Research Article

Green tea polyphenols attenuate resistance exercise-induced increase in pro-inflammatory cytokines in obese men

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Abstract

Green tea polyphenols have been suggested to exert anti-inflammatory actions in in vivo and in vitro studies. The aim of this study was to investigate the effect of green tea extract (GTE) supplementation on pro-inflammatory cytokines during a single bout of resistance exercise (RE) in obese men. Participants were ten obese men who participated in a randomized, double-blind, placebo-controlled (PL) crossover study, administered 14-day GTE (500 mg/day) supplementation and PL with a 14-day washout period. After the supplementation periods, the participants performed the RE protocol, consisting of three sets of six exercises, to failure at 75% of one repetition maximum (1RM) and 2 min rest between sets. The serum samples were collected pre- and post-RE and analyzed for TNF-α, IL-1α, and IFN-γ. RE significantly increased TNF-α and IL-1α in obese men by 15% (p=0.043) and 18.71% (p=0.003) above the pre-RE values in the PL condition, respectively. However, GTE supplementation inhibited acute RE-induced increases in the TNF-α and IL-1α levels in obese men. Moreover, changes in the IFN-γ level during RE tended to be lower in GTE compared to the PL condition. Based on the findings, it can be concluded that 14-day GTE supplementation offers protection against RE-induced increases in pro-inflammatory cytokines in obese men. These immunomodulatory effects of GTE may be, in part, due to the anti-inflammatory properties of GTE in obese men that can be considered as a potential therapeutic factor to ameliorate obesity-associated inflammation.

Key Words: **Green tea extract, Obesity, Pro-inflammatory cytokine, Resistance exercise**

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Received 8 January 2023; Accepted 13 March 2023

Introduction

Obese individuals are at risk of low-grade, chronic inflammation in adipose and liver tissue (Lumeng et al., 2007) that promotes the development of insulin resistance, diabetes, atherosclerosis, and some types of cancer (Johnson et al., &, 2012; Lumeng & Saltiel, 2011). Obesity-induced inflammation is known to be associated with the infiltration of both innate and adaptive immune cells (Duffaut et al., 2009). Type 1 T helper (Th1) cells were found and shown to be associated with adipose inflammation that secretes inflammatory cytokines, including interferon γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1), which lead to the switching of macrophages in adipose tissue and liver from a Type 2 (M2) polarization state (anti-inflammatory) to a Type 1 (M1) polarization state (proinflammatory) (Lumeng et al., 2007). M1 macrophage phenotypes are pro-inflammatory, and their secretion of TNF-α leads to the attenuation of insulin signaling in adipocytes by mitigating the expression of GLUT4 and PPAR-γ (Ye, 2008).

It was demonstrated that obesity is also associated with increased levels of reactive oxygen species (ROS) production (Johnson et al., 2012) which leads to increased macrophage infiltration and inflammatory changes (Furukawa et al., 2004). Furthermore, previous studies have reported that obese individuals were at a greater risk of oxidative stress compared with their non-obese counterparts during acute exercise (Vincent, Morgan, & Vincent, 2004; Vincent, Vincent, Bourguignon, & Braith, 2005). Taken together, elevated levels of pro-inflammatory cytokines and ROS in obesity lead to a state of chronic low-grade inflammation, which may be causal in the development of insulin resistance and the other disorders associated with obesity (Matsuda & Shimomura, 2013). Thus, therapeutic and pharmacological modalities that affect inflammation and ROS production could be beneficial in obese individuals. It has been suggested that the consumption of functional foods containing bioactive polyphenols could be used to mitigate chronic low-grade inflammation associated with obesity (Munir et al., 2013).

Moreover, a large body of evidence suggests a primary role for green tea as a functional food due to its content of flavonoids, which have antioxidant, anti-carcinogenic, anti-inflammatory, antidiabetic and anti-obesity properties (Santhakumar et al., 2014). Polyphenol antioxidants called catechins, found in green tea, include epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) (Ayyadurai & Deonikar, 2021; Bruno et al., 2014). In vitro studies have demonstrated that EGCG had inhibitory effects on the total RNA expression of the pro-inflammatory cytokines TNF-α and IL-1β in white blood cells in cell cultures stimulated with T-cell mitogen concanavalin A (Sehm et al., 2005) as well as that EGCG suppressed the lipopolysaccharide induced expression of TNF-α and IL-1β in human cerebral microvascular endothelial cells (J. Li et al., 2012). Furthermore, in-vivo animal studies have shown that obese rats treated with 12 weeks of green tea polyphenols can attenuate pro-inflammatory IL-2, IL-6, IL-1β, and TNF-α cytokines (Molina et al., 2015), and TNF-α, IL-6 and TLR4 as well (Albuquerque et al., 2016).

To the best of our knowledge, the response of pro-inflammatory cytokines to green tea polyphenol supplementation and resistance exercise (RE) is not well understood in obese people. A few studies have investigated the antioxidant effects of green tea supplementation during exercise in healthy humans (Eichenberger et al., 2009; Jówko et al., 2015; Jówko et al., 2011). However, the findings of the studies are inconsistent, with some reporting no effect (Eichenberger et al., 2009; Jówko et al., 2012) or a significant decrease (Jówko et al., 2015; Jówko et al., 2011) in exercise-induced oxidative stress following green tea supplementation. Furthermore, acute effects of green tea and carbohydrate co-ingestion (Suzuki et al., 2015) and three weeks of green tea extract (GTE) supplementation (Eichenberger et al., 2009) did not influence the inflammatory cytokines (IL-1β, TNF-α, IL-6, and IL12p40) and inflammatory parameters (IL-6 and C-reactive protein) respectively, in well trained men. As noted, the results of in vitro human studies (Y. P. Li & Reid, 2000; Sehm et al., 2005) and in vivo animal studies (Albuquerque et al., 2016; Molina et al., 2015) have evidenced the direct role of green tea as an anti-inflammatory agent. However, to the knowledge of the researchers, no published studies have evaluated the effects of green tea supplementation on systemic pro-inflammatory cytokines during RE in obese men. Therefore, in a randomized double-blind, placebo-controlled, crossover study, the effects of 14 days of GTE supplementation on systemic proinflammatory cytokines during RE in obese men were investigated.

Materials and Methods

Participants

In a randomized, double-blind, placebo-controlled, crossover design, 10 apparently healthy obese men voluntarily participated in this study. After a complete description of the study goals and methods, the participants completed a consent form and a health questionnaire to participate in the study. All procedures followed in this study were in accordance with the ethical standards of the Institutional Ethics Committee on human experimentation. The study protocols were approved by the Ethics Committee of the University UO#95/145P. All subjects completed the study.

The participants' characteristics are presented in Table 1. The participants were nonsmokers, were not receiving drugs or antioxidant supplements or any kind of food rich in polyphenolic compounds for the past four months, had not performed any regular exercise training within the past six months, and had a BMI above 30 kg.m-2.

Procedure

The obese men took part in two 14-day supplementation periods, followed by an RE protocol and one 14-day washout period (Jówko et al., 2011; Panza et al., 2008). One week before the two 14-day supplementation periods, the participants visited the human performance laboratory for familiarization, filling in the Par-Q Health History questionnaire, and undergoing measurement of one repetition maximum (1RM) on bench press, lat pull down, biceps curl, leg flexion, leg extension, and leg press according to a previously described procedure (Rahimi, 2011). All participants were encouraged to avoid any strenuous exercise and not to change their normal diets during the study. All participants completed three-day dietary records prior to RE on Saturday, Monday, and Wednesday. The participants received a copy of their dietary record sheets and were asked to exactly follow the same food intake patterns (as recorded in their dietary record sheets) before the two RE protocols (Rahimi & Falahi, 2017).

During two 14-day supplementation periods, half of the subjects received GTE (two capsules per day) and the other half placebo (PL; two capsules per day), and vice versa. Both the GTE and PL capsules were identical in shape, size, and color. The participants consumed two capsules of GTE (250 mg GTE gelatin capsules,

Table 1. Physical characteristic of the participants.

Variables	Groups	
	Green Tea Extract	Placebo
Age (y)	37.12±5.66	37.12±5.66
Weight (kg)	102.66±14.43	104.2±13.56
Height (cm)	177.25±7.53	177.25±7.53
BMI (kg.m^{-2})	32.53±2.52	32.48±2.39
WHR	0.99±0.03	1.00±0.03

Olimp Labs, Poland) or PL (Maltodextrin) twice a day at breakfast and dinner. One GTE capsule (55% EGCG) was composed of 249 mg polyphenols, which contained 200 mg catechins (137.5 mg EGCG). At the end of each of the two 14-day supplementation periods, participants on Day 15 returned to the exercise physiology laboratory and took an additional capsule of GTE or PL one hour before the RE protocol, which included three sets to exhaustion of bench press, lat pull down, biceps curl, leg flexion, leg extension, and leg press with 75% of 1RM and 2 min rest between sets and exercises (Rahimi & Falahi, 2017). Prior to the RE protocol, all subjects performed a warm-up, which consisted of 3 min of running, and 5–10 repetitions at 50% of the perceived maximum strength and stretching period (Figure 1).

Venous blood samples were obtained from an antecubital vein of each participant before (pre) and immediately after (post) RE. The serum was obtained by centrifugation at 3,000 rpm for 10 min at 4ºC and frozen at −80ºC for later analysis. The pro-inflammatory responses were determined using serum TNF-α (ELISA kit, Cat.No: EK0525), IL-1α (ELISA kit, Cat.No: EK0389) and IFN-γ (ELISA kit, Cat.No: EK0373). The average intra-assay coefficient of variation for TNF-α, IL-1α, and IFN-γ were 3.8%, 2.7% and 6.1%, respectively. The sensitivities for TNF-α, IL-1α, and IFN-γ were 1 pg/mL, 0.5 pg/mL and 2 pg/mL, respectively.

Statistical analysis

The data are expressed as mean ± SD. Statistical evaluation was performed with SPSS (SPSS, Chicago, IL) for Windows. The normality and variance of the data were measured using the Shapiro–Wilk and Levene tests, respectively. The TNF-α, IL-1α, and IFN-γ levels were analyzed using a 2 (groups) × 2 (times) repeated-measures analysis of variance (two-way ANOVA). When the interaction effects were significant ($p \leq 0.05$), the simple main effects were assessed using a one-way ANOVA and a paired t-test. Independent-sample t-tests were performed to determine possible group differences for the following variables: height, body mass, and dietary intake. The significance level was set at $p<0.05$.

Results

The physical characteristics of the participants at baseline and after two weeks of green tea supplementation are presented in Table 1. No significant differences were found between the treatments for age, weight, height, BMI, and waist-to-hip ratio (27). As demonstrated in Figures 1 to 3, the baseline serum inflammatory cytokines of TNF-α, IL-α, and IFN-γ were greater by 20.28%, 16.58%, and 12.23% in PL compared to green tea supplementation in obese men. In response to acute RE, TNF-α

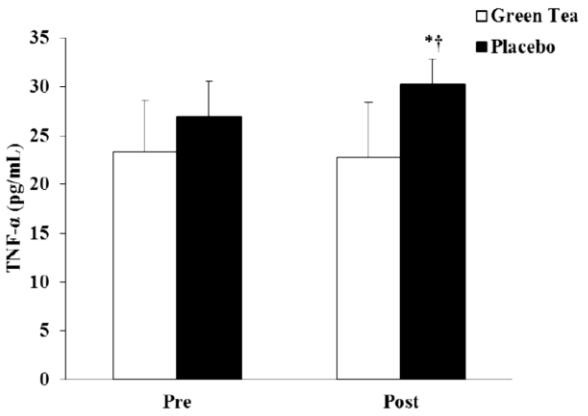

Figure 1. Serum TNF-α concentrations in response to resistance exercise following 14-day green tea extract supplementation in obese men. Values are mean±SD. (*) P<0.05, within-subjects effect versus pre resistance exercise. (†) P<0.05, statistically significant difference compared to green tea treatment.

(12.40%) and IL-α (18.71%) exhibited significantly greater increases in PL compared to green tea supplementation (Figures 1 and 3), whereas no difference was found for IFN-γ between both conditions (Figure 2). In the PL condition, the serum TNF-α and IL-α levels significantly increased from pre- to post-RE (Figures 1 and 2); however, no significant difference was found for IFN-γ from pre- to post-RE (Figure 3). In the green tea supplementation condition, there were no differences in the TNF-α, IL-α, and IFN-γ levels from pre- to post-RE (Figures 1 to 3).

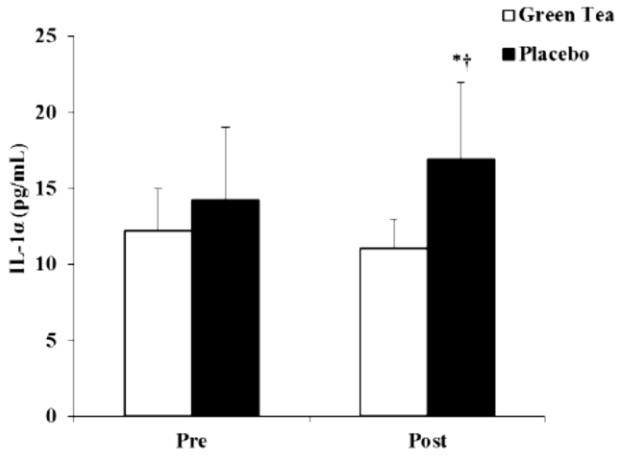

Figure 2. Serum IL-1α concentrations in response to resistance exercise following 14-day green tea extract supplementation in obese men. Values are mean±SD. (*) P<0.05, within-subjects effect versus pre resistance exercise. (†) P<0.05, statistically significant difference compared to green tea treatment.

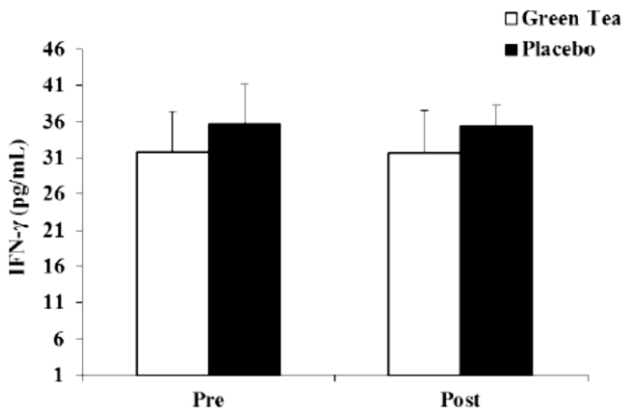

Figure 3. Serum IFN-γ concentrations in response to resistance exercise following 14-day green tea extract supplementation in obese men. Values are mean±SD. There were no significant differences within-, and between- groups.

Discussion

The present study is, to our knowledge, the first study on the anti-inflammatory capacity of GTE in obese humans exposed to acute RE using 14-day GTE supplementation in a randomized, double-blind, placebo-controlled, crossover design. The main findings of the study were that acute RE increased the level of inflammatory cytokines in obese men, while GTE supplementation inhibited increases in inflammatory cytokines induced by acute RE protocol.

In this study, obesity-associated systemic inflammation was elevated by cytokines, including TNF-α, IFN-γ and IL-1α, which have pro-inflammatory and atherogenic properties (Tousoulis et al., 2016; Yokota & Hansson, 1995). TNF-α and IL-1 are secreted by macrophages, lymphocytes, natural killer cells, and vascular smooth muscle cells, and they are potent pro-inflammatory cytokines (Moldoveanu et al., 2001). Proinflammatory signaling of TNF-a and IL-1 is mainly mediated by the p38 mitogen-activated protein kinase (p38MAPK)/nuclear factor kappa-light-chain-enhancer of the activated B-cell (NF- B) pathway (Chan et al., 2000). The activation of these kinases plays a prominent role in the inhibition of insulin signaling associated with obesity (Johnson et al., 2012). IFN-γ is produced to a large extent by Th1 lymphocytes, NK cells, and cytotoxic T lymphocytes (Moldoveanu et al., 2001). All these proinflammatory cytokines drive macrophage polarization toward the M1 macrophage phenotype demonstrated to inhibit insulin sensitivity in adipocytes by mitigating the expression of GLUT4 and PPAR-γ (Ye, 2008).

The results of this study showed prominent and novel effects of GTE supplementation on pro-inflammatory and atherogenic mediators in obese men. As expected, RE with 75% of 1RM triggered a pro-inflammatory response, as demonstrated by increased TNF-α and IL-1α levels. To the knowledge of the researchers, there is no data regarding the inflammatory response to RE in obese individuals. However, previous studies examining the acute effect of RE on inflammatory markers revealed significant elevations (Smith et al., 2000; Townsend et al., 2013) and no changes (Buford et al., 2009; Uchida et al., 2009) in the levels of inflammatory cytokines in other populations. In addition, the effects of acute endurance exercise on pro-inflammatory cytokines in humans showed significant increase in proinflammatory markers (Moldoveanu et al., 2001). It was shown that high levels of circulating inflammatory cytokines such as TNF-α and IL-1α inhibit myogenic differentiation and promote protein catabolism (Dirks & Leeuwenburgh, 2006; Reid & Li, 2001) and are associated with low muscle mass in obese people (Schrager et al., 2007).

GTE supplementation (275 mg EGCG) for 14 days inhibited increases in the TNF-α and IL-1α levels induced by acute RE in obese participants. In addition, the pattern of change for the IFN-γ level during RE tended to be lower in green tea supplementation compared to PL. These findings are in line with previous studies that demonstrated a significant decrease in the total RNA expression of TNF-α and IL-1β in white blood cells (Sehm et al., 2005) and the lipopolysaccharide-induced expression of TNF-α and IL-1β in human cerebral microvascular endothelial cells (J. Li et al., 2012) in vitro. In addition, the anti-inflammatory effects of GTE in obese individuals corroborate previous studies on in vivo animal models, which showed that obese rats treated with 12 weeks of green tea polyphenols can attenuate the levels of proinflammatory IL-2, IL-6, IL-1β, and TNF-α cytokines (Molina et al., 2015), and TNF-α, IL-6 and TLR4 as well (Albuquerque et al., 2016). However, the results of the present study are inconsistent with previous studies which show that GTE supplementation did not affect cytokines such as IL-1β, TNF-α, IL-6, and IL12p40 (Suzuki et al., 2015) and IL-6 and C-reactive protein (Eichenberger et al., 2009) in well-trained men. Taken together, these findings suggest that GTE has anti-inflammatory properties. However, for the first time, the findings of this study have demonstrated the anti-inflammatory properties of GTE after acute RE in obese men.

The possible mechanisms by which GTE inhibits anti-inflammatory properties are not fully elucidated. The possible mechanisms could be related to the inhibition of the toll-like receptor 4 (TLR4) signaling pathway by GTE, which is indicated by the reduced mRNA levels of TLR4 (Molina et al., 2015), there-

thereby decreasing the production of inflammatory cytokines such as TNF-α, IFN-γ, and IL-1α (Byun, Fujimura, Yamada, & Tachibana, 2010). Also, TLR4 signaling provokes the pro-inflammatory response by activation of the NF-κB pathway, leading to increased expression of proinflammatory target genes (Joo et al., 2012; Lee et al., 2004). It was demonstrated that green tea catechins (EGCG) inhibit NF-KB activity by blocking the phosphorylation of IκB-α (J. Li et al., 2012; Melgarejo et al., 2010), which in turn, results in the decline in the expression of inflammatory target gene products such as TNF-α, IL-1, and NO synthase (Melgarejo et al., 2010; Shih et al., 2015). Another mechanism could be due to the antioxidant effects of green tea polyphenols, which are able to scavenge free radicals and increase gene expression of the antioxidant defense system (Melgarejo et al., 2010; Molina et al., 2015). Taken together, the aforementioned mechanisms support the anti-inflammatory properties of GTE; however, a major limitation of the present study was that it did not measure the TLR4 and NF- B signaling pathways in the adipose tissue and skeletal muscle of obese men during RE. Further research is required to elucidate the TLR4 and NF- B signaling response in the adipose tissue and skeletal muscle of obese men to GTE supplementation during RE.

Conclusion

In summary, 14 days of GTE supplementation reduced pro-inflammatory cytokine production during RE in obese men, suggesting that GTE has anti-inflammatory properties. This finding indicates that GTE can be considered as a potential therapeutic factor to ameliorate obesity-associated inflammation. Thus, more studies are necessary to confirm the anti-inflammatory properties of GTE supplementation in humans, especially in obese individuals who are at risk of chronic low-grade inflammation associated with obesity.

What is already known on this subject?

Obesity has been associated with low-grade, chronic inflammation in adipose and liver tissue. Green tea catechins, include epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) have been associated with antioxidant, anti-carcinogenic, anti-inflammatory, antidiabetic and anti-obesity properties.

What this study adds?

It was demonstrated that 2 weeks' green tea polyphenols ingestion may be involved in reduction pro-inflammatory cytokines such as TNF-α, IL-1α, and IFN-γ during RE in obese men.

Acknowledgements

We would like to thank the participants for contribution to the study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Informed consent Informed consent was obtained from all patients for being included in the study.

Author contributions

Conceptualization: MR.R, Sh.ZTL.; Methodology: MR.R, Sh.ZTL.; Software: MR.R, Sh.ZTL.; Validation: MR.R, Sh.ZTL.; Formal analysis: MR.R, Sh.ZTL.; Investigation: MR.R, Sh.ZTL.; Resources: MR.R, Sh.ZTL.; Data curation: MR.R, Sh.ZTL.; Writing - original draft: MR.R, Sh.ZTL.; Writing - review & editing: MR.R, Sh.ZTL.; Visualization: MR.R, Sh.ZTL.; Supervision: MR.R.; Project administration: MR.R, Sh.ZTL.; Funding acquisition: MR.R.

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