The effect of isotretinoin on insulin resistance and serum adiponectin levels in acne vulgaris patients: a systematic review and meta-analysis

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Abstract

Aim: Isotretinoin, the drug of choice for severe - nodulocystic acne, might be associated with an increase in insulin resistance. We aimed to investigate this association. Methods: We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. A systematic search in PubMed/MEDLINE, SCOPUS and Cochrane databases was conducted until the 12th of January 2022 using the PICO tool (Patient, Intervention, Comparison, Outcome). Studies with a published full text in English regarding acne patients under isotretinoin were included. Insulin, glucose and adiponectin serum levels before and after isotretinoin treatment were recorded and insulin sensitivity was assessed using the homeostasis model assessment of insulin resistance (HOMA–IR). For Meta-analysis, the Review Manager (RevMan) 5.4.1 software was utilized. The quality assessment of the included studies was performed using the ROBINS-I tool. Results: Fifteen studies were included. The meta-analysis revealed a statistically significant increase in post-treatment adiponectin [SMD = 0.86; 95% confidence interval (CI) = 0.48 - 1.25, p-value <0.0001; I2 = 58%]. Subgroup analysis by study type revealed the same results [cohort studies pooled SMD = 1.2, 95% CI = 0.81 -1.61, p-value <0.00001; I2 = 8% and case-control studies pooled SMD = 0.53, 95% CI = 0.16 - 0.9, p-value=0.005; I2 = 27%)]. No statistically significant results were shown for insulin, glucose levels and HOMA-IR. Conclusion: Although isotretinoin exposure is not clearly associated with insulin resistance, it seems that it can increase serum adiponectin levels. Further research is needed to clarify this association.

Introduction

Acne vulgaris (AV) is a chronic multifactorial inflammatory disease of the pilosebaceous units of the skin that affects 80% of adolescents and young adults [1]. The four main factors implicated in the pathogenesis of AV are the abnormal follicular desquamation, increased sebum production, Propionibacterium acnes proliferation and inflammation [2].

Isotretinoin (13-cis-retinoic acid) is a systematic retinoid and Vitamin A (retinol) metabolite, which constitutes the only available medication with a potential for a long-term cure of acne, as it acts on all the pathogenic mechanisms of acne [3,4]. Isotretinoin is the first line treatment for severe nodulocystic and papulopustular acne, acne localized both on face and trunk, acne with tendency to scarring and acne with psychological effects, but it is also indicated in cases with mild to moderate acne, unresponsive to other topical or systematic therapy [3].

Although isotretinoin is an effective and relatively well-tolerated medication, many side effects are related

with its intake. In the serum of patients treated with isotretinoin, an increase in the levels of total cholesterol and triglycerides and a decrease in the levels of high density lipoprotein (HDL) are commonly noticed, a phenotype also observed in patients with insulin resistance [5].

Recent studies have shown that adipose tissue, except its main function as an energy-storing organ, has immunological and endocrinological functions. The hormones secreted by fat tissue are called adipocytokines, with the main representative of them, adiponectin. Adiponectin is not only an anti-inflammatory agent, inhibiting inflammation in a wide range of cell types, but also hinders liver glucose production, increases insulin sensitivity and contributes in the maintenance of whole-body's energy homeostasis [6].

Previous studies with subject the influence of isotretinoin on insulin resistance and serum adiponectin levels in patients with AV have given controversial conclusions [7,8]. The objective of this systematic review and meta-analysis is therefore to evaluate the effect of isotretinoin on glucose metabolism, focusing mainly on changes in insulin resistance and levels of adiponectin.

Methods

This systematic review was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[9]. It is in line with the PRISMA checklist. The review protocol has been submitted to PROSPERO (International Prospective Register of Systematic Reviews) without yet been accepted.

Inclusion and Exclusion Criteria

We searched for Randomized Controlled Trials (RCTs), Cohort and Case-Control studies comparing the serum levels of adiponectin, insulin, and glucose, as well as the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) before and after systematic treatment with isotretinoin in patients with acne vulgaris. We included only studies with a published full text in English.

Search Strategy and Sources

The research strategy was designed based on the Peer Review of Electronic Search Strategies (PRESS) checklist [10]using free text and Medical Subject Heading (MeSH) terms and their synonyms. Search terms were "isotretinoin", "acne", "insulin resistance" and "adiponectin" with synonyms and alternatives. Apart from language, no filters, geographical, publication status, and year restrictions were applied (Appendix, Table S1).

The following databases were searched by two reviewers (EP, GNK) independently: Pubmed/ Medline, Scopus, and Cochrane Library. PROSPERO (International Prospective Register of Systematic Reviews) database was likewise searched for ongoing SRMAs. The last searches were conducted on the 12th of January 2022.

Study Selection and Data Extraction

Two reviewers (EP, GNK) conducted study selection and data extraction separately. Any discrepancies were resolved by a third reviewer (TP) through discussion and consensus. Mendeley© (v.1.19.8) was used as a reference manager, and duplicates were removed. Predefined collection forms proposed by Cochrane collaboration for Intervention Reviews [11] were used for data extraction. In case of questions about study eligibility or data provided by the studies, the paper authors were contacted.

Definitions

Acne vulgaris (AV) is a chronic multifactorial inflammatory disease of the pilosebaceous units of the skin [1]. Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population[12]. HOMA-IR is a quantitative assessment of the contributions of insulin resistance and deficient r-cell function to the fasting hyperglycemia, through the comparison of a patient's fasting values with the model's predictions [13].

Risk of Bias Assessment

We used the ROBINS-I Cochrane Tool for assessing the risk of bias in non-randomized studies [14]. Studies with low/moderate risk of bias were included in the quantitative synthesis. A sensitivity analysis was conducted for studies with serious/critical risk of bias. Graphics visualizing the risk of bias were created using the Robins tool[15]. Two reviewers (EP and GNK) independently conducted the risk of bias assessment, and the third reviewer (TP) settled any discrepancies.

Synthesis

The treatment effect of all outcomes was measured using mean/median, SD/IQR with 95% Confidence Interval (CI), as all of them were quantitative data. First, a robust qualitative synthesis was conducted. Second, we conducted a quantitative synthesis with RevMan (v.5.4.1). Different forest plots were created. Statistical heterogeneity was evaluated using the Higgins I^2 test and Chi-Squared Cochran Q-test (α=0.1). When I^2 was over 75%, was regarded as high statistical heterogeneity. Inverse Variance statistical method with standardized mean difference (SMD) as effect measure was conducted. The random-effects model was applied due to the heterogeneity of the studies. We conducted sensitivity analysis (excluding studies of serious/critical risk of bias). Subgroup analyses were performed based on the type of study. In case of missing data, we tried to contact the authors by e-mail.

Publication bias was assessed if [?]10 studies were available per outcome. RevMan 5.4.1 was used to create funnel plots.

Quality of evidence

An assessment of the quality of evidence for each outcome was performed separately by two reviewers (EP and GNK) using the GRADE reporting system (Grading of Recommendations Assessment Development and Evaluation System) [16]. Any discrepancies were resolved by a third reviewer (TP). The assessment was conducted using the online tool GRADEpro GDT [17].

Results

Search results

The PRISMA flow diagram of search results is shown in Figure 1. After the removal of 67 duplicates, 317 studies were screened per Title and Abstract. A total of 16 studies qualified for assessment of eligibility. Finally, 1 study [18] was excluded according to the exclusion criteria, while 15 studies [7,8,19–31] were found eligible for qualitative and quantitative analysis including 380 acne vulgaris patients under systematic isotretinoin.

Study Characteristics

Due to the absence of published RCTs, we used 9 cohort studies[7,19,21,24–28,31] and 6 case-control studies[8,20,22,23,29,30] in our systematic review and meta-analysis. The study characteristics are shown in Table 1. All studies were conducted in Asia and Europe. More precisely, 10 studies[7,8,19–23,29–31] were conducted in Turkey, 3 studies[25,27,28] in Finland, one study [24] in United Kingdom and one study [26] in Switzerland. Regarding gender, in 7 studies [7,8,19,24,28,30,31] the population was mixed, in 5 studies [20–23,29] females only and in 3 studies [25–27] males only. In all studies isotretinoin was administered orally. In 7 studies[8,19,23–27] the dosage of isotretinoin was steady during therapy with range between studies 0.5-1 mg/kg/day, and in one study [22] the dosage was 120-150mg/kg/day. In 5 studies[7,20,21,29,31] increasing dosage was used, while in 2 studies [28,30] the dosage was not mentioned. In five studies [22,23,28,30,31] the treatment duration was 3 months, in 2 studies [19,24] 4 months, in one study[8] 5 months and in 2 studies [20,21] 6 months. In 4 studies [7,25,27,29] the treatment duration was dependent to disease progression. In only one study[26] the duration was 5 days, but in a previously treated population with isotretinoin for acne vulgaris.

Risk of Bias Assessment

For the included observational studies, the results of the risk-of-bias assessment tool are presented in Appendix Figures S1 and S2. Moderate risk of bias was mainly raised in the “Bias due to confounding”, “Bias

in measurement of outcomes", and "Bias in the selection of reported result" domains in almost all studies. Only in a single study[30] serious risk of bias was raised in the "Bias in the selection of reported result" domain, because the authors didn't provide all their results.

Outcome Measures

The assessed outcomes of the studies are shown in Table 2. There is great heterogeneity regarding the measurement values of each outcome. Ten studies [7,19–21,23–26,28,29] assessed insulin levels in serum before and after treatment, 9 studies[7,19,20,23–26,28,29] assessed glucose levels in serum before and after treatment, 6 [8,20,27,28,30,31] studies assessed adiponectin levels in serum before and after treatment. Finally, 6 studies [7,8,19,20,22,29] estimated HOMA-IR before and after treatment, while in 5 studies[23–26,28] the latter was calculated by the reviewers EP and GNK.

Results of Meta-analysis

Glucose

Nine studies [7,19,20,23–26,28,29] that assessed glucose levels in serum before and after treatment with systemic isotretinoin were meta-analyzed. No statistically significant difference was found in glucose levels before and after treatment [pooled SMD: -0.03, 95% CI (-0.23 - 0.17), p-value: 0.76; I^2: 0%] (Appendix, Figures S3 and S4).

Insulin

Ten studies [7,19–21,23–26,28,29] that assessed insulin levels in serum before and after treatment with systemic isotretinoin were meta-analyzed. No statistically significant difference was found in insulin levels before and after treatment [pooled SMD: 0.17, 95% CI (-0.41 - 0.76), p-value: 0.56; I^2: 89%]. Despite the conducted subgroup analysis, the high statistical heterogeneity remained (I^2>75%), with none statistically significant result (Appendix, Figures S5-S7).

Adiponectin

Six [8,20,27,28,30,31] studies assessed adiponectin levels in serum before and after treatment with systemic isotretinoin. Our meta-analysis showed that adiponectin increases significantly after treatment [pooled SMD: 0.86, 95% CI (0.48 – 1.25), p-value <0.0001; I^2: 58%] (Figure 2). We conducted a sensitivity analysis excluding one study[30]that was assessed as having serious risk of bias, with similar results [pooled SMD: 0.90, 95% CI (0.40 – 1.39), p-value: 0.0004; I^2: 67%] (Figure 3), but in our subgroup analysis the meta-analyzed cohort studies revealed a higher and more statistically significant increase of adiponectin levels after treatment [pooled SMD: 1.21, 95% CI (0.81 – 1.61), p-value <0.00001; I^2: 8%] (Figure 4). Two of the meta-analyzed studies [27,28] measured the levels of adiponectin 1-3 months after treatment, and showed that even though isotretinoin increases adiponectin levels, this increase is transient.

HOMA-IR

We meta-analyzed HOMA-IR before and after treatment with systemic isotretinoin from 11 studies[7,8,29,19,20,22–26,28]. No statistically significant difference was found in HOMA-IR before and after treatment [pooled SMD: 0.04, 95% CI (-0.16 - 0.24), p-value: 0.67; I^2: 21%]. Despite the conducted subgroup analysis, none statistically significant result was found (Appendix, Figures S8-S10).

Strength of evidence GRADE reporting system

The results of the quality of evidence assessment regarding the comparison of insulin, glucose and adiponectin levels, as well as HOMA-IR, before and after treatment with systemic isotretinoin are shown in Appendix, Table S2. Adiponectin, insulin, and glucose levels were judged to be of "High" strength of evidence, while HOMA-IR was judged to be of "Moderate" level of evidence.

Discussion

To the best of our knowledge, Tsai et al.[32] conducted the only systematic review and meta-analysis found in the literature regarding the effect of isotretinoin treatment on glucose metabolism in patients with acne. They concluded that treating acne patients with isotretinoin does not substantially change the HOMA-IR values but significantly increases the serum adiponectin level. In our updated systematic review and meta-analysis, we included 3 more subsequently published studies, and our results were consistent to the ones of Tsai et al.'s.

All-trans retinoic acid (ATRA), the result of 13-cis-retinoic acid isomerization by sebocytes, changes gene expression by binding to and activating the retinoic acid receptors (RARs)[33]. In human keratinocytes, both the expression of p53 and proapoptotic caspases are increased by ATRA, which is also responsible for the apoptosis of the former. Furthermore, neutrophil apoptosis caused by ATRA and p53 possibly minimizes inflammation in acne. During treatment, isotretinoin induces the death of sebocytes and consequently reduces sebum production, while the microscopic image of it is the involution of sebaceous glands[34]. In those glands, nuclear levels of Forkhead box protein O1 and O3 (FoxO1, FoxO3) are increased by ATRA as well, further reducing sebum production [35].

Although the exact mechanisms behind the regulation of fluctuation of adiponectin levels in plasma and cells are yet to be revealed, recent studies' results lean towards the possibility that adiponectin is controlled during and post transcription. Peroxisome proliferator-activated receptor-g (PPARγ), CCAAT-enhancer-binding protein a and FoxO1 appear to be transcription factors that increase adiponectin expression while agonists of the nuclear receptor and PPARγ additionally increase its multimerization and secretion[36]. It has also been shown that the activation of the latter not only multiplies small, sensitive to insulin adipocytes by facilitating the process of their creation but increases the response of adipose-derived hormone adiponectin as well [37]. On the other hand, FoxO1, one of the Forkhead box O transcription factors, participates in the adjustment of adipocyte differentiation. More specifically, even though FoxO1 seems to upregulate adiponectin transcription, it also appears to suppress PPARγ gene expression and its interaction with CCAAT/enhancer-binding protein α obscurely increases adiponectin gene transcription [38,39].

Laboratory results were contradictory. To begin with, Landrier et al.[40] observed a decreased expression of adiponectin in white muscle adipose tissue during high in Vitamin A diet while Kovács et al.[20] reported that isotretinoin treatment decreases adiponectin mRNA expression in human sebaceous cells. According to Kalisz et al.[41], treatment with all-trans-retinoic acid increases both synthesis and secretion of adiponectin by perivascular adipose tissue in apolipoprotein E deficient mice, without though significantly increasing its levels in visceral adipose tissue. It is possible that adiponectin is secreted by different cell types and its levels in sebaceous cells do not reflect the ones measured in serum in clinical practice. In addition, the post isotretinoin treatment adiponectin increase in acne patients may be triggered by the anti-inflammatory mechanisms of isotretinoin. More research is needed to clarify these mechanisms and bridge the gap between scientific findings and clinical measurements.

Adipocytes of a growing adipose tissue are the first to develop insulin resistance, while ectopic fat storage in organs such as the liver and muscles as a result of its unsuccessful deposition in the adipose tissue is considered to be the spread mechanism of such resistance in those organs. The above-mentioned ectopic lipid storage appears to be controlled by usual genetic mutations as well [42].

Not long ago, ApoC3 polymorphisms were associated with the lean male population's susceptibility to NAFLD and insulin resistance leading to a rise in ApoC3 plasma levels by approximately 30% and post-prandial hypertriglyceridemia caused by ApoC3's altering effect on lipoprotein lipase activity. It was also found that this alteration consequently increased the amount of chylomicron remnants stored in the liver. In addition, increased hepatic triacylglycerol (TAG)/DAG concentration was observed in transgenic mice on a high-fat diet that overexpressed human ApoC3 in the liver due to the activation of hepatic PKCε (Protein Kinase Cε) and the development of hepatic insulin resistance[43]. The isomerization of isotretinoin to ATRA takes place inside human sebaceous cells, increasing nuclear levels of FoxO1[33,35]. This particular protein raises apolipoprotein C3 levels, which subsequently favorizes the storage of very low-density lipoprotein (VLDL) over lipids into cells, causing hypertriglyceridemia[44]. Both lipid profiles of patients receiving isotretinoin

treatment and those with insulin resistance were found to share the same disorders. More specifically, an increase in triglycerides and decrease in high-density lipoprotein (HDL-C) were the most common laboratory findings. Finally, although FoxO1 plays a major role in the insulin signaling pathway, not much is known about its association with insulin resistance in adipocytes, the most critical cell type in developing it [41,45].

Limitations

Finally, it is important to mention the limitations of the present study. First of all, due to the lack of randomized clinical trials in literature, we based our review and meta-analysis on only cohort and case-control studies with a full-text available in English. This way, articles with content relevant to our study but written in another language may have been omitted. Secondly, the number of studies as well as the population examined was limited and the majority came from only two countries, Turkey and Finland. Thirdly, all included studies had variations concerning the baseline characteristics of the study population (sex, BMI, age, comorbidities) and methodology (dosage, duration of treatment). Such variations may have affected adiponectin and insulin resistance levels and were confusing factors that could not be weighed out. Nevertheless, according to the I^2 test the heterogeneity was low.

It seems that there is not a great interest regarding the effect of isotretinoin on insulin resistance. This is evident by the small number of published studies, as well as from the fact that, even there are a few registered RCTs regarding the safety and efficacy of isotretinoin, none of them assesses the possible role of isotretinoin in insulin resistance.

Conclusion

To conclude, in accordance with the systematic review and meta-analysis performed, isotretinoin treatment in acne patients significantly increases serum adiponectin levels but does not substantially alter insulin resistance (HOMA - IR). Further research including multicenter randomized controlled trials is needed to both reveal the pathophysiological pathway that associates isotretinoin with insulin resistance and the role of serum adiponectin in this correlation.

Authors' Individual Contributions: Eleni Paschalidou and Georgios N. Katsaras: conceived the study, participated in its design, collection and interpretation of the data, and also performed the data collection and extraction, as well as the statistical analyses, and helped to draft the manuscript. Thomas Papoulakis and Evangelia Kalloniati: participated in conceptualization and the design of the study, collection and interpretation of the data; and also performed the data collection and extraction, as well as the statistical analyses, and drafting the manuscript. Dimitrios Kavvadas and Sophia Karachrysafi: contributed to the analysis of the results and in drafting the manuscript. Dorothea Kapoukranidou, Georgios Tagarakis and Theodora Papamitsou: supervised the methodology and statistical analyses and edited the final draft of the manuscript.

All authors critically revised the paper for important intellectual content and approved the final version to be published.

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Table 1. Study characteristics.

Author (Year)
Laker (1987)[24]
Koistinen (2001)[25]
Stoll (2004)[26]
Koistinen (2006)[27]
Heliövaara (2007)[28]
Ertugrul (2010)[7]
Cetinözman (2013)[29]
Karadag (2015)[30]
Cemil (2016)[31]
Saklamaz (2016)[19]
Aydin (2017)[20]
Soyuduru (2019)[8]
Acmaz (2019)[21]
Koçyiğit (2020)[22]
Aktar (2021)[23]

Abbreviations: F, females; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; M, males; N/A, not available. Range ^Mean (SD) **Median (IQR) [1]Previous treatment with isotretinoin on average 5 years earlier (3-10)

Table 2. Outcome measurements of all included studies.

Author (Year)
Laker (1987)[24]
Koistinen (2001)[25]
Stoll (2004)[26]
Koistinen (2006)[27]
Heliövaara (2007)[28]

Ertugrul (2010)[7]
Cetinözman (2013)[29]
Karadag (2015)[30]
Cemil (2016)[31]
Saklamaz (2016)[19]
Aydin (2017)[20]
Soyuduru (2019)[8]
Acmaz (2019)[21]
Koçyiğit (2020)[22]
Aktar (2021)[23]
Abbreviations: HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; N/A, not available; SD, Standard Deviati
All results are presented in Means (SD).
ˆCalculated by the reviewers.
The authors did not provide the measurement.

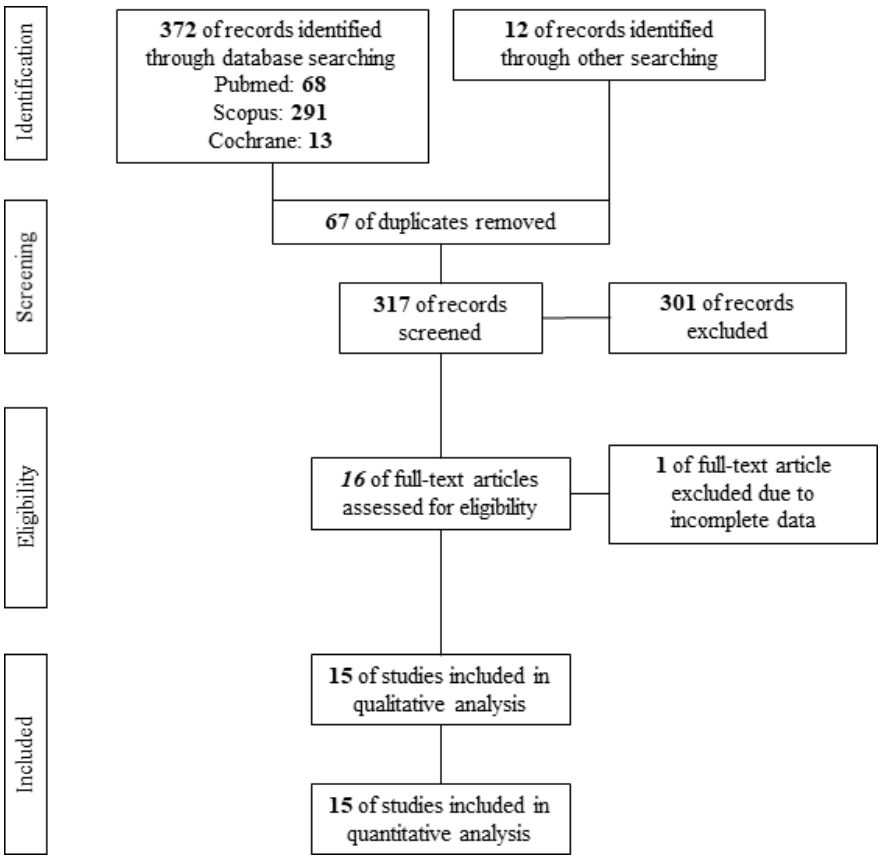
Figure Legends

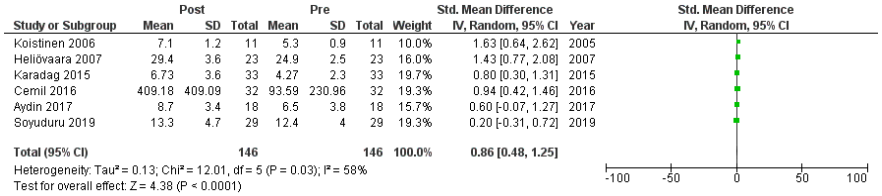
Figure 1. PRISMA flow diagram.

Figure 2. Forest plot: adiponectin levels before and after treatment with systemic isotretinoin.

Figure 3. Forest plot (sensitivity analysis): adiponectin levels before and after treatment with systemic isotretinoin.

Figure 4. Forest plot (subgroup analysis): adiponectin levels before and after treatment with systemic isotretinoin.

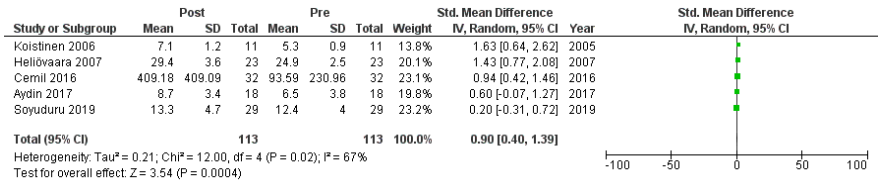




Study or Subgroup	Post Mean	Post SD	Post Total	Pre Mean	Pre SD	Pre Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Koistinen 2006	7.1	1.2	11	5.3	0.9	11	10.0%	1.63 [0.64, 2.62]	2005
Heliövaara 2007	29.4	3.6	23	24.9	2.5	23	16.0%	1.43 [0.77, 2.08]	2007
Karadag 2015	6.73	3.6	33	4.27	2.3	33	19.7%	0.80 [0.30, 1.31]	2015
Cemil 2016	409.18	409.09	32	93.59	230.96	32	19.3%	0.94 [0.42, 1.46]	2016
Aydin 2017	8.7	3.4	18	6.5	3.8	18	15.7%	0.60 [-0.07, 1.27]	2017
Soyuduru 2019	13.3	4.7	29	12.4	4	29	19.3%	0.20 [-0.31, 0.72]	2019
Total (95% CI)			**146**			**146**	**100.0%**	**0.86 [0.48, 1.25]**	

Heterogeneity: Tau² = 0.13; Chi² = 12.01, df = 5 (P = 0.03); I² = 58%
Test for overall effect: Z = 4.38 (P < 0.0001)

Std. Mean Difference
IV, Random, 95% CI
-100 -50 0 50 100



Study or Subgroup	Post Mean	Post SD	Post Total	Pre Mean	Pre SD	Pre Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Koistinen 2006	7.1	1.2	11	5.3	0.9	11	13.8%	1.63 [0.64, 2.62]	2005
Heliövaara 2007	29.4	3.6	23	24.9	2.5	23	20.1%	1.43 [0.77, 2.08]	2007
Cemil 2016	409.18	409.09	32	93.59	230.96	32	23.1%	0.94 [0.42, 1.46]	2016
Aydin 2017	8.7	3.4	18	6.5	3.8	18	19.8%	0.60 [-0.07, 1.27]	2017
Soyuduru 2019	13.3	4.7	29	12.4	4	29	23.2%	0.20 [-0.31, 0.72]	2019
Total (95% CI)			**113**			**113**	**100.0%**	**0.90 [0.40, 1.39]**	

Heterogeneity: Tau² = 0.21; Chi² = 12.00, df = 4 (P = 0.02); I² = 67%
Test for overall effect: Z = 3.54 (P = 0.0004)

Std. Mean Difference
IV, Random, 95% CI
-100 -50 0 50 100