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RESEARCH ARTICLE

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The effect of curcumin and zinc co-supplementation on glycemic parameters in overweight or obese prediabetic subjects: A phase 2 randomized, placebo-controlled trial with a multi-arm, parallel-group design

Majid Karandish¹ | Hassan Mozaffari-khosravi²  |
Seyed Mohammad Mohammadi³ | Bahman Cheraghian⁴ | Maryam Azhdari^{5,6} 

¹Nutrition and Metabolic Diseases Research Center, Clinical Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

²Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

³Endocrinology & Metabolism, School of Medicine, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

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

⁵Department of Nutrition, School of Allied Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

⁶Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Correspondence

Maryam Azhdari, Department of Nutrition,
School of Allied Medical Sciences, Ahvaz
Jundishapur University of Medical Sciences,
Ahvaz, Iran.
Email: azhdari_mar@yahoo.com

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Management of prediabetes is a critical step to prevent type-2 diabetes. Curcumin and zinc have been studied as an antioxidant, antiinflammatory, and antidiabetic agents. In this clinical trial, 84 subjects were randomized into curcumin (500 mg), zinc (30 mg), zinc and curcumin, and placebo groups for 90 days. At the baseline and the end of the study, the outcomes (fasting plasma glucose (FPG), 2-hour postprandial glucose (2hpp), HbA_{1c}, insulin, insulin sensitivity (IS), insulin resistance (IR), β -cell function (BCF), weight, body mass index (BMI), dietary intake, and physical activity (PA)) were measured. A hypocaloric diet and PA were recommended for all subjects. In total, 82 subjects completed the study. After the intervention, dietary intake, PA, weight, and BCF% did not show a significant difference among the groups. However, subjects taking only zinc and zinc and curcumin groups experienced decreased BMI compared to the placebo ($p = .01$ and $.007$, respectively). The three treated groups had improved FPG ($p = .01$), 2hpp ($p = .003$), HbA_{1c} ($p = .004$), insulin ($p = .001$), IS % ($p = .001$), and IR ($p < .001$) compared to the placebo. **Based on these results, zinc and curcumin supplementation exerted a beneficial effect on several key glycemic parameters.**

Abbreviations: ADA, American Diabetes Association; AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; AMPK, AMP-activated protein kinase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; BCF, beta cell function; BMI, body mass index; CONSORT, consolidated standards for reporting trials; COX2, cyclooxygenase-2; DMC, Data Monitoring Committee; Cu/Zn SOD, copper/zinc superoxide dismutase; ELISA, enzyme-linked immunosorbent assay; FFA, free fatty acid; FPG, fasting plasma glucose; G6Pase, glucose-6-phosphatase; GLUT-4, glucose transporter-4; HbA_{1c}, hemoglobin A_{1c}; HPLC, high-performance liquid chromatography; HOMA, homeostasis model of assessment; IDF, International Diabetes Federation; IGT, impaired glucose tolerance; IL-1B, interleukin-B; IL-6, interleukin-6; IPAQ-SF, short form of international physical activity questionnaire; IQR, interquartile range; IRCT, Iranian Registry of Clinical Trials; IR, insulin resistance; IS, insulin sensitivity; LPL, lipoprotein lipase; MET, metabolic equivalent of task; MM, muscle mass; MetS, metabolic syndrome; NCDs, non-communicable diseases; NF- κ B, nuclear factor kappa-light-chain enhancer of activated B-cells; OGTT, oral glucose tolerance test; One-way ANOVA, one-way analysis of variance; PA, physical activity; PEPCK, phosphoenol pyruvate carboxykinase; RCT, randomized clinical trial; SAE, serious adverse events; SD, standard deviation; SPSS, statistical software package; TNF- α , tumor necrosis factor-alpha; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; WHO, World Health Organization; 2hpp, 2 hour post prandial.

KEYWORDS

blood glucose, curcumin, insulin resistance, insulin sensitivity, prediabetes, zinc

1 | INTRODUCTION

Prediabetes or borderline diabetes is an intermediate hyperglycemia condition that typically occurs in overweight or obese people who are otherwise healthy. Fasting plasma glucose (FPG), HbA1C, and oral glucose tolerance test (OGTT) plasma glucose are the main diagnostic criteria for prediabetes ("American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018," 2018). Both insulin resistance (IR) and β -cell dysfunction have been reported in prediabetes, with IR considered the main factor of developing prediabetes. β -cell dysfunction plays a key role in the progression of type-2 diabetes (T2DM; Cai et al., 2019). While the diagnostic criteria for prediabetes are controversial, prediabetes is considered an increased risk for non-communicable diseases (NCDs) including T2DM, heart disease, and stroke. The increasing incidence of NCDs leads to premature death and astronomical economic costs ("American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018," 2018; World Health Organization, 2006). As a result, preventable interventions with relatively low cost and toxicity are essential. Lifestyle and behavioral modifications can control prediabetes and prevent T2DM ("American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018," 2018). Evidence has shown the dietary components (Mazidi et al., 2017) and physical activity (PA; Bird & Hawley, 2017) can reduce T2DM risk by improving glucose homeostasis and insulin sensitivity (IS). There is some controversy in the most predominant factor contributing to the progression of prediabetes, especially among different populations. However, β -cell dysfunction may play a more important role than IR in Asian Indians (Mohan et al., 2013). Likewise, IR was considered the main factor in Koreans (C.-H. Kim et al., 2018). Therefore, the importance of measuring IR, IS, and β -cell function (BCF) is necessary.

Curcumin, also known as diferuloylmethane, is a polyphenolic pigment extracted from the rhizomes of turmeric (*Curcuma longa* L.), a plant in the Zingiberaceae family (Hewlings & Kalman, 2017; Yue et al., 2012). The therapeutic properties of curcumin include anti-diabetic, antioxidant, anticancer, antiinflammatory, antinephrotoxicity, antiproliferative, antiangiogenic, immunomodulatory, and hepatoprotective properties (Hewlings & Kalman, 2017).

The bioavailability of curcumin is low due to poor absorption and rapid elimination, presenting a major challenge for its therapeutic benefits. However, the presence of lipophilic essential oil components (turmerones) from turmeric in combination with curcumin is demonstrated to increase bioavailability. For example, the addition of turmerones to curcumin increased p-glycoprotein activity, thereby increasing the transport of curcumin into human intestinal epithelial Caco-2 cells (Yue et al., 2012).

The favorable effect of curcumin supplementation was previously identified on FPG, HbA1C, OGTT plasma glucose, IS%, IR, BCF%, and insulin for 9 months in elderly prediabetic subjects with comorbidity illnesses. However, the beneficial properties of 3-month curcumin supplementation were observed only on FPG, OGTT, and HbA1C (Chuengsamarn, Rattanamongkolgul, Luechapudiporn, Phisalaphong, & Jirawatnotai, 2012). Further, while curcumin supplementation may improve some glycemic measurements in subjects with metabolic syndrome (Azhdari, Karandish, & Mansoori, 2019) and T2DM subjects (Wojcik, Krawczyk, Wojcik, Cypryk, & Wozniak, 2018), more research is needed in prediabetic subjects. To date, one small trial has evaluated curcumin effects in subjects with prediabetes (Chuengsamarn et al., 2012).

Zinc is an essential nutrient with antioxidant and antiinflammatory properties (Prasad & Bao, 2019; Ruz et al., 2019). Zinc plays a number of essential roles for enzyme function, cell membrane integrity, gene expression, cell signaling, carbohydrate metabolism, insulin action (Ruz et al., 2019), and human islet amyloid polypeptide secretion (Brender et al., 2010). Lower serum zinc levels have been identified in prediabetic subjects, and are related to the reduced IS, β -cell dysfunction, and abnormal secretion of insulin (Islam et al., 2013). The beneficial effects of zinc supplementation on key glycemic parameters in prediabetes or metabolic syndrome may help to prevent the development of T2DM (X. Wang et al., 2019). Other attractive properties of zinc and curcumin supplementation for prediabetes include low-cost and available food sources. This multi-arm, parallel-group, randomized, double-blind placebo-controlled phase 2 clinical trial aimed to evaluate the effect of curcumin and zinc supplementation on glycemic parameters in overweight or obese prediabetic subjects.

2 | MATERIALS AND METHODS

The details of the method were previously published (Karandish, Mozaffari-khosravi, Mohammadi, Azhdari, & Cheraghian, 2020).

2.1 | Study design, intervention, and follow-up

This 90-day randomized, double-blind, controlled phase 2 clinical trial was carried out with a four-parallel arm and reported at the Diabetes Research and Clinical Practice Center of Yazd according to the Consolidated Standards for Reporting Trials (CONSORT) statement.

A convenience sampling technique was used to select subjects. The interventions used in the study were zinc supplement, curcumin supplement, and their respective placebos. The zinc supplement was

provided in the form of a **zinc gluconate tablet (Dineh Company, Iran), containing 30 mg zinc**. The placebo for the zinc supplement was a lactose tablet, made at the School of Pharmacy, Shahid Sadoughi University of Medical Sciences and Health Services, Iran. The curcumin supplement was provided as a capsule, containing 500 mg of a turmeric extract standardized to contain at least 95% curcuminoids, at least 65% curcumin, and naturally occurring levels of turmerones, as BCM95®, also known as Curcugreen®. The turmeric extract was made from botanically identified dry rhizomes of turmeric and extracted with ethyl acetate to form turmeric oleoresin. Curcuminoid crystals were precipitated under low temperature, then combined with turmeric essential oil made by steam distillation and contains turmerones, which make the curcumin supplement more bioavailable. Placebo capsules for curcumin were made of roasted rice powder. Both curcumin supplement and its placebo capsules were supplied by M/s Arjuna Natural Pvt Ltd., India. Placebos were identical in texture and appearance to their corresponding active supplement. Dosages were selected based on previous studies (Asghari, Hosseinzadeh-Attar, Alipour, Sehat, & Mohajeri-Tehrani, 2019; Islam et al., 2016; Panahi et al., 2018).

Eligible subjects were randomized into four groups, including three treatment groups: (a) curcumin group: curcumin supplement with the placebo for zinc, (b) zinc group: zinc supplement with the placebo for Curcumin, (c) zinc and curcumin group: zinc and curcumin supplement, and an untreated group, and (d) placebo group: the placebos for curcumin and zinc.

At the baseline and end of the study (day 90), the outcomes, including biochemistry parameters, anthropometric data, dietary intake, and PA were evaluated for all subjects. According to the allocation, the supplements were delivered to each subject on the 1st, 30th, and 60th day by a blinded assessor. All subjects received a tablet (zinc or placebo) and were advised to consume it before breakfast and a capsule (curcumin or placebo) after breakfast, daily, along with a hypocaloric diet and PA recommendation for 90 days. The lifestyle modification recommending a healthy hypo-caloric diet and PA was administered to all subjects. Daily messaging tools or telephone services were used to remind subjects of their treatment plan. Compliance was assessed by pill counts at the end of each 30-day period.

All adverse events (AE) were documented and reported to the Data Monitoring Committee (DMC) and the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences.

2.2 | Study population and sample size

All subjects were recruited from the Diabetes Research and Clinical Practice Center of Yazd, central Iran. Inclusion criteria were overweight or obese grade I women or men aged (18–50 years) with pre-diabetes diagnosis, according to the American Diabetes Association (ADA) guidelines (“American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018,” 2018). Voluntary written consent was obtained from all subjects prior to the conduct of the trial by the research staff.

Exclusion criteria included a diagnosis of any types of malignancies/cancers, liver, kidney, lung, endocrine, autoimmune, inflammatory, and neurological diseases, effective hereditary disorders of the liver (iron and copper storage disease), medications for blood pressure, glucose, lipid or weight lowering drugs; hormone replacement; supplements for three months before or during the intervention; weight loss surgery in the last year, weight-loss diet in the last 3 months; and lactating, pregnant or planning to get pregnant, compliance less than 80% during the intervention, or no signed informed consent.

This trial was approved by the Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Ethical committee reference code: IRAJUMS.REC.1398.504) and registered in the Iranian Registry of Clinical Trials (IRCT), Registration number: IRCT20190902044671N1 in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

A randomized, parallel design controlled trial formula was used to calculate the sample size (Karandish et al., 2020). Based on the previous trials, the sample size to detect a mean effect of FPG between each supplement with placebo was determined 8 and 19 for the curcumin and zinc group, respectively ($\alpha = .05$, significance), ($\beta = .2$, power) (12,22). Twenty-one subjects were considered in each group (total: 84 subjects).

2.3 | Randomization and blinding

A computer-generated random number sequence was applied using the method of block randomization with a block size of 4 for the randomization of the subjects by an independent statistician. The unique codes were assigned to the eligible subjects for the allocation concealment by the pharmacist who maintained the codes during the study. The assessors, who were involved in the study, were blinded to the treatment allocation. In addition to the assessors, the subjects would not be informed about the type of intervention. A blinded assessor delivered the supplements to the subjects according to the allocation for a 30-day period on the 1st, 30th, and 60th day.

2.4 | Study outcomes

FPG, 2-hour post prandial (2hPP), HbA1c, fasting serum insulin, IR, IS %, and BCF% was considered as the primary outcomes, and the secondary outcomes included dietary intake, serum zinc, and AE (serum alanine transaminase (ALT), and serum aspartate transaminase (AST)).

2.5 | Data collection

Biochemical parameters: The detail of the biochemical assessment was illustrated in the published study protocol (Karandish et al., 2020). A fasting blood sample was collected from all subjects. Then, the serum was immediately obtained to assay the concentration of biochemical parameters after sampling. The concentration of FPG and 2hpp was

measured by the glucose oxidase/oxidase method. High-performance liquid chromatography (HPLC) method was used to assay HbA1C. The serum levels of fasting insulin were evaluated by an enzyme-linked immunosorbent assay (ELISA) kit. International Federation of Clinical Chemistry method was used to assess ALT and AST. The assessment of IR, IS%, and BCF% was conducted by the updated homeostasis model assessment calculator from the University of Oxford (Song, Hwang, Ahn, & Park, 2016). This online calculator is available at <http://www.dtu.ox.ac.uk/homacalculator/index.php>. Serum zinc levels were assessed by flame atomic absorption spectrometry method (Ziest Chem Diagnostics kit, Iran).

Personal characteristics: Demographic and medical information including gender, age, marital status, ethnicity, smoking and medical history, alcohol consumption, family history of diabetes or/and hypertension, and the diagnosis time of prediabetes were obtained from each participant.

Anthropometric data: Body weight was measured to the nearest 500 g using a pre-calibrated electronic scale (Seca, Germany). Height was recorded to the nearest 0.1 cm using a wall-mounted stadiometer in a normal standing position. Body mass index (BMI) (kg/m^2) was calculated as weight (kg) divided by (m^2). All subjects had minimal clothing and no shoes. The mean of duplicate measuring of anthropometric data was recorded by a trained assessor.

Dietary intake: Self-reported dietary intake was assessed using a 24-hr recall for 3-day (two weekdays, one weekend day) by the subjects before and after the intervention period. The nutritional recommendations included adherence to the diet, calorie count, and avoiding excessive intake of high-fat and/or sugar products. Nutritionist IV software (Version I) was used to analyze the daily dietary intake (energy (kcal), carbohydrate (g), protein (g), fat (g), and the percent of energy from carbohydrate, protein, and fat (%)).

Physical activity: The assessment of PA was performed using the short form of the International Physical Activity Questionnaire. PA was categorized into three groups (vigorous-intensity activity, moderate-intensity activity, and low-intensity activity; Craig et al., 2003).

Participant adherence: Adherence to the supplement intake was assessed by remaining pill counts every 30 days. Participant adherence was reported as good, moderate, or poor.

Adverse events: The liver enzymes (ALT and AST) were assessed to monitor the possible adverse effects. Serious AE (SAE) were recorded and reported to the DMC and the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences.

2.6 | Statistical analysis

The normality of data and the homogeneity of variances in quantitative variables were evaluated by the Kolmogorov-Smirnov Test and Leven's tests, respectively. All variables were reported as mean $\pm$ standard deviations (SD), median (interquartile range [IQR]), or frequency (%). Comparisons between the groups were assessed through a one-way ANOVA with post hoc (LSD) analysis for the normal

distribution quantitative variables or Kruskal-Wallis for the non-normal distribution quantitative variables. Changes before and after the intervention within each group were performed using the paired t-test or Wilcoxon signed-rank test, based on the normality assumption. According to the significant correlation values, ANCOVA was applied to control the potential confounding variables (PA before the intervention (pre-PA) and BMI after the intervention (post-BMI)). The three models were used to adjust the potential confounders are as follows: Model 1: the adjustment for pre-PA, Model 2: the adjustment for post-BMI, and Model 3: pre-PA and post-BMI. All data analyzed using a statistical software package (SPSS), version 22.0 (SPSS, Inc., Chicago, IL). Statistical significance was determined at $p < .05$.

3 | RESULTS

In this trial, 84 subjects were allocated to four groups. Eighty-two subjects completed the 90-day protocol. Two subjects could not be evaluated: One participant from the zinc and curcumin group was lost due to poor compliance, and one subject from the placebo group withdrew due to severe abdominal pain. No significant differences in the means of AST, ALT between the treated and untreated groups (Table S1). A small number of subjects from all groups reported minor symptoms such as nausea, headache, hearing impairment, and dizziness (Table S2). Compliance with the treatments was at least 80% in all groups (Table S3).

The CONSORT flow diagram of the study is depicted in Figure 1. The mean $\pm$ SD age of subjects was 35.95 ± 6.57 . Most subjects were female (68.3%). The subjects reported 67.3% and 65.5% history of prediabetes and hypertension, respectively. At baseline, no significant differences among the groups were observed in general characteristics including age, total energy expenditure, duration of prediabetes, gender, material status, alcohol drinking, smoking status, and family history of prediabetes or hypertension. General characteristics of subjects are presented in Table 1.

The comparison of anthropometric measures (weight and BMI), PA, and daily dietary intake of the subjects between and within the groups was also measured (Table 2).

3.1 | Anthropometric measures (weight and BMI)

3.1.1 | Between-group analysis

Baseline: Weight and BMI have revealed no significant difference ($p \geq .05$). The changes remained non-significant after adjusting the PA effect (adjusted $p \geq .05$).

Post-intervention: BMI was showed a significant difference between groups ($p = .03$). A significant reduction in BMI was observed in zinc and zinc and curcumin groups compared to the placebo groups ($p = .01$ and $.007$, respectively). A significant decrease in BMI was observed after adjusting for PA (adjusted $p = .008$). A significant decrease in BMI was observed for the zinc (adjusted $p = .008$)



CONSORT 2010 Flow Diagram

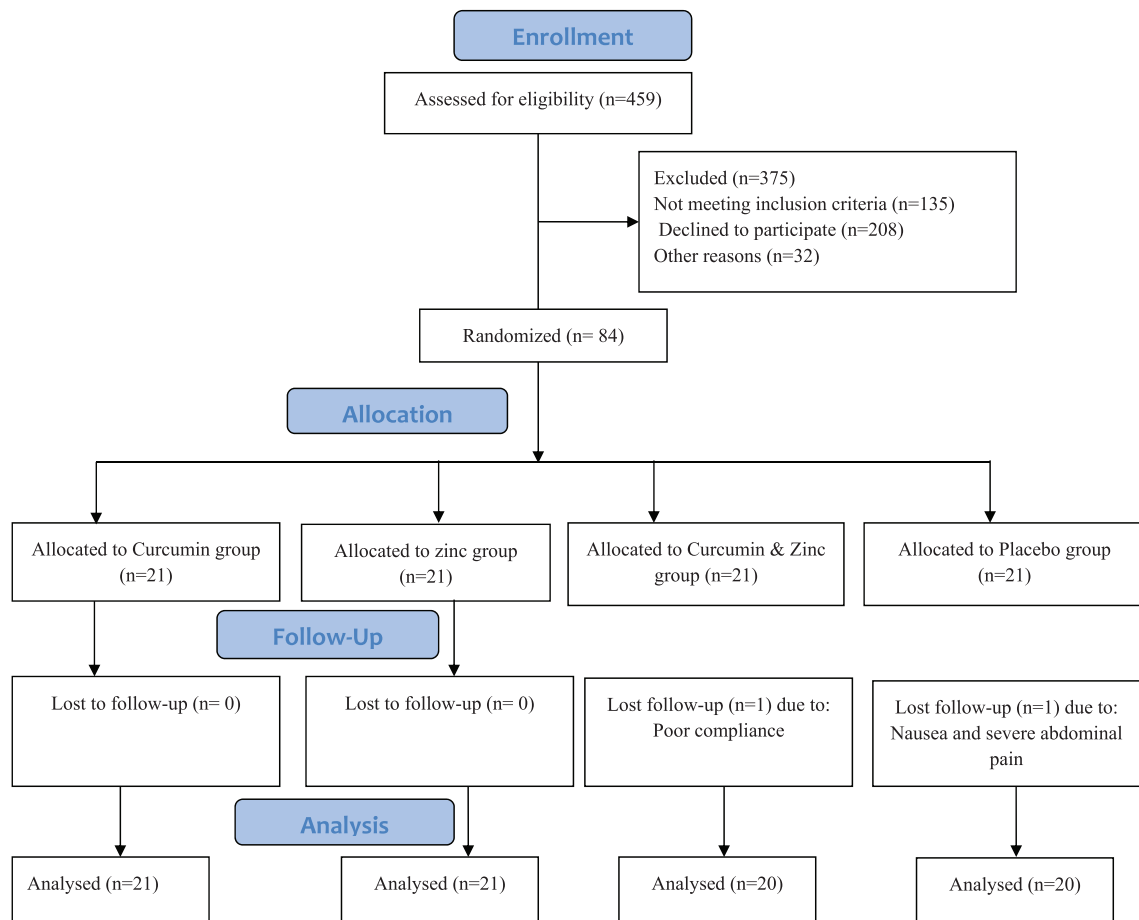


FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow chart-trial protocol [Colour figure can be viewed at wileyonlinelibrary.com]

and zinc and curcumin (adjusted $p = .002$) groups, compared to the placebo group. A trend for reduction in body weight was observed, both before and after removing the effect of PA ($p = .08$ and adjusted $p = .09$, respectively).

Within-group analysis: In all groups, a significant reduction in weight and BMI was observed after the intervention ($p < .001$).

3.2 | Physical activity

3.2.1 | Between-group analysis

Baseline: A significant increase in PA was observed between groups ($p = .02$). A significant increase in PA was observed for the curcumin

group compared to zinc alone ($p = .02$), as well as the zinc and curcumin group ($p = .008$).

Post-intervention: The statistical significance was not revealed in PA levels ($p = .18$). After excluding the PA effect (Model 1), the changes remained non-significant (adjusted $p = .66$).

Within-group: There were no significant differences in all groups from the baseline ($p \geq .05$).

3.3 | Daily dietary intake

3.3.1 | Between-group analysis

Baseline: There were no statistically significant differences in daily dietary intake between the groups ($p \geq .05$). Moreover, any difference in

TABLE 1 General characteristics of the subjects at baseline

	Groups				
Variables	Placebo N = 20	Curcumin N = 21	Zinc N = 21	Zinc and curcumin N = 20	p-Value
Qualitative variables					
Age (year)	34.19 ± 7.03	36.95 ± 7.23	38.19 ± 4.87	34.48 ± 6.45	.14
Total energy expenditure (kcal/day)	1,875.64 ± 454.93	1,908.09 ± 294.74	1,802.73 ± 429.27	1,770.55 ± 283.85	.62
Duration of pre-D (months)	2.33 ± 1.96	2.71 ± 1.62	2.43 ± 2.94	3.14 ± 2.78	.69
Quantitative variables					
Gender (female)	12 (60)	16 (76.2)	15 (71.5)	13 (65)	.837*
Material status					
Married	14 (70)	13 (61.9)	14 (66.6)	13 (65)	.947*
Single	5 (25)	7 (23.3)	6 (28.5)	7 (35)	
Others	1 (5)	1 (4.8)	1 (4.8)	0	
Alcohol drinking (yes)	4 (20)	4 (19)	4 (19)	2 (10)	.818*
Smoking (yes)	8 (40)	6 (28.5)	7 (33.3)	5 (25)	.884*
History of diabetes (yes)	16 (80)	14 (66.7)	15 (71.4)	11 (55)	.394*
History of hypertension (yes)	14 (70)	15 (71.4)	12 (57.1)	12 (60)	.714*

Note: Data are presented as mean ± standard deviation (SD) for quantitative variables and frequency (%) for qualitative variables. *p*-Value was calculated for the comparison variables between four groups using one-way analysis of variance (one-way ANOVA). *p*-Value <.05 was considered significant.

**p*-Value was calculated for the comparison variables between four groups using Kruskal–Wallis.

TABLE 2 Comparison of anthropometric measures, physical activity, and daily dietary intake of the subjects between and within the groups

	Groups				p-Value	p-Value
Variables	Placebo N = 20	Curcumin N = 21	Zinc N = 21	Zinc and curcumin N = 20		Model 1
Weight (kg)						
Before	84.67 ± 9.78	82.6 ± 8.03	81.81 ± 13.08	80.57 ± 10.17	.653*	.56
After	82.08 ± 9.32	77.29 ± 8.02	77.16 ± 12.80	74.79 ± 10.01	.08*	.09
p-Value [†]	<.001	<.001	<.001	<.001		
Body mass index (kg/m ²)						
Before	30.97 ± 2.33	30.46 ± 2.75	29.5 ± 2.82	29.95 ± 2.56	.32*	.11
After	30.05 ± 2.65 ^{a,b}	28.78 ± 2.86	28.1 ± 2.26 ^a	27.86 ± 2.55 ^b	.03*	.008
p-Value [†]	<.001	<.001	<.001	<.001		
Physical activity (MET·min week ^{−1})						
Before	445 (396–853.88)	990 (495–1,860) ^{a,b}	396 (396–1,440) ^a	396 (396–982) ^b	.03 [#]	–
After	742 (544–1,161)	1,188 (742–1,617)	742 (657–1,287)	742 (594–1,170)	.2 [#]	.66
p-Value [†]	.16	1	.52	.17		
Total energy (kcal)						
Before	2,146.5 ± 385.47	2,116.19 ± 250.97	2,115.95 ± 414.64	2,139 ± 237	.99*	.91
After	1,849 ± 274.24	1,846.9 ± 221.7	1,854.8 ± 285.12	1,853.75 ± 232.02	.85*	.73
p-Value [†]	<.001	<.001	<.001	<.001		
Carbohydrate (g)						
Before	314.75 ± 56.32	302.62 ± 34.99	290 ± 43.56	308.5 ± 35.54	.11*	.2
After	274.52 ± 38.69	263.33 ± 33.07	261.19 ± 34.82	262 ± 30.15	.58*	.48
p-Value [†]	<.001	<.001	<.001	<.001		
Percent of energy from carbohydrate (%)						
Before	58.79 ± 3.99	57.38 ± 4.49	55.39 ± 5.01	57.83 ± 4.43	.07*	.73
After	57.61 ± 2.56	57.02 ± 2.24	56.53 ± 2.49	56.69 ± 3.28	.62*	.61
p-Value [†]	.1	.74	.17	.22		

TABLE 2 (Continued)

	Groups					<i>p</i> -Value
Variables	Placebo N = 20	Curcumin N = 21	Zinc N = 21	Zinc and curcumin N = 20	<i>p</i> -Value	Model 1
<i>Protein (g)</i>						
Before	57.4 ± 15.16	56.29 ± 17.77	69.27 ± 33.5	64.36 ± 21.04	.23*	.11
After	53.51 ± 9.59	53.91 ± 9.94	55.98 ± 16.92	54.68 ± 12.8	.93*	.88
<i>p</i> -Value [†]	.42	.58	.007	.01		
<i>Percent of energy from protein (%)</i>						
Before	10.673 ± 2.15	10.59 ± 2.87	12.58 ± 3.57	11.92 ± 3.53	.12*	.05
After	11.38 ± 1.96	11.68 ± 1.67	11.9 ± 2.03	11.7 ± 1.8	.85*	.8
<i>p</i> -Value [†]	.3	.2	.21	.72		
<i>Fat (g)</i>						
Before	73.1 ± 18.27	75.62 ± 14.3	75.43 ± 17.2	71.95 ± 12.82	.85*	.87
After	65.55 ± 13	64.21 ± 9.36	65.12 ± 11.37	64.22 ± 10.8	.98*	.17
<i>p</i> -Value [†]	<.001	<.001	<.001	<.001		
<i>Percent of energy from fat (%)</i>						
Before	30.47 ± 3.85	32.03 ± 3.42	32.03 ± 3.6	30.25 ± 4.1	.26*	.2
After	31 ± 2.64	31.3 ± 2.3	31.58 ± 2.25	31.6 ± 2.67	.86*	.9
<i>p</i> -Value [†]	.33	.28	.5	.04		

Note: Data were presented as mean ± standard deviation or median (interquartile [IQR]). Model 1: p-Value was calculated using ANCOVA or nonparametric ANCOVA, adjusted for physical activity levels at the baseline.

Abbreviation: MET-min week⁻¹, metabolic equivalent of task minute per week.

^{a,b}A significant difference with another group ($p \leq .05$).

*p-Value was calculated for the comparison variables between four groups using one-way analysis of variance (one-way ANOVA) with post hoc (LSD) analysis.

#p-Value was calculated for the comparison variables between four groups using Kruskal–Wallis.

[†]p-Value was calculated for the comparison variables within each group using paired t-test.

[‡]p-Value was calculated for the comparison variables within each group using Wilcoxon.

daily dietary intakes remained non-significant between the study groups after adjustment for the PA (adjusted $p \geq .05$).

Post-intervention: No significant difference in daily dietary intake was observed, even after controlling for PA (adjusted $p \geq .05$).

Within-group: In all groups, a significant reduction in self-reported total energy and carbohydrate and fat intake was observed after the intervention ($p < .001$). A significant decrease was found in protein intake in the zinc ($p = .007$) and zinc and curcumin groups ($p = .01$) from baseline, without any significant difference for other groups. The comparison of the percent of energy from carbohydrate and protein indicated that there was no significant difference ($p \geq .05$). However, the percent of energy from fat increased post-intervention in the zinc and curcumin group ($p = .04$). There was no difference in the percent of energy from fat within other groups ($p \geq .05$).

3.4 | Glycemic parameters

Table 3 indicated the comparison of glycemic parameters between and within the groups. The results (p-values) of the pairwise comparisons of glycemic parameters for significant ANOVA and ANCOVA were projected in Tables S5 and S6, respectively.

3.4.1 | Between-group

Baseline: There was a non-significant difference in all glycemic parameters between the four groups ($p \geq .05$) as well as after adjusting for the PA levels (adjusted $p \geq .05$).

Post-intervention: No significant difference was identified in BCF % ($p = .86$). However, a significant difference was revealed in FPG ($p = .01$), 2hpp ($p = .003$), HbA1C ($p = .004$), insulin ($p = .001$), IS% ($p = .001$), and IR ($p < .001$). The significant decrease in FPG, 2hpp, HbA1C, insulin, and IR and increase in IS% exhibited in the three treated groups compared with the placebo group (Table S5).

As indicated in Table 3, all glycemic parameters except BCF% significantly improved after adjusting by the PA effect (Model 1). Moreover, these changes were observed in the treated groups in comparison with the untreated group (Table S6).

After controlling for BMI (Model 2), a decreases in 2hpp, insulin, and IR and an increase in IS% were observed in the treated groups compared to the placebo group (Table S6). Also, a significant reduction in FPG was observed in both curcumin and zinc groups compared to placebo by excluding confounder variables (Table S6). HbA1C decreased in the curcumin group compared to the placebo group using Models 2 or 3 (Table S5). Improvement in 2hpp, insulin, IS%, and

TABLE 3 Comparison of mean $\pm$ standard deviation (SD) of glycemic parameters of the subjects between and within the groups

	Groups					p-Value		
Variables	Placebo N = 20	Curcumin N = 21	Zinc N = 21	Zinc and curcumin N = 20	p-Value*	Model 1	Model 2	Model 3
FPG (mg/dl)								
Before	111.35 ± 11.38	108.81 ± 12.36	108.67 ± 11.88	112.6 ± 9.57	.62	0.29	–	–
After	110.8 ± 10.46 ^{a,b,c}	103.48 ± 8.87 ^a	103.43 ± 8.9 ^b	106.76 ± 5.45 ^c	.025	0.007	0.02	0.02
p-Value	.38	<.001	<.001	<.001				
2-hpp (mg/dl)								
Before	142.05 ± 22.5	138.95 ± 15.1	145.57 ± 22.35	142.55 ± 19.68	.76	0.35	–	–
After	141.6 ± 13.86 ^{a,b,c}	125.24 ± 13.25 ^a	129.86 ± 18.23 ^b	127.62 ± 13.32 ^a	.004	0.004	0.006	0.006
p-Value	.004	<.001	<.001	<.001				
HbA ₁ C (%)								
Before	5.91 ± 0.23	5.87 ± 0.29	6 ± 0.31	6 ± 0.35	.38	0.69	–	–
After	5.9 ± 0.15 ^{a,b,c}	5.68 ± 0.19 ^a	5.78 ± 0.21 ^b	5.78 ± 0.21 ^c	.004	0.02	0.009	0.007
p-Value	1	<.001	<.001	<.001				
Insulin (μU/ml)								
Before	19.22 ± 5.52	16.95 ± 4.62	16.56 ± 4.55	17.39 ± 4.77	.32	0.13	–	–
After	19.09 ± 4.43 ^{a,b,c}	15.42 ± 2.71 ^a	15.45 ± 2.93 ^b	16.92 ± 2.97 ^c	.002	0.001	0.001	0.001
p-Value	.59	.006	.02	.01				
β-Cell function♦(%)								
Before	118.24 ± 22.72	112.42 ± 33.67	113.29 ± 26.22	108.25 ± 23.34	.71	0.31	–	–
After	119.53 ± 21.46	116.96 ± 20.93	118.34 ± 22.27	117.29 ± 19.83	.86	0.82	0.69	0.73
p-Value	.58	.39	.02	.04				
Insulin sensitivity♦ (%)								
Before	42.2 ± 12.84	50.97 ± 21.12	47.86 ± 10.37	45.54 ± 11.37	.28	0.79	–	–
After	41.16 ± 9.16 ^a	50.45 ± 7.77 ^a	50.23 ± 7.46 ^b	48.19 ± 8.97 ^c	.002	0.001	0.002	0.002
p-Value	.39	.89	.04	.002				
Insulin resistance♦								
Before	2.57 ± 0.74	2.19 ± 0.7	2.21 ± 0.61	2.34 ± 0.63	.25	0.23	–	–
After	2.55 ± 0.59 ^{a,b,c}	2.04 ± 0.38 ^a	2.05 ± 0.39 ^b	2.14 ± 0.39 ^c	.001	<0.001	0.001	0.001
p-Value	.55	.13	.012	.006				

Note: Data were presented as mean $\pm$ standard deviation. *p*-Value was calculated for the comparison variables within group using paired *t*-test. Model 1: *p*-Value was calculated using ANCOVA adjusted for physical activity levels at the baseline. Model 2: *p*-Value was calculated using ANCOVA adjusted for BMI at the end of study. Model 3: *p*-Value was calculated using ANCOVA adjusted for physical activity levels at the baseline and BMI at the end of study. Abbreviations: 2-hpp, 2-hour post prandial; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin A1C.

^{a,b,c}A significant difference with another group (*p* $\leq$.05).

*Calculated by Homeostasis Model Assessment 2 (HOMA-2) calculator.

**p*-Value was calculated for the comparison variables between four groups using one-way analysis of variance (one-way ANOVA) with post hoc (LSD) analysis.

IR was also found in the treated groups compared to the placebo group after removing confounders (Models 2 and 3; Table S6).

Within-group: A significant reduction in FPG, HbA_{1c}, and insulin was observed in three treated groups from before the intervention (*p* < .05; Table 3). However, there was no significant difference in FPG, HbA_{1c}, and insulin in the placebo group (*p* $\geq$ 0.05). A significant decreasing trend in 2hpp was observed from baseline for all four groups (*p* < .05). A significant increase in BCF% and IS%, and a decrease in IR were observed in both zinc and zinc and curcumin groups from the baseline.

3.5 | Serum zinc

3.5.1 | Between-group

Baseline: No differences in serum zinc were observed between the four groups (*p* $\leq$.3; Table S4).

Post-intervention: Serum zinc significantly increased in zinc (*p* = .009) and zinc and curcumin (*p* = .002) groups compared to the curcumin-only group. Moreover, serum zinc increased in the zinc and curcumin group compared to the placebo group (*p* = .039).

Within groups: However, serum zinc increased in both zinc and zinc and curcumin groups ($p < .001$) compared to the baseline, no significant changes were observed in the curcumin and placebo groups ($p = .07$ and $.62$, respectively).

4 | DISCUSSION

Based on existing evidence, combination therapy (lifestyle modification [exercise, healthy diet] and pharmacotherapy) has been shown more impacts and lower side effects than monotherapy to prevent T2DM (24). In this study, subjects taking zinc and curcumin showed a remarkable improvement in FPG, 2hpp, HbA1C, insulin, IS, IR, and BMI. These may be the most important findings of this trial. Further, both the zinc and zinc and curcumin groups displayed a significant reduction in BMI, while the changes in body weight were considered non-significant trends for improvement.

The present trial was performed at a difficult time, during the challenge of COVID-19. Despite the recommendations to adopt a healthy lifestyle, there was no significant change in PA levels from baseline in any group. This is likely due to mandatory quarantine conditions in Iran, which led to inadequate PA. However, daily energy intake decreased within all groups after 90 days, although there were no significant changes between groups. Moreover, self-reported dietary macronutrient intakes were not changed between the groups. This could be due to having more time at home to prepare healthy meals in quarantine conditions, as well as the closure of restaurants and cooking and food distribution centers during this time (Mayasari et al., 2020). The notable weight loss and decreased BMI from baseline in all groups may be a result of more easily adopting a hypocaloric diet during the pandemic, while changes between groups in glycemic parameters are more likely to result from the positive effects of supplements.

The form of both supplements as interventions was effective in creating positive therapeutic results. For example, zinc gluconate has higher absorption compared to other conventional forms of zinc used for supplementation (Wegmüller, Tay, Zeder, Brnić, & Hurrell, 2014). Likewise, the therapeutic effects of the turmeric intervention were likely related to its components, especially the essential oils combined with curcumin, resulting in improved bioavailability (Yue et al., 2012).

Previously, no clinical evidence was available on the combined effect of zinc and curcumin, and their efficacy on glycemic parameters in subjects with prediabetes or metabolic diseases like IFG, IGT, or T2DM. Chuengsamarn et al. (2012) demonstrated the effective role of curcumin supplementation (1,500-mg per day) on FPG, HbA1C, OGTT, IR, and IS% in prediabetic subjects after 3, 6, and 9 months of intervention. However, the reduction in body weight was remarkable after 9 months of the intervention. In a trial conducted by Panahi et al. (2018), a daily 500 mg curcumin supplement administered for 3 months improved FPG, HbA1C, weight, and BMI, without a positive effect on BCF%, IR, or insulin in subjects with T2DM (Panahi et al., 2018). In the trial conducted by Panahi et al. (2018), the dosage and study duration was similar to the present trial, yet all subjects

were diagnosed with T2DM as opposed to prediabetes in this trial. A positive effect of curcumin on the subjects in that trial on IFG, IGT, and MeS was observed at different doses, ranging from 20 to 2,400 mg for a duration of 2–9 months (Azhdari et al., 2019; Chuengsamarn et al., 2012).

Zinc has also shown some promise in lowering glycemic endpoints in T2DM patients. Previously, a dose of 30 mg/day zinc (as zinc sulphate) significantly improved FPG, BCF, IS, and IR (Islam et al., 2016). Following zinc supplementation (30 mg zinc gluconate), no significant differences were found in glycemic control and anthropometric parameters. Serum insulin levels increased significantly compared to baseline in the zinc group. In another study, Asghari et al. (2019) also showed zinc gluconate (30 mg) improves serum zinc levels in subjects with zinc deficiency. In the present study, while no groups had zinc deficiency at baseline, a significant increase was observed in serum zinc levels in groups assigned to zinc intervention.

The results of a meta-analysis of RCT found improvement of zinc as sole or co-supplement on FPG, 2hpp, insulin, IR, and HbA1C in subjects with T2DM and prediabetes (17). Asghari et al. (2019) suggested that zinc gluconate (30 mg) supplementation may be ineffective on glycemic measurements in patients with T2DM.

However, these findings which conflict with the present study may be due to different doses, duration of the study, type of supplement, and more severe glycemic condition of the subjects. The findings from this study suggest that earlier intervention during prediabetes before T2DM is diagnosed may be key to preventing the progression of the disease. Numerous mechanisms support the positive role of curcumin on glycemic parameters, including a) peroxisome proliferator-activated receptor-gamma (PPAR- γ) agonists. The hypoglycemic effect of curcumin supplements including curcuminoids and the essential oil from turmeric may arise from PPAR γ activation (Aggarwal & Harikumar, 2009). Due to the direct action of PPAR- γ on glucose sensing in β -cells and the glucose transporter, (a) the pleiotropic antidiabetic action of curcumin involves several target tissues (Aggarwal & Harikumar, 2009; H.-I. Kim & Ahn, 2004), (b) the suppression of hepatic glucose production by activating AMP-activated protein kinase (AMPK) and inhibiting glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), (c) enhancement of cellular glucose uptake followed by stimulation of the GLUT4 translocation, (d) elevation of hepatic glycogen storage by the enhanced activity of glucokinase, (e) reduction of free fatty acid (FFA) production through the increase in the uptake and oxidation of fatty acids, the up-regulation of fatty acid translocase (CD36), and the stimulation of the skeletal muscle lipoprotein lipase (LPL) activity; and (f) the enhancement of the insulin production by the increased IRS1 tyrosine phosphorylation.

Furthermore, curcumin can play a crucial role in preventing T2DM through a positive impact on body weight (Wojcik et al., 2018). Some proposed mechanisms for weight reduction include: (a) controlling adipose tissue by the suppression of angiogenesis vascular endothelial growth factor (VEGF) and its receptor VEGFR2, (b) stimulation of adipocyte energy metabolism by AMPK activation, (c) enhancement of heat production by inducing brown adipocytes (S. Wang et al., 2015) and producing heat shock proteins (Wojcik et al., 2018).

Several mechanisms by which zinc may prevent the progression of prediabetes to T2DM are as follows: (a) biosynthesis, crystallization, maturation, and secretion of insulin in pancreatic β cell by the zinc transporter ZnT8 (SLC30A8), (b) action of insulin in peripheral tissues by inhibiting of FOXO transcription factors (TF) and the regulation of PEPCK and G6Pase (Ruz et al., 2019), (c) antiinflammatory and antioxidant effects by suppressing the activation of NF- κ B, and the secretion of IL-1 β and TNF- α from both monocytes and macrophages, (d) antioxidant effects by inhibition of oxidation of macro-molecules leading in the down-regulation of ROS production (Prasad & Bao, 2019) and the activation of the antioxidant enzyme (ex, copper/zinc superoxide dismutase [Cu/Zn SOD]; Bjørklund et al., 2020), (e) enhancement of glucose uptake by inhibiting protein-tyrosine phosphatases and translocation of GLUT4 to the plasma membrane, (f) induction of GLUT1 and GLUT4 gene expression by normalization of peroxisome PPARs activation, (g) inhibition of glucagon secretion via changes in potassium and calcium channels in the pancreatic alpha cells and the liver, (h) the inhibition of insulin clearance through the suppression of clathrin-dependent insulin endocytosis in liver, and (i) the stimulation of adipogenic differentiation through key transcriptional regulatory proteins including zinc finger domains, and finally, the enhancement of the phosphorylation of insulin receptors (Ruz et al., 2019).

Taken together, the multiple mechanisms previously demonstrated may justify the therapeutic effects of curcumin and zinc supplementation.

The limitations of this trial follow: (a) the study durations (3 months) seemed to be short in prediabetes, (b) the use of a single dose of each supplement, (c) a single center was considered as the recruitment of participants, (d) the self-reported assessment of the dietary intake, and (e) the lack of the assessment of micronutrients in the diet.

Further RCTs are suggested with longer duration, different doses, diversity in the form of the supplements (i.e., syrup, nano-capsule, nano-tablet, or nano oral solution), and multiple centers.

Despite these limitations, this study is unique due to the use of zinc and curcumin supplements in prediabetic subjects.

5 | CONCLUSION

The present adjuvant therapy (zinc and curcumin supplementation) along with following a hypo-caloric diet could have beneficial effects on all glycemic measurements (except for BCF) and BMI in prediabetic subjects. In addition, each supplement on its own showed an effective role on some glycemic parameters. This study indicated that curcumin and zinc supplementation can be used to improve glycemic parameters for 3 months without any serious AE.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Maryam Azhdari, Majid Karandish, and Hassan Mozaffari-khosravi participated in study design and protocol development. Maryam Azhdari and Seyed Mohammad Mohammadi coordinated recruitment and participant management. Seyed Mohammad Mohammadi confirmed all subjects. Maryam Azhdari collected data adhering to study protocol. Bahman Cheraghian provided statistical advice and input. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Hassan Mozaffari-khosravi  <https://orcid.org/0000-0001-5317-4942>

Maryam Azhdari  <https://orcid.org/0000-0003-2110-9817>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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