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ORIGINAL ARTICLE

The Effects of Two Weeks Quercetin Supplementation in Adolescent Swimmer Girls on The Oxidative Stress and Inflammatory Mediator's Response to Acute Swimming Session

Masoumeh Gholaman[1], Maryam Khodabakhsh Nokola[1], Zahra Ghorbani Ganjeh[1], Shokoufeh Sokhanvardastjerdi[2], Mandana Gholami[1], Maryam Kasiri[1]

[1]*Department of Physical Education and Sport Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran*

[2]*Department of Exercise Physiology, South Branch, Islamic Azad University, Tehran, Iran*

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KEYWORDS

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ABSTRACT: Quercetin could modulate the oxidative stress and inflammation, but its effects on exercise related oxidative stress and inflammation has attracted little attention. The present study conducted aimed to identify the effect of quercetin supplementation on oxidative stress and inflammatory mediator's response following the acute swimming session. In semi-experimental study, the 20 trained swimmer girls (15.1±0.21 yrs old and BMI, 21.05±2.3 kg m^{-2}) randomly allocated in two equal groups including quercetin (n= 10) and placebo (n= 10) groups. Subjects in quercetin group received 1000 mg quercetin daily for two weeks. Subsequently, participants completed the high intensity (>85% MHR) exhausting swimming session. In order to measurement the inflammatory (IL-6, CRP) and oxidative stress related markers, blood samples collected at the baseline, pre (after two-week quercetin supplementation) and immediately after completing the swimming session. Repeated-measures ANOVA test used for data analysis and significant levels considered at $p<0.05$. IL-6 significantly increased immediately after exercise in both groups ($p<0.001$), but IL-6 response to exercise in quercetin group was significantly less than placebo group ($p<0.05$). However, CRP don't show significant changes ($p>0.05$). TAC doesn't change, but significant increase in MDA, SOD, GPx and Catalase were observed in placebo and quercetin group immediately after swimming session ($p<0.05$) and MDA response to exercise session in quercetin group was significantly lower compared to placebo group ($p<0.05$). Quercetin modulated the IL-6 and MDA response after exhausting exercise and Quercetin can be considered as supplement for combating exercise induced inflammation and oxidative stress.

INTRODUCTION

Oxidative stress is mainly defined as an imbalance between oxidative status and antioxidant defense [1]. The most common biomarker for representing the oxidative stress is the evaluation of malondialdehyde (MDA) levels [2], that is an end-product of lipid peroxidation [3]. On the other hand, antioxidants enzymes are involved in the regulating and attenuation oxidative stress that among them, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and heme oxygenase-1 (HO-1) attracted a lot of attention [4]. Oxidative stress closely interrelated to inflammation [5]. Among inflammatory factors, cytokines known as main mediators of inflammation. Cytokines are a diverse family of intercellular signaling molecules that play an important role in regulating the inflammation and immune system [6]. Interleukin 6 (IL-6) and C reactive

*Corresponding author: m.gholami@srbiau.ac.ir (M. Gholami)
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protein (CRP) are important pro-inflammatory cytokines, which dysregulated in different pathological condition [7]. According to previous researches, it seems that oxidative stress and inflammation are involved in different disorders pathogenesis including cardiovascular disease and diabetes [8]. Therefore, investigate the strategies for modulating or attenuation the inflammation and oxidative stress is very important and, in this context, its reported that these processes (inflammation and oxidative exercise) affected by different intervention including diets and acute or chronic exercise training [9, 10].

Oxidative stress, antioxidant activity and inflammation process response and adaptation to exercise training is extremely complex. It's reported that acute high intensity exercise is associated with stimulate and increase in oxidative and inflammatory response [11]. In contrast, regular high intensity interval training (HIIT) attenuates and decrease the baseline inflammation and oxidative stress [12], and result in improve anti-oxidant capacity [13]. In addition to exercise, dietary supplements especially phenolic and polyphenols affected the oxidative system and inflammation and its antioxidant and anti-inflammatory properties has been approved [14]. Quercetin is one of the available plant phenolic compounds [15], that exhibits significant benefits including cardioprotective, protective effect on endothelial function during oxidative stress, preventing inflammatory process and damages [16]. The quercetin antioxidant properties are mainly exerted by its effect on glutathione, signal transduction pathways, enzymatic activity and reactive oxygen species (ROS) production, and quercetin induce the strong antioxidant activity by maintaining the oxidative balance [17]. In regard to quercetin effects on inflammatory and oxidative status response following acute exercise, its reported that two weeks quercetin supplementation decrease exercised induced inflammation (TNF-α) after exhausting exercise session and affected the immune system response [18]. In addition, acute ingestion of polyphenolic antioxidants supplement (2.3 g polyphenols) in trained cyclists were associated with attenuating the exercise-induced oxidative stress after 90 min cycling with 70% VO_{2max} intensity [19]. However, the results are contradictory and some researchers indicated that one week quercetin supplementation had no effect on muscle damage indicators or inflammatory cytokine (such as IL-6 and CRP) response after eccentric exercise [20]. Moreover, its reported that even long-term (8 weeks) quercetin supplementation hasn't a positive effect in athletes [21]. These controversial results can be attribute to many factors related to exercise session or quercetin supplementation and probably different subject properties. According to our knowledge, it's the first time that effects of short-term quercetin supplementation (two weeks) on the levels of inflammatory and oxidative or antioxidant activity following exhausting swimming in adolescent swimmer have been investigated.

MATERIALS AND METHODS

Subjects

Present study is semi-experimental research that conducted on the moderately trained adolescent swimmer girls with the average age of 15.1±0.21 yrs, weight 51.8±3.4 kg and height 155.1±3.7 as a participant, and all of them were in puberty stage. The subjects don't take any medications, anti-oxidant or vitamin supplements exceeding 100% of RDA in three months before intervention and during research protocol. Initially, the subjects and his parent were asked to signing the written informed consent and present study procedures were approved by the science and research branch, Islamic Azad University, Tehran. The subject's characteristics have been reported in Table 1. Healthy adolescent swimmer girls, 3 to 5 years swimming training experience, at least 3-4 training session (each session more than one hour) per week, no drugs or supplement intake and lack of allergy to drugs were considered as inclusion criteria for subjects. The subjects were wanted to continue their routine training program, but they were avoided from intensive exercise in the 48 hours before take part in the exhausting swimming session.

Table 1. The subjects' characteristics in placebo and supplement groups.

Factors	Placebo group	Supplement group	p
Age (yrs)	14.9 ± 0.12	15.3 ± 0.17	0.383
Height (cm)	154.9 ± 0.5	155.4 ± 3.2	0.781
Weight (kg)	52.4 ± 2.6	51.3 ± 3.1	0.739
Body mass index (kg m^{-2})	20.8 ± 2.8	21.3 ± 2.6	0.672
VO_{2max} (ml kg^{-1} min^{-1})	49.6 ± 5.3	51.7 ± 4.8	0.426

Procedures

All participants take part in the present study voluntarily. The participants were avoided from intake the unusual dose of mineral or vitamin supplements (more than 100% of RDA) and ergogenic aids during three weeks period of present research protocol. The researchers were unable to exact controlling participants diet but the subjects were asked to consume similar and certain number of foods especially two days before take part in exhausting protocol. In addition, the subjects recommended sleeping time between 11 pm to 7 am. The participation was randomly divided into two groups including placebo and quercetin groups with 10 swimmers in each group. Research protocol started during the luteal phase of participant's menstrual cycle.

VO_{2max} measurement

In order to measurement the maximal oxygen consumption (VO_{2max}), all of subjects completed Cooper's test and they run and covered as many laps as possible during 12-minute test time in outdoor track. After 12-minute the participants stopped the test [22] and finally by means of Cooper's [23] standardized equation the covered distance by each subject were used to estimate the subjects VO_{2max}.

Quercetin Supplementation

The participants in quercetin group received two quercetin capsules (totally 1000 mg) daily for two weeks period [24]. Quercetin capsules provided from Solaray company, USA (500 mg, 90 Count) and adolescent girls in quercetin group consumed one capsule before breakfast and another before dinner on a daily basis (two capsules daily) to receiving 1000 mg quercetin per day. The placebo group subjects received 1 g dextrose daily.

Exhausting swimming protocol

Participants in placebo and quercetin groups continued their routine training program during study, but 48 hours before exhausting protocol subjects were avoided from intense exercise or physical activity. Participation was called to swimming pool and exercise protocol fully was explained to all participants. In order to subjects familiarization with protocol, the protocol conducted completely by examiner and finally exhausting swimming protocol completed by adolescent swimmers. At the baseline, subjects warmed-up for 10 minutes by low intensity crawl swimming and subsequently crawl swimming protocol conducted with >85 percent of maximum heart rate (MHR) until exhaustion. For this purpose, one minute's bouts of crawl swimming in 12.5 meters' widths pool performed by subjects and each high intensity one minutes bout followed by 30 seconds inactive rest and this process until exhaustion repeated as previously described [18]. Subjects heart rate between bouts checked by polar heart rate monitor.

blood sampling and assays

In the present study, blood samples collected three times including: 1) baseline (before start the placebo or quercetin supplementation), 2) pre (30 minutes before conducting the swimming protocol) and 3) immediately after exercise (as soon as possible after subjects reaching the exhaustion). All blood samples collected from antecubital vein in supine position and after 30-minute seated rest in environment situations. In order to plasma collection, obtained blood samples was poured into EDTA containing tubes and subsequently were centrifuged at 4°C and 3000g for 15 minutes [25]. Collected plasma samples stored at -80°C for later measurement of total antioxidant capacity (TAC), superoxide dismutase (SOD) and malondialdehyde (MDA). In addition, Catalase (CAT) and glutathione peroxidase (GPx) activity was evaluated in erythrocytes.

Plasma and erythrocytes were separated and erythrocytes were washed three times with 0.9% NaCl solution, Distilled water was added to the erythrocytes to obtain a solution of approximately 50% dilution and finally product stored in Eppendorf and -80º C for CAT and GPx measurement, that detailed process described previously [26].

IL-6 and CRP measurement

The plasma levels of IL-6 and CRP were measured by enzyme linked immunosorbent assay (ELISA) methods and using special commercially available kit (R&D Systems, Minneapolis, MN, USA). All procedures conducted according to manufacturer instructions.

Oxidative stress assay

Plasma levels of malondialdehyde (MDA) were measured according to Draper and Hadley method as previously reported [27]. In addition, total antioxidant status (TAS) determined using ferric reducing/antioxidant power (FRAP) assay as previously described [28]. Plasma SOD measured by means of commercial kit from cayman chemical company, USA (cat num: 706002). GPx and Catalase activity were measured in erythrocyte. GPx (cat num: 703102) and Catalase (cat num: 707002) measured using the commercial kit from cayman chemical company, USA in erythrocyte lysate. Finally, the GPx and Catalase activity reported as unit per gram of hemoglobin (U g Hb).

Statistical analysis

All present study results were analyzed using SPSS software, version 24 (SPSS Inc., Chicago, Ill, USA). Our findings expressed as means ± SD in table 2. The normality of data distribution was determined by Shapiro-Wilk test and in order to determine changes in variables at different stages, 2 (groups)×3 (time) repeated measures ANOVA test were used and statistical significance determined at the level of $p< 0.05$.

RESULTS

All participants completed our procedures and all of them were included in the final analysis of data. There is no significant difference between placebo and quercetin group after two weeks supplementations ($p>0.05$) and the levels of all variables was unchanged between baseline and pre-exercise stages in placebo and supplement group. Immediately after swimming protocol, CRP and TAS levels don't has significant changes and their levels remained unchanged compared to pre-exercise ($p>0.05$). CRP and TAS levels in baseline, pre and immediately after exercise reported in Table 2.

Table 2. the levels of variables at different stages (baseline, pre and immediately after).

Groups	Baseline	Pre-exercise	Immediate post-exercise	% Changes (immediately after compared to pre-exercise)	P value	
					P for treatment (quercetin)	P for time; interaction effect
TAS (mmol L^{-1})						
quercetin	0.98 ± 0.16	1.04 ± 0.21	1.01 ± 0.18	% -2.88	0.27	0.19; 0.34
placebo	1.06 ± 0.09	1.02 ± 0.14	0.99 ± 0.2	% -2.94		
MDA (µmol L^{-1})						
quercetin	1.92 ± 0.57	2.01 ± 0.59	3.70 ± 0.72	% 84.07	0.12	< 0.001; 0.027
placebo	2.10 ± 1.10	2.26 ± 0.73	4.98 ± 0.54	% 120.35		
SOD (U mL^{-1})						
quercetin	3.65 ± 1.27	3.82 ± 1.33	4.53 ± 1.46	% 18.58	0.31	0.04; 0.52
placebo	3.24 ± 0.92	3.17 ± 1.08	3.86 ± 1.35	% 21.76		
GPx (U g Hb^{-1})						
quercetin	51.7 ± 6.93	49.3 ± 5.64	63. 8 ± 9.13	% 29.41	0.26	0.01; 0.73
placebo	46.5 ± 8.41	47.60 ± 7.58	59.4 ± 10.36	% 24.78		
Catalase (U g Hb^{-1})						
quercetin	97.4 ± 18.6	96. 3 ± 21.2	136.9 ± 33.0	% 42.15	0.45	< 0.001; 0.21
placebo	103.7 ± 15.5	105.1 ± 19.9	142.8 ± 28.3	% 35.87		
CRP (mg L^{-1})						
quercetin	0.62 ± 0.14	0.57 ± 0.2	0.63 ± 0.35	% 10.52	0.14	0.33; 0.29
placebo	0.73 ± 0.21	0.79 ± 0.19	0.82 ± 0.28	% 3.79		
IL-6 (pg ml^{-1})						
quercetin	1.47 ± 0.62	1.53 ± 0.70	2.96 ± 1.24	% 93.46	0.59	< 0.001; 0.035
placebo	1.59 ± 0.83	1.55 ± 0.77	3.38 ± 1.38	% 118.06		

Immediately after swimming the levels of IL-6 significantly increased in placebo and quercetin group ($p<0.001$), but in quercetin group the increase in IL-6 levels significantly was lower compared to placebo group ($p=0.016$). MDA results indicated significant increase in both groups immediately after exercise ($p<0.001$). However, MDA levels increase in placebo group compared to quercetin group was significantly higher ($p<0.001$). In addition, SOD, GPx and CAT levels significantly increased following swimming exhausting protocol in both placebo and quercetin group ($p<0.05$) and no significant difference observed between placebo and quercetin group for SOD, GPx and CAT response to swimming session ($p>0.05$) (Table 2).

DISCUSSION

Present study conducted aimed to investigate the effect of quercetin supplementation on exercise induced oxidative stress and inflammation. The present study main finding was that two-week quercetin supplementation significantly attenuate the MDA and IL-6 response after exhausting swimming session. However, short term quercetin ingestion doesn't affect antioxidant enzymes (CAT, GPx, SOD) response to acute exercise session. In addition, quercetin supplementation and exercise session hasn't affected the TAS and CRP levels. Finally, two weeks quercetin supplementation wasn't associated with changes in the resting levels of any oxidative stress or inflammation related factors.

In the present study, exhausting exercise in placebo or quercetin group were associated with significant increase in desired variables, except the TAS and CRP levels. Previous studies confirmed present findings and reported that exhausting aerobic exercise as a running in young females with different ethnicity led to significant increase in inflammatory markers (IL-6, TNF-α) and MDA levels [29]. Apart from the type of muscle contraction, the IL-6 upregulation is directly related to exercise intensity, duration, and recruited muscle mass [30] and in present study high intensity exhausting swimming was associated with increase in IL-6 levels in both groups. Upregulation the inflammatory markers including IL-6 following exercise session attributed to its secretion from skeletal muscle (as a myokine) which can play important roles in mediating the exercise related beneficial health effects [31]. Although acute exercise induces inflammatory response, but the regular exercise training decreases the resting levels of IL-6 and CRP by different mechanisms including the downregulation of cytokine secretion from adipose tissue, skeletal muscles, endothelial and circulating mononuclear cells [32]. In contrast, it seems that ingestion of some polyphenolic flavonoids such as quercetin partly reduced exercise induced inflammation [24].

Quercetin exerts many protective functions and specially its anti-inflammatory, antioxidant and its role in inhibition of lipid peroxidation is noticeable [33]. Our results are comparable to previous researches that concluded the quercetin supplementation decrease inflammatory response to exercise. The researchers confirmed the present findings and observed significant decrease in IL-6 and TNF-α response to acute exercise following quercetin supplementation for three weeks period [24]. The same results were observed, though that exercise protocol and quercetin supplementation period was different from present study. In another research and in line with the findings of the present study, its reported that two weeks quercetin supplementations decrease exercise induced inflammatory response (TNF-α) following exhausting swimming and they suggested the quercetin as an effective strategy for attenuate the exercise induced inflammation [18]. Although, our results indicated that IL-6 response was lower significantly in quercetin group compared to placebo group, but the CRP response to acute exercise don't has significant difference between placebo or quercetin group. In another study, present findings about the ineffectiveness of quercetin ingestion on the CRP response to acute exercise were supported and it's reported that even long-term quercetin supplementation (1000 mg daily for 6 weeks) cannot influence the CRP upregulation response following the acute exercise in highly trained subjects [34]. These findings represented that quercetin supplementation has a different effect on various inflammatory factors. Although the exact mechanism by which quercetin decrease exercise induced inflammation is remarkably unknown, according to conducted studies it can be concluded that beneficial

immuno-stimulatory and anti-inflammatory effects of quercetin probably mediated by induction the type 1 helper T Cell (Th-1) derived cytokines or attenuate the type 2 helper T Cell (Th-2) derived cytokines [35]. In addition, quercetin anti-inflammatory effect is partially related to quercetin function in blocking the secretion of IL-6 and inhibition of TNF-α related activating the inflammatory signaling pathways such as ERK, JNK and NF-κB [36]. However, the results about quercetin effects on the inflammation is controversial and some researchers indicated that acute ingestion of quercetin don't attenuate the post exercise inflammation [37]. Moreover, there is some evidence that long terms quercetin supplementation (8 weeks) cannot be effective in decrease inflammatory markers such as IL-6, but quercetin in combination with vitamin C significantly decrease IL-6 levels [38]. These researchers concluded that ingestion of quercetin with pro-oxidants such as vitamin-C can increase the quercetin effectiveness in attenuate the inflammatory signaling.

In the present study, acute exercise was associated with upregulation of antioxidant enzymes. In supporting these findings, significant increase in GPx, CAT and SOD after high intensity interval exercise (cycling) have been observed in healthy men [39]. Some researchers indicated that SOD, CAT and GPx activity significantly increased immediately after exercise. However, the CAT and GPx returned to baseline values after 3 hours. Acute exercise is associated with inducing oxidative stress and anti-oxidant system simultaneously [40]. Therefore, increase in antioxidant enzymes probably is a normal body immune system response to intense exercise and in this regard researchers concluded that increase in blood antioxidant markers levels over recovery period is due to the following reasons: 1) Oxidant production decrease with the stopping exercise session giving antioxidant system an opportunity to return to baseline levels, 2) increase the endogenous antioxidants, and 3) Oxidant upregulation during exercise can result in mobilization of antioxidants from tissue stores to circulation [41].

In contrast to our findings, its reported that aerobic exercise (20 min running with 80 percent of MHR) don't affect the levels of oxidative (GPx, SOD, TAC) and inflammatory (including IL-6, IL-8 and MCP-1) markers in normal weight, overweight and severe obese sedentary subjects [42]. Researchers attribute these findings to the short duration of exercise session. But in contrast to this idea and in line with our findings, the researchers reported that exercise intensity compared to duration of exercise has a greater impact on the oxidative stress and inflammatory cytokines [43]. Other findings of present study were that short term quercetin supplementation doesn't affect the TAS and antioxidant enzymes response to intensive swimming. In another study, the researchers confirmed present findings and reported that acute ingestion the polyphenolic antioxidants (2.3 g polyphenols) has no effect on the TAS response immediately or 45 minutes after 90 min cycling (70% VO_{2max}) on ergometer [19]. In the present study, quercetin as a polyphenolic component had no effect on the antioxidant capacity following swimming session. Moreover, its observed that three weeks quercetin supplementation (250 mg, 4×/day) don't affect the oxidative damage or antioxidant capacity during an ultramarathon challenge [44]. In addition, the researchers suggested that even long terms quercetin supplementation (6 weeks) don't has a significant effect on the antioxidant capacity or prevent oxidative damage after heavy exercise in trained subjects [34]. All these statements confirm our study results. About resting status, it's also evidence exist that 12 weeks quercetin supplementation don't alter the oxidative stress and antioxidant capacity, although the significant increase in quercetin levels were observed [45] and therefore the researchers suggested the quercetin consumption along with other flavonoids such as vitamin C for significant effectiveness and in agreement with this idea previously researchers confirmed this hypothesis [38]. According to these statements it can be recommended for future researchers to investigate the effects of simultaneously consumption of quercetin along with others flavonoids or polyphenols on oxidative damage and inflammatory response to acute exercise. Totally, respect to little number of subjects in present study and researcher's inability to exact control of participants nutrition states, the confident conclusion about role of quercetin supplementation on exercise induced inflammation and oxidative stress needed furthers studies to answer the many unanswered questions in this field.

CONCLUSIONS

Present study findings indicated that although the quercetin supplementation attenuates some inflammatory and oxidative damage related factors (IL-6 and MDA) response following the exhausting exercise, but there is no significant difference between quercetin and placebo group for CRP and antioxidant capacity. It seems that quercetin supplementation at least in short term don't has significant effect on inflammatory status and specially antioxidant capacity after exercise.

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Conflict of interests

There are no conflicts of interest.

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