Can Exercise Training Improve Immune Function in the Aged?

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ABSTRACT: Many strategies have been used to improve immune function in the aged. Unfortunately, many of these interventions have been disappointing, impractical, costly to develop and administer, or accompanied by adverse side effects. Aside from dietary manipulation (caloric restriction without malnutrition or antioxidant supplementation), research involving behavioral preventative or restorative therapies has been lacking. Moderate exercise training has been shown to elicit beneficial outcomes in both the prevention and rehabilitation of many diseases of the elderly. It has been hypothesized that moderate levels of exercise improves, whereas strenuous exercise or overtraining suppresses, various immune function measures. Three general approaches have been implemented to study the impact of exercise on immune functioning in the elderly: (1) cross-sectional studies, (2) longitudinal studies, and (3) animal studies. In general, cross-sectional studies examining highly active elderly have demonstrated improved in vitro T cell responses to polyclonal stimulation when compared to sedentary elderly. This is corroborated by several animal studies that have shown improved splenic T cell responses in vitro. Unfortunately, human prospective studies have failed to demonstrate consistent improvements in various measures of immune function in older adults. However, it should be cautioned that these studies have included small samples followed over a short duration, measuring a limited number of in vitro immune parameters, with some failing to account for potential confounding influences. Although such findings have the potential to be of substantial public health importance, very few systematic studies have been conducted.

KEYWORDS: immune function; exercise; training; aging; elderly; physical activity

INTRODUCTION

The enormous healthcare costs associated with supporting a rapidly growing aged population and the overall concern for the well-being of older persons makes research on aging of vital interest to everyone. Several measures of immunity are altered with aging,1 and this is believed to be a contributing factor in the increased incidence of respiratory, neoplastic, and arthritic diseases2,3 and higher mortality rates...
from bacterial and viral infections. The realization of dysregulated immune function and increased disease incidence in the elderly has been the impetus for interventions designed to improve immune function in the elderly. Unfortunately, pharmacologic/hormonal, genetic, and tissue grafting interventions have been either disappointing, impractical, costly to develop and administer, or accompanied by adverse side effects. For example, despite early enthusiasm for dehydroepiandrosterone (DHEA) treatment in retarding the effects of aging on the immune system, more recent studies have not found it to be a panacea for immunosenescence. Two nutritional paradigms have resulted in improved T cell–mediated immune function in elderly subjects, suggesting that the aged immune system is amenable to change. It has long been known that caloric restriction without malnutrition in rodents has been found to improve T cell functions, including mitogenic proliferation and interleukin (IL)-2 production. Likewise, dietary supplementation with vitamin E for four months in elderly humans can improve delayed-type hypersensitivity (DTH) responses, in vitro T lymphocyte function, and tetanus toxoid and hepatitis B (but not diptheria or pneumococcal) antibody response to vaccination. Aside from dietary manipulation, research involving behavioral preventative or restorative therapies has been lacking.

Alternatively, moderate aerobic exercise training has been shown to elicit beneficial outcomes in both the prevention and rehabilitation of many diseases of the elderly. With respect to immune function, it has been hypothesized that moderate levels of exercise improves, whereas strenuous exercise or overtraining suppresses, various immune function measures. This theoretical model has been called the “inverted J hypothesis” due to the shape of the immune function (Y axis) versus exercise intensity (X axis) curve. The extent to which moderate exercise training or lifelong physical activity influences dysregulated immune function in the elderly is unclear. Despite this, exercise is currently being used by elderly populations to enhance muscle functioning and combat diseases, such as osteoporosis, diabetes, and heart disease. Three general approaches have been implemented to study exercise and immune function in aged populations: (1) human cross-sectional studies comparing master’s athletes with sedentary elderly, (2) human longitudinal studies in which exercise training commenced in old age, and (3) animal studies. Several other studies have examined the effects of single bouts of exercise on various immune parameters in old when compared to young subjects; they will not be reviewed.

**HUMAN CROSS-SECTIONAL STUDIES**

Cross-sectional studies have examined the relationship between a physically active lifestyle and aging in terms of in vitro NK cell activity (NKCA), T cell function, and cytokine production. Basal killing of NK-sensitive K562 cells has been commonly used to assess NKCA in humans and yet there are conflicting reports as to whether basal NKCA is altered in older individuals. Several cross-sectional exercise studies offer conflicting data in regards to basal NK cell function in older adults. Nieman et al. reported a 54% higher basal NKCA in elderly athletes when compared to sedentary controls. This increase was seen in the absence of changes in NK cell number. In this study athletes were highly competitive females, aged 65 to 84, who
had exercised at least an hour a day for a minimum of five years. By contrast, there was no difference in NKCA when Shinkai et al. examined older athletes when compared to age-matched sedentary controls.\textsuperscript{18} The athletes in that study had run recreationally an average of about 1 hour a day, 5 days a week for over 17 years. There is obviously a big difference between recreational runners and highly competitive athletes, which may explain the discrepancy of findings between the two studies. It may be that regularly performed high intensity exercise is needed to alter NKCA. Unfortunately, none of these studies examined the effects of exercise on the known age-related suppression in sensitivity of NK cells to endogenous activators such as IL-2 or IL-12.\textsuperscript{19}

Aging seems to affect functions of T cells the most, particularly in their ability to proliferate \textit{in vitro} in response to polyclonal mitogens, such as concanavalin A (Con A) or phytohemagglutinin (PHA). The cross-sectional data on the impact of exercise on this is clearer, pointing to improved T cell responses in physically active elderly when compared to sedentary controls. Shinkai \textit{et al.}\textsuperscript{18} and Nieman \textit{et al.}\textsuperscript{17} reported very similar increases (~40–50%) when comparing proliferative response to PHA in an elderly exercise group when compared to the sedentary group. Shinkai\textsuperscript{18} studied all male subjects and found decreased proliferative response in the aged, not only to PHA, but also to pokeweed mitogen (PWM) and alloantigens. The aged exercising group had higher proliferative responsiveness to PHA (41%) and PWM (46%) than the aged sedentary group (adjusted to per cell basis). Looking at a different measure, Gueldner \textit{et al.} examined T cell responsiveness in older women and found that CD25 expression in response to fixed anti-CD3 antibody was higher on T cells in the active group when compared to an inactive control group.\textsuperscript{20} The exercise group consisted of subjects who had engaged in long-term moderate exercise in formal exercise classes. DiPietro \textit{et al.} reported an increase in the percentage of peripheral blood mononuclear cells forming rosettes with sheep red blood cells (SRBC) after incubation with PHA in noncompetitive elderly cyclists when compared to sedentary controls.\textsuperscript{21} This indicated that physically active elderly responded more vigorously to PHA with enhanced expression of CD2, the receptor responsible for SRBC binding and a molecule important in T cell costimulation. This was accompanied by alterations in signal transduction through the phosphatidylinositol pathway. Wang \textit{et al.}\textsuperscript{22} found that basal protein kinase C (PKC) activity, phorbol myristate acetate (PMA)-induced redistribution of PKC, and PHA-induced enhancement of PKC activity were reduced in cytosolic and membrane fractions in lymphocytes obtained from older adults, but the magnitude of these reductions was smaller among elderly who were physically fit, as determined by estimated maximal oxygen uptake (VO\textsubscript{2max}) testing. PKC is a serine/threonine kinase important in T cell activation. Taken together, these data indicate that T cells obtained from physically active, cardiovascularly fit older adults may be better able to respond to polyclonal stimulation.

Cytokines are also affected by the aging process, most notably a decrease in production and responsiveness to IL-2. Shinkai \textit{et al.}\textsuperscript{18} confirmed this and reported that PHA-stimulated IL-2, interferon-\(\gamma\), and IL-4 production in elderly runners was higher compared to an elderly sedentary group. This brings up the possibility that older individuals who exercise regularly may have improved type I cytokine responses that may ultimately contribute to improved cell-mediated immunity.
Summary

In addition to the low subject number, a major limitation with these cross-sectional studies is that inclusion of elderly athletes as a comparison group is likely not relevant in determining the effect of moderate physical activity on immune function in older individuals. Most elderly will never realistically become (or desire to become) competitive athletes. Indeed, the recent public health message is that moderate levels of exercise can result in considerable improvements in physiological/psychological functioning in the aged with concomitant reductions in disease. These moderate levels of exercise are likely the ones that can be attained by the majority of elderly persons. Obviously, the major drawback of the cross-sectional approach is that other factors, including nutritional status, genetics, smoking history, and psychosocial factors (among others) exist to explain the relationship between physical activity status and high levels of immune function. However, as a starting point, it would be of interest to determine if cardiovascular fitness (e.g., VO$_{2\text{max}}$) and/or self-reported physical activity are associated in any way with various measures of immune function. Unfortunately, no studies have had sufficient subject numbers to adequately address this issue.

HUMAN PROSPECTIVE STUDIES

Prospective studies can definitively determine whether exercise training improves immune function in older adults. Several studies have examined the impact of either moderate aerobic exercise or resistance training on indicators of immune function in the aged.

Aerobic Exercise

Woods et al. examined 6 months of moderate aerobic training (60–65% of VO$_{2\text{max}}$, 40 min/day, 3 times/wk) or flexibility/toning control (FT-CON) on previously sedentary elderly (65.3 ± 0.8 years) adults. Measures of both T lymphocyte and natural killer cell function were examined. While both groups revealed a small intervention-induced increase in in vitro T cell proliferation to Con A and PHA, the aerobic-trained group showed a higher percentage change over several doses of Con A. Basal NKCA versus K562 cells tended to be higher in the aerobic-trained group, while little change was evident in the FT-CON group. In another study, Fahlman et al. examined the effects of a 10-week endurance-training program (walking at 70% of heart rate reserve 3 d/wk) in elderly (76 ± 5 years) nuns. One clear advantage to the use of this particular population was that all of the subjects lived and ate together, and had similar lifestyle and activity patterns. The short training program was without effect on basal NKCA and Con A–induced proliferation. In a 17-week randomized controlled intervention, Chin et al. combined very mild exercise and enriched foods in frail elderly subjects (79.2 ± 5.9 years). They found no effect of enriched foods, so they combined the exercise and exercise plus enriched foods into one group. Using a DTH skin test, it was shown that exercise had only a small beneficial effect on the DTH response. In effect, the control group significantly declined, whereas the exercise group maintained their cumulative DTH responses to multiple
antigens. This effect was quite small and associated with large variability. Crist et al. examined the effects of 20–30 minutes of chair-callisthenic exercises (three times per week for 16 wks) that were designed to improve functional aerobic capacity and neuromuscular performance in a population of ambulatory seniors (72 years old). Crist and Crist et al. examined the effects of 20–30 minutes of chair-callisthenic exercises (three times per week for 16 wks) that were designed to improve functional aerobic capacity and neuromuscular performance in a population of ambulatory seniors (72 years old). Crist et al. examined the effects of 20–30 minutes of chair-callisthenic exercises (three times per week for 16 wks) that were designed to improve functional aerobic capacity and neuromuscular performance in a population of ambulatory seniors (72 years old). Crist et al. examined the effects of 20–30 minutes of chair-callisthenic exercises (three times per week for 16 wks) that were designed to improve functional aerobic capacity and neuromuscular performance in a population of ambulatory seniors (72 years old). Although it was demonstrated that basal NKCA was 33% higher in trained versus untrained, these measures were only taken posttraining, and it was assumed that initial differences between subjects were equally balanced across the two treatment conditions through the randomization process and that any posttreatment differences were due to the experimental treatment. This is clearly not an ideal study design. Nieman et al. examined the effects of 12 weeks of walking on in vitro immunological responsiveness in aged (73-year-old) sedentary females. Although a significant increase (12.6%) in VO2max was seen following the intervention, no effect in basal NKCA or T cell proliferation to PHA was observed. They suggested that either the duration or the intensity of the exercise prescribed may not have been stimulating enough to elicit any functional immunological change in this population despite the increase in VO2max.

Resistance Training

Resistance or strength training is also being recommended to elderly populations as a means of combating sarcopenia and osteoporosis. Although the majority of exercise intervention studies focus on aerobic exercise as the model, there are a few studies that have examined resistance training as the mode of exercise. Rall et al. found that 12 weeks of progressive resistance training did not affect immune function in young (22–30 years) or healthy elderly (65–80 years) individuals. Training did not induce changes in lymphocyte subsets, in vitro cytokine production (IL-1, IL-2, TNF-α, or IL-6), lymphocyte proliferation, or in vivo DTH responses to multiple antigens. There were eight and six elderly subjects in the exercise and control groups, respectively. This small number and the high variability in the measures would make detection of small differences in immune function difficult. In a later study by Bermon et al., it was demonstrated that 8 weeks of strength training did not modify counts of lymphocyte subsets in previously sedentary elderly (70.1 ± 1.0 years) adults. In both studies, no changes in body composition or body weight were observed, although in the Rall study strength increases were seen in all groups, the variability in strength increases were very high. The inconsistent increases in strength, accompanied by the fact that subjects failed to alter body composition, indicate that the intervention was probably too short to induce significant physiological changes that may have affected immune function measures in these populations. Moreover, Flynn et al. examined the effects of 10 weeks of lower-body resistance training in elderly (67–84 years) women. They found no significant changes in lymphocyte subsets or proliferation or basal NKCA.

Summary

Despite the suggestive results from cross-sectional studies, data from the few prospective studies that have been published appear not to support a role for moderate aerobic or resistance exercise training in imparting a substantial beneficial effect on various measures of immune function in the elderly. However, the studies that have
been performed have been very short in duration (most <12 wks) and limited in statistical power due to small sample number. Moreover, some have used poor designs and have failed to control or account for influential covariates or seasonal variations in immune function. Although they are difficult and costly to administer, there exists a clear-cut need for long-term (>12 months) exercise-intervention studies in older adults to definitively determine if moderate exercise training can improve immune function in the elderly. It cannot be assumed that changes in immune function in response to exercise training, if they occur, take place within the same time frame as improvements in VO$_{2\text{max}}$ or strength.

**Clinical Relevance of Exercise Training–induced Changes in Immune Function**

A limitation of most exercise-immune studies is the use of *in vitro* responses of peripheral blood cells to assess global immune functioning. Unfortunately, most of these measures lack clinical disease correlates. One measure that has demonstrated clinical significance is the DTH response. The DTH response has long been used as an overall indicator of the robustness of cell-mediated immunity,\(^3^0\) and its clinical significance is evidenced by studies demonstrating an association between low DTH response and subsequent mortality.\(^3^1,3^2\) Although several exercise studies have examined DTH responses, the variability associated with this measure is high, making studies with small sample numbers difficult to interpret. Arguably, the most clinically relevant measure would be the response to a defined antigenic challenge. Unfortunately, there are no published studies on measures such as antibody response to influenza vaccination in elderly exercisers versus sedentary controls. Two studies have demonstrated a decrease in upper respiratory tract infection (URTI) rates in active elderly subjects when compared to sedentary controls.\(^1^7,3^3\) However, these studies have been small with respect to epidemiological standards, and the identification of URTI was based on self-report and not clinical diagnosis.

**ANIMAL STUDIES**

Animal models allow for a more direct examination of the host’s overall immunological response to exercise in tissues that are unavailable in human models (e.g., spleen, heart, brain, and bone marrow). Additionally, investigators can control virtually every aspect of the study, including housing, diet, exercise, room temperature, and light cycle. Ultimately, these models allow for the testing of physiological significance of exercise training–induced changes in immune function using relevant disease models. The majority of studies involving exercise, aging, and immune function involve the use of rodents (various mouse or rat strains), although larger animals are sometimes used.

In one of the first papers to measure the effects of exercise on the aged immune system, Pahlavani *et al.* found that six months of twice-a-day swimming (one hour each session) resulted in an age-related decrease in mitogen-induced splenic lymphocyte proliferation in male Fischer 344 rats.\(^3^4\) They found that the age-related decline in proliferation and IL-2 production was less in the exercised rats, but this was due to lower levels in the young exercised rats and not due to any exercise-related protective effect. In a later study using less stressful treadmill training for 16 weeks,
Nasrullah and Mazzeo showed that exercise enhanced splenocyte proliferation and IL-2 production in response to Con A in aged (27-month-old) Fischer 344 rats, while a decreased splenic proliferation and a reduction in IL-2 production were seen in young and middle-aged rats. Further, the authors demonstrated that increased activity levels had little effect on splenic NKCA. This mode of exercise differs greatly from swim training, in that volume and intensity of the stimulus (exercise) can be controlled to a greater degree, and the effects of the water (i.e., a fear of drowning) is eliminated. Barnes et al. followed with a study examining the same strain of rats, also using treadmill running as the exercise stimulus. These investigators concluded that while 10 weeks of endurance training (75% of maximal capacity) resulted in significant increases in VO2max and reductions in the respiratory exchange ratios in both young and aged rats, exercise training did not significantly alter the antibody response to keyhole limpet hemocyanin (KLH), an antigenic protein that is a T cell–dependent antigen.

In a study involving exercise in conjunction with caloric restriction, Utsuyama et al. suggested that lifelong (19 months) physical exercise in addition to dietary restriction might retard certain immunological functions that are shown to decrease with age. They found that 5 of 13 rats (exercised voluntarily by means of a wheel in their cages and fed 80% of the ad libitum–fed group) exhibited a highly proliferative response of T cells to mitogens and that this contributed to higher levels of proliferation when compared to the calorically restricted groups alone. It is worth noting that in this study, rats had to run on an exercise wheel in order to receive food and that they learned to perform this exercise throughout the experiment (a period lasting 21 months). Based on previous studies showing that mature mice that are able to explore a T-shaped maze more quickly have an above-average longevity, De la Fuente et al. divided 70-week-old female outbred Swiss mice into “fast” or “slow” groups. Upon sacrifice (6 ± 1 week later), it was shown that the “fast” mice had a better in vitro immune function than the “slow” mice based on measurements made on macrophages, lymphocytes, and NK cells. These studies bring up the possibility that heterogeneity likely exists in subjects’ alteration of immune responses to exercise training and that this heterogeneity needs to be accounted for when analyzing exercise and aging studies.

In a study by Lu et al., exercise training in the form of treadmill running (18–22 m/min, 45 min/day, 5 day/wk for 16 wks) significantly increased in vitro peritoneal macrophage tumor cytolysis in young and aged mice, although the effect was larger in young mice. This effect could be abrogated by the inducible nitric oxide synthase inhibitor monomethyl-L-arginine. The latter finding suggested that exercise training increased the ability of IFN-γ and LPS-stimulated macrophages to produce nitric oxide and that this was indeed the mechanism that was responsible for the increase in cytoplastic activity. A strength of this study was the documentation of an intracellular mechanism responsible for exercise training–induced changes in in vitro tumor killing.

Summary

Many of the limitations of human immune studies can be reduced or eliminated through the use of animal models. For example, although an exercise protocol may alter activity levels in a human population, activity outside of the researcher’s con-
trol, such as a subject who participates in a supervised exercise program of moderate intensity but works off-peak (shift) hours in a physically laborious occupation, may confound the data because of increased activity levels, as well as adversely affected sleeping cycles. Housing conditions may act as a further confounding variable (e.g., human subjects living alone may have a more structured lifestyle than someone who is caring for children or a dependent). Furthermore, most human studies in exercise immunology are limited to sampling of blood that contains a small fraction of the body’s leukocyte pool and may not reflect sites important in in vivo immune functioning. The animal data regarding exercise and immune function in the aged suggests that exercise-trained animals may manifest improved T cell–mediated immune functions when compared to sedentary controls. Although testable, the physiological significance of these observations is not known.

Potential Mechanisms for an Association Between Exercise and Immune Function

The aging process does not affect the immune system uniformly, and there is a high degree of individual variability that may be associated with confounding factors. There are several factors that have not been adequately accounted for in previous studies of exercise and immune function, including diet, substance abuse, smoking status, psychological stress, underlying disease, recent illness or vaccination, medication usage (including hormone supplements), seasonal/diurnal/assay variation, body composition, and socioeconomic status. These factors have the potential to either confound data interpretation or contribute to an interaction between exercise and immune function, or both. For example, people who are physically active may adopt other healthy behaviors (e.g., not smoking and eating a healthy diet). However, the role these factors play in explaining improved immune function in the physically active elderly is unknown. Likewise, a myriad of physiological mechanisms exist that could potentially explain how exercise training might affect immune function, including changes in neuroendocrine status, altered hematopoiesis, leukocyte apoptosis, muscle damage, metabolic changes including increased protein synthesis or improved glucose utilization, and changes in antioxidant defenses, to name a few. Some of the above factors may lead to alterations in the makeup of leukocyte subsets in such tissues as blood or spleen. Given that the aged manifest higher numbers of memory T cells, at the expense of naive T cells, and that this likely contributes to age dysregulation in T cell immune function, it will be important to examine various subsets of leukocytes in future exercise studies to determine if functional changes are associated with cell subset shifts in the samples obtained. However, testing of the contribution of mechanisms such as these seems premature until we know whether or not exercise-induced changes can be accounted for by other lifestyle variables.

CONCLUSIONS

The limited preliminary evidence from cross-sectional human, prospective human, and animal studies suggests that exercise-trained or physically active elderly subjects have higher in vitro measures of immune function and, perhaps, lower inci-
dence rates and severity of URTIs when compared to sedentary controls. Although such findings have the potential to be of substantial public health importance, very few cross-sectional or randomized prospective trials of exercise and immune function have been conducted to date in the elderly. These studies can be characterized as comprising small samples followed over a short duration, measuring a limited number of in vitro immune parameters whose clinical significance is unknown, and failing to account for potential confounding influences. There is clearly a need for definitive human prospective and animal studies examining the physiological relevance of exercise training–induced changes in immune function with regard to disease models.

REFERENCES