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Acute bouts of exercise induce a suppressive effect on lymphocyte proliferation in human subjects: A meta-analysis

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ABSTRACT

Objective: Lymphocyte proliferative responses are commonly used to assess immune function in clinical settings, yet it is unclear how proliferative capacity is altered by exercise. This analysis aims to quantitatively assess the proliferative response of lymphocytes following an acute bout of exercise.
Methods: Electronic databases were searched for articles containing the keywords "exercise" OR "acute" OR "aerobic" OR "resistance training" OR "immune function" AND "proliferation" AND "lymphocyte." Initial results yielded 517 articles of which 117 were reviewed in full. Twenty-four articles met the inclusion criteria. Calculated standardized mean difference (SMD) and corresponding standard errors (SE) were integrated using random-effect models.
Results: Analyses uncovered evidence for suppression of proliferative capacity following acute exercise in general (SMD = −0.18, 95% CI: −0.21, −0.16) with long duration, high intensity exercise exhibiting a moderate suppressive effect (SMD = −0.55, 95% CI: −0.86, −0.24). Discordant proliferative responses for long duration, high intensity exercise in competitive versus non-competitive settings were identified with enhanced proliferation (SMD = 0.46, 95% CI: 0.03, 0.89) observed following competitive events and a large suppressive effect detected for similar activities outside of a competitive environment (SMD: −1.28, 95% CI: −1.61, −0.96) (p = 0.02).
Conclusion: Evidence suggests lymphocyte proliferation is suppressed following acute bouts of exercise, with exercise lasting longer than one hour having a greater magnitude of effect regardless of exercise intensity. Variations in observed effect sizes across intensity, duration, and competitive environment further highlight our need to acknowledge the impact of study designs in advancing our understanding of exercise immunology.

1. Introduction

Exercise induced alterations of specific immune cell populations and hormonal concentrations are some of, if not the most, commonly reported effects in the area of exercise immunology. The most replicated of these effects is the rapid mobilization of leukocytes and lymphocytes into peripheral circulation during exercise (Dhabhar et al., 1996, 1995, 1994; Fragala et al., 2011). Disruptions in leukocyte trafficking are thought to result from events including increased shear forces and hydrostatic pressure from surges in cardiac output (Foster et al., 1986; Shephard, 2003), additional lymphatic fluid pushed out by forceful muscle contractions (Foster et al., 1986) and as a response to increased concentrations of catecholamines (Benschop et al., 1996) and glucocorticoids (Dhabhar et al., 1996) in the blood.

Exercise associated lymphocytosis and lymphocytopenia have been reported on extensively (Gleeson, 2007; Nielsen, 2003; Nieman, 1997). The characteristic exercise response of blood leukocyte counts involves an initial increase as cells are mobilized from marginal pools and other organs followed by a decrease in total counts as those same cells move into areas like the skin, mucosa, and lymph nodes. Observations of this phenomenon coupled with epidemiological data have produced ideas like the "Open Window" hypothesis whereby individuals are thought to have decreased immune function following intense physical activity (Nieman, 1997; Pedersen and Ullum, 1994).

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Alterations in cell trafficking, however, contribute little information about the overall immunocompetence of an individual. Immunocompetence is better assessed by investigating the ability of lymphocytes to proliferate in response to cognate antigen. Upon encountering cognate antigen, a lymphocyte undergoes clonal expansion to increase the number of lymphocytes present with identical antigen specificity and defend the host from the threat (Kindt et al., 2007). This proliferative capacity of lymphocytes is a crucial feature of the adaptive immune response (Janeway et al., 2001). A failure to proliferate in response to foreign antigen is indicative of impaired immune function, and the host's ability to respond to an immunological challenge can be substantially diminished in these circumstances.

Lymphocyte proliferation can also be induced by factors other than cognate antigen. Plant lectins are carbohydrate-binding glycoproteins that agglutinate cells (Moreira et al., 1991). When added to a cell culture, lectins act as a mitogen to induce lymphocyte proliferation via cross-linking of glycoproteins on the cell surface (Chilson et al., 1984). For decades a simple assay for the ability of human T cells to proliferate in response to the T cell mitogen phytohaemagglutinin (PHA) has been used to evaluate immunocompetence. PHA assays have been routinely used to monitor immune function in potentially immunosuppressed patients including transplant recipients, HIV positive individuals, and others at risk for immunosuppression. Because lymphocytes play a pivotal role in the immune response, it is important that investigations of susceptibility to infection following exercise be conducted within the context of proliferative capacity. For this reason, we used measures of lymphocyte proliferation as a functional assessment of immunocompetence following exercise.

As we have noted above, proliferation assays are a mainstay of clinical diagnostics yet they represent a small proportion of the literature comprising the field of exercise immunology (Nielsen, 2003; Nielsen and Pedersen, 1997). Non-systematic review articles of lymphocyte proliferation report inconsistent findings regarding whether immune function is enhanced or suppressed by exercise (Gleeson, 2007; Nielsen, 2003; Nieman, 1997; Nielsen and Pedersen, 1997). We are not aware of any systematic reviews of lymphocyte proliferation following acute bouts of exercise. Therefore, the purpose of this meta-analysis was to provide a quantitative review of the effects of acute exercise bouts on lymphocyte proliferation. To do this, we conducted a comprehensive review of published studies involving acute (minutes to hours) bouts of exercise and outcomes of lymphocyte proliferation in healthy individuals. We hypothesized that lymphocyte, specifically T cell, proliferative ability would be depressed immediately post exercise with higher intensity exercise having a greater suppressive effect.

2. Materials and methods

Studies were identified by searching the following electronic databases: PubMed, Google Scholar and Web of Science. Subject specific search terms utilized either individually or jointly were: "exercise", "acute", "aerobic", "resistance training", "immune function", "proliferation", "lymphocyte." We included studies that were published up to March 2016. No registered protocol exists for this meta-analysis. We adhered to the PRISMA Guidelines for manuscript preparation. A flow chart of studies evaluated and excluded during the review process is shown in Fig. 1. One hundred seventeen publications were identified as possibly relevant and the reference lists of these articles were forward and backward searched for pertinent articles not identified in the initial electronic searches. Of the 117 articles reviewed in full, 81 either did not have a measure of lymphocyte proliferation or did not utilize an acute training protocol and were excluded from analysis. Authors of papers that did not include sufficient data for calculation of standardized mean differences (SMD) were contacted to request further information. Twenty-four of the retrieved articles were determined to be suitable for inclusion (Bacurau et al., 2002; Bassit et al., 2000; Ceddia et al., 1999; Dohi et al., 2001; Field et al., 1991; Frisina et al., 1994; Fry et al., 1992; Gray et al., 1992; Henson et al., 1999; Henson et al., 1998, 2004; Krzywkowski et al., 2001; Nehlsen-Cannarella et al., 1991; Nieman et al., 1997, 2000, 2006, 1994; Smith et al., 1993; Tossige-Gomes et al., 1992a,b; Vider et al., 2001; Koch et al., 2001; LaVoy et al., 2015) (Table 1).

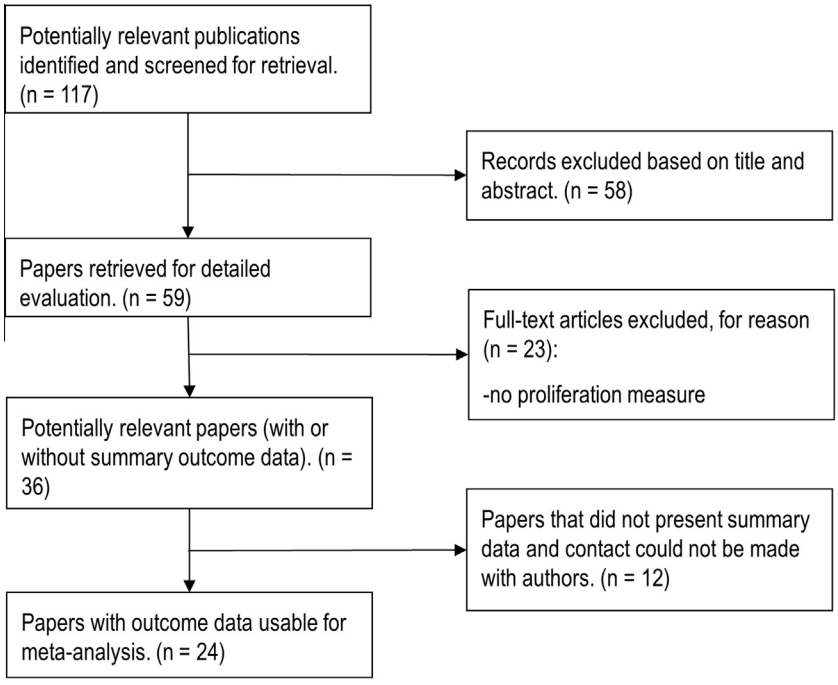

Fig. 1. Flow chart of selection process of reviewed studies.

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