Received: 20 Sep 2023 | **Accepted:** 11 Dec 2023 **Genel Tıp Derg. Volume** 34/**Issue** 1 (February), 94-99
DOI: 10.54005/geneltip.1363466

ORIGINAL ARTICLE

Cytokine Response to Acute Endurance Exercise: Regular Treadmill versus Lower Body Positive Pressure Treadmill

Akut dayanıklılık Egzersizine Sitokin Yanıtı: Normal Koşu Bandına Karşı Alt Vücut Pozitif Basınçlı Koşu Bandı

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How to cite ?

Kırışka MS, Belviranlı M, Okudan N. Cytokine response to acute endurance exercise: Regular treadmill versus lower body positive pressure treadmill. Genel Tıp Derg. 2024;34(1):94-99.

ABSTRACT

Objectives: This study aimed to investigate the cytokine response to acute endurance exercise performed in the lower body positive pressure treadmill (LBPPT) and to compare it with the regular treadmill.
Materials and Methods: Eleven healthy physically active men aged between 18-22 years participated in the study. All subjects performed 45 minutes of running exercise at 70% maximal oxygen consumption (VO2max) on the regular treadmill and LBPPT in random order, one week apart. Blood samples were collected at pre-exercise, immediately post-exercise, 30 min post-exercise, and 2 h post-exercise to analyze serum high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-a), and interleukin-8 (IL-8) levels.
Results: On the regular treadmill, hs-CRP levels were higher immediately, 30 min, and 2 h post-exercise than pre-exercise. In addition, it was lower 2 h post-exercise compared with immediately, and 30 min post-exercise. No significant differences in LBPPT for hs-CRP were observed for any time point. Hs-CRP concentration immediately and 30 min post-exercise was lower in the LBPPT than in the regular treadmill. TNF-a and IL-8 levels were unchanged in response to exercise performed neither on the regular treadmill nor on the LBPPT.
Conclusion: Acute endurance exercise induces a limited systemic inflammatory response in physically active men.

Keywords: Cytokine response, Acute endurance exercise, Lower body positive pressure treadmill, Inflammation

ÖZ

Amaç: Bu çalışma, alt vücut pozitif basınçlı koşu bandı (lower body positive pressure treadmill; LBPPT) ile gerçekleştirilen akut dayanıklılık egzersizine verilen sitokin tepkisini araştırmayı ve normal koşu bandı ile karşılaştırmayı amaçlamıştır.
Gereç ve Yöntem: Çalışmaya 18-22 yaş arası 11 sağlıklı, fiziksel olarak aktif erkek katılmıştır. Tüm denekler, bir hafta arayla rastgele sırayla normal koşu bandı ve LBPPT üzerinde Maksimum oksijen tüketimi (VO2max) değerinin % 70'inde 45 dakikalık koşu egzersizi gerçekleştirdi. Serum yüksek hassasiyetli C-reaktif proteini (hs-CRP), tümör nekroz faktör-alfa (TNF-a) ve interlökin-8 (IL-8) seviyelerini analiz etmek için egzersizden önce, egzersizden hemen sonra, egzersizden 30 dakika sonra ve egzersizden 2 saat sonra kan örnekleri alındı.
Bulgular: Normal koşu bandında, hs-CRP seviyeleri egzersizden hemen sonra, 30 dakika ve 2 saat sonra, egzersiz öncesine göre daha yüksekti. Ek olarak, hemen ve egzersizden 30 dakika sonra ile karşılaştırıldığında egzersizden 2 saat sonra daha düşüktü. Herhangi bir zaman noktasında hs-CRP için LBPPT'de anlamlı fark gözlenmedi. Egzersizden hemen sonra ve 30 dakika sonra hs-CRP konsantrasyonu LBPPT'de normal koşu bandına göre daha düşüktü. TNF-a ve IL-8 seviyeleri, ne normal koşu bandında ne de LBPPT'de yapılan egzersize yanıt olarak değişmedi.
Sonuç: Akut dayanıklılık egzersizi fiziksel olarak aktif erkeklerde sınırlı bir sistemik inflamatuvar yanıta neden olmaktadır.

Anahtar kelimeler: Sitokin yanıtı, Akut dayanıklılık egzersizi, Alt vücut pozitif basınç koşu bandı, İnflamasyon

Introduction

Cytokines are a large family of polypeptides and proteins that are primarily secreted by myocytes, adipocytes, immune cells and endothelial cells. In addition to regulating immune functions, cytokines also play a role in cell proliferation, differentiation, migration, survival and apoptosis processes. Cytokine production can be modulated by a variety of stimuli such as hormonal stress, oxidative stress and exercise (1). Numerous studies have reported that acute exercise either increases or does not affect cytokine levels in both sedentary subjects and endurance trained athletes (2,3). Cytokine response to acute exercise is dependent on the mode, intensity, and duration (1-3). Additionally, in physically active subjects, the cytokine response may depend on the several factors such as training volume (4), body composition (5) and cardiorespiratory fitness (6). In recent years, the use of new technologies and alternative exercise tools developed for rehabilitation, treatment and sportive performance has been increasing. Among these devices, the lower body positive pressure treadmill (LBPPT) is becoming important (7). LBPPTs like AlterG are anti-gravity treadmills that can reduce the load on the musculoskeletal system by up to 80% by creating positive pressure around the lower body, thus allowing treatment or exercise in safe conditions (8). The main goals of this device was to decrease the stress on joints, ligaments, and tendons, and to decrease ground

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
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Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
https://yayinevi.selcuk.edu.tr/

reaction force and the amount of load transmitted through tissues of the lower limbs (9). The result is a decrease in impact forces, an increase in stride length and flight time, and a decrease in contact time while running on the machine (7).

The LBPPT is widely used for rehabilitation purposes to support body weight (10), and its potential effects on cardiovascular and metabolic responses have also been extensively studied. It has been reported that LBPPT exercise causes less metabolic and cardiovascular load (7) compared to regular treadmill exercise at the same speed, and that peak oxygen uptake is reduced with an increase in body weight support (9-13). However, it has been reported that LBPPT is not effective in recovery from exercise-induced muscle damage or endurance exercise (14,15).

The fact that LBPPT exercise has different metabolic and cardiovascular demands compared to regular treadmill exercise of the same intensity suggests that the cytokine response may also be different. Also, to our knowledge, there is no research on cytokine responses to acute endurance exercise performed in LBPPT. The primary objective was to examine the responses of cytokines such as interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-a) and high sensitivity C-reactive protein (hs-CRP) to acute endurance exercise performed on LBPPT with partial body weight support and regular treadmill in physically active men. Our second aim was to compare cytokine responses to regular treadmill and LBPPT.

Materials and Methods

Participants

Eleven healthy male physically active men aged 18-22 years volunteered to participate. The definition of physically active included at least 1.5-2 hours of daily regular activity, 3-5 days a week, for at least 2 years.

The participants were informed and signed informed consent was obtained. The study was approved by the local Ethical Committee (approval No. 2018/452).

Before the exercise tests, all participant's body weights were measured in light clothes with an electronic scale (Philips HF-390/00, China) and their heights were measured.

Research Design

This was a crossover interventional trial. All participants were invited to the laboratory 4 times. These were the familiarization session, aerobic capacity assessment, test session 1 and test session 2 with at least 1 week between visits. In Sessions 1 and 2, all subjects underwent LBPPT or regular treadmill exercise at 70% of VO2max or vice versa. Venous blood samples were collected for the analysis of IL-8, TNF-a and hs-CRP levels.

Exercise Protocols

Measurement of Aerobic Capacity

Aerobic capacity of the participants was estimated using the 20-m multistage shuttle run test (16,17). During this test, subjects were asked to run continuously with a sound signal between two cones placed 20 m apart. The speed increased gradually at each stage. The test was terminated until the subject voluntarily exhausted or failed to reach one of the cones a second time before the corresponding beep. The maximum speed and maximal oxygen consumption (VO2max) reached during the test was determined using the equation proposed by Larsen et al (18).

Exercise Tests

After determining the VO2max values of the subjects, the workload corresponding to 70% of the VO2max was determined for each subject according to the American College of Sports Medicine guidelines (19,20). Both regular and LBPPT exercise sessions started at the same hours of the day, lasted 50 minutes, and the subjects performed both exercise sessions at the same pace.

The regular treadmill exercise consisted of a five-minute warm-up at a self-selected pace followed by a 45-minute running exercise at 70% of the previously calculated VO2max on the regular treadmill (Cosmed T150, Rome, Italy).

LBPPT exercise was performed on a AlterG Anti-Gravity treadmill (Alter-G Inc., Fremont, CA, USA). During the test, the tights necessary for the participants to settle into the treadmill were put on and their connection with the device was provided with the zipper in the tights. The device was calibrated by filling the plastic bag with air. Participants started the session with a warm-up. This included running at a self-selected pace for 5 minutes on a LBPPT without bodyweight support. After that, the device was programmed to 80% body weight support and the running started. The running speed corresponding to 70% of the participant's VO2max was reached gradually in 1 min and they were allowed to run at this speed for 45 minutes.

Blood sampling

Ten milliliter venous blood samples were obtained by a certified phlebotomist pre-exercise, immediately post-exercise, 30 min post-exercise, and 2 h post-exercise to analyze cytokine levels. The samples were stored 30 min until the centrifugation for serum separation, and after that, they were centrifuged at 3000 rpm for 15 min at 4°C. The samples were stored at – 80 °C.

Biochemical analysis

Serum hs-CRP, TNF-a and IL-8 concentrations were analyzed by an ELISA technique, according to the manufacturer's recommendations (Cat no: E-EL-H5134, E-EL-H0109, E-EL-H0048, respectively. Elabscience Biotechnology Co. Ltd, Wuhan, China). The intra-assay coefficient of variance (CV) was 4–6%, whereas the inter-assay CV was 5–7%. The levels of the IL-8, and TNF-a were expressed as pg/mL and levels of the hs-CRP were expressed as mg/L.

Statistical analysis

Statistical analyses were performed using the IBM SPSS v.25.0 (Chicago, IL, USA). Normality of the variables was

assessed with the Shapiro-Wilks test. For analysis of hs-CRP, TNF-a and IL-8 data, repeated-measures ANOVA (2 × 4, group × time) was used. Pairwise comparisons were made to explore the differences between the two groups and the four time points in the parameters in which the interaction was observed. Effect size (ES) transformations were used to assess the magnitude of change. Differences between mean values of cytokines that were observed to be statistically significant by comparing pre-exercise levels and post-exercise levels and values between the two groups for each time point were converted into ESs using Cohen's d. For ESs, changes were categorized as <0.25 trivial, 0.25-0.49 small, 0.50-1.0 moderate, and >1.0 large changes (21). The negative effect size indicates that effect decreases mean of the experiment group. A p value less than 0.05 was accepted as significant.

Results

All participants successfully completed the required exercise tests. Anthropometric and physiological characteristics of the subjects are given in Table 1.

Figure 1 shows the changes in circulating hs-CRP, TNF-a and IL-8 levels in response to regular treadmill and LBPPT exercises. Analysis of blood samples for serum hs-CRP concentrations showed a statistically significant time [F(3, 18) = 14.109, p = 0.000] and group x time [F(3, 18) = 4.464, p = 0.016] interactions. On the regular treadmill, measurements taken for serum hs-CRP immediately post- (p = 0.001), 30 min post- (p = 0.000), and 2 h post- (p = 0.038) exercises were higher than pre-exercise. The magnitude of changes between the pre- and immediately post- (ES = 2.10), pre- and 30 min post- (ES = 2.14), and pre- and 2 h post-(ES = 1.18) exercises were large. In addition, it was lower 2 h post-compared with immediately post- (p = 0.050), and 30 min post-(p = 0.010) exercises. The magnitude of changes between the immediately post-and 2 h post-(ES = - 0.91), and 30 min post- and 2 h post- (ES = - 0.81) exercises were moderate. No significant differences in LBPPT for serum hs-CRP levels were observed for any time point. Serum hs-CRP concentration immediately post- (p = 0.045, ES = - 0.75) and 30 min post- (p = 0.025, ES = - 0.96) exercises were lower in the LBPPT than in the regular treadmill (Figure 1A). Serum hs-CRP levels were within the normal range at all measurement points before and after exercise.

Serum TNF-a concentrations showed no statistically significant time [F(3, 18) = 0.774, p = 0.524] or group x time [F(3, 18) = 0.968, p = 0.429] effect. Analysis of blood samples for serum IL-8 levels demonstrated a statistically significant time [F(3, 18) = 3.810, p = 0.028] but no group x time [F(3, 18) = 0.968, p = 0.429] interaction (Figure 1B). In the LBPPT, serum IL-8 concentration was higher 2 h post-compared to pre- exercise (p = 0.015). The magnitude of changes was large (ES = 1.21). No significant differences were observed in the regular treadmill for any time point (Figure 1C).

Discussion

This study showed a statistically significant increase in the serum hs-CRP concentration following the acute endurance exercise performed on the regular treadmill but not on the LBPPT. Additionally, serum TNF-a levels were unchanged in response to exercise performed neither on the regular treadmill nor on the LBPPT, while serum IL-8 levels were higher 2 h post-exercise than pre-exercise in response to exercise performed on the LBPPT. This study is novel because to our knowledge, there is no study investigating the systemic cytokine response to acute endurance exercise performed in the LBPPT and comparing it with the regular treadmill.

Although various studies examined hs-CRP responses to exercises of different intensities and durations such as marathon (22), ultra-marathon (23), half-marathon (24), triathlon (25) and walking exercise (26), there are only a few reports regarding the acute endurance exercise (27). Our results confirmed that acute endurance exercise leads to elevation in systemic hs-CRP concentration. In our study, the post-exercise increment in hs-CRP after acute endurance exercise was significant and large in magnitude (ES = 2.10, 2.14, and 1.18 immediately post-exercise, 30 min post-exercise, and 2 h post-exercise, respectively). This hs-CRP response to exercise seems to be proportional to the duration and intensity of the exercise as well as muscle injury (3) and it increased between 122% and 2000% immediately after the marathon (22), while it increased by 81% after acute endurance exercise (27), which is in line with our findings. However, no significant changes in hs-CRP levels were observed after 30 min of walking on a treadmill at the 50% VO2max (26). Additionally, Jatene et al (28) claimed that serum hs-CRP levels should be an internal indicator of the exercise load.

CRP is a widely used biomarker of inflammation, and it is considered an indicator of the likelihood of cardiovascular disease. Elevated levels of CRP have been independently associated with the progression of atherosclerosis in humans (29,30). The hs-CRP provides a more sensitive and accurate measurement of CRP at lower concentration levels. In this study, the concentrations of hs-CRP significantly increased in the regular treadmill phases when compared to baseline level. The mechanism in which regular treadmill leads to an increase in hs-CRP may be related to the activation of a pro-inflammatory signaling pathway that is regulated by toll-like receptors (TLRs) and nuclear factor kappa-B (NF-κB) (31). TLRs, one of the innate immune components, are stimulated by exercise and induce the production of inflammatory cytokines. In addition, the NF-κB signaling pathway can be activated in a redox-sensitive manner during muscular contraction, presumably due to increased oxidant production (32).

Our study data show that hs-CRP concentrations were lower at 2 h post-exercise than immediately post-exercise and 30 min post-exercise, respectively. The 2 h post-exercise decrement in hs-CRP levels was significant but moderate in magnitude (ES = - 0.91, - 0.83; immediately post-exercise, and 30 min post-exercise, respectively). Previous studies have shown

Table 1. Anthropometric and physiological characteristics of participants

Characteristics	Mean ± SD
Age (years)	19.54 ± 0.89
Height (m)	1.75 ± 0.06
Weight (kg)	69.10 ± 6.66
VO_{2max} (mL/kg/min)	57.90 ± 2.06
Running speed (km/h)	11.1 ± 0.4

Data are presented as mean ± standard deviation (SD). VO_{2max}: maximal oxygen consumption (VO_{2max}).

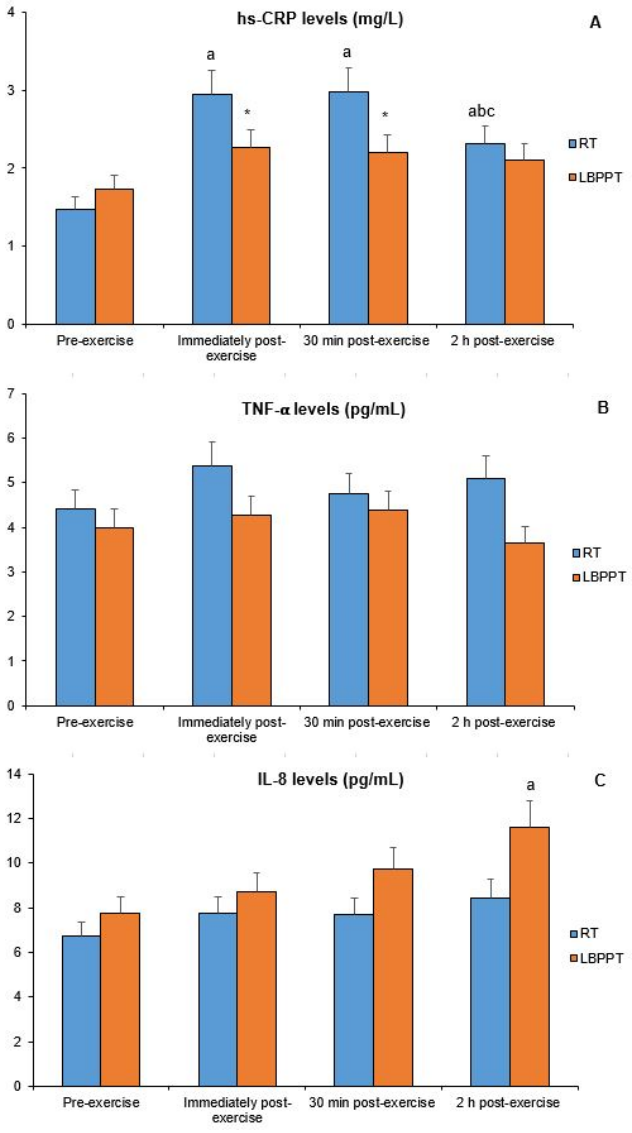

Figure 1. Systemic cytokine concentrations in response to running on the regular treadmill and lower body positive pressure treadmill

Data are presented as mean ± standard deviation (SD). RT: regular treadmill, LBPPT: lower body positive pressure treadmill, hs-CRP: high-sensitivity C-reactive protein, TNF-a: tumor necrosis factor-alpha, IL-8: interleukin-8. [a]p < 0.05 compared to pre-exercise, [b]p < 0.05 compared to immediately post-exercise, [c]p < 0.05 compared to 30 min post-exercise, *p < 0.05 compared to regular treadmill.

that recovery time takes 2-6 days after a marathon race, 48 hours after a football match (28), and 5 days after a 3-stage trial running race (33). These data indicate that recovery time after exercise also depends on the intensity of the exercise.

In this study, serum hs-CRP concentrations did not change in response to acute endurance exercise performed on LBPPT. In addition, hs-CRP levels immediately post-exercise and 30 min post-exercise were lower than exercise performed on a regular treadmill and the effects size of the decrement was - 0.75, and - 0.96, respectively. These data indicate that the exercise performed on the LBPPT causes less systemic cytokine response than the exercise performed on the regular treadmill at the same speed. Previous studies have shown that the metabolic cost of running with body weight support in LBPPT is lower than running at the same intensity on a regular treadmill, and that exercising on such treadmills can reduce metabolic cost as body weight decreases (11,12).

In this study, serum TNF-a levels changed in response to exercise performed neither on the regular treadmill nor on the LBPPT, while serum IL-8 levels were higher 2 h post-exercise than pre-exercise in response to exercise performed on the LBPPT. In addition, there was no significant difference between the normal treadmill and LBPPT in terms of TNF-a and IL-8. It has been reported that the acute responses of the TNF-a and IL-8 to exercise depends on the intensity and duration of effort (34). Studies have shown that circulating TNF-a and IL-8 levels only increase in response to muscle damage during very intense or strenuous exercises such as marathon running, but do not change in response to acute endurance exercises (35,36). In this context, it was reported that IL-8 and TNF-a levels increased immediately after a marathon race (37,38). In addition, Gokbel et al. (39) reported that repeated bouts of supramaximal exercise did not affect plasma TNF-a levels in sedentary subjects. To our knowledge there is no study investigating the TNF-a and IL-8 response to acute endurance exercise performed in the LBPPT and comparing it with the regular treadmill. However, West et al (14) compared the effect of LBPPT with cycling and stretching exercises on TNF-a levels in the recovery period from acute exhaustive exercise and showed that all three exercise types had similar effects and there was no difference between the groups.

Although these results provide new information, we recognize that there are some limitations to our study design. One of the limitations inherent in this study was the lack of funding to conduct more biochemical tests that could provide more information on indicators of immune function such as macrophages, neutrophils and eosinophils. The second limitation was that, due to technical difficulties, exercise intensity was not measured with markers of exercise intensity such as heart rate, oxygen consumption or Borg scale during the LBPPT exercise, and only exercised at 80% body weight support. Although it has been shown in previous studies that exercises performed with different body

weight support cause different metabolic responses, we could not test this situation in our study. The third limitation of our study is the relatively small and only male sample size included in the study. Despite the appropriate sample size calculation, further randomized controlled trials with larger sample sizes are needed to address the limitations of the current study. Another limitation of our study is that we only examined the time up to 2 hours after exercise. To observe changes in cytokine levels in more detail, more samples are needed over a wider time period. Future studies should analyze these factors over a broader time period.

Conclusion

In this study, in response to regular treadmill exercise and LBPPT, there was only a significant change in hs-CRP levels, but no changes in TNF-a and IL-8 levels. This suggests that acute endurance exercise causes a limited systemic inflammatory response in physically active men. However, more comprehensive studies involving more diverse populations are required in the future to clarify the potential effects of LBPPT.

Acknowledgements

The authors would like to thank the participants for volunteering the in time and efforts. This study was produced from the MSc thesis of Muhammet Salih Kırışka

Conflict of Interest

None of the authors has any conflict of interest to disclose.

Author contributions

MSK, MB and NO conceived and designed the study. MSK and MB performed the experiments. MB wrote the paper. NO reviewed and edited the manuscript. All authors read and approved the manuscript for publication

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