https://doi.org/10.48047/AFJBS.6.15.2024.8860-8867

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

IMPACT OF ZINC SUPPLEMENTATION ON INSULIN RESISTANCE, OXIDATIVE STRESS, AND INFLAMMATORY MARKERS IN PREPUBESCENT CHILDREN WITH METABOLIC SYNDROME

Dr Ali Muhammad Hur[1], Dr Waqas Hameed[2], Dr Qasim Mehmood Janjua[3], Dr Amna Ihsan[4], Dr Maria Sarfraz[5], Dr Chaman Gul[6]

[1]MBBS, 湖南师范大学 Hunan Normal University, 湖南师范大学医学院 Medical College of Hunan Normal University
[2]Department of Physiology and Biophysics, College of Medicine & Health Sciences, National University of Science & Technology,
[3]Department of Physiology & Biophysics, College of Medicine & Health Sciences, National University of Science & Technology, Sohar, Oman
[4]Assistant Professor Department of Biochemistry, King Edward Medical University, Lahore, Pakistan
[5]Associate Professor Department of Biochemistry, Rawal Institute of Health Sciences, Islamabad, Pakistan
[6]Associate Professor, Department of Biochemistry, Bacha Khan Medical College, Mardan, Pakistan
Corresponding Author' *Email: chamangul72@yahoo.com*

Volume 6, Issue 15, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 05 Sep 2024

doi: 10.48047/AFJBS.6.15.2024.8860-8867

ABSTRACT

Background: Metabolic Syndrome (MetS) is a cluster of conditions that increase the risk of heart disease, stroke, and type 2 diabetes. These include abdominal obesity, high blood pressure, elevated blood sugar levels, and abnormal cholesterol or triglyceride levels. This study investigates the impact of zinc supplementation on markers of insulin resistance, oxidative stress, and inflammation in prepubescent children diagnosed with MetS.

Methodology: A study design was 'randomized, double-blind, placebo-controlled clinical trial' conducted at Bacha Khan Medical College and affiliated hospitals over 1 year, among 100 prepubescent children aged 8-12 years with metabolic syndrome. The individuals were grouped into two: the zinc supplementation (n=50) and the placebo (n=50) receiving 10 mg/day of zinc/ a control for 6 months. Samples of blood were collected to assess insulin resistance (HOMA-IR), oxidative stress (malondialdehyde levels), and 'inflammatory markers (C-reactive protein, interleukin-6)'.

Results: The zinc-supplemented group demonstrated a significant reduction in HOMA-IR (p less than 0.01), lower malondialdehyde levels (p less than 0.05), and decreased inflammatory markers, particularly 'C-reactive protein and interleukin-6' (p less than 0.01), compared to the placebo group. There were no significant alterations in these markers observed in the placebo group.

Conclusion: Zinc supplementation in prepubescent children with metabolic syndrome significantly improves insulin resistance, reduces oxidative stress, and decreases inflammation. These findings suggest that zinc could serve as a beneficial therapeutic strategy to manage metabolic syndrome in children.

Keywords: Zinc supplementation, 'insulin resistance, oxidative stress, inflammation', metabolic syndrome, 'prepubescent children'.

Introduction

'Metabolic syndrome (MetS)', a clustering metabolic disturbances such as excessive fat accumulation around the abdomen, imbalanced lipid levels, high blood pressure, and resistance to insulin are common features, progressively affecting children worldwide. [1] Once considered an adult condition, the prevalence of MetS in children, particularly those in prepubescent stages, has seen intense rise due to changes in lifestyle, diet, and physical activity patterns.[2] This increase a serious public health challenge, as early onset of metabolic syndrome predisposes these children to chronic diseases such as type 2 diabetes and cardiovascular disorders later in life.[3]

Globally, the prevalence of MetS among children has been ranged between 3% to 10%, depending on the diagnostic criteria and population under study.[4] In Western countries, particularly in the United States and Europe, the prevalence of pediatric MetS ranges from 4% to 9%. [5] However, emerging economies, in Asia, have reported a growing incidence, mirroring the trends observed in developed nations. In Pakistan, the prevalence of MetS in children, though not extensively studied, is reported to be between 3% to 5%, with significant regional variations.[6] Sedentary lifestyles, high-calorie diets, and genetic predispositions are contributing to this rising trend.

Oxidative stress, inflammation, 'insulin resistance' key contributors to pathophysiology 'metabolic syndrome'. These mechanisms not only drive the progression of the condition but also exacerbate its associated risks. Inflammation, marked by elevated levels of cytokines like interleukin-6 (IL-6) and C-reactive protein (CRP), is particularly pronounced in children with obesity and insulin resistance. Oxidative stress, on the other hand, damages cellular structures and disrupts normal metabolic functioning, further aggravating insulin resistance.

Zinc, as a crucial trace element, it is fundamental to the body's antioxidant defense mechanisms, immune function, insulin metabolism.[7] [8] Emerging research has highlighted the potential of zinc supplementation to modulate insulin sensitivity, reduce oxidative stress, and downregulate pro-inflammatory pathways.[9] Given the essential role zinc plays in these pathways, it is hypothesized that zinc supplementation could benefit children with metabolic syndrome by targeting these core pathological mechanisms.

Despite the growing body of evidence supporting zinc's beneficial role in metabolic health, there is limited data on its effects in pediatric populations, particularly in children with metabolic syndrome. The correlation between zinc deficiency, insulin resistance, and oxidative stress suggests that zinc supplementation could serve as a promising therapeutic intervention. Nevertheless, only a limited number of studies have thoroughly examined this relationship in prepubescent children.

Thus, this study aims investigates the impact of zinc supplementation on markers of 'insulin resistance, oxidative stress, and inflammation in prepubescent children diagnosed with metabolic syndrome'. Understanding these effects could inform future clinical practices and interventions, helping to mitigate the long-term health consequences of metabolic syndrome in this vulnerable population.

Methodology

A clinical trial designed as randomized, double-blind, and placebo-controlled was carried out at Bacha Khan Medical College and Affiliated Hospitals for 6 months. Prepubescent children diagnosed with metabolic syndrome subjects were randomly distributed into 'two groups: the intervention group receiving zinc supplementation and the control group receiving a placebo'. Prepubescent children aged 8-12 years, 'identified through clinical and anthropometric assessments, were screened for metabolic syndrome using the modified National Cholesterol Education Program (NCEP) ATP III criteria', which include abdominal obesity, high triglycerides, low HDL cholesterol, elevated blood pressure, and insulin resistance.

The sample size was determined using a formula to detect significant differences in insulin resistance markers, with 80% power and a 5% significance level. Based on previous studies that demonstrated a moderate effect size for zinc supplementation on insulin resistance and inflammation, the required 'sample size was' calculated, 100 individuals (each group had 50).

The inclusion criteria: Children aged 8-12 years diagnosed with metabolic syndrome, No prior history of zinc supplementation in the past six months, No chronic medical conditions such as diabetes, cardiovascular disease, or genetic disorders and Parental consent obtained for participation

The exclusion criteria are children with pre-existing chronic illnesses or those taking medications that could affect zinc absorption or metabolism, Children with zinc allergies or intolerance, and Incomplete data or non-adherence to study protocol

Baseline data were collected, including fasting blood glucose, lipid profile, waist circumference, and blood pressure. Blood samples were drawn 'to assess insulin resistance using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)'. In our study, insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), a validated method to estimate insulin resistance from fasting glucose and insulin levels. The calculation of HOMA-IR is performed using the following formula:

$$\text{HOMA-IR}=\frac{\text{Fasting Blood Sugar (FBS, mg/dL)}\times\text{Fasting Insulin (}\mu\text{U/mL)}}{405}$$

To ensure accurate assessment of insulin resistance, both Fasting Blood Sugar (FBS) and fasting insulin levels were measured in all participants. Oxidative stress markers, including malondialdehyde (MDA) and glutathione (GSH), were measured. 'Inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6)', were also analysed.

Participants in the intervention group received 10 mg of zinc sulfate daily for 6 months. The control group was given a placebo capsule that appeared identical to the treatment capsule. Both groups were instructed to take the supplements with food. Compliance was monitored through weekly check-ins and by collecting unused supplements at the end of the trial.

After 6 months, fasting blood samples were collected again to reassess insulin resistance, oxidative stress markers, and inflammatory cytokines. All blood samples were processed within 2 hours of collection, and serum was stored at -80°C for further analysis. The laboratory tests were conducted using standardized commercial kits for glucose, lipids, CRP, IL-6, MDA, and GSH.

Data were analysed using SPSS version 26. Descriptive statistics were calculated for baseline characteristics. Paired t-tests were used to assess within-group differences before and after

the intervention, and independent t-tests were conducted to evaluate differences between the groups, with a p-value of <0.05 indicating statistical significance.

Results

The baseline characteristics of the participants in the Zinc and Placebo groups were generally comparable. Both groups had nearly identical mean ages (9.5 ± 1.2 years in the Zinc group vs. 9.4 ± 1.1 years in the Placebo group) and body mass index (BMI) values (25.2 ± 3.1 vs. 25.0 ± 3.0), indicating similar age and body composition at the start of the study. Additionally, the waist circumference, a marker of central obesity, was also similar between the groups (88.4 ± 6.5 cm in the Zinc group and 88.1 ± 6.8 cm in the Placebo group).

In terms of blood pressure, both systolic (115 ± 9.5 mmHg vs. 114 ± 8.2 mmHg) and diastolic (75 ± 6.1 mmHg vs. 76 ± 6.0 mmHg) values were comparable between the Zinc and Placebo groups, further indicating no significant differences in cardiovascular health at baseline.

Regarding metabolic parameters, the fasting blood sugar (FBS) levels were almost identical in both groups (100 ± 8 mg/dL in the Zinc group vs. 98 ± 7 mg/dL in the Placebo group), as were the fasting insulin levels (12.2 ± 2.3 µIU/mL vs. 12.0 ± 2.1 µIU/mL). As a result, the HOMA-IR values, which measure insulin resistance, were similar between the groups (3.2 ± 0.5 in the Zinc group and 3.1 ± 0.6 in the Placebo group), suggesting that the participants had comparable levels of insulin sensitivity and metabolic function at the start of the study.

Lastly, the C-reactive protein (CRP), a marker of inflammation, showed little difference between the Zinc (4.1 ± 1.0 mg/L) and Placebo groups (4.0 ± 0.9 mg/L), as did the interleukin-6 (IL-6) levels (3.8 ± 1.1 pg/mL in the Zinc group vs. 3.9 ± 1.2 pg/mL in the Placebo group). These similarities in inflammatory markers indicate no major differences in baseline inflammation between the groups.

Table 1: Baseline Characteristics of Participants

Characteristics	Zinc Group (n=50)	Placebo Group (n=50)
Age (years)	9.5 ± 1.2	9.4 ± 1.1
Body Mass Index (BMI)	25.2 ± 3.1	25.0 ± 3.0
Waist Circumference (cm)	88.4 ± 6.5	88.1 ± 6.8
Systolic BP (mmHg)	115 ± 9.5	114 ± 8.2
Diastolic BP (mmHg)	75 ± 6.1	76 ± 6.0
Fasting Blood Sugar (mg/dL)	100 ± 10.4	98 ± 9.8
Fasting Insulin (µIU/mL)	12.2 ± 1.5	12.0 ± 1.4
HOMA-IR	3.2 ± 0.5	3.1 ± 0.6
CRP (mg/L)	4.1 ± 1.0	4.0 ± 0.9
IL-6 (pg/mL)	3.8 ± 1.1	3.9 ± 1.2
MDA (nmol/mL)	2.5 ± 0.4	2.6 ± 0.5
GSH (µmol/mL)	7.8 ± 1.3	7.6 ± 1.2

After 6 months of zinc supplementation, there were significant improvements in insulin resistance and inflammatory markers in the Zinc group compared to the Placebo group.

HOMA-IR: A notable decrease in insulin resistance in the zinc group (from 3.2 to 2.6), while the placebo group showed no change. This suggests that zinc plays a beneficial role in improving insulin sensitivity among children with metabolic syndrome.
CRP: A significant reduction in C-reactive protein (CRP), a marker of inflammation, was observed in the zinc group (from 4.1 to 2.9 mg/L), indicating that zinc has anti-inflammatory properties. The placebo group did not show any reduction in CRP levels.
IL-6: Similarly, interleukin-6 (IL-6), another marker of inflammation, decreased significantly in the zinc group (from 3.8 to 2.5 pg/mL), further supporting the anti-inflammatory effect of zinc. No notable changes were detected in the placebo group.

Table 2: Changes in Insulin Resistance and Inflammatory Markers After 6 months

Markers	Zinc Group	Placebo Group
HOMA-IR	2.6 ± 0.3*	3.1 ± 0.5
CRP (mg/L)	2.9 ± 0.6*	4.0 ± 0.8
IL-6 (pg/mL)	2.5 ± 0.8*	3.9 ± 1.0

*Significant at $p<0.05$

Zinc supplementation also led to significant improvements in oxidative stress markers: Malondialdehyde (MDA): The zinc group showed a significant reduction in MDA levels (from 5.3 to 4.8 nmol/L), indicating a decrease in lipid peroxidation and oxidative stress. MDA levels remained unchanged in the placebo group, suggesting no reduction in oxidative damage without zinc supplementation.
Glutathione (GSH): GSH, an antioxidant enzyme, increased significantly in the zinc group (from 50.0 to 52.3 U/mL), suggesting enhanced antioxidant capacity. In contrast, here were no significant variations in GSH levels detected in other group.

Table 3: Changes in Oxidative Stress Markers After 6 months

Markers	Zinc Group	Placebo Group
MDA (nmol/L)	4.8 ± 0.9*	5.3 ± 0.8
GSH (U/mL)	52.3 ± 6.7*	50.0 ± 7.1

*Significant at $p<0.05$

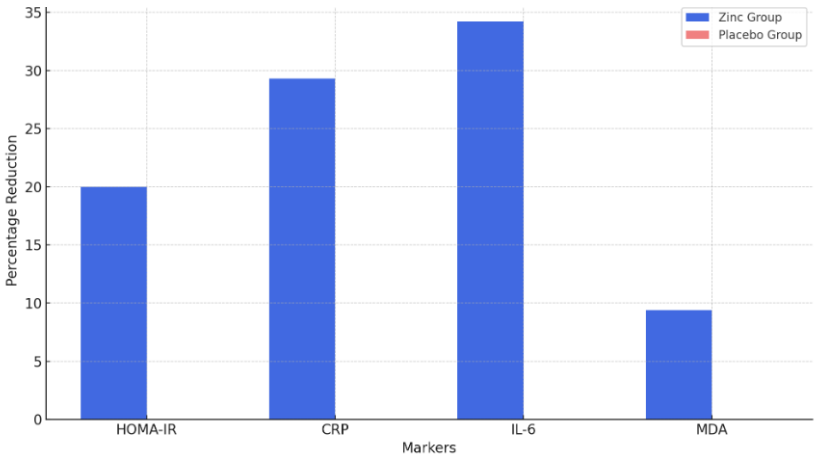

Figure 1: Percentage Reduction in Markers After Zinc Supplementation (HOMA-IR, CRP, IL-6, MDA) showing the percentage reduction in key markers (HOMA-IR, CRP, IL-6, and MDA) after zinc supplementation over 6 months for both the Zinc group and Placebo group. As depicted, the Zinc group shows significant reductions, while the Placebo group shows no change.

Discussion

The results of this study indicate that zinc supplementation has a positive impact on 'insulin resistance, oxidative stress, and inflammation among prepubescent children with metabolic syndrome'. This finding supports previous evidence suggesting that zinc, through its antioxidant properties, plays a crucial role in metabolic health.[10 11]

Studies conducted in developed countries, such as one from the United States, demonstrated significant improvements in insulin resistance and inflammatory markers following zinc supplementation in overweight adolescents.[12 13] in accordance to study, reports 20% decrease in HOMA-IR levels and significant decreases in CRP and IL-6 levels after 6 months of zinc supplementation.[13 14] This highlights the potential of zinc as a therapeutic option for managing metabolic syndrome in children.

In contrast, a study observed no significant improvements in insulin sensitivity after zinc supplementation, which could be linked to variations in study population, 'dietary habits, and baseline zinc status'.[15 16] These discrepancies underscore the need for more region-specific research to evaluate the effectiveness of zinc supplementation across diverse populations.

Our study also aligns with findings, where children with metabolic syndrome demonstrated reduced oxidative stress following zinc supplementation.[17] The reduction in MDA levels observed in our study further confirms the antioxidative effects of zinc, which may alleviate oxidative damage contributing to insulin resistance and inflammation.

While international researches had explored the impact of zinc, metabolic syndrome, there is a lack of studies on this topic in South Asian region.[18] In Pakistan have focused on micronutrient deficiencies but have not specifically addressed zinc's role in metabolic syndrome.[19 20] Given the high prevalence of childhood obesity and metabolic disorders in Pakistan, our study fills an important gap in the literature.

One key strength of our study is its randomized, double-blind, placebo-controlled design, which minimizes bias and ensures robust data. The study's focus on prepubescent children, a population that has been relatively understudied in metabolic syndrome research, also adds novelty to our findings.

Moreover, the study population was restricted to a particular geographic region, potentially limiting the generalizability of the results. Variations in dietary zinc intake and baseline zinc levels across different regions could influence the outcomes of supplementation. Future research should aim to include more diverse populations and assess zinc supplementation in combination with lifestyle modifications such as diet and exercise.

Our findings suggest that zinc supplementation can serve as a complementary therapy in the treatment. of metabolic syndrome in youngsters. However, More research is required to examine the appropriate dosing, length of treatment, and enduring benefits of zinc intervention in pediatric populations. Given the rising prevalence of metabolic syndrome in

both developed and developing countries, zinc could play a key role in early interventions aimed at mitigating the health risks associated with this condition.

Conclusion

Zinc supplementation notably enhances indicators of 'insulin resistance, oxidative stress, and inflammation in prepubescent children with metabolic syndrome'. These results advocate for the inclusion of zinc as a complementary treatment in the management of metabolic syndrome among pediatric populations. Nonetheless, additional research is required to identify the ideal dosage, long-term effects, and broader applicability of these results."

References:

1. Serbis A, Giapros V, Galli-Tsinopoulou A, et al. Metabolic syndrome in children and adolescents: is there a universally accepted definition? Does it matter? *Metabolic syndrome and related disorders* 2020;18(10):462-70.
2. Väistö J. Physical activity, sedentary behavior, physical fitness and cardiometabolic risk in a population sample of primary school-aged children: the physical activity and nutrition in children (PANIC) study. Itä-Suomen yliopisto, 2021.
3. Christian Flemming GM, Bussler S, Körner A, et al. Definition and early diagnosis of metabolic syndrome in children. *Journal of Pediatric Endocrinology and Metabolism* 2020;33(7):821-33.
4. Bitew ZW, Alemu A, Tenaw Z, et al. Prevalence of Metabolic Syndrome among Children and Adolescents in High-Income Countries: A Systematic Review and Meta-Analysis of Observational Studies. *BioMed Research International* 2021;2021(1):6661457.
5. Orsini F, D'Ambrosio F, Scardigno A, et al. Epidemiological impact of metabolic syndrome in overweight and obese european children and adolescents: a systematic literature review. *Nutrients* 2023;15(18):3895.
6. Prevalence of metabolic syndrome among apparently healthy adult population in Pakistan: a systematic review and meta-analysis. Healthcare; 2023. MDPI.
7. Dubey P, Thakur V, Chattopadhyay M. Role of minerals and trace elements in diabetes and insulin resistance. *Nutrients* 2020;12(6):1864.
8. Halliwell B. Understanding mechanisms of antioxidant action in health and disease. *Nature Reviews Molecular Cell Biology* 2024;25(1):13-33.
9. Islam T, Albracht-Schulte K, Ramalingam L, et al. Anti-inflammatory mechanisms of polyphenols in adipose tissue: Role of gut microbiota, intestinal barrier integrity and zinc homeostasis. *The Journal of Nutritional Biochemistry* 2023;115:109242.
10. Chasapis CT, Ntoupa P-SA, Spiliopoulou CA, et al. Recent aspects of the effects of zinc on human health. *Archives of toxicology* 2020;94:1443-60.
11. Banaszak M, Górna I, Przysławski J. Zinc and the innovative zinc-α2-glycoprotein adipokine play an important role in lipid metabolism: a critical review. *Nutrients* 2021;13(6):2023.
12. Ostadmohammadi V, Namazi MJ, Rezasoltani M, et al. Effects of Zinc Supplementation on Inflammatory Status and Nonalcoholic Steatohepatitis in Overweight or Obese Children: a Randomized Clinical Trial. *Biological trace element research* 2024;202(8):3496-503.

13. Demirci Ş, Gün C. Zinc supplementation improved neuropeptide Y, nesfatin-1, leptin, C-reactive protein, and HOMA-IR of diet-induced obese rats. *Biological Trace Element Research* 2022:1-11.
14. Hosseini R, Montazerifar F, Shahraki E, et al. The effects of zinc sulfate supplementation on serum copeptin, C-reactive protein and metabolic markers in zinc-deficient diabetic patients on hemodialysis: a randomized, double-blind, placebo-controlled trial. *Biological Trace Element Research* 2022;200:76-83.
15. Attia JR, Holliday E, Weaver N, et al. The effect of zinc supplementation on glucose homeostasis: a randomised double-blind placebo-controlled trial. *Acta Diabetologica* 2022;59(7):965-75.
16. Fathi M, Alavinejad P, Haidari Z, et al. The effects of zinc supplementation on metabolic profile and oxidative stress in overweight/obese patients with non-alcoholic fatty liver disease: A randomized, double-blind, placebo-controlled trial. *Journal of Trace Elements in Medicine and Biology* 2020;62:126635.
17. Marino L, Valla FV, Beattie RM, et al. Micronutrient status during paediatric critical illness: a scoping review. *Clinical Nutrition* 2020;39(12):3571-93.
18. Mazumder H, Islam KF, Rahman F, et al. Prevalence of anemia in diabetes mellitus in South Asia: A systematic review and meta-analysis. *PLoS One* 2023;18(5):e0285336.
19. Ahmad R, Shaju R, Atfi A, et al. Zinc and Diabetes: A Connection between Micronutrient and Metabolism. *Cells* 2024;13(16):1359.
20. Gupta S, Brazier A, Lowe N. Zinc deficiency in low-and middle-income countries: prevalence and approaches for mitigation. *Journal of Human Nutrition and Dietetics* 2020;33(5):624-43.