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Combined Effects of Curcumin and Zinc Co-Supplementation on Inflammatory and Oxidative Stress Biomarkers in Prediabetes: A Double-Blind, Randomized, Placebo- Controlled Trial

Maryam Azhdari

azhdari_mar@yahoo.om

Shahid Sadoughi University of Medical Sciences

Majid Karandish

Ahvaz Jundishapur University of Medical Sciences

Hassan Mozaffari-khosravi

Shahid Sadoughi University of Medical Sciences

Bahman Cheraghian

Ahvaz Jundishapur University of Medical Sciences

Seyed Mohammad Mohammadi

Shahid Sadoughi University of Medical Sciences, Iran

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Combined Effects of Curcumin and Zinc Co-Supplementation on Inflammatory and Oxidative Stress Biomarkers in Prediabetes: A Double-Blind, Randomized, Placebo-Controlled Trial

Maryam Azhdari [1,2*], Majid Karandish[3], Hassan Mozaffari-khosravi[1], Bahman Cheraghian[4], Seyed Mohammad Mohammadi[5]

[1]Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[2] Researcher, Nutrition and Beauty and Amino Company, Yazd, Iran

[3] Nutrition and Metabolic Diseases Research Center, Clinical Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[4] Department of Biostatistics and Epidemiology, School of Health Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

[5] Shahid Sadoughi Hospital, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

***Corresponding Author:** Maryam Azhdari

Email: azhdari_mar@yahoo.com

Abstract

Background:

Prediabetes is associated with an increased risk of metabolic comorbidities and all-cause mortality. Given the limitations of conventional therapies in preventing disease progression, many individuals seek complementary and alternative medicine (CAM) approaches. Curcumin and zinc, which are recognized for their antioxidant and anti-inflammatory properties, may provide therapeutic benefits. This study evaluated the effects of curcumin and zinc co-supplementation on inflammatory and antioxidant biomarkers in overweight or obese individuals with prediabetes.

Methods:

In this 90-day, single-center, double-blind, randomized, placebo-controlled trial, 84 adults with prediabetes (body mass index [BMI] 25–35 kg/m²; men aged 18–50 years and premenopausal women aged ≥18 years) were randomly assigned to four groups (n = 21 each): curcumin (500 mg/day), zinc (30 mg/day), curcumin plus zinc, or placebo. The study protocol was approved by the Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1398.504). Written informed consent was obtained prior to enrollment.

Primary outcomes included malondialdehyde (MDA), high-sensitivity C-reactive protein (hs-CRP), superoxide dismutase (SOD), interleukin-1β (IL-1β), and total antioxidant capacity (TAC). Secondary outcomes included serum and urinary zinc levels.

Results:

Of the 84 participants, 82 completed the study. Curcumin and zinc co-supplementation significantly increased serum (p=0.001) and urinary (p=0.04) zinc levels. After adjusting for baseline physical activity, co-supplementation significantly increased TAC and SOD and significantly decreased IL-1β (all adjusted P=0.001) and hs-CRP (adjusted P=0.04) compared with placebo. However, the reduction in MDA did not reach statistical significance (p=0.097).

After adjusting for baseline physical activity, co-supplementation significantly increased TAC and SOD and significantly decreased IL-1β (all adjusted P=0.001) and hs-CRP (adjusted P=0.04) compared with placebo. However, the reduction in MDA did not reach statistical significance (p=0.097).

Conclusion

Curcumin and zinc co-supplementation significantly decreased IL-1β and hs-CRP while enhancing TAC and SOD in overweight or obese individuals with prediabetes. These findings suggest that this curcumin and zinc co-supplementation may represent a safe and well-tolerated complementary strategy.

Trial registration

The study protocol was prospectively registered in the Iranian Registry of Clinical Trials (IRCT20190902044671N1) on October 11, 2019.

Keywords

antioxidant biomarkers, curcumin, inflammatory biomarkers, Oxidative Stress, prediabetes,

1. Background

Prediabetes, an intermediate metabolic state between normal glucose regulation and type 2 diabetes mellitus (T2DM), is estimated to affect approximately 720 million people worldwide, and its prevalence steadily increasing (1, 2).

This condition is associated with a significantly increased risk of progression to T2DM and serious complications, including cardiovascular disease, chronic kidney disease, and elevated all-cause mortality (2, 3). Impaired insulin sensitivity and β-cell dysfunction are key contributors to T2DM pathogenesis, often manifesting years before clinical diagnosis (3).

Effective and sustainable interventions to prevent or delay T2DM progression are urgently needed (2). However, adherence to lifestyle modifications, such as dietary changes and physical activity (PA), is typically low due to behavioral, socioeconomic, and environmental barriers (5). Consequently, many individuals with prediabetes seek complementary and alternative medicine (CAM) approaches, particularly dietary supplements, as adjunctive strategies (5, 6).

Curcumin, a bioactive compound derived from turmeric (Curcuma longa L.), and zinc, an essential trace element, have been identified as promising CAM agents because of their antioxidant and anti-inflammatory properties (7, 8).

Curcumin and zinc have demonstrated beneficial effects on metabolic health. Curcumin has been widely studied for its anti-inflammatory, antioxidant, and glucose-modulating properties (7).

Curcumin supplementation has been shown to improve glucose homeostasis, lipid profiles (e.g., total cholesterol (TC), triglyceride (TG)), and inflammatory markers (e.g., C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP), and monocyte chemoattractant protein-1 (MCP-1) as well as antioxidant biomarkers (e.g., malondialdehyde (MDA), superoxide dismutase (SOD)), in individuals with obesity, polycystic ovary syndrome (PCOS), T2DM, nonalcoholic fatty liver disease (NAFLD) and other chronic conditions (3, 7, 9 -12).

Evidence from animal studies suggests that curcumin reduces interleukin-1β (IL-1β) secretion by inhibiting the NLRP3 inflammasome (13). Similarly, zinc enhances antioxidant defense through increased superoxide dismutase (SOD) activity and modulating inflammatory pathways, thereby improving glycemic markers, lipid profiles, CRP, hs-CRP and total antioxidant capacity (TAC) in prediabetes, T2DM, and gestational diabetes (8, 14 -16).

However, the effects of zinc on maternal MDA levels and TNF-α remain inconclusive (16, 17). Zinc deficiency has been associated with increased IL-1β production, with plasma cytokine levels responding dose-dependently to zinc intake (18, 19).

Despite these findings, approximately 5–10% of individuals with prediabetes progress to T2DM annually, even with lifestyle interventions (2). The synergistic effects of curcumin and zinc in prediabetes management have largely been unexplored in human clinical trials. Therefore, this randomized controlled trial was designed to evaluate the combined effects of curcumin and zinc co-supplementation on inflammatory and oxidative stress biomarkers in overweight or obese individuals with prediabetes, addressing a critical gap in the management of this condition.

2.Methods

2.1 Study design and setting

This 90-day, double-blind, randomized, placebo-controlled trial was conducted at a single center, the Diabetes Research and Clinical Practice Center in Yazd, Iran. Participants were recruited via convenience sampling through multiple communication channels, including email, telephone, SMS, and social media platforms such as Telegram and WhatsApp. Methods and findings related to glycemic indices, dietary intake, and lipid profiles were previously reported (20, 21, 22); the present study represents a predefined secondary analysis focusing on inflammatory and oxidative stress biomarkers. Key details are summarized to provide context for the current sub-study.

Eligibility was assessed through medical record review and physician referrals. After confirmation of baseline criteria, participants were randomized. The study was carried out in accordance with Good Clinical Practice (GCP) guidelines.

2.2 Ethical considerations

The study protocol was approved by the Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1398.504) and prospectively registered in the Iranian Registry of Clinical Trials (IRCT20190902044671N1). The trial adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Supplementary S.3), and the participant flow diagram is presented in Figure 1 . Written informed consent was obtained prior to enrollment.

2.3 Participant selection

A total of 84 participants who met the predefined inclusion and exclusion criteria (23, 24) were enrolled. Eligible participants were men aged 18 to 50 years and premenopausal women aged 18 years or older who were diagnosed with prediabetes based on the American Diabetes Association (ADA) criteria: fasting plasma glucose (FPG) of 100–125 mg/dL, 2-hour postprandial glucose (2hPG) of 140–199 mg/dL, or glycated hemoglobin (HbA1c) of 5.7– 6.4% (11). Additional criteria included a body mass index (BMI) of 25 to 35 kg/m² and the provision of written informed consent.

Exclusion criteria were as follows: a history of malignancies, autoimmune diseases, chronic or acute hepatic disorders, biliary diseases, hereditary liver disorders, renal diseases, pulmonary diseases, thyroid dysfunctions (hypothyroidism or hyperthyroidism), Cushing's syndrome, inflammatory diseases, neurological diseases, or hypertension (defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg); use of medications affecting blood pressure, glucose, or lipid levels within the previous three months; use of multivitamin or mineral supplementation within three months before the intervention, bariatric surgery within the past year; and participation in weight-loss programs within the previous three months, pregnancy,

lactation, or unwillingness to adhere to the study protocol. Individuals with hypertension were excluded to minimize potential confounding effects of antihypertensive medications and hypertension-related vascular inflammation on oxidative stress and inflammatory biomarkers. Participants were withdrawn if they had less than 80% adherence, experienced adverse events, or withdrew voluntarily.

2.4 **Sample size**

The required sample size was calculated based on FPG, the most variable outcome in the broader project. Because inflammatory outcomes required smaller samples, the FPG-based calculation was chosen as the most conservative approach.

Using WinPepi (Version 11.4; Abramson, 2011), with 80% power, a two-sided alpha level of 0.05, and prior standard deviation (SD), the minimum required sample size was estimated at 76 participants (19 per group). Allowing for 10% attrition, the final sample size was increased to 84 participants (21 per group), which was deemed sufficient to detect clinically meaningful differences.

2.5 Randomization and Blinding

A computer-generated random number table was used by an independent statistician to allocate participants using block randomization (block size = 4), stratified by sex and BMI. Allocation was concealed in sealed, opaque envelopes prepared by a pharmacist who was not otherwise involved in the trial. Both participants and study assessors remained blinded to group assignment throughout the intervention period. To maintain blinding, supplements were dispensed by a blinded assessor at baseline, day 30, and day 60.

2.6 Intervention

Eligible participants were assigned to one of four groups using a 2x2 factorial design: Curcumin Group: Received 500 mg BCM-95® curcumin (Curcugreen capsule, Arjuna Natural Pvt Ltd., India) (25) plus a zinc placebo; Zinc Group: Received 30 mg zinc gluconate (Dineh Company, Iran) (26) plus a curcumin placebo; Curcumin and Zinc Group: Received both 500 mg BCM-95® curcumin and 30 mg zinc gluconate; Placebo Group: Received placebos for both curcumin and zinc.

Details of BCM-95® curcumin analysis and the Ultra Performance Liquid Chromatography (UPLC) results are shown in the Supplementary S1 and Figure S.1, respectively. Curcumin placebo (roasted rice powder) was provided by Arjuna Natural Pvt Ltd., India. Zinc placebo (lactose) was formulated at Shahid Sadoughi University of Medical Sciences, Iran.

Participants were instructed to take curcumin capsule after breakfast and the zinc tablet before breakfast (or their corresponding placebo), daily for 90 consecutive days.

All participants received lifestyle counseling, including a personalized hypocaloric diet and guidance to perform 150 minutes/week of PA (21, 26, 27). Additional lifestyle counseling details were provided in the Supplementary S.2. Supplements and lifestyle counseling were provided on days 1, 30, and 60.

2.7 Follow-up and adherence

Participants were followed through daily messages (Telegram or WhatsApp) or weekly phone calls. They were reminded to take their assigned supplement each morning (or later if missed). Adherence was assessed via pill counts and self-maintained diaries on days 1, 30, and 60. Adverse events were promptly documented and reported to the Data Monitoring Committee and the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences.

2.8 Data collection and outcome measures

Baseline demographics and medical history data, including sex, age, marital status, smoking history, alcohol use, and duration of prediabetes, were collected using standardized forms for each participant. Anthropometric measurements, including weight, height, and BMI, were obtained in duplicate using calibrated equipment. Measurements were conducted by trained research staff. Mean values of anthropometric variables were used for statistical analysis. BMI (kg/m^2) was calculated using the standard formula: weight (kg) / (height (m)) ^{2}.

Primary outcomes included TAC, MDA, SOD, IL-1β, and hs-CRP. Secondary outcomes included serum and urinary zinc levels. Assessments were performed at baseline and after 90 days. Height was measured only at baseline. Monthly monitoring was used to assess adherence.

2.9 Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). A two-tailed $p < 0.05$ was considered statistically significant.

2.9.1 Data distribution and descriptive statistics

Data normality was tested using the Kolmogorov-Smirnov test, and homogeneity of variance was assessed with Levene's test. Except for PA, all continuous variables were normally distributed. Normal data were expressed as mean ± SD. Categorical variables were summarized as frequencies and percentages.; non-normally distributed variables as median (interquartile range IQR); and categorical variables as frequencies (percentages).

2.9.2 Between-group comparisons

For normal data, between-group comparisons were conducted with one-way ANOVA and Least Significant Difference (LSD) post hoc tests. For non-normal data, the Kruskal-Wallis test was applied.

To support the selection and interpretation of covariates in the statistical models, relevant baseline data from a previously published dataset (20, 21) were included in the Supplementary, Table S1. These data were used exclusively for covariance modeling and were not incorporated into the primary statistical analyses of the current study.

To account for potential baseline differences in PA levels and key metabolic parameters including glycemic parameters (FPG, 2hPG, and HbA1C) (21) as well as lipid profile components (TC, serum low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-C)) (21), univariate analysis of covariance (ANCOVA) was performed using two models: Model 1 (adjusted for baseline PA levels) and Model 2 (adjusted for changes in weight, BMI, FPG, 2hPG, HbA1C, TC, LDL-C, TG, and HDL-C).

Covariates were selected based on clinical relevance and statistically significant baseline differences. Further details of baseline variations and covariates are provided in the Supplementary, Table S1.

3. Results

Of the 84 participants enrolled, 82 completed the 90-day trial (56 women (68%) and 26 men (32%)). Two participants withdrew due to non-compliance and adverse effects, one from the curcumin and zinc group due to nausea and one from the placebo group due to severe abdominal pain. Mean adherence, assessed by pill count, was 88.87 ± 1.93%. Compliance was comparable across groups ($p = 0.21$) (Supplementary, Table S2).

The CONSORT flow diagram is shown in Figure 1. No severe adverse reactions were reported during the intervention. The mean duration of prediabetes was 2.31 ± 1.37 years, and the average age was 36.04 ± 6.61 years.

At baseline, no significant differences were identified in terms of family history of diabetes or hypertension, alcohol consumption, glycemic parameters (FPG, 2hPG, HbA1C, serum insulin), lipid profiles (TC, LDL-C, TG, HDL-C), or dietary intake (carbohydrates, fats, proteins, and total energy) ($p \geq 0.05$). However, PA levels differed between groups (Supplementary, Table S3).

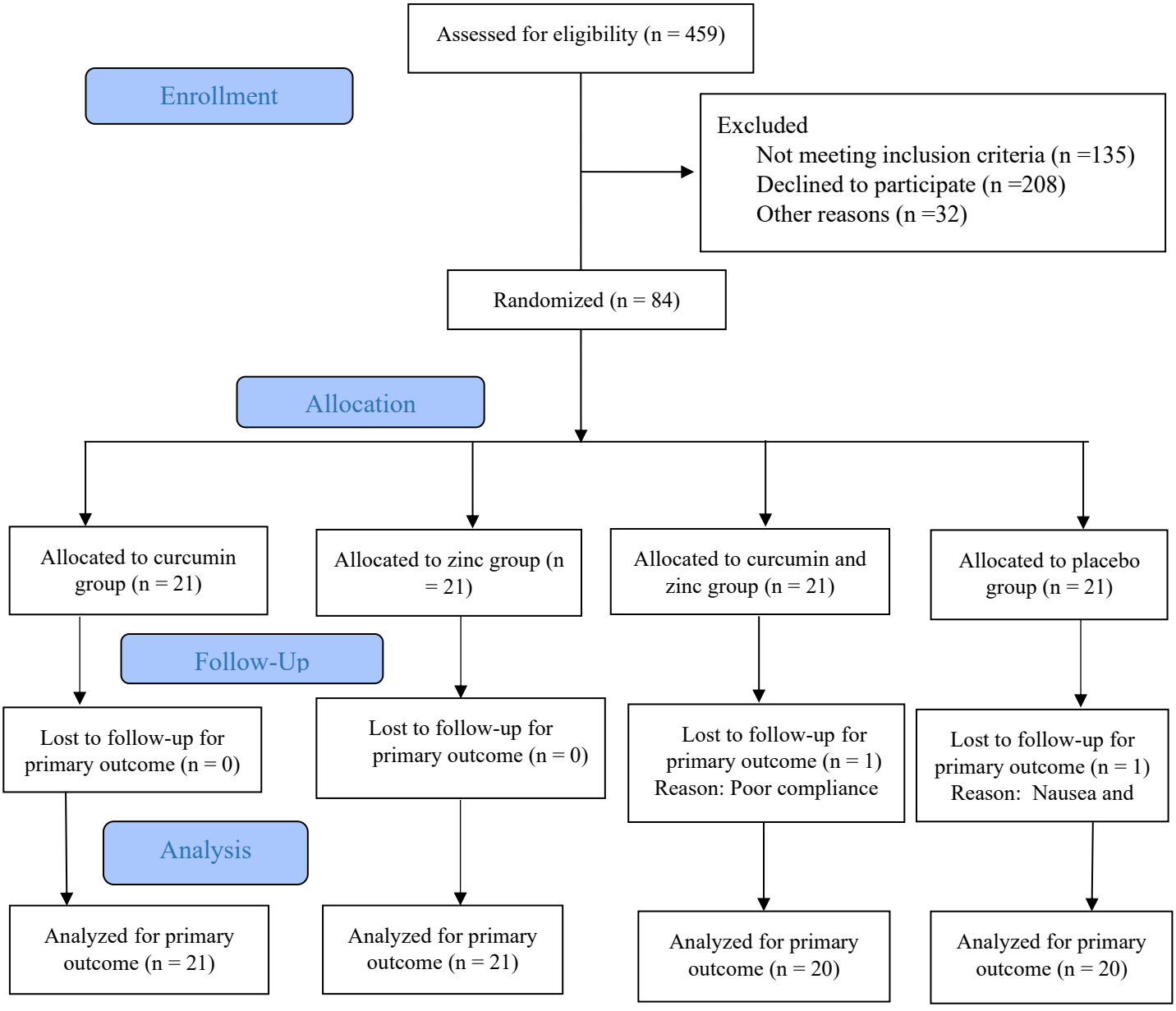


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of participant enrollment, allocation, and analysis. A total of 459 individuals were assessed for eligibility, of whom 135 did not meet inclusion criteria, 208 declined to participate, and 32 were excluded for other reasons. Eighty-four participants were randomly assigned to four groups (n = 21 each): curcumin (500 mg/day), zinc (30 mg/day), curcumin plus zinc, or placebo. During the trial, one participant in the curcumin and zinc group was lost to follow-up due to nausea and severe abdominal pain, and one in the placebo group due to poor compliance. A total of 82 participants (56 women and 26 men) completed the trial and were included in the final analysis.

Significant between-group differences were detected for changes in FPG (p= 0.002), 2hPG (p = 0.004), HbA1c (p = 0.018), SBP (p < 0.001), TC (p = 0.005), LDL-C (p < 0.001), TG (p = 0.007), and HDL-C (p = 0.007) (Supplementary, Table S1). After PA adjustment (Model1), improvements remained significant in FPG (adjusted p = 0.0026), 2hPG (adjusted p = 0.02), HbA1c (adjusted p = 0.029), SBP (adjusted p < 0.001), LDL-C (adjusted p = 0.035), TG (adjusted p = 0.001), and HDL-C (adjusted p < 0.001); however, TC was also not significant after adjustment (Adjusted p ≥ 0.05) (Supplementary, Table S1).

No significant between-group differences were observed for changes in serum insulin, DBP, ALT, AST, or dietary intake (carbohydrates, fats, proteins, and total energy) either before or after PA adjustment (p ≥ 0.05) (Supplementary, Table S1).

For zinc status, significant between-group differences were observed in serum (p < 0.001) and urinary (p = 0.04) levels (Table 1). Pairwise analyses showed significant increases in serum zinc in the zinc compared to both placebo (p < 0.001) and curcumin (p < 0.001) groups, and in the curcumin and zinc group compared to the curcumin (p < 0.001) and placebo (p = 0.001) groups. No significant difference was observed between the zinc group and the curcumin and zinc group (p ≥ 0.05) (Supplementary, Table S4).

Table 1: Between-group comparison of changes in serum and urinary zinc levels from baseline to day 90.

Variables	**Groups**				**P**
	Placebo N= 20	**Curcumin N= 21**	**Zinc N= 21**	**Curcumin and zinc N= 20**	
Serum zinc (µg/dL)	-0.25 ± 5.9 [a,b]	0.43 ± 3.89 [c,d]	6.29 ± 5.1 [a,c]	5.9 ± 4.46 [b,d]	**< 0.001**

Urinary zinc (µg/dL)	1 ± 6.16[a]	1.9 ± 20.81 [b]	7.29 ± 7.77	11.4 ± 10.98 [a,b]	**0.04**

Data are expressed as mean ± standard deviation (SD).

Between-group comparisons were analyzed using one-way analysis of variance (ANOVA) followed by LSD post hoc test.

Different superscript letters (a, b, c, d) indicate statistically significant differences between groups ($P \leq 0.05$).

For urinary zinc, pairwise comparisons showed no differences for zinc compared to others ($p \geq 0.05$); however, the curcumin and zinc group showed a significant increase in urinary zinc levels compared to the curcumin ($p = 0.012$) and zinc ($p = 0.021$) groups (Supplementary, Table S4).

Between-group comparison for inflammatory (IL-1β and hs-CRP) and antioxidant (TAC, MDA, and SOD) biomarkers were presented in Table 2. TAC was significantly increased ($p < 0.001$) in all treatment groups compared to placebo (Supplementary, Table S5).

Table2. Between-groups comparison of changes in inflammatory and antioxidant biomarkers from baseline to day 90

Variables	**Groups**	**P**	***Adjusted P** (Model 1)	****Adjusted P** (Model 2)

	Placebo N= 20	Curcumin N= 21	Zinc N= 21	Curcumin and zinc N= 20			
TAC	25.05 ± 16.72 [a,b,c]	140.8 ± 103.6 [a]	170.73 ± 107.46 [b]	187.26 ± 158.92 [c]	**< 0.001**	**0.003**	**< 0.001**
MDA	-0.79 ± 0.41 [a,b]	-1.92 ± 1.42 [a]	-1.32 ± 0.76	-1.85 ± 1.31 [b]	**0.004**	**0.004**	0.097
SOD	0.09 ± 1.81 [a,c]	11.77 ±9.79 [a,b]	18.61 ± 4.83 [a]	23.44 ± 5.77 [a,b,c]	**< 0.001**	**< 0.001**	**< 0.001**
IL-1B	-0.2 ±0.69 [a,b,c]	-1.2 ± 0.89 [a,d]	-1.67 ± 1.27 [b]	-1.96 ± 1.03 [cd]	**< 0.001**	**< 0.001**	**< 0.001**
hs-CRP	-0.13 ± 0.1 [a,b]	-0.48 ± 0.16 [a,c]	-0.23 ± 0.16 [c,d]	-0.39 ± 0.2 [b,d]	**< 0.001**	**< 0.001**	**0.041**

Abbreviations: hs-CRP: high-sensitivity C-reactive protein; IL-1 β: Interleukin-1-beta; MDA: malondialdehyde; SOD: superoxide dismutase; TAC: total antioxidant capacity.

Data were presented as mean ± standard deviation (SD).

$P \leq 0.05$ was considered statistically significant. Between-group comparisons were performed using one-way analysis of variance (ANOVA) followed by LSD post hoc test.

Different superscript letters (a, b, c) indicate significant pairwise differences ($P \leq 0.05$).

For covariate-adjusted models:

* Model 1: Adjusted for baseline physical activity using ANCOVA.

** Model 2: Adjusted for changes in weight, Body mass index (BMI), Fasting Plasma Glucose (FPG), 2-hour Postprandial Glucose (2hPG), Hemoglobin A1c (HbA1c), Total

Cholesterol (TC), Low-Density Lipoprotein (LDL-C), Triglyceride (TG), and High-Density Lipoprotein-cholesterol (HDL) using ANCOVA.

MDA levels were significantly reduced across all groups ($p < 0.001$), with significant reductions in the curcumin ($p = 0.001$) and curcumin and zinc ($p = 0.002$) groups compared to placebo (Supplementary, Table S5).

SOD levels increased more in all active intervention groups compared with placebo ($p < 0.001$). Post hoc pairwise comparisons confirmed significant increases in SOD levels in each active group versus placebo. The combination showed greater improvements than curcumin ($p < 0.001$) and zinc alone ($p = 0.016$) (Supplementary, Table S5). Pairwise comparisons revealed significant reductions in all active intervention groups versus placebo group, with the combination demonstrating the greatest reduction.

Significant between-group differences were also identified in IL-1β levels ($p < 0.001$). Pairwise comparisons showed significant reductions in the curcumin ($p = 0.001$), zinc ($p < 0.001$), and curcumin and zinc ($p < 0.001$) groups compared to placebo. Furthermore, the curcumin and zinc group showed a significant reduction in IL-1β levels compared to the curcumin group ($p = 0.012$) (Supplementary, Table S5).

A significant reduction in hs-CRP levels was also observed ($p < 0.001$). Reductions were significant in the curcumin ($p < 0.001$), curcumin and zinc ($p = 0.001$) groups compared to placebo. Both the curcumin ($p = 0.003$) and curcumin and zinc ($p = 0.044$) groups showed significantly greater reductions compared to the zinc group (Supplementary, Table S5).

After adjusting in Model 1 (PA adjustment), significant between-group differences persisted for IL-1β, hs-CRP, and SOD ($p < 0.001$), as well as for TAC ($p = 0.003$), and MDA ($p = 0.004$). After full adjustment in Model 2 (adjusted for changes in weight, BMI, FPG, 2hPG,

HbA1c, TC, LDL-C, TG, and HDL-C), significant between-group differences remained for IL-1β, SOD, and TAC ($p < 0.001$), and hs-CRP ($p = 0.041$), but not for MDA ($p = 0.097$).

4. Discussion

This randomized, double-blind, placebo-controlled clinical trial evaluated the effects of 90-day co-supplementation of curcumin and zinc in overweight or obese adults with prediabetes. The key findings demonstrated that co-supplementation: (1) significantly reduced circulating levels of pro-inflammatory biomarkers (IL-1β and hs-CRP) compared to placebo, (2) enhanced antioxidant capacity (SOD activity and TAC) compared to placebo, and (3) showed numerically greater improvements over monotherapies, with a larger reduction in IL-1β than curcumin alone and higher SOD activity than zinc alone. These results suggest potential additive effects, though formal interaction analysis was not performed.

Mechanistic insights elucidate these synergistic effects. The observed antioxidant synergy likely arises from zinc's role in potentiating curcumin-mediated activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathways via inhibition of Kelch-like ECH-associated protein 1 (Keap1) ubiquitination, thereby amplifying SOD upregulation. Concurrently, the anti-inflammatory synergy stems from the combination's ability to suppress nuclear factor-kappa B (NF-κB) activation more effectively than either agent alone, accounting for the pronounced reduction in IL-1β and hs-CRP.

The observed antioxidant and anti-inflammatory effects may involve zinc-mediated potentiation of curcumin-induced Nrf2 activation and suppression of NF-κB signaling, as suggested by preclinical studies. Notably, the lack of a significant MDA decrease may be explained by stage-specific pathophysiology (lower lipid peroxidation in prediabetes compared with T2DM) or methodological factors (e.g., dose, duration). No severe adverse events were reported, supporting the intervention's tolerability.

This contrasts with prior studies in advanced metabolic disease (3, 10, 28-29) and warrants further dose-duration investigations.

These findings extend previous evidence by demonstrating synergy in prediabetes, a stage where oxidative stress and inflammation drive β-cell dysfunction. (3, 10, 18, 28, 30–33). The greater reduction in IL-1β highlights the potential for attenuating NOD-like receptor protein 3 (NLRP3) inflammasome-mediated β-cell apoptosis. Curcumin's direct Nrf2 activation (via Keap1 interaction) and NF-κB suppression (35) and zinc's stabilization of Nrf2/IL-1β modulation (4, 6, 8, 19, 28, 30, 33) align with the observed effects. Additionally, curcumin upregulates gene expression related to oxidative stress, thereby reducing lipid peroxidation by scavenging free radicals (29).

Zinc further contributes to antioxidant and anti-inflammatory activity by stabilizing Nrf2 through Keap1 ubiquitination inhibition, reducing IL-1β maturation, and supporting enzymatic processes critical for oxidative balance and inflammation control (4, 6, 8, 19, 28, 30).

However, some studies have reported inconsistent effects of either curcumin or zinc on inflammatory markers, possibly due to differences in formulation, bioavailability, or baseline metabolic status of participants. This underscores the need for further stratified analyses to identify subgroups most likely to benefit.

In summary, the observed concordance between elevated SOD/TAC and reduced IL-1β/hs-CRP underscores the potential of this combination as an adjunctive therapy for oxidative-inflammatory dysregulation; larger, multicenter trials are warranted. However, larger, multicenter trials with extended follow-up and functional metabolic endpoints are warranted to confirm its integration into preventive strategies for T2DM.

4.1 Strengths and limitations

A key strength of this study lies in its rigorous design as a randomized, double-blind, placebo-controlled trial, which strengthens the validity of the findings. The multi-arm approach allowed for a comprehensive comparison between individual and combined interventions, providing insights into their potential as adjunctive therapies in managing prediabetes. Furthermore, the use of high-bioavailability BCM-95® may have contributed to efficacy.

Several limitations should be acknowledged. Although the sample size was sufficient to detect differences in the primary outcomes of the parent trial, the study may have been underpowered to detect smaller effect sizes in certain inflammatory biomarkers. Moreover, the relatively homogeneous sample and limited demographic diversity may restrict the generalizability of the findings.

The 90-day intervention period may not be adequate to assess long-term metabolic outcomes, including progression to T2DM or sustained glycemic improvements. Additionally, the single-center design, conducted in Yazd, Iran, may introduce regional influences related to genetic background, dietary patterns, and lifestyle factors, potentially limiting external validity.

The use of fixed doses of curcumin (500 mg/day) and zinc (30 mg/day) precluded dose-response analysis, which would be valuable for optimizing therapeutic strategies. Furthermore, individuals with hypertension were excluded to minimize potential confounding effects of antihypertensive medications and hypertension-associated vascular inflammation on oxidative stress and inflammatory biomarkers; however, this exclusion may limit generalizability to the broader prediabetic population, in which hypertension frequently coexists.

Moreover, Adherence assessment, dietary intake, and PA were assessed using self-reported questionnaires, which are prone to recall bias or reporting inaccuracies. The absence of detailed data on micronutrient intake, particularly dietary antioxidants, limited the ability to control for potential confounding effects on oxidative stress and inflammation. Finally, the study did not include a formal assessment of blinding (e.g., asking participants or assessors to guess group

assignments), which could have introduced performance or detection bias, particularly in outcomes influenced by perception or behavior.

4.2 Future directions

While the present findings demonstrate promising anti-inflammatory and antioxidant effects of curcumin-zinc co-supplementation, several key research gaps remain for future investigation. Future studies should employ larger, multicenter, randomized controlled trials with longer follow-up periods to evaluate the long-term safety and efficacy of curcumin and zinc supplementation. Such studies should incorporate dose-ranging designs to establish optimal individual and combined dosing regimens, while exploring innovative delivery systems such as syrup or nano-formulations (e.g., nano-capsule, nano-tablet, or nano-oral solution) is warranted to optimize bioavailability and therapeutic outcomes.

Furthermore, subsequent research should enroll more diverse prediabetic populations, particularly high-risk subgroups with concurrent cardiometabolic comorbidities to improve clinical generalizability. Complementary mechanistic studies should further elucidate the interplay between Nrf2 and NF-κB pathways underlying the observed synergistic effects. Additionally, pragmatic trials should assess their application in real-world clinical settings. Collectively, these investigations will substantially advance our understanding of curcumin-zinc supplementation as a potential adjunctive therapy for prediabetes management.

5. Conclusion

Curcumin (500 mg/day) and zinc (30 mg/day) co-supplementation over 90 days significantly improved key inflammatory (IL-1β, hs-CRP) and antioxidant (SOD, TAC) biomarkers in overweight or obese adults with prediabetes. The findings highlight the potential complementary benefits of co-supplementation, along with an excellent safety profile,

supporting its role as an adjunctive strategy for managing prediabetes and mitigating diabetes-related risks. These results emphasize the need for larger, multicenter, long-term trials to confirm the efficacy and safety of curcumin and zinc co-supplementation in prediabetes management.

List of abbreviations

2-hour Postprandial Glucose (2hPG)
American Diabetes Association (ADA)
Body Mass Index (BMI)
Complementary and Alternative Medicine (CAM)
Consolidated Standards of Reporting Trials (CONSORT)
C-Reactive Protein (CRP)
Diastolic Blood Pressure (DBP)
Fasting Plasma Glucose (FPG)
Good Clinical Practice (GCP)
Hemoglobin A1c (HbA1c)
High-Density Lipoprotein-Cholesterol (HDL)
High-Sensitivity C-Reactive Protein (hs-CRP)
Interleukin-6 (IL-6)
Interleukin-1β (IL-1β)
Interquartile range (IQR)
Kelch-like ECH-Associated Protein 1 (Keap1)
Least Significant Difference (LSD)
Low-Density Lipoprotein (LDL-C)
Malondialdehyde (MDA)
Monocyte Chemoattractant Protein-1 (MCP-1)
Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)
One-way Analysis of Variance (ANOVA)
Polycystic Ovary Syndrome (PCOS)

Physical Activity (PA)

Serum Low-Density Lipoprotein Cholesterol (LDL-C)

Superoxide dismutase (SOD)

Systolic Blood Pressure (SBP)

Total antioxidant capacity (TAC)

Total Cholesterol (TC)

Triglyceride (TG)

Tumor Necrosis Factor-Alpha (TNF-α)

Type 2 diabetes mellitus (T2DM),

Ultra Performance Liquid Chromatography (UPLC)

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (approval code: IR.AJUMS.REC.1398.504). Written informed consent was obtained from all participants prior to enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions statement

M.A.: Conceptualization, Methodology, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Project Administration;

M.K.: Conceptualization, Methodology, Validation, Supervision, Writing – Review & Editing;

B.C.: Formal Analysis, Validation, Writing – Review & Editing;

H.M-k.: Conceptualization, Methodology, Supervision, Writing – Review & Editing;

S.M.M.: Resources, Investigation, Project Administration, Validation, Writing – Review & Editing.

All authors read and approved the final manuscript.

Authors' information (optional)

M.A.:

- Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
- Researcher, Nutrition and Beauty and Amino Company, Yazd, Iran

M.K.:

- Nutrition and Metabolic Diseases Research Center, Clinical Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

H.M-k.:

- Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

B.C.:

- Department of Biostatistics and Epidemiology, School of Health Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

S.M.M.:

- Shahid Sadoughi Hospital, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Supplementary

Figure S.1. Ultra-Performance Liquid Chromatography (UPLC) chromatogram of bioavailable turmeric extract (BCM-95®) detected at 420 nm, showing retention times of curcumin (3.439 minutes), demethoxycurcumin (3.122 minutes), and bisdemethoxycurcumin (2.831 minutes).

Supplementary S1: Certificate of Analysis for BCM-95® turmeric extract supplement.

Supplementary S2: Standardized healthy lifestyle recommendations provided to all participants.

Supplementary S3: CONSORT 2010 Checklist

Table S1. Between-group changes in liver enzymes, blood pressure, glycemic parameter, lipid profiles, and physical activity from baseline to day 90.

Table S2. Supplement compliance rates (%) by intervention groups during 90 days.

Table S3. Baseline of physical activity levels between the four groups

Table S4. Post-hoc pairwise comparisons of serum and urinary zinc changes following significant ANOVA results.

Table S5. Post-hoc pairwise comparisons of changes in inflammatory and antioxidant biomarkers following significant ANOVA results.

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