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Frequent participation in high volume exercise throughout life is associated with a more differentiated adaptive immune response

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ABSTRACT

Exercise induces changes in the immune system depending on its intensity and duration. For example, transient states of immunodepression can be induced after acute intense physical activity whereas beneficial anti-inflammatory effects of moderate chronic exercise on many diseases and longevity have been described. To study the impact of high volume exercise over a lifetime on aspects of immunity we compared immunological features of 27 young and 12 elderly athletes with 30 young and 26 elderly non-athletes stratified by their CMV serostatus. We characterized blood leukocyte and lymphocyte subpopulations by flow cytometry, quantified TREC content, and measured activation and proliferation ability of T-lymphocytes in the presence of anti-CD3. NK-cells functionality was determined in response to K-562, 721.221 and 721.221-AEH cell-lines. High volume physical activity reduced the total number of circulating leukocytes, neutrophils, and lymphocytes. In the lymphocyte compartment, athletes had higher frequencies of NK-cells and CD8+ T-lymphocytes, whereas CD4+ T-lymphocytes were present at significantly lower levels in CMV-seropositive athletes. We found, in the high volume physical activity individuals, a higher degree of differentiation in CD4+ T-lymphocytes. CD8+ T-lymphocytes from young athletes had reduced TREC content and lower frequencies of recent thymic emigrants. Furthermore, the functional ability of CD4+ and CD8+ T-lymphocytes was significantly impaired in young but not in elderly athletes, and may be compensated for significantly higher activation and degranulation of NK-cells.

In conclusion, high volume exercise throughout life appears to be associated with increased levels of biomarkers that are associated with an aging immune system, which are partially reduced with physiological aging.

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1. Introduction

Exercise involves a series of changes in the status of an individual's immune system that vary with the type, intensity, and duration of the activity undertaken over a lifetime. In general, exercise alters the distribution, trafficking, and functional capabilities of different types of immune cell, as well as local and systemic levels of various soluble mediators (interleukine (IL)-2, IL-4, IL-6, CRP) (Romeo et al., 2008; Simpson et al., 2012; Walsh et al., 2011). These aspects clearly differ depending on whether the study is conducted after short-term high intensity exercise, after prolonged submaximal exercise, or at rest in trained individuals. In fact, transient states of immunodepression are induced after acute intense physical activity and beneficial anti-inflammatory effects of moderate chronic exercise on many diseases and longevity have been described (Woods et al., 1999b).

The relationship between exercise and susceptibility to infection has been modeled on a "J" curve (Nieman, 1994), suggesting that moderate activity increases immunity and reduces the risk of illness with respect to sedentary individuals (Matthews et al., 2002). Conversely, excessive volumes of strenuous endurance exercise may induce a reduction in the protective capacity of the

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immune system, thereby increasing the risk of illness (Cox et al., 2008; Mackinnon and Hooper, 1996). The cause of this immunodepression is probably multifactorial, with hormonal, nutritional, and inflammatory factors interacting. Intense exercise induces transient inflammatory responses in the exercised muscles, which are involved in repair processes, hypertrophy, and muscular angiogenesis secondary to exercise. However, the repetition of these inflammatory reactions can cause intense and chronic local inflammatory conditions, and may even have systemic consequences (Peake et al., 2005a,b). This systemic effect results in an acute phase response to inflammation and, when intense and sustained over time, alters the immune capacity of athletes and can lead to situations of immunodepression (Helenius et al., 2005; Reid et al., 2004). Another cause of this immunodepression could be the anti-inflammatory effect that occurs during prolonged exercise, with elevations of IL-6, IL-10, IL-1Ra, and sTNFR (Gleeson et al., 2011; Petersen and Pedersen, 2005). These anti-inflammatory mediators may have opposite effects, causing transient immunodepression but long-term beneficial effects that decrease the low-grade chronic inflammation and the risk of chronic diseases. Numerous observational studies have demonstrated the salutary effects of exercise in patients with various diseases and even on comorbidity and survival in older individuals (Braith and Stewart, 2006; Manini et al., 2006; Thompson et al., 2003). Sedentary elderly individuals have a greater risk of mortality than those with intermediate or high levels of physical activity, whereas moderate levels of physical activity are associated with a reduced risk of coronary heart disease, neurodegeneration, cancer incidence, and disability (functional impairment) (Hambrecht et al., 2000; Simpson et al., 2012; Speelman et al., 2011).

There are certain parallels between the immune system of athletes undergoing intense training programs and elderly individuals. Sedentary elderly people also experience a chronic inflammatory state that is considered responsible for many of the changes that occur in the immune system as a result of aging (Franceschi et al., 2000; Simanek et al., 2011). Aging of the immune system is associated with increased susceptibility to infections and cancer, as well as increased morbidity and mortality (Simanek et al., 2011). Over a lifetime, as the immune system suffers repeated encounters with the same antigens and the degree of thymic atrophy increases, levels of highly differentiated cells increase. T-cells can be separated into functionally distinct populations using combinations of cell-surface markers such as the tyrosine phosphatase isoform CD45RA and the chemokine receptor CCR7. With these markers, T-lymphocytes are subdivided into naïve (NAÏVE; CD45RA+CCR7+), central memory (CM; CD45RA-CCR7+), effector memory (EM; CD45RA-CCR7−), and effector memory cells that re-express CD45RA (EMRA; CD45RA+CCR7−) (Sallusto et al., 1999). Meanwhile, EM and EMRA are heterogeneous populations, and the staining with two additional markers, CD27 and CD28, can distinguish between less-differentiated (CD27+ and/or CD28+) and more-differentiated ($CD27^{null}CD28^{null}$) cells (Koch et al., 2008). EM T-cells can be divided into EM1 (CD27+CD28+), EM2 (CD27+$CD28^{null}$, only in CD8+T-cells), EM3 ($CD27^{null}CD28^{null}$), and EM4 ($CD27^{null}$CD28+) cells. Functionally, EM1 and EM4 are very similar and exhibit memory-like properties and EM2 are intermediate, whereas EM3 display effector-like properties. Similarly, the EMRA subset can be subdivided into very poorly differentiated pre-effector-1 (pE1, CD27+CD28+), pre-effector-2 (pE2, CD27+$CD28^{null}$, only in CD8+T-cells), and the most differentiated T-cell subset, effector (E, $CD27^{null}CD28^{null}$). In these highly mature T-lymphocytes, mainly $CD28^{null}$ T-cells, oligoclonal expansions against CMV and other chronic antigens are evident (Clambey et al., 2005). Studies have associated the changes in the number of lymphocytes expressing activation and differentiation markers both with age and with CMV seropositive status and antibody titer against the virus (Looney et al., 1999; Roberts et al., 2012). Moreover, these cells are less effective in generating potent immune responses against antigens due to the restricted number of antigens that they can recognize and their reduced functional abilities (Lynch et al., 2009).

These findings prompted us to study whether self-reported scores of habitual exercise training are associated with an enhanced state of their immune system, providing evidence of the beneficial effect of physical activity or, conversely, if it contributes to more acute or premature differentiation degree of the immune system in athletes than in individuals who undertake moderate or low levels of physical activity.

2. Materials and methods

2.1. Study population

Ninety-five volunteers were recruited to the study. In all cases, at least 18 h had elapsed since the last training session before the blood sample was extracted, in a fasted state. Individuals in the study were divided into four groups: young non-athletes (30), young athletes (27), elderly non-athletes (26), and elderly athletes (12). The young athlete group consisted of rowers that performed a program of training specifically involving water rowing training, running and resistance training. The athletes performed 6.2 ± 1 days a week, an average of 125.3 ± 41.5 min a day, for 13 ± 4.2 years (mean ± SD). Exercise intensity in this group, based on the records of past season training, was 60% easy-moderate, 30% intense and 10% very intense exercise or competition. Training period preceding the blood drawn was a period of general adaptation or pre-season training and incremental exercise tests, performed using the blood lactate concentration, did not show performance decrements. All individuals included in the young non-athlete group were recruited from the Centro de Transfusiones del Principado de Asturias (Oviedo, Spain) and the selection criteria were not performing 150 min or more of moderate weekly exercise or 75 min or more of intense exercise. For the elderly athlete group, we selected people aged over 65 years who were involved in athletic activities such as endurance exercise, stretching and body core exercises. Also, elderly athletes performed some resistance training exercises less frequently, usually with low loads. To estimate physical activity in the senior athletes, we asked them about their physical sports activities through their lives by mean of a quantitative and qualitative semi-structured interview including the following questions: What is your main sports activity? What is your secondary sports activity? How many years have you been training routinely? How many days a week do you exercise? What is the average length of time that you train daily? What is the average intensity that you perform routinely? From this interview we determined that senior athletes trained 4.9 ± 1 days a week, an average of 79 ± 29.9 min per day, for 45.1 ± 11 years with an easy-moderate intensity (mean ± SD). The elderly non-athlete group consisted of older people living at the Santa Teresa nursing home (Oviedo, Spain) and who were judged to be physically fit. The functional abilities of the subjects were assessed using the Barthel Index of Activities of Daily Living (BI) (Mahoney and Barthel, 1965). Each person was evaluated at 10 tasks that measured daily functioning for various activities of daily living and mobility. The highest BI score (100) meant that the person needed no assistance in any part of the tasks. All the participants in the study had a BI of 90 or more. Each participant also provided his physical activity score using a questionnaire, which assigns numerical value (physical activity rating; PA-R) for infrequent (0–1), moderate (2–3) and vigorous (4–7) exercisers. Cardiorespiratory fitness was measured as the maximal oxygen uptake (VO_{2max}) that is the maximum capacity of an indi-

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