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Exercise, stress, and inflammation in the growing child: from the bench to the playground

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Purpose of review

It is becoming increasingly clear that physical activity in children plays a critical role in growth and development, therapy for certain chronic diseases and disabilities, and in the pediatric origins of a variety of bone, metabolic, and cardiovascular diseases. New mechanistic insights have created the opportunity for a phase shift in understanding of the links between exercise and health in the context of the growing child.

Recent findings

Exercise even in healthy children profoundly alters stress, immune, and inflammatory mediators including peripheral blood mononuclear cells and circulating pro- and anti-inflammatory cytokines (like interleukin-6). Moreover, exercise even in healthy adults stimulates the production of reactive oxygen species (ROS) and mediators that attenuate them. Oxidative stress, in turn, alters growth and stress mediators. Both ROS and stress/inflammatory factors interact with powerful growth mediators like growth hormone and insulinlike growth factor-I. These findings suggest specific ways in which the balance between pro- and anti-inflammatory, catabolic, and anabolic factors associated with exercise can influence health and growth in children.

Summary

To address the current epidemic of physical inactivity and obesity in children and to optimize the therapeutic effects of exercise in children with disease and disability will require real changes in environments (*eg*, schools and playgrounds); innovative approaches to rehabilitation of children with chronic disease and disability; and enlightened training of child health professionals. Identifying novel exercise mechanisms involving stress, inflammation, and growth factors will help guide these efforts.

Keywords

physical activity, stress, inflammation, innate immunity, oxidative stress, growth hormone, insulinlike growth factor

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Abbreviations

CATCH	Child and Adolescent Trial for Cardiovascular Health
GH	growth hormone
IGF-I	insulinlike growth factor-I
IL-6	interleukin-6
ROS	reactive oxygen species

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Introduction

Although the idea that "exercise is good for children" seems axiomatic, translating this vague notion into specific, scientifically based guidelines that actually influence health has proved to be difficult. Never before has the need for such guidelines been so great. We find ourselves in the midst of an emerging epidemic of pediatric obesity, type 2 diabetes, and the metabolic syndrome [1–3,4••], all, in large measure, ominous consequences of unprecedented levels of physical inactivity in children [5•]. At the same time, therapeutic advances have created an increasing number of childhood survivors of premature birth, congenital heart disease, lung disease, burn injury, and cancer. For these children, physical activity is beneficial [6–10], but only if the "exercise dose" does not exacerbate underlying inflammatory, metabolic, or physiologic abnormalities. Identifying optimal levels of exercise must be based on a better understanding of the mechanisms that link exercise with health and disease in the growing child.

It has become abundantly clear that the biologic mechanisms linking exercise to health in children are multifactorial. Attempting to identify the clinically relevant mechanisms is challenging, but a set of related, recent discoveries and technological advances has created the opportunity for a "phase shift" in our understanding of this problem, and to form specific hypotheses about novel mechanisms that link exercise and health in the context of the growing child. These exciting observations are:

- The translation of physical activity to health effects rests on the interaction of seemingly dichotomous anabolic and catabolic mediators and cell signaling

pathways including growth factors like insulinlike growth factor-I (IGF-I) and proinflammatory cytokines like interleukin-6 (IL-6).

- Exercise even in healthy children profoundly alters stress, immune, and inflammatory mediators including peripheral blood mononuclear cells and circulating pro- and anti-inflammatory cytokines. These mediators are now known to play important roles in a variety of pediatric and adult diseases.
- Exercise even in healthy adults stimulates the production of reactive oxygen species (ROS) and mediators that attenuate them. Oxidative stress alters growth and stress mediators, and the balance between ROS and their mitigating factors is now known to play a key role in the development of metabolic syndrome, type 2 diabetes, hypertension, and cardiovascular disease.
- There exist critical periods of growth and development during which the effect of exercise on growth mediators and stress/inflammatory factors would have long-term health effects. Such periods occur early in life (particularly in premature babies) and in the pubertal transition. The magnitude and quality of these effects are profoundly altered by gender.

The purpose of this review is to highlight how these insights can be used to form new research directions and clinical applications focused on health effects of exercise in children.

The role of physical activity in growth and development

It is increasingly recognized that physical activity in children is not merely play; rather, it is an essential component of healthy growth and development. We now recognize that the absence of sufficient exercise during childhood leads to inadequate bone mineralization and markedly greater risk for osteoporosis later in life [11••]. Levels of physical activity markedly affect body composition, and sedentary lifestyles in children are a major cause of the current epidemic of childhood obesity and its accompanying comorbidities [12]. As levels of physical activity progressively decline in children [13•], it is reasonable to speculate that sarcopenia, the debilitating loss of muscle mass observed in the elderly [14], will ultimately be found to have roots in inadequate muscle development during childhood, a sad echo of our current understanding of osteoporosis.

Levels of physical activity during childhood can influence growth and development of muscle, fat, and bone. Recent data suggest that exercise alteration of the growth hormone→insulinlike growth factor-I axis (GH→IGF-I), a system of hormones and mediators that modulates growth in many tissues, may be involved. Basal levels of IGF-I are correlated with muscle mass and fitness in prepubertal children, adolescents, and adults [15–17] .

There is increasing evidence in both children and adults, however, that even relatively brief periods of aerobic exercise training (5 weeks) can lead to reductions, rather than expected increases, in basal, resting levels of IGF-I even when muscle mass increases [16,18,19]. Thus, training in children initially seems to create a state of GH resistance (*ie*, reduced GH binding protein and IGF-I), more often associated with catabolic rather than anabolic hormonal activity [20].

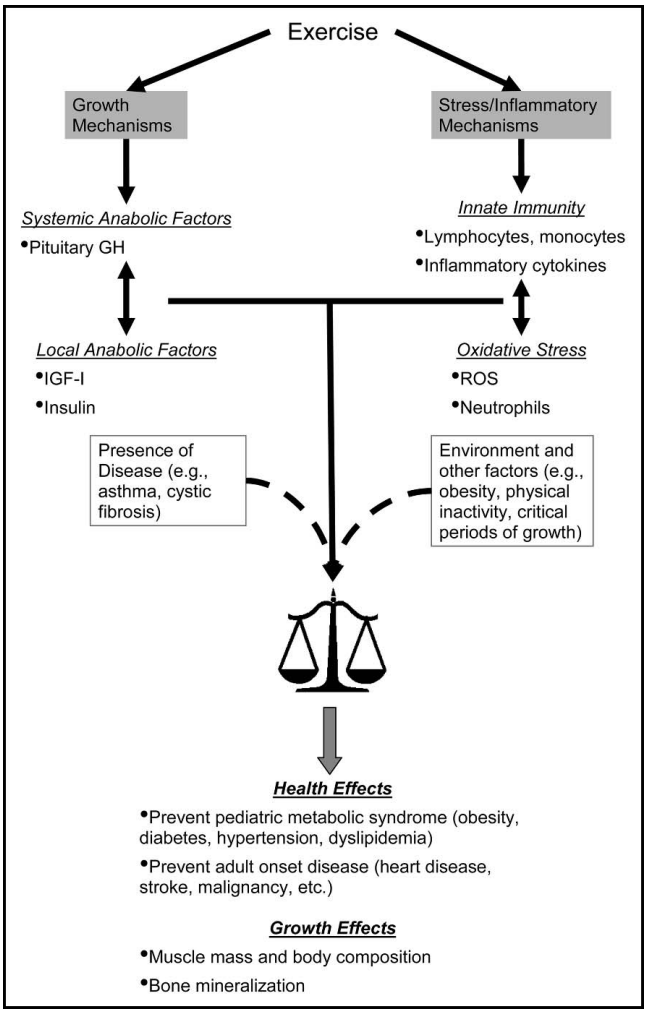
This paradox led us to the idea that single bouts of exercise in children could, as in adults [21,22], stimulate proinflammatory cytokines known to directly inhibit anabolic activity of the GH→IGF-1 axis (*ie*, IL-6, IL-1β, and tumor necrosis factor-α). In adults, Ostrowski *et al.* [23] noted that strenuous exercise stimulated proinflammatory mediators, but simultaneously, "…cytokine inhibitors and anti-inflammatory cytokines restrict the magnitude and duration of the inflammatory response to exercise." The cumulative effect of these individual exercise perturbations would be to lower basal levels of IGF-I, because inflammatory cytokines like TNF-α and IL-6 are now known to inhibit both GH and IGF-I [24–33]. As an extreme example of this paradigm, in children with systemic inflammatory diseases [34–36] chronically elevated IL-6 leads to reduced basal IGF-I and impaired somatic growth.

The exercise response paradox in children: relation to disease and prevention

There is mounting evidence that physical activity plays its most substantial role in diseases that have in common altered stress, inflammation, and leukocyte function, such as asthma and arthritis in children and atherosclerosis in adults [37,38•,39]. Exercise can lead to a substantial perturbation of cellular homeostasis including a profound metabolic acidosis, markedly altered oxygen and substrate flux in tissue and mitochondria, and, on occasion, frank tissue injury. Not surprisingly, exercise results in what appears to be a "danger" type activation of innate immune responses [40–42] that involves increased levels of circulating cytokines and leukocytes typically associated with catabolic, rather than anabolic, states [28,43]. In contrast, the salient features of the healthy adaptation to repeated exercise are both anti-inflammatory and anabolic, consisting of increased muscle mass, angio- and arteriogenesis, increased bone strength, and the formation of new mitochondria.

Thus, the paradigm of a paradoxical pro- and anti-inflammatory, anabolic–catabolic, response to exercise provides new insights into the mechanisms that link physical activity with growth and health in children (Fig. 1). There are also increasing data supporting the idea that there exist "critical periods" of development during

Figure 1. Relation of exercise to health and growth in children.



GH, growth hormone; IGF-I, insulinlike growth factor-I.

which a variety of stimuli can alter the overall programming of developmental processes [44,45].

Intriguingly, the impact of physical activity on these critical periods need not be limited to the ambulating child. A number of studies now show that assisted exercise in preterm infants can increase body weight and improve bone strength (Fig. 2). "Assisted exercise" in this context is defined as systematic manipulation of the upper and lower extremity joints consisting of flexion and extension with gentle compression and passive range of motion movements [46]. This observation corroborates work that started several decades ago in both human and animal models demonstrating that certain types of stimuli very early in life can beneficially alter growth and development even through maturity [47,48]. Because weight gain is so critical a determinant of healthy outcomes in the neonatal intensive care unit, interventions that improve body mass accrual could substantially reduce length of stay and influence standard of care.

We examined the correlation between IL-6 and IGF-I in healthy adolescents and preterm infants. The preliminary results of this study are shown in Figure 3. Remarkably, despite the large (expected) difference in circulating IGF-I between the preterm infants and the adolescents, there appears to be an inverse relation between IL-6 and IGF-I in these two seemingly diverse populations. Clearly, further studies of this relation in a larger group of infants need to be done.

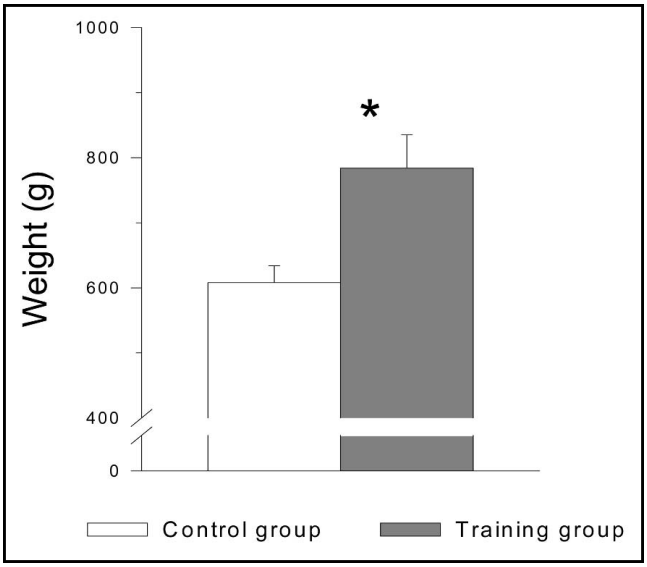
The human immune system is remarkably adaptable, and the molecular processes that enable to the immune system to distinguish self from nonself typify the concept of immunologic "memory." Recent epidemiologic observations about asthma and atopy suggest that critical periods exist for the development of other aspects of the immune system as well. Although as yet unproven, the "hygiene hypothesis" has been proposed recently to explain the fact that the incidence of asthma and atopy is higher in children who were *not* exposed early in life to multiple viruses, helminthes, and bacteria [49•]. The lack of exposure may impair the natural development of putative lymphocytes that modulate T-helper type 2 functions and, therefore, leads to an exaggerated T-helper 2 immune cell response, and, consequently, an increase in asthma and atopy. As noted, physical activity can stimulate a variety of immune-related processes leading to the general hypothesis that physical inactivity early in life may contribute to the development of asthma in children. Indeed, obesity and asthma are known to be linked in children, and each is related to physical inactivity [50]. Moreover, the compelling role of immune, inflammatory, and oxidative mechanisms in the development of the components of the metabolic syndrome and the impact of physical activity on these factors further support the focus of the proposed studies.

Exercise and oxidative stress

Closely tied to the innate immune activation that occurs with exercise is the effect of exercise on oxidative stress. Oxidative stress is an imbalance between production of ROS—a normal part of physiologic metabolic processes—and antioxidant defenses. By attacking, denaturing, and modifying structural and functional molecules, ROS cause cytotoxicity, tissue injury, and dysfunction and provoke an inflammatory response. These molecular effects contribute to the pathogenesis of tissue complications of numerous human diseases such as atherosclerosis, infection, inflammation, cancer, degenerative disorders, metabolic disease (obesity, metabolic syndrome, diabetes), radiation injury, ischemia-reperfusion, and hypertension [51–53,54••].

Mitochondrial O_2 flow increases up to 100-fold during intense exercise, and up to 4% is diverted to form ROS [55], rendering this the primary source of ROS during exercise. We now know that metabolic and physiologic

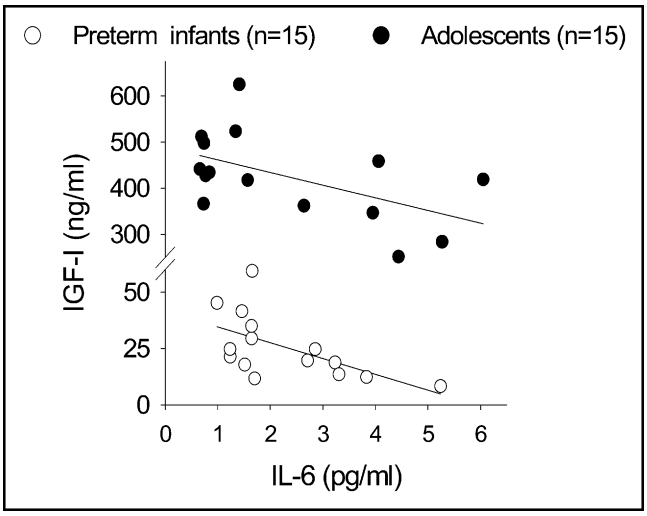
Figure 2. The effect of 4 weeks of assisted exercise on weight gain in preterm infants.



Data from Nemet *et al.*
*P < 0.05

effects of exercise are indeed different in children compared with adults in a manner that could influence the exercise-specific component of the exercise stress response. Studies from our and other laboratories demonstrate a greater oxygen cost of exercise in children [56]. Moreover, ^{31}P-magnetic resonance spectroscopy studies have shown that the changes in intramuscular pH and the ratio of inorganic phosphate to phosphocreatine are smaller during exercise in children [57]. Collectively, these observations indicate that the flow of oxygen to working muscles is greater in children and, consequently, end-organ oxidative stress from exercise may differ.

Figure 3. Correlation between circulating level of interleukin-6 (IL-6) and insulinlike growth factor-I (IGF-I) in healthy preterm infants and adolescents.



Despite the large differences in IGF-I, significant inverse relationships were found in both healthy adolescents ($r = -0.543$, $P < 0.036$) and in the preterm infants ($r = -0.591$, $P < 0.02$). The impact of exercise on the relationship between growth and inflammatory factors may be an important mechanism in the overall impact of physical activity in the pediatric age range.

Among other extramitochondrial sources [58] of ROS (xanthine oxidase pathway [59,60•], catecholamine and prostanoid metabolism), the contribution by circulating neutrophils is quantitatively the most important. Circulating neutrophils contain large amounts of oxidative enzymes (indeed this oxidative capacity is the base of neutrophil-mediated defense against bacteria and other offensive agents) and migrate during exercise from peripheral sites (*eg*, the lung) to the central circulation and to active skeletal muscles. Elevated circulating levels of neutrophil-derived oxidative enzymes myeloperoxidase and elastase [61–65] and greater generation of superoxide by neutrophils are well documented in adults [66]. Moreover, neutrophilia persists for hours after exercise, when mitochondrial O_2 flow has returned to basal levels, potentially rendering neutrophil-derived ROS the main source of oxidative stress in the postexercise state [64,67]. Confirming data from adults, we have observed robust increases in circulating neutrophils in healthy and obese children during a variety of exercise formats (Fig. 4). However, the effect of exercise and physical activity on oxidative stress in children remains largely uninvestigated.

Exercise and the pediatric origin of adult disease

Closely tied to the concept of critical periods of growth and development, exercise-associated inflammatory responses and exercise-associated oxidative stress is the theme of pediatric origins of adult disease. A number of salient studies have clearly demonstrated this phenomenon. With regards to cardiovascular disease and the potential protective effects of childhood exercise, the following observations are particularly important:

> *"The existing evidence indicates that primary prevention of atherosclerotic disease should begin in childhood."*—American Heart Association Scientific Statement: Guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease Beginning in Childhood [68••]

> *"…immunologic-inflammatory cells are present in the earliest stages of atherogenesis in 15–34-year-old subjects, arguing in favor of an initiating role of the immune system in atherosclerosis development."* [69]

> *"Our findings suggest that IGF-I may be involved in the pathogenesis of ischemic heart disease."* [70]

"Inflammatory cytokines are systemically increased following relatively brief exercise in healthy children. This increase may alter critical anabolic agents such as IGF-I and its binding proteins." [26]

In addition, new data are emerging supporting the notion that adult pulmonary, nutritional (*eg*, obesity), metabolic, and bone diseases are all highly correlated with pathologic metabolic events that occur early in life [11••,71–73].

Exercise, stress/inflammatory responses, and children with chronic disease

The role of exercise as therapy in children with a variety of chronic diseases and disabilities is becoming increasingly recognized. However, the clinician attempting to prescribe a program of exercise training for children and adolescents with chronic diseases faces a dilemma. For example, in cystic fibrosis, a debilitating congenital pulmonary disease, exercise may promote health in part by stimulating growth factors and tissue anabolism (enhanced bone mineralization, increased muscle hypertrophy, mitochondrial density and capillarization, and increased insulin sensitivity [74,75]). In contrast, it is now known that the same process of exercise, if sufficiently intense, can stimulate inflammatory cytokines and lead to a catabolic state [18,76–78]. Finding the optimal level of physical activity in children and adolescents with cystic fibrosis is difficult because the underlying disease is associated with increased basal energy expenditure [79,80], hypoxemia, malnutrition, and inflammation, all of which promote tissue catabolism even at rest. The cystic fibrosis dilemma typifies the problem that exists in implementing exercise therapy for children with a variety of inflammatory/catabolic conditions like pediatric arthritis, severe burns, and cancer in which there is increasing interest in developing truly beneficial and safe exercise interventions [81,82,83•].

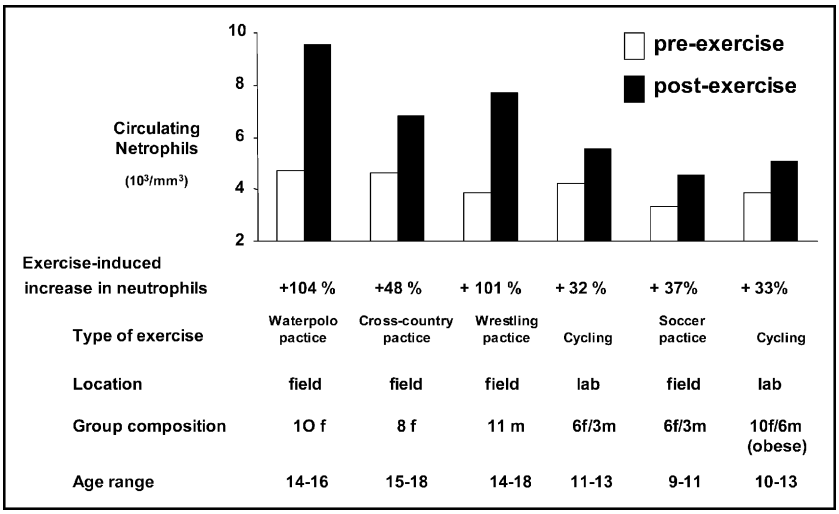
Conclusion

Translating scientific discoveries into successful applications of physical activity in children has proved to be a daunting task. Although there is abundant evidence that children (and infants) can be "trained" in controlled, supervised conditions, efforts to change the exercise environment for children in the real world have not been as successful. A variety of approaches have been used to increase levels of physical activity in children and adolescents under field conditions in schools [84,85], but only modest increases, if any, in traditional measures of cardiopulmonary performance have generally been observed. Recently, Kelder *et al.* [86] noted that major barriers, such as insufficient training and lower importance of physical education compared with other academic areas, frustrate attempts to maintain school physical activity goals derived from one of the largest studies ever undertaken to improve physical activity in schools, the Child and Adolescent Trial for Cardiovascular Health (CATCH).

We believe that sufficient impetus to alter policy that can change the environment for exercise and physical activity in schools and communities and as a rehabilitative tool for children with chronic diseases must ultimately rest on sound scientific and clinical findings. A modern understanding of what constitutes "physical fitness" in the context of the growing child and new insights into growth, stress, and inflammatory mechanisms may constitute the first steps toward achieving these necessary goals.

Figure 4. Circulating levels of neutrophils in different groups of children before (*white bars*) and at the end of (*black bars*) varied exercise protocols, in a laboratory setting as well as in the field during regular sports practice.

Data from [24] and preliminary studies.



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