Nutrição sob a Ótica Teórica e Prática 2

Vanessa Bordin Viera
Natiéli Piovesan
(Organizadoras)

Atena Editora
Ano 2021

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Editora Chefe: Profª Drª Antonella Carvalho de Oliveira
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Revisão: Os Autores
Organizadores: Vanessa Bordin Viera
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Dados Internacionais de Catalogação na Publicação (CIP)

N976 Nutrição sob a ótica teórica e prática 2 / Organizadoras Vanessa Bordin Viera, Natiéli Piovesan. – Ponta Grossa - PR: Atena, 2021.

Formato: PDF
Requisitos de sistema: Adobe Acrobat Reader
Modo de acesso: World Wide Web
Inclui bibliografia
ISBN 978-65-5706-951-6
DOI 10.22533/at.ed.516210104

1. Nutrição. 2. Pesquisa. I. Viera, Vanessa Bordin (Organizadora). II. Piovesan, Natiéli (Organizadora). III. Título.
CDD 613

Elaborado por Bibliotecária Janaina Ramos – CRB-8/9166

Atena Editora
Ponta Grossa – Paraná – Brasil
Telefone: +55 (42) 3323-5493
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Atena Editora
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Ciências Biológicas e da Saúde

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APRESENTAÇÃO

O *e-book* “Nutrição sob a Ótica Teórica e Prática 2" traz 20 artigos científicos com temáticas atuais como alimentos biofortificados, análises de composição nutricional de cardápios, gordura trans, hábitos alimentares; dietas da moda, transtornos alimentares; aleitamento materno; vitamina D, alimentação saudável, entre outros assuntos que envolvem diversas áreas da nutrição.

Convidamos todos para uma leitura visando obter conhecimento e promover reflexões sobre os temas deste *e-book.*

Vanessa Bordin Viera
Natiéli Piovesan

SUMÁRIO

CAPÍTULO 7

EFFICACY OF SUPPLEMENTATION WITH MYO-INOSITOL IN THE TREATMENT OF POLYCYSTIC OVARY SYNDROME - META-ANALYSIS

Data de aceite: 29/03/2021
Data de submissão: 04/01/2021

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ABSTRACT: Objective- Statistically analyze the hypothesis that the efficacy of interventions with myo-inositol, in polycystic ovary syndrome, is superior or similar to metformin, considering, as comparative parameters, the index of the model for the evaluation of homeostasis, serum glucose, insulin, luteinizing hormone and follicle stimulating hormone. **Methods-**This is a meta-analysis, according to the PRISMA protocol. Twelve articles were select from the databases for data extraction. Subsequently, the mean difference test was perform for continuous data. The tests were performed with the STATA® 16.0 software, considering the significance limit of 5% (p=0.05). **Results-** The effectiveness of metformin related was to the highest concentration (2,550 mg), on the other hand, all interventions, with myo-inositol, showed significant results, with emphasis on the intervention with 2 g of myo-inositol associated with 200 μg of folic acid, which was efficient in the control of luteinizing hormone and follicle stimulating hormone. Thus, considering 2 g of myo-inositol associated with 200 μg of folic acid, the differences between means were: for the index of the homeostasis assessment model, MD= 1.4 (p=0.00); for insulin, MD= 5.9 (p=0.00); for follicle stimulating hormone, MD= 2.5 (p=0.00); and for luteinizing hormone, MD= 4.9 (p=0.00). The intervention using 4 g of myo-inositol, with 400 μg of folic acid, showed a reduction in the serum glucose level, with MD= 6.2 (p=0.00). **Conclusion-** The results of this meta-analysis point to myo-inositol as a treatment option for polycystic ovary syndrome, considering the absence of side effects and the efficacy similar or superior to metformin.

KEYWORDS: Myo-Inositol, Metformin, Polycystic Ovary Syndrome.

EFICÁCIA DA SUPLEMENTAÇÃO COM MIO-INOSITOL NO TRATAMENTO DA SÍNDROME DO OVÁRIO POLICÍSTICO - METANÁLISE

RESUMO: Objetivo- Analisar estatisticamente a hipótese de que a eficácia das intervenções com mio-inositol, na síndrome do ovário policístico, é superior ou semelhante à metformina, considerando, como parâmetros comparativos, o índice do modelo para avaliação da homeostase, glicose sérica, insulina, hormônio luteinizante e hormônio folículo estimulante. **Método-** Trata-se de uma meta-análise de acordo com o protocolo PRISMA. Doze artigos foram selecionados das bases de dados para extração de dados. Posteriormente, foi realizado o teste de diferença entre médias para dados contínuos. Os testes foram realizados no software STATA® 16.0, considerando o limite de significância de 5% (p = 0,05). **Resultados-** A eficácia da metformina foi relacionada à maior concentração (2.550 mg), por outro lado, todas as intervenções, com mio-inositol, apresentaram resultados significativos, com destaque para a intervenção com 2 g de mio-inositol associado a 200 μg de ácido fólico, que foi eficiente no controle do hormônio luteinizante e hormônio folículo estimulante. Assim, considerando 2 g de mio-inositol associado a 2 μg de ácido fólico, as diferenças entre as médias foram: para o índice do modelo de avaliação da homeostase, MD = 1,4 (p = 0,00); para insulina, MD = 5,9 (p = 0,00); para o hormônio folículo estimulante, MD = 2,5 (p = 0,00); e para o hormônio luteinizante, MD = 4,9 (p = 0,00). A intervenção com 4 g de mio-inositol, com 400 μg de ácido fólico, resultou na redução da glicemia sérica, com MD = 6,2 (p = 0,00). **Conclusão-** Os resultados desta metanálise apontam para o mio-inositol como opção de tratamento para a síndrome do ovário policístico, considerando a ausência de efeitos colaterais e eficácia semelhante ou superior à metformina.

PALAVRAS-CHAVE: Mio-inositol, Metformina, Síndrome do Ovário Policístico.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex disease related to endocrine and metabolic dysfunction (LAVEN *et al.,* 2002; FIGUROVÁ *et al.,* 2017). PCOS can originate from a set of genetic, metabolic and environmental factors (DUMESIC *et al.,* 2015), affecting mostly women between menarche and menopause, reaching a prevalence of 6 to 16% of women of childbearing age (ROSA-e-SILVA, 2018).

Women with PCOS may present reproductive, metabolic, psychological disorders, increased risk for cardiovascular diseases, dyslipidemia, visceral obesity, depression (FACCHINETTI *et al.,* 2019; DI SEGNI *et al.,* 2017), infertility (LEGRO *et al.,* 2013) and, very commonly, insulin resistance and hyperinsulinemia, which reaches 80% obese women and 30 to 40% of thin women with PCOS (NEHRA *et al.,* 2017).

Insulin resistance is a consequence of the excess of ovarian estrogens, which eventually affects the translation of the insulin signal, reducing the functionality of this signaling (COSTANTINO *et al.,* 2009). Insulin signaling can be affected by the deficiency or insufficiency of inositol phosphoglycans, which are insulin mediators (ROMERO; LARNER *et al.,* 1993).

The measurement of the degree of insulin resistance is performed by calculating

the index of the homeostasis assessment model (HOMA). Insulin resistance generates hyperinsulinemia that can alter follicle stimulating hormone (FSH) and luteinizing hormone (LH), impairing the selection of dominant ovarian follicle (ARTINI *et al.,* 2013; YANG *et al.,* 2018). Hyperinsulinemia can also alter sensitivity to LH, causing an increase in androgen production (NELSON *et al.,* 2001; ORTEGA-GONZALEZ *et al.,* 2005), directly interfering with fertility and altering the menstrual cycle. Insulin resistance may be a key factor in the pathogenesis of PCOS and the use of insulin sensitizers has been shown to be a viable treatment option. Two likely insulin sensitizers are metformin and myo-inositol (ANGIK *et al.,* 2015).

Inositol is a vitamin of the B complex and can be synthesized endogenously or consumed through the diet, through bran and seeds (BIZZARRI *et al.,* 2016). There are nine possible forms of steroid isomers, they are: scilo-, mucous-, epi, neo, allo-, cis-, D-chiro, L-chiro-inositol and myo-inositol. The isomers mio and d-chiro-inositol have the characteristic of insulin sensitizers. In addition to insulin sensitizer, myo-inositol improves ovulation, oocyte quality and reduces androgen levels, consequently improving the fertility parameter (NELSON *et al.,* 2001; ROSA-e-SILVA, 2018).

Metformin is an insulin sensitizer, commonly used for the treatment of type II diabetes, aids in weight loss and, when used in women with PCOS, may show improvements in menstruation and ovulatory cycle, with a reduction in serum androgens and body weight, however, the drug can cause gastrointestinal problems, such as nausea, poor appetite and diarrhea (SOARES-JUNIOR; DE SÁ, 2014), justifying the meta-analysis in question.

The purpose of this meta-analysis was to evaluate the efficiency of interventions with myo-inositol in PCOS, comparing it with metformin interventions, considering HOMA index, serum glucose and insulin levels and LH / FSH hormonal control as comparative parameters.

METHODS

It is a systematic review and meta-analysis, with an analytical and descriptive aspect. Consultations were held with the Health Sciences Descriptors (DeCS) and the Medical Subject Heading (MeSH), where the descriptors were identified: Myo-inositol, Metformin and Polycystic Ovary Syndrome. For the search for articles, the Boolean operators “AND”, “AND NOT” and “OR” were considered. Time limitation was not considered for systematic review and meta-analysis. However, for bibliographic review, articles published in the period from 1993 to 2020 were considered, giving preference to publications from the last 4 years, thus, considering the updated information. The articles were found in the databases: Scientific Electronic Library Online (SciELO), PubMed, on the National Center for Biotechnology Information (NCBI) website, using the identified descriptors.

In SciELO, 25 references were found and in PubMed, 453 references, all with

availability of the title, year, place of publication and summary. The repetitions and publications that were not related to the topic were excluded, resulting in 31 references, where 12 contributed data for systematic review and meta-analysis (Figure 1). The references obtained that constituted this sample were cataloged and analyzed.

Selection strategy

The selection was made through the analysis of abstracts and methods, considering the research protocol described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) (MOHER *et al.,* 2009). The exclusion criteria were: master's dissertations, doctoral theses, articles that did not address the topic in a satisfactory way and research that did not adopt the randomized method. The following inclusion criteria were adopted: randomized research, research using the double-blind method, articles that discussed the relationship between the effect of myo-inositol and metformin, in the serum markers of insulin, glucose, LH and FSH, as well as the HOMA index. The adopted strategy allowed the selection of high quality research.

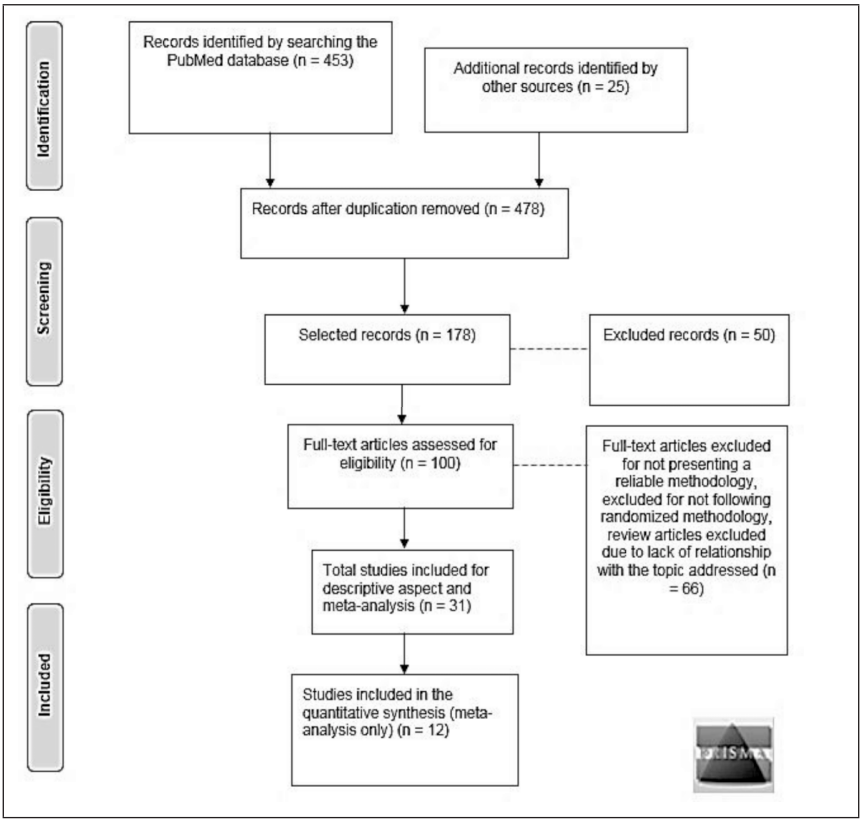

Figure 1. Flowchart: selection process of articles used in systematic review and meta-analysis.

Source: Source: Authors, (2021), adapted from Moher *et al*., (2009).

Data synthesis and Analysis

After selecting the studies, according to the inclusion and exclusion criteria, data from the articles used in the meta-analysis were extracted and tabulated. Statistical analyzes were subdivided according to the administered concentrations of the drug metformin or myo-inositol supplement, considering the association with folic acid. Thus, being able to determine through the results in subgroups, which concentration was more effective in reducing the considered parameters. In this way, references from the total sample were segregated for data extraction, in order to demonstrate the efficiency of myo-inositol, comparing metformin results, in the treatment of PCOS. For this, the means of glucose, insulin, HOMA index, LH and FSH were compared, considering the difference between means before and after interventions. Some units of measurement conversions were performed, aiming at an assertiveness between the averages of the differences of the statistical tests. Statistical analyzes were performed with the aid of the STATA® 16.0 software, using the statistical test for continuous data mean difference, adopting the fixed and random effects, according to the heterogeneity between the data collected for each analysis.

Assessed hypotheses

Taking into account the antecedents, the present research had to evaluate the hypotheses: a) the supplement myo-inositol presents efficacy equal or superior to metformin for HOMA index and in the serum control of glucose and insulin; b) the myo-inositol supplement associated with folic acid is efficient in hormonal control (LH / FSH).

Determination of heterogeneity

To determine heterogeneity, the chi-square test of heterogeneity (c^2) and the Higgins and Thompson test (I^2) were used. Although the c^2 test determines significance or insignificance of heterogeneity, it has its efficiency compromised when the sample is small. On the other hand, the I^2 test shows assertive results when the sample is small. Thus, the association of the two tests, in determining heterogeneity, presents a greater chance of assertiveness, in the choice of the adopted effect. When the p-value is <0.05, in the c^2 test, it is understood that the sample is heterogeneous, thus adopting the randomized effect. However, if the p-value is> 0.05, the hypothesis is accepted that the sample does not have significant heterogeneity, considering the fixed effect. The I^2 test follows the same principle, however, it is evaluated according to the percentage presented: 0% without heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity and 75% or more, high heterogeneity (HIGGINS; THOMPSON, 2002; HIGGINS *et al.,* 2003). For all statistical analyzes, a significance coefficient of 5% ($p <0.05$) was considered for accepting the hypotheses.

RESULTS

The extracted data referenced the following analyzes: glucose for myo-inositol, five studies, resulting in 119 participants (n = 119); glucose for metformin, four searches (n = 107), insulin for myo-inositol, four searches (n = 81); insulin for metformin, seven searches (n = 187), HOMA index for myo-inositol, eight searches (n = 155); HOMA index for metformin, seven searches (n = 197), LH for myo-inositol, five searches (n = 105) and FSH for myo-inositol, four searches (n = 85) (Table 1).

Glucose: Data on treatment with myo-inositol (mg/dL)						
Author, Years	(N)	Ab ± SD	Aa ± SD	Age years	Research time	Administered concentration
(PKHALADZE et al., 2016)	20	83.60 ± 11.71	79.09 ± 10.09	15.95±1.85	3months	4g of myo-inositol and 400mg of folic acid
(NEHRA et al., 2017)	30	88.96 ± 2.79	82.00 ± 2.46	23.8± 0.69	6months	2g of myo-inositol
(DE LEO et al., 2013)	20	100.00 ± 1.40	95.00 ± 2.10	24 to 32	6months	3g of myo-inositol
(COSTANTINO et al., 2009)	23	87.60 ± 4.0	81.60 ± 4.0	18 to 40	3 to 4months	4g of myo-inositol and 400μg of folic acid
(SHOKRPOUR et al., 2019)	26	97.5±6.60	89.80±8.50	28.3 ± 4.9	3months	4g of myo-inositol and 400μg of folic acid
Combined	**119**					
Insulin: Myo-inositol treatment data (mU/mL)						
(GENAZZANI et al., 2008)	10	12.40±2.20	6.50±1.10	Not included	3months	2g of myo-inositol and 200μg of folic acid
(PKHALADZE et al., 2016)	20	8.50±6.70	5.20±3.04	15.95±1.85	3months	4g of myo-inositol and 400μg of folic acid
(ARTINI et al., 2013)	25	11.40±2.20	5.50±1.10	34.9±2.1	3months	2g of myo-inositol and 200μg of folic acid
(SHOKRPOUR et al., 2019)	26	13.00±3.40	10.80±3.00	28.3 ± 4.9	3months	4g of myo-inositol and 400μg of folic acid
Combined	**81**					
HOMA Index: Data on myo-inositol treatment						
(GENAZZANI et al., 2008)	10	2.8±0.6	1.4±0.3	not included	3months	2g of myo-inositol and 200μg of folic acid
(PKHALADZE et al., 2016)	20	1.81±1.38	1.03±0.64	15.95±1.85	3months	4g of myo-inositol and 400μg of folic acid
(ARTINI et al., 2013)	25	2.5±0.6	1.1±0.3	34.9±2.1	3months	2g of myo-inositol and 200μg of folic acid
(FRUZZETTI et al., 2017)	24	2.1±0.5	1.5±0.4	21.6±6.6		4g of myo-inositol and 400μg of folic acid
(SHOKRPOUR et al., 2019)	26	3.1±0.9	2.6±0.8	28.3 ± 4.9	3months	4g of myo-inositol and 400μg of folic acid
(DE LEO et al., 2013)	20	3.8±0.3	2.7±0.3	24 to 32	6months	3g of myo-inositol
(NEHRA et al., 2017)	30	4.18±0.41	2.88±0.27	23.8± 0.69	6months	2g of myo-inositol
Combined	**155**					

LH: Data regarding treatment with myo-inositol (mIU/mL)						
(ARTINI et al., 2013)	25	13.5±2.2	8.6±1.6	34.9±2.1	3months	2g of myo-inositol and 200μg of folic acid
(GENAZZANI et al., 2008)	10	14.5±2.2	9.6±1.6	Not included	3months	2g of myo-inositol and 200μg of folic acid
(PKHALADZE et al., 2016)	20	9.11±5.70	7.56±4.50	15.95± 1.85	3months	4g of myo-inositol and 400μg of folic acid
(DE LEO et al., 2013)	20	11.1±0.7	8.6±0.4	24 to 32	6months	3g of myo-inositol
(NEHRA et al., 2017)	30	12.62±1.62	11.28±1.44	23.8± 0.69	6months	2g of myo-inositol
Combined	**105**					
FSH: Data regarding treatment with myo-inositol (mIU/mL)						
(ARTINI et al., 2013)	25	5.5±0.5	3.0±0.3	34.9±2.1	3months	2g of myo-inositol and 200μg of folic acid
(GENAZZANI et al., 2008)	10	6.5±0.5	4.0±0.3	Not included	3months	2g of myo-inositol and 200μg of folic acid
(DE LEO et al., 2013)	20	5.5±0.2	6.1±0.3	24 to 32	6months	3g of myo-inositol
(NEHRA et al., 2017)	30	6.8±0.51	7.4±0.53	23.8± 0.69	6months	2g of myo-inositol
Combined	**85**					
Glucose: Metformin treatment data (mg/dL)						
(NEHRA et al., 2017)	30	88.93±2.41	82.76±2.18	23.26±1.03	6months	1500mg of metformin
(ZAHRA et al., 2016)	20	100.2±9.5	100.8±5.3	25.8 ± 6.1	3months	1500mg of metformin
(SHOKRPOUR et al., 2019)	27	97.00±7.60	94.80±9.70	27.7 ± 3.2	3months	1500mg of metformin
(ORTEGA-GONZALEZ et al., 2005)	30	94.7±3.0	91.0±2.5	28.6±0.7	6months	2550mg of metformin
Combined	**107**					
Insulin: Metformin treatment data (mU/mL)						
(NEHRA et al., 2017)	30	18.98±1.48	14.04±1.10	23.26± 1.03	6months	1500mg of metformin
(JAVANMANESH et al., 2015)	48	10.65±3.03	10.40±2.64	29.37±4.6	6months	1500mg of metformin
(SHOKRPOUR et al., 2019)	27	12.6±2.2	11.9±2.4	27.7 ± 3.2	3months	1700mg of metformin
(ZAHRA et al., 2016)	20	17.2±9.2	14.1±9.3	25.8 ± 6.1	3months	1500mg of metformin
(DE LEO et al., 2013)	20	15±0.7	10.9±0.6	24 to 32	6months	1700mg of metformin
(FIGUROVÁ et al., 2017)	12	18.63±11.68	6.26±11.27	27.6±4.96	6months	1700 a 2550mg of metformin
(ORTEGA-GONZALEZ et al., 2005)	30	31.1±1.6	18.9±4.0	28.6±0.7	6months	2550mg of metformin
Combined	**187**					
HOMA index: Metformin treatment data						
(FRUZZETTI et al., 2017)	22	2.4±0.3	2.0±0.3	22.3±6.0	6months	1500mg of metformin
(NEHRA et al., 2017)	30	4.38±0.43	2.99±0.29	23.26± 1.03	6months	1500mg of metformin
(SHOKRPOUR et al., 2019)	27	3.0±0.7	2.8±0.7	27.7 ± 3.2	6months	1500mg of metformin
(JAVANMANESH et al., 2015)	48	2.23±0.73	2.09±0.69	29.37±4.6	6months	1500mg of metformin
(ZAHRA et al., 2016)	20	4.2±2.3	3.5±2.3	25.8 ± 6.1	3months	1500mg of metformin
(DE LEO et al., 2013)	20	3.2±0.4	2.4±0.3	24 to 32	6months	1700mg of metformin

(ORTEGA-GONZALEZ et al., 2005)	30	7.31±0.57	4.41±1.0	28.6±0.7	6months	2550mg of metformin
Combined	**197**					

Legend: Average before the intervention (Ab), Average after the intervention (Aa), Standard Deviation (SD).

Table 1. Data extracted and considered for meta-analysis after systematic review

Source: Authors, (2021).

Statistical analyzes were carried out according to the concentrations of drugs used in the interventions, thus, it was possible to assess which one showed greater efficiency in reducing or controlling the analyzed substances.

For serum glucose level after intervention with metformin, two concentrations of the drug were assessed in this meta-analysis. The results regarding the intervention with 1,500 mg of metformin, were not statistically significant, however, the intervention with 2,550 mg, was effective in the reduction of serum glucose with MD = 3.70 (95% CI = 2.30-5.10; $p < 0.05$), indicating a reduction of approximately 4 mg of glucose. Likewise, for serum insulin, the concentrations: 1,500 mg and 1,700 mg were not effective for serum hormone control, on the other hand, the 2,550 mg intervention showed statistically significant results, with MD = 12.20 (95% CI = 10.66-13.74; $p < 0.05$). The HOMA index showed a reduction, after the interventions, with 1,700 mg and 2,550 mg of metformin, the results were MD = 0.80 and MD = 2.90, respectively ($p < 0.05$) (Figure 2).

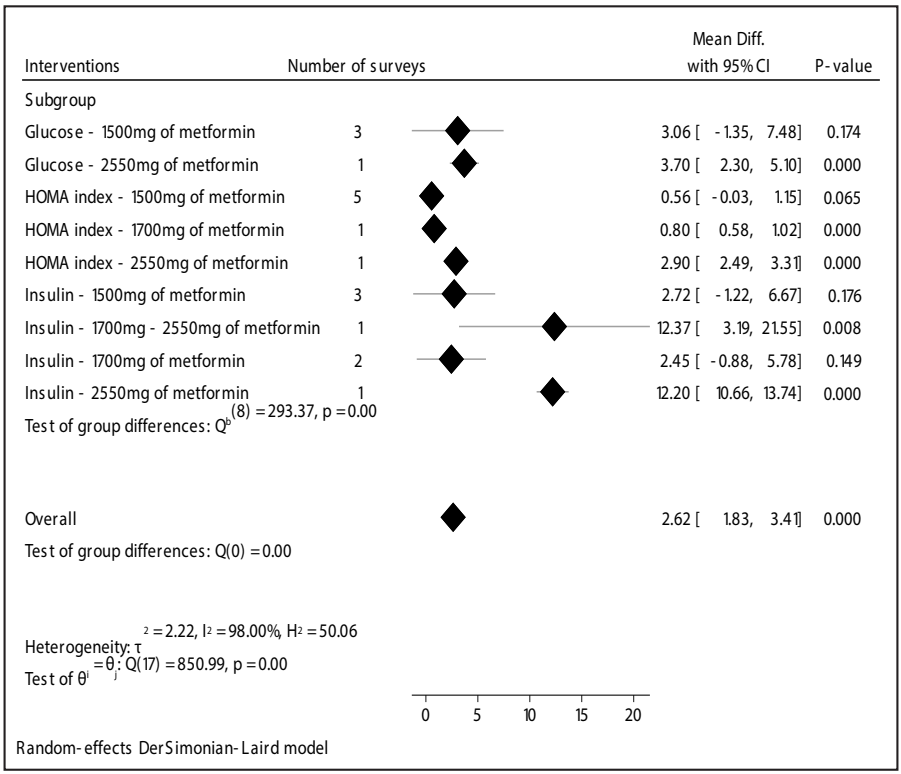

Figure 2. Glucose, Insulin and HOMA index: Comparison between treatments with metformin.

Source: Authors, (2021).

Myo-inositol showed efficiency in serum glucose reduction, interventions using 2 g and 3 g showed, respectively, an average reduction of 7 mg and 5 mg of glucose. The association of 4 g of myo-inositol, with 400 μg of folic acid, resulted in MD = 6.25 (95% CI = 4.32-8.18, p <0.05), that is, after intervention, the serum glucose reduction is on average 6 mg. Also, insulin concentrations were analyzed after the interventions, with 2 g of myo-inositol, associated with 200 μg of folic acid, and 4 g of myo-inositol, associated with 400 μg of folic acid, the interventions presented, respectively, MD = 5.9 and MD = 2.4 (p <0.05), determining greater effectiveness of the intervention with 2 g of myo-inositol associated with 200 μg of folic acid. The HOMA index decreased after all interventions with myo-inositol, with or without an association with folic acid. The intervention with 2 g of myo-inositol, associated with 200 μg of folic acid, showed an average reduction of 1.4 in the HOMA index. Likewise, the concentrations 4 g of myo-inositol, associated with 400 μg of folic acid, 2 g of myo-inositol and 3 g of myo-inositol, pointed, respectively, MD = 0.60; MD = 1.30; and MD = 1.10 (p <0.05) (Figure 3).

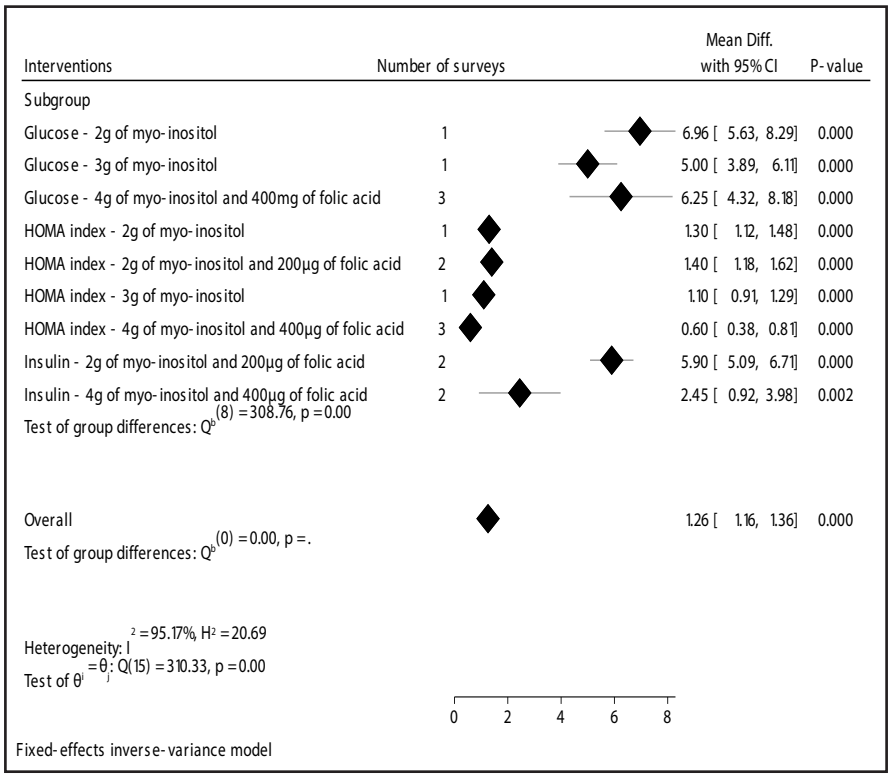

Figure 3. Glucose, Insulin and HOMA index: Comparison between treatments with myo-inositol.

Source: Authors, (2021).

The hormones LH and FSH were also analyzed, considering the interventions used the concentrations: 2 g of myo-inositol, associated with 200 µg of folic acid; 4 g of myo-inositol, associated with 400 µg of folic acid; 3 g of myo-inositol; and 2 g of myo-inositol. According to the statistical analyzes, the intervention with 2 g of myo-inositol, associated with 200 µg of folic acid, showed greater efficacy, in hormonal control of LH and FSH, with MD = 4.90 and MD = 2, respectively, 50 ($p < 0.05$). On the other hand, the concentrations of 2 g and 3 g of myo-inositol were effective only in controlling LH, with an increase in FSH after interventions. The intervention with 4 g of myo-inositol, associated with 400 µg of folic acid, did not present a significant result, with MD = 1.55 (95% CI = - 1.63-4.73, $p > 0.05$) (Figure 4).

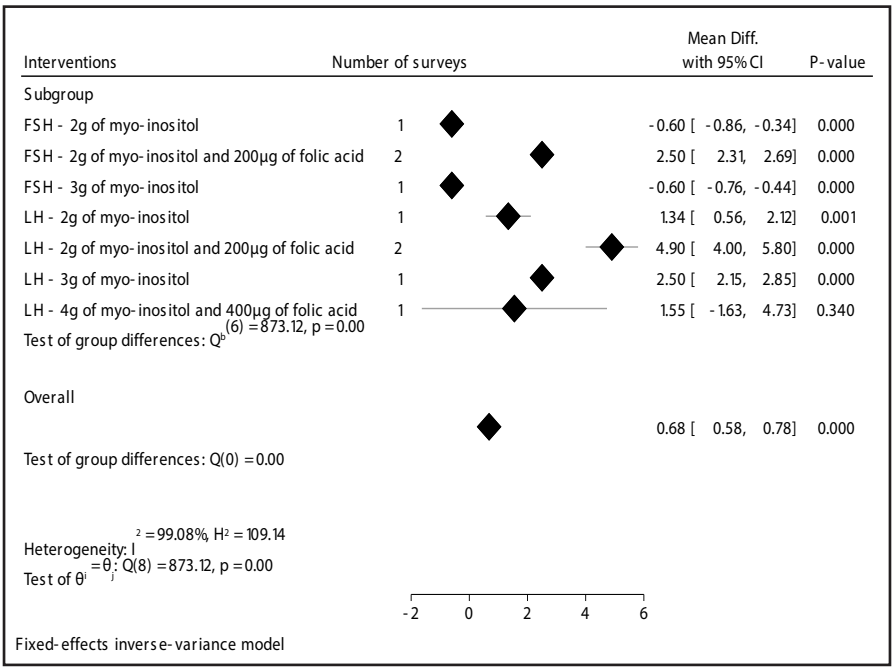

Figure 4. LH and FSH: Comparison between treatments with myo-inositol.

Source: Authors, (2021).

DISCUSSION

The diagnosis of PCOS is based on the criteria established in the ESRHE / ASRM Rotterdam consensus in 2003. For the diagnosis of the syndrome, it is necessary to have two of the following three characteristics: oligo ovulation, hyperandrogenism and presence of ovarian cysts (FAUSER *et al.,* 2004). However, although hyperinsulinemia and insulin resistance are not diagnostic criteria, these two physiological changes are prevalent in women with PCOS, usually associated with the pathogenesis of the syndrome, determining the importance of treating insulin resistance and hyperinsulinemia, usually done with insulin sensitizers. After analyzing the effects of the myo-inositol and metformin sensitizers, it was possible to observe that both had beneficial effects, effective in the treatment of PCOS, with regard to the serum reduction of insulin, glucose and improvement of the HOMA index.

Velazquez *et al.,* (1994), initially evaluated metformin supplementation at a dose of 1,500 mg per day for six months in 26 obese patients, the reported results were: weight loss and reduced androgen levels, improvement in menstrual cycle induction and ovulation. Metformin works by reducing glucose absorption, increasing insulin sensitivity, increasing peripheral glucose uptake without producing direct implications for pancreatic insulin production. Myo-inositol has recently been used as an insulin sensitizer. Glucose

metabolism is controlled by enzymes activated by an inositol phosphoglycan molecule, so when there is an enzyme deficiency, the mechanism is consequently compromised. Nehra *et al.,* (2017), found improved insulin sensitivity, glucose tolerance and reduced glycemic stimulus after the administration of myo-inositol, in the same way, Genazzani *et al.,* (2008), showed improvement in glucose level after supplementation of myo-inositol.

Insulin is an important parameter to be observed in patients with PCOS. The maintenance of hyperinsulinemia causes several complications characteristic of this pathology, such as ovulation problem, reduced quality of oocytes, increased production of androgens, altered menstrual cycle and reduced fertility (ANGIK *et al.,* 2015). According to Fruzzetti *et al.,* (2017), both metformin and myo-inositol are effective, improving insulin sensitivity, weight loss and reducing metabolic disorders.

The HOMA index measures insulin resistance by calculating the glucose-to-insulin ratio. Insulin resistance is determined by the demand for insulin greater than normal for the performance of physiological processes, due to a defect in the binding of insulin with its receptors or failure in the transmission of the insulin signal, causing increased insulin excretion, characterizing compensatory hyperinsulinemia, and at the same time, serum glucose levels remain within the reference values (BREMER; MILLER, 2008).

The present meta-analysis showed ineffectiveness of metformin in the reduction of the HOMA index, serum reductions in insulin and glucose, when administered 1,500 mg, showing statistically significant results when administered 2,550 mg. The importance of these results is in the relationship between drug concentration and increased risk of side effects, since the concentration is directly related to the time of the drug in the body. On the other hand, myo-inositol, associated or not with folic acid, showed statistically significant results for all concentrations, with a reduction in the HOMA index, serum reductions in insulin and glucose. Thus, the use of myo-inositol has advantages, considering the absence of side effects.

The excess of androgen is an important characteristic in the clinical picture of PCOS, and, therefore, the regulation of these hormones is fundamental for an improvement in signs and symptoms. In the study by Artini *et al.,* (2013), the intervention with myo-inositol for 6 to 8 weeks had beneficial effects in the reduction of androgens, gonadotropin and serum lipid, reducing 66% of the total testosterone and reduction of androstenedione. The intervention with myo-inositol was also related to an improvement in hirsutism and regulation of the menstrual cycle (ARTINI *et al.,* 2013).

In this meta-analysis, serum LH and FSH levels were analyzed after the administration of myo-inositol. The results showed a reduction of LH in the interventions using the concentrations 2 g, 3 g and 2 g associated with 200 μg of folic acid. On the other hand, myo-inositol without the association with folic acid was not efficient in reducing FSH, however, the administration of 2 g associated with 200 μg of folic acid, was effective in reducing the mean FSH. About 55 to 77% of women with PCOS have a high LH / FSH ratio. One of the

roles of FSH is to promote the growth of ovarian follicles. When LH is increased and FSH is reduced, the antral follicles suffer premature growth arrest and the oocytes lose their quality, thus compromising fertility (KALRO; LOUCKS; BERGA, 2001). Thus, for the control of FSH, the association of myo-inositol with folic acid becomes essential.

Metformin and myo-inositol showed equal efficiency as insulin sensitizers, improved HOMA index and reduced hyperinsulinemia. However, the use of metformin can cause gastrointestinal problems such as nausea, lack of appetite and diarrhea, and its use should be suspended within 48 hours before surgical cases with a risk of developing metabolic acidosis, therefore, adherence to treatment is compromised, determining the importance of researching other methods of treatment of insulin resistance, as effective as. According to Lin *et al.* (2019), women with PCOS have the same eating habits as women without PCOS, despite the fact that women with the syndrome have a high body mass index (BMI). It was also found a low fiber intake and high sodium intake. Something to note is the risk of developing diabetes and cardiovascular disease in women with PCOS (LIN *et al*., 2019).

Guidance on healthy eating together with the encouragement of physical activity is essential and recommended by the International Guideline, Based on Evidence for the Evaluation and Management of PCOS. The nutritionist professional must act to improve the clinical picture of PCOS, and the nutritional intervention must be based on the possibility of supplementation of myo-inositol, in the objective of losing 5 to 10% of the original weight for overweight and obese women (TEEDE *et al*., 2019). Still according to El Hayek *et al*., (2016), lifestyle modification is one of the first-line treatments.

CONCLUSION

The present meta-analysis found efficacy of metformin, when administered a higher dosage. On the other hand, myo-inositol was efficient in reducing the HOMA index and serum insulin and glucose levels, regardless of dosage. When associated with folic acid, myo-inositol had potential to reduce FSH and LH. The results of this research are very relevant in the decision-making of the nutritionist, however, research is necessary considering environmental and genetic factors, considering samples that statistically represent the population with PCOS.

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