

# Zinc supplementation for the prevention of type 2 diabetes mellitus (Review)

Beletate V, El Dib R, Atallah ÁN



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[Intervention Review]

# Zinc supplementation for the prevention of type 2 diabetes mellitus

Vânia Beletate<sup>1</sup>, Regina El Dib<sup>2</sup>, Álvaro N Atallah<sup>3</sup>

<sup>1</sup>Programa de graduação de Medicina Interna e Terapêutica, Universidade Federal de São Paulo, Piracicaba, Brazil. <sup>2</sup>McMaster Institute of Urology, St. Joseph's Healthcare Hamilton, Toronto, Canada. <sup>3</sup>Brazilian Cochrane Centre, Universidade Federal de São Paulo / Escola Paulista de Medicina, São Paulo, Brazil

Contact address: Vânia Beletate, Programa de graduação de Medicina Interna e Terapêutica, Universidade Federal de São Paulo, Aquilino Pacheco 1516, apto 43, Piracicaba, Brazil. [vaniabeletate@uol.com.br](mailto:vaniabeletate@uol.com.br).

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## ABSTRACT

### Background

The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. Insulin resistance is a fundamental aspect of the aetiology of type 2 diabetes. Insulin resistance has been shown to be associated with atherosclerosis, hypertriglyceridaemia, glucose intolerance, dyslipidaemia, hyperuricaemia, hypertension and polycystic ovary syndrome. The mineral zinc plays a key role in the synthesis and action of insulin, both physiologically and in diabetes mellitus. Zinc seems to stimulate insulin action and insulin receptor tyrosine kinase activity.

### Objectives

To assess the effects of the zinc supplementation in the prevention of type 2 diabetes mellitus.

### Search methods

Studies were obtained from computerised searches of MEDLINE, EMBASE, LILACS and *The Cochrane Library*.

### Selection criteria

Studies were included if they had a randomised or quasi-randomised design and if they investigated zinc supplementation in adults living in the community, 18 years or older with insulin resistance (compared to placebo or no intervention).

### Data collection and analysis

Two authors selected relevant trials, assessed methodological quality and extracted data.

### Main results

Only one study met the inclusion criteria of this review. There were 56 normal glucose tolerant obese women (aged 25 to 45 years, body mass index  $36.2 \pm 2.3$  kg/m<sup>2</sup>). Follow-up was four weeks. The outcomes measured were decrease of insulin resistance, anthropometric and diet parameters, leptin and insulin concentration, zinc concentration in the plasma and urine, lipid metabolism and fasting plasma glucose. There were no statistically significant differences favouring participants receiving zinc supplementation compared to placebo concerning any outcome measured by the study.

## Authors' conclusions

There is currently no evidence to suggest the use of zinc supplementation in the prevention of type 2 diabetes mellitus. Future trials will have to standardise outcomes measures such as incidence of type 2 diabetes mellitus, decrease of the insulin resistance, quality of life, diabetic complications, all-cause mortality and costs.

## PLAIN LANGUAGE SUMMARY

### Zinc supplementation for the prevention of type 2 diabetes mellitus

Currently no evidence to suggest the use of zinc for the primary prevention of type 2 diabetes. Diabetes mellitus is associated with long-term complications, especially eye, kidney, nerve, heart and blood vessel disease. Type 2 diabetes is mainly characterised by a reduced ability of the hormone insulin to stimulate glucose uptake in body fat and muscles (insulin resistance) and affects most people suffering from diabetes. Type 2 diabetes may not cause symptoms for some time and may remain undetected for many years. Zinc, an important mineral, plays a relevant role in the synthesis and action of insulin. The human body does not produce zinc on its own, so it must be obtained from outside sources. The mineral zinc can be found in both animal and plant food sources, but the richest source of zinc comes from animal food sources.

We assessed the effects of the zinc supplementation in the prevention of type 2 diabetes mellitus. Only one relevant study was detected. There were no significant differences favouring people receiving zinc supplementation compared to placebo concerning any outcome measured in the study. Thus, there is currently no evidence to suggest the use of zinc supplementation in the prevention of type 2 diabetes mellitus.

## BACKGROUND

### Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased (ADA 1999). For a detailed overview of diabetes mellitus, please see under 'Additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About', 'Cochrane Review Groups (CRGs)'). For an explanation of methodological terms, see the main glossary in *The Cochrane Library*.

There are two major forms of diabetes, insulin-dependent diabetes mellitus (IDDM, type 1 diabetes) and non-insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes) (ADA 1999). Type 2 diabetes, the most prevalent form of the disease, is often asymptomatic and may remain undiagnosed for many years (ADA 1998). Type 2 diabetes may be seen in children and young adults. In type 2 diabetes the pancreatic islet cells are capable of compensating

insulin resistance (see below) and producing larger quantities of insulin, at least in the beginning of the disease (Chausmer 1998).

### Prevalence and costs

The worldwide prevalence of diabetes has been estimated to be around 171 million people (WHO 2000), reaching 299 million by the year 2025 (WHO 1997). Diabetes accounts for over 77 billion EURO (U.S. \$98) in health care costs (Tracey 2003).

### The risk of developing type 2 diabetes and insulin resistance

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. Insulin resistance is a fundamental aspect of the aetiology of type 2 diabetes (Barbara B 2000). The majority of patients who develop type 2 diabetes are insulin resistant, and hyperglycaemia occurs when these patients can no longer support the degree of compensatory hyperinsulinemia required to prevent gross decompensation of glucose homeostasis (Tracey 2003). Insulin resistance has been shown to be associated with prevalent atherosclerosis (Howard 1996), hypertriglyceridaemia (Moro 2003), glucose intolerance, dyslipidaemia, hyperuricaemia, hypertension (Bonora 1998) and polycystic ovary syndrome (Barbara B 2000).

Insulin resistance can be mensurated by using the glucose clamp technique (DeFronzo 1979) which is considered the "gold standard" in the assessment of insulin sensitivity (Karelis 2004), how-

ever, this method is laborious, expensive and inadequate for large-scale or epidemiological studies (Bonora 2000). Matthews et al developed the "Homeostasis Model Assessment" (HOMA) method, that derives an estimate of insulin sensitivity by taking fasting plasma glucose and insulin concentrations into account. HOMA is supposed to evaluate the insulin resistance and the function of the  $\beta$ -cells. Insulin resistance is calculated with the following formula: (fasting serum insulin ( $\mu$ U/ml) x fasting plasma glucose (mmol/L)) / 22.5 (Matthews 1985).

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are associated with the insulin resistance. IFG and IGT refer to an intermediate metabolic stage between normal glucose homeostasis and diabetes. This stage includes individuals with fasting glucose levels equal or greater than 110 mg/dl but lower than 126 mg/dl or after an oral glucose tolerance test with 2-h values equal or greater than 140 mg/dl but lower than 200 mg/dl.

## Description of the intervention

Every single cell in the body needs zinc for structural and energy producing functions. Zinc is an essential trigger for many biochemical reactions and also for protein production. Zinc plays an important role in cell division, growth, and repair. It helps with wound healing and maintaining a normal sense of taste and smell. Zinc works as an immune booster and can be instrumental in fighting colds, flu, and other infections. Zinc is a component of more than 200 enzymes, most of them involved in protein and DNA synthesis. Zinc has beneficial effects on sex and thyroid hormones. The male prostate gland has strong concentrations of zinc and this gland manufactures prostatic fluid in which sperm cells are mixed to make semen. Furthermore, zinc helps regulate the metabolism of testosterone in the prostate, as well as sex drive. It is also believed to enhance fertility in both men and women. The human body does not produce zinc on its own, so it must be obtained from outside sources. The mineral zinc can be found in both animal and plant food sources, but the richest source of zinc comes from animal food sources.

The daily recommended dose of zinc is 12 mg for women and 15 mg for men. Studies suggest an oral supplementation of zinc sulphate from 30 to 200 mg per day. The effect of supplementation with zinc was assessed in 10 patients with liver cirrhosis. Supplementation was approximately 136 mg zinc per day. The patients presented with impaired glucose tolerance and zinc deficiency. The study showed that zinc supplementation produced a significant improvement in glucose disposal. The action of zinc seemed to be related to the increased activities of insulin independent glucose transporters (Marchesini 1998).

### Adverse effects of the intervention

Amounts of two gram per day or more can cause gastrointestinal irritation and vomiting (Marchesini 1998;Marreiro 2004).

## How the intervention might work

Zinc ions have an insulin-like effect. A particularly sensitive target of zinc ions is protein tyrosine phosphatase 1B (PTP 1B), a key regulator of the phosphorylation state of the insulin receptor (Haase 2005). Several studies have investigated the role of zinc status in insulin secretion and metabolism. The zinc seems to stimulate insulin action and insulin receptor tyrosine Kinase (IRTK) activity ( Marchesini 1998; Rossetti 1990).

## Why it is important to do this review

In vitro studies show that insulin may form a complex with zinc improving the solubility of this hormone in the pancreatic  $\beta$ -cells. Moreover, the binding ability of insulin to its receptor may be increased. Alterations in zinc concentrations and distributions in tissues, as well as improvements of insulin sensitivity after supplementation with this element have been demonstrated. Thus, the metabolic role of zinc in insulin resistance and obesity should be further investigated (Marreiro 2004b).

## OBJECTIVES

To assess the effects of the zinc supplementation for the prevention of type 2 diabetes mellitus.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised and quasi-randomised controlled clinical trials with minimal duration of four weeks.

#### Types of participants

Non-diabetic adults living in the community, 18 years or older with insulin resistance.

#### Diagnostic Criteria

Insulin resistance was required to be measured by the "Homeostasis Model Assessment" (HOMA) or glucose clamp technique.

Diagnostic criteria of type 2 diabetes mellitus should have been established using the standard criteria valid at the time of the beginning of the trial. Ideally, diagnostic criteria should have been described. If necessary, authors' definition of type 2 diabetes mellitus were used.

### Types of interventions

- Zinc versus placebo or no intervention;
- Different doses of zinc versus placebo or no intervention.

### Types of outcome measures

#### Primary outcomes

- incidence of type 2 diabetes mellitus.

#### Secondary outcomes

- decreased insulin resistance;
- quality of life;
- all-cause mortality;
- diabetic complications;
- costs;
- adverse effects;
- cholesterol levels, LDL cholesterol levels, HDL cholesterol levels, triglycerides, leptin concentration.

#### Timing of outcomes measures

Short term (four weeks or less), medium term (more than four weeks to less than four months) and long term (four months or more) .

### Search methods for identification of studies

#### Electronic searches

We used the following sources for the identification of trials:

- *The Cochrane Library* (issue 3, 2005);
- MEDLINE (until June 2005);
- EMBASE (until June 2005);
- LILACS (Literature Latino-Americana e do Carib em Ciências da Saúde) (until June 2005).

We also searched databases of ongoing trials: Current Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com) - with links to other databases of ongoing trials), the National Research Register (<http://www.update-software.com/National/>) and Clinical Research Studies (<http://clinicalstudies.info.nih.gov>).

The described search strategy (see for a detailed search strategy under [Appendix 1](#)) was used for MEDLINE. For use with EMBASE and the other databases this strategy was slightly adapted.

#### Reference lists

References of the identified relevant studies were scrutinized for additional citations.

#### Searching other resources

Authors of relevant identified studies and other experts were contacted in order to obtain additional references, unpublished trials, ongoing trials or obtain missing data not reported in the original trials.

### Data collection and analysis

#### Selection of studies

Two authors (VB and RPED) independently scanned the titles or abstract of every record retrieved. Full articles were retrieved for further assessment if the information given suggested that the study: 1. included patients with insulin resistance, 2. compared zinc intervention with placebo. Where differences in opinion existed, they were resolved by a third party (ANA). If resolving disagreement was not possible, the article was added to those 'awaiting assessment' and authors were contact for clarification.

In future updates interrater agreement for study selection will be measured using the kappa statistic (Cohen 1960) and an adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection will be attached (Moher 1999).

#### Data extraction and management

For studies that fulfilled the inclusion criteria, two authors (VB and RPED) independently abstracted relevant population and intervention characteristics, using a standard data extraction template. Any disagreements were resolved by discussion, or required by a third reviewer (ANA). Any relevant missing information on the trial was sought out the original author(s) of the article, if required.

Data extracted included the following:

- general information: published or unpublished, title, authors, source, contact address, country, language of publication, year of publication, duplicate publications.
- trial characteristics: design, duration, randomisation (and method), allocation concealment (and method), blinding (participants, people administering treatment and outcome assessors), check of blinding.
- intervention characteristics: zinc intervention, comparison placebo (method, timing).
- patients characteristics: sampling (random or convenience), exclusion criteria, total number and number in comparison groups, gender, age, diagnostic criteria of diabetes, similarity of

groups at baseline, assessment of compliance, withdrawals and losses to follow-up (reasons or description), subgroups.

- outcomes: outcomes specified above, what was the main outcome assessed in the study, other events, length of follow-up.
- results: for outcomes and times of assessment, intention-to-treat analysis.

### Assessment of risk of bias in included studies

Two authors (VB and RPED) assessed each trial independently. Possible disagreement was resolved by consensus, or with consultation of a third reviewer in case of disagreement (ANA). We planned to explore the influence of individual quality criteria in a sensitivity analysis (see under 'sensitivity analyses'). In cases of disagreement, the rest of the group was planned to be consulted and a judgement made based on consensus. Interrater agreement for key quality indicators was planned to be calculated using the kappa statistic (Cohen 1960).

The methodological quality of the included trials in this review was measured using an adaptation of the Cochrane criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005), since scales are not a reliable method to assess the validity of a primary study (Juni 1999). In particular, the following factors were studied:

1. Minimisation of selection bias - a) was the randomisation procedure adequate? b) was the allocation concealment adequate? c) was there a systematic difference between comparison groups?

A. Adequate allocation concealment

B. Unclear - not described in the publication and information impossible to be acquired from the authors of the primary study.

C. Inadequate.

D. Not used

2. Minimisation of detection bias

(1) Met: assessors unaware of the assigned treatment when collecting outcome measures;

(2) Unclear: blinding of assessor not reported and cannot be verified by contacting investigators;

(3) Not met: assessors aware of the assigned treatment when collecting outcome measures.

3. Minimisation of attrition bias

(1) Met: less than 20% and equal for both groups;

(2) Unclear: not reported in publication or by authors;

(3) Not met: greater than 20% or not equal for both comparison groups, or both.

4. Minimisation of performance bias - were participants, caretakers or people responsible for administration of medication blinded to the allocation?

Based on these criteria, studies were broadly subdivided into the following three categories:

- low risk of bias: all quality criteria met;
- moderate risk of bias: one or more of the quality criteria only partly met;

- high risk of bias: one or more criteria not met.

We also planned to explore the influence of individual quality criteria by means of sensitivity analysis.

### Measures of treatment effect

#### Dichotomous data

In future updates, dichotomous outcomes (for example mortality yes/no) will be expressed as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI).

#### Continuous data

Continuous outcomes (for example leptin concentration) were expressed as mean differences with 95% CI.

#### Time-to-event data

In future updates, time-to-event outcomes (for example time until death) will be expressed as hazard ratios (HR) with 95% CI.

#### Unit of analysis issues

In future updates, different units of analysis (for example OR and RR) will be subjected to a sensitivity analysis.

#### Dealing with missing data

Relevant missing data were obtained from authors, if feasible. Evaluation of important numerical data such as screened, eligible and randomised patients as well as intention-to-treat and per-protocol population were carefully performed. Drop-outs, misses to follow-up and withdrawn study participants were investigated. Issues of last-observation-carried-forward (LOCF) were critically appraised and compared to specification of primary outcome parameters and power calculation.

#### Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study, we tried to maximise yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) obtained priority.

### Assessment of heterogeneity

It was not necessary to measure heterogeneity in this version of the review. In future updates, inconsistency among the pooled estimates will be quantified using the  $I^2$  statistic. This illustrates the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error (Higgins 2003; Higgins 2005).  $I^2$  demonstrates the percentage of total variation across studies due to heterogeneity and will be used to judge the consistency of evidence.  $I^2$  values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity is found, we plan to determine potential reasons for it by examining individual study characteristics and those of subgroups of the main body of evidence.

### Assessment of reporting biases

Due to only one study included in this review we were not able to assess publication bias by drawing a funnel plot (trial effect versus trial size). If a sufficient number of studies were available in future updates, small study bias will be assessed.

Funnel plots will be used in an exploratory data analysis to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies (Sterne 2001) and publication bias. Thus, this exploratory data tool may be misleading (Tang 2000; Thornton 2000) and we will not place undue emphasis on this tool.

### Data synthesis

In this review it was not appropriate to combine results. Data were planned to be summarised statistically if they were available, sufficiently similar and of sufficient quality. Statistical analysis was planned to be performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005). Pooled results were planned to be analysed using primarily a random-effects model.

### Subgroup analysis and investigation of heterogeneity

There were insufficient data to allow for any subgroup analyses. Should sufficient data in future permit, the following subgroup analyses would be of interest:

- gender (female/male);
- age (depending on data but especially older versus younger patients);
- patients with or without co morbidities (for example heart attack, stroke, peripheral vascular disease);
- duration of intervention;
- different anthropometric parameters;
- different status of lipid metabolism;

- different nutrients;
- different concentrations of zinc;
- different urinary volume and urinary excretion of zinc;
- different insulin, leptin, and glucose concentrations.

Subgroup analyses will be mainly used to explore clinical or methodological or statistical heterogeneity.

### Sensitivity analysis

There were insufficient data to allow any sensitivity analysis. Sufficient data in the future would permit us to analyse the following informations:

- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of study quality, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country;
- different study design (parallel versus cross-over).

The robustness of the results will also be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio etc.) and different statistical models (fixed and random effects models).

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

### Results of the search

Altogether 192 titles were evaluated. Following assessment of full articles only two publication were considered for inclusion in this review. One study was excluded (Marchesini 1998) and one study which met minimal methodological requirements was included in this review (Marreiro 2002).

### Included studies

This study was a quasi-randomised clinical trial. Fifty-six normal glucose tolerant obese women, aged 25 to 45 years with a body mass index of  $36.2 \pm 2.3$  kg/m<sup>2</sup> participated. Follow-up was four weeks. Treatment with zinc consisted of oral intake of 30 mg per day for four weeks (n=28) or placebo (n=28). Outcome measures were decrease in insulin resistance, anthropometric parameters,



diet parameters, leptin concentration, insulin concentration, zinc concentration in erythrocytes, zinc concentration in urine, lipid metabolism and fasting plasma glucose.

### Excluded studies

One study is described in the 'Table of excluded studies' (Marchesini 1998). The main reason for exclusion was that the study was not a randomised controlled trial but a case series.

### Risk of bias in included studies

The single included trial (Marreiro 2002) did not describe the method of allocation concealment. Generation of allocation was described as sequential why we defined this study as a quasi-randomised trial. The study was consequently graded B (unclear) regarding quality of allocation concealment and inadequate (C) regarding generation of allocation. Blinded assessment details were described in the publication as the assessor being unaware of the assigned treatment when collecting outcome measures. Attrition bias was not reported.

### Effects of interventions

#### Comparison of zinc supplementation versus placebo

##### Anthropometric parameters

The anthropometric parameters measured in the Marreiro 2002 study after treatment were body mass index, body perimeter, body constitution, skinfold thickness below the scapula, skinfold thickness above the hip bone and skinfold thickness of the upper arm. There was no statistically significant difference favouring participants receiving zinc supplementation compared to placebo.

##### Lipid metabolism

The lipid metabolism parameters measured in the Marreiro 2002 study were triglycerides, total cholesterol, very low density, low density and high density lipoprotein cholesterol. There was no statistically significant difference favouring participants receiving zinc supplementation compared to placebo.

#### Comparison of energy and of nutrients in obese women

The energy and nutrients in the obese women measured in the Marreiro 2002 study were energy intake, proteins, carbohydrates, lipids and zinc. There was no statistically significant difference favouring participants receiving zinc supplementation compared to placebo.

#### Limitation of the study

Four weeks were not sufficient to assess a long-term process like the development of glucose intolerance and diabetes.

## DISCUSSION

This systematic review offers up-to-date but limited evidence supported by only one randomised controlled trial regarding the effects of zinc supplementation for the prevention of type 2 diabetes mellitus (Marreiro 2002).

The relationship between obesity and insulin resistance is seen across all ethnic groups and is evident across the full range of body weights. Insulin resistance is thought to be a major feature of type 2 diabetes, particularly since high basal plasma insulin concentrations often found in obese type 2 diabetic patients. However, in our review we did not find any differences between the two groups evaluated (zinc supplementation versus placebo) regarding plasma insulin concentrations.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is currently no evidence to suggest the use of zinc supplementation for the prevention of type 2 diabetes mellitus.

### Implications for research

There was only one included study evaluating the effects of zinc supplementation for the primary prevention of type 2 diabetes mellitus. Future randomised controlled clinical trials should have standardised outcomes measures such as incidence of type 2 diabetes mellitus, decrease of insulin resistance, diabetic complications, quality of life, all-cause mortality and costs. Drop-outs and losses to follow-up need to be clearly reported.

## ACKNOWLEDGEMENTS

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bias in meta-analysis. *Journal of Clinical Epidemiology* 2000;**53**:477–84.

**Thornton 2000**

Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *Journal of Clinical Epidemiology* 2000;**53**:207–16. 2000;**53**:207–16.

**Tracey 2003**

Tracey L, McLaughlin MD, Gerald M, Reaven MD. Beyond type 2 Diabetes: The need for a clinically useful way to identify insulin resistance. *The American Journal of Medicine* 2003;**114**:501–2.

**WHO 1997**

World Health Organization. *The World Health Report*. WHO. Geneva, 1997.

**WHO 2000**

World Health Organization. *Prevalence of Diabetes WorldWide 2000,2030*. available: [http://www.who.int/diabetes/facts/world\\_figures/](http://www.who.int/diabetes/facts/world_figures/) assessed in 21 de junho de 2005.

\* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Marreiro 2002

Methods	Design: quasi-randomised clinical trial. Single-centre. Setting: Hospital das Clínicas da FMUSP, São Paulo, Brazil. Sample size: not reported. Generation of allocation: unclear. Allocation concealment: inadequate (sequential). Blinded assessment of treatment allocation: met. Withdrawals: unclear. Intention-to-treat analysis: not reported. Follow-up: four weeks	
Participants	56 normal glucose tolerant obese women (age: 25-45 years, BMI = 36,2 ± 2,3 kg/m <sup>2</sup> ). Inclusion criteria: 25-45 years; IMC>40 kg/m <sup>2</sup> ; absence of hormonal reposition and use of oral contraceptives. Exclusion criteria: patients with 110 mg/dl of glucose; subjects who were taking any drug or another vitamin-mineral supplement; smokers and diabetes mellitus type 2, polycystic ovary syndrome, arterial hypertension and chronic kidney failure	
Interventions	56 normal glucose tolerant obese women were randomized to treatment with zinc 30 mg daily orally for 4 weeks (n=28) or placebo daily orally for 4 weeks (n=28)	
Outcomes	Decrease of the insulin resistance, anthropometric parameters, diet parameters, leptin concentration, insulin concentration, zinc concentration in erythrocytes plasma, zinc concentration in urine, lipid metabolism and glucose fasting	
Notes	Both groups at baseline were not different in age, BMI, lipid parameters, body composition, caloric intake, leptin and insulin concentration, insulin resistance, zinc concentration on diet, plasma, urine and erythrocytes	
<i>Risk of bias</i>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear

### Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Marchesini 1998	Case series

## DATA AND ANALYSES

### Comparison 1. Zinc supplementation versus placebo

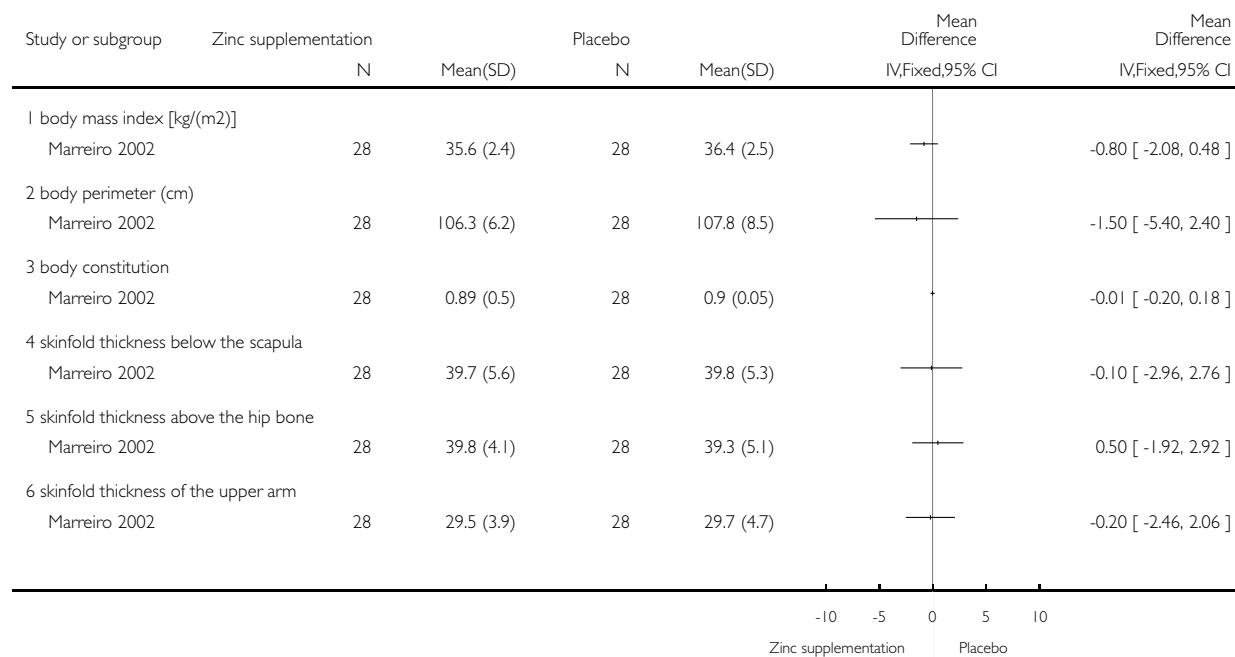
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anthropometric parameters after treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 body mass index [kg/(m <sup>2</sup> )]	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 body perimeter (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 body constitution	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.4 skinfold thickness below the scapula	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.5 skinfold thickness above the hip bone	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.6 skinfold thickness of the upper arm	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Lipid metabolism	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 triglycerids	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 total cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.3 cholesterol (very low density lipoprotein)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.4 cholesterol (low density lipoprotein)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.5 cholesterol (high density lipoprotein)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Comparison of the energy and of the present nutrients in obese women	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 energy (kcal)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 protein	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.3 carbohydrates	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.4 lipids	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.5 zinc (mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

**Analysis 1.1. Comparison 1 Zinc supplementation versus placebo, Outcome 1 Anthropometric parameters after treatment.**

Review: Zinc supplementation for the prevention of type 2 diabetes mellitus

Comparison: 1 Zinc supplementation versus placebo

Outcome: 1 Anthropometric parameters after treatment

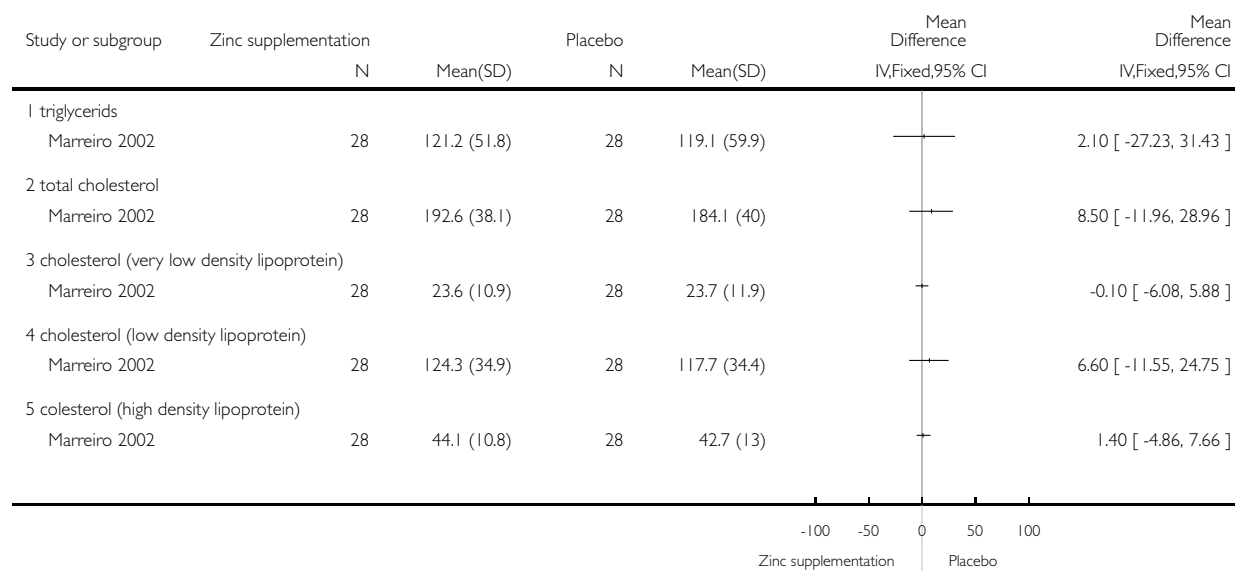


## Analysis 1.2. Comparison 1 Zinc supplementation versus placebo, Outcome 2 Lipid metabolism.

Review: Zinc supplementation for the prevention of type 2 diabetes mellitus

Comparison: 1 Zinc supplementation versus placebo

Outcome: 2 Lipid metabolism

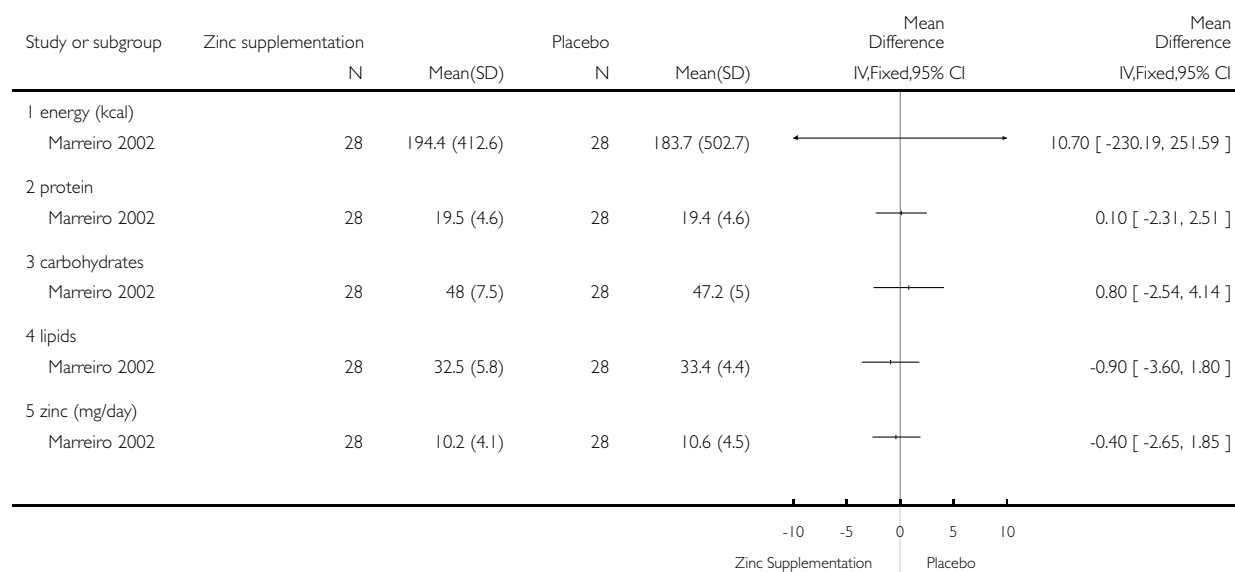


### Analysis 1.3. Comparison 1 Zinc supplementation versus placebo, Outcome 3 Comparison of the energy and of the present nutrients in obese women.

Review: Zinc supplementation for the prevention of type 2 diabetes mellitus

Comparison: 1 Zinc supplementation versus placebo

Outcome: 3 Comparison of the energy and of the present nutrients in obese women



## APPENDICES

### Appendix I. Search strategy

#### Search terms

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign (\$) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent

#### MEDLINE:

1. "Glucose Intolerance"[MeSH]
2. "Diabetes Mellitus, Type II/prevention and control"[MeSH]
3. "Glucose Tolerance Test"[MeSH]
4. "Insulin Resistance/drug effects"[MeSH]
5. "Metabolic Syndrome X"[MeSH]
6. "impaired fasting glucose" [tw]



(Continued)

7. "impaired fasting blood glucose" [tw]
8. "impaired fasting bloodglucose" [tw]
9. "impaired fasting glycaemia" [tw]
10. "impaired fasting glycemia" [tw]
11. impaired glucose toleran\* [tw]
12. impaired glucose stat\* [tw]
13. impaired glucose-respons\* [tw]
14. impaired glucose control\* [tw]
15. IGT [tw]
16. glucose intoleran\* [tw]
17. impaired glucose regul\* [tw]
18. impaired glucose metab\* [tw]
19. impaired glucose homeost\* [tw]
20. reduced glucose metabolism\* [tw]
21. reduced glucose toleran\* [tw]
22. glucose intolerant\* [tw]
23. glucose tolerance test\* [tw]
24. prediabet\* [tw]
25. praediabet\* [tw]
26. "pre diabetes" [tw]
27. "prae diabetes" [tw]
28. "pre diabetic" [tw]
29. "prae diabetic" [tw]
30. "pre diabetics" [tw]
31. "prae diabetics" [tw]
32. metabolic syndr\* [tw]
33. "syndrome X" [tw]
34. borderline diabet\* [tw]
35. mild diabet\* [tw]
36. insulin resistan\* [tw]
37. impaired insulin secret\* [tw]
38. reduced insulin secret\* [tw]

39. or /1-38

39. and (zinc or (serum zinc level))

40. and (randomized controlled trial [Publication Type] OR controlled clinical trial [Publication Type] OR randomized controlled trials [MeSH Terms] OR random allocation [MeSH Terms] OR double blind method [MeSH Terms] OR single blind method [MeSH Terms] OR clinical trial [Publication Type] OR clinical trials [MeSH Terms] OR (clinical\* [Text Word] AND trial\* [Text Word]) OR single\* [Text Word] OR double\* [Text Word] OR treble\* [Text Word] OR triple\* [Text Word] OR placebos [MeSH Terms] OR placebo\* [Text Word] OR random\* [Text Word] OR research design [MeSH Terms] OR comparative study [MeSH Terms] OR evaluation studies [MeSH Terms] OR follow-up studies [MeSH Terms] OR prospective studies [MeSH Terms] OR control\* [Text Word] OR prospectiv\* [Text Word] OR volunteer\* [Text Word])

## WHAT'S NEW

Last assessed as up-to-date: 29 June 2005.

Date	Event	Description
13 October 2008	Amended	Converted to new review format.

## HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 1, 2007

## CONTRIBUTIONS OF AUTHORS

Vânia Beletate (VB) was responsible for elaboration of the clinical question. Álvaro Nagib Atallah (ANA) was responsible for coordinating this protocol. VB and Regina Paolucci El Dib (RPED) were responsible for the search strategy, running the searches, screening the search results, obtaining papers, screening the retrieved papers against inclusion criteria, appraising the quality of the papers and extracting the data. VB was responsible for writing to the authors of papers for any additional information and locating potentially relevant unpublished or ongoing studies. VB was responsible for the data management of the review. VB and RPED analysed and interpreted data and wrote up the results, whilst seeking clinical, methodological and implications for practice and research.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Brazilian Cochrane Center, Brazil.

### External sources

- No sources of support supplied

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

\*Dietary Supplements; Diabetes Mellitus, Type 2 [\*prevention & control]; Zinc [\*administration & dosage]

### **MeSH check words**

Humans