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Original article

Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial

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ABSTRACT

Background: Cytokines are involved in the development of metabolic abnormalities that may result in metabolic syndrome (MetS). Since curcumin has shown anti-inflammatory properties, the aim of this study was to evaluate the effect of curcumin supplementation on serum cytokines concentrations in subjects with MetS.

Methods: This study was a post-hoc analysis of a randomized controlled trial in which males and females with diagnosis of MetS, according to the criteria defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines, were studied. Subjects who met the inclusion criteria were randomly assigned to either curcumin (daily dose of 1 g/day) or a matched placebo for a period of 8 weeks.

Results: One hundred and seventeen subjects were assigned to either curcumin ($n = 59$) or placebo ($n = 58$) groups. Within-group analysis revealed significant reductions in serum concentrations of TNF-α, IL-6, TGF-β and MCP-1 following curcumin supplementation ($p < 0.001$). In the placebo group, serum levels of TGF-β were decreased ($p = 0.003$) but those of IL-6 ($p = 0.735$), TNF-α ($p = 0.138$) and MCP-1 ($p = 0.832$) remained unaltered by the end of study. Between-group comparison suggested significantly greater reductions in serum concentrations of TNF-α, IL-6, TGF-β and MCP-1 in the curcumin versus placebo group ($p < 0.001$). Apart from IL-6, changes in other parameters remained statistically significant after adjustment for potential confounders including changes in serum lipids and glucose levels, and baseline serum concentration of the cytokines.

Conclusion: Results of the present study suggest that curcumin supplementation significantly decreases serum concentrations of pro-inflammatory cytokines in subjects with MetS.

1. Introduction

Metabolic syndrome (MetS) was described initially by Reaven in 1988 as Syndrome X, characterized by insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein cholesterol (HDL-C), and elevated triglyceride levels [1]. Then, several definitions were proposed including obesity as a principal feature, focusing on visceral obesity since excess adipose tissue is associated with MetS components [2]. Both overweight and obesity are linked to chronic low-grade inflammation although underlying molecular mechanisms are still unclear [3]. Hypertrophied adipocytes and infiltrating macrophages and

Abbreviations: MetS, metabolic syndrome; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; TGF-β, transforming growth factor beta; BMI, body mass index; SD, standard deviation; ANCOVA, univariate analysis of covariance; MCP-1, monocyte chemoattractant protein-1; SBP, systolic blood pressure; DBP, diastolic blood pressure; Lp(a), lipoprotein(a); hs-CRP, high-sensitivity C-reactive protein.

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lymphocytes contribute to the release of pro-inflammatory cytokines [4]. Tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) are considered as the most important cytokines responsible for chronic low-grade systemic inflammation, also called "metabolic inflammation", that is commonly associated with metabolic disturbances such as type 2 diabetes [5]. Pro-inflammatory cytokines may induce the development of insulin resistance by altering the insulin signaling pathway or via triggering inflammatory pathways [6,7]. In addition, chronic systemic inflammation plays an important role in the pathogenesis of atherosclerosis and cardiovascular disease [8–10]. Although it has been suggested that the inflammatory process induced by obesity may lead to comorbidities such as atherosclerosis, dyslipidemia, hypertension, diabetes, and insulin resistance that characterize MetS; the pathophysiological mechanisms have remained unexplained yet.

Curcumin is the bioactive yellow pigment with a polyphenolic structure that is present in turmeric (*Curcuma longa* L.). Hitherto, several medicinal effects of curcumin have been described [10–22]. Curcumin interacts with various molecular targets including cytokines, growth factors, proteins, enzymes, and receptors [23,24]. Furthermore, this polyphenol has anti-inflammatory, antioxidant, and anti-tumor effects [25–27]. Although curcumin has been investigated in different clinical conditions, clinical trials evaluating its effect in individuals with MetS are scarce [28,29]. Therefore, in this study, we evaluate the curcumin effect on serum cytokines concentrations in subjects with MetS.

2. Material and methods

2.1. Subjects

This study is a post-hoc analysis performed on the samples obtained from our previous investigation [28]. 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 as 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 glucose ≥6.1 mmol/L [30].

Exclusion criteria were pregnancy or breastfeeding, lack of compliance with the study medication (defined as not using the medication for >1 week according to the participans' self-report), participation in a concomitant trial, hypersensitivity to the study medication, presence of inflammatory and systemic diseases, 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 designed as a randomized double-blind placebo-controlled trial with a parallel-group design. Subjects who met the inclusion criteria were randomly assigned to either curcumin (Curcumin C3 Complex®, Sami Labs LTD, Bangalore, India; n = 59) or matched placebo (n = 58) for a period of 8 weeks. Randomization was performed via alternative allocation of participants to capsule bottles (identical in shape, size and color) labelled as "code A" or "code B". Curcumin was administered at a daily dose of 1 g (500 mg b.i.d.), a dose that was found to be effective and safe in previous trials [17,31]. Both administering physician and the patients were blinded to the assigned intervention. In order to improve the bioavailability problem of curcumin, 5 mg piperine (Bioperine®; Sami Labs LTD, Bangalore, India) was added to each 500 mg curcumin capsule [32]. Placebo capsules contained lactose plus equal amount (5 mg) of piperine. C3 Complex® preparation that was used in the present study contained three major curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin in a patented ratio. The purity of the three major curcuminoids was determined using HPLC assay.

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

Measurement of waist circumference was performed at the level of the umbilicus, i.e. the midway between the lower rib margin and the iliac crest. Weight was measured with the subjects dressed in light clothing after an overnight fasting using a standard scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (m^2) [33–35]. Serum glucose concentrations were determined using glucose oxidase method [36]. Serum concentrations of cholesterol, triacylglycerol, LDL-C and HDL-C were measured using enzymatic methods on an automated analyzer. For the measure of serum total cholesterol concentrations, a sterol esterase–cholesterol oxidase assay was used as previously described [37]. Serum LDL-cholesterol concentrations were measured directly using the sterol esterase–cholesterol oxidase method, after selective precipitation of LDL and removal of non-LDL lipoproteins. Serum HDL-C concentrations were measured with the same sterol esterase–cholesterol oxidase method used for serum cholesterol, after removal of non-HDL apoB-containing lipoproteins with magnesium–dextran sulfate precipitation [38]. Serum triglycerides concentration was measured by hydrolyzing the triacylglycerol and subsequent determination of the released glycerol [39]. Serum high-sensitivity C-reactive protein (hs-CRP) was measured using an immunoturbidimetric assay with a commercial kit [40].

Serum concentrations of IL-6, TNF-α, transforming growth factor beta (TGF-β) and chemoattractant protein-1 (MCP-1) were determined the enzyme linked immunoassay technique with commercial kits. The intra-assay coefficients of variation for the measurement of IL-6, TNF-α, MCP-1 and TGF-β were 6.2%, 8.5%, 7.7% and 3.2%, respectively. The inter-assay coefficients of variation for the measurement of IL-6, TNF-α, MCP-1 and TGF-β were 7.0%, 9.8%, 6.2% and 4.9%, respectively.

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 performed using paired samples *t*-test (for normally distributed data) or Wilcoxon signed-ranks test (for non-normally distributed data). Between-group comparisons were performed using independent samples *t*-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data). Categorical variables were compared using Chi-square test. Univariate analysis of covariance (ANCOVA) using general linear model was used to adjust for the effect of potential confounders on the association between curcumin supplementation and changes in serum levels