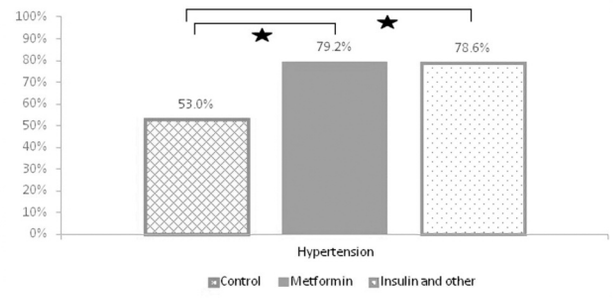

Figure 7. — Comparison of frequency of the applied radiotherapy in the control group, the metformin-treated group, and the group treated with insulin or other antidiabetic agents ($p < 0.05$).

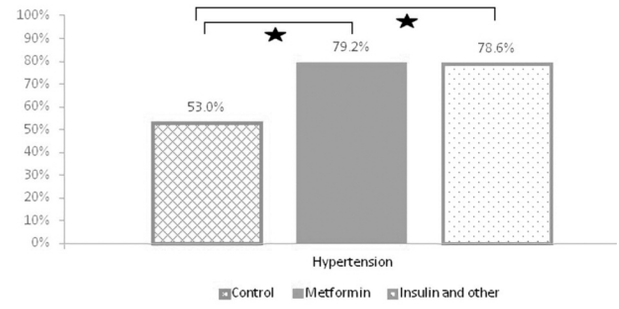

Figure 8. — Comparison of frequency of hypertension in the control group, metformin-treated group, and the group treated with insulin or other antidiabetic agents ($p < 0.05$).

control, $p < 0.0001$). Conversely, the group of patients with BMI < 30 kg/m^2 was significantly more often seen in patients without diabetes in comparison with diabetic metformin users (52.6% vs. 32.6%, $p < 0.0001$) or patients treated with insulin or other antidiabetic agents (52.6% *vs.* 26.9%, $p < 0.0001$). In patients with BMI index between 30 and 39 kg/m^2, a higher percentage of diabetic patients treated without metformin was found (56.6% insulin and other *vs.* 40.6% control, $p = 0.0003$). There was no difference between groups of patients with diabetes treated with different antidiabetic drugs ($p = 0.2857$ for BMI < 30 kg/m^2, $p = 0.1417$ for BMI < 30-39 kg/m^2, and $p = 0.5221$ for BMI > 40 kg/m^2) (Figure 2).

In the present study the authors did not find any differences in the number of pregnancies between women in analysed groups ($p > 0.05$); 19.98% of women in the control group, 24.31% of metformin users, and 24.83% of patients treated with insulin or other antidiabetic drugs had three or more pregnancies. One or two deliveries included 68.01%, 61.81%, and 68.97% women, respectively. Nulliparous women were less frequent in EC patient with diabetes treated insulin or other drugs (6.21%), compared with 13.89% of women using metformin and 12.01% of women without diabetes, but it was not statistically significant.

In the three groups of patients investigated, no statistically significant differences were disclosed at early FIGO stages (for Stage IA metformin *vs.* control $p = 0.43$, insulin and other *vs.* control $p = 0.82$, metformin *vs.* insulin and other $p = 0.67$; for Stage IB metformin *vs.* control $p = 0.64$, insulin and other *vs* control $p = 0.97$, metformin *vs.* insulin and other $p = 0.71$; for Stage IC metformin *vs.* control $p = 0.81$, insulin and other *vs.* control $p = 0.06$, metformin *vs.* insulin and other $p = 0.21$) (Figure 3).

Patients in advanced Stage IIIC were detected statistically less frequently in the group of women treated with metformin compared to the control group or the cohort treated with other antidiabetic agents. EC in Stage IV in metformin users was rarely detected, although this was not statistically significant due to the low number of patients in each subgroup at Stage IV (Figure 4).

Worth mentioning is the fact that between the studied groups of patients, there was no statistical difference in percentage of endometrioid type of cancer [(87% in the control group, 91% in patients with diabetes treated with metformin, and 85.5% in non-metformin users (metformin *vs.* control $p = 0.18$, insulin and other *vs.* control $p = 0.62$, metformin *vs.* insulin and others $p = 0.15$)]. There was also no statistical difference between groups of patients according to grade of cancer cell histopathological differentiation (Figure 5).

In the group of women with EC treated with metformin, TAHBSO was performed significantly less frequently than

in the control group ($p = 0.001$) (Figure 6). Metformin users were more frequently subjected to other types of surgery or diagnostic procedure only - hysteroscopy or curettage of the endometrium.

The group of patients treated with metformin more frequently underwent post-operative radiotherapy than the remaining patient groups (59.7% metformin *vs.* 47.3% control $p = 0.005$, 54.5% insulin and others *vs.* 47.3% control $p = 0.26$, 59.7% metformin *vs.* 54.5% insulin and others $p = 0.37$) (Figure 7).

The patients diagnosed with diabetes, both treated with metformin or insulin and other drugs, were statistically more likely to suffer from hypertension than the control group (metformin *vs.* control $p < 0.0001$, insulin, and others *vs.* control $p < 0.0001$). There was no difference in frequency of hypertension between two groups of diabetic patients ($p = 0.91$) (Figure 8).

Discussion

Recent studies have demonstrated that metformin applied in women with type 2 diabetes affects the development and course of EC. According to a number of observational studies, metformin results in a reduced risk of developing EC, improves both PFS and OS [15, 24, 26-29]. However, other studies, including retrospective case-controls, in 92,366 women obtained from a diabetic register, the application of metformin was linked to increased incidence, involving EC (type I EC) [30]. In another study, PFS and OS did not differ between the control group and the group of metformin-treated women [31]. In the present study the authors investigated and analysed age upon cancer diagnosis, BMI, parity, FIGO stage, histology of EC (type I and type II), grading, and therapeutic management factors affecting both the risk of developing EC and its course.

Analysis related to age upon EC diagnosis demonstrated that women with diabetes, both treated with metformin and other drugs, developed EC significantly later than in the control group (67.0 *vs.* 62.2 and 68.1 *vs.* 62.2 years of age), but no difference in age was found between metformin users and women with type 2 diabetes treated with other antidiabetic agents. In studies by Hilli *et al.* [31] and Hall *et al.* [32] there was also no difference in the mean age at the time of diagnosis of EC between patients with diabetes treated with metformin or other antidiabetic agents. Similar results were presented in the Dutch ZODIAC study [33].

Obesity is closely linked to the development of EC [3, 7]. In the present study, patients with EC and diabetes treated with metformin and other antidiabetic agents had significantly less frequently BMI index < 30 than the control group.

By comparison, a higher percentage of women with morbid obesity (BMI > 40) was detected in the group of women with diabetes, with no difference between treated with metformin or other drugs. A significantly higher BMI index (BMI > 30 and BMI > 40) was also detected in women with EC and type 2 diabetes in other studies [31-33].

One of principal prognostic factors affecting the course of EC involves FIGO stage. Most ECs (around 80%) are diagnosed at early FIGO stages [3, 7, 31, 32, 34]. According to the retrospective studies presented above, no difference was noted in FIGO stages nor in grading in the group of patients without diabetes or among those with diabetes treated with metformin [31, 32]. The present study disclosed no difference in early FIGO stages between the women treated with metformin and the control group, nor was any difference in grading detected. However, a difference in advanced FIGO stages was noted. In the group of women with type 2 diabetes treated with metformin, FIGO Stages IIIC was detected significantly less frequently in the group of metformin users. Only one case of FIGO Stage IV was recorded in the group treated with metformin.

Of the present entire cohort, the group of patients treated with metformin underwent TAHBSO significantly less frequently in comparison to the control group and the group of women treated with other antidiabetic agents. The metformin-treated group was subjected to other types of surgical procedures more frequently.

In 43 women in an advanced stage of EC or with comorbidities only diagnostic procedures were performed (hysterectomy or classic uterine abrasion). This group affected in part the lower frequency of the TAHBSO procedure, reflecting in turn the higher frequency of applied radiotherapy. Such a relationship – a higher frequency of radiotherapy application in patients with type 2 diabetes treated with metformin has not been previously observed by other investigators [30]. The application of radiotherapy alone, was due to other comorbidities, mainly morbid obesity and hypertension. In the present results, hypertension was the most frequent disease accompanying EC in the cohort of patients with type 2 diabetes treated with metformin affecting over 79% of patients.

Several studies demonstrated that women with EC, in addition to diabetes, also suffer from hypertension more often [3, 4, 34-36] as the present study also shows. The results obtained by Arima *et al.* [25] in a cohort of 1,215 women, of whom 19% were metformin-users due to type 2 diabetes, indicated the reduced mortality of this group due to comorbidities.

Conclusion

Age at diagnosis, BMI, and hypertension are related to type 2 diabetes, not to the applied treatment for diabetes mellitus. In women with EC and type II diabetes, metformin-users were less frequently diagnosed in advanced stages of EC. Further long-term studies on the effect of metformin in women with EC and type 2 diabetes are necessary.

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