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Evaluation of the Effects of Nanoparticles in the Treatment of Diabetes Mellitus: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: Due to the importance of the issue in the treatment and prevention of diabetes mellitus, in the present study, it is decided to investigate the role of nanoparticles in the treatment or prevention of the development of diabetes mellitus. The aim of the present study was to evaluate the effects of nanoparticles in the treatment of diabetes mellitus.

Material and methods: The present study is a systematic review and meta-analysis based on PRISMA 2020 Checklist. Databases of PubMed, Scopus, Web of Science, EBSCO, ISI Web of knowledge, and Embase were searched for systematic literature until 20 November 2022. A 95% confidence interval for mean differences with the random effect model and REML method were calculated. Meta-analysis was performed using Stata/MP v.17 software.

Results: In the initial review, duplicate studies were eliminated, abstracts of 219 studies were reviewed, and two authors reviewed the full text of 184 studies. Finally, nine studies were selected. The mean differences in Fasting blood sugar between the silver nanoparticles group and zinc oxide nanoparticles vs. group was -209.92 (MD: -209.92 95% CI; -272.56, -147.28; p=0.00) and -1.58 (MD: -1.58 95% CI; -2.38, -0.78; p=0.00), respectively.

Conclusions: Based on the present meta-analysis, administering silver nanoparticles and zinc oxide nanoparticles in animal models can have antidiabetic effects and reduce fasting blood sugar levels.

1. Introduction

Diabetes is a complex metabolic disorder caused by a lack of insulin secretion, defects in insulin function, or insensitivity of cells to insulin.[1] In fact, in diabetes, there is a disturbance in the transfer of glucose to the cell, the blood glucose level increases, and hyperglycemia occurs, which in turn causes glycosylation of body proteins and leads to secondary complications in the eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy) and arteries of the body.[2] Type 2 diabetes is a heterogenetic disorder resulting from the interaction of genetic and environmental factors due to insulin deficiency and insulin resistance. The liver plays an important role in maintaining normal blood glucose levels. Liver damage caused by insulin resistance may contribute to the development of type 2 diabetes. In this way, type 2 diabetes and disturbances in liver fat metabolism can lead to insulin resistance, which aggravates diabetes, increases liver fat deposits, and ultimately leads to liver damage and increased liver enzymes.[3] The mechanism of diabetes mellitus is based on insulin deficiency and insulin resistance, which can lead to certain complications such as micro and macrovascular disorders.[4] Studies have shown that oral medications, diet modification, exercise, and insulin therapy can reduce disease processes.[5] Evidence shows that non-treatment or long-term use of several anti-diabetes Mellitus drugs in preventing diabetes mellitus complications can lead to hospitalization and death. Therefore, it is important to explore different treatment options that reduce complications.[6] During the last decade, studies have shown promising results of nanoparticles in the treatment of diabetes mellitus. A study has shown that in an animal model, the use of zinc oxide nanoparticles can have anti-oxidative and anti-hyperglycemic effects.[7] Another study also showed that gold, silver, selenium, and zinc oxide nanoparticles positively affect the treatment of diabetes mellitus.[8]

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Silver nanoparticles are among the most widely used nanoparticles in that studies have reported antidiabetic results.[9] According to the available literature, there are different methods for producing silver nanoparticles.[10, 11] Recent studies have shown that silver nanoparticles effectively treat diabetes mellitus.[6] It should be mentioned that most of the studies are animal; In a study with an animal model, it was observed that silver nanoparticles have antidiabetic activity by increasing the activation of the glucose transporter-2 gene, liver glucokinase activity, and serum insulin level.[12] Also, the size of nanoparticles is one of the factors that make their use and disposal easier.[13] Some studies have also shown that the administration of nanoparticles may have possible toxic effects because their distribution in several organs, including the liver, kidneys, lungs, and brain, has been reported.[14, 15] Considering the conflicting findings of the studies and the lack of consensus in the results, and due to the importance of the issue in the treatment and prevention of diabetes mellitus, in the present study, it is decided to investigate the role of nanoparticles in the treatment or prevention of the development of diabetes mellitus. The present study aimed to evaluate the effects of nanoparticles in treating diabetes mellitus.

2. Material and methods

Search strategy

The present study is a systematic review and meta-analysis based on the PRISMA 2020 Checklist.[16] All international databases, PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase using keywords related to the objectives of the study until 20 November 2022 were reviewed. Google Scholar search engine was also used to find related articles. MeSH keywords:

((((((((((("Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Mellitus, Lipoatrophic"[Mesh] OR "Diabetes Mellitus, Experimental"[Mesh]) OR ("Diabetes Mellitus/prevention and control"[Mesh] OR "Diabetes Mellitus/statistics and numerical data"[Mesh])) AND "Nanoparticles"[Mesh])) AND "Silver"[Mesh]) OR "Zinc Oxide"[Mesh]) OR "Gold"[Mesh]) OR "Selenium"[Mesh]) OR "ceric oxide" [Supplementary Concept]) AND "Blood Glucose"[Mesh]) AND "Pregnancy-Associated Plasma Protein-A"[Mesh]) AND "Lipids"[Mesh].

Data items, data collection, and selection process

Using a checklist that included the author's name, year of publication, Species and sex, sample size, Drugs, Type of nanoparticle, and Characteristics of nanoparticles were extracted from the studies. All articles were selected based on the inclusion criteria, two reviewers independently screened each record, and each report was retrieved.

Eligibility criteria

Inclusion criteria: Articles published in English, animal studies, and Access to the full text.

Exclusion criteria: in-vitro, case studies, case reports, review papers, and letters to editors.

Study risk of bias assessment

In the current study, only animal studies were included, and the quality of these studies was evaluated using the CAMARADES criteria(17). The scores of this tool are between 0 and 10, and a higher score (⩾4) showed a higher quality of the study.

Data analysis

Data analysis was performed using STATA/MP. V17 software. A 95% confidence interval for mean differences with the random effect model and REML method were calculated. Random effects were used to deal with potential heterogeneity, and I2 showed heterogeneity. I2 values less than 50% indicate low heterogeneity, and above 50% indicate moderate to high heterogeneity.

3. Results

Study selection

In the initial search, 219 articles related to the keywords were found. Of these, 17 studies were Duplicate records, 8 articles were removed due to Records marked as ineligible by automation tools, and 10 articles were records removed for other reasons. In the next step, abstracts of 184 articles were reviewed, and finally, 101 articles were excluded from the research according to the exclusion criteria. The full text of 83 articles was reviewed, and according to the inclusion criteria, 46 studies were excluded, and finally, 9 studies were selected (Fig. 1).

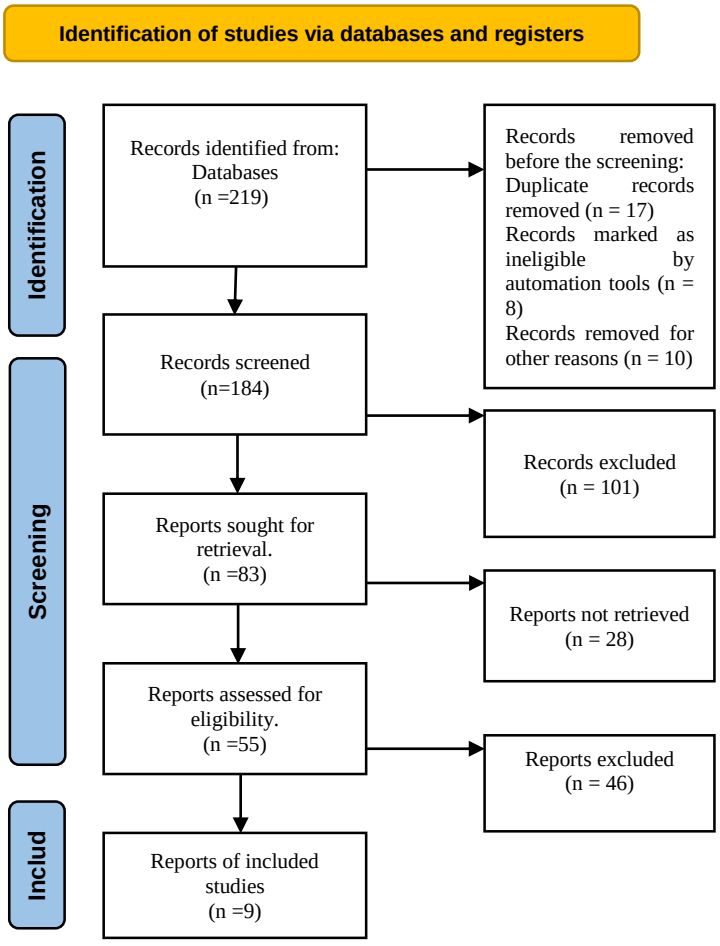

Fig. 1. PRISMA 2020 Checklist.[16]

Study characteristics

The data extracted from the studies are reported in Table 1. The intervention and control groups' sample sizes were 171 and 120, respectively, a total of 291. Wistar albino rats, Sprague–Dawley rats, Albino mice, Wistar rats, and Albino rats were used to perform the experiments of included studies. Eight studies were conducted on rat species, and one study worked

on mice. Eight studies tested the male gender, and one study used the female gender. Six studies were treated with the silver nanoparticle; one study used Zinc oxide nanoparticles along with silver nanoparticles, and two studies were treated with Zinc oxide nanoparticles.

Table 1. Data extraction from included studies.

No	Study. Years	Sample Size		Species	Sex	Drugs/Dose (mg/kg)	Nanoparticle				
		Intervention	Control				Type	Size	Shape	Time (days)	Particle (mg/kg)
1	Haq et al., 2022 [18]	20	5	Wistar rats	Male	Glibenclamide/0.5	Ag-NPs	NR	NR	NR	NR
2	Olojede et al., 2022 [19]	18	18	Sprague–Dawley rat	Male	Tenofovir disoproxil fumarate/300	Ag-NPs	NR	NR	NR	NR
3	Gadoa et al., 2022 [20]	48	12	albino rats	Male	Pyrazolopyrimidine/5	ZnONPs	NR	NR	30 d	65
4	Virgen-Ortiz et al., 2020 [21]	48	48	Wistar rats	Male	Streptozotocin and nicotinamide	ZnONPs	NR	NR	5 h	NR
5	Prabhu et al., 2018 [22]	6	6	albino Wistar rats	Female	Streptozotocin/ 50	Ag-NPs	20, 80 and 110	NR	28 d	NR
6	Sengottaiyan et al., 2016 [9]	5	5	Wistar albino rats	Male	Alloxan/ 200	Ag-NPs	4-25	Spherical	21 d	10
7	Ansari et al., 2015[23]	8	8	Albino mice	Male	NR	Ag-NPs	181	NR	14 d	NR
8	virgen-Ortiz et al., 2015 [6]	8	8	Wistar rats	Male	Streptozotocin/ 150	Ag-NPs	9	Spherical	30 d	NR
9	Alkaladi et al., 2014 [12]	10	10	Albino rats	Male	Streptozotocin/ 100	ZnONPs, Ag-NPs	20	NR	30	10

Ag-NPs: silver nanoparticle; NR: not reported; Ag-NPs: Zinc oxide nanoparticles.

Fasting Blood Sugar

The mean differences in Fasting blood sugar between the silver nanoparticles group and control group was -209.92 (MD: -209.92 95% CI; -272.56, -147.28; p=0.00) with high heterogeneity (I^2=98.95). A significant difference was observed in terms of the mean difference between the groups (p=0.00) (Fig. 2).

The mean difference in Fasting blood sugar between the Zinc oxide nanoparticles group and the control group was -1.58 (MD: -1.58 95% CI; -2.38, -0.78; p=0.00) with low heterogeneity (I^2=0). A significant difference was observed in terms of the mean difference between the groups (p=0.00) (Fig. 3).

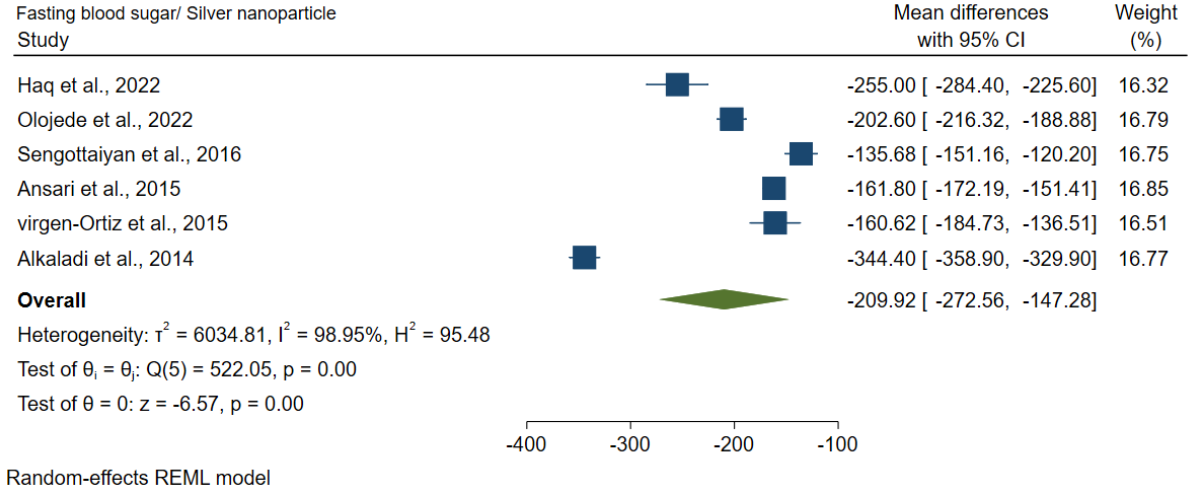

Fig. 2. The Forest plot showed mean differences between silver nanoparticles and the control group.

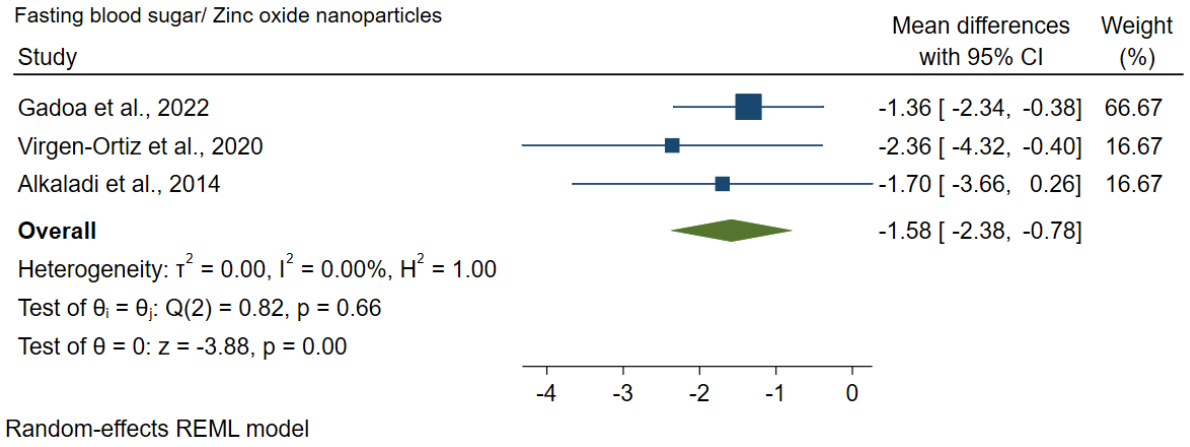

Fig. 3. The forest plot showed mean differences between Zinc oxide nanoparticles and the control group.

4. Discussion

In the present study, the effects of administering silver nanoparticles and zinc oxide nanoparticles on fasting blood sugar in diabetic animals were investigated. Meta-analysis showed that administering silver nanoparticles and zinc oxide nanoparticles positively affects fasting blood sugar in diabetic animals. Previous studies investigated the antibacterial, antioxidant, and antiplatelet properties of silver and zinc oxide nanoparticles. Most available studies are based on animal models, and in-vitro and RCT studies were not found. It is suggested to be carried out in future studies of toxicity and zinc oxide nanoparticles.[24, 25] Nanoparticles can be introduced into human tissues through several routes.[26] The findings of selected studies and meta-analysis showed that silver nanoparticles and zinc oxide nanoparticles could significantly reduce fasting blood sugar. Studies have shown that silver nanoparticles have antidiabetic activity.[22, 27] Also, studies have shown that after treatment with nanoparticles, a significant increase in the level and cholesterol level of Alkaline Phosphatase is observed.[28, 29] A study also showed that there is a significant increase in high-density lipoprotein, a study also showed that there is a significant decrease in cholesterol and triglyceride levels. According to research findings, silver nanoparticles can increase serum insulin.[6, 12] Also, using silver nanoparticles in the dose can cause histopathological apoptotic cells.[30] Recent studies have shown that silver nanoparticles can induce cytotoxicity; these findings should be further investigated to provide strong evidence. In the present study, the heterogeneity between the studies in investigating the effects of silver nanoparticles was high; therefore, citing the findings of the present study should be done with caution. Also, few studies were found investigating the effects of zinc oxide nanoparticles; more is needed to confirm the current evidence. The present study had some limitations, one of which was that animal models were used instead of human studies in the selected studies. However, human studies related to the purpose of the study were not found, or there are very few.

5. Conclusion

According to the present meta-analysis, administering silver nanoparticles and zinc oxide nanoparticles in animal models can have antidiabetic effects and reduce fasting blood sugar levels. These findings show that these treatments can be used in the future; However, more studies are needed to confirm the present evidence.

Conflict of Interest

The authors declared that there is no conflict of interest.

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