Clinical Investigation / Araştırma

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Effect of metformin on proliferative markers in women with endometrial carcinoma: Systematic review and meta-analysis

Metforminin endometriyal karsinomlu kadınlarda proliferatif belirteçler üzerine etkisi: Sistematik derleme ve meta-analiz

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Abstract

Objective: Endometrial carcinoma (EC) is the most common gynecologic malignancy in the USA and Western Europe. Surgery is the mainstay of both staging and treatment of EC. Fertility sparing medical therapies are often offered to young women who desire fertility. Metformin has been suggested to be an anti-cancer agent as evidenced by previous studies. It decreases Antigen Ki-67 (Ki-67) proliferation and expression which is associated with proliferative activity of malignant tumors. In this systematic review and meta-analysis, we assessed the efficacy of metformin on patients with EC.

Materials and Methods: We searched PubMed, Cochrane CENTRAL, Web of Science, and SCOPUS for relevant clinical trials and excluded observational studies. The quality appraisal was evaluated according to GRADE, and we assessed the risk of bias using Cochrane's risk of bias tool. We conducted the analysis of continuous data using mean difference (MD). We included the following outcomes: Ki-67 index, glucose, insulin, P-S6, body mass index (BMI), C-peptide, Insulin-like growth factor (IGF-1), leptin, and hemoglobin.

Results: Nine studies were eligible for our meta-analysis. We found that compared to the control group, metformin is highly effective in reducing Ki-67 proliferation and expression [MD=-10.14 (-19.10, -1.17)], (p=0.03), P-S6 [MD=-1.82 (-3.17, -0.46)], (p=0.009), plasma glucose level [MD=-1.76 (-4.88, 1.37), p=0.27], and BMI [MD=-1.07 (-1.49, -0.65)], (p<0.001).

Conclusion: We conclude that metformin administration is effective in patients with EC. It decreases Ki-67 proliferation and expression, serum glucose, and p-S6 significantly.

Keywords: Metformin, glucophage, dimethylbiguanide, endometrial carcinoma, meta-analysis

Öz

Amaç: Endometriyal karsinom (EK), ABD ve Batı Avrupa'da en sık görülen jinekolojik malignitedir. EK'nin hem evrelemesinin hem de tedavisinin temeli cerrahidir. Doğurganlığı koruyucu tıbbi tedaviler genellikle doğurganlık isteyen genç kadınlara sunulur. Metforminin, önceki çalışmalardan elde edilen kanıtlara göre bir anti-kanser ajanı olduğu öne sürülmektedir. Metformin malign tümörlerin proliferatif aktivitesi ile ilişkili Antijen Ki-67 (Ki-67) proliferasyonunu ve ekspresyonunu azaltır. Bu sistematik derleme ve meta-analizde, metforminin EK'li hastalardaki etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: İlgili klinik araştırmalar için PubMed, Cochrane CENTRAL, Web of Science ve SCOPUS'yi taradık ve gözlemsel çalışmaları hariç tuttuk. Kalite değerlendirmesi GRADE'ye göre değerlendirildi ve biz de Cochrane'nin yanlılık riski aracını kullanarak yanlılık riskini değerlendirdik. Ortalama farkı (MD) kullanarak sürekli verilerin analizini gerçekleştirdik. Şu sonuçları dahil ettik: Ki-67 indeksi, glukoz, insülin, P-S6, vücut kitle indeksi (VKİ), C-peptid, insülin benzeri büyüme faktörü (IGF-1), leptin ve hemoglobin.

PRECIS: Metformin is effective in patients with endometrial carcinoma. It significantly decreases Ki-67 proliferation and expression, serum glucose, and p-S6.

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Bulgular: Dokuz çalışma meta-analizimiz için uygun bulundu. Kontrol grubu ile karşılaştırıldığında metforminin Ki-67 proliferasyonunu ve ekspresyonunu [MD=-10,14 (-19,10, -1,17)], (p=0,03), P-S6 [MD=-1,82 (-3,17, -0,46), (p=0,009), plazma glukoz düzeyini [MD=-1,76 (-4,88, 1,37), p=0,27] ve VKİ'yi [MD=-1,07 (-1,49, -0,65)], (p<0,001) azaltmada oldukça etkili olduğunu bulduk.

Sonuç: EK'li hastalarda metformin uygulamasının etkili olduğu sonucuna varılmıştır. Metformin Ki-67 proliferasyonunu ve ekspresyonunu, serum glukozunu ve p-S6'yı önemli ölçüde azaltmaktadır.

Anahtar Kelimeler: Metformin, glukofaj, dimetilbiguanid, endometriyal karsinom, meta-analiz

Introduction

Endometrial carcinoma (EC) is the most common gynecologic malignancy in the USA and Western Europe[1]. The main symptoms of EC are dysfunctional uterine bleeding and infertility[2]. EC is divided into two major types. Type I, known as estrogen-dependent or endometrioid, is the more common type. It is associated with unopposed hyperestrogenemia and is often preceded by endometrial hyperplasia. Moreover, type II, known as estrogen-independent or non-endometroid, has a poorer prognosis and less differentiation than type I[3]. Many factors increase the risk for developing both low-grade and high-grade EC, including obesity, diabetes especially type II (which is associated with insulin resistance), menstrual irregularity, anovulation, and infertility[4]. Fortunately, most women are usually diagnosed at an early stage in which the disease is limited to the uterine corpus. Therefore, about 75% of women survive for 5 years[5,6].

Treatment options for EC vary depending on the stage and grade of the disease. Surgery is the mainstay of both staging and treatment of EC. Surgery includes hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment[7]. Fertility sparing medical therapies are often offered to young women who desire fertility. The standard conservative medical treatment of EC is high-dose oral progestin such as megestrol acetate or medroxyprogesterone acetate[8]. However, women experience many side effects, including liver damage, weight gain, thrombosis, and progesterone resistance, which limits the usage of this drug[9].

Metformin is the first-line medication for treating type 2 diabetes mellitus[10]. It has been suggested to be an anticancer agent[11]. Previous studies reported the anti-carcinogenic properties of metformin on gastric cancer, medullary thyroid carcinoma, pancreatic cancer, and EC[12,13]. A recent study revealed that metformin and progestins have a synergistic effect on the inhibition of proliferation of EC cells[14]. Metformin also affects Adenosine monophosphate-activated protein kinase (AMPK)-independent pathways responsible for tumor growth and cell proliferation. Therefore, it decreases Antigen Ki-67 (Ki-67) proliferation and expression[15,16]. Expression of Ki-67 is associated with proliferative activity of malignant tumors, so it has been used as a marker for tumor aggressiveness[17,18].

There are no sufficient data from previous trials regarding the effect of metformin on endometrial neoplasms. Therefore, we performed this systematic review and meta-analysis to estimate the effect of metformin on the proliferation and expression of tumor cells and the change of tumor markers in cases of EC.

Materials and Methods

In this meta-analysis, We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[19] guidelines and conducted every step in this study according to the Cochrane Handbook for Systematic Reviews of Interventions[20]. The ethics statement is not applicable because this study is based exclusively on published literature.

Literature Search

We searched four databases: Web of Science, SCOPUS, Cochrane CENTRAL, and PubMed, from inception until October 2020. We followed this search strategy with no restriction on time or languages: (metformin OR glucophage OR dimethylbiguanide OR dimethylguanylguanidine) AND (endometrial cancer OR EC OR endometrial hyperplasia OR endometrial proliferation OR endometrial thickness).

Eligibility Criteria

We included studies according to these eligibility criteria: (I) **Population:** Patients with EC or endometrial hyperplasia with atypia, (ii) **Intervention:** Metformin regardless of the dose and mode of administration, (iii) **Comparator:** Placebo or no treatment, (IV) **Outcomes:** Ki-67 proliferation and expression index as a primary outcome. The secondary outcomes were plasma glucose level, body mass index (BMI), p-S6, insulin, C-peptide, insulin growth factor (IGF-1), Leptin, p-AKT, p-4EBP1, hemoglobin. (v) **Study design:** We included only randomized clinical trials (RCTs). Our exclusion criteria were (1) non-randomized controlled clinical trials, (2) studies that did not report data or measures for our selected outcomes (3) single-armed trials, or (4) that with no available full-text.

Screening of Results

After retrieving the search results, we exported the data into EndNote X8.0.1 (Build 1044), with the automatic removal of any duplicates. We screened the included articles through two steps, the first step was the title and abstract screening, and the second was full-text screening. Two independent authors performed the screening steps and obtained the full-text files for all included studies based on our criteria for eligibility criteria. A third author solved any deflection.

Data Extraction and Analysis

After the screening process, we performed the data extraction step. We extracted the data into three main categories: 1) baseline and demographic data of patients in each study, including age, BMI, myometrium invasion, and menopausal

state. 2) Data about Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging and tumor grades, and 3) Data for analysis including outcome values of Ki-67 proliferation and expression index, glucose level, BMI, p-S6, insulin, c-peptide, IGF-1, Leptin, p-AKT, p-4EBP1, hemoglobin. In addition to the previous three categories, we extracted the data about the seven domains assessing the risk of bias according to Cochrane's risk of bias.

Statistical Analysis

We performed our analysis using Review Manager Software (RevMan 5.4.1) under the Inverse variance method. Continuous data were expressed using mean difference (MD) and standard error, relative to 95% confidence interval (CI), while dichotomous outcomes were expressed using percentage and total. Two main tests indicate inconsistency among studies[21], the I-square test (I^2) and the p-value of the chi-square test. The outcomes with I^2>50%, p<0.1 were considered heterogeneous, while outcomes with I^2<50%, p>0.1 were considered homogeneous, according to the Cochrane Handbook. Homogenous data were analyzed using a fixed-effects model, while heterogeneous outcomes were analyzed using the random-effects model.

Quality Assessment

Quality assessment of this meta-analysis was performed using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). We included only the controlled trials and excluded the observational evidence. We used Cochrane's risk of bias tool to perform the risk of bias assessment for the included studies[22]. The tool depends on the following domains for the assessment of the risk of bias: 1) proper randomization, 2) blinding allocation of the included patients into each group, 3) blinding of patients only (single-blinding), blinding of both personnel and participants (double-blinding), or not blinding at all, 4) attrition bias, 5) selection bias (outcomes reported matches with that of the protocol or not), 6) awareness of the outcome assessor (whether blinded or not), 7) other bias. The total risk of bias for the studies has been assessed as well.

Results

Summary of Included Studies

Figure 1 shows a PRISMA flow diagram of our literature search. In our study, we performed an analysis of 397 patients from nine studies[23-31]. A total of 221 patients were allocated to receive metformin, and 176 patients entered the control group. The mean age of the percipient in the treatment group was 56.4±8.8 years, while that of the control group was 60±7.5. The mean BMI of the patients in the metformin group was 34.14±6.1, while that of the control group was 32.84±9.7. Table 1 shows a detailed summary of the included participants, their demographic data, and the menopausal state. Additionally, Table 2 illustrates the FIGO staging and Tumor grade.

Results of Risk of Bias Assessment

The result of the risk of bias assessments yielded an overall low risk of bias, according to Cochrane's tool[22]; Figure 2 summerizes the quality assessment of included studies. Regarding randomization, all studies were at low risk of randomization, except Sivalingam et al.[24], and Mitsuhashi et al.[25] were non-randomized trials. As for the allocation concealment, three studies[23,27,29] reported adequate allocation concealment; therefore, there were put to a low risk of bias. Five studies[24-26,30,31] did not report enough data about allocation concealment, thus put to an unclear risk of bias. One study reported no allocation concealment. Most included studies[23,24,26,27,29,30] were blinded, and only three studies[25,28,31] did not report enough data about blinding of the participants and personnel, thus put to an unclear risk of bias. Six studies[23,24,26,27,29,30] were at low risk of blinding of outcome assessment. Zhao et al.[31] and Pabona et al.[28] did not report enough data about blinding of outcome assessment. The remaining domains of the Cochrane tool were all at low risk of bias, except two studies: Zhao et al.[31] did not report enough evidence aonthe attrition bias domain, and Tehranian et al.[29] did not report enough evidence on the reporting bias domain.

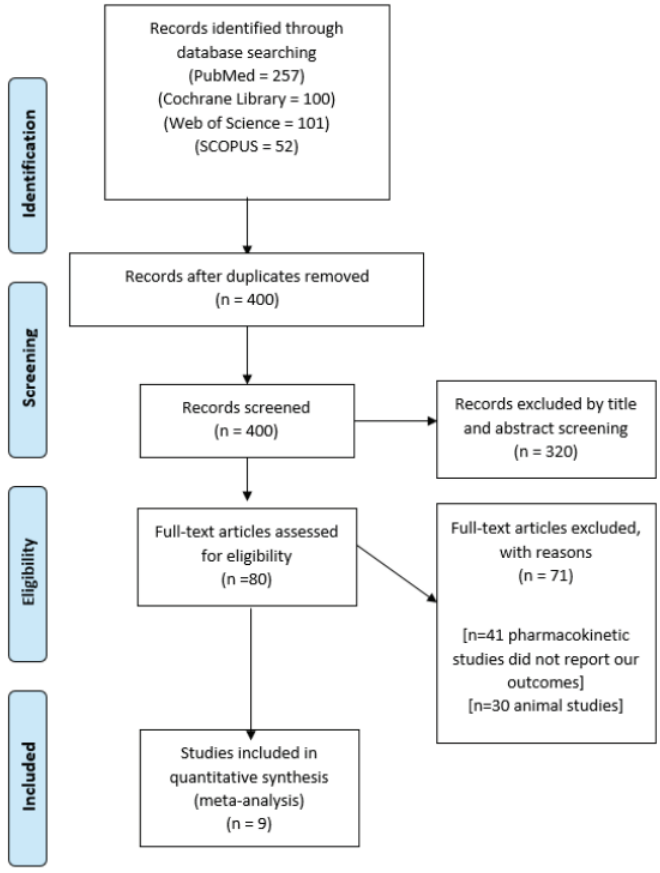

Figure 1. Shows a PRISMA flow diagram of our literature search

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Analysis of Outcomes

1-Ki-67 index:

Ki-67 index was reported by six studies[23-26,28,31].The overall mean difference favored the metformin group over the control group [MD=-10.14 (-19.10, -1.17)], (p=0.03). Pooled analysis was heterogeneous (p<0.001); I^2=89% as shown in Figure 3A.We solved the heterogeneity by the exclusion of Pabona et al.[28] (p=0.53); I^2=0%. The pooled analysis after the exclusion also favored the metformin group significantly [MD=-11.82 (-15.22, -8.42)], (p=0.01). Figure 3B illustrates the analysis after the exclusion of one study.

2-P-AKT:

Two studies[24,31] reported P-AKT. There was no significant difference between both groups [MD=0.40 (-1.32, 2.13)]. Pooled analysis was homogenous (p=0.97); I^2=0% as shown in Figure 4.

3- P-S6

Two studies reported p-S6 outcome[24,26]. P-S6 was significantly decreased in the metformin group [MD=-1.82 (-3.17, -0.46)], (p=0.009). Analysis was homogenous (p=0.15); I^2=52% as shown in Figure 5.

4-P-4EBP1

p-4EBP1 was reported in two studies[24,31]. The overall analysis did not show any variation between both groups [MD=-2.28 (-5.75, 1.20)], (p=0.20). Data were homogeneous (p=0.90); I^2=0% as shown in Figure 6.

5-Hemoglobin (g/dL)

Two studies reported hemoglobin outcome[29,30]. The analysis did not show any significant difference between both groups [MD=-0.03 (-0.33, 0.26)], (p=0.82). Data were homogenous, (p=0.65); I^2=0% as shown in Figure 7.

6-Glucose (mg/dL)

Glucose outcome was reported in five studies[23,24,27,29,30]. The overall mean difference did not reveal any difference between both groups [MD=-1.76 (-4.88, 1.37)], p=0.27. Analysis was heterogeneous (p=0.07); I^2=54% as shown in Figure 8A. To solve heterogeneity we excluded Tehranian et al.[29] (p=0.75); I^2=0%. The total mean difference after solving heterogeneity also favored metformin group [MD=-0.40 (-0.68, -0.11)], (p=0.006) as shown in Figure 8B.

7-Insulin (mUI)

Three studies reported insulin outcome[24,27,30]. The total analysis showed increased insulin level in the metformin group than the control group [MD=1.99 (1.86, 2.12)], (p<0.001), Data were homogeneous (p=0.40); I^2=0% as shown in Figure 9.

8-BMI

Three studies reported BMI[24,29,30]. The total mean difference favored BMI significantly [MD=-1.07 (-1.49, -0.65)], (p<0.001).

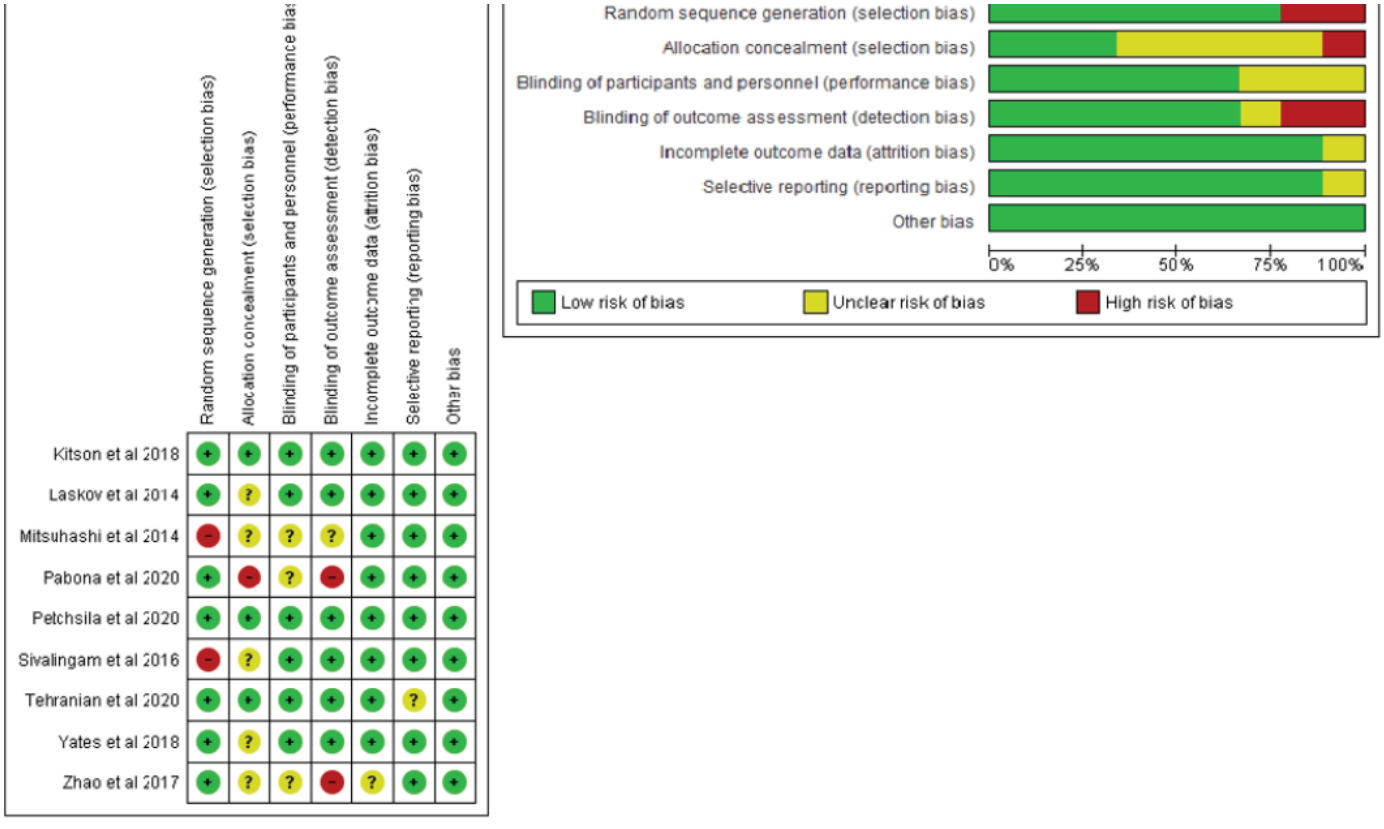

Figure 2. Shows both a summary and a graph of the risk of bias of the included studies

Table 1. Shows a detailed summary of the included participants, their demographic data, and the menopausal state

Study ID	Age, years (mean ± SD)/ median (range)		BMI kg/m² (mean ± SD)/ median (range)		Post-menopausal n (%)		Myometrial invasion, n (%)			
							<50		≥50	
	MFM	C	MFM	C	MFM	C	MFM	C	MFM	C
Kitson et al. 2018[27]	64.375±13.525	64.8±11.35	31.0 (20.2-54.2)	32.0 (17.8-47.6)	36 (80.0)	36 (83.7)	NR	NR	NR	NR
Laskov et al. 2014[26]	61±6.5	68.25±4.75	28.6 (20.5-34.9)	28.8 (25-40)	11 (100)	10 (100)	NR	NR	NR	NR
Mitsuhashi et al. 2014[25]	50.25±11.25		NR	NR	NR	NR	NR	NR	NR	NR
Pabona et al. 2020[28]	55.4±4.7	60.5±1.8	42.5±4.9	38.2±2.8	NR	NR	NR	NR	NR	NR
Petchsila et al. 2020[23]	55.5±10.0	54.9±11.9	NR	NR	17 (68.0)	15 (62.5)	13 (52.0)	18 (75.0)	10 (40.0)	6 (25.0)
Sivalingam et al. 2016[24]	63.6±8.9	67.8±9.2	35.5±11.3	32±5.9	NR	NR	22 (78.6)	7 (58.3)	6 (21.4)	3 (25.0)
Tehranian et al. 2020[29]	44.85±6.80	43.16±6.08	NR	NR	3 (9.4)	4 (16)	NR	NR	NR	NR
Yates et al. 2018[30]	60.0±4.5	55.8±5.2	36.7±5.5	38.3±5.1	NR	NR	NR	NR	NR	NR
Zhao et al. 2017[31]	NR	NR	27.4 (23.7-36.1)	26.9 (24.5-35.6)	24 (72.7)	22 (68.75)	26 (78.7)	24 (75)	7 (21.2)	8 (25)

Data are reported as mean ± SD or n (%) unless otherwise specified. NR: Unreported, MFM: Metformin, C: Control group, BMI: Body mass index, SD: Standard deviation

Table 2. Illustrates the FIGO staging and tumor grade

Study ID	FIGO Stage n (%)				Tumor grade n (%)					
	Early stage (I-II)		Advanced stage (III-IV)		G1		G2		G3	
	MFM	C	MFM	C	MFM	C	MFM	C	MFM	C
Kitson et al. 2018[27]	34 (75)	38 (88.3)	9 (25)	3 (6.9)	26 (57.8)	23 (53.5)	10 (22.2)	12 (27.9)	6 (13.3)	6 (14.0)
Laskov et al. 2014[26]	9 (81)	2(11)	9 (90)	1 (10)	2 (18)	5 (50)	5 (45)	2 (20)	4 (36)	3 (30)
Mitsuhashi et al. 2014[25]	26 (80)		5 (20)		NR	NR	NR	NR	NR	NR
Pabona et al. 2020[28]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Petchsila et al. 2020[23]	20 (80.0)	21 (87.5)	5 (20.0)	3 (22.5)	15 (60.0)	17 (70.8)	6 (24.0)	5 (20.8)	4 (16.0)	2 (8.3)
Sivalingam et al. 2016[24]	23 (83)	10 (100)	5 (17)	0(0)	14 (50.0)	1 (8.3)	13 (46.4)	6 (50.0)	1 (3.6)	3 (25.0)
Tehranian et al. 2020[29]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yates et al. 2018[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhao et al. 2017[31]	23 (69.6)	19 (59.3)	10 (30.3)	13 (39.3)	19 (57.5)	18 (56.25)	8 (24.4)	7 (21.8)	6 (18.1)	7 (21.8)

Data are reported as mean ± SD or n (%) unless otherwise specified. NR: Unreported, MFM: Metformin, C: Control group, FIGO: Fédération Internationale de Gynécologie et d'Obstétrique. SD: Standard deviation

Pooled analysis was homogeneous (p=0.17); I^2=43% as shown in Figure 10.

9-C-peptide (pg)

The C-peptide outcome was reported in two studies[24,30]. The combined mean difference did not show any significant difference between both groups [MD=-93.12 (-422.60, 236.36)], (p=0.58) Data were heterogeneous (p=0.01); I^2=84% as shown in Figure 11. We could not solve heterogeneity because only two studies reported this outcome.

Discussion

In our meta-analysis, we investigated the effect of metformin on tumor markers of EC. Six studies[23-26,28,31] evaluated the association of metformin use with Ki-67 proliferation and expression. Out of the six studies that reported the Ki-67 index, five studies[23-26,31] found that metformin significantly decreased the positive rate of Ki-67. Pabona et al.[28] found that metformin did not affect Ki-67 proliferation, which may be due to a short-term metformin administration and/or the non-diabetic status of the patients.

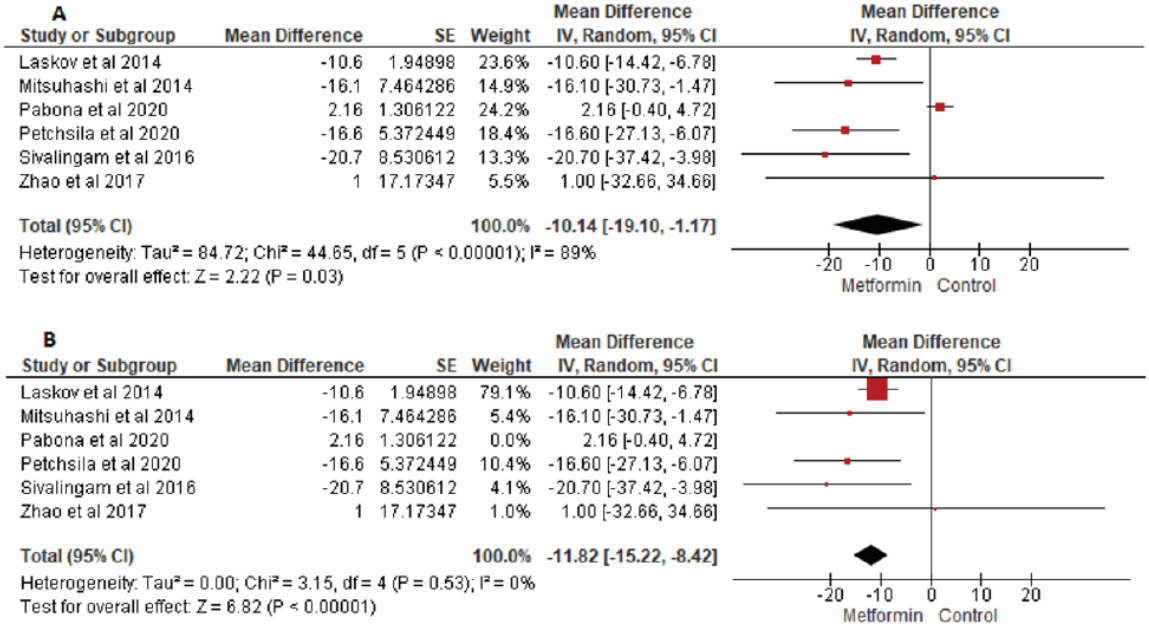

Figure 3. Shows the Ki-67 proliferation index outcome

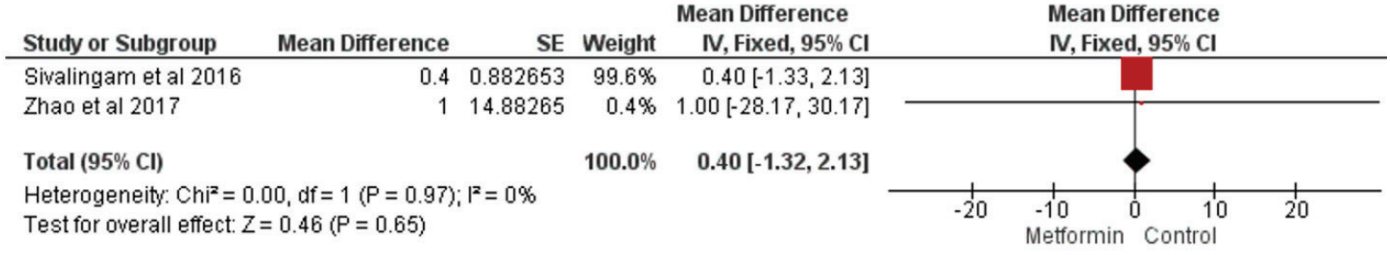

Figure 4. Shows the P-AKT outcome

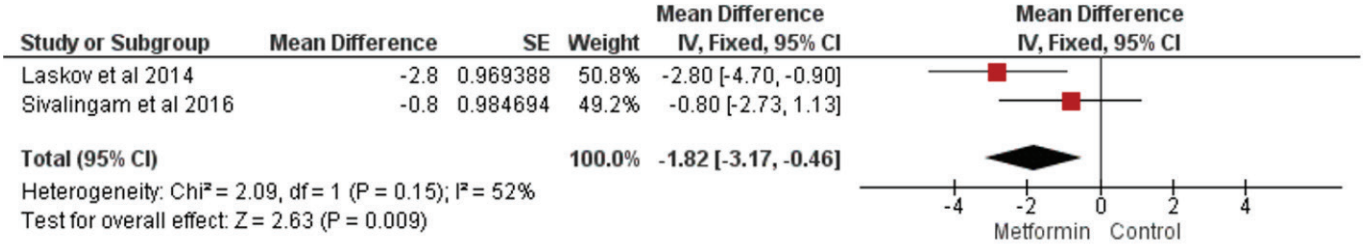

Figure 5. Shows the P-S6 outcome

Ki-67 protein is a proliferation marker for many human tumors for decades. Recently, we have understood the molecular functions of the Ki-67 protein[32]. Ki-67 affects the active phases of the cell cycle. It accumulates only during S, G2, and M phases but is absent from resting cells G0; therefore, it is an excellent marker for cell proliferation[33]. Zhao et al.[31] and Sivalingam et al.[24] reported the effect of metformin on p-AKT expression. The two studies showed that metformin significantly decreased the rate of p-AKT. Akt is a serine kinase that participates in the PI3K signaling pathway. It can be activated by various growth signals. Once activated, Akt modulates the function of many proteins involved in cellular proliferation, survival, metabolism, -and angiogenesis.

Two studies[24,26] showed that reduction of pS6 expression was evident in all patients who received metformin. The expression of ps6 was increased in abnormal epithelial glands compared to the normal endometrium. Five studies that reported glucose level showed a significant decrease in glucose level after metformin administration as expected[23,24,27,29,30]. The main underlying mechanism is that metformin improves insulin sensitivity and prevents gluconeogenesis, lowering plasma glucose[34]. A previous study found impaired glucose

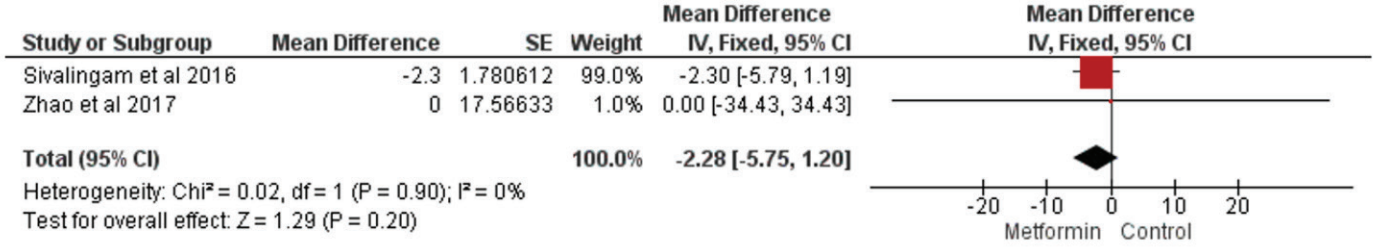

Figure 6. Shows the p-4EBP1 outcome

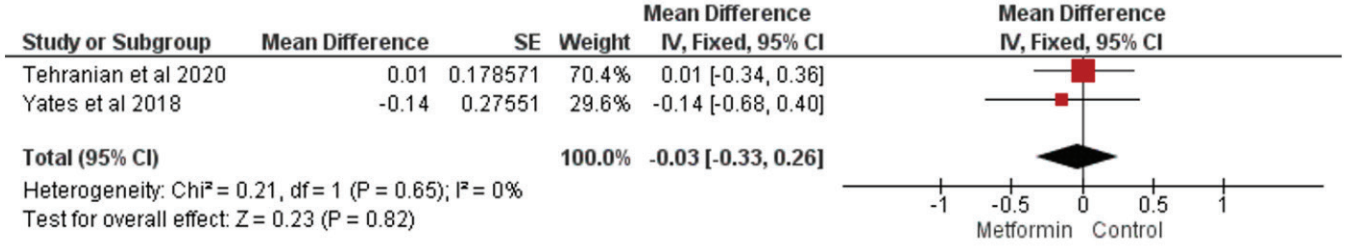

Figure 7. Shows the hemoglobin (gm) outcome

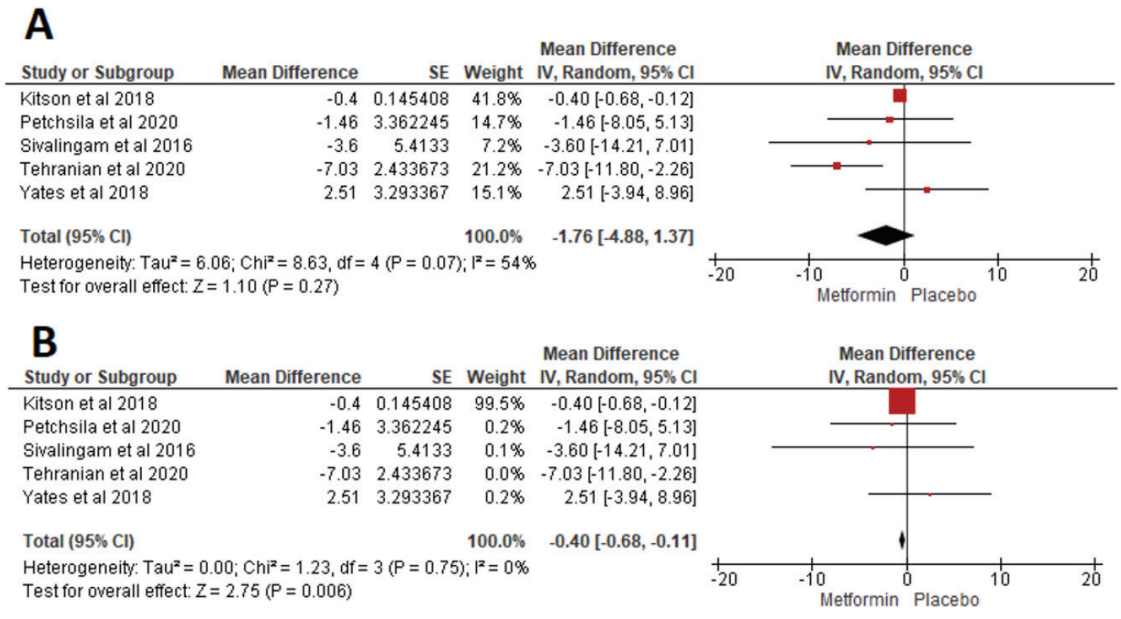

Figure 8. Shows the glucose (mg/dL) outcome

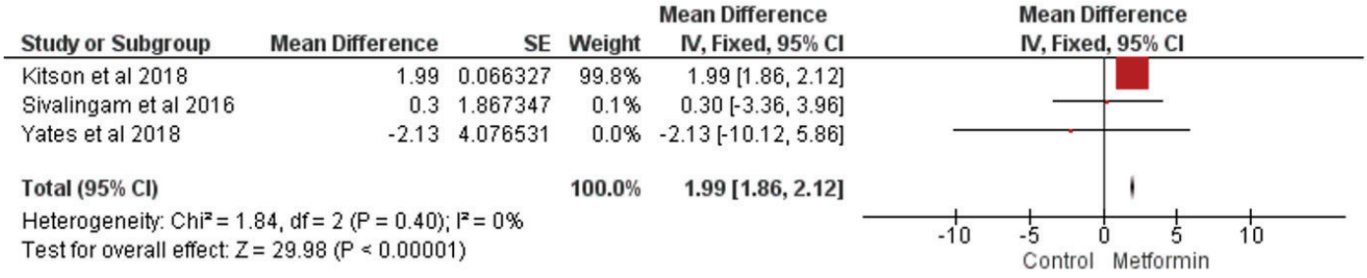

Figure 9. Shows the insulin (mIU) outcome

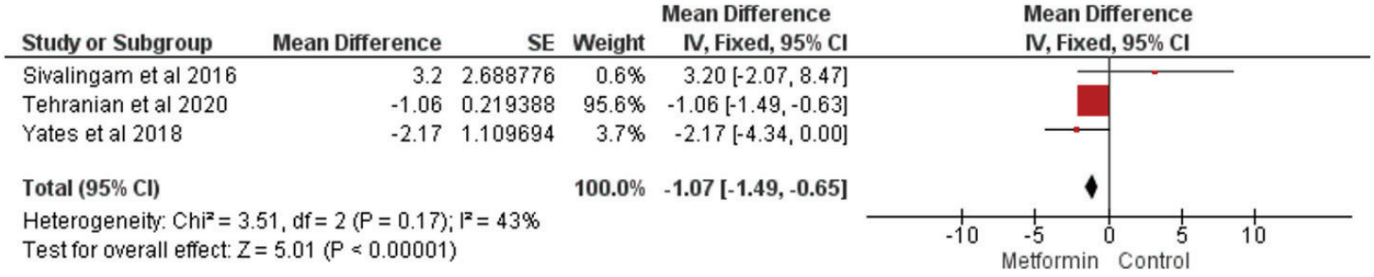

Figure 10. The BMI (kg/m^2) outcome

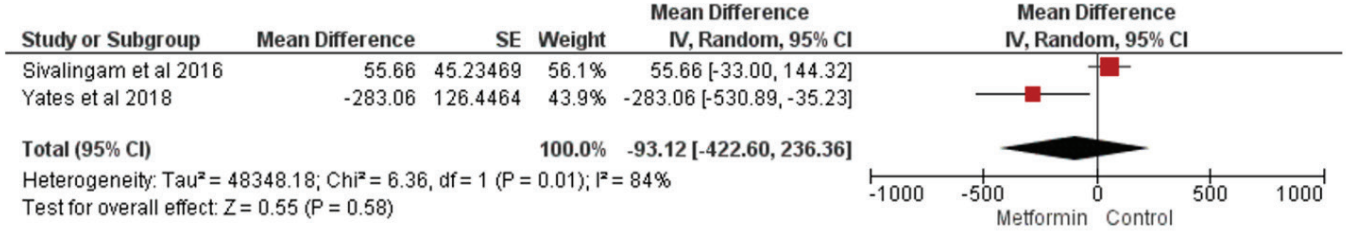

Figure 11. The c-peptide (pg) outcome

tolerance and insulin resistance may induce the initiation and progression of EC. Therefore, Adequate diabetes control by metformin is suggested to prevent EC[35]. There is a debate on whether metformin increases or decreases plasma insulin levels. Two studies reported that metformin decreases insulin levels[24,30,36], while another study found that metformin did not affect insulin-signaling pathways[27].

The main point of strength in our study is the inclusion of clinical trials only while excluding other observational evidence. It is well-known that data from clinical trials are considered the strongest evidence, according to Cochrane's handbook. We found an overall low risk of bias among the included trials, which further supports the accuracy of our findings. Most of the analyzed outcomes were homogeneous, and this favors the true interpretation of data.

Study Limitations

The major limitation of this study is the relatively small sample size (397 participants). Other limitations include some heterogeneous secondary outcomes and the fact that two trials were not randomized. Additionally, no data were reported regarding the safety parameters of administering metformin in patients with EC. So, we highly recommend the initiation and conduction of further clinical trials with a larger sample size and considering safety endpoints.

Conclusion

As a summary, the evidence from the included studies shows that metformin administration in patients with EC significantly decreases Ki-67 proliferation and expression, reduces serum glucose levels and p-S6.

Ethics

Ethics Committee Approval: The ethics statement is not applicable because this study is based exclusively on published literature.

Informed Consent: Not necessary.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.A.S., A.A.S., A.T.A., A.T.M., A.M.F., H.M., Design: M.A.S., A.A.S., A.T.A., A.T.M., A.M.F., H.M., Data Collection

or Processing: M.A.S., A.A.S., A.T.A., A.T.M., A.M.F., H.M., Analysis or Interpretation: M.A.S., A.A.S., A.T.A., A.T.M., A.M.F., H.M., Literature Search: M.A.S., A.A.S., A.T.A., A.T.M., A.M.F., H.M., Writing: M.A.S., A.A.S., A.T.A., A.T.M., A.M.F., H.M.

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