



EFFECTIVENESS OF ZINC SUPPLEMENTATION FOR TYPE II DIABETES PREVENTION: A SYSTEMATIC REVIEW

EFEKTIVITAS SUPLEMENTASI ZINK UNTUK PENCEGAHAN DIABETES TIPE II: TINJAUAN SISTEMATIS

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ABSTRACT

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Background: The incidence of prediabetes is predicted to continue to increase. Approximately 25% of prediabetes patients develop type 2 diabetes mellitus (T2DM) within 3–5 years. Zinc is known to have a role in the synthesis, storage, secretion, and action of the insulin hormone.

Purpose: The aim of the study is to know about the impact of zinc supplementation in type 2 diabetes mellitus (DM) prevention.

Methods: A systematic literature search was performed using the PubMed, Cochrane, and EBSCOHost search engines. The inclusion study includes systematic review and metaanalysis of randomized clinical trials study and randomized clinical study, and we only include the research of the last 10 years.

Results: Three RCTs were selected from 175 articles to undergo a critical review with a total of 353 patients with a duration of 6-12 months (level of evidence II-III). The incidence of T2DM in the intervention group decreased significantly (OR: 0.37 [95% CI 0.7-0.8]; RR: 0.44; ARR: 14% [95% CI 3.5-24.5%]; NNT: 7.14 [4-29]) in one study. Zinc supplementation significantly reduced Fasting Blood Sugar (FBS) in two studies (mean difference -17.3 and -5.76) and oral glucose tolerance test (OGTT) in one study (MD -22.6).

Conclusion: Administration of zinc in prediabetes patients to prevent the development of T2DM still requires further study with a larger sample, longer duration, and control variables by design and statistics.

Keywords: Glycemic Control; Prediabetes; Prevention of Type 2 Diabetes Mellitus; Supplementation; Zinc

ABSTRAK

Pendahuluan: Angka kejadian prediabetes diprediksi akan terus meningkat. Sekitar 25% pasien prediabetes berkembang menjadi diabetes mellitus tipe 2 (T2DM) dalam waktu 3-5 tahun. Zink diketahui memiliki peran dalam sintesis, penyimpanan, sekresi, dan aksi hormon insulin.

Tujuan: Penelitian ini bertujuan untuk mengetahui dampak suplementasi zink dalam pencegahan diabetes mellitus (DM) tipe 2.

Metode: Sebuah pencarian literatur sistematis dilakukan dengan menggunakan mesin pencari PubMed, Cochrane, dan EBSCOHost. Studi inklusi mencakup tinjauan sistematis dan meta-analisis dari studi uji klinis acak dan studi klinis acak, dan peneliti hanya memasukkan penelitian 10 tahun terakhir.



Hasil: Tiga RCT dipilih dari 175 artikel untuk menjalani tinjauan kritis dengan total 353 pasien dengan durasi 6-12 bulan (tingkat bukti II-III). Insiden T2DM pada kelompok intervensi menurun secara signifikan (OR: 0,37 [95% CI 0,7-0,8]; RR: 0,44; ARR: 14% [95% CI 3,5-24,5%]; NNT: 7,14 [4-29]) dalam satu studi. Suplementasi zink secara signifikan mengurangi Gula Darah Puasa (GDP) dalam dua penelitian (perbedaan rata-rata -17,3 dan -5,76) dan tes toleransi glukosa oral (TTGO) dalam satu penelitian (MD -22,6).

Kesimpulan: Pemberian zink pada pasien prediabetes untuk mencegah berkembangnya T2DM masih memerlukan penelitian lebih lanjut dengan sampel yang lebih besar, durasi yang lebih lama, dan variabel kontrol berdasarkan design dan statistik.

Kata kunci: Kontrol Glikemik; Pencegahan Diabetes Mellitus tipe 2; Prediabetes; Suplementasi; Zink

BACKGROUND

Prediabetes is a condition where blood sugar exceeds the normal criteria but does not meet the criteria for Diabetes Mellitus (DM). The diagnosis of prediabetes is made on conditions of fasting blood glucose 100-125 mg/dL or impaired fasting blood glucose, plasma glucose 2 hours after Oral Glucose Tolerance Test (OGTT) 140-199 mg/dL or Impaired Glucose Tolerance (IGT), or HbA1c value of 5.7- 6.4%. Fasting Blood Sugar Test (FBST) and IGT conditions can also occur simultaneously.¹

The prevalence of IGT in the world according to the International Diabetes Federation (IDF) is estimated to reach 7.5% (374 million) in 2019 and is predicted to increase to 8% (454 million) in 2030 and 8.6% (548 million) in 2045.² In the United States, one in three adults ($\pm 33.9\%$) is diagnosed with prediabetes and 90% are unaware that they have the condition.³ According to the results issued by Riskesdas 2018, the proportion of Indonesia's population with FBST reached 13.1% and the proportion of the Indonesian population with IGT reached 19.7%.⁴ Prediabetes can progress to type 2 DM in 70% of cases and this process occurs within 3-5 years in 25% of cases. Prediabetes and diabetes conditions have major implications for the quality of life of patients and also the economic burden of a health system. Compared to the population with normal blood glucose, prediabetes patients have a higher risk of developing coronary heart disease, stroke, and chronic kidney disease.⁵ Diabetes and prediabetes also accounted for 2.1% (US\$ 403.9 billion) of the total gross domestic product in the United States in 2017.³ The difference in total costs for prediabetic and diabetic patients is estimated at \$7,000/year.⁶ Therefore, before prediabetes develops into diabetes, non-pharmacological and pharmacological interventions need to be carried out.

Lifestyle modification can reduce the risk of progression of prediabetes to diabetes for 10 years.⁷ Studies have shown that diabetes is associated with micronutrient deficiencies such as

magnesium, vitamin D, and zinc.⁸⁻¹⁰ Zinc is a mineral with an important role in the synthesis, storage, secretion, and action of the insulin hormone. One of the zinc levels in the body are concentrated in the Langerhans cells of the pancreas. In beta cells, zinc will form a complex with insulin and form an insulin-zinc-hexamer. This structure can stabilize insulin structure and facilitate insulin storage in pancreatic beta-cell granules. When exocytosis occurs in the extracellular space in the pancreas, the hexameric structure dissociates into zinc ions and the active monomer of insulin. These zinc ions can then work in a paracrine manner as a regulator of glucagon secretion in pancreatic alpha cells.¹⁰

As a signaling molecule, zinc plays a role in glucose translocation into cells. In mouse adipocytes, zinc can activate cAMP phosphodiesterase and mobilize glucose transporters to the cell plasma membrane.¹⁰ Additionally, zinc can inhibit protein tyrosine phosphatase 1B (PTP1B). PTP1B is a negative regulator of insulin and leptin signal transduction pathways. If PTP1B is inhibited by zinc, activation of the signal transduction pathway by insulin may last longer. Zinc is also able to modulate glycogen synthesis, lipogenesis, and is able to inhibit gluconeogenesis and lipolysis. It is proved that the addition of zinc to insulin solutions can prolong insulin action.¹¹ Epidemiological studies have shown an association between low zinc levels and hyperglycemia.¹² Meta-analysis has also shown significant differences in levels of FBS, HbA1c total cholesterol, and LDL in diabetic patients who received zinc supplementation.¹³

The results of these studies bring zinc as a candidate for pharmacological therapy that is useful for prediabetes patients. Therefore, this systematic review was conducted to assess the medical evidence from currently available translational studies regarding zinc effectiveness in the prevention of the progression of prediabetes.



PICO Formulation

Based on the explanation which was mentioned in the background, the PICO formulation proposed in this systematic review is "Can zinc supplementation prevent type 2 diabetes mellitus."

Table 1. PICO Formulation

Patient/ Problem (P)	Intervention (I)	Comparison (C)	Outcome (O)
Prediabetes patient aged 18 years old	Zinc	Placebo	The incidence of type 2 DM
Clinical question types	Intervention		
Study design	A meta-analysis, systematic review, randomized controlled trial (RCT)		

RESEARCH METHOD

Search Strategy

A literature search was conducted on September 16 through 3 search engines: 1) PubMed, 2) Cochrane Library, and 3) EBSCOhost. The search strategy and the number of articles selected for each database are elaborated in Table 2.

Table 2. Literature Search Strategy

Databases	Search Strategy	Finding
Pubmed	((Zinc[MeSH Terms]) OR (zinc supplementation)) AND ("Diabetes Mellitus, Type 2/blood"[Mesh] OR "Diabetes Mellitus, Type 2/diagnosis" [Mesh] OR "Diabetes Mellitus, Type 2/prevention and control" [Mesh]) AND ((prediabetic state [MeSH Terms]) OR (Impaired glucose tolerance) OR (impaired fasting glucose) OR (impaired glucose control) OR (impaired glucose homeostasis) OR (impaired glucose regulation) OR (prediabetes) OR (pre-diabetes))	35
Cochrane Library	("zinc" or "zinc supplementation") and ("diabetes type 2" or "diabetes mellitus type 2" or "diabetes 2" or "T2D" or "T2DM") and ("prediabetes" or "impaired glucose tolerance" or "impaired fasting glucose" or "prediabetic state" or "early stage diabetes" or "borderline diabetes")	27

EBSCOhost	(zinc OR zinc supplement) AND (diabetes mellitus type 2 or diabetes mellitus type 2 or diabetes 2 or T2D or T2DM) AND (prediabetic state OR Prediabetes OR Pre-diabetes OR Impaired glucose tolerance OR impaired fasting glucose OR impaired glucose control OR impaired glucose homeostasis OR impaired glucose regulation)	40
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Eligibility Criteria

This literature applied inclusion and exclusion criteria for the basis of literature screening, with the following criteria:

Inclusion Criteria:

1. Meta-analysis studies, systematic reviews, or randomized clinical trials
2. Relevant to clinical questions
3. Patient population aged 18 years with prediabetes
4. Subjects were given zinc supplementation
5. There is a placebo group for comparison
6. The study includes the results of diabetes mellitus tests, such as HbA1c, FBS, OGTT, or random blood sugar

Exclusion Criteria:

1. Full text is not available
2. The study is not available in Indonesian and English
3. The study has not been completed

Article Selection

Based on a search using predefined keywords and databases, 102 articles were obtained. There were 35 articles from PubMed, 27 articles from Cochrane, and 40 articles from EBSCOhost. There were 18 articles that were eliminated due to duplication. The next step was conducting the stage 1 screening, specifically titles and abstracts screening based on eligibility criteria. There were 74 articles omitted due to discrepancies in population, intervention, outcome, study design, and incomplete studies. Next on the order was Full-Text screening which resulted in 10 articles where 6 articles were omitted as there was 1 article with unsuitable clinical questions, 2 articles with unsuitable population, 1 article with unsuitable intervention, 1 article with unsuitable outcome,

and 2 articles were unfinished. At the end of the screening, 3 articles passed the selection (Figure 1).

DISCUSSION

Study Summary

After the screening was conducted, three literatures were obtained with a randomized controlled trial study design. The studies were written by Attia JR in 2022¹⁴, Ranasinghe P in 2017¹⁵, Islam MR in 2016.¹⁶ The characteristics of the selected studies are illustrated in Table 3.

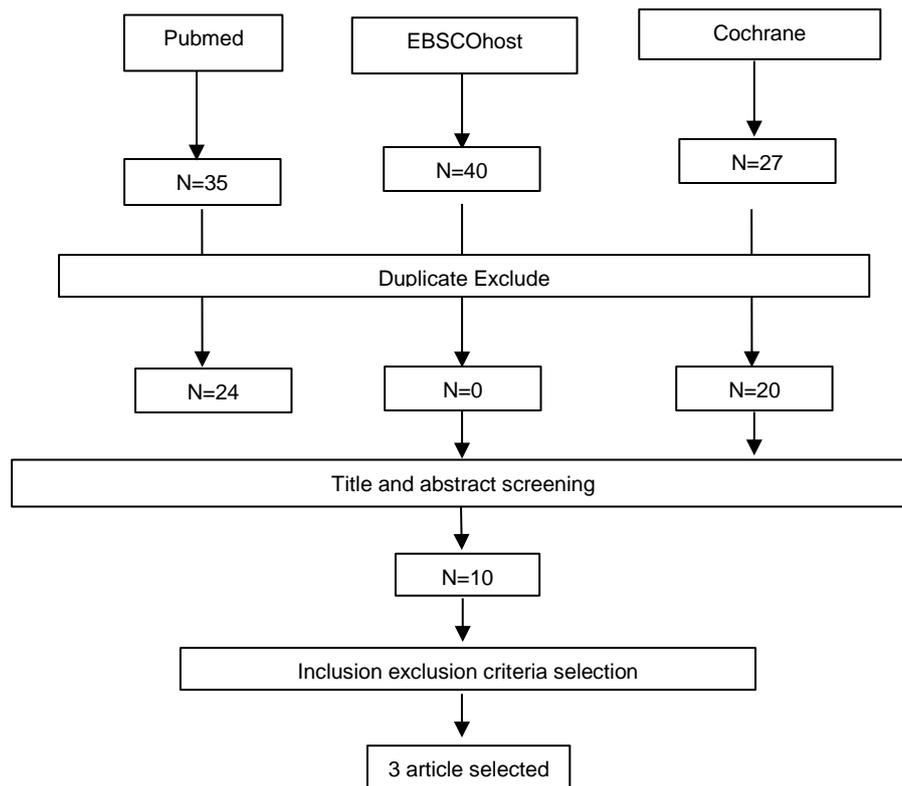


Figure 1. Search Strategy Flowchart

Table 3. Characteristics of Selected Studies

Author, year	Location, duration, number of samples	Intervention	Outcome (related to glycemic control)		Non-glycemic output
			Primary	Secondary	
Attia, 2022	Australian, 12 months, 98	Zinc gluconate 1x30 mg	HbA1c and GDP 12 months	Incidence of T2DM, HbA1c and GDP at 1 and 6 months, HOMA parameters (insulin resistance, insulin sensitivity, beta cell function)	Lipid profile, anthropometry, compliance
Ranasinghe, 2017	Sri Lanka, 12 months, 200	Zinc 1x20 mg	Changes in GDP and 12-month TTGO	Incide of T2DM, HbA1c, serum insulin, insulin resistance	Lipid profile, anthropometry, blood pressure, serum creatinine, liver enzymes, and bilirubin
Islam, 2016	Bangladeshi, 6 months, 55	Zinc sulfate 1x30 mg	Change in GDP 6 months	Incidence of T2DM, HOMA parameters (insulin resistance, insulin sensitivity, function) beta cells)	Lipid profile, serum zinc

T2DM: type 2 diabetes mellitus; FBS: fasting blood sugar; OGTT: oral glucose tolerance test; HOMA: Homeostasis Model Assessment



All studies were double-blind RCTs, with moderate-high quality of evidence (LOE II-III), and were designed to have minimal risk of bias through a series of blinding methods and intention-to-treat analyses, except the study by Ranasinghe et al.,¹⁵ who performed the analysis on the remaining patients in each examination period. Ranasinghe, et al., study¹⁵ also had the highest dropout rate (31%) compared to the other two studies. Each study reported that the baseline characteristics of the subjects, in general, did not differ significantly across various demographic, clinical, and biological (laboratory) parameters. A study conducted by Attia et al.,¹⁴ did not report any significant differences in subject baseline characteristics; Ranasinghe on the variables of LDL, triglycerides, and daily protein intake; and Islam et al.,¹⁶ on monthly income and expenditure variables and lipid profiles. The same treatment for intervention or control subjects in the form of healthy lifestyle modification education which was given routinely either during visits for examinations or through communication channels was also carried out in each study.

The study of Attia et al., found the incidence of T2DM with (OR 1.04; 95% CI 0.2-5.4). In the study of Ranasinghe et al., the incidence of T2DM was found with (OR 3.7; 95% CI 0.7-0.8), RR 0.44; ARR 14% (3.5-24.5%); NNT 7.14 (4-29). Meanwhile, the study of Islam et al., did not include T2DM outcomes.¹⁴⁻¹⁶ While there is a tendency to improve glycemic control parameters, not all studies give similar results. Attia's¹⁴ research on an Australian population did not support the two previous clinical trials (Asian populations: Bangladesh and Sri Lanka) – as she found no significant effect of zinc supplementation on almost all glycemic control parameters (HbA1c, FBS). Only the Ranasinghe study reported the progression of prediabetes to T2DM for further analysis.¹⁵ The risk of progression of prediabetes to T2DM was 63% lower (ARR: 14%, NNT: 7.14). The same study also found the largest decline in FBS. Only Islam et al., showed a significant improvement in beta-cell function.¹⁶

Molecularly, zinc can control plasma glucose concentration in several ways: 1) Catalyst, zinc plays a role in the metabolism of macronutrients such as glucose by stimulating glycolysis and inhibiting gluconeogenesis; 2) A signaling molecule, zinc is involved in the synthesis, storage, secretion, and action of insulin; and 3) Modulator of inflammation through suppression of NADPH oxidase expression which increases GSH expression (antioxidant) or decreases TNF-alpha and IL-6, AP-1, and NF-kB expression.¹⁷ However, in clinical trials, there are still many issues that require further studies.

Diabetes is a complex disease with a long course. Although only 25% of prediabetes patients will be diagnosed with diabetes within 3-5 years, the disease process has occurred over the past 20 years, starting from glucose dysregulation to a significant increase in FBS 10 years before the diagnosis of diabetes.^{5,6,18} Due to the long duration of the disease course, research to see the effect of therapy should be carried out over a longer term, both the intervention period and the follow-up period.

Unfortunately, even though only the Ranasinghe study found a significant proportion of prediabetic patients progressing to T2DM, this study did not perform an intention-to-treat analysis. In addition, there is no information in any of the studies regarding how long the diagnosis of prediabetes has been made. However, it is necessary for subgroup analysis based on the duration of prediabetes.

A study by Karandish et al.,¹⁹ on the zinc and curcumin supplementation effect on the lipid profile of prediabetic patients assessed the duration of prediabetes diagnosis, which was only 2.31 ± 1.37 years. Approximately 25% of patients without intervention are likely to have diabetes over a 12-month period study. Sticking to the 25% progression of prediabetes to diabetes within 3-5 years, this rate is not different from the progression rate found in the Ranasinghe study (placebo group).

Ranasinghe et al.,¹⁵ studies mentioned that the incidence of T2DM in the intervention group decreased significantly (OR: 0.37 [95% CI 0.7-0.8]; RR: 0.44; ARR: 14% [95% CI 3.5-24.5%]; NNT: 7.14 [4-29]). However, the study of Attia et al.,¹⁴ and Ranasinghe et al.,¹⁵ could not illustrate a significant difference in diabetes progression between the intervention and placebo groups. This could be due to a large number of samples being inadequate to determine the effect of disease progression and the high dropout rate in the study. The higher rate of progression in the control group may have occurred as a result of the higher baseline metabolic risk in that group. Meanwhile, the study conducted by Islam et al.,¹⁶ does not include T2DM outcomes but displays an analysis of glycemic control parameters.

The three clinical trials conducted showed that some glycemic control parameters improved in prediabetes patients after zinc supplementation, although the clinical significance remains to be studied. Even two studies showed a significant decrease in FBS, one study that assessed the OGTT showed a significant decrease, and none of the studies showed a significant improvement in HbA1c. Whereas HbA1c is a measure that can describe long-term glycemic control (3 months).



The findings of the Attia study showed that in the Australian (Caucasian) population, there was no significant improvement in FBS and HbA1c which was hypothesized to be related to genetic and lifestyle differences. Zinc is mostly obtained from the consumption of plant products, while Caucasians consume more animal products. These findings must be a concern to provide zinc supplementation in the right population. In addition, a meta-analysis involving 32 studies (1,700 subjects) by Wang showed that zinc supplementation improved glycemic control in patients already diagnosed with T2DM, are Asian (Eastern) population, and were given in doses <30 mg.²⁰

Patients in the cases are according to the population studied in all three clinical trials. Zinc at a dose of 20 mg per day for 12 months can be given, needless to say, while still providing education on lifestyle modification: diet and physical activity. Other laboratory tests must also be carried out, especially the lipid profile which is closely related to dysglycemia and will experience improvement after zinc administration based on existing studies. Supplementation is more likely to have a positive impact considering that the patient also comes from a non-Caucasian race.

The search for therapeutic agents for prediabetes is still a relevant issue considering that the administration of metformin—the only drug which can be given to prediabetic patients according to the ADA recommendations—in prediabetic patients is still much debated.²¹ The three studies in this systematic review can provide an overview of how zinc, although it is a potential therapeutic agent in prediabetes patients given its benefits in terms of improving glycemic control parameters, as well as anthropometry, lipid profile, and inflammatory conditions still has to go through further high-quality research with a longer duration.¹⁷ Moreover, Attia's study mentioned that medication adherence was closely related to improved glycemic control.¹⁴ Although labeling a supplement makes a drug more acceptable to patients, managing prediabetes requires lifestyle modification and awareness of the risks posed by the disease not getting worse.

CONCLUSION

The use of zinc as supplementation in prediabetes patients to suppress the progression or prevent the development of T2DM requires further study. Although it can improve glycemic control, the results between studies are mixed so that zinc administration should be done wisely to the right target to obtain the full advantage.

SUGGESTIONS

High-quality clinical trial studies with larger sample sizes and the use of various doses and types of zinc preparations are vital to obtain optimal supplementation type. Control of confounding variables, both demographic, clinical (especially duration of prediabetes), and laboratory by design and through statistical analysis should be carried out to discover which group will give the best response to zinc supplementation.

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