Clinical Nutrition 34 (2015) 1101–1108

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized control trials

Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis

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ARTICLE INFO

Article history:
Received 12 November 2014
Accepted 29 December 2014

Keywords:
Curcuma longa
Turmeric
Cardiovascular disease
Antioxidant
Randomized controlled trial

SUMMARY

Background: Oxidative stress and inflammation have been proposed as emerging components of metabolic syndrome (MetS). Curcuminoids are natural polyphenols with strong antioxidant and anti-inflammatory properties.

Objective: To study the effectiveness of supplementation with a bioavailable curcuminoid preparation on measures of oxidative stress and inflammation in patients with MetS. Our secondary aim was to perform a meta-analysis of data from all randomized controlled trials in order to estimate the effect size of curcuminoids on plasma C-reactive protein (CRP) concentrations.

Methods: In this randomized double-blind placebo-controlled trial, 117 subjects with MetS (according to the NCEP-ATPIII diagnostic criteria) were randomly assigned to curcuminoids (n = 59; drop-outs = 9) or placebo (n = 58; drop-outs = 8) for eight weeks. Curcuminoids were administered at a daily dose of 1 g, and were co-supplemented with piperine (10 mg/day) in order to boost oral bioavailability. Serum activities of superoxide dismutase (SOD) and concentrations of malondialdehyde (MDA) and CRP were measured at baseline and at study end. Regarding the importance of CRP as a risk marker and risk factor of cardiovascular disease, a random-effects meta-analysis of clinical trials was performed to estimate the overall impact of curcuminoid therapy on circulating concentrations of CRP. The robustness of estimated effect size was evaluated using leave-one-out sensitivity analysis.

Results: Supplementation with curcuminoid-piperine combination significantly improved serum SOD activities ($p < 0.001$) and reduced MDA ($p < 0.001$) and CRP ($p < 0.001$) concentrations compared with placebo. Quantitative data synthesis revealed a significant effect of curcuminoids vs. placebo in reducing circulating CRP concentrations (weighed mean difference: −2.20 mg/L; 95% confidence interval [CI]: −3.96, −0.44; $p = 0.01$). This effect was robust in sensitivity analysis.

Conclusions: Short-term supplementation with curcuminoid-piperine combination significantly improves oxidative and inflammatory status in patients with MetS. Curcuminoids could be regarded as natural, safe and effective CRP-lowering agents.

Abbreviations: ARE, antioxidant response element; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; FBS, fasting blood sugar; GRAS, generally recognized as safe; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; MDA, Malondialdehyde; MetS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel III; ROS, reactive oxygen species; SBP, systolic blood pressure; SOD, superoxide dismutase.

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http://dx.doi.org/10.1016/j.clnu.2014.12.019
0261-5614/

1. Introduction

Metabolic syndrome (MetS) is a global health problem that arises as a consequence of the co-occurrence of several cardiometabolic risk factors including hyperglycemia, hypertension, abdominal obesity and dyslipidemia [1]. Accumulation of these risk factors significantly increases the risk of coronary heart disease (CHD) and its equivalents such as Type 2 diabetes [2]. Oxidative stress can be considered as a unifying feature of the seemingly discrete components of metabolic syndrome [3,4]. Accumulating evidence from experimental and clinical works indicate a strong association between metabolic syndrome and oxidative stress [3,4]. Numerous studies have shown overproduction of reactive oxygen species (ROS), elevated biomarkers of lipid peroxidation and protein oxidation, and depleted levels of both enzymatic and non-enzymatic antioxidants in patients with MetS [5–7]. What is more, there is evidence indicating that oxidative stress is not merely a risk marker of MetS but an active contributor to the early steps of the disease, owing to the pathologic role of ROS in insulin resistance, visceral adiposity, endothelial damage and lipoprotein metabolism [3,8]. Therefore, restoration of impaired redox state by antioxidant therapy has been proposed as a promising therapeutic strategy for patients with MetS. Inflammation is another pathomechanism that may serve as a mechanistic link among metabolic syndrome components. A low-grade inflammatory status commonly underlies MetS and is characterized by elevated levels of pro-inflammatory cytokines and C-reactive protein (CRP) in plasma [9,10]. Serum CRP concentrations have been repeatedly reported to be directly associated with several cardiovascular as well as metabolic diseases. Mounting evidence indicates that oxidative stress can activate NF-κB and trigger the release of pro-inflammatory cytokines and CRP [11]. On the other hand, leukocytes that are infiltrated in response to inflammation are a rich source of ROS. Therefore, inflammation and oxidative stress are highly inter-related and cross-promote each other in a vicious cycle, resulting in the progression of MetS to cardiometabolic outcomes [4]. Owing to the pivotal role of oxidative stress and inflammation in the pathogenesis of MetS, concomitant targeting of both these factors would be of paramount importance in the management of disease.

Curcuminoids are bioactive principles of the famous dietary spice, turmeric. Having a polyphenolic structure, curcuminoids have been extensively studied in different diseases including experimental models of metabolic and cardiovascular diseases [12]. Among the myriad of biological activities of curcuminoids [13–24], antioxidant [25–27] and anti-inflammatory [28,29] activities are of particular interest owing to the pivotal role of these parameters in the pathogenesis of MetS. Curcuminoids are known to inhibit several transcription factors (e.g. NF-κB) and enzymes (e.g. p38 MAPK and JNK) involved in inflammation, decrease expression and release of pro-inflammatory cytokines and acute phase reactants, scavenge ROS, reduce lipid peroxidation and up-regulate antioxidant enzymes [30–32]. In spite of these beneficial actions [33,34], no study has yet assessed the antioxidant and anti-inflammatory effects of curcuminoids in patients with MetS. The single evidence is our recent study, in which we showed a significant effect of supplementation with a bioavailability-enhanced preparation of curcuminoids in improving serum concentrations of lipoproteins in patients with MetS [35]. The present study aimed to extend our understanding of the benefits of curcuminoid therapy in MetS by measuring serum activities of superoxide dismutase (SOD; as a measure of systemic antioxidant capacity), malondialdehyde concentrations (MDA; as a measure of lipid peroxidation) and CRP (as a measure of systemic inflammation) as measures of systemic oxidative stress and inflammation. In addition, regarding the importance of CRP as a risk marker and risk factor of cardiovascular disease, a meta-analysis of randomized controlled trials was performed to estimate the effect size of curcuminoid therapy in changing circulating concentrations of this protein.

2. Materials and methods

2.1. Subjects

Participants were recruited from the Cardiology and Endocrinology Clinics of the Baqiyatallah Hospital (Tehran, Iran). Inclusion criteria were males and females who were not originally receiving lipid-lowering therapy, for whom a diagnosis of MetS was made according to the criteria defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines a follows: ≥3 of the following conditions: waist circumference ≥102 cm (male) or ≥88 cm (female), blood pressure ≥130/85 mmHg, triglycerides ≥1.7 mmol/L, HDL-C <1.03 mmol/L (males) or <1.29 mmol/L (females), fasting blood sugar (FBS) ≥6.1 mmol/L [36].

Exclusion criteria were pregnancy or breastfeeding, lack of compliance with the study medication (defined as not using the medication for >1 week), participation in a concomitant trial, hypersensitivity to the study medication, presence of malignancies and impossibility to give informed consent. The study protocol was given approval by the institutional Ethics Committee and written informed consent was obtained from participants.

2.2. Study design

This study was a phase III randomized double-blind placebo-controlled trial with a parallel-group design. After assessing for eligibility, subjects who met the inclusion criteria were randomly allocated to either curcuminoids (Curcumin C3 Complex®, Sami Labs LTD, Bangalore, India; n = 59) or matched placebo (n = 58) for a period of eight weeks. Curcuminoids were administered at a daily dose of 1 g (500 mg b.i.d.). In order to address the poor bioavailability problem of curcuminoids, 5 mg piperine (Bioperine®; Sami Labs LTD, Bangalore, India) was added to each 500 mg curcuminoid capsule [37]. C3 Complex® preparation that was used in the present study contains three major curcuminoids i.e. curcumin, demethoxycurcumin and bisdemethoxycurcumin in patented ratio.

2.3. Blood sampling

Overnight fasting blood samples were collected at baseline and at study end. The samples were allowed to clot for about 30 min and then centrifuged at 750 g for 10 min to obtain serum. Sera were aliquoted and frozen at −80 °C until measurements.

2.4. Measurements

Serum activities of SOD and concentrations of MDA were determined spectrophotometrically using routine methods. Serum high-sensitivity C-reactive protein (hs-CRP) was measured using an immunoturbidimetric assay with a commercial kit. Weight, height, and systolic and diastolic blood pressures were measured according to standard procedures [38]. To calculate BMI, weight (in kilograms) was divided by height (in squared meters [m^2]).

2.5. Statistical analysis

Statistical analyses were performed using the SPSS software version 11.5 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean ± SD or number (%). Within-group comparisons were