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The power of the placebo effect in diabetes: A systematic review and meta-analysis

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ABSTRACT

This review aims to identify the magnitude of the placebo effect in people with type 2 diabetes mellitus. Literature research was conducted Medline, Embase and Virtual Health Library for studies published between the date of inception and June 2021. The eligibility criteria included randomized controlled trials, showing comparison to placebo, having participants with type 2 diabetes mellitus, and having glycated hemoglobin (HbA1c) as the primary outcome. Meta-analysis was conducted with the effect of changing HbA1c in relation to the baseline. Exploration of heterogeneity was performed.The meta-analysis showed an increase in the average of HbA1c compared to the baseline of 0.14% (95% CI: 0.07–0.21). There was a significant difference between follow-up times ($p = 0.03$) and between administration routes ($p = 0.01$), with an increase in HbA1c in the oral route [0.15% (95% CI: 0.07–0.23)]. The meta-regression of the year of publication showed a significant downward trend ($p = 0.01$) of the increase in HbA1c compared to the baseline.In this study, the expected placebo effect of Hba1c reduction was not found; instead, higher Hba1c levels were observed in the control groups, although this effect was reduced over the years.

Registration: PROSPERO ID CRD42020172797

1. Introduction

Type 2 diabetes mellitus is a chronic disease characterized by hyperglycemia with high prevalence worldwide [1]. Glycemic control is extremely important to reduce acute symptoms and related chronic micro and macrovascular complications [2,3]. The ultimate goal of diabetes management is to keep the patients' glycemic level as close to normal as possible, which involves lifestyle changes and

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antihyperglycemic agents [4], based on randomized controlled trials (RCTs) which have compared these interventions to placebo. Interestingly, since the classic study by Beecher et al. [5] it is well known that placebo is associated with symptomatic improvements similarly to the index therapy in several health conditions. It is plausible to consider that the same may occur in therapies for diabetes [6].

Previous data on interventions for diabetes showed a growing response to placebo over the years and a possible relation to the baseline glycated hemoglobin (Hba1c) levels [7]. However, this analysis focused on studies published during a short period of time (1999–2015) from only one database. Another publication which sought to better understand the placebo effect in diabetes according to ethnicity showed no differences among groups [8]. Thus, given the evidence of possible responses to placebo in diabetes - with only a few studies evaluating this effect - and the growing prevalence of the disease [9], more studies are needed to evaluate the pattern of the placebo effect in this condition.

This systematic review aimed to identify the magnitude of the placebo effect in people with type 2 diabetes included in RCTs conducted to assess the effectiveness of drug interventions, and to measure its clinical impact over time. Moreover, we aimed to evaluate whether the pharmaceutical form of the placebo, its route of administration, follow-up time or the year of its publication would be related to these effects. Our hypothesis was that, as in patients with other health conditions, patients with diabetes also would experience the placebo effect at some level.

2. Methods

2.1. Protocol and registration

This is a systematic review developed based on the Preferred Reporting Items for Systematic Review and Meta-analysis: The PRISMA Statement [10] and registered in the International Prospective Register of Systematic Reviews (Prospero) under the number CRD42020172797 on 10/15/2020, available in Supplementary Material A.

2.2. Eligibility criteria

Eligible studies were RCTs conducted to assess the effectiveness of anti-hyperglycemic drug interventions compared to placebo, performed in patients with type 2 diabetes with HbA1c changes in relation to the baseline as the primary outcome, minimum follow-up time of 12 weeks, and published in English, Spanish, or Portuguese. To avoid interference with the placebo effect, studies in which the control group received a placebo associated with an active drug were excluded. Under-analyzed data from published RCTs, letters and other types of studies were also excluded.

2.3. Information sources

Research was conducted in electronic databases without restriction on the period of publication. The last search was carried out in June 2021 and covered the following databases: Pubmed, Embase, and Biblioteca Virtual Health Libray (VHLBVS).

2.4. Search strategy

The search was conducted in English using the descriptors: “randomized controlled trial”; “placebo”; “acarbose”; “metformin”; “glyburide”; “sulfonylurea compounds”; “gliclazide”; “chlorpropamide”; “thiazolidinediones”; “insulin”; “pramlintide”; “alogliptin”; “glimepiride”; “tolbutamide”; “exenatide”; “dapagliflozin”; “vildagliptin”; “sitagliptin”; “repaglinide”; “nateglinide”; “meglitinide”; and “type 2 diabetes mellitus”. Terms related to type 2 diabetes mellitus were also searched to obtain the greatest possible number of results. The Pubmed search strategy is available in Supplementary Material B.

2.5. Selection of studies

Articles were evaluated in two stages: firstly, their titles and abstracts were read using the EndNote software by two pairs of reviewers (M.B.F, L.P and R.P.B, M.D). After that, the selected articles were read entirely and considered eligible or ineligible by two pairs of reviewers (M.B.F, P. T. and R.P.B, M.D) in duplicate. In both stages a third reviewer (A.N.G) was consulted in cases of disagreement.

2.6. Data extraction process

A standardized, pre-piloted form (Excel) was used to extract data from the included studies for evidence synthesis. Two independent reviewers (M.B.F and R.P.B) extracted the data using a clinical record previously prepared by the authors. The third reviewer (A.N.G) deliberated on the disagreements in the comparison phase of these data in duplicate. In some cases, the authors were contacted to obtain data.

2.7. List of extracted data

The data extracted from each study comprised three blocks: 1 - basic characteristics of the studies and the population: location (continent); year of data collection; average age and age group; participants’ gender; and time of diagnosis of diabetes. 2 - data for quality analysis with six domains for analyzing the risk of bias: generation of random sequence; allocation concealment; blinding of participants and professionals; blinding of the evaluators; incomplete outcome data; and selective reporting. 3 - characteristics of the studies regarding the outcome and other analyses: sample size at the beginning and at the end of the study; follow-up time; comparative medication; pharmaceutical class; route of administration and dosage; HbA1c at the beginning and at the end of the study; standard deviation; standard error; and limits of the confidence interval.

2.8. Risk of bias and publication bias assessment

The risk of bias was assessed in all included articles using the Cochrane Collaboration tool, inserted in the Review Manager software (version 5.3) [11]. Then, two reviewers (M.B.F and R.P.B) in duplicate evaluated the methodology used in the following items: generation of random sequence; allocation concealment; blinding of participants and professionals as well as outcome evaluators; incomplete outcomes; reports of selective outcomes; and other sources of bias. The third reviewer (A.N.G) was consulted in cases of disagreement.

2.9. Effect measures

Change of HbA1c compared to the baseline was the measure used. It was calculated considering the average baseline and the longest follow-up period values when not available. In these cases, the standard error was calculated considering zero correlation between the baseline and follow-up measurements.

2.10. Summary of results

Narrative and quantitative analyses were performed to describe the results. The meta-analyses were performed with the RStudio software using a random effects model with a DerSimonian and Laird estimator for the variability between studies and the inverse variance method for calculating the summary estimate. The results were showed using forest plots with combined values, 95% confidence intervals (CI), and 95% prediction intervals (PI). Heterogeneity was measured using the I^2 statistic, the Cochran’s Q test, and the PI. Since PI shows the variability in the unit of the measure of effect, it supports the assessment of heterogeneity.

2.11. Subgroup and sensitivity analyses

Exploration of the expected heterogeneity was performed considering the follow-up time (meta-regression and time subgroups), route of administration (oral or parenteral), pharmaceutical form (tablet or solution for injection), and year of publication (meta-regression).

We also performed sensitivity analyses to assess whether any bias influenced the results obtained in the main metanalysis, further exploring heterogeneity. We have considered allocation concealment, blinding of participants, professionals and outcome evaluators, incomplete outcomes, reports of selective outcomes, the randomization process and missing data for these analyses.

3. Results

3.1. Selection of studies

The search identified a total of 15,850 studies (6955 via Pubmed, 903 articles from the VHL database, and 7992 via Embase.) Out of these, 1599 were duplicated, thus, a total of 14,251 articles were included for later analysis. After reviewing titles and abstracts, 12,860 were excluded. From these studies, 1391 were identified as potentially meeting the inclusion criteria. After examination of these full text articles, 91 studies were included in the systematic review (Fig. 1).

3.2. Study characteristics

From the 15,850 studies identified, 91 RCTs met all the inclusion criteria. Out of these, four studies did not describe the number of patients included and one did not mention the participants' average age, thus totaling 8233 participants with an average age ranging from 47 to 72 years. The average time of diagnosis of diabetes ranged from 0.5 to 8.6 years. Articles were published from 1988 to 2018, and data collection time interval was from 1989 to 2015, although this information was missing in many studies. Table 1 shows the characteristics of the included studies.

3.3. Risk of study bias

Fig. 2 shows the evaluation of the risk of bias. Considering the seven domains for this analysis, none of the included studies demonstrated a low risk of bias for all the evaluated criteria. The generation of random sequence and allocation concealment, both assessing selection bias, showed low risk of bias in only 36.6% and 30.0% of the studies, respectively. Most studies (90%) were classified as having an uncertain risk of bias in the domain that assesses the blindness of the outcome evaluators, since very few authors described this item. Only three studies demonstrated a high risk of bias for the incomplete outcomes of the domain, which assesses the complete description of losses throughout the study. Complete information of the risk of bias for each study is available in Supplementary Material C.

3.4. Results of the analyses

In total, 91 studies were included in the meta-analyses, and only data regarding the placebo groups were analysed. Fig. 3 shows that placebo was associated with higher levels of HbA1c [0.14% (95% CI: 0.06–0.23), p-value: 0.001] although a high heterogeneity among the studies

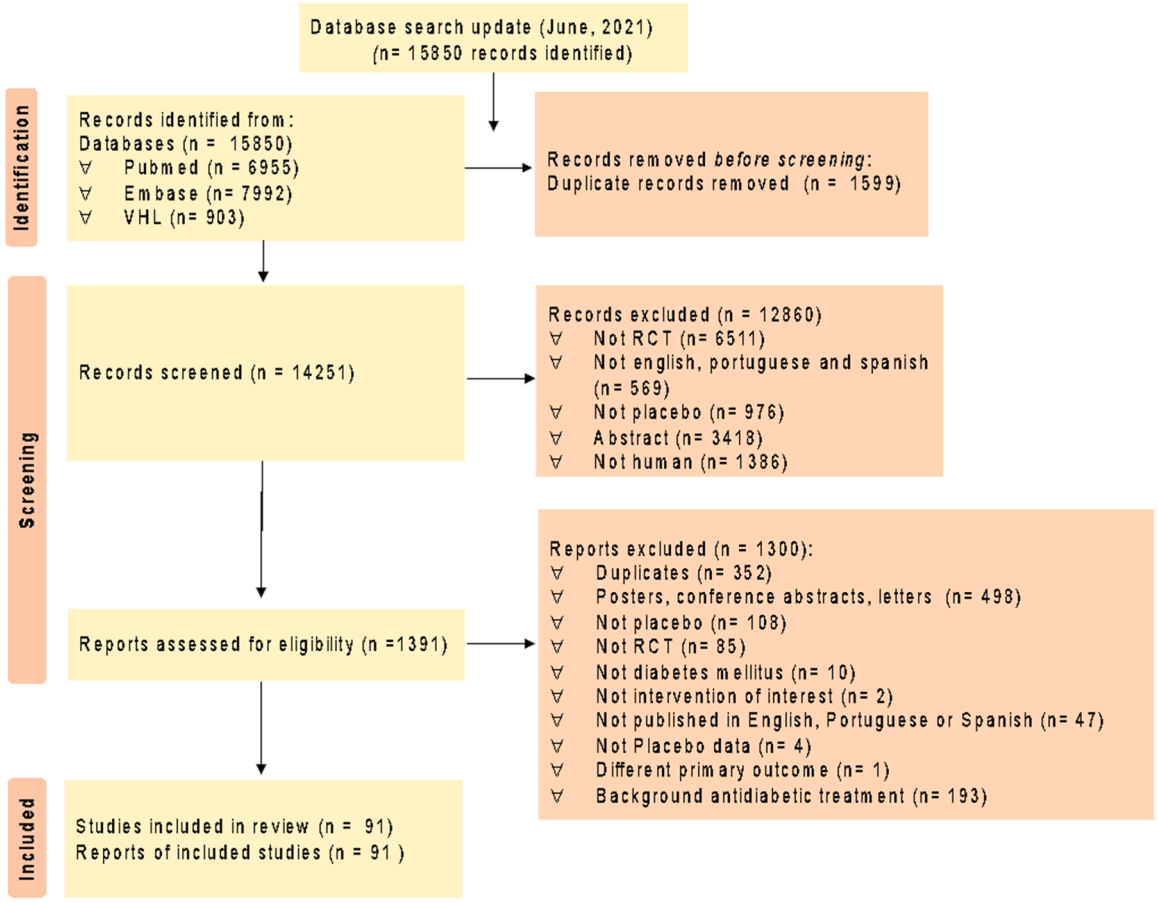

Fig. 1. Flowchart illustrating how articles were identified and selected for inclusion in the meta-analysis. (VHL: Virtual Health Library/ RCT: Randomized Controlled Trial).

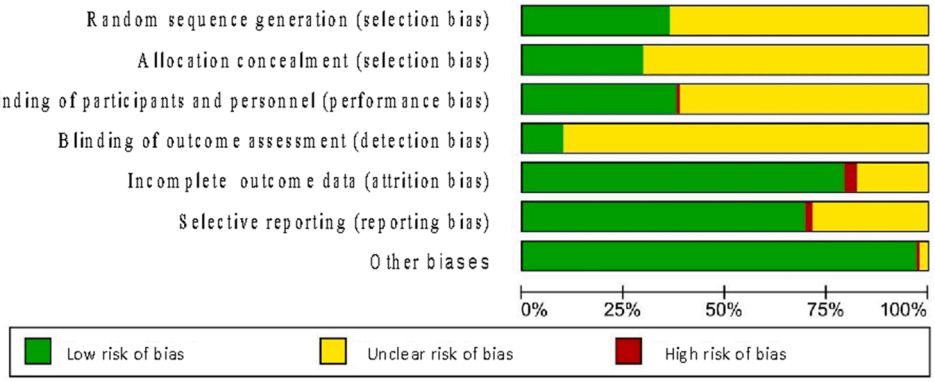

Fig. 2. Risk of bias assessment.

was observed (I^2: 97%; τ^2: 0.0846; p-value: 0% and 95% PI: −0.55 to 0.83), indicating that, possibly, the studies selected had different populations where the placebo effect was experienced differently. The follow-up time shows a behavior pattern with a greater increase in HbA1c in studies lasting less than 24 weeks (Fig. 4). An association between the oral route administration of the placebo with higher HbA1c levels (Fig. 4) was observed, [0.15 (95% CI: 0.07–0.23), p-value: 0.0143], a difference not observed in placebo administered parenterally [− 0.07 (95% CI: −0.23; 0.09), p-value> 0.05].

Metaregression (Fig. 5) shows a significant linear decreasing ($p = 0.01$) in the association between placebo and HbA1c considering the year of publication (i.e., less HbA1c elevation by placebo in 2018, more HbA1c elevation by placebo in 1988). This association can be better interpreted based on the estimates (Fig. 6) presented by year of publication and duration of therapy. For example, it is estimated that the average increase in HbA1c was 1.67% (95% CI: 1.26 – 2.08) in 1988 when study duration was higher than 24 weeks and that, by a linear trend, it decreased to 1.13% (95% CI: 0.97 – 1.29) in 2018. Moreover, the PI shows the estimated variation in the increase in HbA1c between the different populations. It is observed that the predicted increase in HbA1c in studies with duration of more than24 weeks was 1.67 (95% PI: 0.67; 2.66) and decreased to 1.13 (95% PI: 0.50; 1.76).

Sensitivity analyses performed did not change the results (Supplementary Material D).

4. Discussion

This systematic review aimed to identify the magnitude of the possible placebo effect in people with type 2 diabetes who participated in clinical trials of antidiabetic agents compared to placebo. Our hypothesis was that these patients would experience the placebo effect at some level, however, this was not shown. Patients with diabetes who participated in those trials had higher and not lower HbA1c levels, as expected, when used placebo and not the active drug. The literature suggests several other health conditions showing not only the experience of the placebo effect, but also an increasing pattern over time [7, 12].

This meta-analysis did not demonstrate a reduction of HbA1c in response to placebo; on the other hand, it showed an average increase of 0.14% of HbA1c. This result may indicate that the placebo effect may vary according to the disease. Some studies report that placebo improves symptomatic manifestations of diseases, but does not alter the pathophysiology of the disease, as for example in cases of cancer, in which the placebo does not reduce tumor size, but may reduce symptoms and side effects such as nausea and fatigue [13].

Our results go in the opposite direction of those of Guo et al. (2018) who described significant reductions of HbA1c with the use of placebo vs. sulfonylurea (−0.683%), placebo vs. DPP4 inhibitors (−0.193%), and placebo vs. SGLT2 inhibitors (−0.230%) in a white population. In an Asian population, the use of placebo resulted in significant decreases of HbA1c in trials that used DPP4 inhibitors (−0.162%) and GLP-1 agonist receptors (−0.269%). Moreover, placebo reduced body weight significantly in these patients. However, the above clinical trials evaluated antidiabetic agents as compared with placebo and another active treatment. This is especially important, since the effect assigned to placebo was not really caused by a placebo effect, but indeed by the active treatment of the “placebo arm.” Our systematic review excluded studies with active agents as compared to the antidiabetic evaluated, thus, we indicate that the information provided is more accurate.

Our meta-analysis also identified high heterogeneity among the evaluated trials, suggesting that there were distinct populations among the studies and that their responses to placebo were also different, some experiencing an increase and others a reduction in HbA1c in response to placebo. To clarify whether there was any pattern of behavior among these different populations, we conducted subgroup analyses. Although placebos are essential for accurate evaluation of new drugs, placebo composition is frequently not described and varies from inert or active substances, which may hamper interpretation of some trial results [14].

When analyzing the relationship between the studies follow-up time and the response to placebo, we observed a significant difference between groups, although we still cannot identify this difference. In contrast with previous evidence [7], the follow-up time may influence HbA1c response to placebo; however, further studies are necessary to better understand this influence. The follow-up factor may be related to the researchers’ care relationship with patients: more time receiving health care from researchers can motivate and generate positive expectations. An approach focused on care and empathy is responsible for psychosocial and biological adaptations related to the placebo effect [15]. Similarly, it can be expected that when the relationship does not develop positively over time, it can generate negative expectations, possibly causing the nocebo effect. Situations in clinical practice demonstrate that patients with colds, for instance, reported more severe symptoms with longer duration when they do not perceive empathy by their health care professionals [16].

As the response to placebo is a complex phenomenon with many variables [13], analyses regarding the pharmaceutical form and the route of administration were also conducted. In other health situations, a more invasive intervention had a more pronounced placebo effect [11, 12]. In our review, there were differences between oral and parenteral routes (p-value: 0.0143), with less invasive routes presenting a tendency for raising HbA1c by placebo. Since only few studies had interventions with parenteral administration in this review, further studies are necessary to analyze better this behavior. The response to placebo treatment was related to its active comparator, with injectable placebo GLP-1ra showing a relevant response on weight, whereas oral placebo DPP4i showing no significant response [17].

Headache, anxiety [5], Parkinson’s disease [18], and post-surgical and neuropathic pain [5,12] are examples of health conditions that

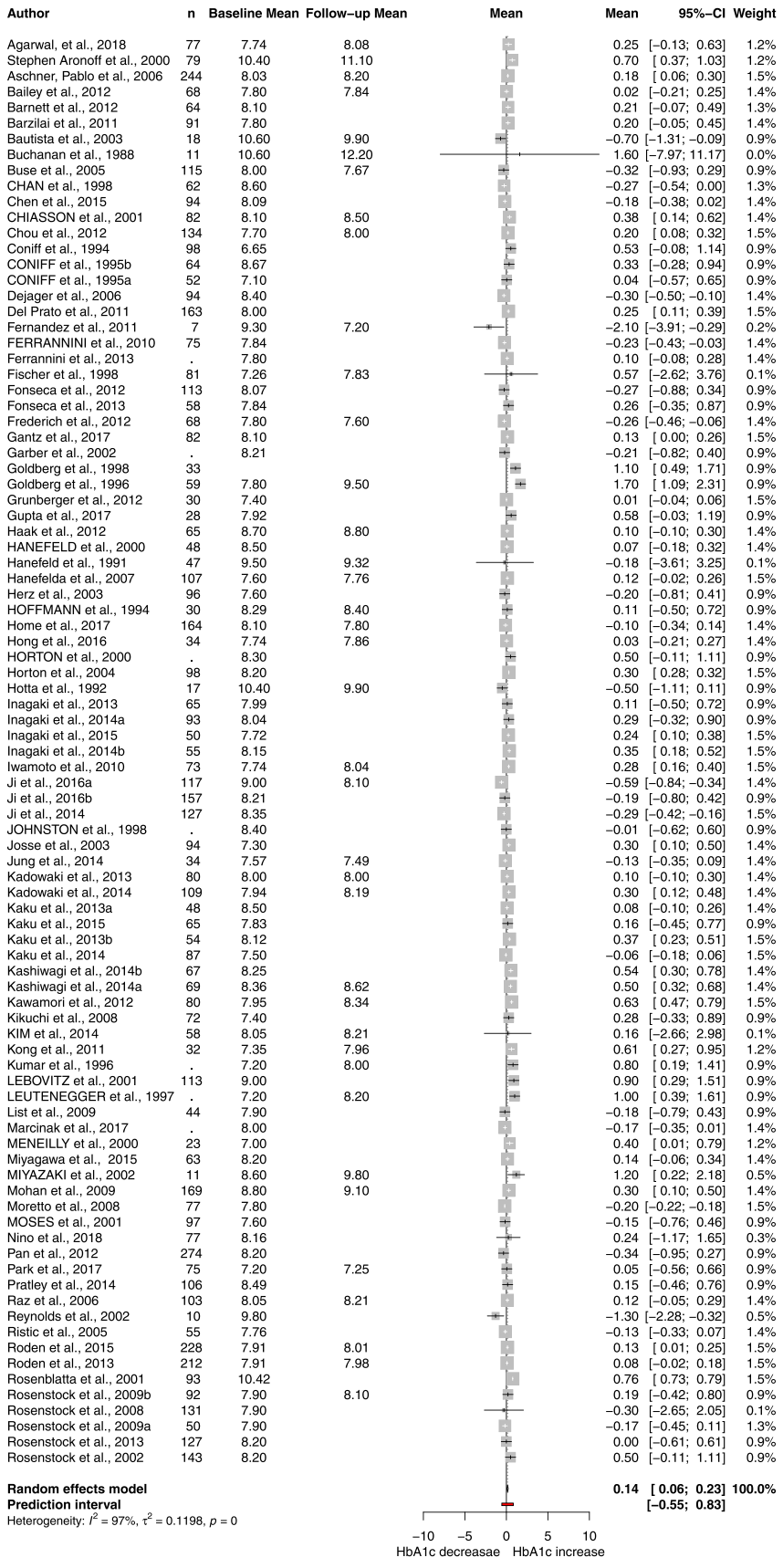

Fig. 3. Placebo effect on HbA1c changes.

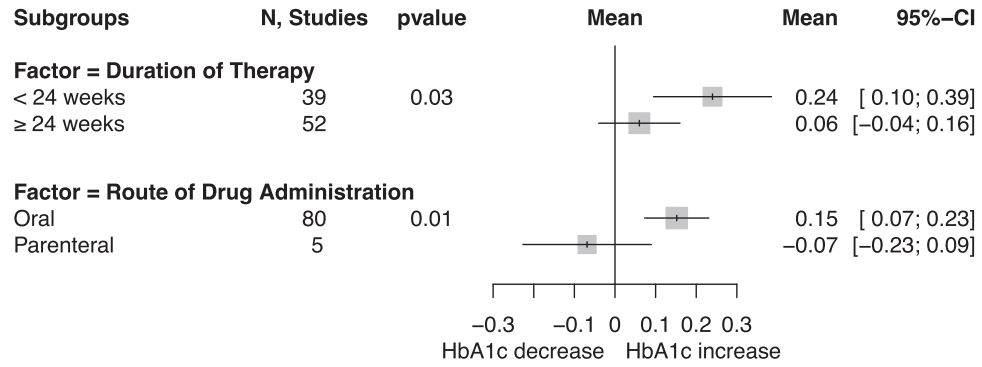

Fig. 4. Changes in HbA1c for individual studies included in the placebo group before vs. after intervention in patients with type 2 diabetes according to follow-up time and route of administration (oral or parenteral). CI: confidence interval.

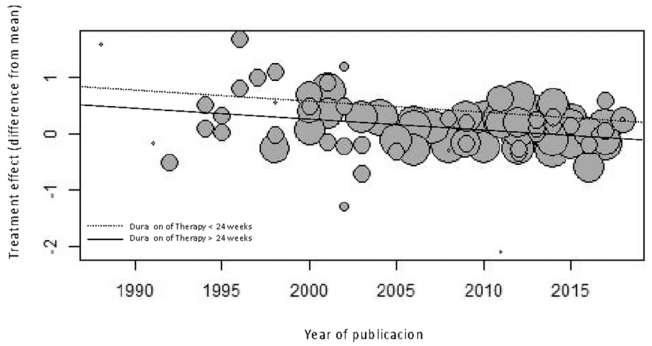

Fig. 5. Meta-regression by year of publication and time of follow-up.

showed increased response to placebo over the years. Although we already have evidence suggesting the same pattern in type 2 diabetes [7, 8], data are scarce. The sub-analysis on the year of publication does not corroborate this previous evidence, since over time the higher HbA1c response to placebo decreased (p-value: 0.01), with a total reduction of 0.5% in HbA1c from the first to the last year of publication of the analyzed articles. However, it was also shown that the reductions in HbA1c - although clinically important - are still positive, since the average increased less over time.

The possible increasing response to placebo over time can be explained by the improvement in the design and execution of RCTs [6], to the increase in advertising the involved drugs, and to the length of follow-up of clinical trials [12]. From the year 2000 onwards, the number of clinical trials increased considerably worldwide compared to previous decades [19], and, simultaneously, research received more investments, reaching diverse and larger populations. Moreover, regulatory factors were also intensified at major research sites, outlining good practices involving research with human beings and improving the performance of trials, such as the 2001/20/CE and 2003/94/CE directives in Europe, the International Harmonization Conference to align centers in the European Union, Japan, and the United States [19], and the Consolidated Standards of Reporting Trials which encompasses several initiatives developed by the CONSORT Group to improve quality of trials [20].

Economic, regulatory, and cultural factors seek to indicate assumptions about how the passing of the years has increased the placebo effect in RCTs. We can also assume greater visibility of the patients' individual characteristics, such as the hope of improvement, conditioning, and their personal preferences. A study [21] evaluating anticipation and experience of pain showed that when the participants were informed that they would receive the analgesic ointment before a pain stimulus, areas of their brains linked to the perception of pain had less activity on magnetic resonance imaging, and patients described feeling pain relief. If the same patients received the opposite information suggesting the ointment did not have an active substance, the same areas showed more activity; these responses differed even though patients received similar placebo ointment applied to their skin. This suggests that expectation of a cure or improvement is critical for the response to the placebo. Likewise, conditioning may increase response to placebo. Trials for testing placebo in analgesia have shown that the expectation of pain relief is so complex that even interaction with neurochemical factors, generating a specific analgesic effect, can be present. Moreover, the learning capacity associated with the response to placebo, where specific subsystems conditioned to receiving the analgesic, activated this learning when receiving a placebo and triggered the analgesia. Recently, specialized entities such as the American Diabetes Association and the European Association for Diabetes Studies have come to value more subjective parameters in the treatment of type 2 diabetes, going beyond the standardized goals and recommending actions that place the patient in the center of the care. The focus is now on a care model that includes and respects the patients' preferences and needs, leading to faster clinical improvement and satisfaction of the patient and the health team [22].

In the two existing systematic reviews in the literature, the lack of description of the methodological quality of the included studies limits the interpretation of the results. According to our findings, several articles were published with an uncertain risk of bias, demanding criticism on our evaluation process. Moreover, while HbA1c is the standard method for long-term glycemic control in patients with diabetes, there are different methods for measurement of HbA1c and not all laboratories use the reference method [high-performance liquid chromatography (HPLC)]. Furthermore, the amount of missing data, as well as the language restrictions -which included only English, Portuguese, and Spanish - are both limiting factors.

Another important factor that we should mention is the choice of clinical study designs involving placebo. A placebo study conducted by Cochrane [23] revealed that the best choice to verify this effect would be to use studies with three arms; however, due to the difficulty of finding studies with this design and without a co-treatment in recent years, the group decided on two-arm clinical trials without co-treatments. The limitation of this methodological choice is that the effect of the placebo intervention could not be distinguished from the natural course of the disease: progressive beta-cell failure is expected, and thus, a worst metabolic control, with HbA1c raise. Moreover, factors such as regression to the mean could be operating. Understanding these questions would help the clinician in providing a treatment regimen that considers the various stages of diabetes, an important contribution of the present study.

In conclusion, the expected placebo effect of HbA1c reduction was not found; instead, higher HbA1c levels were observed in the control groups, although this effect was reduced over the years. It was also possible to identify that the form and route of administration influence the response to the placebo, with higher HbA1c levels when using the

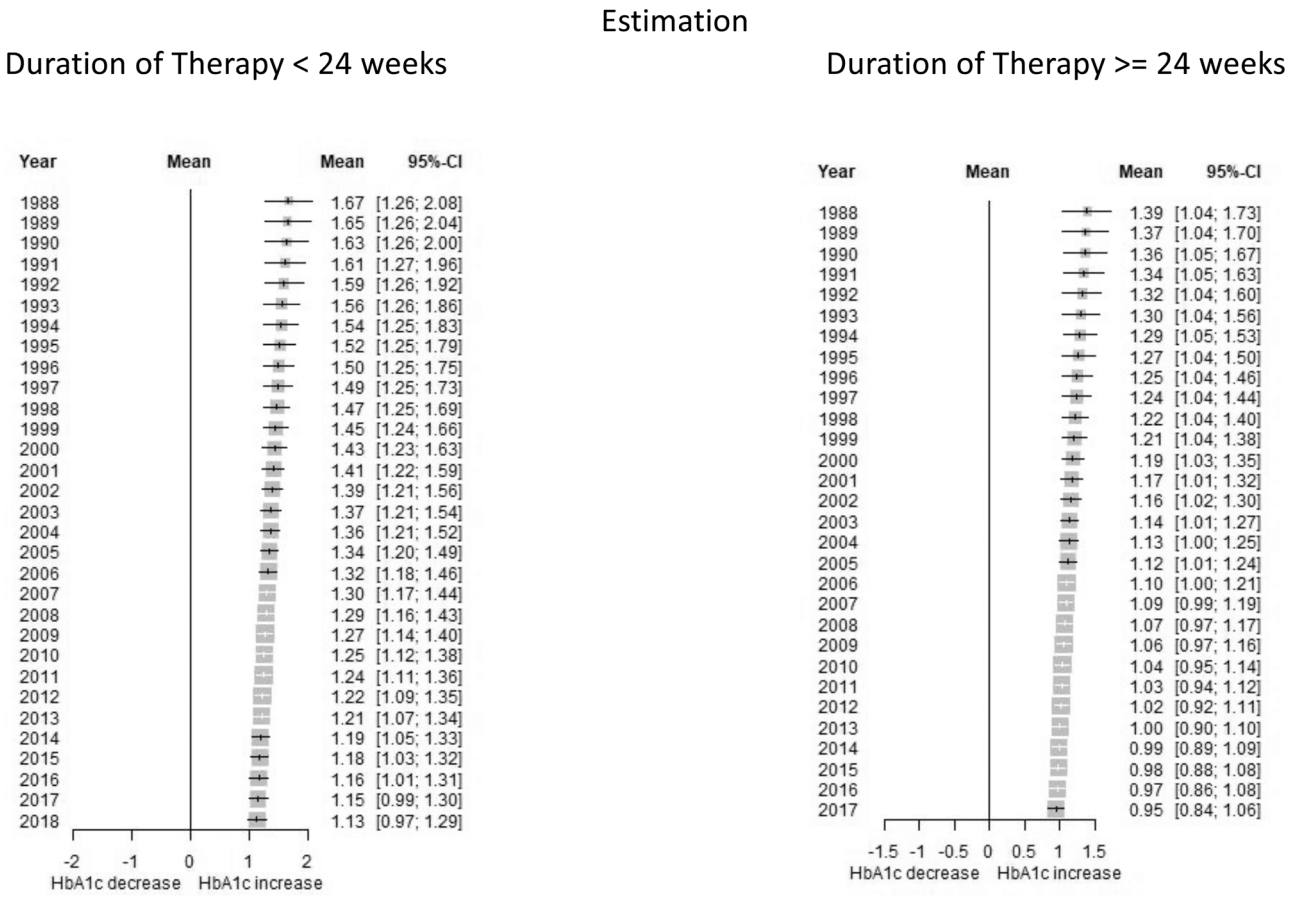

Fig. 6. Estimates presented by year of publication and study duration.

oral route. Finally, follow-up time of the studies seems to be an important factor influencing the response to placebo in patients with type 2 diabetes.

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Conflict of interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pcd.2023.03.006.

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