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Technical Note

A Pilot Study on Cannabidiol (CBD) and Eccentric Exercise: Impact on Inflammation, Performance, and Pain

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ABSTRACT

International Journal of Exercise Science 16(2): 109-117, 2023. Cannabidiol (CBD) is a non-psychoactive cannabinoid purported to reduce symptoms of discomfort. Individuals are now using CBD to treat symptoms of multiple sclerosis, seizures, and chronic pain. Animal models indicate that CBD may be effective at reducing inflammation post fatiguing exercise. However, little evidence is available to evaluate these findings in humans. Therefore, the purpose of this investigation was to evaluate the impact of two doses of CBD oil on inflammation (IL-6), performance, and pain after an eccentric loading protocol. Participants (n = 4) participated in three conditions (placebo, low dose, and high dose), in this randomized, counterbalanced design. Each condition took 72 hours to complete, with a 1-week washout period between conditions. At the beginning of each week, participants were subjected to a loading protocol of six sets of ten eccentric only repetitions in the single-arm bicep curl. Participants consumed capsules of either a placebo, low dose (2mg/kg) or high dose (10mg/kg) of CBD oil immediately following the session and continued every twelve hours for 48 hours. Venipunctures were taken before exercise and repeated at 24, 48, and 72 hours post exercise. Blood samples were centrifuged for 15 minutes in gel and lithium heparin vacutainers. Plasma was separated from cells and stored at -80° until analysis. Samples were analyzed using an immunometric assay for IL-6 (ELISA). Data were analyzed using a three (condition) by four (time) repeated measure ANOVA. There were no differences in inflammation between conditions ($F(2,6) = 0.726$, $p = 0.522$, $n_p^2 = 0.195$) or across time ($F(3,9) = 0.752$, $p = 0.548$, $n_p^2 = 0.200$), handgrip strength between conditions ($F(2,6) = 0.542$, $p = 0.607$, $n_p^2 = .153$) or across time ($F(3,9) = 2.235$, $p = .153$, $n_p^2 = .427$), or bicep curl strength between conditions ($F(2,6) = 0.675$, $p = 0.554$, $n_p^2 = .184$) or across time ($F(3,9) = 3.513$, $p = .150$, $n_p^2 = .539$). There were no differences in pain between conditions ($F(2,6) = 0.495$, $p = 0.633$, $n_p^2 = .142$), but there was a difference across time ($F(3,9) = 7.028$, $p = .010$, $n_p^2 = .701$). There were no significant interactions to note. Although there was no statistical significance between conditions (likely due to the low sample size), there was a visible increase in IL-6 48 (4.88 ± 6.53) and 72 hours (3.12 ± 4.26) post exercise in the placebo condition which was not observed in the low (48: 0.35 ± 2.22; 72: 1.34 ± 5.6) and high dose condition (48: 1.34 ± 1.34; 72: -0.79 ± 5.34). Future investigations should consider implementing eccentric resistance training across a larger portion of the body to improve ecological validity of the exercise. A larger sample would reduce risk of researchers committing a type II statistical error and give strength to detecting differences between conditions.

KEY WORDS: Negatives, inflammatory cytokine, cannabinoids, sport recovery

INTRODUCTION

Resistance training (RT) is a chronic process where an individual acts against an external load in an effort to improve musculoskeletal strength, endurance, and/or power. The American College of Sports Medicine (ACSM) prescribes RT to more than just athletes, as they suggest healthy and special populations engage in this modality at least twice per week (15). Exercise is a relatively safe activity for most individuals, but it can be accompanied by uncomfortable side effects such as muscle soreness/fatigue, potentially causing avoidance behaviors (20).

Greater loads applied during RT provide a strong anabolic stimulus that leads to prolonged muscle protein synthesis. This formation of new protein and subsequent muscle growth benefits all populations, ranging from athletes to older adults. The positive outcomes associated with RT are partially attributed to the skeletal muscle damage it causes, as the rate of protein remodeling that follows exercise is correlated to the damage inflicted. Muscle soreness after exercise results from microtrauma to the muscular proteins and neurotrophic factors (as reviewed in (18), leading to inflammatory and immune reactions. This series of events is considered normal and important to the remodeling process, but individuals may take NSAIDs to counteract the discomfort. Consumption of non-steroid anti-inflammatory drugs (NSAIDs) post exercise, however, attenuates the protein remodeling necessary for muscular improvement (27).

Cannabidiol (CBD) has been associated with analgesic effects as well as anti-inflammatory properties (1). Unlike other cannabinoids found in the sativa plant (e.g., Tetrahydrocannabinol [THC]), CBD has no psychotropic actions or effects as it contains less than 0.3% THC. CBD has recently been approved to treat patients with epilepsy, symptoms of multiple sclerosis, and chronic pain. For reference, dosing of Epidiolex (synthesized CBD) is recommended at 2.5 mg/kg or greater (up to 25 mg/kg) twice per day (11, 26). Although athletes self-report taking CBD to promote recovery and avoid muscular discomfort (13), very little information is available verifying the validity of these purported claims in humans. Of the studies available, they are limited to animal models reviewed in (17) or assessments were considered "noninvasive" and potentially not sensitive enough to detect differences between CBD conditions after exercise (5).

It is postulated that CBD inhibits oxidative stress and inflammation due to its interaction with CB1 and CB2 adenosine receptors (23). Antagonizing these receptors may block immune cell migration (22), thus leading to less inflammation and pain post-exercise (2, 10). When left untreated, this exercise-induced muscle damage that precedes release of inflammatory cytokines leads to prolonged (1-14 days) loss of muscle strength (as reviewed in (7)). Supplementing with CBD may serve as an alternative anti-inflammatory therapy that does not impair desired protein remodeling following exercise (1). This may be of particular importance to athletes seeking a competitive edge as CBD is no longer a banned substance by the NCAA. Diminished soreness and increased recovery (by reducing inflammation) may allow individuals to train more frequently leading to greater overall volume of work (more positive adaptations).

The field is urging scientists to evaluate any potential beneficial effects of CBD on sport and RT related muscle soreness, including studies to establish an effective dose (4). Therefore, the purpose of this investigation was to gather metrics of effect of two doses of CBD oil on measures of pain, performance, and inflammation after an eccentrically biased resistance training session.

METHODS

Participants

Four eccentric-naïve adults (2 men and 2 women) were recruited from the local university. All procedures followed the ethical standards of the Helsinki Declaration and *International Journal of Exercise Science* (19). All procedures followed an approved IRB (#1887256-1; 03.18.2022) and participants freely gave informed consent. Participant demographics are provided in Table 1.

Table 1. Participant demographics

	Mean	Standard Deviation
Height (cm)	171.38	9.60
Weight (kg)	71.89	16.30
Body Composition (%)	22.82	7.44

Protocol

This exploratory investigation was executed with the intent of identifying the effect (n_p^2) of CBD supplementation after an eccentrically exhaustive exercise bout. The study followed a double-blind, repeated measures crossover design wherein participants were randomized into a placebo (soybean vegetable oil, Cincinnati OH), low-dose (2 mg/kg) or high-dose (10 mg/kg) of CBD (Cloud N9ne CBD, Las Vegas, NV). The USA produced, broad spectrum CBD oil was verified to have no psychoactive cannabinoids present when independently tested (DB Labs, Las Vegas, NV). Oil was placed in vegetarian capsules and quantity of pills for placebo and low-dose (CBD + vegetable oil) matched the prescribed high-dose. Each condition took 72 hours to complete, with a one-week washout period between conditions. Timeline of events are presented in Table 2.

Table 2. Study protocol timetable

Baseline	Trial 0	Trial 24	Trial 48	Trial 72
Anthropometrics Pain Range of Motion Interleukin-6 Handgrip Bicep Curl Eccentric Load Determination	Interleukin-6 6x10 Eccentric Protocol Supplementation: immediately after and 12 hours later	Pain Interleukin-6 Range of Motion Handgrip Bicep Curl Supplementation: immediately after and 12 hours later	Pain Interleukin-6 Range of Motion Handgrip Bicep Curl Supplementation: immediately after and 12 hours later	Pain Interleukin-6 Range of Motion Handgrip Bicep Curl
One Week Washout				
Repeat procedures with assigned CBD or placebo supplementation				
One Week Washout				
Repeat procedures with assigned CBD or placebo supplementation				

Anthropometrics: Height and body mass were assessed unshod using a stadiometer (SECA, Hamburg, Germany) and scale (COSMED, Concord, CA), respectively. Body composition was taken by an experienced technician via three-site skinfold at the triceps, suprailiac crest, and thigh for females and chest, abdomen and thigh for males (15).

VAS and Range of Motion: Upon daily arrival, participants were asked to make a vertical mark on a 10 cm visual analog scale (VAS) representing pain in the affected arm (25). Range of motion was assessed using a long-arm goniometer rotating at the elbow and aligning with the acromion clavicular joint and the head of the radius while standing in the anatomical position. Participants were asked to allow their arm to hang in a relaxed position while measurements were taken.

Handgrip and Bicep Curl Strength: Participants were asked to perform isometric strength assessments on handgrip and back dynamometers. The handgrip strength assessment followed traditional methods wherein participants maximally squeezed the dynamometer for two to three seconds while holding the analog dynamometer away from the body (Smedley III, (24). Participants stood with their elbow flexed at 90 degrees where the hand and dynamometer were perpendicular to the body. Three consecutive measurements were taken for each limb with at least one minute rest between attempts.

A back and leg dynamometer (T-16K, Japan) using a single arm grip attachment was set up so that the participants' arm was flexed at 90°. With their back and arm fixed against a wall, participants were asked to flex at the elbow with maximal force for two to three seconds. Three attempts were made per arm (or only the affected arm after baseline) with a minimum of one minute rest between attempts. See Figure 1a for a visual depiction of the apparatus.

Interleukin-6: Venipunctures were assessed after the participant had the opportunity to sit and rest for five minutes. Blood was captured either from an antecubital vein or from the hand. Blood samples were centrifuged for 12 minutes in gel and lithium heparin vacutainers. Plasma was separated from cells and stored at -80° until analysis. Samples were analyzed in duplicate using immunometric assay for Interleukin-6 (IL-6) (ELISA; Cayman Chemicals, Ann Arbor, MI) following manufacturer guidelines. IL-6 is a common measure of systemic inflammation.

Eccentric Loading: Load was determined on the initial baseline training session; experimental weight was determined by identifying a weight that could be concentrically curled using the biceps with both arms and lowered eccentrically with one arm for a minimum of three seconds, but no more than five seconds. This protocol is unique to this investigation and was developed to mimic the degrees/second experienced on isokinetic dynamometers (6).

At the beginning of each week, participants were subjected to a loading protocol of six sets of ten eccentric only repetitions in the single-arm bicep curl. Participants lowered the weight with one arm (counterbalanced between weeks) for three to five seconds (verified by use of a metronome). An investigator returned the weight to the upright, fully flexed position and released the weight for the participant to lower independently. Bicep curls were completed on

functional trainer weight machine (Rep Fitness, Denver, CO) while wearing a bicep isolator (RDX Sports, Stafford, TX) (Figure 1b).

A.  B. 

Figure 1. Demonstration of methodologies; A. isometric bicep curl strength; B. eccentric loading

Statistical Analysis

A 3 (condition) × 4 (day) repeated-measures analysis of variance (ANOVA) was performed to determine main effects for isometric handgrip and bicep curl strength, pain, ROM, and IL-6. Sphericity was assessed using Mauchly's test and corrected using a Greenhouse-Geisser correction. Because the purpose of the study was to gather metrics to guide future CBD research, no post-hoc analyses were carried out. Additionally, partial eta squared (η_p^2) was calculated as a measure of effect for the main and interaction effects of the ANOVA. All data was analyzed using SPSS v28.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was determined a priori at $\alpha \leq 0.05$. Data reported as mean ± SD unless otherwise stated.

RESULTS

Table 3. Test statistic, *p*-value, and partial-eta squared

	Condition			Time			Condition x Time		
	$F_{2,6}$	*p*	η_p^2	$F_{3,9}$	*p*	η_p^2	$F_{6,18}$	*p*	η_p^2
Interleukin-6	0.726	0.522	0.195	0.752	0.548	0.2	0.599	0.727	0.166
Handgrip	0.542	0.607	0.153	2.235	0.153	0.427	1.963	0.125	0.369
Bicep Curl	0.675	0.554	0.184	3.513	0.15	0.539	0.937	0.493	0.238
Pain	0.495	0.633	0.142	.028	0.01	0.701	0.521	0.785	0.148
ROM	0.192	0.742	0.06	3.279	0.165	0.522	0.850	0.548	0.221

Table 4. Means and standard deviations of outcome measures

		Baseline	24h	48h	72h
Interleukin-6 (ng/dL)	Placebo	-0.6 ± 4.51	-0.03 ± 6.22	4.88 ± 6.53	3.11 ± 4.26
	Low	0.75 ± 1.31	2.01 ± 2.44	0.35 ± 2.22	0.47 ± 5.61
	High	0.44 ± 0.51	1.69 ± 1.75	1.34 ± 1.34	-0.79 ± 5.34
Handgrip (kg)	Placebo	33.4 ± 8.8	35.2 ± 8.7	35.3 ± 8.8	36.1 ± 8.4
	Low	32.2 ± 8.3	34.3 ± 11.1	33.6 ± 10	34.1 ± 9
	High	34.7 ± 8.6	30.6 ± 8	34 ± 8.3	34.9 ± 9.9
Bicep Curl (kg)	Placebo	26.4 ± 13	19.3 ± 15.8	23.6 ± 16.4	23.9 ± 14.5
	Low	24.8 ± 14.7	21.8 ± 16.8	25.3 ± 17.7	26.5 ± 16.7
	High	29.1 ± 13.2	23.3 ± 15.9	24.7 ± 16.7	26.3 ± 17.1
Pain (a.u.)	Placebo	0 ± 0	27.3 ± 14.9	23 ± 19.4	7.6 ± 7.4
	Low	0 ± 0	23.5 ± 22.3	8.5 ± 10.1	3.8 ± 4.5
	High	0.3 ± 0.5	28 ± 25.6	13 ± 14.4	9.5 ± 9.1
Range of Motion (°)	Placebo	171.5 ± 8.5	164.8 ± 10	166 ± 8.7	168.5 ± 8.3
	Low	176 ± 7	163.8 ± 13.5	166.3 ± 8.8	172 ± 2.9
	High	174.3 ± 5	163.8 ± 8.5	164.5 ± 5.2	166.8 ± 2.4

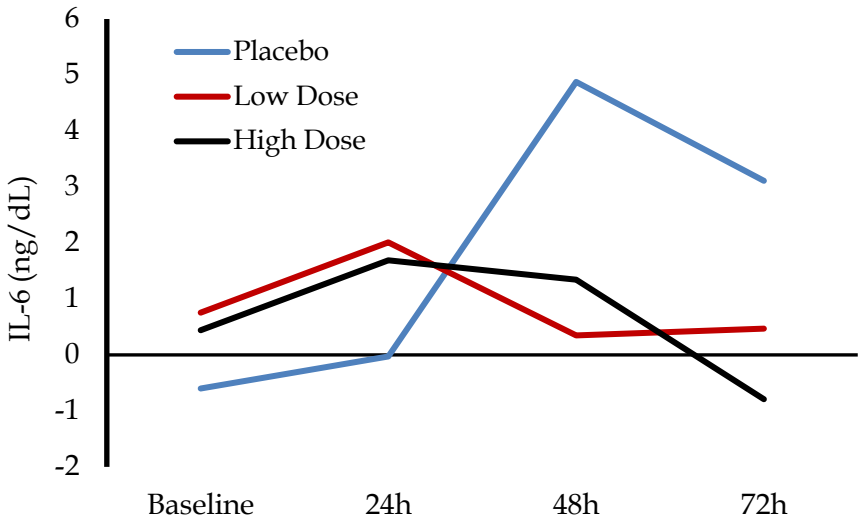

Figure 2. Interleukin-6 across the study duration between placebo, low, and high dose CBD.

DISCUSSION

The primary purpose of this investigation was to determine the effect of CBD supplementation on inflammation, range of motion, pain, and strength following fatiguing eccentric exercise bout. Although not detectable with the current sample, it appears that inflammation, as measured by IL-6, may be attenuated by CBD supplementation following an intense bout of eccentric exercise when compared to a placebo. It does not appear that pain or muscle strength (performance) are impacted by CBD supplementation. Readers should be aware that the presentation of data from the current study should simply inform future researchers when

developing new investigations rather than interpreting data as "findings," due to the small sample size.

CBD is rapidly being adopted by individuals in and out of the sporting arena. Despite the growing implementation of CBD, the full gambit of physiological effects are yet to be defined (23). There is growing evidence, however, that CBD brings about a therapeutic effect for those with diabetes, Parkinson's disease, rheumatoid arthritis, and Alzheimer's (3, 8, 12, 21, 28). The main mode of action is the antagonistic nature of CBD to endocannabinoids. Activation of cannabinoid receptor two (CB_2) brings about appetite suppression, anxiety relief, and anti-inflammatory responses (23). Binding of CBD to CB_2 may override the potential cytokine storm that follows intense muscle damage, leading to antinociception (22).

The current investigation evaluated IL-6 as a metric of systemic inflammation following a damaging bout of exercise. It appears, when looking at visual depictions of the data, that supplementation of CBD attenuates systemic inflammation, regardless of dose. It would be interesting to evaluate CBD's effect on inflammation following a bout of exercise that taxed larger muscle groups (e.g., lower extremities, chest and arms) to determine if higher doses of CBD are necessary to ameliorate greater inflammatory responses. The current investigation recruited eccentric-naïve individuals to prevent evaluating those who have gone through the "repeated bout effect," or the acclimation to eccentric exercise resulting in reduced muscle damage secondary to ERT (16). It would be interesting if future investigations evaluated the impact of CBD in those with and without experience with ERT.

It is anticipated that the use of CBD in and outside of sport will continue to grow despite the lack of scientific evidence supporting its efficacy. This pilot investigation is not without its limitations. Future investigations may consider evaluating a larger sample as parametric testing was limited in this study. Researchers may also consider assessing other biomarkers such as IL-1, IL-10, TNF-α, myoglobin, advanced oxidation protein products, and the ratio of reduced and oxidized glutathione (oxidative stress). Additionally, researchers should seek to determine the impact of chronic CBD use on liver and muscle function as this was not assessed in the current investigation (4). Moreover, future investigations may consider choosing an alternative control oil as soybean may impact IL-6 concentrations (9). However, previous interventions found that this dose makes little to no impact on markers of inflammation (5). Though unlikely to have occurred from the intervention, there is the possibility that muscular strength could have changed due to outside factors during the study. Investigators may also consider evaluating the impact of CBD supplementation on muscle growth patterns in humans, as only animal models are available for appraisal at this time (14).

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