



## Positive Effects of Six Months Training Program on Inflammatory Mediators in Young Soccer Players

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### ABSTRACT

Despite the worldwide popularity of football, there is still insufficient data on the effects of the training process on the immune system, followed via serum values of cytokines measured during or following constant exercise. This study aims to assess the effects of a six-month programmed physical activity, on activity of inflammatory mediators in young footballers. The study included 26 players, male, aged 12-13 years, who participated in the six-month training program and 26 sedentary boys who are not entering of the previously mentioned program. Blood samples, which measured levels of the inflammatory mediators TNF- $\alpha$  (tumor necrosis factor alpha) and IL-6 (interleukin six) were taken before and after a six-month training programs. Significantly low values of IL-6 serum ( $34,73 \pm 33,23$ ;  $12,52 \pm 3,35$ ;  $p=0,000^{**}$ ) were measured, while the concentration of TNF in the serum did not significantly alter after a 6-month training process. The results obtained in this way can be of an invaluable value in the organizing and dosing of physical activities in young football players.

**Keywords** inflammatory response; cytokines; exercise; soccer players; training programme

### Academic Discipline And Sub-Disciplines

Exercise Physiology

### SUBJECT CLASSIFICATION

Sport's medicine

### TYPE (METHOD/APPROACH)

A prospective study

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## INTRODUCTION

Soccer is without question the world's most popular sport with 265 million registered players [1]. When compared with continuous exercise, intermittent exercises such as sporting games (soccer, basketball and handball) involve both aerobic and anaerobic metabolism [2]. Physical activity has a huge role in the balancing of a child's organism. A good-quality exercise program to a large degree improves a child's physical, psychomotor and intellectual abilities. Health depends largely on physical activities, which improve a balanced development in children [3]. In the last two decades, participation in competitive sports events has become a basic feature of childhood in western countries [4]. To successfully carry out technical-tactical activities during a football match, it is necessary for the players to have maximally developed functional and motor abilities. The game of football most often involves aerobic and anaerobic capacity, strength, flexibility and agility [5]. This is demonstrated by several studies which researched the appearing of an inflammatory reaction in significantly extreme physical activities such as running the marathon and the ultramarathon (6, 7, 8, 9). These studies conclude that the appearing of inflammation in athletes who participate in the mentioned sports events can be connected to an increased incidence of infection in the period after the loading. Namely, a two to six time higher frequency was noted in the upper respiratory tract in athletes after a marathon, in comparison with control runners who did not participate in these races [6, 7, 8, 9]. Also, intense physical activities result in reactions of the organism which are by many criteria very similar to those caused by infections, sepsis, or trauma [10]. The response of the organism is reflected in the existing of a significant increase of cyclic leucocytes, primarily lymphocytes and neutrophils, with direct proportionality between increasing of their values and the increase of the workout intensity and duration. Along with this, during muscle work there is also an increased production of reactive oxygen species (ROS). The main sources of ROS during exercising are the respiratory chain in the mitochondria, cytosol as well as membrane NADH oxidase (nicotinamide adenine dinucleotide) and xanthine oxidase [11, 12]. ROS can instigate the development of inflammatory reactions, as it mediates in the appearing of numerous pro-inflammatory cytokines, especially IL-6 [13].

All the mentioned data points to the fact that intense and long-lasting exercise cause changes of the inflammatory response level within the system circulation, in the sense of prevailing pro-inflammatory cytokines, which in the end causes an inflammatory reaction of the muscle tissue, reflecting negatively on recovery after training and sports performance. Nevertheless, the number of data which is involved with the occurrence of inflammation caused by intense physical activity, especially in children and adolescent is scarce, and with conflicting results.

Taking into consideration the unquestionable significance of a well-timed discovery of possible inflammatory processes during childhood, the aim of this research is to determine the activities of inflammatory cytokines in young football players in order to assess the effects of a six-month training process on their inflammatory response.

## MATERIALS AND METHODS

### Subjects 2.1

The research was carried out within a group of 26 male athletes (aged 12-13 years, with minimum 5 years of sports experience), involved in the six-month training programme. Control group included 26 age-matched young non-athletes who did not participate in training.

All participants were healthy, had no special eating habits, and did not use medications or supplements, except additional protein intake. During the six-month training programme all the athletes had approximately 90 g of protein per day, i. e. each meal consisted of 15 g of protein (eggs, meat, bacon, fish, cheese, milk, yoghurt). After each training session they got a protein shake (30 g of protein plus 5 g of glutamine in 500 ml of water). They also had two snacks, each consisted of 7 g of protein, and 400 g of vegetables (raw, grilled and boiled) were included in each meal. A piece of fruit was eaten after each training session (300 g).

Because of possible adverse effects of UV radiation and pollens, training sessions were performed in the sports hall during autumn and winter seasons.

All participants and their parents gave written informed consent.

The study was approved by the Faculty of Medical Sciences Ethics Committee, University of Kragujevac.

### Protocol 2.2

Examination was conducted in the beginning of the pre-competition stage as initial measurement and after the completion of the six-month training programme. Both examinations were performed using the same protocol. The examinations started at 8 a.m. in the morning and consisted of standard sports medical examination and blood sampling.

Training programme was realised as physical activity running over six months and undertaken for at least 12 hours per week. Trainings lasted for 75-90 minutes. The training sessions were divided into three parts: warm up (15 min.), basic training (50-65 min.) and cool down (10 min.). Warm up focused on exercises with the ball and lower extremities. Middle stage included basic techniques of ball control – individually, in pairs, and in groups of four players as the maximum number of players per team. The heart rate at this stage of training did not exceed 160 beats per minute. Final phase consisted of stretching muscles and the entire body.



### Biochemical assays 2.3

Blood sample was taken before and after six-month training programme. The gathered serums were stored and frozen to -20°C to defrost directly before the test. The serum levels IL-6, IL-17 and TNF- $\alpha$  were measured with a highly sensitive enzymatic immunosorbent assay (ELISA) by human interleukin kits (R&D Systems Minneapolis, MN). Before use, the standards were dissolved in PBS (pH 7.2), so that the initial concentrations were 2000 pg/ml for TNF- $\alpha$ , IFN- $\gamma$  and IL-4, and 1000 pg/ml for IL-17. The created stocks were serially 7 times twofold diluted in Reagent Diluent in order to get a standard curve with 7 points. 100 $\mu$ l of work concentration of a capture antibody was poured into the wells of polystyrene microtiter plate-MTP. The plates were sealed, incubated and left overnight at room temperature, after which they were wash buffered. All the samples were dissolved in solvent, in a 1:4 ratio. The dissolved samples and prepared standards were poured into MTP, covered with adhesive foil and left for 2 hours at room temperature. After incubation and rinsing, the well, following an adding of 100 $\mu$ l of work concentration of a detection antibody, were once more covered by adhesive foil and left for another 2 hours at room temperature. After a new incubation and rinsing, Streptavidin-HRP (Streptavidin horseradish peroxidase) was added (100  $\mu$ l). The incubation was interrupted after 20 minutes at room temperature, without being exposed to direct sunlight. Following that, 100  $\mu$ l of Substrate Solution was poured in as well as 50  $\mu$ l of Stop Solution (2N H<sub>2</sub>SO<sub>4</sub>). The optical density was measured by a Microplate reader set at 450 nm [14, 15].

### Statistics 2.4

Descriptive statistics were used to calculate arithmetic mean (X) with dispersion measures (standard deviation SD and standard error SE), 95% confidence intervals, median, and minimum (min) and maximum (max) values of analysed properties.

Depending on distribution checked by Shapiro-Wilk, Paired Samples T-test, or Wilcoxon signed rank sum tests were used to assess the difference between parameters gathered in two different points of time (before and after the training programme).

## RESULTS

With the athletes and the non-athletes in our research, neither one of the two measured inflammatory cytokines (IL-6 and TNF- $\alpha$ ), showed any statistical significance (Figure 1 and 2).

The serum level of IL-6 in athletes in relation to non-athletes was statistically lower after a six-month training process with mean values (12,52 $\pm$ 3,35; 36,40 $\pm$ 28,39; p=0,000\*\*) (Figure 3).

Due to the impact of the training process, there was a significant difference in the IL-6 level, in the sense of reduced values after programmed six-month physical activities (34,73 $\pm$ 33,23; 12,52 $\pm$ 3,35; p=0,000\*\*) (Figure 4).

Anthropometric and functional capacities characteristics of participants are shown in Table 1,2. Athletes had statistically lower percentage of fat and body weight values as well as statistically higher percentage of muscle and body height values compared with non-athletes (Table 1). Aerobic power was significantly increased after training programme in the group of examined athletes (Table 2).

## DISCUSSION

In our research, the values of pro- and anti-inflammatory cytokines in plasma of athletes in relation to non-athletes, showed no significant differences when measured in basal conditions (Table 1).

Comparing the cytokine levels measured in plasma of athletes and non-athletes of young football players aged 12-13, after 6-month programmed physical activities, we observed that the IL-6 levels from athletes, after the training process, were significantly lower compared to non-athletes (Figure 1).

Previous reports have shown that during and after long-lasting and strenuous sports events, there is a significant increase of the level of cytokines in the plasma [16, 17, 18, 19], including pro-inflammatory cytokines such as TNF- $\alpha$ , inflammatory protein-1 originating from macrophages, IL-1 $\beta$ , anti-inflammatory cytokines IL-6, IL-10, antagonist receptor for IL-1 and C-reactive protein (CRP) [20]. However, the degree of changes in the cytokine concentration in plasma depends on the exercise intensity and duration, as well as on the type of muscle contraction involved. The main finding during and after strenuous exercise is enhanced production of reactive oxygen species followed by leukocyte infiltration into skeletal muscles and subsequent tissue injury [21]. IL-6 is well-studied cytokine produced by variety of cell types including contracting myocytes. It is a potent regulator of immune response, acting both in the pro-inflammatory and the anti-inflammatory manner. Elevated production of IL-6 accompanied with physical activity plays a central role in the control of oxidative stress and acute-phase response by exhibiting anti-inflammatory and antioxidant effects [22]. On the other hand, IL-6 is known as classical pro-inflammatory cytokine and chronic exposure to higher levels of IL-6 generates low-grade inflammation involved in the pathogenesis of numerous metabolic disorders [23]. While, the exercise itself provokes significant acute increase in IL-6 production by muscle in contraction, prolonged exercise training reduces circulating levels of IL-6, but also increases expression of receptor for IL-6 and enhances muscle response to IL-6 [24]. Some studies have shown that during exercise there is an increase of IL-6 concentration in the blood plasma [20, 25], and others have shown that there is an increase of IL-6 concentration after acute exercise, while the plasma concentration of TNF- $\alpha$  remains unchanged, based on the inhibitory effect of IL-6 on pro-inflammatory TNF- $\alpha$  production [26]. Additional studies show that exercise does not induce increased TNF- $\alpha$  levels in plasma, unless the exercise is extremely strenuous [27]. The producing of IL-6 from monocytes [28] as well as IL-2 and IFN- $\gamma$  (but not IL-4) from T lymphocytes was reduced during and several hours after longer-lasting physical loading [29, 10]. However, a large increase of IL-6 concentration in plasma was noticeable after exercise based on hitherto findings, which can be explained by releasing cytokines from

muscle fibers which contract [20]. Elevated IL-6 level in plasma stimulates production of anti-inflammatory cytokines such as IL-1 receptor antagonist and IL-10 [30].

Some research has shown that a significantly increased level of IL-6 during and after strenuous exercise depends on the intensity and nature of muscle contractions [31, 32]. Although plasma IL-6 levels significantly increases after the handball game in male players, it decreases to baseline levels within the 24 hours after the game [33]. Based on the fact that different exercise protocols induce significant changes in athletes oxidative stress homeostasis, it has been reported that sport-specific activity of longer duration may not induce disturbances in athletes redox state [34]. The appropriate balance between duration, intensity and volume of physical activity could influence the inflammatory response and subsequent cytokine production, including IL-6, which is in line with our findings.

While the IL-6 level is increased, the response of the muscle damage - a reduced level of IL-6 - can have a positive impact on the recovery time from physical exercise. There is evidence that the production of cytokines after muscle damage is linked with DOMS (a delayed onset of pain in the muscles) [31,32,35,36]. Pedersen and associates [32], and the later research of Richards and coauthors [35], show that the IL-6 inflammatory response in the post-exercise period is not useful, nor necessary for muscle development.

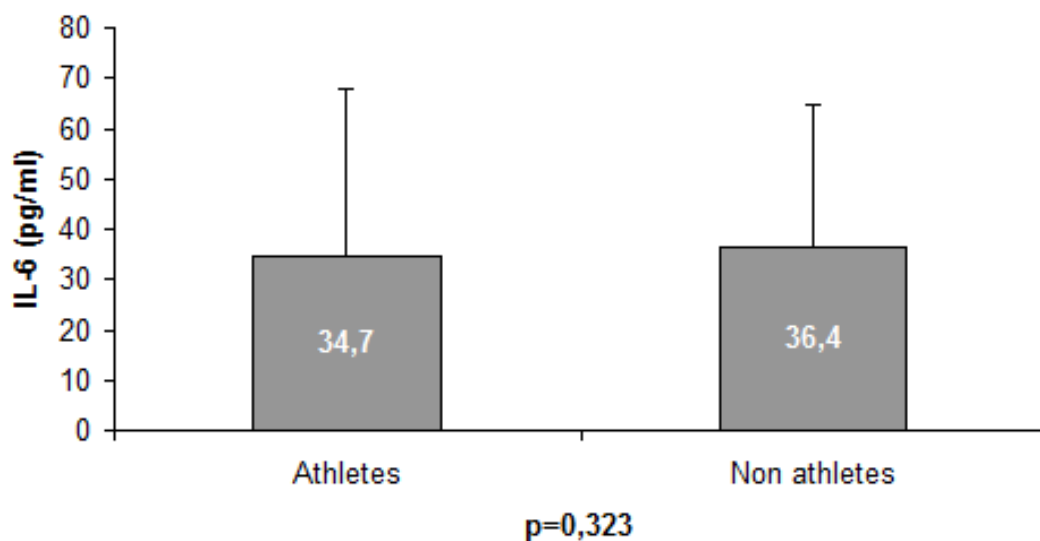
In this study, we have obtained results which suggest that after the six-month training cycle in athletes aged 12-13 the production of IL-6 can be reduced, while the concentration of TNF- $\alpha$  before and after the conducted program does not statistically differ. Our results confirm the hypothesis that a carefully and professionally planned training process balances an inflammatory response and oxidative stress homeostasis which enables a quick recovery in athletes (Figure 2).

## CONCUSLION

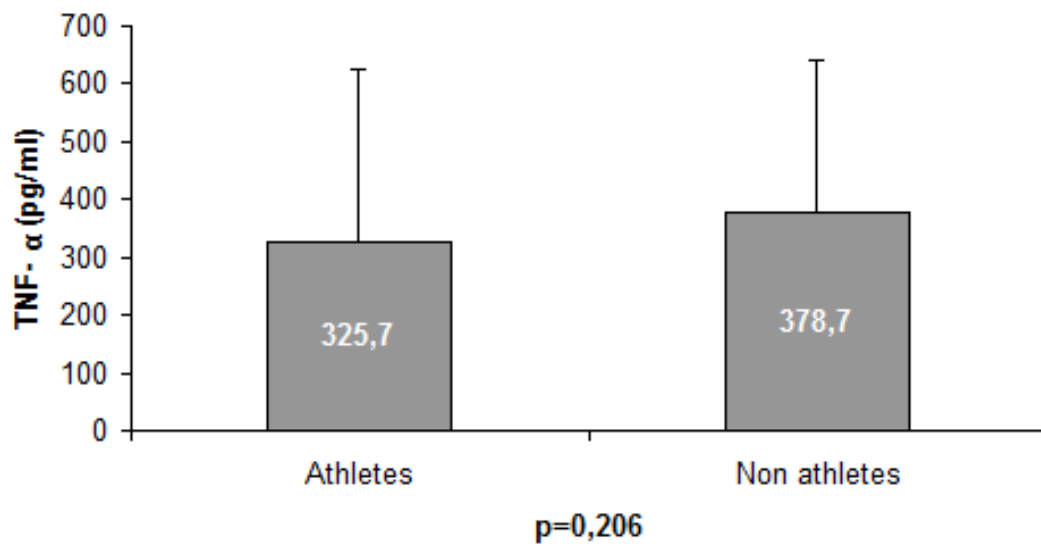
The results of the present study unequivocally confirm our hypothesis that, if planned carefully and carried out professionally, programmed physical activity can reduce the inflammatory response of the organism to physical stress and contribute to a proper psychological and physical development of young sportsmen, thereby improving their sports performance.

## ACKNOWLEDGEMENTS

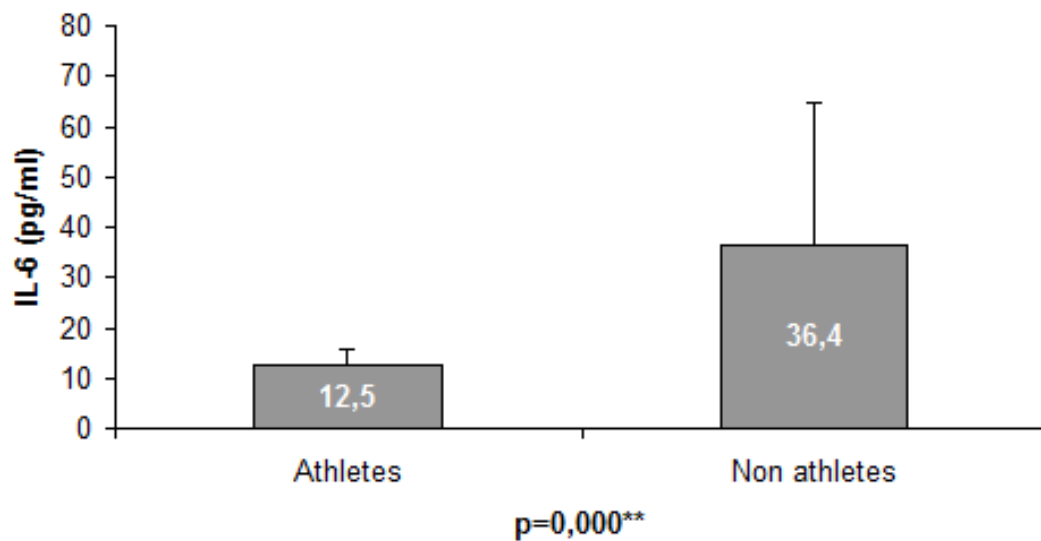
This work was supported by the Ministry of Science and Technical Development of the Republic of Serbia (Grant No. 175043) and the Faculty of Medical Sciences, University in Kragujevac (Junior Project No. 09/11).



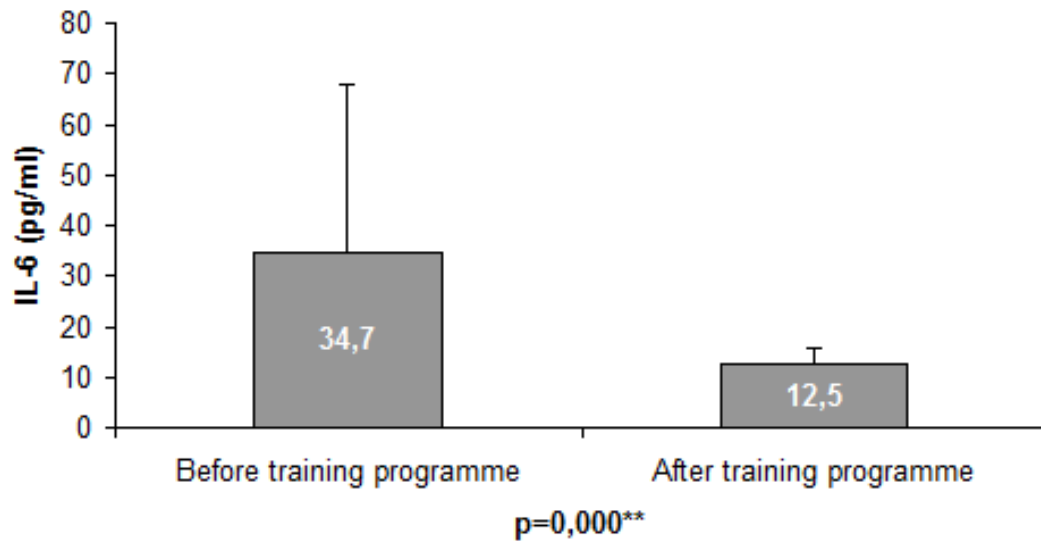
**Figure 1, 2.** Pro / anti-inflammatory markers in the blood of different groups of subjects in basal conditions (athletes with the first measurement prior to the program)



**Figure 2.**With the athletes and the non-athletes in our research, neither one of the two measured inflammatory cytokines (IL-6 and TNF- $\alpha$ ), showed any statistical significance (Figure 1 and 2).



**Figure 3.** Pro / anti-inflammatory markers in the blood of different groups of subjects: athletes after a training process and non-athletes in basal conditions



**Figure 4.** Changes in pro and anti-inflammatory markers in the blood of athletes before and after the training process

**Table 1.** Anthropometrical and morphological characteristics of non-athletes and athletes after six-month training programme

| Table 1.                   | X±SD       | Min - Max     | Med   | Test                  |
|----------------------------|------------|---------------|-------|-----------------------|
| <b>Body height (cm)</b>    |            |               |       | <b>Paired T- test</b> |
| <b>Athletes (n=28)</b>     | 157,3±8,3  | 143,7 - 173,3 | 157,5 | <b>P=0,013*</b>       |
| <b>Non-athletes (n=28)</b> | 164,2±11,2 | 139,5 - 183,5 | 163,0 | <b>t= -2,567</b>      |
| <b>Body weight (kg)</b>    |            |               |       | <b>Paired T- test</b> |
| <b>Athletes (n=28)</b>     | 45,2±7,6   | 33,0 - 60,2   | 43,5  | <b>P=0,025*</b>       |
| <b>Non-athletes (n=28)</b> | 52,5±13,8  | 29,3 - 83,1   | 47,1  | <b>t= -2,337</b>      |
| <b>BMI</b>                 |            |               |       | <b>Mann-whitney</b>   |
| <b>Athletes (n=28)</b>     | 18,1±1,7   | 15 - 21,5     | 18,1  | <b>P= 0,682</b>       |
| <b>Non-athletes (n=28)</b> | 19,2±3,6   | 15,2 - 28,4   | 18,2  | <b>Z = -0,410</b>     |
| <b>% body fat</b>          |            |               |       | <b>Mann-whitney</b>   |
| <b>Athletes (n=28)</b>     | 12,9±4,9   | 6,4 - 26,1    | 12,1  | <b>P=0,002**</b>      |
| <b>Non-athletes (n=28)</b> | 18,5±7,4   | 10,4 - 38,7   | 15,2  | <b>Z = -3,056</b>     |
| <b>% body muscles</b>      |            |               |       | <b>Paired T- test</b> |
| <b>Athletes (n=28)</b>     | 47,3±2,7   | 40,5 - 51,6   | 47,0  | <b>P=0,001**</b>      |
| <b>Non-athletes (n=28)</b> | 43,6±4,6   | 37,2 - 52,8   | 43,4  | <b>t= 3,427</b>       |



Table 2. Functional characteristics of athletes before and after six-month training programme

| Table 2.                             | X±SD         | Min - Max   | Med    | Test                   |
|--------------------------------------|--------------|-------------|--------|------------------------|
| <b>VO<sub>2</sub>max (ml/kg/min)</b> |              |             |        | <b>Wilcoxon's test</b> |
| <b>Before training programme</b>     | 48,7±11,1    | 23,2 - 84,3 | 49,9   | <b>P=0,012*</b>        |
| <b>After training programme</b>      | 53,9±8,4     | 38,8 – 76,9 | 54,4   | <b>Z= -2,527</b>       |
| <b>VO<sub>2</sub>max (ml/kg)</b>     |              |             |        | <b>Paired T-test</b>   |
| <b>Before training programme</b>     | 2197,1±443,8 | 1084 - 2841 | 2211,5 | <b>P=0,000**</b>       |
| <b>After training programme</b>      | 2523,1±421,7 | 1724 - 3609 | 2568,0 | <b>t= -4,118</b>       |

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