TIME-COURSE OF BLOOD INTERLEUKINE 6 AFTER EXERCISE

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INTRODUCTION

It has becoming clearer that the comprehensive benefits of regular exercise on immune system [1-3] are tightly associated with exercise effects on cells metabolism [4, 5]. Although many chronic exercise benefits on immune system have been associated with long term adaptations such as reduction in fat mass and increase in muscle mass [6], another part of exercise benefits are generated in each exercise session.

Elevation of cortisol and adrenaline during physical exercise stimulate leukocyte circulation, release of cytokines, chemokines, and increased lymph flow, in turn facilitating antigen recognition, processing, and presentation, as well as cell migration to lymph nodes and cell differentiation [7]. In addition to the elevation of adrenaline that is critical in mobilizing NK cells to reduce tumour growth, the release of muscle IL-6 and other factors produced and released by muscle during exercise also mediate the positive immune response to exercise [8-11]. At this time, IL-6 regulates myocyte growth and differentiation (for hypertrophy and myogenesis), modifies the energy homeostasis of lipid, carbohydrate and protein metabolism, and regulates inflammation and communication between organs [8, 12, 13].

Interleukin 6 (IL-6) is a key energetic regulator produced and released by muscles to attend the energetic requirements during exercise [12, 14, 15]. For this reason, the carbohydrate supplementation during exercise is one of the main factors affecting the magnitude of IL-6 release [15], but other factors also influence its magnitude of change with exercise. Even though, more than 300 studies have been conducted to test the effect of exercise on blood IL-6, not many has been conducted in a controlled design and characterize the true effect of exercise on blood IL-6 is the first step to understand the role of exercise in the metabolism of the immune cells.

OBJECTIVE

The objective of this work was to identify the kinetics of blood IL-6 following an exercise session by meta-analysis of previous literature. The second aim was to identify the influence of different types of exercise and energy supplementation on the IL-6 kinetics.

METHODS

The search was performed in the following databases: PubMed, Scopus, Embase, Web of Science, Cochrane, CINAHL, ScienceDirect, in May, 2021. We searched from acute exercise interventions in humans, assessing blood IL-6 before and after exercise, up to 120h.

We extracted mean and standard deviation of IL-6 concentrations before and after intervention in each exercised and control group, as well as the number of participants in each group.

The meta-analysis was performed at the software Comprehensive Meta-Analysis (CMA) software, version 3.3.070. The main meta-analyses compared pre exercise levels of blood IL-6 with each post-exercise time-point in which blood IL-6 was assessed in the studies included (0h, 30min, 1h, 2h, 4h, 24h, 48h, 72h, 96h and 120h). The standardized mean difference (SMD) and 95% confidence iterval (95%CI) were calculated by mean, standard deviation and sample size of blood IL-6 in each time point. When there was significant heterogeneity ($p \leq 0.05$), we calculated the randomized effect and when there was no significant heterogeneity ($p > 0.05$) we used fixed effects.

RESULTS AND DISCUSSION

From 1131 papers retrieved, 17 controlled trials were included for meta-analysis (Figure 1).

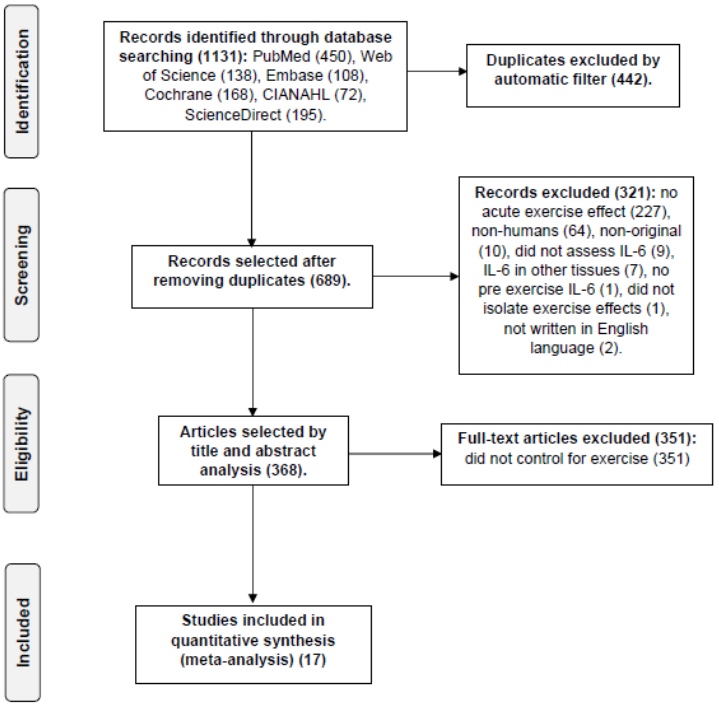

Figure 1. Flowchart of the studies selected.

Figure 2, shows a significant higher blood IL-6 only immediately (SMD 0.62 [0.20;1.03], P = 0.003) and 1h after exercise (SMD 0.38 [0.18; 0.58], P < 0.001) when compared to control.

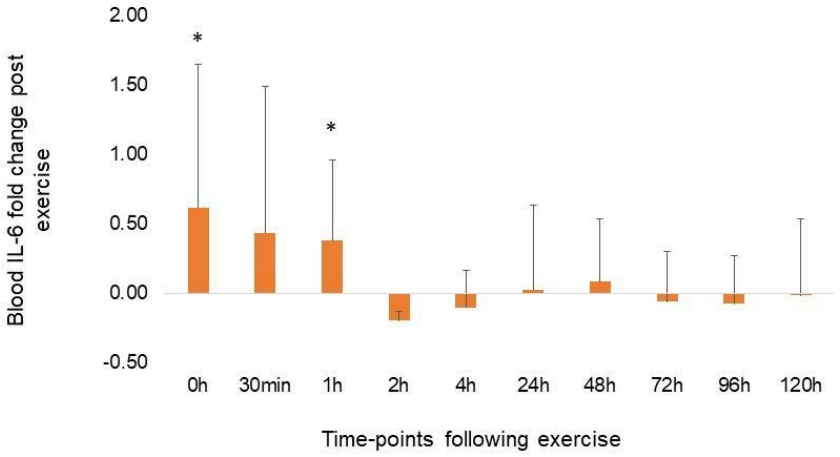

Figure 2. IL-6: Interleukine 6; error bars represent the upper limit of 95% confidence interval; *significant difference from baseline.

As has already been reported, any inflammatory event can be generated by a stimulus of a physical, chemical, or microbiological nature [16], each one different from each other according to the inflammatory microenvironment characterized by various combinations of cytokines and chemokines as well as the order of their appearance, all this to protect the system and/or recover homeostasiss [16-19].

In this article we focus on the microenvironment generated by exercise, where the stimulus would initially be mechanical on the muscle fibres due to the movement performed in the different exercise protocols. If we consider the muscle as an organ that produces IL-6, as suggested in many works, the release of IL-6 could be responsible for the changes in the metabolism of glucose, fatty acids, lipids, as well as alterations in thermoregulation [1, 14, 20]. Also, we considered than high levels of IL- 6 would correspond to processes related to generation of a "protective" anti-inflammatory response due to cell wear in muscle fibers since IL-6 promote the production of IL-1ra is a natural antagonistic cytokine that competes with IL-1 for receptor binding without inducing signal transduction. Furthermore, it has been shown that IL-6 and G-CSF are involved in neutrophil mobilization from bone marrow reserves to the circulation after exercise [21, 22].

Currently, there are many studies that have consistently shown that IL-1ra, IL-6, IL-8, and IL-10 are markedly increased after long-duration endurance exercise (such as marathons and triathlons). compared with short duration intensive exercise or eccentric contraction exercise. This has generated controversy, since there are reports suggesting that the inflammatory environment is generated by muscle damage, which would explain the high levels of IL-6 at prolonged times, 24, 48 hours after exercise, as has been suggested by some reports [23, 24].

On the other hand, the highest levels of Il-6 at times early may not depend on muscle damage induced by exercise, but might be related to the intensity of exercise (physiological load/stress). In fact, it has been known that the response of IL-6 to resistance exercise depends on factors such as the decrease in cellular energy levels, heat stress and changes in hormones related to cellular stress. It is known that IL-6 enhances the utilization of energy substrates such as glucose and free fatty acids, which contribute to endurance performance. Since it is a cytokine, it also affects immune cells and IL-6 during exercise correlated with neutrophil count, whereas neutrophil mobilization was correlated with changes in the muscle damage markers, Creatine Kinase (CK) and myoglobin [22].

In addition, another meta-analysis of our group (in preparation) recent showed significant increase of muscle IL-6 up to 72 hours post exercise, suggesting that long lasting production of muscle IL-6 might has an autocrine function after 1 hour.

CONCLUSIONS

Increase in blood IL-6 post exercise only last 1h when compared to control sessions. Thus, is likely that uncontrolled studies that previously showed longer lasting effects of exercise on blood IL-6 could have been caused by bias due to lack of control.

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