Immune Responses to Exercise in Children: A Brief Review

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Despite significant advances in exercise immunology over the last two decades, our understanding of immune responses to exercise in children remains sparse. This review outlines and discusses commonly reported aspects of the immune response to exercise, with emphasis on child–adult differences. Compared with adults, children generally experience smaller perturbations to the immune system (e.g., NK cells and IL-6) in response to exercise of the same duration and intensity. Children also demonstrate a faster recovery of immune components (e.g., neutrophil and IL-6) after exercise. The health and clinical relevance of exercise-induced changes in a child’s immune system remain to be determined.

Introduction

A detailed characterization and understanding of immune responses to exercise in humans has several important health implications. In addition to its defining role in protection against pathogens, the immune system is intimately linked to health disorders such as obesity, Type 2 diabetes mellitus (T2DM), and cardiovascular disease. In today’s society, physical inactivity among children and adolescents is a serious problem and is strongly associated with high rates of obesity (61) and adult-type health problems such as T2DM (41,48) and vascular dysfunction (42,65). To what extent the early onset of these adult-type disorders during childhood is linked to development of the immune system is unknown. Moreover, it is unclear whether regular exercise during childhood is protective against infection and illness, as has been suggested for adults (24). Given the well-documented age-related changes in the immune system throughout childhood (2,3,14,15), it is reasonable to expect similar growth-related changes in the immune response to exercise during childhood. Despite the expanding field of exercise immunology, however, study participants have been mostly young adult males, and investigations devoted to children remain sparse. The purpose of this article is to briefly review commonly reported aspects in the exercise immunology literature as derived from the pediatric population. In the interest of space, only responses to acute bouts of exercise are included. Where possible, the findings are discussed in light of child–adult differences, and areas for future work are proposed.

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Historical Perspective

Exercise immunology as a scientific discipline has its roots in data collected more than 100 years ago. In their 1935 review of the literature, Garrey and Bryan (22), for example, discussed an 1893 publication by Schulz who reported that muscular activity caused an increase in the leukocyte count. Indeed, a substantial amount of literature reviewed in the 1930s (22, 29, 55) described variations in leukocyte counts in response to physical activity and training. Some years later, a renaissance of this discipline was catalyzed by anecdotal evidence from athletes and coaches indicating that intense training resulted in an increased frequency of illness and infection. In a brief review article published in 1984 (47), Dr. Harvey Simon challenged the notion that regular exercise was protective against infection, thus providing strong incentive to further clarify this issue. Consequently, the early 1990s experienced an exponential increase in the frequency of exercise immunology publications (36). From a historical perspective, and to the best of this author’s knowledge, the earliest published data reporting a leukocytosis of physical activity in young children appear to be those of Christensen and Rothstein (9) published in 1979. In a way these authors were the first to determine the effect of exercise intensity on immune changes by comparing the total leukocytosis and neutrophilia in newborn babies in response to three conditions: circumcision, chest physical therapy, and heel puncture. The most robust increases in circulating total leukocyte (∼46%) and neutrophil (∼48%) counts were observed after the “most violent physical activity” (i.e., circumcision), with a full recovery of cell counts to resting levels by 60 min after the procedure (9). Later, in 1987, the same authors documented exercise-induced changes in the blood concentrations of leukocyte populations in teenage athletes (8). Since 1996, however, the number of publications devoted to children and adolescents remains relatively low (Figure 1).

Responses To Acute Exercise

Salivary Immunoglobulin A (sIgA)

IgA determined in saliva is an important marker of mucosal immunity and, given its anatomical location, sIgA is a first-line defense against pathogens. In the adult literature, a link between depressed sIgA levels and risk of upper respiratory tract infection (URTI) among athletes has been demonstrated (23). In boys, acute bouts of basketball exercise were associated with slight but significant increases in sIgA after practice and game situations in pre- and postpubescent boys (56). Changes in total protein, however, were not corrected for in this study. In pediatric studies in which sIgA concentrations were expressed relative to total protein in the sample, young girls (20) and older adolescent girls and boys (35) demonstrated a significant reduction after exercise similar to what has been reported in adults. Exercise intensity might also be an important determinant of the sIgA response in children inasmuch as sIgA levels were depressed after high-intensity (75% VO₂max) exercise, but enhanced after moderate-intensity (50% VO₂max) exercise (16). To date, however, no strong evidence is available to support child–adult differences in the sIgA response to acute exercise. Clearly, more work is required to investigate acute
changes in mucosal immunity in response to exercise in children and adolescents and its association with long-term risk of URTI.

**Natural Killer (NK) Cells**

NK cells demonstrate potent cytotoxicity (11) and play important innate roles in antiviral (4) and anticancer (7) defenses. They are generally characterized as lymphocytes with a CD3<sup>-</sup>CD16<sup>+</sup>CD56<sup>+</sup> immunophenotype and are the cell type most responsive to exercise (37) because of a high density of β-adrenergic receptors on the cell surface (25). Several pediatric studies have reported changes in NK cells in response to various durations and intensities of exercise (5,6,17,32,34,35,39,46,58,59,64), with the magnitude of change ranging from −20% (35) to +425% (6) above pre-exercise values. It is also noteworthy that, similar to the adult literature (45), the magnitude of increase in NK cells after 60 min of constant load exercise is no greater than after 30 min in children and adolescents (59), suggesting that cellular mobilization is relatively rapid.

With regard to child–adult differences, a study by Shore and Shephard (46) was the first to compare NK cell responses between children and adults. Unfortunately, the two groups of participants apparently completed exercises of different duration and different intensities, and different cell surface markers were used to enumerate NK cells in each group. Notwithstanding these methodological limitations, the children’s response after 30 min of exercise was ~40% less than that of the adults after the same amount of exercise time (46). Work from our laboratory clearly demonstrated child–adult differences in the NK cell response to standardized, high-intensity exercise (58). It is interesting to note that the magnitude of the NK cell

![Figure 1 — Publication frequency of pediatric studies describing immune responses to an acute bout of exercise. Data are derived from a PubMed search, reference lists of relevant articles, and the author’s personal library.](image-url)
response after 60 min of cycling at 70% VO₂max in 9- and 10-year-old boys was also ~40% less than in 20- to 25-year-old men (58). The mechanisms for this age difference are unknown but might be related to an increase in β-adrenergic receptor density on NK cells with advancing chronological age (21,43). Alternatively, the catecholamine response to exercise might also be less in children than in adults, but there is no strong evidence to support this possibility. The immunological significance of transient increases in NK cells in response to acute bouts of exercise is unclear. Given the antiviral (4) and anticancer (7) functions of NK cells, regularly active children might therefore improve their defenses against certain infections and malignancy. The apparent child–adult difference in NK cell sensitivity to physiological stress, however, also suggests that the signals that initiate NK cell recruitment are smaller in children, and that any protection against infection and malignancy offered by exercise might be less during childhood than in adulthood.

**Neutrophils**

Neutrophils are another important component of the innate immune system. Few pediatric exercise studies, however, have reported the effects of exercise on neutrophil function. Twenty-four hours after 20 min of treadmill running, *in vitro* neutrophil chemotaxis was reduced in untrained prepubertal girls (62). The magnitude of this reduction in function, however, was ~64% less than the magnitude of reduction reported by the same research group for untrained women performing similar exercise (63). Thus, there is some evidence that certain aspects of neutrophil function are maintained better in children than in adults after an acute bout of aerobic exercise. Whether this apparent age difference in immune function translates into improved protection for younger individuals against infection during a training season, for example, remains to be determined.

A classical immune-related response to high-intensity exercise apparent in the adult literature is a sustained neutrophilia during the recovery period (i.e., 1 to 3 hrs after termination of exercise; 37). Studies conducted with children have been reluctant to include recovery time points to investigate the kinetics of exercise-induced neutrophil changes. Although Shore and Shephard (46) did report recovery of neutrophil counts to be faster in children, interpretation of this finding is restricted by the methodological limitations previously described. In our work comparing boys and men (58), the recovery of neutrophils 60 min after high intensity exercise was clearly faster in the boys, thus confirming the work of Shore and Shephard (46). Postexercise neutrophil recovery is also faster in children than in adolescents (59). Together, these studies provide compelling evidence that young children might be resistant to a major inflammatory-related response to acute exercise. Whether the above differences in postexercise neutrophilia are the result of age-related differences in muscle damage is unknown, but previous studies (1,28,49) have shown that markers of muscle damage after eccentrically biased exercise are lower in children than in adults.

**Interleukin-6 (IL-6)**

In recent years, IL-6 responses to exercise have received considerable interest in the adult literature. Following the observation that IL-6 can be released from skeletal muscle during contraction (54), the role of this cytokine in metabolic
adjustments to exercise has been extensively studied (19). In addition, IL-6 is considered an anti-inflammatory cytokine, and its release from muscle might reflect the anti-inflammatory properties of exercise (40). In children and adolescents, most studies (33,34,35,38,44) have investigated the impact of exercise on circulating IL-6 levels under field-type conditions. The IL-6 response in children cycling at a defined work-rate (60), however, was 50% lower than what had previously been reported for adults (10,51) under similar exercise conditions (Figure 2), and direct comparisons of boys and men confirm a child–adult difference (58).

In metabolic terms, there are a number of possibilities that might help explain this age-related finding. First, a smaller total muscle mass performing work might contribute to smaller amounts of IL-6 released during contraction. Second, clearance of IL-6 by the hepatosplanchnic bed, which occurs in adults (18), might be greater in children, thus lowering the peripheral balance. Third, the signaling for IL-6 production within skeletal muscle might be less in children than in adults. In this regard, IL-6 is thought to be released from muscle during exercise as a potential regulatory hormone to increase liver gluconeogenesis, for example, when muscle glycogen content is low (52). We (57) and others (27,30) have clearly demonstrated that children preferentially oxidize fat rather than carbohydrate as a source of endogenous fuel during exercise. Thus, if children’s muscle glycogen levels are not lowered during exercise, the intracellular signaling for IL-6 release might also be reduced. In immunological terms, the lower IL-6 response during and following exercise (58) is consistent with a lower inflammatory response in younger children.

**Tumor Necrosis Factor-α (TNF-α)**

TNF-α is a prototypical proinflammatory cytokine involved in inflammatory reactions and implicated in insulin resistance (12) and reduced protein synthesis.

![Figure 2](image-url)

**Figure 2** — IL-6 response to acute exercise in children and adults. Values are means of the change (Δ) in plasma IL-6 levels from pre- to postexercise. Data taken from references (10,51,60).
Exercise can increase systemic levels of this cytokine, but generally only during long duration exercise tasks such as marathon running (31). In children, the magnitude of exercise-induced changes in TNF-α concentration is generally quite low (33,44,58,60) and might even be negative (34). Recently, it was demonstrated that IL-6 produced during exercise might function as an antagonist to TNF-α (50). Indeed, TNF-α is expressed in, but not released from, skeletal muscle during contraction (53). Therefore, the ratio of IL-6 to TNF-α might be a useful marker of the inflammatory environment during and after exercise.

Figure 3 highlights this “anti-inflammatory ratio” in 9- and 10-yr-old boys and 20- to 25-yr-old men at rest, after 60 min of exercise, and again after 60 min of recovery (Timmons and Bar-Or, unpublished observations). These findings show that a) the anti-inflammatory ratio at rest is higher in boys than in men, and b) the anti-inflammatory ratio increases over time in the men but not in the boys. The consistently higher anti-inflammatory ratio in the boys is further support for the notion that children are relatively resistant to a major inflammatory insult during and after strenuous exercise. Given the antagonism between inflammation and growth (13), this “inflammatory protection” would allow for the anabolic effects of exercise to take priority, thus reflecting an overall positive response from a growth perspective. To this end, we have recently reported that the growth-promoting cytokine IL-8 increases during recovery from strenuous exercise in children and adolescents (59).

Summary and Future Areas for Research

In this article we have briefly reviewed and discussed commonly reported aspects of immune responses to acute bouts of exercise as derived from the pediatric

![Figure 3](image.png)

**Figure 3** — Anti-inflammatory ratio in response to acute exercise in boys and men. Data are derived from reference number 58. Values are means ± SEM. *Significantly different than rest within men, p < .05. Data were analyzed with a 2-way ANOVA (Group × Time) and Tukey’s post-hoc test for significant differences.
population. In summary, children tend to be resistant to major exercise-induced perturbations to the immune system. This has been characterized by smaller NK cell and IL-6 responses to exercise. Similar to other physiological functions (e.g., heart rate), children’s immune systems tend to recover more quickly than those of adults. Although the number of exercise immunology studies devoted to children has increased in recent years, there is still an immense need for further evaluation. Indeed, the future is wide open for research in pediatric exercise immunology and could take several avenues. Studies are required to determine whether puberty influences the effects of exercise on immune function during childhood. A clearer understanding of the relationship between physical activity level and immune health (i.e., resistance to infection) among children and adolescents is also of great interest. The ability of exercise to mobilize cytokines (e.g., IL-8) with growth-promoting properties might be an essential link among regular exercise, the immune system, and tissue adaptation in growing children; this also represents a fruitful area for future study.

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References


