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The influence of metformin on IGF-1 levels in humans: A systematic review and meta-analysis

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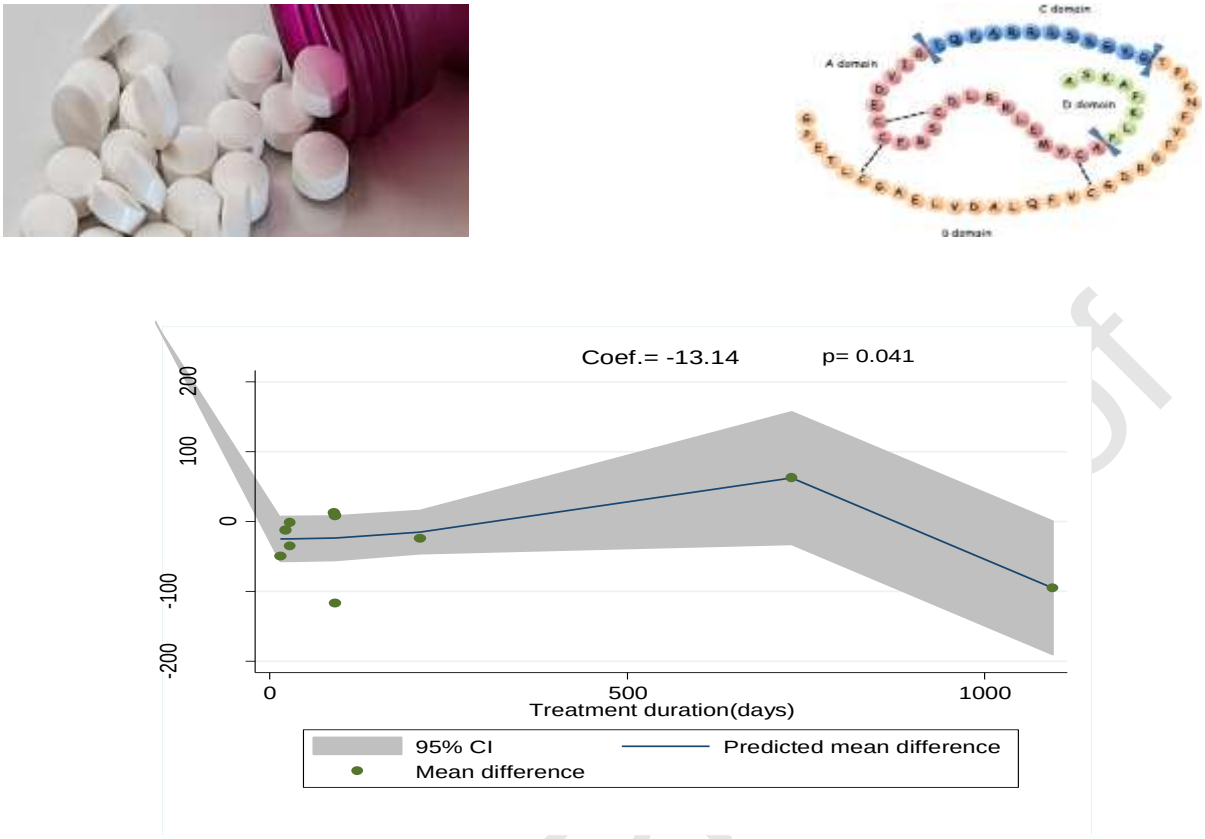
Graphical abstract



Abstract

Background: A meta-analysis is needed to comprehensively consolidate findings from the influence of metformin on IGF-1 levels. The present study was conducted with the objective to accurately evaluate the influence of metformin intake on IGF-1 levels via a meta-analysis of randomized controlled trials.

Methods: A comprehensive systematic search was carried out in PubMed/MEDLINE, Web of Science, SCOPUS and Embase from inception until June 2019. Weighted mean difference (WMD) with the 95% CI were applied for estimating the effects of metformin on serum IGF-1 levels.

Results: 11 studies involving a total of 569 individuals reported changes in IGF-1 plasma concentrations as an outcome measure. Pooled results demonstrated an overall non-significant decline in IGF-1 following metformin intake (WMD: -8.292 ng/ml, 95% CI: -20.248, 3.664, p= 0.174) with heterogeneity among (p=0.000,I^2=87.1 %). The subgroup analyses displayed that intervention duration >12 weeks on children (WMD:-55.402ng/ml, 95% CI: -79.845, -30.960, I2=0.0%) significantly reduced IGF-1. Moreover, in age 18 > years older metformin intake (WMD: 15.125 ng/ml, 95% CI: 5.522, 24.729, I2=92.5%) significantly increased IGF-1 than 18 ≤ years older (WMD:-1.038 ng/ml,95% CI: -3.578,1.502,I^2=78.0%). Following dose-response evaluation, metformin intake reduced IGF-1 (coefficient for dose-response analysis= -13.14, P= 0.041 and coefficient for liner analysis= -0.066, P= 0.038) significantly based on treatment duration.

Conclusion: We found in children, intervention duration >12 weeks yielded significant reductions in IGF-1, whilst paradoxically, in participants >18 years old, metformin intake significantly increased IGF-1. We suggest that caution be taken when interpreting the findings of this review, particularly given the discordant supplementation practices between children and adults.

Keyword: meta-analysis, metformin, IGF-1, insulin-like growth factor I, biguanidine

1. Introduction

Insulin-like growth factor 1 (IGF-1) is an anabolic hormone produced mainly in the liver. The hormone plays an important role in regulating biological activities related to growth hormone (GH), such as insulin metabolism and cell proliferation, differentiation and apoptosis[1]. As such, IGF-1 has been commonly implicated in various human diseases. For example, an elevated level

of serum IGF-1 has been found to be associated with an increased risk of many cancers [2]. In contrast, a lower level of serum IGF-1 has been associated with diabetes and cardiovascular diseases[3, 4]. Besides, epidemiological evidence and animal studies have demonstrated the role of the IGF-1/GH pathway in longevity and aging process[5-9]. These findings indicate that a proper balance in the level of IGF-1 is essential for optimal health.

Metformin is an insulin-sensitizing biguanide drug that is commonly used for treatment of type 2 diabetes after dietary and exercise interventions have failed[10]. Metformin has an excellent safety profile due to its negligible risk of hypoglycemia and clinically-relevant drug interactions (in other words, there will be minimal, if any, side effects or changes in the effectiveness of metformin when it is used in conjunction with other drugs or agents)[10]. Besides bringing down the level of blood glucose, recent evidence has shown that metformin also possesses some anti-cancer properties. The use of metformin has been found to be associated with a decreased incidence and mortality of various cancers[11-13]. Metformin achieves its anti-hyperglycemic and anti-cancer effects through highly complex mechanisms, which include suppressing the hepatic fatty acid oxidation, increasing insulin sensitivity, reducing intestinal absorption of glucose, decreasing inflammation, and inhibiting mitochondrial oxidative phosphorylation through the LKB1–AMPK pathway[14-17]. A number of studies have also demonstrated that metformin induces apoptosis and inhibits cell proliferation by interacting with the IGF-1 pathway [18-20].

For this reason, several studies have been conducted to examine the influence of metformin intake on the levels of IGF-1 in humans. Nevertheless, different studies have reported inconsistent and sometimes contradictory findings with regard to the relationship between metformin and IGF-1 levels. For example, while Cai et al. [21]and Hamed et al. [22]found that metformin intake could lead to a significant reduction in IGF-1 level, Díaz et al. [23] and Yates et al. [24] did not find any significant changes in IGF-1 level following metformin intervention. The conflicting results

obtained in different studies could be attributed to various factors, such as the small sample size in each individual trial, different characteristics of the study participants, as well as dose and duration of metformin intervention. A meta-analysis is needed to comprehensively consolidate findings from different studies. The present systematic literature review was conducted with the objective to accurately evaluate the influence of metformin intake on IGF-1 levels via a meta-analysis of randomized controlled trials.

2. Methods

2.1. Search strategy

The current study was performed across the PRISMA [Preferred Reporting Items for Systematic Review and Meta-analysis] protocols [25]. A comprehensive systematic search was carried out in PubMed/MEDLINE, Web of Science, SCOPUS and Embase by two independent reviewers (JR and HKV) from inception until June 2019 without using time or language restrictions. We considered randomized controlled trials (RCTs) that measured the effects of metformin on circulating IGF-1 concentrations. Search strategy details were provided in Supplementary Table 1.

2.2. Selection criteria

We considered the participant, intervention, comparison, outcome, time, and study design (PICOTS) criteria to ascertain study inclusion criteria. Endnote Reference Manager X8© was used for citation management. Two independent authors (JR and HKV) reviewed the abstract of all studies to choose eligible trials and subsequently screened the full texts of included studies. The following inclusion criteria were applied: 1. Trials that had a controlled trial design; 2. Studies which provided circulating IGF-1 serum in the form of mean differences (MD) with the 95% confidence intervals (95% CI). In addition, studies not reporting IGF-1 concentrations before and

after administration; animal studies; non-randomized study designs; studies without a control group; reviews, commentaries, conference abstracts and case-reports were excluded.

2.3. Data extraction

Two independent researchers (HKV and JR) extracted the data and an additional reviewer resolved any disagreements. The following information was retrieved: author, year of publication, country, number of cases and controls, participants' gender, mean age (year), study design, duration of intervention, dose of metformin intervention, and means and standard deviations of IGF-1 levels at baseline, post treatment and/or changes between baseline and post treatment.

2.4. Quality assessment

The Cochrane Collaboration's tool for quality assessment of randomized controlled trials was used to assess the risk of bias in all eligible studies (Higgins et al., 2011). The quality assessment tool encompasses the following domains: allocation concealment, random sequence generation, blinding of participants and personnel, incomplete outcome data, blinding of outcome assessment, selective reporting and other probable sources of biases.

2.5. Statistical analysis

Weighted mean difference (WMD) with the 95% CI were applied for estimating the effects of metformin on serum IGF-1 levels. When the SD of the mean difference was not provided in the studies, we obtained it using the following formula: SD_{change}= square root [($SD_{baseline}^{2}$+SD_{final}^{2}) -(2×R× $SD_{baseline}$× SD_{final})] [26]. Combined WMD from eligible studies was calculated with derSimonian and Laird random-effects method. We assessed heterogeneity between study-specific estimates using the Q-test, the I-squared (defined as significant when a p value < 0.10). Subgroup analysis was performed to specify the source of heterogeneity among studies. The potential effects of metformin dosage and intervention duration were surveyed using fractional polynomial modelling in non-linear dose-response analysis and meta-regression analysis. Publication bias was

ascertained using funnel plot inspection as well as Egger's and Begg's tests. All statistical tests were executed using the Stata software (Stata Corp. College Station, Texas, USA) and a p value of 0.05 or less was reported as statistically significant. One-way ANOVA and Tukey-Kramer Multiple Comparison tests was used to compare IGF-1 levels and daily metformin intake (mcg/d) in participants.

3. Results

Primary systematic search identified 560 studies from PubMed/MEDLINE, Web of Science, Scopus, and Embase (Supplementary Fig. S1). Duplicated studies were removed and 380 studies remained. During the primary screening, which was based on review of study titles and abstracts, 338 studies were excluded and 42 studies remained for full text extraction. During the secondary screening, 31 studies were excluded for the following reasons: 1) non trial design, 2) and studies included no data of interest. 11 studies were included in the quantitative meta-analysis [21-23, 27-34].

3.1. Study characteristics

Characteristics of the eligible studies are presented in Table 1. one studies were performed in China [21], two in Spain [23, 31], two in Italy [28, 34], one in Egypt[22], one in Brazil [30], one in Sweden [32] , one in Germany [33], and two in USA [27, 29]. All studies were published between the years 1999–2018. The mean duration of interventions was 226 days. All studies were randomized controlled clinical trials. Dose of metformin intake ranged between 425 and 2000 mg/day. Studies were conducted on different population three on cancer patients [21, 27, 28], three on children [23, 29, 31], women with polycystic ovary syndrome[22, 30], one on type 1 diabetes patient [32], and two healthy adults [33, 34]. The results of the quality assessment of eligible studies are accessible in Table 2. The risk of bias was attributed to randomization processes of included studies.

3.2. Meta-analysis results

11 studies involving a total of 569 individuals (case=279, control=290) reported changes in IGF-1 plasma concentrations as an outcome measure. Pooled results using the random-effects model demonstrated an overall non-significant decline in IGF-1 following vitamin metformin intake (WMD: -8.292 ng/ml, 95% CI: -20.248, 3.664, p= 0.174; Fig. 1). However, a significant degree of heterogeneity among studies was observed (p= 0.000, I2= 87.1 %).

3.4. Subgroup analysis

We subsequently stratified studies based on metformin dosage, intervention duration (week), Age (years) of participants and Type of study population (Table 3). These analyses showed that intervention duration (week) and Type of study population were possible source of heterogeneity. In addition, intervention duration >12 weeks on children (WMD: -55.402 ng/ml, 95% CI: -79.845 , -30.960, I2=0.0%) significantly reduced IGF-1. Moreover, in age 18 > years older metformin intake (WMD: 15.125 ng/ml, 95% CI: 5.522, 24.729, I2=92.5%) significantly increased IGF-1 than 18 ≤ years older (WMD: -1.038 ng/ml, 95% CI: -3.578, 1.502, I2=78.0%).

3.5. Dose-response and meta-regression

Subsequent analysis of the relationship between intervention duration with plasma IGF-1 alterations revealed a negative correlation in non-liner dose response (Coefficient for dose-response analysis= -13.14, P= 0.041; Fig.2) and linear association (Coefficient for liner analysis= -0.066, P= 0.038). Significant associations were not observed for other outcomes.

3.6. Publication bias and sensitivity analysis

The Begg's and Egger's tests did not find a significant publication bias among the studies (p=0.392 and p=0.235, respectively). Evaluation of publication bias by visual inspection of funnel plot illustrated no evidence of publication bias (Supplemental Fig. 2). To discover the impact of each single study on the combined effect size, we removed each trial at a time from the analysis and

accounted for their individuality. We observed no significant effects of any individual study on the combined effect sizes.

4. Discussion

It has been asserted that higher IGF-1 bioactivity may be correlated with an increased risk of several types of cancer, including prostate [35, 36], colorectal [37], and breast cancers [38]. Given the potential contrasting roles of the IGF-1 axis on overall indices of health, a deciated effort is required to better understand the determinants of IGF-1 biological activity, particularly in relation to widely used medications. Several studies have investigated the influence of metformin intake on IGF-1 levels in humans, however, much of the literature is equivocal. For example, while Cai et al. (Cai et al., 2016) and Hamed et al. (Hamed, Hasan, Ahmed, & Ahmed, 2010) reported that metformin intake could yield significant reductions in IGF-1 levels, Díaz et al. (Diaz, Bassols, Lopez-Bermejo, de Zegher, & Ibanez, 2015) and Yates et al. (Yates et al., 2018) reported contrary evidence. The incongruent results obtained in different studies could be attributed to various factors, such as small sample sizes, varying participant characteristics, in addition to variable doses and duration of metformin interventions. Clearly, a meta-analysis is warranted to comprehensively consolidate findings from different studies; thus, the present study sought to evaluate the influence of metformin intake on IGF-1 levels via a meta-analysis of randomized controlled trials. In accord with the aforementioned aim, we found an overall non-significant decline in IGF-1 following metformin intake; however, a significant degree of heterogeneity was observed among studies, attributable to intervention duration (week) and study population. We found that, in children, intervention duration >12 weeks led to significant reductions in IGF-1; whilst in participants >18 years old, metformin intake significantly increased IGF-1, compared to those aged ≤ 18 years.

Although no, overall, significant effect was manifest, sub-group analyses demonstrated, that when stratified by age and supplementation duration, significant alterations in IGF-1 were evident. Metformin is an insulin-sensitizing biguanide, considered appropriate for treatment of pediatric type 2 diabetics. The mechanism of action of metformin is multifaceted, where it can facilitate insulin-induced suppression of gluconeogenesis, moreover, it can induce expression of glucose transporters, which subsequently increases glucose utilization [39]. We found that longer term interventions yielded significant reductions in IGF-1 in children, although in independent trials, studies have generally reported variable and modest improvements in children when using metformin for 4–6 months [40-42]. Interestingly, of all the included studies in this meta-analysis, those that focused on child participants tended to utilize much longer intervention durations, than in adult populations. In fact, [29] reported that children with obesity, but no other co-morbidities, had noticeable increases in highly sensitive C-reactive protein, interleukin 6 (IL-6), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1), which represents a pro-inflammatory and pro-thrombotic state, and is manifest prior to the onset of any other metabolic syndrome symptoms and the onset of puberty, as compared to normal-weight, age-matched controls [43]. Moreover, Mauras et al [29] asserted that currently available data support the use of aggressive interventions in children, irrespective of other comorbidities, which may conceivably explain the protracted interventions employed in the included studies. As noted above, a significant degree of heterogeneity was observed among studies, which was attributable to intervention duration (week) and study population, highlighting the discrepant treatment duration with metformin in children vs. adults.

Putative mechanism

Cancer cells can elicit an increase in the level of insulin circulating in the blood, and stimulate IGF signaling pathways, which consequently leads to growth of cancerous cells [44]. Metformin elicits

its therapeutic effect through numerous mechanisms, where it can reduce insulin resistance and elicit optimal glycemic control [45]. Metformin acts through inhibition of the mTOR pathway; where autonomous AMP-activated protein kinase (AMPK) is activated, which results in phosphorylation of tuberous sclerosis complex protein 2. Consequently, this elicits a decrease in cell growth and protein synthesis [46-48]. Moreover, metformin can reduce HOMA and leptin levels, respectively, where high concentration of the aforementioned is associated with deleterious health outcomes. Leptin purportedly acts on the OB-2 receptor, which can result in activation of the STAT signaling pathway and, indeed, Ras–Raf MEK signaling. Metformin may indirectly reduce leptin levels, subsequently inhibiting the OB-2 receptor pathway. Further suggested mechanisms of action through which metformin may elicit anti-cancer effects are through increases in TUNEL, which is an apoptosis biomarker and can reduce Ki-67, which is a biomarker of proliferation [46, 49]. Furthermore, metformin may contribute to weight loss through improving moderators of insulin resistance, regulation of fat oxidation, decreases in hepatic glucose output, and inhibition of gluconeogenesis. In turn, this positively impacts blood glucose control, and reduces caloric intake and intestinal glucose absorption [50-52]. However, as to why metformin appears to elicit greater effects in children vs. adults, this requires more detailed evaluation, beyond supplement duration discrepancies.

Strengths and limitations

This meta-analysis has numerous strengths and limitations. Firstly, the foremost strength of the present study is the use of only randomized-controlled trials to investigate the association between intervention and outcome. We investigated sources of heterogeneity among the included studies using subgroup analyses, and were based on intervention duration, participants age and metformin dose, and conducted a sensitivity analysis. However, there were some limitations that must be

addressed. Although we utilized a robust quality assessment tool, such judgements were qualitative in nature, and inter-rater reliabilities were not further investigated. Another conceivable limitation is the dearth of studies available for subgroup analysis, however, this was beyond the operational control of the study. This highlights that larger studies with adequately powered sample sizes are needed to inform definitive conclusions.

Conclusion

We found an overall non-significant decline in IGF-1 following metformin intake; however, a significant degree of heterogeneity was observed among studies, attributable to intervention duration (week) and study population. In sub-group analyses, in children, intervention duration >12 weeks yielded significant reductions in IGF-1, whilst paradoxically, in participants >18 years old, metformin intake significantly increased IGF-1. We suggest that caution be taken when interpreting the findings of this review, particularly given the discordant supplementation practices between children and adults. We strongly recommend that evidence from longitudinal studies is needed to make conclusive clinical recommendations, for both child and adult populations.

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Conflicts of interest

The authors hereby declare that they have no conflicts of interest in relation to the completion of this work.

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Fig. 1. Forest plot of randomized controlled trials investigating the effects of metformin on IGF-1 levels.

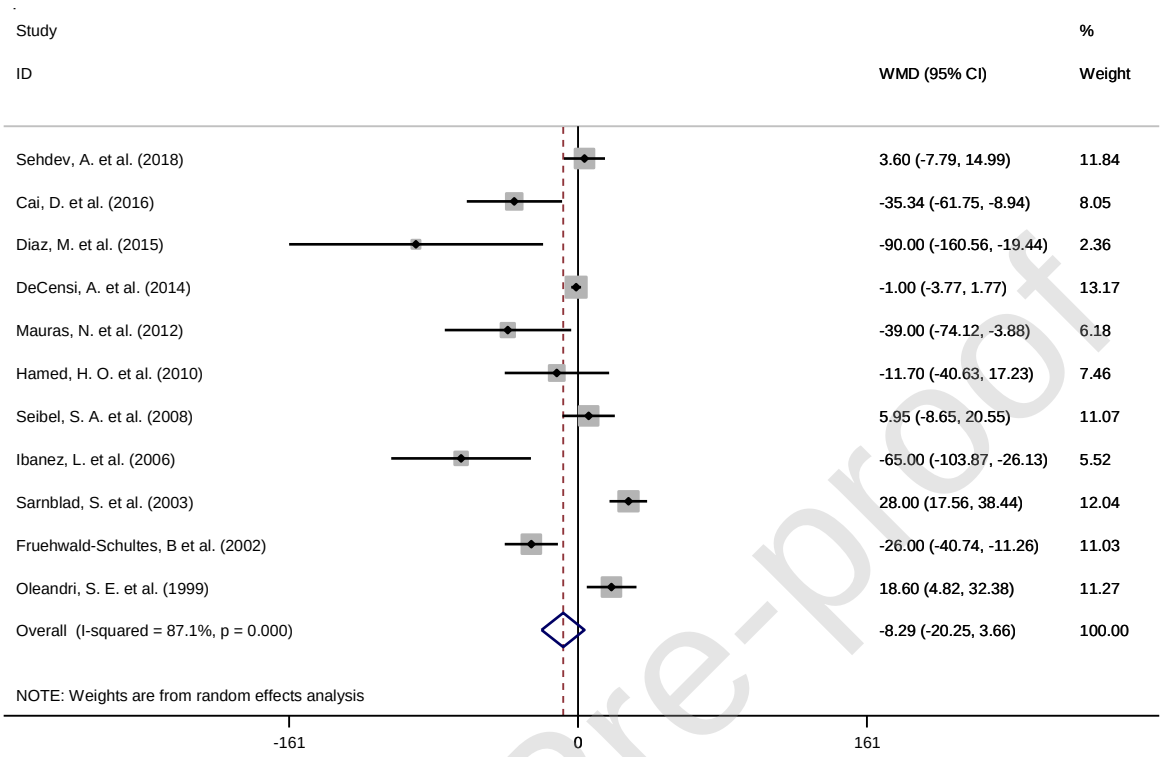
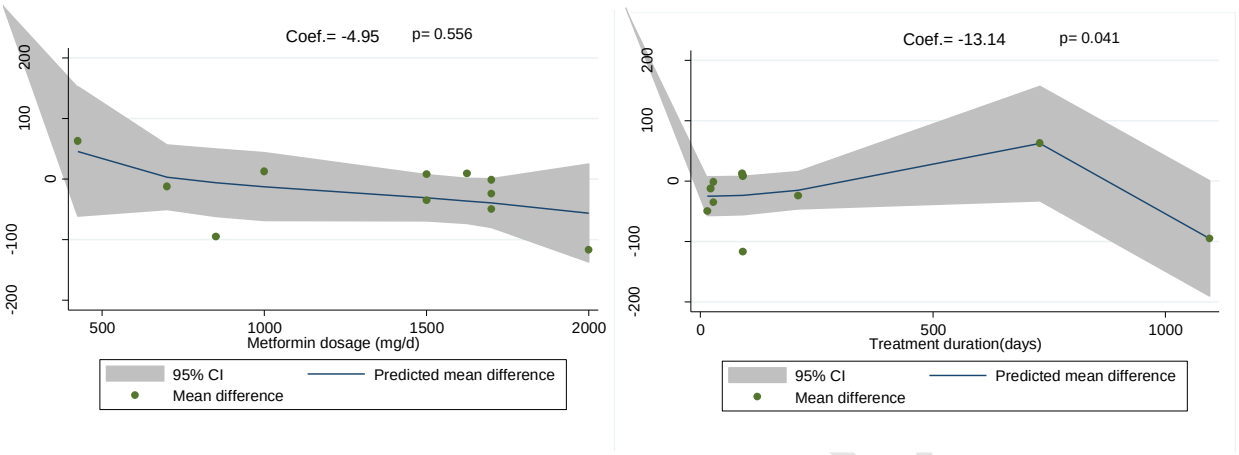


Fig2. A) Dose-response analysis - metformin **dosage (IU/day)** and **Intervention duration (week) with** IGF changes. Weighted mean difference, WMD., B) Meta regression analysis (Metformin dosage (IU/day) and Intervention duration (week) with IGF changes).

A)



B)

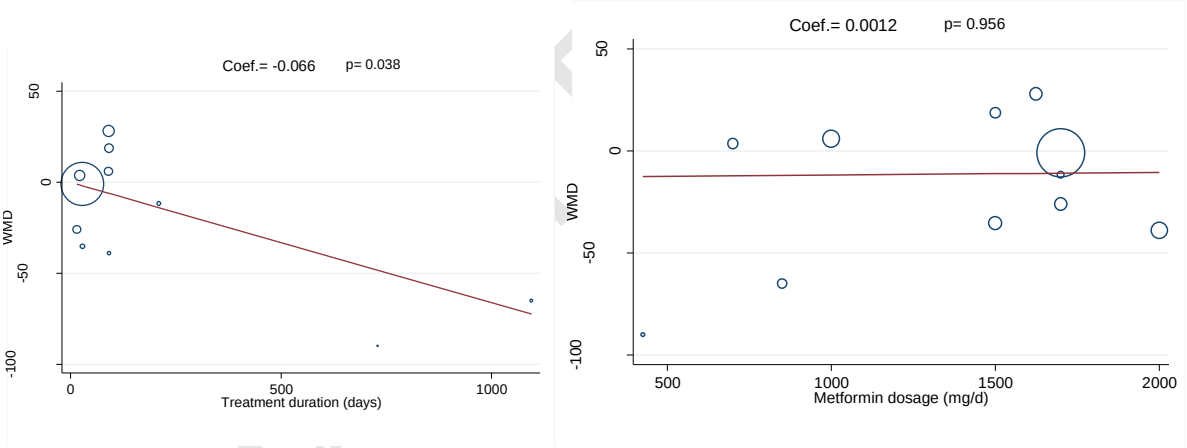


Table 1. Characteristics of included studies

Author	Country(year)	Study Design	Duration	Age(year)	study population	Sample Size case/placebo	Dose (mg/day)
Sehdev, A. et al.	USA(2018)	parallel	22days	57	patients with advanced solid tumors	8/10	700
Cai, D. et al.	China(2016)	parallel	4weeks	45	Human Endometrial Cancer	30/30	1500
Diaz, M. et al.	Spain(2015)	parallel	24months	7.8	prepubertal children	6/14	425
DeCensi, A. et al.	Italy(2014)	parallel	4 weeks	≥18	women with stage I-IIa breast cancer candidate to elective surgery	97/99	1700
Mauras, N. et al.	USA(2012)	parallel	6 months	12	children with obesity	23/19	2000
Hamed, H. O. et al.	Egypt(2010)	parallel	30 weeks	23	women with polycystic ovary syndrome	54/55	1700
Seibel, S. A. et al.	Brazil(2008)	parallel	90 days	≥18	obese patients with polycystic ovary syndrome	15/15	1000
Ibanez, L. et al.	Spain(2006)	parallel	36 months	8.6	Low-Birth-Weight Girls with Early-Normal Onset of Puberty	10/12	850
Sarnblad, S. et al.	Sweden(2003)	parallel	3months	17	type 1 diabetes	11/13	1625
Fruehwald-Schultes, B et al.	Germany(2002)	cross over	15 days	26	normal-weight healthy men	15/15	1700
Oleandri, S. E. et al.	Italy(1999)	parallel	3months	47.5	obese patients	10/8	1500

Table 2: Quality assessment of study included in this study

Table 3. Pooled estimates of effects on IGF-1 within different subgroups.

Group	No of comparisons	WMD (95% CI)			P value	P-heterogeneity	I^2 (%)
Metformin intake **dosage (IU/day)**							
<1000	3	-3.890	-14.690	6.910	0.480	0.000	88.2
≥1000	8	0.232	-2.290	2.754	0.857	0.000	88.3
Intervention duration (week)							
≤12	8	0.584	-1.884	3.053	0.643	0.000	87.4
>12	3	-55.402	-79.845	-30.960	0.000	0.369	0.0
Age(years)							
18 >	4	15.125	5.522	24.729	0.002	0.000	92.5
18 ≤	7	-1.038	-3.578	1.502	0.423	0.000	78.0
Type of study population							
Cancer	3	-1.099	-3.779	1.581	0.422	0.028	71.9
Children	3	-55.402	-79.845	-30.960	0.000	0.369	0.0
women with polycystic ovary syndrome	2	2.365	-10.672	15.402	0.722	0.286	12.3
healthy	2	-2.206	-12.274	7.863	0.668	0.000	94.7