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Examine.com

Research Digest

Issue 40, Vol 1 of 2 ◆ February 2018

Zinc: An alternative path away from type 2 diabetes?

Zinc supplementation in prediabetes: A randomized double-blind placebo-controlled clinical trial

Introduction

Prediabetes is a condition of elevated blood glucose that is above normal, healthy levels but not so high as to meet criteria for type 2 diabetes. Two definitions of prediabetes are summarized in Figure 1. Currently, the World Health Organization defines prediabetes as having a fasting blood glucose level of 110-125 mg/dL (6.1-7.0 mmol/L) or a two-hour blood glucose value of 140-200 mg/dL (7.8-11.1 mmol/L) during an oral glucose tolerance test. The American Diabetes Association has similar criteria, with the the additional parameter of HbA1c being 5.7-6.4%.

The Center for Disease Control reports approximately one in three U.S. adults to have prediabetes. The prevalence increases with age, to about 48% of adults 65 years or older. Rising levels of blood sugar have also been noted worldwide in both developed and developing countries. Ultimately, about 70% of people with prediabetes will progress to develop type 2 diabetes, making prediabetes a critical period for intervention.

Lifestyle interventions for prediabetes primarily target fat loss, but improvements to diet and increases in physical activity are also key for preventing progression to diabetes. Although effective and cost-efficient, lifestyle interventions can be difficult for some people to adhere to.

Treatment with zinc may provide a cost-effective alternative. Zinc is thought to have multiple effects, summarized in Figure 2, that could help with both diabetes and prediabetes. It plays an important role in beta-cell function, insulin signal transduction, and is involved in insulin biosynthesis. Moreover, some people with type 2 diabetes have low zinc absorption and high urinary zinc excretion. This may, in part, explain why people with type 2 diabetes have lower levels of serum zinc.

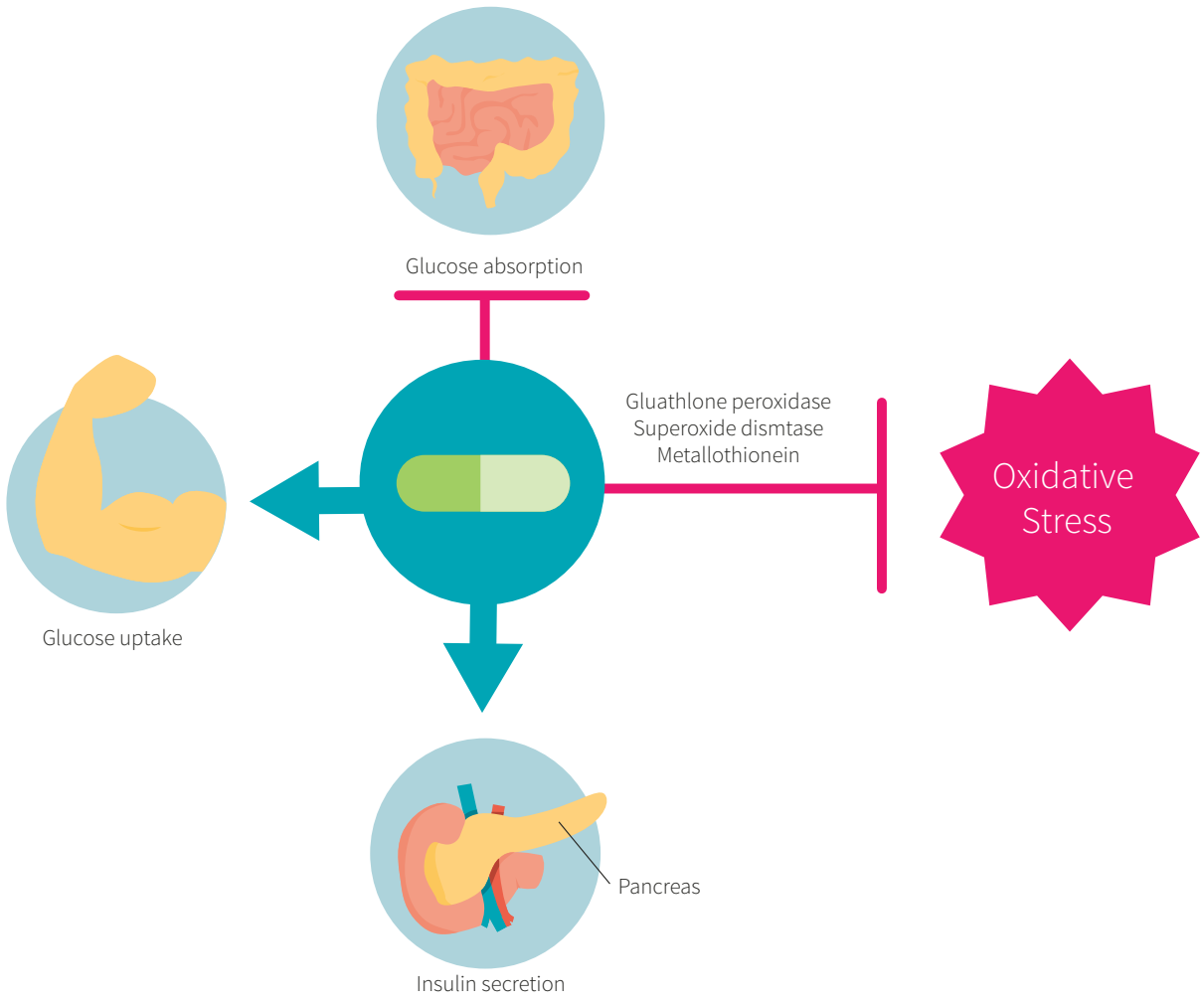
A meta-analysis of zinc supplementation studies in participants with type 2 diabetes reported significant benefits for glycemic control and blood lipids. These findings were supported by a separate meta-analysis involving primarily patients with type 2 diabetes, but also insulin resistant and healthy adults. However, a systematic review looking only at people with insulin resistance without diabetes reported no significant benefit from zinc supplementation. Limited research looking specifically at adults with prediabetes exists. One pilot study reported that zinc supplementation benefits glycemic control in this population. The study under review sought to build upon this research to determine the effects of zinc supplementation in a large group of people with prediabetes over a 12-month period.

Prediabetes represents an important checkpoint on the path to type 2 diabetes. Zinc is involved in proper glucose metabolism and supplementation has been shown to benefit glycemic control in people with type 2 diabetes. Less certainty exists regarding its effects in people with prediabetes. The study under review sought to address this knowledge gap.

Figure 1: Two definitions of prediabetes

	Fasting blood glucose		2-hour glucose		HbA1c
WHO	110-125 mg/dL	6.1-7.0 mmol/L	140-200 mg/dL	7.8-11.1 mmol/L	--
ADA	100-125 mg/dL	5.6-6.9 mmol/L	140-200 mg/dL	7.8-11.1 mmol/L	5.7-6.4%

Figure 2: Theoretical benefits of zinc supplementation in people with diabetes



Reference: Ranasinghe P. Daru. 2015 Sep.

Who and what was studied?

This was a double-blind, randomized controlled trial involving 200 adults with prediabetes. None of the participants were taking vitamin or mineral supplements, and none had a history of diabetes or other metabolic diseases. Participants were randomly assigned to take either 20 milligrams of elemental zinc per day or an identical placebo for 12 months. They were given a one month supply and instructed to take the capsule one hour before breakfast. All participants were given information for lifestyle improvements.

The prespecified primary outcomes were differences between groups in fasting blood glucose and two-hour glucose levels following an oral glucose tolerance test. Secondary outcomes included between-group differences in HOMA-IR (a measure of insulin resistance), HOMA-B (a measure of beta cell function), blood lipids, blood pressure, and anthropometrics (bodyweight, BMI, waist and hip circumference, and waist to hip ratio). Vital signs, liver enzymes, and kidney function were assessed as safety parameters.

All outcomes were assessed at baseline and again after one, three, six, and 12 months. An a priori power analysis suggested that 138 participants (69 in each group) were required to detect a 20% difference in fasting glucose between groups. Although 200 began the intervention and completed the one-month follow-up, only 171 were present at three months, 140 at six months, and 138 at 12 months.

Importantly, there were no corrections for multiple comparisons. Moreover, only the absolute variables were statistically compared between groups, as opposed to comparing the changes from baseline that each group experienced.

This double-blind, randomized controlled trial investigated the effects of supplementing 20 milligrams of elemental zinc per day on glycemic control in people with prediabetes over 12 months. The primary outcomes were fasting glucose and two-hour postprandial glucose. Secondary outcomes were blood lipids, blood pressure, and insulin resistance.

What were the findings?

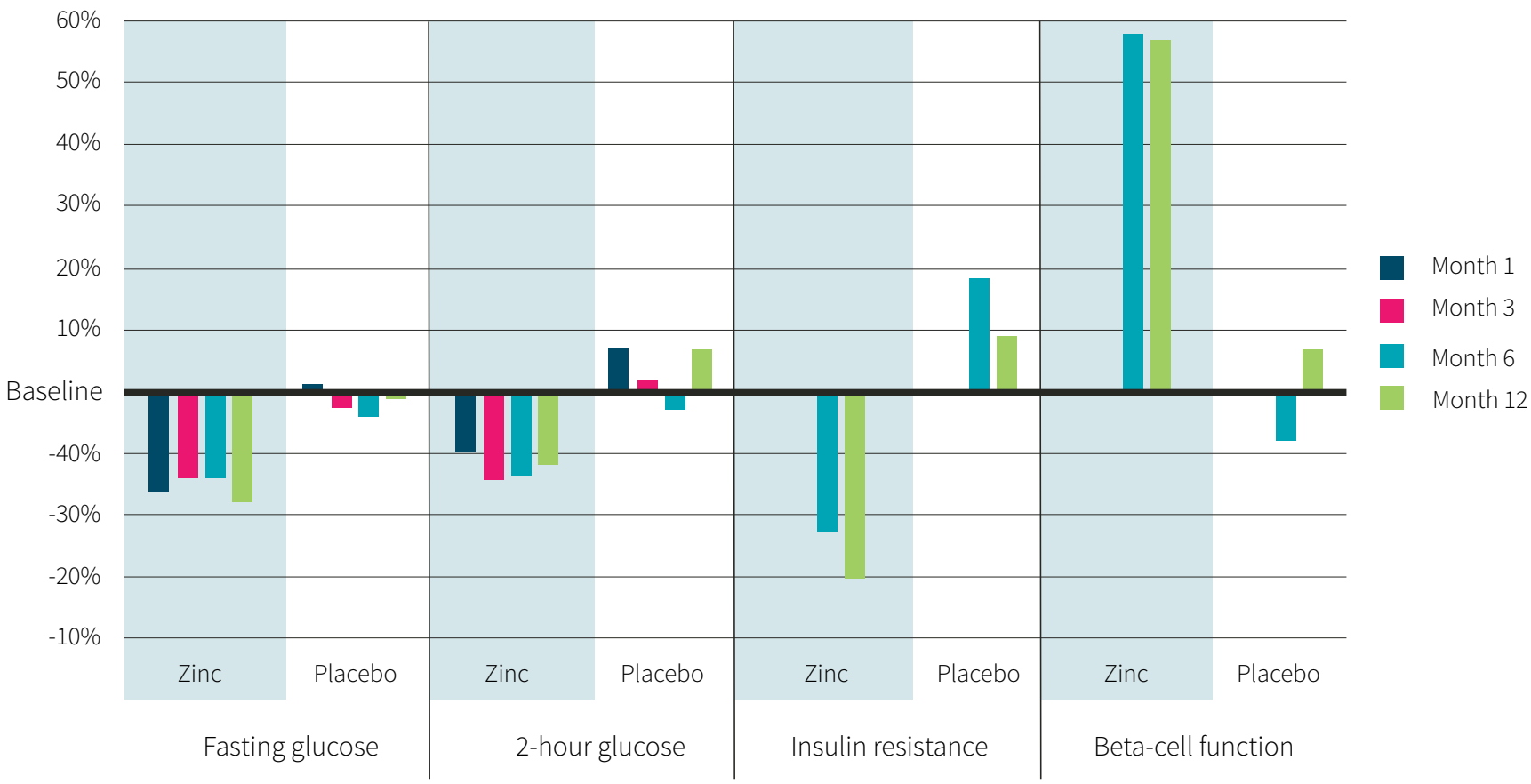
The main findings and their time course are summarized in Figure 3. Fasting blood glucose in the zinc group fell significantly by 16% after one month and was sustained around that level throughout all 12 months. A similar rapid initial drop of 10% and sustained reduction thereafter was observed in the two-hour postprandial glucose level. All changes were significantly different from the placebo group, which experienced no changes in fasting glucose and a significant 7% increase in two-hour glucose after 12 months.

The improvements in glycemic control in the zinc group were accompanied by significant 12-month reductions in HOMA-IR (-30%) and increases in beta cell function (57%), both of which were significant compared to the control group. Ultimately, 25% of the placebo group developed type 2 diabetes over the intervention period, which was significantly greater than the 11% rate observed in the zinc group.

After 12 months, the zinc group experienced a significant reduction in total and LDL cholesterol levels compared to the placebo group. There were no differences between groups for changes in HDL-cholesterol, triglycerides, blood pressure, or anthropometric variables.

At baseline, the average zinc status was considered deficient. As expected, serum zinc levels were increased significantly with zinc supplementation (by 72%) to normal levels and unchanged with placebo. Diet and physical activity remained constant during the 12-month intervention in both groups. Compliance

Figure 3: Theoretical benefits of zinc supplementation in people with diabetes



with the interventions was over 90%, and zinc was well tolerated; there were no adverse events or issues with liver and kidney function.

Zinc supplementation significantly improved glycemic control compared to placebo supplementation over 12 months. Modest reductions in total and LDL cholesterol were also noted, but most other parameters, such as anthropometric variables and blood pressure, remained unchanged.

What does this study really tell us?

This study has several strengths. For example, the researchers only recruited participants with confirmed prediabetes as defined by the World Health Organization. It must also be noted that this was the longest and largest trial assessing zinc in a prediabetic cohort to date. High compliance may have resulted from regular appointments with researchers and an allotment of only one month's supply at a time. Compliance was not only confirmed through pill counting, but researchers also performed serum analysis and evaluated each participant's typical diet for changes in zinc intake.

Nonetheless, there are some issues with the study design, data analysis, and reporting that diminish this study's quality. First, the calculation of sample size was well explained. Unfortunately, it was based off of a calculated 20% decrease in FPG using an expected 0.5-1.25% improvement in HbA1c observed with metformin. Calculation of the primary aim using HbA1c was also an odd choice, as FPG is readily reported from studies in this field. Second, HbA1c would have been a very valuable indicator of long-term glycemic control but the current study did not report this value at any time point. Third, it may have also been overly ambitious to base sample size for a supplement study using pharmaceutical data. However, published studies utilizing zinc treatments for insulin resistance lacked substantial effects to base a sample size upon 6 years ago during the planning of this study. Lastly, the researchers not only did not report HbA1c values, they also failed to report insulin data. It is unknown whether HbA1c was assessed, however insulin on the other hand is needed to calculated both insulin resistance and β-cell function values. Therefore, insulin was assessed but researchers withheld this data for an unknown reason.

Despite the trial's high compliance and size, the authors slightly underestimated the number of dropouts along with the number of participants which ended up discontinuing due to disease progression (27% in the zinc group and 35% in the placebo group - an overall 30% dropout rate was assumed). As such, the sample fell below the number of participants needed to retain statistical power in the placebo group. Conducting a last observation carried forward or an intention to treat analysis could have helped retain statistical power. However, this would have likely diluted the treatment effect compared to baseline values and zinc treatment may have no longer been favored.The placebo group had higher discontinuation rate as a result of developing diabetes. This could explain why there were some unexpected improvements in blood pressure in the placebo group. For example, those with more advanced prediabetes may have also had higher blood pressure. It is feasible to assume that these prediabetic cases may have had a higher likelihood of advancing to type two diabetes without treatment of zinc. Excluding these potential cases of high blood pressure from analysis due to diabetes development may have driven the entire sample mean lower than baseline values in the placebo group.

In addition, some questions about the researchers' statistical analysis remained unaddressed. For instance, the researchers did not define how they accounted for baseline differences observed for LDL cholesterol, triglycerides, and daily protein intake. These between

group comparisons are extremely important to determine significance between the treatment and placebo groups. However, they presented the between group significance as a side note. The entire purpose of having a placebo group is to compare it to the treatment group. Such comparisons are imperative in long-term trials as outcomes may change over time. Between group comparisons are also necessary in interventional trials involving a supplement or medication, as the placebo effect can be a major driver. Lastly, the authors chose to use a paired t-test. This would have been appropriate for a short-term study with only one follow-up visit. However the researchers repeatedly compared 4 time points over time. Repeating t-test statistics over and over at each time point is a major cause for concern since it increases the likelihood for significant values. As a consequence, this method could result in the occurrence of false positives. As an alternative, the researchers should have used a statistical test known as an ANOVA that is designed to safeguard against this problem.

> “[...] the study population was primarily of Southeast Asian descent and the study findings may not be generalizable to other ethnic populations.”

While not explicitly discussed, this study was conducted in Sri Lanka. This means, the study population was primarily of Southeast Asian descent and the study findings may not be generalizable to other ethnic populations.

Finally, this study provided 20 milligrams of elemental zinc per day. The recommended dietary allowance (RDA) for men and women is 11 milligrams per day and eight milligrams per day, respectively. The tolerable upper limit is 40 milligrams per day. In instances of zinc deficiency, two to three times the RDA is recommended. The zinc dose in the present study is rather modest. So it comes to no surprise that there were minimal side effects over the course of 12 months.

This was the largest and longest study to date assessing zinc treatment for glycemic control in a population with prediabetes. The researchers took several measures to ensure and confirm compliance to the assigned treatment. However, some statistical and reporting issues exist in the analysis. Also, the study was done in Sri Lanka, and its results may not generalize to other ethnicities.

The big picture

This study helps to clarify whether or not zinc is solution to better glycemic control in prediabetes. Work from studies intervening in type 2 diabetes previously indicated that zinc could help improve FPG and HbA1c along with total cholesterol and LDL cholesterol. However, the studies from this body of work are quite

variable from each other, and studying a population with diabetes is also more complicated, as there may be concurrent use of multiple pharmaceutical treatments. The pathology of insulin resistance is also much more progressed in diabetes, compared to prediabetes. As such, it's not appropriate to generalize findings from studies in type 2 diabetes to prediabetes as the physiological effect of zinc is likely different.

There was one previous review which complied results from three studies in populations with obesity, two of which specified that the participants had normal glucose tolerance. Not surprisingly, the authors of the review concluded that zinc had no effect on glycemic control. Regardless, this group of studies is also not reflective of how zinc may help people with prediabetes regulate blood glucose.

One pilot study lasting six months in prediabetic participants using a higher does of zinc (30 milligrams per day) also showed improvements in FPG. Additionally, this study indicated an improvement in β-cell function and insulin resistance. It is possible that the higher dose in the pilot study may have enhanced the effect.

Interestingly, the -14% to -18% improvement in FPG in this study is comparably higher than the -4.5% improvement noted with metformin treatment from a large meta-analysis. The improvements in LDL cholesterol (-30%) may also be higher with zinc than metformin (-5.6%). However, it would be hasty to compare the two, as these comparison were not made in a randomized clinical trial, and metformin treatment has a considerably higher number of trials contributing to this data summary (31 studies) compared to this single zinc trial reviewed here. Additionally, the metformin treatment reduced the incidence of new-onset type 2 diabetes by 40%. Low sample size prevented this calculation from being made in the currently study. Incidence was 11% in the zinc group, and 25% in the placebo group. While this may seem like a substantial difference, 11% is on the high end of the expected incidence rate of new onset diabetes without treatment (5-10% per year).

It is also interesting that these improvements were experienced without weight loss. Research has indicated that approximately 5-10% weight loss is needed to observe metabolic improvements. However, this and other studies have shown improvements without significant weight loss.

The treatment effect may also be influenced by the zinc status of the participants. In the currently study, the average serum zinc concentration at baseline was considered deficient. Conversely, in a study of type 2 diabetic participants, 240 milligrams of elemental zinc was administered (over 10x the dose used in the present study) with no change in glycemic control parameters. While zinc concentrations increased substantially with the mega dose of zinc, these participants had normal serum zinc concentrations.

Several other studies have reported mild gastrointestinal (GI) disturbances with zinc supplementation. For example, in the study administering 240 milligrams per day, 15 out of 20 participants reported GI issues that subsided after about three days of zinc usage. High doses of zinc also have the potential to decrease serum copper. The 240 milligram dose did not affect copper status, and neither did smaller doses of 30 milligrams per day.

This work adds to a very small body of literature suggesting that zinc is able to improve glycemic outcomes, specifically FPG, in people with prediabetes, without deleterious health consequences.

Frequently asked questions

Can zinc treatment improve glycemic control in polycystic ovarian syndrome?

Polycystic ovarian syndrome is a metabolic condition marked by insulin resistance, elevated blood lipids, and dysfunctional sex hormone profiles. A 2015 study reported similar improvements in a placebo-controlled study with 52 women diagnosed with PCOS. After eight weeks of treatment using 50 milligrams of elemental zinc, FPG, insulin, β-cell function, and indicators of insulin sensitivity and resistance improved.

Can zinc reduce oxidative stress in type 2 diabetics?

Type 2 diabetes is associated with an increase in oxidative stress due, in part, to elevated blood glucose, insulin, and cholesterol. Zinc is a component in superoxide dismutase, an antioxidant in the body. It may also decrease oxidation by displacing pro-oxidant metals in the body, such as copper and iron. Theoretically, this means zinc has the potential to reduce oxidative stress. However, the effectiveness of zinc to reduce oxidative stress may depend on the zinc status of the population studied. Two studies where 30% of the population may have been zinc deficient showed a 13.6-15% decrease in oxidative stress in adults with diabetes supplementing 30 milligrams of zinc a day. In opposition, a placebo-controlled study in type 2 diabetic males with normal zinc levels noted no improvements in measures of oxidative stress after four months of treatment with 240 milligrams of zinc.

What should I know?

Prediabetes represents a turning point for many, as it represents a path to diabetes that could be cut off at the pass. Lifestyle interventions focusing on weight loss are crucial to prevent diabetes development in at-risk individuals. However, such changes can be difficult to initiate and maintain. While pharmaceutical inventions have also been shown to help control glycemic outcomes in prediabetes, this option may not be accessible or affordable to everyone in need. Zinc supplementation may be a more accessible and easier to maintain option to decrease FPG and improve lipid parameters. Some studies support the use of zinc for type 2 diabetes and other conditions of insulin resistance. However, this was the first study to assess the long-term use of zinc in prediabetes.

This study suggests zinc can be used long term as an ongoing treatment to control blood sugar and improve blood lipids in prediabetic users without adverse side effects. However, the way in which the researchers chose to evaluate the study statistics diminishes overall quality. Additionally, the placebo group did not retain statistical power due to a high proportion of participants being discontinued from the study after developing diabetes. Further research should explore responder compared to non-responder characteristics. It is possible that zinc supplementation only helps people with prediabetes who are also zinc deficient. ◆

This study had major strengths and some weaknesses. Do you think the weaknesses were enough to take the results with a larger-than-average grain of salt? Have your say, and see what others think, in the ERD Facebook forum.

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