Lipid profile and blood glucose in patients with Diabetes Mellitus treated with Cinnamon - Systematic Review and Meta-analysis with randomized clinical research

Perfil lipídico e glicemia em portadores de Diabetes Mellitus tratados com Canela – Revisão Sistemática e Meta-análise com pesquisas clínicas randomizadas

Perfil lipídico y glucemia en pacientes con diabetes mellitus tratados con canela - Revisión sistemática y metaanálisis con ensayos clínicos aleatorizados

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Abstract
This study aimed to measure the efficiency of cinnamon in patients with Type 2 Diabetes Mellitus (DM2), comparing fasting plasma glucose averages and lipid profiles with a placebo group through a meta-analysis. Four databases were the source of the research to find the articles used, including: Medline / PubMed, LILACS and NCBI. 11 randomized clinical trials that evaluated cinnamon on glycemic and lipid parameters were included in this study. Meta-analysis was performed with the aid of the STATA® 16.0 software, which determined the difference in glucose means and lipid profiles compared to a placebo group. Cinnamon at concentrations of 250 mg twice a day decreased blood glucose with MD = -0.25 (95%CI = - 0.36 to -0.14; *p<0.00001*) and in the intervention with 2 g 3 times a day with MD = -5.60 (95%CI = -6.98 to -4.22; *p<0.00001*). Total cholesterol was significant with 2 g 3 times a day with MD = 0.98 (95%CI = -1.27 to -0.69), followed by LDL-cholesterol MD = 0.64 (95%CI = 0.88 to 0.40; *p<0.00001*), and HDL-cholesterol with 500 mg 3 times daily with MD = 0.12 (95%CI = 0.05 to 0.19). High-dose supplementation of

cinnamon can reduce glucose and lipid profiles in patients with DM2. This supporting treatment can be useful when added to the diet plan of patients with DM2.

Keywords: Type 2 Diabetes Mellitus; Cinnamon; Blood glucose; Lipid profiles.

Resumo

Esse presente estudo teve como finalidade mensurar a eficiência da canela em portadores de Diabetes Mellitus tipo 2 (DM2), comparando as médias de glicose no plasma em jejum e os perfis lipídicos com um grupo placebo através de uma Metanálise. Quatro bancos de dados foram fonte das pesquisas para achados dos artigos utilizados, incluindo: Medline/PubMed, LILACS e NCBI. 11 ensaios clínicos randomizados que avaliaram a canela nos parâmetros glicêmicos e lipídicos, foram incluídos nesse estudo. A Metanálise foi realizada com o auxílio do software STATA® 16.0, que determinou a diferença das médias de glicose e perfis lipídicos comparando com um grupo placebo. A canela nas concentrações de 250 mg 2 vezes ao dia diminuiu a glicemia com MD= -0,25 (IC95% = - 0,36 a -0,14; $p<0,00001$) e na intervenção com 2 g 3 vezes ao dia com MD= -5,60 (IC95% = -6,98 a -4,22; $p<0,00001$). Colesterol total obteve significância com 2 g 3 vezes ao dia com MD = 0,98 (IC95% = -1,27 a -0,69), seguido do LDL-colesterol MD = 0,64 (IC95% = 0,88 a 0,40; $p<0,00001$), e HDL-colesterol com 500 mg 3 vezes ao dia com MD = 0,12 (IC95% = 0,05 a 0,19). A suplementação com altas doses de canela pode reduzir a glicemia e os perfis lipídicos em pacientes com DM2. Esse pode ser um tratamento coadjuvante útil quando adicionado ao plano alimentar de pacientes com DM2.

Palavras-chave: Diabetes Mellitus tipo 2; Canela; Glicemia; Perfis lipídicos.

Resumen

Este estudio tuvo como objetivo medir la eficacia de la canela en pacientes con Diabetes Mellitus tipo 2 (DM2), comparando los perfiles medios de glucosa plasmática y lípidos en ayunas con un grupo de placebo a través de un metanálisis. Cuatro bases de datos fueron la fuente de investigación para los hallazgos de los artículos utilizados, incluyendo: Medline / PubMed, LILACS y NCBI. En este estudio se incluyeron 11 ensayos controlados aleatorios que evaluaron la canela en parámetros glucémicos y lipídicos. El metanálisis se realizó con la ayuda del software STATA® 16.0, que determinó la diferencia en los perfiles medios de glucosa y lípidos en comparación con un grupo de placebo. La canela a concentraciones de 250 mg dos veces al día disminuyó la glucosa en sangre con MD = -0,25 (IC del 95% = -0,36 a -0,14; $p <0,00001$) y en la intervención con 2 g 3 veces al día al día con MD = -5,60 (IC del 95% = -6,98 a -4,22; $p<0,00001$). El colesterol total fue significativo con 2 g 3 veces al día con MD = 0,98 (IC del 95% = -1,27 a -0,69), seguido de MD de colesterol LDL = 0,64 (IC del 95% = 0,88 a 0,40; $p <0,00001$), y Colesterol HDL con 500 mg 3 veces al día con MD = 0,12 (IC del 95% = 0,05 a 0,19). La suplementación con altas dosis de canela puede reducir los perfiles de glucosa y lípidos en sangre en pacientes con DM2. Este puede ser un tratamiento coadyuvante útil cuando se agrega al plan de alimentación de los pacientes con DM2.

Palabras clave: Diabetes Mellitus tipo 2; Canela; Glucosa; Perfiles lipídicos.

1. Introduction

Type 2 diabetes mellitus, DM2, is a serious disease that affects thousands of people and is a worldwide health problem. It is characterized by an increase in blood glucose (hyperglycemia) due to resistance to insulin, the pancreatic hormone responsible for glucose uptake in cells such as muscle and adipose tissue. Hyperglycemia can trigger a series of chronic complications, such as: heart problems, nephropathy, retinopathy, neuropathy and even limb amputations. There are many treatments for diabetes, including weight loss, dietary changes, physical activity and drug treatment (Tang et al., 2019).

However, some of the obstacles to good adherence to treatments include the precarious economic conditions, low educational level and high drug prices (Tang et al., 2019). Due to these factors, the strategy of using alternative therapy with medicinal plants and herbal medicines is gaining strength and is growing daily. In Brazil, in 2006 the National Policy for Complementary Integrative Practices was created, with the intention of, based on scientific data, introducing these treatments in the Unified Health System (Neto et al., 2020). Among the various complementary practices, one of the most widespread is herbal medicine, that uses medicinal plants for the prevention and treatment of diseases.

Cinnamon is an aromatic plant that deserves attention among medicinal plants that have scientific support for its beneficial biological effects (Namazi et al., 2019). Cinnamon has been shown to have biological properties similar to insulin. Its action in glycemic control probably occurs through activation of the insulin-kinase receptor, with insulin receptor autophosphorylation improving its sensitivity and glycogen synthase enzyme activity (Zare et al., 2018).

The articles report two main species of cinnamon, Cassia cinnamon (*Cinnamomum aromaticum*) and Ceylon cinnamon (*Cinnamomum zeylanicum*) (Zare et al., 2018). Cinnamon has in its bark, several botanical compounds, including polyphenols, which perform excellent antioxidant activity, among others. It has been studied and used to improve general health and to treat various diseases such as DM2. In addition to its anti-diabetic properties, cinnamon is also efficient in its use as an anti-inflammatory, antibacterial and antioxidante (Sahib, 2016). The main active ingredient in cinnamon that contributes to glycemic control, as well as to the improvement of lipid and anthropometric profiles, is cinnamaldehyde, a phenolic compound. The effects of cinnamaldehyde are investigated in promoting improved insulin sensitivity and better use, regulation of protein tyrosine phosphatase and insulin receptor kinase (Namazi et al., 2019).

The objective of the study was to analyze if T2DM patients treated with cinnamon, when compared to a placebo-controlled group, present a significant result between the means in relation to glycemic and lipid parameters.

2. Methodology

This is a systematic review and meta-analysis, with descriptive aspects, based on electronic databases, to simultaneously assess several investigations from different studies on the same topic. Meta-analysis resides in placing several studies together in a database using statistical and analytical methods, in order to elucidate changes in the results. Its benefits are: increased objectives and number of investigated studies (Moher et al., 2009).

For the systematic review and meta-analysis, clinical articles that assessed serum glucose and lipid parameters of DM2 patients supplemented with cinnamon were chosen, comparing them with placebo-controlled DM2 patients. For a descriptive aspect, articles were collected that reported the active principles of cinnamon and its mechanism of action in relation to DM2. In the health sciences descriptors, the keywords were found: Cinnamon, Diabetes mellitus type 2 and Glycemic index. Searches for articles were performed in the PubMed database on the National Center for Biotechnology Information (NCBI) website and in the Virtual Health Library (VHL) databases, considering the Literature Latin American and Caribbean in Health Sciences (LILACS). For advanced searches the Booleans 'AND' and 'OR' were used. In LILACS 4 references were found and in PubMed 34 references. Repetitions or articles that were not in accordance with the proposed theme were excluded, resulting in 20 references, in which 11 contributed to the meta-analysis (Figure 1). The articles chosen for meta-analysis had no restrictions on the year of publication. Now, for the described aspect of the study, only articles published in the period from 2016 to 2020 were used, without language restrictions.

Inclusion criteria for articles were: randomized clinical trials evaluating cinnamon supplementation with results in at least three parameters. Fasting plasma glucose, total cholesterol and LDL/HDL-cholesterol, with populations over 18 years of age, with type 2 Diabetes Mellitus, considering both genders. The criteria for exclusion from the studies were: Non-randomized research, doctoral theses, monographs, books and master's dissertations, studies that used cinnamon with another herbal medicine or cinnamon added to a cooking recipe, patients under 18 years of age and without Diabetes Mellitus type 2 or with more complications. All data collection, as well as the development of the systematic review and meta-analysis, were carried out based on the instructions and recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

The flowchart model adopted was found in PRISMA. After selecting the articles, according to the inclusion and exclusion criteria, data from 11 studies were extracted and tabulated, referring to the following analyses: fasting plasma glucose (11), total cholesterol (9), LDL-cholesterol (9) and HDL Cholesterol (8) (Table 1). The measurement units were standardized in mmol/L, to express confident and assertive results (Moher et al., 2009).

The STATA® 16.0 software was used for statistical analysis of data, using the fixed effects test for continuous data,

with the purpose of allocating the differences in mean serum glucose, total cholesterol and LDL/HDL-cholesterol, comparing DM2 patients treated with placebo and DM2 patients supplemented with cinnamon. The software was also responsible for making the graphics (Forest Plot). An alpha value of p<0.05 was considerable and statistically significant, thus it was considered a range or 95% confidence interval (95%CI). The □2 test of heterogeneity associated with the Higgins and Thompson test (I^2) was used to confirm the heterogeneity between studies, adopting the randomized effect. When the □2 test presented p≤0.05, the randomized effect was applied. Likewise, when the I^2 test showed a result of ≥50%, the randomized effect was applied.

Figure 1. PRISMA Flowchart showing systematic selection of articles for meta-analysis and descriptive aspect.
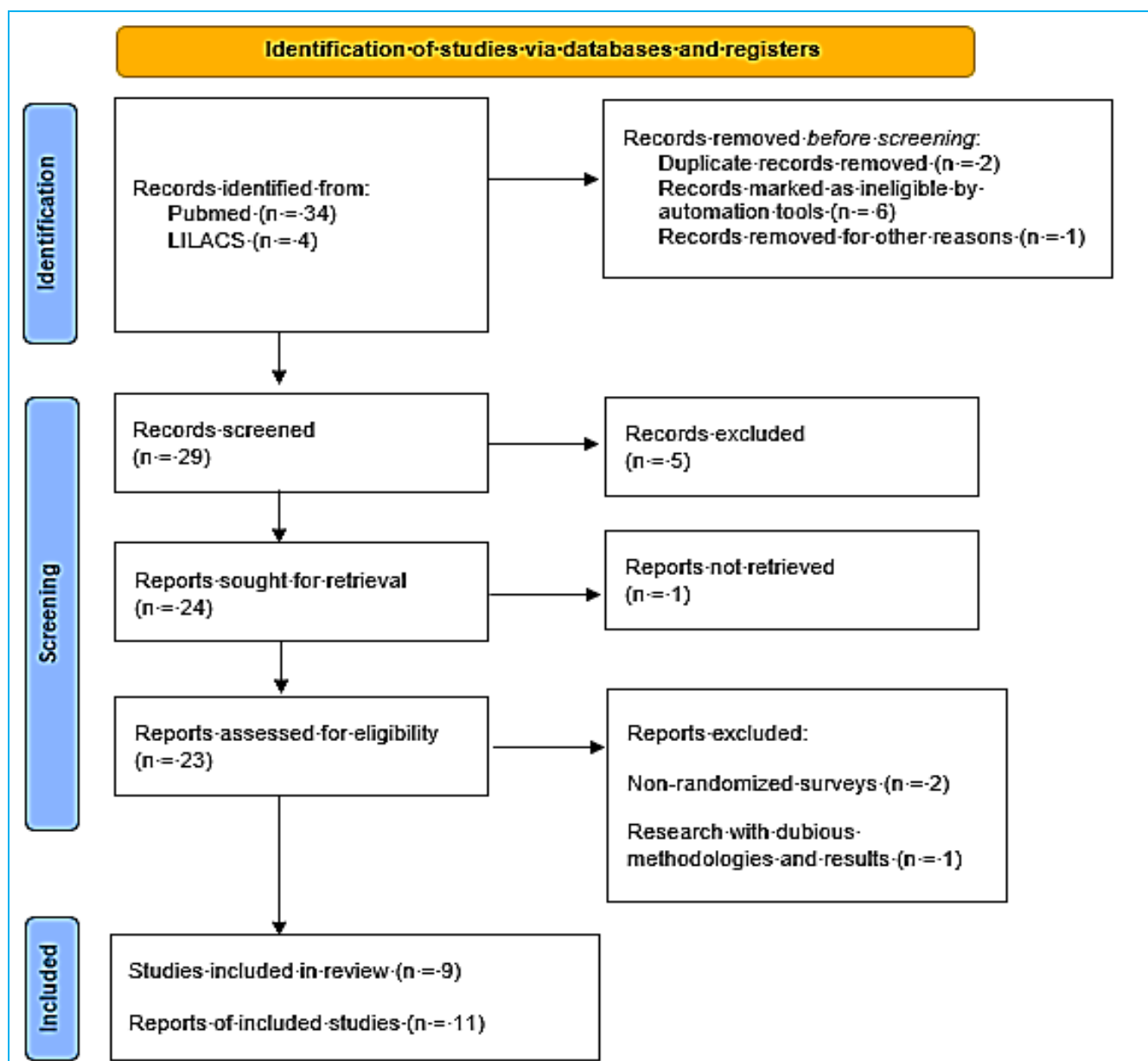
Source: Authors (2021) adapted from Moher et al., (2009).

The main idea of the study was to analyze if DM2 patients treated with cinnamon, when compared to a placebo-controlled group, present a significant result between the means in relation to glycemic and lipid parameters. Thus, the mean serum levels of: fasting glucose in the case groups (N=341) and control groups (N=365), total cholesterol in the case groups

(N=275) and in the control groups (N=295), LDL-cholesterol case groups (N=275) and control groups (N=295) and finally HDL-cholesterol case groups (N=245) and control groups (N=265).

Table 1. Information of selected surveys for meta-analysis.

Author	Intervention
Hasanzade et al., (2013)	Blood glucose: After treatment with 500 mg twice times a day
Khan et al., (2003)	Blood glucose: After treatment with 500 mg twice times a day
Mirfeizi et al., (2015)	Blood glucose: After treatment with 500 mg twice times a day
Khan et al., (2003)	Blood glucose: After 1g treatment three times a day
Mang et al., (2006)	Blood glucose: After 1g treatment three times a day
Talaei et al., (2017)	Blood glucose: After 1g treatment three times a day
Vafa et al., (2012)	Blood glucose: After 1g treatment three times a day
Sengsuk et al., (2015)	Blood glucose: After 500mg treatment three times a day
Vanschoonbeek et al., (2006)	Blood glucose: After 500mg treatment three times a day
Anderson et al., (2015)	Blood glucose: After 250 mg treatment twice daily
Akilen et al., (2010)	Blood glucose: After 500 mg treatment four times a day
Lu et al., (2012)	Blood glucose: After 60 mg treatment six times a day
Khan et al., (2003)	Blood glucose: After 2 g treatment three times a day
Mirfeizi et al., (2015)	Total Cholesterol: After treatment with 500 mg twice times a day
Khan et al., (2003)	Total Cholesterol: After treatment with 500 mg twice times a day
Mang et al., (2006)	Total Cholesterol: After 1g treatment three times a day
Vafa et al., (2012)	Total Cholesterol: After 1g treatment three times a day
Khan et al., (2003)	Total Cholesterol: After 1g treatment three times a day
Sengsuk et al., (2015)	Total Cholesterol: After 500 mg treatment three times a day
Vanschoonbeek et al., (2006)	Total Cholesterol: After 500 mg treatment three times a day
Anderson et al., (2015)	Total Cholesterol: After 250 mg treatment twice daily
Akilen et al., (2010)	Total Cholesterol: After 500 mg treatment four times a day
Lu et al., (2012)	Total Cholesterol: After 60 mg treatment six times a day
Khan et al., (2003)	Total Cholesterol: After 2 g treatment three times a day
Mang et al., (2006)	HDL: After 1g treatment three times a day
Vafa et al., (2012)	HDL: After 1g treatment three times a day
Sengsuk et al., (2015)	HDL: After 500 mg treatment three times a day
Vanschoonbeek et al., (2006)	HDL: After 500 mg treatment three times a day
Anderson et al., (2015)	HDL: After 250 mg treatment twice daily
Akilen et al., (2010)	HDL: After 500 mg treatment four times a day
Lu et al., (2012)	HDL: After 60 mg treatment six times a day
Mirfeizi et al., (2015)	HDL: After treatment with 500 mg twice times a day
Khan et al., (2003)	LDL: After treatment with 500 mg twice times a day
Mirfeizi et al., (2015)	LDL: After treatment with 500 mg twice times a day
Mang et al., (2006)	LDL: After 1g treatment three times a day
Vafa et al., (2012)	LDL: After 1g treatment three times a day
Khan et al., (2003)	LDL: After 1g treatment three times a day
Sengsuk et al., (2015)	LDL: After 500 mg treatment three times a day
Vanschoonbeek et al., (2006)	LDL: After 500 mg treatment three times a day
Anderson et al., (2015)	LDL: After 250 mg treatment twice daily
Akilen et al., (2010)	LDL: After 500 mg treatment four times a day
Lu et al., (2012)	LDL: After 60 mg treatment six times a day
Khan et al., (2003)	LDL: After 2 g treatment three times a day

Source: Authors (2021).

3. Results

According to the exclusion and inclusion criteria, data from 11 randomized clinical trials were tabulated for meta-analysis, the combination of trials resulted in 321 participants in the intervention group and 345 in the placebo group. Different interventions with cinnamon were analyzed, 500 mg twice a day, 1g three times a day, 500 mg three times a day, 250 mg twice a day, 500 mg four times a day, 60 mg six times a day and 2 g three times a day. The efficiency of interventions was evaluated according to blood glucose and lipid profile.

Total cholesterol after interventions with 1 g, 2 g administered three times a day and 500 mg twice a day, showed a higher concentration in the placebo group, that is, they were efficient in reducing total cholesterol in the intervention group, with emphasis on the intervention with 2 g of cinnamon, administered three times a day, MD = -0.98 (95%CI= -1.27 to -0.69) (Figure 2).

Figure 2. Total Cholesterol: Comparison between placebo group and intervention group.
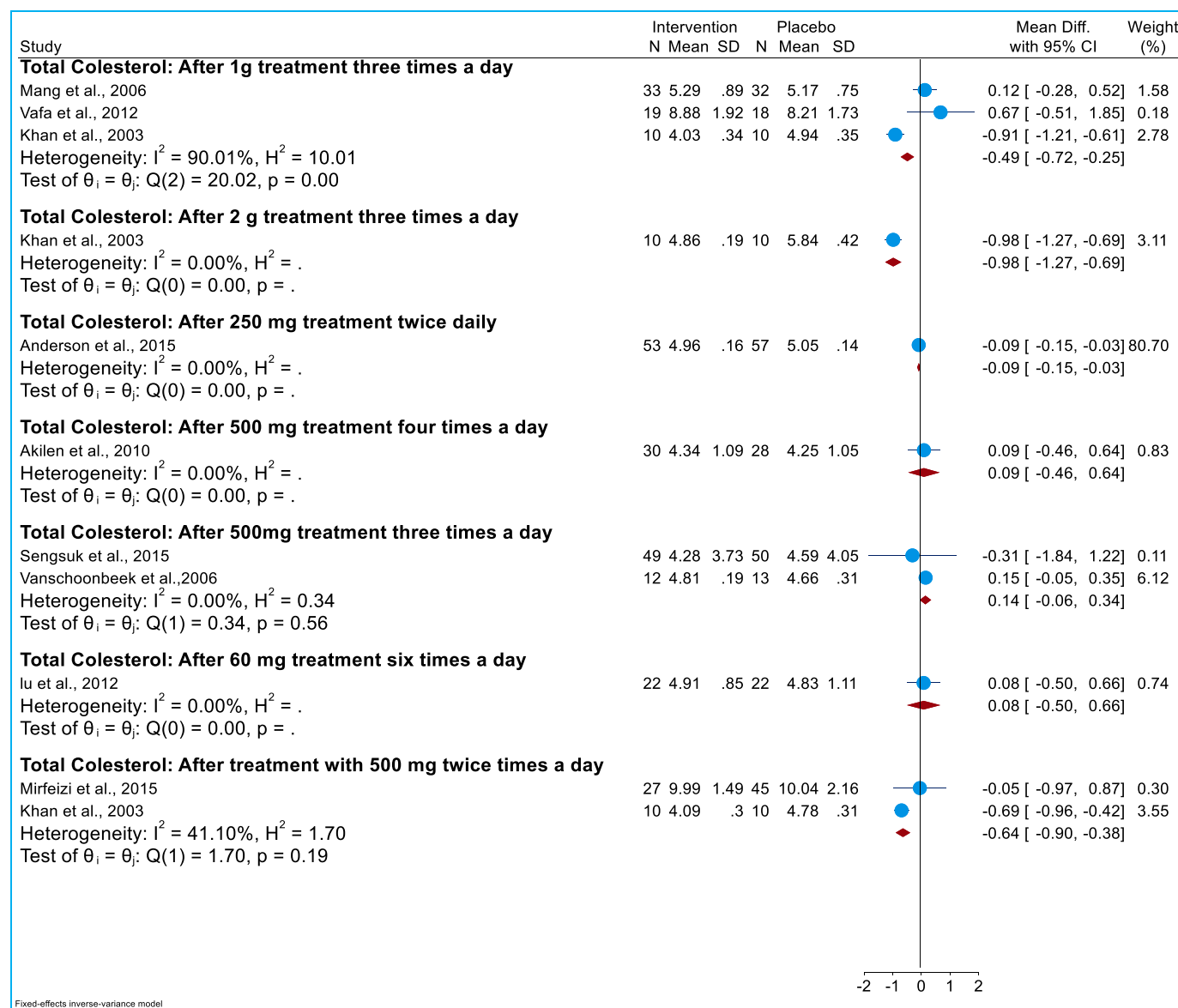
Source: Authors (2021).

Similarly, for LDL cholesterol, interventions with 1 g and 2 g demonstrated efficacy in reducing it with mean differences -60 and -64, respectively (Figure 3).

For HDL cholesterol, 500 mg of cinnamon three times a day was effective with increased HDL concentration in the intervention group, MD = 0.12 (95%CI = 0.05 to 0.19). The other interventions did not show efficiency for the difference between means (Figure 4).

Figure 3. LDL: Comparison between placebo group and intervention group.
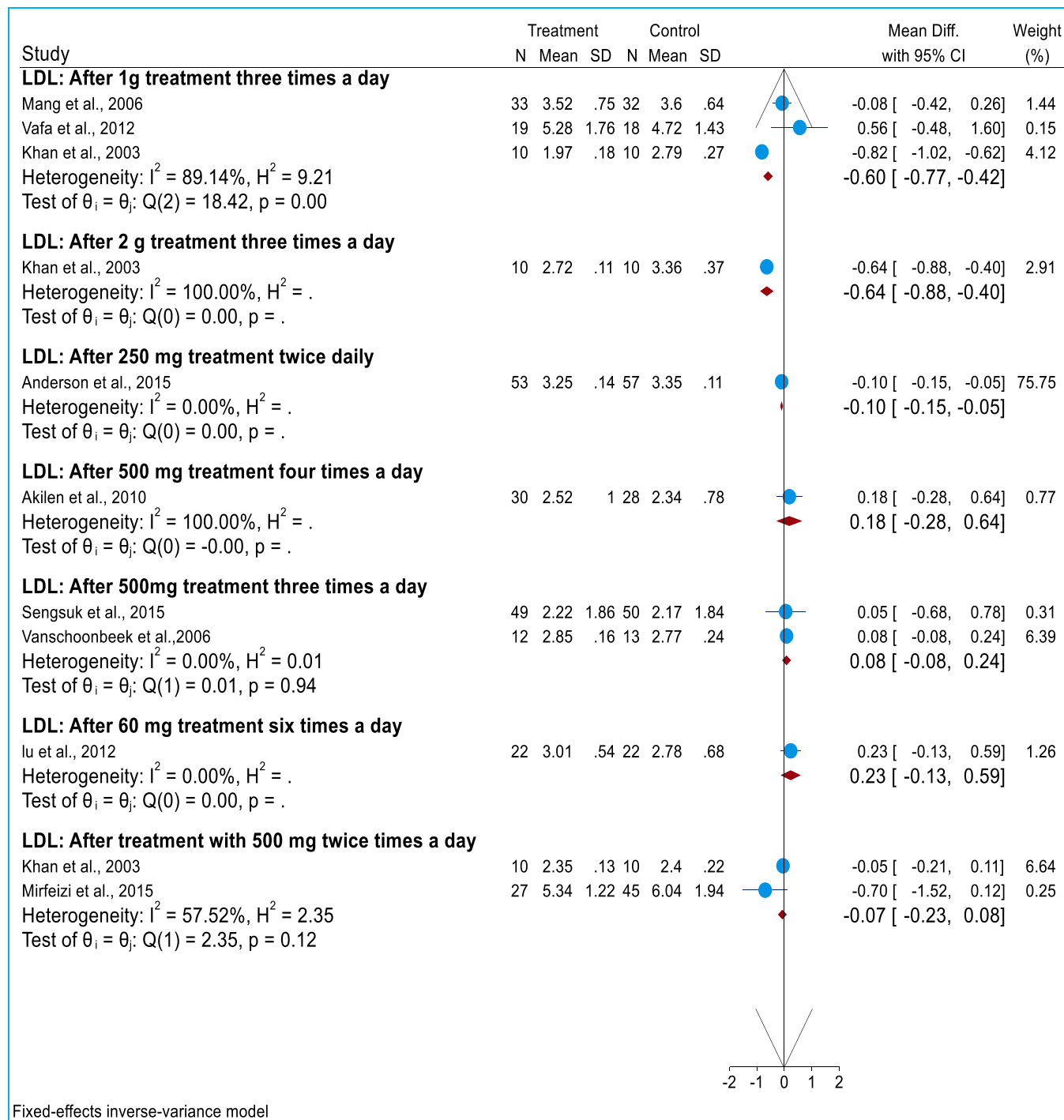
Source: Authors (2021).

Figure 4. HDL: Comparison between placebo group and intervention group.
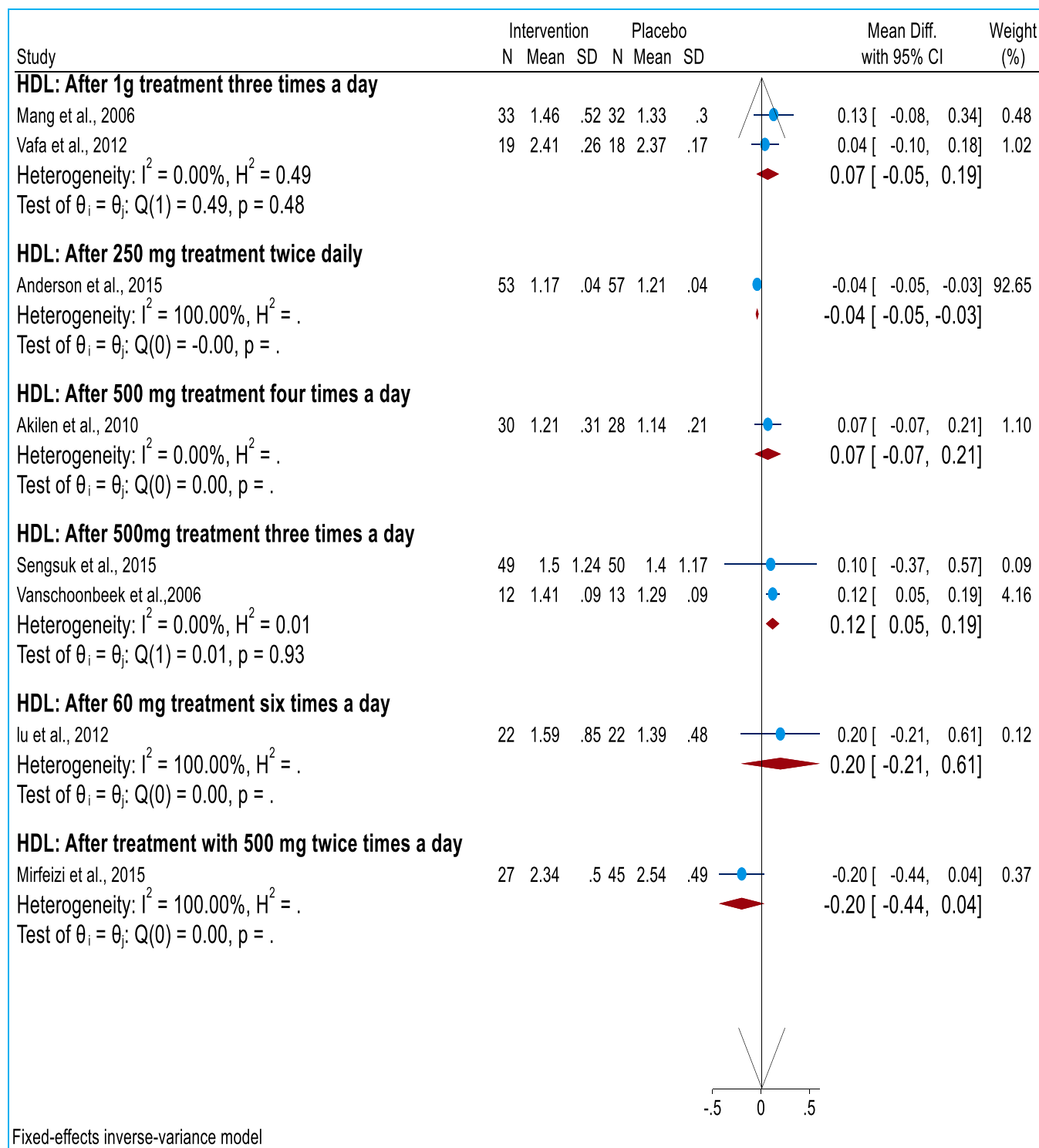
Source: Authors (2021).

Interventions with 1 g, 2 g and 500 mg twice a day were effective in reducing glycemic levels. After interventions, serum glucose means were higher in the placebo group with MD = -0.58 for 1g given three times a day, MD = -5.60 for 2 g given three times a day and MD = -1.05 for 500 mg administered twice a day (Figure 5).

Figure 5. Blood glucose: Comparison between placebo group and intervention group.

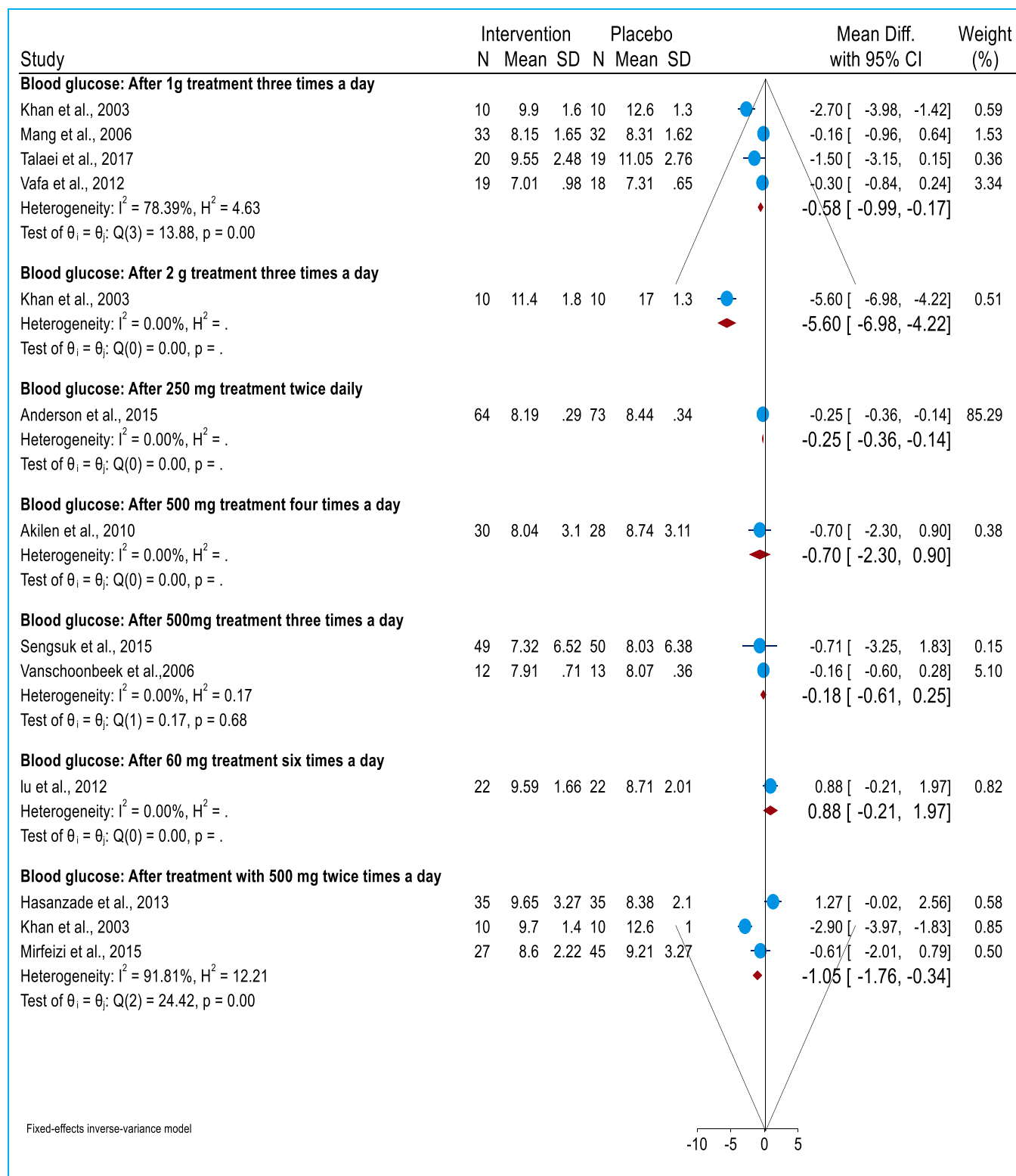| Study	Intervention N	Mean	SD	Placebo N	Mean	SD	Mean Diff. with 95% CI	Weight (%)
Blood glucose: After 1g treatment three times a day								
Khan et al., 2003	10	9.9	1.6	10	12.6	1.3	-2.70 [-3.98, -1.42]	0.59
Mang et al., 2006	33	8.15	1.65	32	8.31	1.62	-0.16 [-0.96, 0.64]	1.53
Talaei et al., 2017	20	9.55	2.48	19	11.05	2.76	-1.50 [-3.15, 0.15]	0.36
Vafa et al., 2012	19	7.01	.98	18	7.31	.65	-0.30 [-0.84, 0.24]	3.34
Heterogeneity: $I^2 = 78.39\%$, $H^2 = 4.63$							-0.58 [-0.99, -0.17]	
Test of $\theta_i = \theta_j$: Q(3) = 13.88, p = 0.00								
Blood glucose: After 2 g treatment three times a day								
Khan et al., 2003	10	11.4	1.8	10	17	1.3	-5.60 [-6.98, -4.22]	0.51
Heterogeneity: $I^2 = 0.00\%$, $H^2 = .$							-5.60 [-6.98, -4.22]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .								
Blood glucose: After 250 mg treatment twice daily								
Anderson et al., 2015	64	8.19	.29	73	8.44	.34	-0.25 [-0.36, -0.14]	85.29
Heterogeneity: $I^2 = 0.00\%$, $H^2 = .$							-0.25 [-0.36, -0.14]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .								
Blood glucose: After 500 mg treatment four times a day								
Akilen et al., 2010	30	8.04	3.1	28	8.74	3.11	-0.70 [-2.30, 0.90]	0.38
Heterogeneity: $I^2 = 0.00\%$, $H^2 = .$							-0.70 [-2.30, 0.90]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .								
Blood glucose: After 500mg treatment three times a day								
Sengsuk et al., 2015	49	7.32	6.52	50	8.03	6.38	-0.71 [-3.25, 1.83]	0.15
Vanschoonbeek et al.,2006	12	7.91	.71	13	8.07	.36	-0.16 [-0.60, 0.28]	5.10
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 0.17$							-0.18 [-0.61, 0.25]	
Test of $\theta_i = \theta_j$: Q(1) = 0.17, p = 0.68								
Blood glucose: After 60 mg treatment six times a day								
lu et al., 2012	22	9.59	1.66	22	8.71	2.01	0.88 [-0.21, 1.97]	0.82
Heterogeneity: $I^2 = 0.00\%$, $H^2 = .$							0.88 [-0.21, 1.97]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .								
Blood glucose: After treatment with 500 mg twice times a day								
Hasanzade et al., 2013	35	9.65	3.27	35	8.38	2.1	1.27 [-0.02, 2.56]	0.58
Khan et al., 2003	10	9.7	1.4	10	12.6	1	-2.90 [-3.97, -1.83]	0.85
Mirfeizi et al., 2015	27	8.6	2.22	45	9.21	3.27	-0.61 [-2.01, 0.79]	0.50
Heterogeneity: $I^2 = 91.81\%$, $H^2 = 12.21$							-1.05 [-1.76, -0.34]	
Test of $\theta_i = \theta_j$: Q(2) = 24.42, p = 0.00								

Fixed-effects inverse-variance model

-10   -5   0   5

Source: Authors (2021).

4. Discussion

The results of this research showed that cinnamon at certain concentrations is efficient in the regulation of serum parameters: fasting glucose, total cholesterol, LDL-cholesterol and HDL-cholesterol. The intervention with 500 mg three times a day determined efficacy in almost all parameters. The clinical trials included in this meta-analysis showed good adherence to

cinnamon supplementation, which is well tolerated by patients. Some clinical trials such as the one by Sahib, (2016), randomized and controlled by placebo, showed significant results when supplementing 500mg of cinnamon twice a day in Iranian diabetic patients. After 6 and 12 weeks, fasting plasma glucose decreased by 12% ($p<0.001$) and 17.4% ($p<0.001$) respectively, compared to the placebo group. However, in this meta-analysis, the dosage of 500mg of cinnamon twice a day, evaluated after the combination of three studies, did not show statistical significance when compared to the placebo group. The combination of systematically selected research results in a larger sample group, with this, the result referring to intervention with 500 mg twice a day, presents greater assertiveness when compared to research with small sample size.

Higher dosage of cinnamon can directly influence its efficiency, the concentration of 2 g of cinnamon 3 times a day can reduce serum glucose levels by 5.6% ($p<0.00001$), compared to the placebo group (Khan et al., 2003). Cinnamon's efficiency in reducing serum glucose is a consequence of the presence of components capable of activating insulin receptors, thus causing their autophosphorylation. There is also an increase in the activation of the glucose transporter (GLUT-4), blocking of the pancreatic amylase enzyme, increased hepatic glycogen synthesis, improvement in insulin sensitivity and lipid profiles, positively altering serum glucose levels (Costello et al., 2016).

In relation to total cholesterol and LDL-cholesterol, the intervention with 2g 3 times a day showed, respectively, serum reductions of 0.98 and 0.64 mmol/L, when compared to the placebo group. Cinnamon can increase UCP3 gene expression in muscle and adipose tissue. The encoding of the UCP3 gene increases the number of proteins in the inner mitochondrial membrane responsible for regulating metabolism. When there is a higher level of gene expression in these tissues, there is a greater oxidation of carbohydrates and fatty acids, affecting thermogenesis (Zare et al., 2018).

In addition to concentration, another factor to be considered is quality. Cinnamon Cassia (*Cinnamomum aromaticum*) has a higher content of coumarins, a hepatotoxic substance, and because of this, high concentrations are not used for long periods, requiring further clinical studies to have greater reliability in patient compliance (Iwata et al., 2016).

A very relevant finding in this research was the increase in HDL-cholesterol in patients supplemented with cinnamon. After treatment with 500 mg 3 times a day with cinnamon, the result was in favor of the intervention group, with MD = 0.12 mmol/L more when compared to the control group (Figure 9), thus suggesting that cinnamon may increase HDL-cholesterol in DM2 patients, being an important point for the prevention of heart problems.

5. Conclusion

According to this research, high doses of cinnamon were effective in decreasing fasting plasma glucose, total cholesterol and LDL-cholesterol and promoted an increase in HDL-cholesterol in patients with DM2. However, caution is still needed in interpreting the results due to the high heterogeneity in some analyses. However, the results obtained show greater reliability in relation to the efficiency of cinnamon as an adjunct in the treatment of people with DM2. Future clinical trials for more assertive specification are needed. The best species of cinnamon to be used is *Cinnamomum aromaticum*, considering the time, dosage in the treatment and safety of cinnamon for long periods of intervention.

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