Effects of Curcumin Supplementation on Exercise-Induced Oxidative Stress in Humans

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Abstract

The purpose of this study was to investigate the effects of curcumin supplementation on exercise-induced oxidative stress in humans. 10 male participants, ages 26.8±2.0 years (mean±SE), completed 3 trials in a random order: (1) placebo (control), (2) single (only before exercise) and (3) double (before and immediately after exercise) curcumin supplementation trials. Each participant received oral administration of 90 mg of curcumin or the placebo 2 h before exercise and immediately after exercise. Each participant walked or ran at 65 % of VO₂max on a treadmill for 60 min. Blood samples were collected pre-exercise, immediately after exercise and 2 h after exercise. The concentrations of serum derivatives of reactive oxygen metabolites measured immediately after exercise were significantly higher than pre-exercise values in the placebo trial (308.8±12.9 U. CARR, P<0.05), but not in the single (259.9±17.1 U. CARR) or double (273.6±19.7 U. CARR) curcumin supplementation trials. Serum biological antioxidant potential concentrations measured immediately after exercise were significantly elevated in the single and double curcumin supplementation trials compared with pre-exercise values (P<0.05). These findings indicate that curcumin supplementation can attenuate exercise-induced oxidative stress by increasing blood antioxidant capacity.

Introduction

Reactive oxygen species (ROS) play an important role in the maintenance of homeostasis through immune function and cellular signals [37]. However, excessive amounts of ROS can damage DNA, proteins and lipids [5,12]. Exercise, for instance, has been suggested to increase oxygen utilization 200-fold above resting levels in active muscles, and endurance exercise of sufficient intensity and duration can further induce oxidative stress [16,29]. Evidence has also suggested a link between oxidative stress and fatigue, or muscle damage, which can affect exercise performance [10,23,28]. Therefore, it is important to prevent these damages by increasing the dietary content of nutritional antioxidants.

For several years, some studies have reported that high-dose antioxidant supplementation can inhibit the up-regulation of endogenous antioxidant capacity in response to exercise training [13,32]. These findings have focused on whether antioxidant supplementation is useful for preventing oxidative stress in response to high-intensity exercise or detrimental by interfering with beneficial physiological effects of ROS during exercise training. Moreover, pretreatment with several antioxidants to improve muscle function and exercise performance has provided limited evidence for prevention of oxidative stress [28]. One possible reason is related to the bioavailability of antioxidants taken as supplements, which may not be absorbed at sufficient levels to produce any biological effects. In addition, the majority of previous studies did not adhere to all the accepted features of a high-quality trial (i.e., placebo-controlled, double-blind, randomized design) [23,28]. Therefore, it is necessary to examine the effects of an antioxidant with high oral bioavailability on exercise-induced oxidative stress in a high-quality trial.

Curcumin is a component of the spice turmeric responsible for the yellow color of curry, which has been known to possess antioxidant, anti-inflammatory, anticancer and antibacterial qualities [2]. It is a diferuloylmethane with 2 β-unsaturated β-diketone (heptadiene-
The ROS scavenging activity of curcumin can arise either from the phenolic OH groups or from the CH₂ group of the β-diketone moiety [1]. Specifically, some studies reported that the phenolic OH groups of curcumin are essential for the ROS scavenging activity and that the presence of the methoxy groups further increase the activity [31,35]. However, the low oral bioavailability of curcumin has been a major issue [34,39]. Recently, curcumin with high oral absorption capacity and bioavailability (Theracurmin®) have been developed [34]. Sasaki et al. has reported that the oral high bioavailability of Theracurmin® was 27-fold higher than that of curcumin powder in humans [34]. Few studies have examined the effects of curcumin supplementation on exercise-induced oxidative stress and exercise performance. Davis et al. have shown that curcumin can offset the muscle damaging effects of downhill running on inflammation and whole body exercise performance in mice [7]. In addition, one study has reported that curcumin administration can improve oxidative stress status induced by ischemia/reperfusion injury in rat skeletal muscle [2]. However, no information is available regarding the effect of curcumin supplementation on exercise-induced oxidative stress in humans. The purpose of this study was to determine whether oral curcumin supplementation may be sufficient to ameliorate oxidative stress induced by exercise in a randomized controlled trial.

Methods

Participants

10 healthy men ages 23–30 years participated in this study after giving written informed consent. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the ethics committees of Waseda University. This study also followed the ethical standards of the journal [15]. Participants were recruited only if they met the following criteria: non-smoking, no known history of cardiovascular disease, body mass index (BMI) < 25 kg/m², and no intake of any medication or antioxidant supplements. All volunteers completed a questionnaire on physical activity, exercise, dietary intake, lifestyle and health history prior to the study. While none of the study subjects were trained athletes competing in any sporting events, some participants were recreationally active. The physical characteristics of participants were as follows (expressed as mean ± standard error of mean (SE)): age, 26.8 ± 2.0 years; height, 1.73 ± 0.05 m; body mass, 67.7 ± 5.3 kg; and BMI, 22.5 ± 1.5 kg/m².

Baseline measurements and determination of maximal oxygen consumption

On their first visit to the laboratory, subjects’ height, weight, blood pressure, heart rate (HR) and percent body fat were measured by the same experimenter. Following these measurements, each participant performed a graded maximal oxygen consumption test (VO₂max) using the Bruce protocol on a motorized treadmill. During exercise, a 12-lead electrocardiogram was electronically recorded (Stress Test System ML-6500; Fukuda Denshi, Japan), and heart rate was derived from the R-R interval. In addition, ratings of perceived exertion (RPE) were determined at the end of each minute of exercise and recovery. Pulmonary gas exchange (oxygen uptake [VO₂], carbon dioxide output [VCO₂], minute ventilation [VE], and respiratory exchange ratio [RER]) were determined breath-by-breath by a gas analyzer (AE-300 S, Minato Medical Science, Japan).

To ascertain that VO₂ max was attained, the following 3 criteria had to be met: (1) VO₂ plateaued despite increasing exercise intensity, (2) the highest HR measured during the last minute of exercise was >90% of the predicted maximal heart rate (220 − age [in years]), and (3) the highest RER was >1.10 during the final stage of incremental exercise. Data from the maximal test were used to determine 65% of VO₂ max for each participant. Some studies have reported that this exercise intensity increased the blood oxidative stress markers [4,14,16].

Main trials

A double-blind, placebo-controlled, counterbalanced crossover design was used. Each participant underwent 3 laboratory-based trials in a randomized order: (1) placebo (control), (2) single curcumin supplementation (only before exercise) and (3) double curcumin supplementation (before and immediately after exercise). The interval between trials was at least 1 week apart. Curcumin was provided by the Theravalues Corporation (Tokyo, Japan). The curcumin capsule in this study consisted of 10% curcumin, 2% curcuminoids without curcumin, 3.2% gum ghatti, 0.27% citric acid, 54.53% dextrin and 30% maltose. The placebo capsule consisted of 5% tartrazine, 3.5% gum ghatti, 0.3% citric acid, 59.2% dextrin and 32% maltose. Participants orally received 90 mg of curcumin or the same capsules of placebo from the experimenter either 2 h before exercise or both 2 h before and immediately after exercise. A previous study has shown that the plasma concentrations of curcumin increased at 1–2 h after administration [18]. Therefore, participants in this study were given curcumin or placebo capsules 2 h before exercise. Each participant walked or ran at 65% VO₂ max on a treadmill for 60 min. HR was monitored throughout the test using short-range telemetry (Polar RS400; Polar Electro, Finland), and RPE were assessed periodically during the test. On the day of trials, all participants ate the same diet and took either curcumin or placebo capsules 2 h before exercise. The trials were performed at approximately the same time of the day to avoid diurnal variation. Participants were instructed to refrain from strenuous exercise and alcohol intake on the day before trials and were asked to maintain their normal diet without antioxidant supplementation during the experimental period.

Blood collection and analysis

Venous blood samples were taken from the antecubital vein immediately before and after exercise, as well as 2 h after exercise. For measuring serum blood markers, samples were allowed to clot for 30 min at room temperature and then centrifuged at 3000 rpm for 10 min at 4°C. Obtained serum was dispensed into plain microtubes and stored at ~80°C until the assay. For measuring plasma blood markers, blood samples collected into tubes containing ethylenediaminetetraacetic acid (EDTA) were immediately centrifuged and stored at ~80°C until the assay. Hemoglobin and hematocrit were determined in EDTA-treated venous blood using an automatic blood cell counter (poch-100i, Sysmex, Japan). Plasma curcumin concentrations were measured as previously described [18,36]. Serum concentrations of derivatives of reactive oxygen metabolites (d-ROMs) and the biological antioxidant potential (BAP) were measured using assay kits from Diacron (Italy). Plasma concentrations of thioredoxin-1 (TRX-1) were also measured by an enzyme-linked immunosorbent assay (Redox Bio Science, Inc., Japan). Plasma...
concentrations of thiobarbituric acid-reactive substances (TBARS), reduced and oxidized glutathione (GSH and GSSG, respectively), along with activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GR) were measured using assay kits from Cayman Chemicals (USA). Changes in plasma volume during the acute bout of exercise were calculated using the method outlined by Dill and Costill [8].

Statistical analysis
Data were presented as mean ± SE. The Kolmogorov-Smirnov test was used to check for normality of distribution of all blood parameters. The distribution of these parameters did not differ significantly from normal. Using 2-way repeated measures ANOVA, we analyzed data for the main effects of trial and time, as well as the interaction of time × trial. When significant main or interaction effects were detected, we used the Tukey’s test (honestly significant difference) for post-hoc comparisons. Statistical significance was set at P < 0.05. Data analysis was performed using PASW Statistics 18 software (SPSS Japan Inc., Japan).

Results
Heart rate (HR), ratings of perceived exertion (RPE) score
There were no statistically significant differences in HR or RPE among trials. HR and RPE immediately after exercise were 161 ± 6 beats/min and 14 ± 1, respectively, in the placebo trial, 164 ± 4 beats/min and 14 ± 1, respectively, in the single curcumin supplementation trial, and 164 ± 5 beats/min and 14 ± 1, respectively, in the double curcumin supplementation trial.

Plasma concentrations of curcumin
For plasma curcumin concentrations, 2-factor ANOVA revealed a significant trial × time interaction (P = 0.001) (Fig. 1). Post-hoc tests showed that plasma curcumin concentrations at baseline were significantly higher in the single and double curcumin supplementation trials than in the placebo trial (post-hoc tests; single vs. placebo, P = 0.001; double vs. placebo, P = 0.001). In addition, plasma curcumin concentrations after exercise and 2 h after exercise were significantly higher in the single and double curcumin supplementation trials than in the placebo trial (post-hoc tests; single vs. placebo, P = 0.001; double vs. placebo, P = 0.001). Moreover, the plasma curcumin concentrations in the double curcumin supplementation trial 2 h after exercise were significantly higher than those in the single curcumin supplementation trial (post-hoc tests; double vs. single, P = 0.015).

Plasma and serum oxidative stress markers
At baseline, there were no statistically significant differences in the concentrations of serum d-ROMs or plasma TRX-1, TBARS and GSSG among trials. For serum d-ROMs concentrations, 2-factor ANOVA revealed a significant trial × time interaction (P = 0.023). Post-hoc tests showed that serum d-ROM concentrations after exercise were significantly higher than pre-exercise values (placebo trial; 282.7 ± 11.8 U. CARR, single curcumin supplementation; 281.3 ± 19.2 U. CARR, double curcumin supplementation; 295.2 ± 21.0 U. CARR) in the placebo trial (308.8 ± 12.9 U. CARR, P = 0.05), but not in the single (259.9 ± 17.1 U. CARR) or double (273.6 ± 19.7 U. CARR) curcumin supplementation trials (P < 0.1) (Fig. 2d). For plasma SOD, CAT, GPX, and GR activity, 2-factor ANOVA revealed that there was a main effect of time (P < 0.01). For plasma GSH concentrations, 2-factor ANOVA revealed a significant trial × time interaction (P = 0.037). Post-hoc tests showed that serum BAP concentrations after exercise were significantly higher than pre-exercise values in the single and double curcumin supplementation trials (P < 0.05; Table 1). Plasma GSH concentrations 2 h after exercise were significantly higher than pre-exercise values in the single curcumin supplementation trial (P < 0.05) and tended to be higher in the double curcumin supplementation trial (P < 0.1) (Fig. 2b). For plasma SOD, CAT, GPX, and GR activity, 2-factor ANOVA revealed that there was a main effect of time for CAT activity (P < 0.01). While plasma CAT activity after exercise was significantly higher than pre-exercise values in all trials, the patterns of changes were not significantly different between the trials (P < 0.05). At 2 h after exercise, plasma GPX activity was significantly increased in the placebo trial (P < 0.05) but not in the single or double curcumin supplementation trials (Table 2). Plasma GR activity after exercise were significantly lower than the pre-exercise values in the...
placebo trial (P<0.05) but not in the single or double curcumin supplementation trials (Table 2). There were no statistically significant differences in plasma SOD activity, irrespective of supplementation or exercise (Table 2).

**Table 1** Changes in thiobarbituric acid reactive substances (TBARS) and oxidized glutathione (GSSG), before (Pre), immediately after (Post) and 2 h after exercise (Post 2 h).

<table>
<thead>
<tr>
<th>Parameter (μM)</th>
<th>Pre</th>
<th>Post</th>
<th>Post 2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBARS</td>
<td>1.03 ± 0.13</td>
<td>1.05 ± 0.14</td>
<td>1.10 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>1.09 ± 0.13</td>
<td>1.00 ± 0.11</td>
<td>0.98 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>1.09 ± 0.13</td>
<td>1.04 ± 0.11</td>
<td>1.01 ± 0.11</td>
</tr>
<tr>
<td>GSSG</td>
<td>8.07 ± 0.86</td>
<td>7.31 ± 0.86</td>
<td>7.71 ± 0.95</td>
</tr>
<tr>
<td></td>
<td>6.14 ± 0.99</td>
<td>7.40 ± 1.08</td>
<td>9.98 ± 2.21</td>
</tr>
<tr>
<td></td>
<td>6.79 ± 1.11</td>
<td>7.10 ± 1.15</td>
<td>7.17 ± 1.05</td>
</tr>
</tbody>
</table>

Values are means ± SE
Placebo: placebo trial, Single: single curcumin supplementation (2 h before exercise [90 mg]), Double: double curcumin supplementation (2 h before exercise [90 mg] and immediately after exercise [90 mg]).

**Table 2** Changes in superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GR), before (Pre), immediately after (Post) and 2 h after exercise (Post 2 h).

<table>
<thead>
<tr>
<th>Parameter (U/ml)</th>
<th>Pre</th>
<th>Post</th>
<th>Post 2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD</td>
<td>19.4 ± 0.7</td>
<td>19.2 ± 1.3</td>
<td>18.5 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>18.8 ± 1.3</td>
<td>17.3 ± 1.3</td>
<td>17.1 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>21.0 ± 1.0</td>
<td>17.6 ± 1.2</td>
<td>17.4 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>120.7 ± 17.4</td>
<td>156.1 ± 16.9*</td>
<td>150.2 ± 13.7</td>
</tr>
<tr>
<td></td>
<td>133.0 ± 20.9</td>
<td>175.0 ± 22.1*</td>
<td>155.6 ± 18.1</td>
</tr>
<tr>
<td></td>
<td>139.5 ± 20.3</td>
<td>180.6 ± 24.1*</td>
<td>152.5 ± 16.3</td>
</tr>
<tr>
<td></td>
<td>197.3 ± 36.9</td>
<td>208.2 ± 30.7*</td>
<td>269.3 ± 9.3*</td>
</tr>
<tr>
<td></td>
<td>257.3 ± 22.1</td>
<td>272.9 ± 23.4</td>
<td>283.0 ± 14.0</td>
</tr>
<tr>
<td></td>
<td>271.3 ± 23.0</td>
<td>301.0 ± 18.0</td>
<td>278.5 ± 12.0</td>
</tr>
<tr>
<td></td>
<td>9.0 ± 1.1</td>
<td>5.6 ± 0.6*</td>
<td>7.9 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>6.2 ± 0.5</td>
<td>7.1 ± 0.9</td>
<td>6.1 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>7.3 ± 0.9</td>
<td>7.2 ± 1.1</td>
<td>8.6 ± 2.3</td>
</tr>
</tbody>
</table>

Values are means ± SE
*Significantly different from the Pre values, P<0.05
Placebo: placebo trial, Single: single curcumin supplementation (2 h before exercise [90 mg]), Double: double curcumin supplementation (2 h before exercise [90 mg] and immediately after exercise [90 mg]).

**Fig. 2** Serum concentrations of derivatives of reactive oxygen metabolites (a d-ROMs), plasma thioredoxin-1 (b TRX-1) concentrations, serum concentrations of biological antioxidant potential (c, BAP), and reduced glutathione (d, GSH) before (Pre), immediately after (Post) and 2 h after (Post 2 h) exercise. Placebo, placebo trial; Single, single curcumin supplementation (2 h before exercise [90 mg]); Double, double curcumin supplementation (2 h before exercise [90 mg] and immediately after exercise [90 mg]). Data represent mean ± SE. *P<0.05 and **P<0.01, significantly different from the pre-exercise values.
Discussion

To the best of our knowledge, the present study is the first to examine the effects of curcumin supplementation on oxidative stress and antioxidant capacity in response to acute endurance exercise in humans. Our main findings are as follows: (1) curcumin supplementation attenuated the exercise-induced serum concentrations of d-ROMs and TRX-1, (2) concentrations of serum BAP and plasma GSH after exercise were increased by curcumin supplementation. These findings indicate that curcumin supplementation may attenuate exercise-induced oxidative stress markers by increasing antioxidant capacity.

A number of studies have reported that curcumin possesses ROS scavenging activity [3,31,40]. However, no information is available regarding its effects on exercise-induced oxidative stress in humans. One possible reason may be its low bioavailability [39]. In this study, highly bioavailable curcumin resulted in a significant increase in plasma curcumin concentrations, which supports the prior work of Sasaki et al. [34].

In the present study, we showed that curcumin supplementation attenuated the exercise-induced elevation of the serum concentrations of oxidative stress markers d-ROMs. In fact, the validity of d-ROMs as an oxidative stress marker has been demonstrated in several studies that evaluated the bioavailability and antioxidant activity of some food supplements and the intensity-dependency of exercise-induced oxidative stress [6,16]. The phenolic compound acts as a scavenger of reactive oxygen species and a quencher of the lipid peroxidative side chain [35]. Thus, the phenolic OH groups of curcumin may have reduced lipid hydroperoxides assessed by d-ROMs. In addition, TRX-1 has been suggested to be a sensitive oxidative stress marker during acute exercise [21,22]. One study has reported that the plasma TRX concentrations were elevated in the ultra-marathon race [22]. In the present study, curcumin supplementation attenuated the exercise-induced elevation of the plasma TRX-1. The mechanism for this change is not clear. Some studies have reported that TRX-1 was induced by oxidative stress [22,38]. Thus, TRX-1 may be down-regulated under the limited oxidative stress by curcumin supplementation. It is also noted that plasma TBARS concentrations were not influenced by either exercise or curcumin supplementation. Consistent with our results, previous studies have reported that TBARS, a nonspecific oxidative stress marker of lipid peroxidation, was not changed by antioxidant supplementation or exercise [30]. Furthermore, it is important to note that plasma and serum oxidative stress markers at baseline were not significantly different between the trials and that curcumin supplementation taken immediately after exercise showed no additive effects on the attenuation of oxidative stress markers.

Some studies have reported a link between oxidative stress and fatigue, or muscle damage, which can affect exercise performance [10,23,28]. However, there were no statistically significant differences in HR or RPE among trials. Thus, there is little direct data to support these relationships in this study. In addition, previous studies have shown that elevated oxidative stress is an independent risk factor for atherosclerosis, lifestyle-related diseases and cardiovascular diseases [11,24,27]. A previous study has reported that patients with type 2 diabetes mellitus (345±64 U. CARR) showed significantly higher d-ROMs concentrations than controls (328±64 U. CARR) [19]. Thus, a small change in d-ROMs concentrations brought about by curcumin supplementation could have clinical importance from the point of view of reducing several lifestyle-related disease risks. However, there is a need to establish the minimal clinically important difference in concentrations which can improve oxidative stress status to impact several disease risks.

In addition to the ROS scavenging activity of curcumin, the reduction of exercise-induced oxidative stress may also be explained by the increased activities of antioxidant enzymes and non-enzymatic antioxidants induced by curcumin supplementation. Avcı et al. have demonstrated that curcumin supplementation increased tissue GSH levels, as well as SOD and CAT activities, in a rat hind limb model of ischemia/reperfusion (2). Moreover, Kalpana et al. suggested that curcumin supplementation exerts its protective effect against nicotine-induced oxidative stress, thereby augmenting the antioxidant defense system in rats [17]. Taken together, these findings suggest that curcumin supplementation may improve the antioxidant defense system.

In this study, we found that serum BAP concentrations after exercise, as well as the GSH concentrations at 2h after exercise, were significantly increased by curcumin supplementation. BAP is assessed as the ferric reducing ability such as uric acid, vitamin C, vitamin E, polyphenol and GSH in the serum [26]. In addition, reduced GSH provides protection against oxidative stress and helps maintain intracellular redox homeostasis [9]. Supporting our results, some reports have indicated that increased concentrations of GSH were induced by curcumin [2,3]. This protein has thiol groups, and plays an essential role in reducing oxidative stress directly via their antioxidant effects [9,21]. A previous study has reported that the presence of hydroxyl groups of curcumin increases antioxidant capacity through intermolecular hydrogen involving the -SH group of GSH [36]. Moreover, GR recycles GSSG to GSH with the simultaneous oxidation of β-nicotinamide adenine dinucleotide phosphate (β-NADPH). Our results showed that curcumin supplementation attenuated the exercise-induced decline of the GR activity. Interestingly, curcumin supplementation taken immediately after exercise showed no additive effects on antioxidant capacity, due possibly to the exercise-induced induction of endogenous antioxidant capacity. Overall, our findings indicate that curcumin supplementation leads to increases in other antioxidant systems, including BAP, GSH and GR, during exercise. Some investigators have also reported increases in enzymatic antioxidants, such as SOD, CAT and GPX, by curcumin supplementation in rat skeletal muscle, lung, liver and kidney [2,17]. However, in this study, we observed that acute curcumin supplementation did not influence enzymatic antioxidant capacity responses induced by exercise, even though plasma CAT and GPX activities were increased after exercise. It is unclear as to why curcumin supplementation in our experiments had no effects on the enzymatic antioxidant system. One possible reason for this discrepancy might be the differences in the tissues and species tested and the intensity/duration of exercise [2,17]. Similar to the results of oxidative stress markers, plasma and serum levels of enzymatic and non-enzymatic antioxidant capacity markers at baseline were not significantly different between the trials. In contrast, previous studies have demonstrated that curcumin supplementation increased resting SOD, CAT activity and GSH concentrations [25,33]. This inconsistency may be explained by the fact that most of these studies investigated the effects of curcumin supplementation on several anti-
oxidant capacity markers for a longer period of time (ranging
from a few days to several weeks) compared to our current study
[25, 33]. Therefore, more long-term curcumin supplementation
may be effective in improving resting oxidative stress or enzy-
matic antioxidant capacity.

Conclusion

Our current study demonstrates that acute curcumin supple-
mentation can not only attenuate exercise-induced oxidative
stress but also increase antioxidant capacity responses to exer-
cise in humans.

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Conflict of interest: All authors declare that there is no conflict
of interest.

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