Trials

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# Effect of nano-curcumin supplementation on cardiometabolic risk factors, physical and psychological quality of life, and depression in patients with coronary slow flow phenomenon: a randomized double-blind clinical trial

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## Abstract

**Background** Extensive evidence has suggested the cardio-protective properties of the polyphenol curcumin. The aim of this study was to investigate the effects of a highly bioavailable curcumin supplement on cardiometabolic risk factors, health-related quality of life, and depression in patients with coronary slow flow phenomenon (CSFP).

**Methods** This randomized double-blind placebo-controlled clinical trial was conducted in 42 patients with CSFP (age 35–70 years, 25 ≤ body mass index < 40 kg/m$^2$). Patients received either 80 mg/day nano-curcumin or placebo for 12 weeks. Serum levels of visfatin, high-sensitivity C-reactive protein (hs-CRP), and glycemic indices were measured before and after the intervention. The short form 36-item quality of life (SF-36) and Beck's Depression Inventory-II (BDI-II) questionnaires were assessed, as well.

**Results** No significant improvements were observed in circulating hs-CRP and visfatin following the intervention. A significant increase was observed in pre- to post-fasting blood glucose (−0.9 ± 12.2 vs. 7.7 ± 12.4 mg/dl, $p = 0.02$) and hemoglobin A1C (−0.1 ± 0.8 vs. 0.5 ± 0.8%, $p = 0.04$) levels, in the placebo compared with the intervention group. Physical (8.2 ± 8.1 vs. − 1.2 ± 6.5, $p < 0.001$) and mental (6.8 ± 11.8 vs. − 1.1 ± 10.4, $p = 0.02$) component summary scores were significantly improved in the nano-curcumin than the placebo group. Additionally, the number of patients with lower degrees of depression was significantly better in the intervention than the placebo group following the supplementation ($p = 0.046$).

**Conclusion** Curcumin supplementation prevented deterioration of glycemic control and improved physical and psychological quality of life and depression in patients with CSFP.

**Trial registration** Iranian Registry of Clinical Trials (IRCT20131125015536N8), June 19, 2019.

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**Keywords** Curcumin, Coronary slow flow phenomenon, Cardiometabolic risk factors, Quality of life, Depression, Glycemic control

## Introduction

Coronary slow flow phenomenon (CSFP), which was described for the first time in 1972 [1], is an angiographic diagnosis seen in 1–7% of patients candidate for coronary angiography. This clinical condition is characterized by delayed contrast opacification of the distal vasculature with no evident coronary stenosis. Despite the well-diagnosis of CSFP by interventional cardiologists, the underlying mechanisms are poorly understood [2]. Endothelial dysfunction, oxidative stress, inflammation, and metabolic disturbances are proposed to be involved in the pathogenesis of CSFP [2–5].

A potential relationship has been proposed between inflammatory status and CSFP [6, 7]. High-sensitivity C-reactive protein (hs-CRP) is a systemic inflammatory biomarker, which is thought to be a valuable prognostic factor and a target of therapy in many cardiovascular diseases (CVDs) including atherosclerosis, coronary artery disease (CAD), heart failure, acute coronary syndrome, and cardiovascular events [8]. Therefore, high levels of CRP reported in CSFP compared to healthy group (0.27 ± 0.16 vs. 0.22 ± 0.11 mg/l) are probably indicating the involvement of inflammatory mechanisms in the pathogenesis of this condition [7]. Visfatin is another inflammatory biomarker that is significantly higher in CSFP patients (17.038 ± 8.86) compared to those with normal coronary flow (9.175 ± 4.63) [9]. This adipokine is increased in obesity and CVDs and could negatively affect inflammation, atherosclerosis, and endothelial dysfunction [10]. Glucose intolerance, hypertension, and obesity are frequently seen in patients with CSFP [4]. However, few clinical studies have been implemented to target these disorders [11–13], and medical treatments and complementary approaches are not well established in CSFP despite the fact that recurrent chest pain and hospital readmissions substantially impair the quality of life of these patients [14]. Moreover, it has been proved that CSFP is correlated with psychological distresses such as depression and anxiety [15].

Additionally, unlike other cardiovascular disorders, there is a significant lack of studies investigating nutritional management and therapeutic interventions in CSFP. In the past decades, plant-derived compounds such as micronutrients, phytochemicals, spices, and herbs have attracted a growing attention thanks to their multiple effects in various diseases especially CVDs.

Curcumin is a lipophilic polyphenol derived from the rhizome of the plant *Curcuma longa* or turmeric [16]. On one hand, it is recognized for its wide range health capacity including, anti-inflammatory, anti-carcinogenic, cardio-protective, anti-ischemic, vasodilatory, and hypoglycemic effects [17, 18] as well as improving psychological disorders [19]. On the other hand, previous evidence showed favorable effects of curcumin on visfatin, CRP, and glycemic indices [20–22]. Although it seems promising strategy to invest on, so far, no data is available regarding the potential advantage of curcumin supplementation in patients with CSFP, and present study is based on hypothesis of curcumin benefits for further CFSP patients' treatment improvement. Hence, this double-blind randomized placebo-controlled clinical trial was conducted to investigate the efficacy of nano-curcumin supplementation on some cardiometabolic risk factors as well as quality of life and depression in patients with CSFP.

## Method

### Study participants

Fifty overweight and obese individuals (25 ≤ body mass index (BMI) < 40 kg/m$^2$), aged 35–70 years, diagnosed with CSFP by a cardiologist, were enrolled in this randomized, double-blind, placebo-controlled, parallel-design clinical trial. The calculation of sample size based on relevant formula for randomized clinical trials (RCT) showed 21 patient in each group. Sample sized was calculated for 2 major endpoints including hs-CRP and visfatin, and the maximum sample size was estimated for hs-CRP. Considering a drop-out rate of 20%, 25 participants in each group would be adequate to have a power of 80% to observe 0.46 difference in hs-CRP levels with a type I error of 0.05 [23].

The diagnosis of CSFP was documented by angiography based on corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) method higher than 27 for one or more coronary vessels while patients had normal coronary vessels with coronary stenosis less than 40% and left ventricular ejection fraction (LVEF) equivalent or higher than 45%. CTFC is the gold standard quantitative assessment of coronary blood flow for three main coronary arteries [24], describing the disorder as one-, two-, or three-vessel slow coronary flow.

The exclusion criteria consisted of active gastrointestinal bleeding and ulcers, premature menopause, drug addiction or alcohol consumption, individuals under treatment with non-steroidal anti-inflammatory drugs (NSAIDs),

corticosteroids or immune-suppressants, and anticonvulsants, routine consumption of aphrodisiac medication within the past 9 months, omega 3 fatty acid supplements (>1 gr/day), vitamin $B_{12}$, folic acid or vitamin $B_6$ containing multi-vitamins, curcumin supplements or unusual consumption of turmeric, as well as athletes or those having regular exercise, and those with a history of hypothyroidism or hyperthyroidism, malignancies, systemic and autoimmune diseases, heart, renal or liver failures or transplantation, myocardial infarction, revascularization procedures such as coronary artery bypass graft, cardiac or coronary vessels anomalies, and hematologic disorders. Participants were excluded from the study if they had reported adverse reactions following nano-curcumin consumption including nausea, headache, diarrhea, rash, and yellow stool [25], did not participate in the study visits, did not consume more than 10% of the supplements, or were not willing to continue the study.

### Study design

In this trial, patients were randomly assigned to two groups to receive either 80 mg/day nano-curcumin (Exir Nano Sina Co., Iran) (nano-curcumin $n=25$) or placebo containing polysorbate 80, soy oil, sorbitol 70, methylparaben, propylparaben, and purified water (Exir Nano Sina Co., Iran) as placebo ($n=25$), for 12 weeks. The nano-curcumin supplements include a curcuminoid mixture, polysorbate, vitamin E, vitamin C, and natural oil. The curcuminoid powder contain 79.4% curcumin, 17.6% dimethyl curcumin (DMC), and 3% bisdemethoxycurcumin (BDMC) with a purity of at least 95%. Containers and the supplement and placebo capsules were exactly the same in appearance and differentiated only by codes A and B assigned by a colleague not involved in randomization and sampling. The allocation of patients was performed using stratified permuted block randomization with random block sizes of 2 or 4, provided by the study statistician who was not involved in patients' recruitment. Fifty recruited samples were stratified based on sex and the risk level of the disease. The risk level was assessed by summing up different characteristics of the participants including (1) a family history of coronary artery disease, (2) diabetes, (3) hypertension, or (4) dyslipidemia and (5) smoking. The absence or presence of each condition received a score of 0 and 1, respectively. Moreover, points 0 and 1 were assigned to using or not using any of the medications angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARBs), beta-blockers, statins, anticoagulants, calcium channel blockers (CCBs), and nitrates. The total score ranged 0 to 6; patients with scores $\leq 3$ were considered as low risk, and those with scores $>3$ were considered as high risk. Patients and assessors were blinded about grouping, as both directions were not aware about grouping, allocated intervention (placebo or nano-curcumin), or any baseline participant's characteristics.

Patients were visited at baseline, end of week 6, and end of the trial (week 12) and were also followed up by phone calls during the study period. They were asked to return the empty container on the second visit and receive the rest of supplements for the next 6 weeks of the study. Participants were supposed to consume one capsule daily after the meal they did not consume any other medicine. Consuming less than 90% of the allocated intervention was considered as non-fulfilled protocol framework. During the study, they were asked to maintain their regular diet and physical activity. Remaining capsules were counted in weeks 6 and 12 to monitor the compliance rate. All participants in both groups received standard care throughout the study.

### Assessments

Anthropometric parameters including weight, height, BMI, and waist circumference (WC) were measured for all the patients at the beginning and at the end of the intervention based on standards.

A 3-day 24-h dietary recall (1 weekend and 2 weekdays) was completed for each patient during the first and last weeks of the intervention to assess dietary intake. Dietary reported intakes were analyzed using the Nutritionist IV Software (The Hearst Corporation, San Bruno, CA, USA).

After overnight fasting (12–14 h), a venous blood sample (10 ml) was taken from all the participants at baseline and following 12 weeks of the intervention. Hemoglobin A1C (HbA1C) was measured in a blood sample collected in tubes with an anticoagulant agent. Additionally, the serum was separated by centrifuging the whole blood at 3000 rpm for 10 min and stored at −80° C for the rest of biochemical analyses. Commercial enzyme-linked immunosorbent assay (ELISA) kits were used to assess serum levels of hs-CRP (Lavor Diagnostika Nord GmbH & Co., Germany), visfatin (Crystal Day Biotech Co., China), and fasting insulin (Infinitumbiotech, USA).

Serum fasting blood glucose (FBG) was measured using a commercial enzymatic colorimetric kit (Pars Azmoon Inc., Iran). HbA1C levels were measured by immunoturbidimetric assay (Automatic Analyzer 917, Audit Diagnostics Co. Ireland). Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated by related formulas [26]. A calibrated digital sphygmomanometer (B.well Inc. Swiss) was used to assess systolic/diastolic blood pressure (SBP/DBP) in sitting position and after a 15-min rest. Measurement was repeated after 5 min, and the mean of two values was recorded.

The international short form 36-item (SF-36) questionnaire of quality of life (QOL) [27] and Beck's depression inventory-II (BDI-II) questionnaire [28] were completed for participants at the baseline and end of the intervention. Each scale of the SF-36 questionnaire ranged 0–100, with higher scores indicating better health status. BDI-II is consisted of 21 items, each ranged from 0 (no symptom) to 3 (severe symptom). Final score is categorized as 0–13, minimal, 14–19, mild, 20–28, moderate, and 29–63 severe depression.

### Statistical analysis

Normal distribution of the variables was assessed using Shapiro–Wilk test. Data were reported as mean ± standard deviation (SD) or frequency (%), as appropriate. Differences in baseline values and pre- to post- changes between the two study groups were compared using independent samples *t*-test (variables with normal distribution), Mann–Whitney (non-parametric variables), chi-square, or Fisher's exact test (nominal variables). Analysis of covariance (ANCOVA) was used to assess post-intervention differences adjusted for baseline values between the two groups. In order to determine within groups changes throughout the study period, Wilcoxon signed rank test or paired *t*-test was used, as appropriate. SPSS Software version 25.0 (SPSS Inc., Chicago, IL) was used for data analyses. *p*-value < 0.05 was considered as statistically significant.

## Results

Totally, 50 participants were recruited to this clinical trial (25 in the NC group and 25 in the placebo group). At the end of the intervention, data from 21 participants in each group was available for the analyses. Four patients in each group did not complete the study due to COVID-19 or other medical conditions. None of the patients reported gastrointestinal or other side effects during the intervention (Fig. 1).

### General characteristics and dietary intakes

Baseline characteristics of the study participants have been presented in Table 1. Each group included 17 males and 4 females with a mean age of 54 ± 9 years in the NC and 55 ± 8 years in the placebo group (all *p* values > 0.05). There were no statistically significant differences between the two study groups in LVEF, education level, underlying disorders, smoking status, family history for coronary artery disease, drug history, mean CTFC (mCTFC), and number of slow flow arteries.

Baseline anthropometric measurements showed no significant differences between the nano-curcumin and placebo groups (weight 85.9 ± 15.3 vs. 86.3 ± 10.8 kg, $p = 0.99$; BMI: 29.7 ± 3.1 vs. 30.6 ± 3.8 kg/m$^2$, $p = 0.45$; and WC 102.4 ± 11.7 vs. 102.9 ± 8.3 cm, $p = 0.85$, respectively). In addition, pre- to post-changes of weight (−0.3 ± 1.7 vs. −0.7 ± 2.0 kg, $p = 0.43$), BMI (−0.1 ± 0.6 vs. −0.2 ± 0.7 kg/m$^2$, $p = 0.49$) and WC (−0.3 ± 1.8 vs. −0.5 ± 2.3 cm, $p = 0.76$) were not statistically different between the nano-curcumin and placebo groups.

Data analyses showed no baseline significant differences between the NC and placebo groups in terms of mean daily intakes of energy (2123 ± 537 vs. 2295 ± 567 kcal, $p = 0.32$), carbohydrate (285.4 ± 76.6 vs. 323.1 ± 86.5 gr, $p = 0.14$), protein (87.3 ± 21.2 vs. 88.1 ± 24 gr, $p = 0.9$), fat (71.7 ± 23.4 vs. 73.6 ± 21.9 gr, $p = 0.87$), and fiber (14.8 ± 5.3 vs. 14.6 ± 5 gr, $p = 0.91$). Additionally, there were not any statistically significant differences in dietary reported intakes between the two groups at week 12 (all *p* values > 0.05).

### Cardiometabolic outcomes

As shown in Table 2, no significant differences were seen between the study groups at the beginning or at the end of the intervention regarding hs-CRP and visfatin serum levels. FBG and HbA1C pre- to post- changes had a rising trend in the placebo group, which was statistically significant compared to the intervention group (7.7 ± 12.4 vs. -0.9 ± 12.2 mg/dl, $p = 0.02$ and 0.5 ± 0.8 vs. −0.1 ± 0.8%, $p = 0.04$, respectively). In addition, within-group analysis confirmed that FBG and HbA1C levels increased significantly in the placebo, but not in the nano-curcumin group, at the end of the trial compared to the baseline values ($p = 0.01$ and $p = 0.008$, respectively). No other significant differences were observed in glucose homeostasis parameters or blood pressure following the supplementation.

### SF-36 QOL and BDI-II questionnaires

Changes in SF-36 and BDI-II are shown in Tables 3 and 4. The results showed that pre- to post- changes of physical and mental component summary scores ($p < 0.001$ and $p = 0.02$, respectively), as well as physical functioning ($p < 0.001$), role physical ($p = 0.04$), bodily pain ($p < 0.001$), and social functioning ($p = 0.01$) dimensions of QOL, improved significantly in the NC compared to the placebo group. Furthermore, at the end of the trial, mental health score was significantly higher in the intervention compared with the placebo group ($p = 0.04$) (Table 3).

Following 12 weeks of nano-curcumin supplementation, the frequency of patients in the categories of severity of depressive symptoms, indicated by BDI-II score, was significantly better in the intervention compared with the placebo group. The number of patients with minimal BDI-II score increased considerably throughout the study period in the NC than control patients (Table 4).

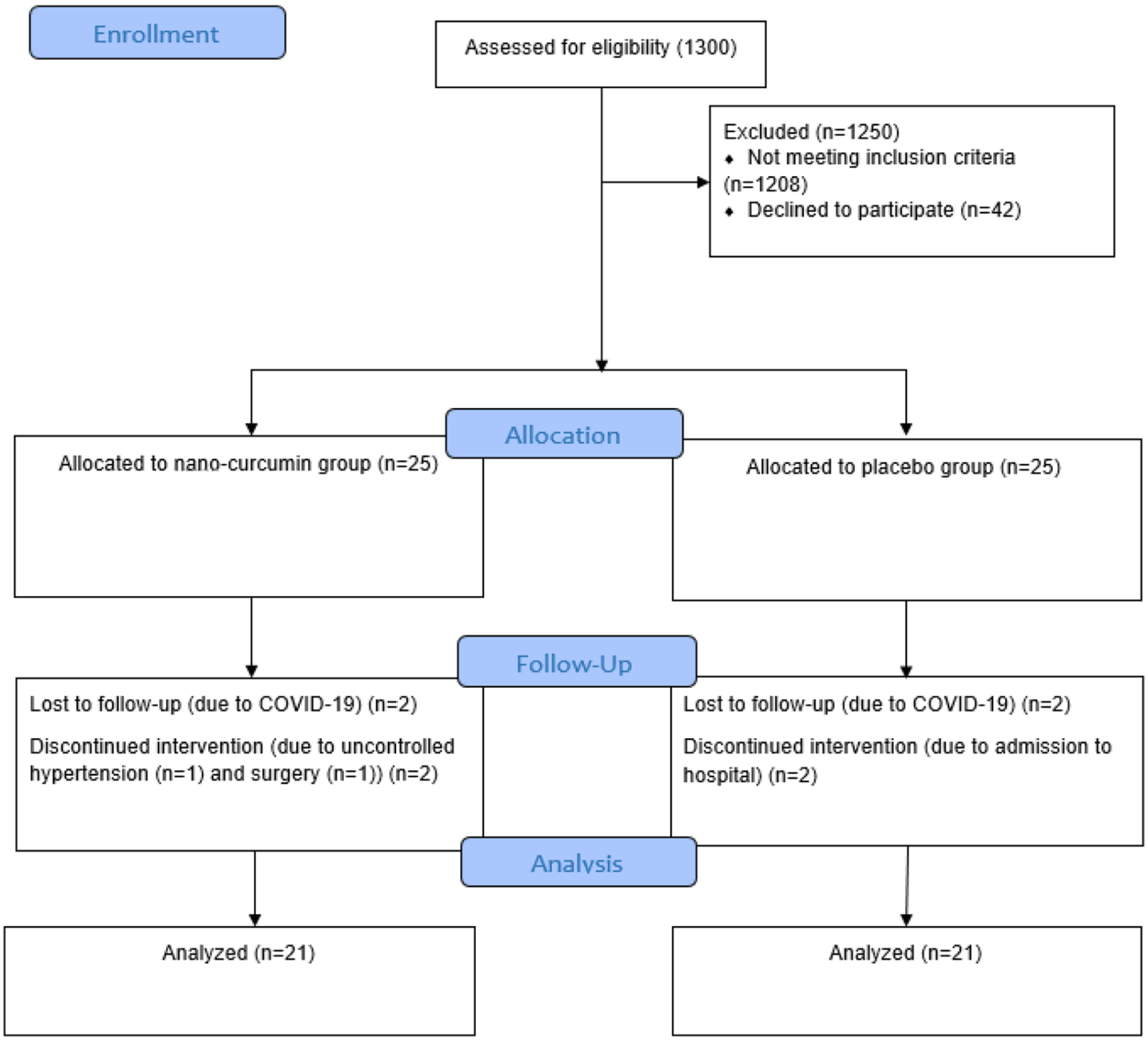


**Fig. 1** CONSORT flow chart

## Discussion

To the best of our knowledge, the present study is among the first researches investigating a nutritional supplement as a complementary treatment in patients with CSFP. This research showed that taking 80 mg of nano-curcumin supplements for 12 weeks did not decrease the levels of hs-CRP and visfatin. However, it stopped the concentrations of FBG and HbA1C from rising more than in the placebo group during the study period. Additionally, several aspects of quality of life and depressive symptoms improved considerably compared to the placebo group following the intervention.

Curcumin was suggested to have beneficial effects on glycemic control by increasing insulin release from pancreatic beta cells [29], protecting against oxidative stress, improving insulin signaling, and increasing gene expression of glucose transporter (GLUT) 4, GLUT2, and GLUT3 and, hence, increasing glucose uptake by tissues [30]. An RCT showed that 12 weeks' supplementation with 300 mg/day curcuminoids could improve FBG, HbA1C, and HOMA-IR in patients with type 2 diabetes compared to the placebo group [31]. Another RCT in diabetes confirmed the beneficial effects of 80 mg/day nano-curcumin supplementation for 3 months on decreasing FBG and HbA1C compared to placebo [32]. In contrast, 6 weeks' supplementation with 1000 mg/day curcumin in polycystic ovarian syndrome did not change FBG, insulin, HOMA-IR, and

**Table 1** Demographic and general characteristics of the study participants at baseline

| Parameter | | Group | | *p*-value |
|---|---|---|---|---|
| | | Placebo ($n=21$) | Nano-curcumin ($n=21$) | |
| Age (years) | | 55 ± 8 | 54 ± 9 | 0.93[a] |
| Sex | Female | 4 (19) | 4 (19) | 1.00[b] |
| | Male | 17 (81) | 17 (81) | |
| Education | Up to high school | 7 (33.3) | 6 (28.6) | 0.57[a] |
| | Diploma | 8 (38.1) | 7 (33.3) | |
| | University degree | 6 (28.6) | 8 (38.1) | |
| Diabetes | No | 15 (71.4) | 13 (61.9) | 0.51[c] |
| Hypertension | No | 11 (52.4) | 13 (61.9) | 0.53[c] |
| Dyslipidemia | No | 6 (28.6) | 9 (42.9) | 0.33[c] |
| LVEF (%) | | 51.2 ± 3.1 | 51.2 ± 2.7 | 0.94[a] |
| Family history of CAD | No | 11 (52.4) | 6 (28.6) | 0.12[c] |
| Smoking | No | 15 (71.4) | 14 (66.7) | 0.74[c] |
| Nitrates | No | 21 (100) | 18 (85.7) | 0.23[b] |
| ACEIs | No | 18 (85.7) | 20 (95.2) | 0.61[b] |
| ARBs | No | 16 (76.2) | 14 (66.7) | 0.50[c] |
| CCBs | No | 17 (81 | 17 (81) | 1.00[b] |
| Aspirin | No | 7 (33.3) | 4 (19) | 0.29[c] |
| Anticoagulants | No | 20 (95.2) | 19 (90.5) | 1.00[b] |
| Statins | No | 6 (28.6) | 8 (38.1) | 0.51[c] |
| BBs | No | 15 (71.4) | 16 (76.2) | 0.73[c] |
| mCTFC | | 34.81 ± 6.01 | 37.43 ± 6.69 | 0.19[a] |
| Number of slow flow arteries | 1-vessel slow flow | 9 (42.9%) | 5 (23.8%) | 0.24[a] |
| | 2-vessel slow flow | 7 (33.3%) | 9 (42.9%) | |
| | 3-vessel slow flow | 5 (23.8%) | 7 (33.3%) | |

Data are presented as mean ± standard deviation or frequency (%)

*LVEF* left ventricular ejection fraction, *ACEIs* angiotensin-converting enzyme (ACE) inhibitors, *ARBs* angiotensin II receptor blockers, *CCBs* calcium channel blockers, *BBs* beta blockers, *mCTFC* mean corrected thrombolysis in myocardial infarction frame count or mean TIMI frame count

[a] Mann-Whitney test

[b] Fisher exact test

[c] Chi-square test

quantitative insulin sensitivity check index (QUICKI) levels compared to the placebo group [33]. Similarly, in another RCT study in patients with diabetes, 600 mg/day curcuminoids for 8 weeks did not improve FBG and HbA1C [34]. The discrepancies in results among these studies with each other and with the current trial might be due to differences in the pathophysiology of the underlying diseases, formulation, bioavailability and dosage of the supplements, study duration and sample size, and other unknown covariates.

The current trial did not show that nano-curcumin has a decreasing effect on FBG and HbA1C in patients with CSFP. However, the placebo group had a significant increase in FBG and HbA1C throughout the study period, compared with the intervention group. In other words, nano-curcumin supplementation prevented the significant increase in these markers and deterioration of glycemic control. Previous studies indicated that higher HbA1C levels are associated with increased incidence and risk of slow coronary flow and slower coronary flow velocity [35, 36], which suggests HbA1C as a promising target in the management of CSFP.

Visfatin, which is highly expressed by visceral adipose tissue, is positively correlated with obesity, metabolic disorders and inflammation. Visfatin can induce the release of inflammatory biomarkers such as interleukin (IL)-1, IL-6, tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) through mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-kB) and phosphatidylinositol 3 kinase (PI3K) pathways [37]. The treatment of breast cancer cells with 0, 5, 30, and 50 (μM) curcumin for 0, 4, 8, 16, and 24 h downregulated the mRNA and protein levels of visfatin time and dose-dependently through inhibition of NF-kB pathway [20]. In an experimental study of rats with non-alcoholic fatty liver disease (NAFLD), 50, 100,

**Table 2** Changes in cardiometabolic risk factors at baseline and following 12 weeks of intervention

| Parameter | | Group | | Mean difference | 95% CI | | *p* |
|---|---|---|---|---|---|---|---|
| | | Placebo (*n* = 21) | Nano-curcumin (*n* = 21) | | Lower | Upper | |
| **Visfatin (ng/ml)** | Before | 22.4 ± 40.5 | 16.0 ± 27.4 | 6.4 | − 15.1 | 28.0 | 0.64[a] |
| | After | 22.3 ± 40.8 | 15.6 ± 25.8 | 6.7 | − 14.6 | 28.0 | 0.76[b] |
| | Change | − 0.1 ± 3.3 | − 0.4 ± 3.6 | 0.2 | − 1.9 | 2.4 | 0.91[a] |
| | P-within | 0.20[c] | 0.74[c] | | | | |
| **hs-CRP (mg/l)** | Before | 1.1 ± 0.5 | 1.1 ± 0.5 | − 0.1 | − 0.4 | 0.3 | 0.84[a] |
| | After | 1.1 ± 0.6 | 1.1 ± 0.5 | 0.0 | − 0.3 | 0.3 | 0.58[b] |
| | Change | 0.0 ± 0.4 | − 0.1 ± 0.4 | 0.1 | − 0.2 | 0.3 | 0.87[a] |
| | P-within | 0.36[c] | 0.25[c] | | | | |
| **FBG (mg/dl)** | Before | 107.2 ± 21.8 | 117.2 ± 26.7 | − 10.0 | − 25.2 | 5.3 | 0.22[a] |
| | After | 114.9 ± 24.3 | 116.3 ± 24.4 | − 1.4 | − 16.6 | 13.8 | 0.06[b] |
| | Change | 7.7 ± 12.4 | − 0.9 ± 12.2 | 8.6 | 0.9 | 16.2 | 0.02[a] |
| | P-within | 0.01[c] | 0.49[c] | | | | |
| **Insulin (μIU/ml)** | Before | 11.5 ± 8.7 | 10.6 ± 6.0 | 0.9 | − 3.8 | 5.6 | 0.70[d] |
| | After | 10.6 ± 5.9 | 12.6 ± 7.2 | − 2.0 | − 6.1 | 2.2 | 0.09[b] |
| | Change | − 0.9 ± 5.4 | 2.0 ± 5.6 | − 2.9 | − 6.3 | 0.6 | 0.10[d] |
| | P-within | 0.46[e] | 0.12[e] | | | | |
| **HbA1C (%)** | Before | 5.8 ± 0.9 | 6.3 ± 1.2 | − 0.5 | − 1.2 | 0.1 | 0.16[a] |
| | After | 6.3 ± 0.8 | 6.3 ± 0.8 | 0.0 | − 0.5 | 0.5 | 0.13[b] |
| | Change | 0.5 ± 0.8 | − 0.1 ± 0.8 | 0.5 | 0.1 | 1.0 | 0.04[a] |
| | P-within | 0.008[c] | 0.74[c] | | | | |
| **HOMA-IR** | Before | 3.2 ± 2.7 | 3.2 ± 2.2 | 0.0 | − 1.6 | 1.5 | 0.47[a] |
| | After | 3.0 ± 1.9 | 3.7 ± 2.5 | − 0.7 | − 2.1 | 0.7 | 0.13[b] |
| | Change | − 0.1 ± 1.5 | 0.6 ± 1.8 | − 0.7 | − 1.7 | 0.3 | 0.21[a] |
| | P-within | 0.90[c] | 0.12[c] | | | | |
| **SBP (mmHg)** | Before | 121.2 ± 15.2 | 121.6 ± 14.2 | − 0.4 | − .9.6 | 8.8 | 0.93[d] |
| | After | 125.3 ± 11.8 | 124.8 ± 12.2 | 0.5 | − 7.0 | 8.0 | 0.85[b] |
| | Change | 4.1 ± 14.0 | 3.2 ± 15.7 | 0.9 | − 8.4 | 10.2 | 0.84[d] |
| | P-within | 0.19[e] | 0.36[e] | | | | |
| **DBP (mmHg)** | Before | 81.8 ± 10.1 | 81.8 ± 10.5 | 0.0 | − 6.4 | 6.5 | 0.99[d] |
| | After | 85.0 ± 12.1 | 84.6 ± 7.6 | 0.5 | − 5.8 | 6.8 | 0.86[b] |
| | Change | 3.2 ± 10.5 | 2.8 ± 7.2 | 0.4 | − .5.2 | 6.0 | 0.88[d] |
| | P-within | 0.17[e] | 0.09[e] | | | | |

*hs-CRP* high sensitivity C-reactive protein, *FBG* fasting blood glucose, *HbA1C* hemoglobin A1C, *HOMA-IR* homeostatic model assessment for insulin resistance, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

[a] Independent sample *t*-test

[b] ANCOVA test

[c] Paired *t*-test

[d] Mann-Whitney test

[e] Wilcoxon signed rank

and 200 mg/kg/day curcumin consumption for 4 weeks attenuated the increased expression of visfatin in liver tissue, although it did not return to normal levels [38]. Despite the experimental evidence indicating the beneficial effect of curcumin on modulating visfatin levels [20, 38], no clinical trial is available in the field. The results of the current trial did not show any significant change in circulating visfatin following nano-curcumin supplementation. Since visfatin can be secreted from damaged endothelial cells, local evaluation of visfatin might be helpful to understand its paracrine activity. Further clinical researches are needed to investigate the efficacy of curcumin on visfatin levels. Moreover, increased serum levels of resistin, another adipokine with similar features

**Table 3** Changes in SF-36 quality of life at baseline and following 12 weeks of intervention

| Parameter | | Group | | Mean difference | 95% CI | | *p* |
|---|---|---|---|---|---|---|---|
| | | Placebo ($n=21$) | Nano-curcumin ($n=21$) | | Lower | Upper | |
| **Physical component summary** | Before | 66.6 ± 19.5 | 61.7 ± 26.1 | 4.9 | −9.5 | 19.4 | 0.70[a] |
| | After | 65.4 ± 20.4 | 69.9 ± 22.4 | −4.5 | −17.9 | 8.9 | < 0.001[b] |
| | Change | −1.2 ± 6.5 | 8.2 ± 8.1 | −9.4 | −14.0 | −4.9 | < 0.001[a] |
| | P-within | 0.35[c] | < 0.001[c] | | | | |
| **Mental component summary** | Before | 62.0 ± 19.0 | 64.0 ± 24.7 | −2.0 | −15.8 | 11.7 | 0.77[d] |
| | After | 60.9 ± 19.9 | 70.9 ± 20.4 | −10.0 | −22.5 | 2.5 | 0.01[b] |
| | Change | −1.1 ± 10.4 | 6.8 ± 11.8 | −8.0 | −14.9 | −1.1 | 0.02[d] |
| | P-within | 0.62[e] | 0.01[e] | | | | |
| **Physical functioning** | Before | 70.7 ± 21.2 | 63.3 ± 28.7 | 7.4 | −8.3 | 23.1 | 0.47[a] |
| | After | 68.3 ± 22.3 | 70 ± 24 | −1.7 | −16.1 | 12.8 | 0.003[b] |
| | Change | −2.4 ± 8.9 | 6.7 ± 8.7 | −9.0 | −14.5 | −3.6 | < 0.001[a] |
| | P-within | 0.16[c] | 0.003 [c] | | | | |
| **Role physical** | Before | 64.3 ± 36.7 | 59.5 ± 45.1 | 4.8 | −20.9 | 30.4 | 0.85[a] |
| | After | 63.1 ± 38.4 | 69.0 ± 39.5 | −6.0 | −30.2 | 18.3 | 0.06[b] |
| | Change | −1.2 ± 18.5 | 9.5 ± 16.7 | −10.7 | −21.7 | 0.3 | 0.04[a] |
| | P-within | 0.76[c] | 0.02[c] | | | | |
| **Bodily pain** | Before | 75.8 ± 18.4 | 66.3 ± 29.1 | 9.5 | −5.7 | 24.7 | 0.36[a] |
| | After | 73.5 ± 20.0 | 80.2 ± 21.7 | −6.8 | −19.8 | 6.2 | < 0.001[b] |
| | Change | −2.4 ± 9.3 | 13.9 ± 15.3 | −16.3 | −24.2 | −8.4 | < 0.001[a] |
| | P-within | 0.20[c] | 0.001[c] | | | | |
| **Role emotional** | Before | 50.8 ± 40.3 | 54.0 ± 41.5 | −3.2 | −28.7 | 22.3 | 0.81[a] |
| | After | 50.8 ± 41.7 | 66.7 ± 40.8 | −15.9 | −41.6 | 9.9 | 0.09[b] |
| | Change | .0 ± 25.8 | 12.7 ± 24.7 | −12.7 | −28.4 | 3.1 | 0.10[a] |
| | P-within | 1.00[c] | 0.04[c] | | | | |
| **Social functioning** | Before | 69.6 ± 20.8 | 67.3 ± 30.7 | 2.4 | −14.0 | 18.7 | 1/00[a] |
| | After | 67.9 ± 21.5 | 77.4 ± 21.9 | −9.5 | −23.0 | 4.0 | 0.002[b] |
| | Change | −1.8 ± 11.4 | 10.1 ± 14.6 | −11.9 | −20.1 | −3.7 | 0.01[a] |
| | P-within | 0.47[c] | 0.01[c] | | | | |
| **General health** | Before | 55.7 ± 22.7 | 57.5 ± 17.9 | −1.9 | −14.6 | 10.8 | 0.76[d] |
| | After | 56.7 ± 20.9 | 60.5 ± 18.8 | −3.6 | −16.0 | 8.8 | 0.39[b] |
| | Change | 1.2 ± 4.7 | 2.9 ± 8.6 | −1.7 | −6.0 | 2.7 | 0.44[d] |
| | P-within | 0.26[e] | 0.14[e] | | | | |
| **Vitality** | Before | 63.6 ± 17.5 | 64.8 ± 27.0 | −1.2 | −15.4 | 13.0 | 0.87[d] |
| | After | 62.9 ± 17.9 | 67.4 ± 22.2 | −4.5 | −17.1 | 8.0 | 0.11[b] |
| | Change | −0.7 ± 6.6 | 2.6 ± 9.0 | −3.3 | −8.3 | 1.6 | 0.18[d] |
| | P-within | 0.62[e] | 0.20[e] | | | | |
| **Mental health** | Before | 64.0 ± 20.3 | 70.1 ± 19.3 | −6.1 | −18.5 | 6.3 | 0.33[d] |
| | After | 61.9 ± 20.9 | 72.0 ± 14.5 | −10.1 | −21.3 | 1.1 | 0.04[b] |
| | Change | −2.1 ± 6.6 | 1.9 ± 9.3 | −4.0 | −9.1 | 1.1 | 0.12[d] |
| | P-within | 0.16[e] | 0.36[e] | | | | |

[a] Independent sample *t*-test

[b] ANCOVA test

[c] Paired *t*-test

[d] Mann-Whitney test

[e] Wilcoxon signed rank

**Table 4** Changes in BDI-II depression score at baseline and following 12 weeks of intervention

| | Group | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo ($n=21$) | | | | Nano-curcumin ($n=21$) | | | | $p^a$ |
| | Minimal | Mild | Moderate | Severe | Minimal | Mild | Moderate | Severe | |
| **Before** | 13 (61.9%) | 6 (28.6%) | 2 (9.5%) | 0 (0.0%) | 12 (57.1%) | 6 (28.6%) | 1 (4.8%) | 2 (9.5%) | 0.66 |
| **After** | 8 (38.1%) | 10 (47.6%) | 2 (9.5%) | 1 (4.8%) | 16 (76.2%) | 2 (9.5%) | 1 (4.8%) | 2 (9.5%) | 0.046 |

[a] Mann-Whitney test

of visfatin, was observed in CSFP. While the exact relationship between CSFP and resistin has not been demonstrated yet, it is proposed that resistin may be involved in the pathogenesis of CSFP independently or in correlation with endothelial dysfunction, atherosclerosis, or vascular resistance [39]. It is worth noting that in an RCT study, 500 mg curcumin supplementations for 4 weeks beneficially lowered resistin levels (another adipokine contributed to obesity and diabetes mellitus) in obese children [40].

CRP can induce vascular damage and endothelial dysfunction, plaque remodeling, pro-thrombotic state, oxidative stress, and inflammatory processes [8] through activation of NF-kB signaling and complement cascade and reduction of bioavailability of nitric oxide and thus exert detrimental effects on CVDs [41]. Some RCTs including a 12-week supplementation with 120 mg/day nano-curcumin in patients with hemodialysis [42] as well as 3 months supplementation with 80 mg/day nano-curcumin in patients with NAFLD [43] showed significant reduction in hs-CRP levels compared to the placebo group. However, the current trial showed no significant improvement in hs-CRP levels in CSFP patients receiving nano-curcumin. In line with our findings, 24 weeks supplementation with 180 mg Theracurmin (a curcumin with high bioavailability) in patients with chronic obstructive pulmonary disease did not improve hs-CRP levels significantly [44]. In another RCT study in CrossFit athletes, consumption of 2 g/day curcumin plus 20 mcg/day BioPerine for 28 days was not beneficial in decreasing hs-CRP level [45]. Additionally, a recent meta-analysis showed no significant reduction in CRP and hs-CRP concentrations by curcumin/turmeric supplementation in chronic inflammatory diseases [46]. Probably, the bioavailability, dose and duration of supplementation, the degree of inflammation, and severity of the underlying and concomitant diseases could explain part of these controversies. The mean hs-CRP levels were about 1 mg/l in both the study groups at baseline, which is not considered as a high inflammatory status.

The current study showed significant improvement in many aspects of QOL as well as depressive symptoms following nano-curcumin supplementation. Subjective outcomes such as QOL and depression have not been considered much enough in many clinical trials, especially in less studied conditions like CSFP. It has been stated that curcumin can alleviate pathological pain induced by inflammation, thanks to its anti-inflammatory properties [47]. Pain has a pivotal role in health-related QOL. Similar to our study, 160 mg/day nano-curcumin supplementation for 3 months significantly improved QOL in patients with Parkinson disease, based on Parkinson's Disease Questionnaire–39 (PDQ-39), in comparison with the placebo group [48]. Another RCT study in patients with cirrhosis showed the beneficial effect of 12 weeks intervention with 1000 mg/day curcumin on improving total mental and physical health scores and all dimensions of QOL (except for role emotional), based on SF-36 questionnaire, compared to the placebo group [49]. Six months' supplementation with 240 mg/day nano-curcumin in children with cystic fibrosis also showed significant improvement in QOL, assessed by pediatric quality of life inventory (PedsQL) 4.0, compared with the placebo group [50]. A recent meta-analysis has illustrated that short term (< 5 months) supplementation with highly bioavailable curcumin has beneficial effects on health-related quality of life in healthy adults and different diseases [51]. Contrary to these studies, a 160-mg/day curcumin supplement with or without 2000 mg docosahexaenoic acid + 400 mg eicosapentaenoic acid/day for 16 weeks did not improve QOL, based on the SF-36 scale, in middle-aged and older adults. However, vigor and subjective memory complaints (SMC) have been improved compared to the placebo group [52].

Inflammatory cascades especially NLR family pyrin domain containing 3 (NLRP3) inflammasome are involved in depression through increased production of inflammatory cytokines and neuro-inflammation. Curcumin reduces the activation of NF-kB and therefor blocks NLRP3 activation [53]. Similar to our results, some previous trials using 500–1000 mg curcumin or curcuminoid for 6–12 weeks have shown promising effects on depression and anxiety in patients with major depression [54–56]. On the other hand, an RCT study did not show any significant improvement in depression and anxiety following 1000 mg/day curcumin

supplementation for 12 weeks in patient with coronary heart disease and type 2 diabetes [57]. Another RCT study in patients with metabolic syndrome revealed that there were no significant differences in depression and anxiety between the patients received either 1 g/day phospholipidated or unformulated curcumin and the placebo group after 6 weeks. However, severe anxiety was improved significantly in the intervention groups compared to the placebo [58]. According to a recent meta-analysis, curcumin supplementation has a beneficial effect on depression and anxiety in patients with depression [59].

This study had some strengths including being among the first studies investigating the role of nutritional interventions on cardiometabolic health as well as physical and psychological well-being in CSFP. The randomized double-blind placebo-controlled design of this trial minimized potential biases. Additionally, using a nano-formulation of the supplement could overcome low bioavailability, which is a major concern with curcumin, and therefore, enhance the efficacy of the intervention [60].

This trial had some limitations that should be considered. Although the relatively low prevalence and diagnosis of CSFP cause time and financial constraints in conducting large trials, including larger sample sizes is suggested in future studies to understand the role of covariates and better judgment of the results. In addition, as a primary study in the field, we used the dosage of 80 mg/day nano-curcumin, which may not be enough to induce a significant change in some outcomes. Measuring more cardiometabolic and inflammatory markers as well as other adipokines at the cellular and biochemical level could help clarify the efficacy of supplementation with nano-curcumin. Finally, angiography is the gold standard method to evaluate the clinical changes in CSFP; however, it was not available at the end of this trial study due to the invasive nature of the procedure and ethical issues.

## Conclusion

The results of the current clinical trial suggest that supplementation with 80 mg/day nano-curcumin for 12 weeks improved physical and psychological quality of life and depression and prevented deterioration of glycemic control. However, circulating visfatin and hs-CRP levels did not change significantly in this trial. Further studies should be conducted to elucidate the effects of curcuminoids on inflammation and oxidative stress, endothelial dysfunction, adipose tissue function, and other potential underlying mechanisms involved in CSFP pathogenesis and outcomes.

## Supplementary Information

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Supplementary Material 1.

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**Authors' contributions**
M.S, M.R, and E.A: contributed to writing the first draft. M.S and M.R: contributed to data gathering. M.S, M.R, and M.Y: contributed to all data and statistical analysis and interpretation of data. M.H, A.F, and S.R: contributed to the research concept, supervised the work, and revised the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**
To protect study participant privacy, data cannot be shared openly, but data are available through a reasonable request from the corresponding author. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Declarations

**Ethics approval and consent to participate**
This study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1398.278) and registered with the Iranian Registry of Clinical Trials (IRCT20131125015536N8). At the beginning, written consent was obtained from all participants voluntarily.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's Note