The effects of acute and chronic exercise on inflammatory markers in children and adults with a chronic inflammatory disease: a systematic review

Hilde E. Ploeger[1,3], Tim Takken[2,3], Mathieu H.G. de Greef[1], Brian W. Timmons[3]

[1] Institute of Human Movement Sciences, University of Groningen, Groningen, The Netherlands

[2] Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

[3] Children's Exercise and Nutrition Centre, Department of Pediatrics, McMaster University, Hamilton, ON, Canada

ABSTRACT

Background: *Chronic inflammatory diseases strike millions of people all over the world, and exercise is often prescribed for these patients to improve overall fitness and quality of life. In healthy individuals, acute and chronic exercise is known to alter inflammatory markers; however, less is known about these effects in patients with a chronic inflammatory disease.*

Objective: *The purpose of this review is to clearly define the effects of acute and chronic exercise on inflammatory markers in patients compared with healthy controls to determine whether exercise elicits an abnormal inflammatory response in those patients.*

Data sources: *A literature search was conducted through MEDLINE and EMBASE (until January 2009).*

Study selection: *A distinction was made between children and adults, acute (i.e., single exercise session) and chronic exercise (i.e., training) and endurance and resistance exercise. To evaluate and compare the exercise responsiveness of various reported inflammatory markers, pre- to post-test effect sizes were calculated.*

Data extraction: *A methodological quality scoring as well as an assessment of the quality of exercise paradigms were both made.*

Results: *In total, 19 studies were included in this systematic review (children, n=7; adults, n=12). Of these, 7 were acute exercise studies in children, 8 were acute exercise in adults, 5 were chronic endurance exercise training studies, and*

Corresponding author:

Brian W. Timmons Ph.D. Children's Exercise & Nutrition Centre

McMaster University and McMaster Children's Hospital

Chedoke Hospital, Evel Bldg, Room 469

Sanatorium Road, P.O. Box 2000, Hamilton, ON Canada L8N 3Z5

Tel: 905-521-2100, ext 77218 or 77615, Fax: 905-385-5033

Email: timmonbw@mcmaster.ca

1 was a chronic resistance exercise training study. No exercise training studies were found involving children. Single bouts of exercise might elicit an aggravated inflammatory response in patients; this was reported for patients with type I diabetes mellitus, cystic fibrosis and chronic obstructive pulmonary disease. More severely affected patients may experience a more aggravated inflammatory response. Levels of inflammatory markers, principally IL-6 but also T-cells, total leukocytes and lymphocytes, remained elevated longer into the recovery period following an acute bout of exercise in patients compared with healthy controls. Evidence was found that chronic endurance exercise training programs can attenuate systemic inflammation in patients with chronic heart failure and type 2 diabetes mellitus.

Conclusions: *In patients with a chronic inflammatory disease, both acute and chronic exercise might elicit different inflammatory responses (i.e., exaggerated after acute exercise & attenuated after training) compared to healthy matched controls. However, the results reveal a major gap in our knowledge regarding the effects of acute and chronic exercise on inflammatory markers in patients with a chronic inflammatory disease. Results are often inconsistent, and differences in training programs (intensity, frequency and duration), heterogeneity of disease populations studied, and analytic methods may be just some of the causes for these discrepancies. To optimize exercise prescriptions and recommendations for patients with a chronic inflammatory disease, more research is needed to define the nature of physical activity that confers health benefits without exacerbating underlying inflammatory stress associated with disease pathology.*

INTRODUCTION

Chronic inflammatory diseases strike millions of people all over the world. Chronic inflammatory disease is an overall term for a variety of chronic diseases such as rheumatoid arthritis (RA), asthma, chronic hearth failure (CHF), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diabetes mellitus type 1 and 2 (T1DM and T2DM), inflammatory myopathies (e.g., idiopathic polymyositis, dermatomyositis, inclusion body myositis), inflammatory bowel disease (IBD) (e.g., Crohn's disease (CD), ulcerative colitis (UC)), juvenile idiopathic arthritis (JIA), McArdle's disease and multiple sclerosis (MS). Despite common characteristics of systemic inflammation, these disorders have a variety of underlying deficiencies while the aetiology and pathogenesis is mostly unknown. In CD, JIA, MS, RA, T1DM and inflammatory myopathies, chronic systemic inflammation is related to underlying autoimmune disorders. COPD might have an autoimmune component, however the origin of systemic inflammation in COPD is mostly unclear (5). Moreover, cigarette smoke is thought to be the predominant contributor of systemic inflammation in patients with COPD (5, 66). CF is a hereditary disease and recently T2DM is considered to be related to low-grade systemic inflammation (25). Whether inflammation is a cause or a consequence of T2DM remains controversial (47). It is interesting to see, in spite of

the different backgrounds and symptoms related to the various diseases, all systemic chronic inflammatory diseases share common characteristics, including elevated circulating levels of cytokines TNF-α and IL-6 under basal or resting conditions (6, 15, 44, 48, 59, 97, 102). Indeed, the source of these inflammatory markers (e.g., TNF-α) depends on the disease. T2DM is associated with an overproduction of TNF-α by the adipocyte, whereas in diseases with an autoimmune component macrophages and T cells are the principal source (2). Nevertheless, the main objective in treating patients with an inflammatory disease is to suppress inflammation and deal with secondary consequences in order to improve the quality of life. A down regulation of pro-inflammatory cytokines might have both disease specific and general effects in patients. If the pro-inflammatory cytokine production is of sufficient magnitude as to enter the bloodstream, circulating cytokines can act at distant sites in an endocrine fashion causing several secondary problems such as cachexia and fever (2). However, a down regulation of pro-inflammatory cytokines from the primary source (e.g., bowel in IBD, joints in RA) can also have disease specific benefits. In both situations, treatment focuses predominantly on medication and cardiac and pulmonary rehabilitation (27, 42, 46, 106). However, progress in exercise immunology highlights the potential of regular exercise as an anti-inflammatory therapy for both healthy individuals and patients with an inflammatory disease (71, 88, 89).

Altered levels of cytokines are not only seen in inflammatory disease; acute exercise has an effect on cytokine responses and inflammation in healthy individuals. The intensity, duration and the type of exercise (e.g., endurance vs. resistance training) and acute vs. chronic exercise can all influence various immune parameters, which are also associated with chronic inflammatory diseases (67, 71, 89). Acute exercise, for example, has an effect both during and after exercise on the immune system and is reviewed in detail by Pedersen and Hoffman-Goetz (67). During acute exercise muscles release IL-6, and levels can increase significantly (71). Leukocyte subsets as neutrophils, lymphocytes (including their subsets T, B and NK cells) and monocytes, as well as plasma concentrations CRP and both pro- and anti-inflammatory cytokines TNF-α, IL-1, IL-1ra, IL-10 and sTNF-r can increase to various magnitudes during a bout of exercise. Following the cessation of intense exercise, neutrophils and monocytes can continue to increase into the recovery period. During this same time, other leukocyte subsets decrease in number, while plasma concentrations of the above-mentioned cytokines stay elevated for some more hours. Strenuous and eccentric exercise seem to exert the most prominent changes in immune parameters (57, 60, 67, 84, 105). Extreme exercise such as marathons, and frequently executed training programs have been associated with a depression in immune function (36), which may increase the elite athlete's susceptibility to infection. The pro-inflammatory markers TNF-α and IL-1β do not seem to increase in short periods of moderate intense exercise, although conflicting results have been documented (60, 67). It is therefore clear that acute bouts of exercise exert various effects on the immune system and are typically transient in nature. The extent to which these changes occur in patients with a chronic inflammatory disease is important to address to ensure that exercise is performed in a safe manner where inflammation is not being further amplified. In an almost paradoxical way, however, participation in regular exercise (i.e., training) can reduce basal or resting levels of many inflammatory markers (50).

The effects of regular or chronic exercise on basal levels of inflammatory markers have been used to recommend exercise as an anti-inflammatory therapy (17, 71). Compared to acute bouts of exercise, chronic exercise effects on inflammatory markers have been less investigated. However, as in acute bouts of exercise, the effect of training on inflammatory markers also seems to dependent on the intensity of exercise, training status, age and involvement of disorders (36). Baseline measurements of circulating inflammatory markers do not seem to differ greatly between healthy untrained and trained adults (35, 67, 89). However basal or resting levels of NK cells, an important lymphocyte subset and very responsive to acute exercise, can be elevated with low-intensity training and their cytolytic activity has also been shown to increase in trained individuals, compared with matched healthy untrained controls (69, 70). Low intensity training in healthy elderly persons can reduce resting levels of pro-inflammatory markers such as monocytes, CRP and IL-6 (62, 87). Moreover, it appears that exercise training can attenuate or blunt the response of a single bout of exercise (38, 105). Whereas exercise of moderate intensity is associated with anti-inflammatory effects, strenuous exercise affects resting levels of inflammatory markers during and after a period of intensive training (35, 56).

In addition to the problems with trying to understand the acute effects of single sessions of exercise and the chronic effects of regular exercise training, special attention must also be given to the effects of exercise with regard to age and gender (94-96). During childhood, the immune system is subject to developmental changes due to maturation and increased antigenic 'experience'. At the other end of life, aging also impacts the immune system. For example, plasma levels of TNF-α, IL-6, IL-1ra, sTNF-r and CRP have all been shown to increase with aging (22). While exercise in children and older adults generally impacts the same types of cells and cytokines, the responsiveness of inflammatory parameters can be different (16, 71, 89). In children, acute exercise brings about an increase in leukocytes, lymphocytes, NK cells, IL-6, TNF-α, IL-1β, IL-1ra and lymphocyte expression of CD95 (14, 61, 76, 90). Chronic exercise on the other hand has been shown to increase resting levels of TNF-α and IL-1β in children (77, 83). There is also accumulating evidence for a gender-related difference in immune changes with exercise. For example, a greater exercise-induced response of total leukocyte, lymphocyte and NK cell counts in adolescent girls compared to adolescent boys (95). Moreover, the female cycle plays an important role on immunological effects of exercise. Distinctly different patterns are found between women (specifically contraceptive users) and men and women in their luteal phase compared to women in their follicular phase, both under resting conditions and in response to exercise (91, 65). In the luteal phase, the concentration of leukocyte and lymphocyte subsets tend to be higher at rest and also after exercise, a statistically significant different pattern of gene regulation is found, with particularly an up regulation of pro-inflammatory genes for non contraceptive using woman compared to both men and women in their follicular phase (65). Given these documented differences in the effects of exercise on immune responses according to age and gender, it is important to consider these factors when investigating immune responsiveness to exercise performed by patients with a chronic inflammatory disease. If exercise is to be used clinically, for example, it might be necessary to individualize prescription according to age and gender. Moreover it high-

lights the necessity to match for those variables doing an intervention study involving control subjects as well as to control for the use of oral contraceptives and menstrual stage in female subjects.

In light of our expansive knowledge about the effects of exercise on immune function and cytokines in healthy individuals, it is unfortunate that more attention has not been given to patients with a chronic inflammatory disease in whom inflammation is, to some extent, dysregulated. Most studies have examined the beneficial effects of exercise in terms of overall health, muscle strength, reduced risk of chronic diseases (e.g., cardiovascular disease), controlling obesity and T2DM, self esteem and body image (28, 80). In fact, Pedersen and Saltin (68) reviewed literature concerning the effects of exercise as a therapy in several chronic diseases in order to provide the evidence for exercise as therapy. Effects of exercise were divided into effects on pathogenesis, symptoms specific to the disease, physical fitness or strength and quality of life. However, evidence-based recommendations could not be made for every disease and there was a particular paucity of evidence regarding effects of training on disease pathology. Consequently, exercise has many beneficial effects for patients with a chronic inflammatory disease, but the impact of exercise on measures of inflammation remains understudied.

To fill this gap in our understanding relevant to patients with a chronic inflammatory disease, we conducted a systematic review of the literature pertaining to the effects of acute and chronic exercise on inflammation in children and adults with a systemic chronic inflammatory disease. We further compared the findings to those of healthy individuals who were investigated in the same study. Our goal was to clearly define the effect of exercise on inflammation in patients, compared with healthy controls, to determine whether exercise elicits an abnormal inflammatory response in those patients. We believe that safe and effective exercise is that which confers the benefits of being active (improved fitness, muscle strength) without exacerbating underlying inflammation associated with the disease pathology. Understanding this balance is necessary to provide an evidence-based approach to exercise prescription for individuals with a chronic inflammatory disease. Given the complexities of the literature, we also make recommendations for improving methodological quality and quality of reporting for future studies of exercise immunology in patient populations.

METHODS

Literature search

Chronic inflammatory diseases comprise a very heterogeneous group of chronic diseases. For this review the literature search included all chronic inflammation diseases. A literature search was conducted through MEDLINE (to January 2009) and EMBASE (to January 2009) by 1 investigator (HEP). The search included the MeSH terms exercise OR physical activity AND inflammation OR cytokines OR immune AND asthma OR arthritis OR chronic heart failure OR chronic kidney disease, OR COPD OR cystic fibrosis OR diabetes mellitus OR inflammatory bowel disease OR McArdle's disease OR myositis OR multiple sclerosis. In addition, the reference lists from the included studies were screened for additional

studies. When the title and abstract suggested that a study was potentially eligible for inclusion, a full-text copy of the report was obtained. A flow-chart outlining the search for this review is depicted in Figure 1.

Two independent assessors performed the quality assessment (HEP, TT). Disagreements between the two reviewers regarding a study's eligibility or quality assessment were resolved by discussion until consensus was reached. Data extraction was performed by one investigator (HEP); when insufficient data were provided in the full-text publications, the original authors were contacted to obtain additional data.
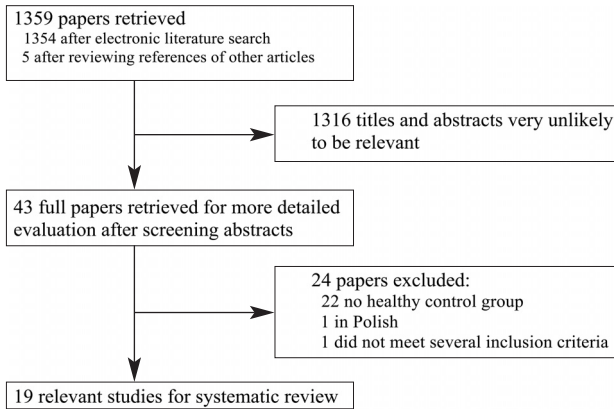
```
┌────────────────────────────────────┐
│ 1359 papers retrieved              │
│   1354 after electronic literature │
│         search                     │
│   5 after reviewing references of  │
│         other articles             │
└────────────────────────────────────┘
            │
            │         ┌────────────────────────────────────┐
            ├────────▶│ 1316 titles and abstracts very      │
            │         │ unlikely to be relevant             │
            │         └────────────────────────────────────┘
            ▼
┌────────────────────────────────────┐
│ 43 full papers retrieved for more  │
│ detailed evaluation after          │
│ screening abstracts                │
└────────────────────────────────────┘
            │
            │         ┌────────────────────────────────────┐
            ├────────▶│ 24 papers excluded:                 │
            │         │   22 no healthy control group       │
            │         │   1 in Polish                       │
            │         │   1 did not meet several inclusion   │
            │         │         criteria                    │
            │         └────────────────────────────────────┘
            ▼
┌────────────────────────────────────┐
│ 19 relevant studies for systematic │
│ review                             │
└────────────────────────────────────┘
```

Figure 1: Flow-chart of the study selection

Inclusion and exclusion criteria

This review included studies in which the effects of acute and/or chronic exercise on markers of inflammation were examined in children or adults with a systemic chronic inflammatory disease and healthy control subjects. Outcome measures of interest included cytokines, total leukocyte count, granulocytes, monocytes, lymphocytes, and lymphocyte subsets such as $CD3^+$ and $CD4^+$ and NK cells. Although a distinction was made between children (age ≤ 18) and adults (age >19), a distinction between younger and older adults could not be made because most adult studies included a broad age-range without partitioning age-related effects. Studies reporting on subjects with an inflammatory disease in combination with obesity (BMI ≥ 25) were excluded, except for those with T2DM and obesity. However, if these latter studies demonstrated a significant weight loss in their patients after an exercise training program they were excluded, because it would be impossible to tease out the effects of exercise vs. weight loss on inflammation. Both randomized controlled trials and case-control studies were included.

Evaluation and classification procedure

Due to the heterogeneity of studies retrieved, distinctions were made between children vs. adults, chronic vs. acute exercise and endurance vs. resistance exercise. If studies investigated both chronic and acute exercise, the study was reviewed twice. Acute exercise was defined as a single bout of exercise perform-

ance where inflammation was assessed up to 24 hours post exercise. Chronic exercise was defined as a training program lasting at least 8 weeks of repeated exercises of either an endurance or resistance type (8), where inflammation markers were examined >24 hours after the last exercise session to assess possible adaptations of basal or resting levels of inflammatory markers to the training program (36, 67). Endurance training was defined as exercise training aimed to improve an individual's peak oxygen uptake (VO_{2peak}). Resistance training was defined as exercise training to improve both muscle size and force production.

To evaluate study outcomes, the results were first assessed for methodological quality using a modified PEDro scale (1, 33, 41) complemented with criteria specific for this review. From the original PEDro scale the following items were used: 1) blinding of assessor who measured at lest one key outcome, 2) outcomes from >85%, and 3) between group comparison. The additional criteria concerned: 1) the quality of the intervention (e.g., exercise protocol properly described, sufficient training and/or exercise bout and sufficient blood sample time point), 2) the analytic methods used, and 3) the reporting of the results. A proper description of the exercise protocol was met when frequency, intensity and duration of either the training program and/or exercise bout was given. The training was considered sufficient when patients exercised at ≥40% of their VO_{2peak} for 30 minutes each time and at least two times a week (20, 85, 103). In order to compare the direct effect of exercise between studies, there had to be a blood sample collected immediately at the end of the exercise. Measurement methods were considered insufficient when using micro bead immunoassay to detect circulating cytokines. This method has been shown to lack sensitivity to the low levels of cytokines in resting human serum and especially to exercise-induced changes in cytokines (92). Results were reported sufficiently when the mean concentration of inflammatory markers in the blood were given, as well as the standard deviation (SD) or a unit that could be used to derive the SD. Our main goal was to compare inflammatory markers within studies based on the statistical information provided by the authors. However, to complement our interpretation of studies, pre- to post-exercise or pre- to post-training effect sizes (ES) were calculated to standardize the interaction effects that would allow an evaluation of different inflammatory markers (e.g., lymphocytes compared with neutrophils). ESs were calculated using pooled baseline and post-exercise (or post-training) SD scores and mean values from patients and controls with a MatLab script in order to minimize errors. ESs below 0.2 were classified as small, from 0.2 to 0.5 as medium and above 0.5 as large, based on Cohen's recommendation (21). A negative effect size either means a greater increase in patients compared to controls (e.g., seen after acute bout of exercise) or a greater decrease in controls compared to patients. A positive effect size either means a greater increase in controls compared to patients or a greater decrease in patients compared to controls (e.g., seen after training intervention). Thus, we did not attempt to use the ESs in a formal analysis (e.g., meta-analysis), but are provided for descriptive purposes only. Because of the heterogeneity of the included studies (e.g., differences in diagnosis, exercise challenge, training program, analytic methods), no attempt was made to pool the obtained ES from the included studies.

RESULTS

In total, 1,359 publications were identified, whereof 12 adult studies and 7 child studies were included in this review. The methodological quality of the studies is shown in Table 1. Three studies used a microbead immunoassay to analyze cytokines (19, 55, 75). Although this method was rated as insufficient, studies were not excluded since we were particularly interested in the interaction effect of the exercise (i.e., patients compared with controls) and not necessarily in the absolute values.

Table 1: Methodological quality of the studies

	Blinding of assessor who measured at least one key outcome	Outcomes from >85%	Between group comparison	Exercise protocol properly described	Training sufficient	Exercise bout sufficient	Measurement methods sufficient	Blood sample collection sufficient	Sufficient result reporting
Adults									
Adamopoulos et al. (3)	+	NR	+	+	+	NA	+	-	+
Castellano et al. (19) acute	NR	-	+	+	NA	+	-	-	-
Castellano et al. (19) chronic	NR	-	+	+	+	NA	-	+	-
Dekker et al. (26)	NR	+	+	+	+	NA	+	+	+
Heessen et al. (43)	NR	-	+	-	+	+	+	+	-
Ionescu et al. (48)	NR	+	+	+	NA	-	+	+	-
Kinugawa et al. (55)	NR	NR	+	+	NA	-	+	-	+
Lucia et al. (55)	NR	+	+	+	NA	+	-	+	+
Niebauer et al. (63)	NR	+	+	+	+	NA	+	-	+
Rabinovich, et al. (73)	NR	+	+	+	+	+	+	+	+
Rall et al. (74)	NR	+	+	+	+	NA	+	+	+
Van Helvoort et al. (100)	NR	+	+	-	NA	-	+	+	+
Van Helvoort et al. (99) submax	NR	+	+	-	NA	+	+	+	+
Van Helvoort et al. (99) max	NR	+	+	+	NA	-	+	+	+
Children									
Boas et al. (12)	NR	+	+	-	NA	-	+	+	-
Boas et al. (13)	NR	+	+	-	NA	-	+	+	+
Galassetti et al. (30)	NR	+	+	+	NA	+	+	+	+
Rosa et al. (75)	NR	+	+	+	NA	+	-	+	+
Schwindt et al. (79)	NR	+	+	-	NA	-	+	+	+
Tahan et al. (86)	NR	+	+	-	NA	-	+	+	+
Tirakitsoontorn et al. (97)	NR	+	+	+	NA	+	+	+	-

Legend: NR, Not Reported; NA, Not Applicable; +, sufficient reporting; -, insufficient reporting. Please see text for descriptions of each characteristic.

Acute exercise in children

In total, seven studies were found that studied the effects of acute exercise on inflammatory markers in children with a chronic inflammatory disease. Healthy children were compared to children with CF in four studies (12, 13, 86, 97), to T1DM in two studies (30, 75) and to asthma in two studies (mild to moderate persistent asthma (79) and stable asthma in children, both negative and positive responding to exercise (86)). The ESs for the acute exercise response (baseline vs. immediately after exercise) are reported in Table 2, ESs calculated from blood collection points other than the end of the exercise are given, where possible, in the text.

Cystic Fibrosis: Boas et al. (13) reported non-statistically significant interaction effects in the measured leukocytes and lymphocyte subsets after a graded maximal bicycle test until exhaustion. A 1-h post exercise assessment showed the number of leukocytes returned to baseline levels in control subjects, while total leukocyte count in the CF group remained elevated (ES –0.91). This trend was also observed for total granulocyte count (ES –0.60). In another study, Boas et al. (12) reported similar increases in healthy controls and children with CF directly after a graded maximal bicycle test. Tirakitsoontorn et al. (97) found a significant interaction effect for TNF-α and IL-6, with a significantly higher increase in TNF-α and IL-6 for the children with CF (non-NSAID users) after ten 2-min bouts of cycling at 50% of their VO_{2peak} with 1-min rest intervals between the bouts (p < 0.05). For IL-6, the increase took place during 90 min of recovery, whereas TNF-α increased immediately after exercise. ESs, however, could not be calculated from the published results. Tahan et al. (86) investigated the effect of exercise in several chemokines, a family of cytokines in patients with CF and healthy controls. They could not find any exercise changes in both the control group and patient group directly after, 6 and 24 h after a 6-min, submaximal bout of exercise on an ergometer. Data were not shown and ESs could not be calculated.

Type 1 Diabetes Mellitus: Galassetti et al. (30) reported a significant increase in circulating IL-6 30 min after the end of exercise, while control subjects did not (ES –0.3). No exercise effect was seen directly after a 30-min bout of cycling at 80% of VO_{2peak}. Rosa et al. (75) found greater and more rapidly activated responses for generally all measured cytokines in children with T1DM compared with healthy controls. In control subjects, all cytokine values initially decreased, whereas in patients with T1DM the onset of exercise increased cytokines concentrations. This course was seen during the 30 min of exercise, which consisted of ten 2-min bouts of cycling at 80% of VO_{2peak} with 1-min rest intervals between the bouts. At the end of the exercise, plasma concentration of cytokines decreased in patients with T1DM and increased in healthy controls, resulting in small differences between the groups. Only a large ES was found for MCP-1, concentrations were higher in patients with T1DM compared with controls. ESs for 30 min post exercise measures were all small; IL-6 (ES 0.00), TNF-α (ES -0.11), IL-1a (ES 0.00), IL-4 (ES –0.03), IL-12p70 (ES –0.18), IL-17 (ES –0.07), GM-CSF (ES –0.12), IL-8 (ES 0.08), MCP-1 (ES –0.18), MIP-1α (ES –0.18), IP10 (ES –0.22), Eotaxin (ES –0.12).

Asthma: Schwindt et al. (79) reported a significant interaction effect for basophils, CD4+CD45RO+RA+ and CD8+CD29+CD45RO+ after a 6-min bout of cycling. They reported that basophils decreased insignificantly in the asthma group, while they increased significantly after exercise in the control group. CD4+CD45RO+RA+ and CD8+CD29+CD45RO+ increased only significantly in the control group. In the study by Tahan et al. (86), who also investigated the effect of exercise on chemokines in children with asthma with positive and negative responses to exercise, no exercise-related changes were found directly after, 6 and 24 hours after a 6-min, submaximal bout of exercise on an cycle-ergometer. However, data were not shown and ESs could not be calculated.

Acute exercise in adults
In seven studies, the effects of acute exercise on inflammatory markers in adults were investigated (Table 3). Healthy adults were compared to adults with MS in two studies (19, 43), to COPD in three studies (73, 99, 100) and to patients with CF (48), CHF (51) and McArdle disease (55) in only one study each.

Multiple Sclerosis: Castellano et al. (19) reported an increase in IFN-γ 30 min after a 30-min bout of cycling at 60% of VO_{2peak} only for healthy controls compared with patients with MS. Two and 3 h post-exercise this interaction effect was washed out (ES respectively 0.29 and 0.25), and IFN-γ values declined significantly below baseline values for both patients with MS and controls at 2 h post exercise. Unfortunately, no blood samples were taken directly after the end of the exercise. For IL-6 and TNF-α, the MS and control group showed similar changes: IL-6 increased significantly, but this effect was washed out after 2 h; TNF-α decreased significantly for both groups after 2 h and a decline remained evident after 3 h (ES at 2 and 3 h were 0.32 and -0.31, respectively). Heesen et al. (43) examined the effects of a single bout of cycling exercise at 60% of VO_{2peak} in both trained and untrained patients with MS. The trained patients had undergone an 8-week cycling program where they exercised twice a week with an interval-training schedule for 30 min at a maximal intensity of 75% of the maximal workload taken from the initial progressive exercise test. ESs could not be calculated from the published results, however. No significant interaction effects were reported, however no further interpretation is possible.

Chronic Obstructive Pulmonary Disease: Rabinovich et al. (73) reported a statistically significant increase in TNF-α in trained and untrained patients with COPD, whereas levels in healthy controls did not change immediately after 11 min of cycling at 40% of W_{peak}. 20 min post exercise measures, revealed a return to baseline levels for TNF-α in patients with COPD (ES 0.16). A training intervention of 8 weeks, 5 days a week, 60 min endurance training (blocks of 2-5 min cycling at 90% of peak work load (W_{peak}) for an effective period $>= 30$ min, recovery periods cycling at 60% of W_{peak}) did not wash out the effect of acute exercise on TNF-α. Plasma levels of sTNFr55, sTNFr75 and IL-6 did not change during or 20 min after the bout of exercise and the authors did not report the data. In the studies of Van Helvoort et al. (99, 100) large ESs were found for total lymphocytes after a graded cycling test until exhaustion. Exercise-induced increases were significantly greater in controls than in patients with COPD (99, 100). In the

study of 2005 (99) this effect was attributed to a lack of increase in NK and B-lymphocytes at W_{peak} for both patients with muscle and non-muscle-wasted COPD. In the study of 2006, only a lack of increase in NK cells was seen (99). About 30 min after exercise, values decreased to baseline levels in both groups (99). Monocytes increased more in patients with COPD than in controls (100). This difference was reduced 30 min after the end of exercise (ES –0.18), and disappeared completely 1 h after the end of exercise (ES -0.04). For T-lymphocytes, an interaction effect was seen 2 h after the end of exercise (ES -1.24) with a more prolonged elevated level in patients with COPD compared with controls (100), although this observation was not made in their later publication (99). In the 2006 report muscle-wasted, non-muscle-wasted and healthy controls performed both a maximal progressive cycle test and a 30 min submaximal bike test at 50% of W_{peak} (99). An aggravated response of IL-6 in patients with muscle-wasted COPD compared with patients with non-muscle-wasted COPD and healthy controls after the maximal test was reported; however, the ES (-0.15) was small. Comparing the submaximal and maximal tests, both tests elicited an increase in circulating leukocytes and IL-6 in patients with muscle-wasted and non-muscle-wasted COPD, whereas in healthy controls only a maximal test induced an increase in leukocytes and IL-6 (99).

Cystic Fibrosis: Ionescu et al. (48) found, after having corrected for the total work performed, a significant greater increment for IL-6, IL-6sr and TNF-αsrI in patients with CF compared with healthy controls. Only for IL-6 a large ES (-0.62) was found. Values showed that, after 120 min of recovery, IL-6 remained significantly elevated in patients (Δ1.1 pg/ml), whereas this elevation was non-significant in healthy controls (Δ0.05 pg/ml) (post exercise ESs could not be calculated from the published results).

Chronic Heart Failure: Kinugawa et al. (51) found similar significant increases after a graded cycling test until exhaustion for IL-6 and TNF-α in patients with CHF and healthy controls. In addition, patients with CHF started with significantly higher level of baseline circulating cytokines.

McArdle Disease: Lucia et al. (55) reported similar exercise responses in patients with McArdle disease and healthy controls except for IL-7. Subjects first performed a maximal test followed by 12 min of cycling at a work load eliciting the ventilatory threshold, with 10-min rest between the two exercise tests. In the control subjects, IL-7 increased more than in the patients with McArdle disease (medium ES, 0.37).

Chronic exercise in children
No studies could be found reporting the effects of exercise training on inflammatory markers in children with a chronic inflammatory disease.

Chronic exercise in adults
Six studies were available for the assessment of the effect of exercise training on basal or resting levels of inflammatory markers. Five of the six focused on endurance training, with the remaining study focusing on resistance training

(Table 4). Healthy adults were compared to patients with MS (19), CHF (3, 63), COPD (73), T2DM (26) and RA (74).

Multiple Sclerosis: Castellano et al. (19) reported a significant increase in basal or resting levels of TNF-α and IFN-γ only in the MS group at the end of an 8-week endurance training program. An assessment after only 4 weeks of training did not reveal significant interaction effects for TNF-α, IFN-γ and IL-6 (ES respectively 0.41, 0.44 and 0.14).

Chronic Heart Failure: In a double blind RTC, Adamopoulos et al. (3) reported a significant decrease in all measured inflammatory markers in patients with CHF after a 12-week endurance training program consisting of cycling for 30 min 5 times a week. In healthy control subjects, basal or resting levels of inflammatory markers after training were not changed from pre-training values. Niebauer et al. (63) could not find changes in measured cytokines either in patients with CHF or in healthy controls. The participants were randomized to start with either 8 weeks of exercise training or 8 weeks of rest. The exercise training was a home based program. In addition to this program, participants were asked to do nine exercises in the Canadian Airforce XBX program, a physical fitness program in which the work load increases as physical fitness improves.

Chronic Obstructive Pulmonary Disease: Rabinovich et al. (73) investigated the effect of acute exercise both before and after an endurance training program as outlined earlier. Comparing resting levels of inflammatory markers before and after the exercise program no change in plasma levels of TNF-α, sTNFr55, sTNFr75 and IL-6 was found.

Type 2 Diabetes Mellitus: Dekker et al. (26) reported non-significant interaction effects ($p > .05$) in obese subjects after a 12-week endurance training program without weight loss. However the ES for PAI-1 was large (ES 0.76) and values decreased in obese subjects by 26% compared with 12% in lean subjects, suggesting low statistical power. Similarly, in the obese T2DM group, a decrease was reported of 52% in IL-6 compared with 32% in the control group (ES 0.72, not significant).

Rheumatoid Arthritis: Rall et al. (74) examined the effects of resistance training (3 sets of 8 repetitions on 5 different machines with 2 min rest between the sessions for approximately 45 min) on peripheral blood mononuclear cell subsets and pro- and anti-inflammatory cytokines. They showed that resistance training did not significantly ($p > .05$) alter the basal or resting values of these inflammatory markers in patients with RA (74).

Table 2: Effects of acute exercise on inflammatory markers in children with an inflammatory disease compared to healthy children

Author	Exercise challenge	Measure point	Inflammatory markers	Patients Baseline – Post exercise Mean±SD	Controls Baseline – Post exercise Mean±SD	Effect size
Boas et al. (13)	Graded cycling test to exhaustion	3 min post exercise	(cells x10^9 per liter)	CF n=15	Healthy n=15	
			Leukocytes	$9.25\pm2.83 - 12.37\pm4.34^{\#}$	$5.17\pm0.96 - 7.26\pm1.81^{\#}$	-0.49
			Lymphocytes	$2.57\pm0.94 - 3.65\pm1.19^{\#}$	$2.06\pm0.32 - 3.34\pm0.66^{\#}$	0.29
			Granulocytes	$6.44\pm2.5 - 8.12\pm3.68^{\#}$	$2.91\pm0.88 - 3.56\pm1.21^{\#}$	-0.17
			Monocytes	$0.59\pm0.21 - 0.92\pm0.34^{\#}$	$0.41\pm0.13 - 0.65\pm0.22^{\#}$	-0.52
			CD3^{+}	$1.95\pm0.84 - 2.45\pm1.03^{\#}$	$1.49\pm0.30 - 1.99\pm0.45^{\#}$	0.00
			CD3^{+}CD4^{+}	$1.06\pm0.42 - 1.26\pm0.44^{\#}$	$0.87\pm0.21 - 1.03\pm0.26^{\#}$	-0.12
			CD3^{+}CD8^{+}	$0.66\pm0.37 - 0.97\pm0.55$	$0.54\pm0.14 - 0.79\pm0.22$	-0.22
			CD19^{+}	$0.46\pm0.29 - 0.49\pm0.20$	$0.36\pm0.10 - 0.46\pm0.21^{\#}$	0.32
			CD3^{-}CD56^{+}CD16^{+}	$0.21\pm0.07 - 0.71\pm0.34^{\#}$	$0.19\pm0.08 - 0.87\pm0.32^{\#}$	2.40
Boas et al. (12)	Graded cycling test to exhaustion	3 min post exercise		CF n=12	Healthy n=12	
			Leukocytes	Δ 38%[2]	Δ 33%[2]	IR[4]
			WBC	NA[4]	NA[4]	IR[4]
			Granulocytes	NA[4]	NA[4]	IR[4]
			Lymphocytes	Δ 61%[2]	Δ 79%[2]	IR[4]
			Monocytes	NA[4]	NA[4]	IR[4]
			CD3^{+}	NA[4]	NA[4]	IR[4]
			CD3^{+}CD4^{+}	Δ 36%[2]	Δ 29%[2]	IR[4]
			CD3^{+}CD8^{+}	Δ 65%[2]	Δ 61%[2]	IR[4]
			CD19^{+}	Δ 36%[2]	Δ 39%[2]	IR[4]
			CD3^{-}CD56^{+}CD16^{+}	Δ 316%[2]	Δ 439%[2]	IR[4]

table 2 continued

Study	Protocol	Timing	Measure	CF (No NSAIDs) n=14	Healthy n=14	
Tirakit-soontorn et al. (97)	10 times 2 min cycling @ 50% of VO_{2peak}, 1 min resting intervals between bouts	Directly after exercise	TNF-α (pg/ml)[1]	Δ 1.5±1.6[#]	Δ 0.27±1.0	IR[4]*
			IL-6 (pg/ml)[1]	Δ 2.3±3.4[#]	Δ 1.08±0.8[3#]	IR[4]*
			IL-1β (pg/ml)[1]	0.66±0.8 – NA[4]	1.47±2.8 - N/A[4]	IR[4]
			IL-1ra (pg/ml)[1]	352.4±217.4 - NA[4]	290.6±134.3 - N/A[4]	IR[4]

Study	Protocol	Timing	Measure	CF n=14 & Asthma n=30	Healthy n=11	
Tahan et al. (86)	6 min cycling submaximal	Directly after exercise	Eotaxin	NA[4]	NA[4]	IR[4]
			RANTES	NA[4]	NA[4]	IR[4]
			TARC	NA[4]	NA[4]	IR[4]
			IP-10	NA[4]	NA[4]	IR[4]

Study	Protocol	Timing	(cells/µl)	Asthma n=14	Healthy n=12	
Schwindt et al. (79)	6 min cycling	Directly after 6 min exercise	Leukocytes	6007.1±1327.9 – 8964.3±2021.2[#]	6550.0±1570.7 – 9714.3±2186.3[#]	0.14
			Lymphocytes	2144.3±676.1 – 3652.8±1189.8[#]	2386.7±396.2 – 3936.1±782.0[#]	0.07
			Monocytes	381.1±150.0 – 629.2±200.2[#]	422.8±107.8 – 707.5±175.1[#]	0.28
			Neutrophils	3155.9±803.3 – 4274.8±1100.0[#]	3444.1±1257.9 – 4654.4±1820.7[#]	0.09
			Eosinophils	288.9±160.5 – 377.3±209.2[#]	268.1±128.3 – 372.5±178.5[#]	0.11
			Basophils	37.0±26.6 – 30.3±11.6	28.2±14.6 – 43.8±18.3[#]	1.04*
			CD3+	1473.1±492.0 – 2115.5±854.6[#]	1508.9±200.2 – 2153.3±440.0[#]	0.01
			CD4+	789.4±232.4 – 1021.7±380.2[#]	844.2±202.4 – 1091.9±288.9[#]	0.07
			CD8+	546.5±238.3 – 855.2±471.8[#]	531.7±105.9 – 833.3±253.7[#]	-0.04
			CD19+	345.1±171.0 – 529.4±230.1[#]	415.1±154.5 – 635.9±232.0[#]	0.22
			CD4+CD45RA+	467.1±207.3 – 603.0±319.2[#]	489.3±209.2 – 632.3±275.0[#]	0.03

table 2 continued

Reference	Protocol	Timing	Marker	T1DM	Healthy	r
			CD4+CD45RO+	358.1±98.4 – 456.7±150.0[#]	384.4±96.2 – 506.3±148.9[#]	0.24
			CD4+CD45RO+RA+	39.8±31.4 – 42.0±27.7	37.2±20.6 – 56.7±28.8[#]	0.65*
			CD8+CD45RA+	389.5±177.7 – 614.2±299.0[#]	391.9±89.4 – 633.1±182.2[#]	0.12
			CD8+CD45RO+	161.4±129.1 – 249.8±257.4[#]	153.6±71.8 – 237.0±129.8[#]	-0.05
			CD8+CD45RO+RA+	19.5±18.8 – 30.9±31.8[#]	31.8±31.1 – 54.8±57.6[#]	0.45
			CD4+CD29+[a]	106.0±71.4 – 145.6±90.4[#]	132.6±63.7 – 196.7±91.0[#]	0.36
			CD4+CD29+CD45RA+[a]	58.9±67.9 – 76.8±79.3[#]	64.3±42.1 – 102.2±57.1[#]	0.35
			CD4+CD29+CD45RO+[a]	50.8±17.3 – 74.2±23.22[#]	73.9±29.9 – 106.5±48.2[#]	0.38
			CD8+CD29+[a]	110.9±75.5 – 161.1±94.6[#]	178.2±110.6 – 320.2±229.4[#]	0.97
			CD8+CD29+CD45RA+[a]	75.7±74.8 – 109.8±92.8[#]	91.3±70.4 – 163.6±132.8[#]	0.53
			CD8+CD29+CD45RO+[a]	36.1±19.1 – 51.4±28.1[#]	71.4±62.4 – 118.3±120.6	0.69*
			CD4+CD62L+	720.9±227.9 – 924.4±262.7[#]	773.6±206.9 – 988.4±283.6[#]	0.05
			CD4+CD62L+CD45RA+	461.5±206.2 – 595.6±317.3[#]	484.3±209.9 – 623.8±277.6[#]	0.03
			CD8+CD62L+	394.2±166.1 – 525.9±257.8[#]	385.4±92.0 – 530.6±186.0[#]	0.10
			CD8+CD62L+CD45RA+	316.4±156.0 – 416.6±225.2[#]	309.5±85.3 – 426.0±152.6[#]	0.13
Galassetti et al. (30)	30 min cycling @ 80% of VO_{2peak},	Directly after 30 min exercise		T1DM n=12	Healthy n=12	
			IL-6 (pg/ml)	5.0±4.5 – 5.3±4.2[2]	1.9±2.1 – 2.7±3.5[2]	0.14
Rosa et al. (75)	10 bouts of 2 min cycling @ 80% of VO_{2peak}, 1 min resting intervals between bouts	Directly after 30 min exercise		T1DM n=21	Healthy n=21	
			IL-6 (pg/ml)	144.8±174.1 – 152.7±178.7[2]	162.7±105.4 – 168.1±100.8[2]	-0.02
			TNF-α (pg/ml)	6.4±6.4 – 8.0±12.4[2]	20.3±19.7 – 18.4±16.5[2]	-0.24
			IL-1α (pg/ml)	557±889.0 – 569±991.9[2]	1105±1118.1 – 1178±1196.1[2]	0.06
			IL-4 (pg/ml)	1384±2195.1 – 1438±2282.1[2]	1053±884.4 – 996±898.2[2]	-0.07
			IL-12p70 (pg/ml)	7.9±10.5 – 10.9±12.4[2]	65.9±114.6 – 58.5±96.2[2]	-0.13

table 2 continued

IL-17 (pg/ml)	$6.2\pm6.9 - 8.6\pm11.0^2$	$48.6\pm56.4 - 54.2\pm60.5^2$	0.08
GM-CSF (pg/ml)	$10.7\pm12.8 - 12.2\pm13.33^2$	$34.2\pm30.2 - 33.3\pm25.7^2$	-0.11
IL-8 (pg/ml)	$34.6\pm45.8 - 33.8\pm44.5^2$	$54.4\pm35.7 - 58.9\pm36.7^2$	0.13
MCP-1 (pg/ml)	$103.4\pm87.1 - 155.7\pm169.6^2$	$170.3\pm77.9 - 165.9\pm68.7^2$	-0.69
MIP-1α (pg/ml)	$29.1\pm21.5 - 38.0\pm27.5^2$	$51.7\pm28.0 - 54.8\pm34.4^2$	-0.23
IP-10 (pg/ml)	$195.7\pm123.7 - 199.9\pm114.6^2$	$274.4\pm119.1 - 298.5\pm146.6^2$	0.16
Eotaxin (pg/ml)	$108.4\pm155.8 - 127.0\pm155.8^2$	$237.0\pm110.0 - 221.0\pm128.3^2$	-0.26

Legend: *$p<0.05$ interaction effect, [#] $p<0.05$ main effect of exercise, [a] Asthmatic group n=7 and control group n=12, [1] Estimated from figure in manuscript, [2] Main effect of exercise not given, [3] Increase took place during a 90min observation period after exercise, [4] NA=Not Available & IR= insufficient results to calculate.

Table 3: Effects of acute exercise on inflammatory markers in adults with an inflammatory disease compared to healthy adults

Author	Exercise challenge	Measure point	Inflammatory markers	Patients Baseline – Post Exercise Mean±SD	Controls Baseline – Post Exercise Mean±SD	Effect size
Castellano et al. (19)	30 min cycling @ 60% VO_{2peak}	30 min after exercise		MS n=11	Healthy n=11	
			TNF-α (pg/ml)[1]	5.7±1.1 – 6.0±0.5	7.6±1.1 – 7.8±0.3	-0.14
			IL-6 (pg/ml)[1]	13.6±0.8 – 15.9±0.7[#]	13.6±0.8 – 15.9±0.7[#]	0.00
			IFN-γ (pg/ml)[1]	28.3±6.1 – 27.1±7.8	19.0±6.1 – 25.6±7.5	1.28
Heesen et al. (43)	30 min cycling @ 60% VO_{2peak}	Directly after 30 min exercise		MS untrained n=13	Healthy n=20	
			TNF-α (pg/ml)[1]	Δ -20.0±108.2[2] (Δ-6.0±115.8)[2, 4]	Δ 50.0±134.2 (Δ85.3±143.1)[2,4]	IR[5]
			IFN-γ (pg/ml)[1]	Δ 11.5±13.7[2] (Δ10.5±24.2)[2,4]	Δ 25.9±50.1 (Δ8.7±12.5)[2,4]	IR[5]
			IL-10 (pg/ml)[1]	Δ -2.6±12.2[2] (Δ1.5±24.2)[2,4]	Δ -2.3±25.5 (Δ9.7±32.6)[2,4]	IR[5]
Heesen et al. (43)	30 min cycling @ 60% VO_{2peak}	Directly after 30 min exercise		MS trained[3] n=15	Healthy n=20	
			TNF-α (pg/ml)[1]	Δ 46.7±116.2[2] (Δ-3.3±126.6)[2,4]	Δ 50.0±134.2[2] (Δ85.3±143.1)[2,4]	IR[5]
			IFN-γ (pg/ml)[1]	Δ 15.8±14.7[2] (Δ12.6±24.4)[2,4]	Δ 25.9±50.1[2] (Δ8.7±12.5)[2,4]	IR[5]
			IL-10 (pg/ml)[1]	Δ 10.1±13.2[2] (Δ5.5±24.4)[2,4]	Δ -2.3±25.5[2] (Δ9.7±32.6)[2,4]	IR[5]
Ionescu et al. (48)	Box-stepping at 20 cm at 15 steps/min for a maximum of 20 min	Directly after end exercise		CF n=11	Healthy n=12	
			TNF-α (pg/ml)	3.30±2.5 – 3.34±2.2	1.78±0.8 – 1.79±1.0	-0.02
			IL-6 (pg/ml)	3.73±2.8 – 5.23±3.1[#]	1.01±0.7 – 1.24±0.7[#]	-0.62[‡]
			TNF-α srI (ng/ml)	1971.6±1030.5 – 2319.2±1166.3[#]	1543.6±898.4 – 1898.2±1810.5	0.01[‡]
			TNF-α srII (ng/ml)	5111.0± 1821.8 – 5028.5±1858.8	3019.1±1429.1 – 3158.7±1882.0	0.14
			IL-6 sr (pg/ml)	42.8±7.5 – 47.6±10.5[#]	36.7±14.1 – 41.7±12.0[#]	0.02[‡]

table 3 continued

Study	Exercise protocol	Timing	Marker	CHF n=80 / McArdle disease n=31	Healthy n=33 / Healthy n=29	Correlation
Kinugawa et al. (51)	Graded cycling test to exhaustion	After end of exercise, not specified	TNF-α (pg/ml)[1]	3.8±1.8 – 4.2±1.9#	2.7±1.1 – 3.1±1.3#	0.00
			IL-6 (pg/ml)[1]	2.4±2.7 – 3.9±4.0#	1.3±1.1 – 2.3±1.3#	-0.24
Lucia et al. (55)	Graded cycling test to exhaustion, 10 min rest, 12 min cycling @ power output eliciting the ventilatory threshold	Directly after end exercise	TNF-α (pg/ml)	51.9±76.28 – 54.6±81.29	22.8±19.93 – 20.4±15.08	-0.09
			IL-1ra (pg/ml)	674.2±1223.24 – 712.4±1474.90	211±241.79 – 184±242.87	-0.07
			IL-1β (pg/ml)	14.4±37.86 – 14.9±43.99	7.3±4.31 – 8.44±8.62	-0.01
			IL-2 (pg/ml)	41.8±116.37 – 44.8±126.39	37.0±49.54 – 35.8±44.16	-0.05
			IL-4 (pg/ml)	14.9±40.64 – 14.2±38.42	14.4±29.08 – 14.8±28.00	0.03
			IL-5 (pg/ml)	2.7±2.78 – 2.6±2.23	2.2±0.54 – 2.2±0.54	0.05
			IL-6 (pg/ml)	38.8±105.79 – 48.0±140.31#	17.4±19.39 – 21.6±19.39#	-0.07
			IL-7 (pg/ml)	15.9±7.79 – 16.0±6.68	14.5±7.54 – 17.4±8.08#	0.37*
			IL-8 (pg/ml)	240.7±269.48 – 128.8±131.40#	240.8±193.33 – 107.9±121.70#	-0.09
			IL-9 (pg/ml)	183.3±190.97 – 142.3±126.39#	131.9±100.70 – 119.5±91.01	0.19
			IL-10 (pg/ml)	24.2±18.93 – 27.3±24.50#	14.8±4.85 – 14.5±4.85	0.25
			IL-12 (pg/ml)	30.6±15.03 – 31.2±16.70	22.6±7.00 – 22.5±8.62	-0.06
			IL-13 (pg/ml)	17.9±36.75 – 13.1±18.93	8.2±5.92 – 7.4±4.31	0.15
			IL-15 (pg/ml)	10.6±6.12 – 8.6±7.24#	8.9±7.54 – 8.0±5.92	0.16
			IL-17 (pg/ml)	15.3±13.36 – 14.4±13.36	9.0±5.39 – 9.8±5.39	0.17
			RANTES (pg/ml)	20701±9710.18 – 30615±32571.42#	26938±25024.86 – 30251±25062.56	-0.35
			IFN-γ (pg/ml)	76.4±55.12 – 72.0±46.77	62.3±51.16 – 58.0±40.39	0.00
			IP10 (pg/ml)	360.9±153.67 – 352.8±197.10	358.4±214.33 – 350.5±194.94	0.00
			MCP1 (pg/ml)	213.0±94.10 – 204.3±89.08	163.8±87.24 – 164.9±94.24	0.11
			MIP-1 (pg/ml)	11.9±10.58 – 9.1±6.12	8.1±3.23 – 8.1±4.31	0.36
			MIP-1b (pg/ml)	204.7±104.67 – 195.6±120.60	163.4±49.00 – 153.1±51.70	-0.01

table 3 continued

Study	Protocol	Timepoint	Measure	COPD n=11	Healthy n=6	
Rabinovich et al. (73)	11 min cycling @ 40% of W_{peak}	Directly after 11 min exercise	TNF-α (pg/ml)[1]	17.3±9.3 – 22.3±9.2#	17.0±14.8 – 17.6±10.4	-0.36*
			TNF-α (pg/ml)[1,3]	16.1±9.5 – 22.2±13.3#	16.8±3.4 – 16.1±4.3	-0.95*
			sTNFr55	NA[5]	NA[5]	IR[5]
			sTNFr75	NA[5]	NA[5]	IR[5]
			IL-6	NA[5]	NA[5]	IR[5]

Study	Protocol	Timepoint	Measure	COPD n=16	Healthy n=11	
Van Helvoort et al. (100)	Graded cycling test to exhaustion	At W_{peak}	Leukocytes (10^9/l)	7.62±2.97 – 9.23±3.68#	5.22±0.73 – 7.21±0.88#	0.18
			Neutrophils (10^9/l)	5.10±2.65 – 5.73±3.18#	3.14±0.81 – 3.61±0.97#	-0.08
			Lymphocytes (10^9/l)	1.64±0.49 – 2.24±0.72#	1.64±0.22 – 2.95±0.54#	1.87*
			Monocytes (10^9/l)	0.51±0.30 – 0.70±0.30#	0.31±0.08 – 0.41±0.15#	-0.41
			NK-cells (10^9/l)	0.19±0.08 – 0.66±0.31#	0.25±0.15 – 0.91±0.40#	1.58
			T-lymphocytes (10^9/l)	1.23±0.31 – 1.71±0.48#	1.17±0.17 – 1.65±0.38#	0.00
			B-lymphocytes (10^9/l)	0.14±0.15 – 0.19±0.18#	0.17±0.04 – 0.24±0.08#	0.18
			CRP (10^9/l)	9.81±6.61 – 9.89±6.93	2.67±1.37 – 2.83±1.69	0.02
			TNF-α (pg/ml)	0.06±0.05 – 0.07±0.05	0.03±0.02 – 0.03±0.02	-0.26

Study	Protocol	Timepoint	Measure	COPD n=10	Healthy n=10	
Van Helvoort et al. (99)	Graded cycling test to exhaustion	At W_{peak}	Leukocytes (10^9/l)	9.17±2.66 – 10.64±3.89#	5.96±1.01 – 8.67±1.36#	0.62
			Neutrophils (10^9/l)	6.06±2.47 – 6.58±2.78[2]	3.98±089 – 4.71±1.14[2]	0.11
			Lymphocytes (10^9/l)	2.35±0.47 – 3.17±1.14[2]	1.53±0.28 – 3.21±0.76[2]	2.22
			Monocytes (10^9/l)	0.54±0.28 – 0.67±0.35[2]	0.34±0.13 – 0.51±0.19[2]	0.18
			B-lymphocytes (10^9/l)	0.22±0.13 – 0.31±0.16[2]	0.17±0.03 – 0.24±0.06[2]	-0.21

table 3 continued

				Muscle-Wasted COPD n=10	Healthy n=10	
			TNF-α (pg/ml)	0.46±0.19 – 0.51±0.28	0.70±0.40 – 0.70±0.28	-0.13
			IL-6 (pg/ml)	2.03±1.26 – 2.72±1.83#	1.90±1.87 – 2.48±1.93#	-0.07
			IL-8 (pg/ml)	8.73±4.36 – 7.2±2.95	3.32±1.47 – 3.97±2.75	0.35
			IL-1ra (pg/ml)	0.79±0.35 – 0.64±0.25	0.72±0.29 – 0.67±0.21	0.32
Van Helvoort et al. (99)	Graded cycling test to exhaustion	At W_{peak}	Leukocytes (10^9/l)	8.06±2.53 – 9.78±3.07#	5.96±1.01 – 8.67±1.36#	0.51
			Neutrophils (10^9/l)	5.55±2.28 – 6.64±2.81[2]	3.98±089 – 4.71±1.14[2]	-0.21
			Lymphocytes (10^9/l)	1.79±0.44 – 2.47±0.41[2]	1.53±0.28 – 3.21±0.76[2]	2.71
			Monocytes (10^9/l)	0.52±0.19 – 0.66±0.19[2]	0.34±0.13 – 0.51±0.19[2]	0.18
			B-lymphocytes (10^9/l)	0.33±0.28 – 0.40±0.28[2]	0.17±0.03 – 0.24±0.06[2]	0.00
			T-lymphocytes (10^9/l)	1.45±0.66 – 1.70±0.85[2]	1.10±0.25 – 1.69±0.44[2]	0.68
			NK-cells (10^9/l)	0.23±0.13 – 0.47±0.41[2]	0.27±0.09 – 1.18±0.51[2]	5.99
			TNF-α (pg/ml)	0.39±0.31 – 0.42±0.24	0.70±0.40 – 0.70±0.28	-0.08
			IL-6 (pg/ml)	3.63±3.51 – 4.64±4.49#	1.90±1.87 – 2.48±1.93#	-0.15*
			IL-8 (pg/ml)	11.15±8.35 – 10.09±8.29	3.32±1.47 – 3.97±2.75	0.34
			IL-1ra (pg/ml)	0.65±0.34 – 0.67±0.18	0.72±0.29 – 0.67±0.21	-0.23
				COPD n=10	Healthy n=10	
Van Helvoort et al. (99)	30 min @ 50% of W_{peak}	Directly after 30 min exercise	Leukocytes (10^9/l)	NA[5]	NA[5]	IR[5]
			Neutrophils (10^9/l)	NA[5]	NA[5]	IR[5]
			Lymphocytes (10^9/l)	NA[5]	NA[5]	IR[5]
			Monocytes (10^9/l)	NA[5]	NA[5]	IR[5]
			B-lymphocytes (10^9/l)	NA[5]	NA[5]	IR[5]

table 3 continued

		Muscle-Wasted COPD n=10	Healthy n=10
	T-lymphocytes (10^9/l)	NA[5]	IR[5]
	NK-cells (10^9/l)	NA[5]	IR[5]
	TNF-α (pg/ml)	NA[5]	IR[5]
	IL-6 (pg/ml)	NA[5]	IR[5]
	IL-8 (pg/ml)	NA[5]	IR[5]
	IL-1ra (pg/ml)	NA[5]	IR[5]
Van Helvoort et al. (99) 30 min @ 50% of W_{peak} — Directly after 30 min exercise	Leukocytes (10^9/l)	NA[5]	IR[5]
	Neutrophils (10^9/l)	NA[5]	IR[5]
	Lymphocytes (10^9/l)	NA[5]	IR[5]
	Monocytes (10^9/l)	NA[5]	IR[5]
	B-lymphocytes (10^9/l)	NA[5]	IR[5]
	T-lymphocytes (10^9/l)	NA[5]	IR[5]
	NK-cells (10^9/l)	NA[5]	IR[5]
	TNF-α (pg/ml)	NA[5]	IR[5]
	IL-6 (pg/ml)	NA[5]	IR[5]
	IL-8 (pg/ml)	NA[5]	IR[5]
	IL-1ra (pg/ml)	NA[5]	IR[5]

Legend: *p<0.05 interaction effect, †p<0.05 interaction effect after correcting for the total work performed, ES are calculated without having corrected for the total work performed, #p<0.05 within group effect of exercise, compared with baseline, [1]Determined from figure in manuscript, [2]Main effect of exercise not given, [3]A single bout of exercise after 8 weeks of training, [4]30 min post exercise, [5]NA=Not Available & IR= insufficient results to calculate.

Table 4: Effects of chronic endurance and resistance exercise on inflammatory markers in adults with an inflammatory disease compared to healthy adults

Author	Training program	Measure point	Inflammatory markers	Patients Baseline – Training Mean±SD	Controls Baseline – Training Mean±SD	Effect size
Chronic endurance exercise						
Adamopoulos et al. (3)	Cycling @ ±60-80% of HR_{max} 12 weeks, 5 times a week, 30 min	Post-training, not specified		CHF n=24	Healthy n=20	
			TNF-α (pg/ml)	7.4±3.9 – 4.6±3.4[#]	3.6±0.9 – 3.7±1.3	1.02*
			TNFsr I (ng/ml)	3.5±1.0 – 2.7±1.0[#]	1.2±0.4 – 1.2±0.9	1.01*
			TNFsr II (ng/ml)	2.7±1.0 – 2.3±1.0[#]	1.6±0.4 – 1.5±0.4	0.39*
			IL-6 (pg/ml)	8.1±4.9 – 5.9±3.9[#]	3.0±0.9 – 2.9±0.9	0.60*
			IL-6sr (ng/ml)	35.5±14.7 – 29.2±14.7[#]	6.0±1.3 – 5.8±0.9	0.58*
Niebauer et al. (63)	Cycling @ 70-80% of HR_{max} 8 weeks, ≥ 5 times a week, 20 min	Not specified		CHF n=18	Healthy n=9	
			TNF-α (pg/ml)	2.7±1.5 – 2.5±0.4	1.4±0.4 – 1.6±0.3	0.36
			TNF-α srI (pg/ml)	915±397 – 900±218	701±111 – 750±240	0.22
			TNF-α srII (pg/ml)	1573±470 – 1620±405	962±292 – 1050±225	0.10
			IL-6 (pg/ml)	31±37 – 30±19	23±22 – 11±16	-0.36
Rabinovich et al. (73)	Blocks of 2-5 min cycling @ 90% of W_{peak}, (recovery @ 60% of W_{peak}) 8 weeks, 5 times a week, >=30 min	Post-training, not specified		COPD n=11	Healthy n=6	
			TNF-α (pg/ml)[1]	17.3±9.3 – 16.1±9.5	17.0±14.8 – 16.8±3.4	0.08
			sTNFr55	NA[3]	NA[3]	IR[3]
			sTNFr75	NA[3]	NA[3]	IR[3]
			IL-6	NA[3]	NA[3]	IR[3]

table 4 continued

Study	Intervention	Timing	Parameter	Disease group	Control group	Effect
Castellano et al. (19)	Cycling @ 60% of VO_{2peak} 8 weeks, 3 times a week, 30 min	>24 hour after end of training intervention	TNF-α (pg/ml)[1]	MS n=11: 7.3±3.8 – 9.6±5.4[#]	Healthy n=11: 5.0±3.7 – 5.0±3.8	-0.62*
			IL-6 (pg/ml)[1]	13.6±15.9 – 10.5±15.0	16.8±17.3 – 14.5±15.0	0.21
			IFN-γ(pg/ml)[1]	24.8±21.9 – 40.4±21.0[#]	16.2±17.1 – 14.3±12.8	-0.89*
Dekker et al. (26)	Cycling ±60% of VO_{2peak} 12 weeks, 5 times a week, 60 min	4 days after end of training intervention	IL-6 (pg/ml)	Obesity with T2DM n=8: 6.2±4.2 – 3.0±2.0[#]	Healthy n=7: 2.8±1.6 – 1.9±1.1[#]	0.72
			CRP (mg/ml)	2.5±1.7 – 2.8±2.5	1.0±0.8 – 1.5±1.1	0.15
			PAI-1 (ng/ml)	79.5±34.7 – 72.1±43.0	50.8±24.6 – 44.5±18.0	0.04
Dekker et al. (26)	Cycling @ 60% of VO_{2peak} 12 weeks, 5 times a week, 60 min	4 days after end of training intervention	IL-6 (pg/ml)	Obesity n=8: 5.2±4.2 – 4.4±1.7[#]	Healthy n=7: 2.8±1.6 – 1.9±1.1[#]	-0.03
			CRP (mg/ml)	3.8±2.3 – 4.3±2.8	1.0±0.8 – 1.5±1.1	0.00
			PAI-1 (ng/ml)	93.4±24.0 – 68.7±28.3	50.8±24.6 – 44.5±18.0	0.76

Chronic resistance exercise

Study	Intervention	Timing	Parameter	Disease group	Control group	Effect
Rall et al. (74)	Resistance training @ 80% of their one-repetition maximum 12 weeks, 2 times a week, 45 min	24-48 hours after end training	TNF-α (ng/ml)[a]	RA n=8: 0.10±0.05 – 0.10±0.05[2]	Young Healthy n=8: 0.09±0.07 – 0.07±0.05[2]	-0.28
			b	0.19±0.17 – 0.31±0.28[2]	0.10±0.11 – 0.11±0.12[2]	-0.77
			IL-6 (ng/ml)[c]	0.18±0.09 – 0.18±0.09[2]	0.30±0.23 – 0.26±0.19[2]	-0.23
			e	2.2±2.1 – 2.3±2.1[2]	2.0±2.1 – 1.3±1.4[2]	-0.38
			IL-1β (ng/ml)[a]	0.09±0.05 – 0.06±0.03[2]	0.14±0.11 – 0.09±0.07[2]	-0.23
			b	0.12±0.08 – 0.10±0.07[2]	0.13±0.11 – 0.10±0.08[2]	0.10
			IL-1ra (ng/ml)[a]	4.0±2.2 – 3.71±2.0[2]	2.1±1.5 – 2.05±1.6[2]	0.13
			b	5.9±3.6 – 5.07±3.1[2]	2.3±1.9 – 4.7±3.9[2]	1.12

table 4 continued

IL-2 (kU/l)[d]	$17.9\pm15.1 - 10.5\pm8.9^{2}$	$15.1\pm11.1 - 10.6\pm7.8^{2}$	0.23
[e]	$5.6\pm3.2 - 5.1\pm2.9^{2}$	$7.5\pm5.6 - 5.6\pm4.2^{2}$	-0.31
Lymphocytes (ccpm[6])[4,d]	$72795\pm25401 - 67554\pm23572^{2}$	$63412\pm18445 - 59597\pm17335^{2}$	0.06
[e]	$31699\pm13442 - 30727\pm13030^{2}$	$25359\pm8400 - 21850\pm7238^{2}$	-0.23
CD3^{+} (%)[7]	$78.6\pm6.4 - 77.1\pm6.3^{2}$	$78.7\pm6.9 - 78.2\pm6.9^{2}$	0.15
CD4^{+} (%)[5,7]	$57.2\pm6.1 - 54.3\pm5.8^{2}$	$51.7\pm6.4 - 54.8\pm6.8^{2}$	0.96
CD8^{+} (%)[5,7]	$23.3\pm6.1 - 23.7\pm6.2^{2}$	$25.0\pm4.0 - 24.7\pm4.0^{2}$	-0.14
CD19^{+} (%)[7]	$8.9\pm2.5 - 8.7\pm2.5^{2}$	$11.2\pm3.6 - 12.7\pm4.1^{2}$	0.55

Legend: *p<0.05 interaction effect, [#] p<0.05 main effect of exercise, [1]Value estimated from figure, [2]SD calculated on the basis of baseline values, [3]NA=Not Available & IR= insufficient results to calculate, [4]n=6, [5]n=7, [6]ccpm=corrected counts per minute, [7]Percentage of Peripheral blood mononuclear cell subsets, [a]Unstimulated Secreted, [b]Unstimulated Cell-associated, [c]Unstimulated, [d]PHA, [e]Con.

DISCUSSION

Regular exercise and physical activity have been considered important components of therapy for many chronic diseases (68). The impact of exercise on immune activation in diseases with an underlying inflammatory burden is less clear. We believe that safe and effective exercise is that which confers the benefits of being active (improved fitness, muscle strength) without exacerbating underlying inflammation associated with the disease pathology. Therefore, the purpose of this systematic review was to investigate the effects of both acute and chronic (i.e., training) exercise on systemic inflammation in patients with various inflammatory diseases compared with healthy controls. All available immunologic outcome measures used in the studies (such as total leukocytes and leukocyte subpopulations including their subsets) were analyzed to investigate if exercise elicits abnormal inflammatory responses in the patient groups compared to healthy controls.

Overview of Evidence for Acute Exercise

Acute bouts of exercise generally activate a global immune change in all subjects (children and adults) irrespective of disease state.

In child studies of inflammatory disease, Rosa et al. (75) found a greater increase in inflammatory markers in the pediatric patients with T1DM compared with healthy controls during acute exercise. Whereas Rosa et al. (75) and Galassetti et al. (30) reported similar changes directly after acute exercise in T1DM and healthy controls. In children with CF a greater increase in TNF-α and IL-6 was reported directly after the end of the exercise compared to healthy controls (97). Another marked finding is that five out of eleven studies (both children and adults studies) which performed a second post recovery measurement after an acute bout of exercise, found that the patients' level of inflammatory markers (principally IL-6, and T-cells, total leukocytes and lymphocytes as well) remained significantly elevated while levels of control subjects already had returned to baseline values (13, 30, 48, 97, 99).

In adult studies of inflammatory disease, no consensus was reached concerning the effects of acute bouts of exercise. Marked immune changes were reported in three studies which involved patients with CF and COPD (48, 73, 99). The aggravated response was attributed to IL-6 in the study of Van Helvoort et al. (99) and Ionescu et al. (48) and TNF-α in the study of Rabinovich et al. (73). Rabinovich et al. (73) could not find an exercise-induced effect on IL-6 and the ES found for IL-6 in the study of Van Helvoort et al. (99) was small. Ionescu et al. (48) also reported a greater increase for TNF-αsrI and IL-6sr in patients with CF compared with healthy controls after values were corrected for the total work performed.

One study included in this systematic review performed within patient comparisons to determine the effect of disease severity on immune responses. For acute bouts of exercise, van Helvoort et al. (99) made a comparison between more and less severely affected patients with COPD and found an exaggerated exercise-induced effect in more severely affected patients. Two other studies made such a subgroup analysis, however without the use of a healthy control group. Spruit et al. (82) could not detect an exercise effect at all in patients with COPD after

cycling at 70% of W_{peak} until symptom limitation (median bicycle exercise time ~7 min). Galassetti et al. (31) found in children with T1DM, that a high morning plasma glucose level (>300 mg/dl) resulted in a significantly higher increase in IL-6 after 30 min cycling at 80% of VO_{2peak} (pre–post 3.5±2.1–4.2±3.4) compared to those with the lowest plasma glucose levels (<150 mg/dl) (ES -0.27). In children with plasma glucose levels <150 mg/dl, cytokine levels did not change significantly after exercise (pre–post 0.7±0.3–1.0±0.3). Plasma values under 100 mg/dl are considered as normal (32). Also 30 minutes post-exercise circulating IL-6 remained elevated in the T1DM group with high morning glucose levels (ES −1.7). Besides the role of disease severity, the use of medications that might differ with patient populations needs to be considered. For example, Tirakitsoontorn et al. (97) investigated the exercise responsiveness of cytokines in children with CF who used ibuprofen or who did not. Compared with users, inflammatory responses in the non-users were significantly lower for IL-6 and TNF-α; however, exercise-induced increases in IL-6 and TNF-α were still greater in the users when compared to healthy control children.

The clinical consequences or relevance of the exaggerated immune responses after acute bouts of exercise in chronic inflammatory disease are not clear. In healthy subjects and subjects with an inflammatory disease, exercise elicits the same inflammatory cytokines as seen in the pathology in chronic inflammatory disease. Many cytokines however have both pro- and anti-inflammatory properties. For example, IL-6 as elevated in the pathology of inflammatory disease is known to exert pro-inflammatory activities. However, in healthy subjects IL-6, a prominent exercise induced cytokine, is thought to play a role in growth processes, the stimulation of anti-inflammatory cytokines and the inhibition of TNF-α production (71, 93). Therefore one could assume that an exaggerated inflammatory response does not necessarily have to make the inflammation concerning the pathology worse in the case of IL-6. However, the magnitude of the response might account for specific exerted effects. When comparing the IL-6 response in children and adults after a similar exercise bout, children experience a 50% smaller increase than adults (93). The physiological reason for such a magnitude difference is not clear; however one can speculate that a greater exercise response might change the positive effects and, for example, inhibit growth factors. One should keep in mind that the effects of exercise training, interestingly, might blunt the effect of an acute bout of exercise (38, 105).

Overview of Evidence for Chronic Exercise
An emerging theme from this systematic review is that exercise training effects found for a particular inflammatory disease are not necessarily generalizable to other inflammatory diseases. For example TNF-α was assessed in four training studies. After the training intervention in patients with CHF, both a decrease (3) and no effects (63) in circulating levels were reported. In patients with MS, significantly higher levels of TNF-α were found (19), whereas in patients with RA no significant effect was reported (74). Castellano et al. (19) prescribed the increase as a possible disease-specific effect of MS. However, the only known study that also measured TNF-α in patients with MS reported a slight decrease (p=0.069) after 8 weeks of progressive strength training (102) (no control group used).

Whereas Niebauer et al. (63) could not find training effects, the anti-inflammatory effects of training programs in patients with CHF can be confirmed by other studies that did not include a healthy control group (4, 23, 34, 53, 54, 72) and were, therefore, not included in this review. A positive trend was seen for endurance exercise training programs to attenuate systemic inflammation in patients with CHF and T2DM with obesity. In healthy individuals on the other hand, little effect was reported after the same training program. The exercise training programs were of moderate intensity (~60% of VO_{2peak}), so the potential for significant physiological adaptation in already healthy persons might be low (10, 64).

The nature and the intensity of the training stimulus are undoubtedly influential to the interpretation of studies representing different diseases. Whereas cycling at 60% of VO_{2peak} could not bring about an acute effect in patients with MS, effects were seen at 75% of W_{peak} in patients with MS (19, 43). Similarly, resistance training might elicit a different exercise-induced response than endurance training (74). Notwithstanding these differences, exercise training has been shown to positively influence circulating levels of inflammatory cytokines in patients with chronic kidney disease and coronary heart disease (18, 39). In concert with the findings of Rall et al. (74), studies that looked at the effect of an aerobic exercise training program on basal or resting levels of inflammation in asthma, MS, COPD, RA, and sporadic inclusion body myositis concluded that exercise improves health-related characteristics without changing levels of inflammation (9, 11, 78, 81, 101). These studies were not included in this review because they did not include a healthy control group.

While the purpose of this systematic review was to clearly define the effects of acute and chronic exercise on inflammatory markers of patients compared with healthy controls to determine whether exercise elicits an abnormal inflammatory response in those patients, it is reasonable to offer some speculation as to the potential mechanisms that might be involved in the relationship between exercise and inflammation in a chronic inflammatory disease. Since no cure has yet been found for the diseases included in this review, treatment remains focused on dampening inflammation using immunosuppressive medication that acts specifically on targets such as TNF-α. Many of these pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are produced by the activation of Toll-like receptors (TLRs) present at different antigen-presenting cells (37). TLRs are known to play a major role in different systemic inflammatory diseases (24) as they are thought to be important targets for therapeutic interventions (45). It is therefore interesting to find that exercise can decrease TLR expression (37), possibly through transient alterations in circulating cytokines that alter the expression of TLRs (52). In the case of chronic inflammatory diseases, one possible mechanism of exercise training benefits may occur via down-regulation of TLR expression, thereby attenuating production of pro-inflammatory cytokines that play a role in the pathogenesis of several inflammatory conditions.

Limitations

When interpreting the results of this systematic review, a number of methodological characteristics must be taken into account. There were a variety of different markers of inflammation, type of chronic diseases, and type of exercise programs

used in the studies that were included, and measurement methods also varied between studies. Analytic methods used are the likely cause for some discrepancies in the findings (e.g., not able to detect changes or deviating values) (92). Moreover, several studies had a small sample size, and in two studies the dropout exceeded 15% (19, 43). Such a study may be insufficiently powered to detect statistically significant changes. Another limitation was in the way of estimating the mean values of measured pre- and post- inflammatory markers, when these results were presented in figure format only. However, any error in this method would be similar for disease and control groups. Unfortunately not all the mean values on cell counts could be retrieved; therefore it was not possible to calculate ESs for a number of studies. Although it was not the intention of this paper to use ESs in a formal analysis (e.g., meta-analysis), this information would have been useful in evaluating different inflammatory markers.

FUTURE RESEARCH

In light of these limitations, we propose a number of considerations for future work. Future studies should use blinded-observers to analyze samples. Furthermore, they should describe the dropout rate, if any, and missing data. The quality of reporting can be improved with a better description of the nature of the acute or chronic exercise stimulus (in terms of frequency, intensity, time and type of exercise) and how the amount of work performed between patients and controls was standardized. Future studies should consider the relevance of investigating the immune-related changes in response to a maximal exercise test to exhaustion. A maximal exercise test does not reflect a training session that will be incorporated into daily life or rehabilitation of patients with chronic inflammatory disease. In addition, the duration of a maximal test will vary for every individual, making it impossible to control the actual work performed. We also suggest that researchers clearly specify the time points at which blood samples are collected before and after exercise.

Another important issue to take into consideration is the use of contraceptives in females and the point of testing during the female hormonal cycle. None of the studies that tested females controlled for these two issues. Blood sample timing during the female hormonal cycle should be taken into consideration (91). Moreover, emphasis should be placed on matching gender and pubertal status among the groups, since both gender and age are variables that account for differences in immune responses.

While all of the exercise training studies were found for the adult population only, we make a number of recommendations for researchers to consider in the design of their next study. Missing from most of the literature is a longer follow-up time and the extent to which training-induced changes in inflammatory markers might be related to clinical status or disease severity. Information on these issues should help individualize exercise prescription and recommendations. How quickly the benefits of an exercise training program on inflammatory markers are lost has not been studied, although this information holds important clinical relevance since some patients may not be able to exercise because of disease complications or other factors. Whether exercise training can alleviate the acute inflam-

matory response to a single bout of exercise in some patients remains an open question. Only one study investigated this topic, but did not demonstrate an effect of training on the acute response (73). Likewise, a study that compared trained patients, untrained patients and healthy control found no differences in the acute response (43).

In this systematic review, we found no studies investigating the effects of exercise training on inflammatory markers in children with a chronic inflammatory disease. Since physical activity is a fundamental component of healthy growth and development, more studies are urgently needed so that safe and effective exercise can be recommended to pediatric patients, especially concerning the relationship between inflammatory cytokines and growth mediators. Circulating inflammatory markers (e.g., TNF-α) can impair the regulation of skeletal muscle protein turnover (29, 107). Reduced levels of IGF, found in children with a chronic inflammatory disease, may further contribute to sub-optimal tissue growth (29, 104). Both chronic and acute exercise in healthy children has been shown to stimulate anabolic processes by increasing growth factors such as, IGF-1 and 2 and GH (30, 40, 49, 58, 97) and is therefore of importance to combat muscle catabolism. Children are not small adults. Not only do they differ in immunological and growth factor responses to a same bout of exercise, but their daily physical activity patterns are different than those of adults (7, 98). This is of significance regarding the creation of exercise programs when one wants to provide challenging and safe, but effective exercise opportunities that can be incorporated in daily life and sustained.

Based on the results of this systematic review, no evidence was found to suggest that the inflammatory response to acute exercise in children with a chronic inflammatory disease is any different than that of their adult patient counterparts in term of exacerbated immune response.

We propose that future research should be focused on the frequency, intensity and duration of exercise that can be safe (i.e., does not exacerbate underlying inflammation) and effective (i.e., improves fitness and quality of life, promotes growth (in children)) for individuals with a chronic inflammatory disease.

CONCLUSION

In this systematic review of the literature we investigated the effects of acute and chronic exercise on various inflammatory markers in patients with a chronic inflammatory disease. It appears that training programs can attenuate chronic inflammation in some of these patients; however, single bouts of exercise might elicit an aggravated inflammatory response. The exercise training-induced response appears highly dependent on the type of disease, severity of the disease and the frequency, duration and intensity of the exercise intervention. This review highlighted a number of strengths and weaknesses of the studies analyzed and will serve to design future studies in this field. Results of this review reveal a major gap in our knowledge regarding the evidence for safe but effective exercise for patients with a chronic inflammatory disease.

ACKNOWLEDGEMENTS

REFERENCES

1. PEDro Scale. http://www.pedro.fhs.usyd.edu.au/scale_item.html. 2009.
2. Abbas AK, Lichtman AH and Pillai S. Cellular and Molecular Immunology, 6th Edition. WB Saunders, 2007.
3. Adamopoulos S, Parissis J, Karatzas D, Kroupis C, Georgiadis M, Karavolias G, Paraskevaidis J, Koniavitou K, Coats AJ and Kremastinos DT. Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure. J Am Coll Cardiol 39: 653-663, 2002.
4. Adamopoulos S, Parissis J, Kroupis C, Georgiadis M, Karatzas D, Karavolias G, Koniavitou K, Coats AJ and Kremastinos DT. Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. Eur Heart J 22: 791-797, 2001.
5. Agusti A, MacNee W, Donaldson K and Cosio M. Hypothesis: does COPD have an autoimmune component? Thorax 58: 832-834, 2003.
6. Arnardottir S, Alexanderson H, Lundberg IE and Borg K. Sporadic inclusion body myositis: pilot study on the effects of a home exercise program on muscle function, histopathology and inflammatory reaction. J Rehabil Med 35: 31-35, 2003.
7. Baquet G, Stratton G, Van PE and Berthoin S. Improving physical activity assessment in prepubertal children with high-frequency accelerometry monitoring: a methodological issue. Prev Med 44: 143-147, 2007.
8. Baquet G, van Praagh E and Berthoin S. Endurance training and aerobic fitness in young people. Sports Med 33: 1127-1143, 2003.
9. Baslund B, Lyngberg K, Andersen V, Halkjaer KJ, Hansen M, Klokker M and Pedersen BK. Effect of 8 wk of bicycle training on the immune system of patients with rheumatoid arthritis. J Appl Physiol 75: 1691-1695, 1993.
10. Baum M, Klopping-Menke K, Muller-Steinhardt M, Liesen H and Kirchner H. Increased concentrations of interleukin 1-beta in whole blood cultures supernatants after 12 weeks of moderate endurance exercise. Eur J Appl Physiol Occup Physiol 79: 500-503, 1999.
11. Bearne LM, Scott DL and Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology (Oxford) 41: 157-166, 2002.
12. Boas SR, Danduran MJ, McBride AL, McColley SA and O'Gorman MR. Postexercise immune correlates in children with and without cystic fibrosis. Med Sci Sports Exerc 32: 1997-2004, 2000.
13. Boas SR, Danduran MJ, McColley SA, Beaman K and O'Gorman MR. Immune modulation following aerobic exercise in children with cystic fibrosis. Int J Sports Med 21: 294-301, 2000.

14. Boas SR, Joswiak ML, Nixon PA, Kurland G, O'Connor MJ, Bufalino K, Orenstein DM and Whiteside TL. Effects of anaerobic exercise on the immune system in eight-to seventeen-year-old trained and untrained boys. J Pediatr 129: 846-855, 1996.

15. Brennan FM, Maini RN and Feldmann M. TNF alpha--a pivotal role in rheumatoid arthritis? Br J Rheumatol 31: 293-298, 1992.

16. Bruunsgaard H. Effects of tumor necrosis factor-alpha and interleukin-6 in elderly populations. Eur Cytokine Netw 13: 389-391, 2002.

17. Bruunsgaard H. Physical activity and modulation of systemic low-level inflammation. J Leukoc Biol 78: 819-835, 2005.

18. Castaneda C, Gordon PL, Parker RC, Uhlin KL, Roubenoff R and Levey AS. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. Am J Kidney Dis 43: 607-616, 2004.

19. Castellano V, Patel DI and White LJ. Cytokine Responses to Acute and Chronic Exercise in Multiple Sclerosis. J Appl Physiol 2008.

20. Chin APM, van Poppel MN, Twisk JW and van MW. Once a week not enough, twice a week not feasible? A randomised controlled exercise trial in long-term care facilities [ISRCTN87177281]. Patient Educ Couns 63: 205-214, 2006.

21. Cohen J. Statistical power analysis for the behavioral sciences (2nd ed). Hillsdale, NJ: Erlbaum, 1988.

22. Colbert LH, Visser M, Simonsick EM, Tracy RP, Newman AB, Kritchevsky SB, Pahor M, Taaffe DR, Brach J, Rubin S and Harris TB. Physical activity, exercise, and inflammatory markers in older adults: findings from the Health, Aging and Body Composition Study. J Am Geriatr Soc 52: 1098-1104, 2004.

23. Conraads VM, Beckers P, Bosmans J, De Clerck LS, Stevens WJ, Vrints CJ and Brutsaert DL. Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease. Eur Heart J 23: 1854-1860, 2002.

24. Cristofaro P and Opal SM. Role of Toll-like receptors in infection and immunity: clinical implications. Drugs 66: 15-29, 2006.

25. Dandona P, Aljada A and Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol 25: 4-7, 2004.

26. Dekker MJ, Lee S, Hudson R, Kilpatrick K, Graham TE, Ross R and Robinson LE. An exercise intervention without weight loss decreases circulating interleukin-6 in lean and obese men with and without type 2 diabetes mellitus. Metabolism 56: 332-338, 2007.

27. Fendrick AM and Greenberg BP. A review of the benefits and risks of nonsteroidal anti-inflammatory drugs in the management of mild-to-moderate osteoarthritis. Osteopath Med Prim Care 3: 1, 2009.

28. Fletcher GF, Balady G, Blair SN, Blumenthal J, Caspersen C, Chaitman B, Epstein S, Sivarajan Froelicher ES, Froelicher VF, Pina IL and Pollock ML. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation 94: 857-862, 1996.

29. Franch HA and Price SR. Molecular signaling pathways regulating muscle proteolysis during atrophy. Curr Opin Clin Nutr Metab Care 8: 271-275, 2005.

30. Galassetti PR, Iwanaga K, Crisostomo M, Zaldivar FP, Larson J and Pescatello A. Inflammatory cytokine, growth factor and counterregulatory responses to exercise in children with type 1 diabetes and healthy controls. Pediatr Diabetes 7: 16-24, 2006.

31. Galassetti PR, Iwanaga K, Pontello AM, Zaldivar FP, Flores RL and Larson JK. Effect of prior hyperglycemia on IL-6 responses to exercise in children with type 1 diabetes. Am J Physiol Endocrinol Metab 290: E833-E839, 2006.

32. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J and Zimmet P. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 26: 3160-3167, 2003.

33. Giacomini MK and Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 284: 357-362, 2000.

34. Gielen S, Adams V, Mobius-Winkler S, Linke A, Erbs S, Yu J, Kempf W, Schubert A, Schuler G and Hambrecht R. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. J Am Coll Cardiol 42: 861-868, 2003.

35. Gleeson M. Immune system adaptation in elite athletes. Curr Opin Clin Nutr Metab Care 9: 659-665, 2006.

36. Gleeson M. Immune function in sport and exercise. J Appl Physiol 103: 693-699, 2007.

37. Gleeson M, McFarlin B and Flynn M. Exercise and Toll-like receptors. Exerc Immunol Rev 12: 34-53, 2006.

38. Gokhale R, Chandrashekara S and Vasanthakumar KC. Cytokine response to strenuous exercise in athletes and non-athletes--an adaptive response. Cytokine 40: 123-127, 2007.

39. Goldhammer E, Tanchilevitch A, Maor I, Beniamini Y, Rosenschein U and Sagiv M. Exercise training modulates cytokines activity in coronary heart disease patients. Int J Cardiol 100: 93-99, 2005.

40. Gulmans V, van der LJ, Wattimena D, van DJ, Oostveen D, Berger R and de MK. Insulin-like growth factors and leucine kinetics during exercise training in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 32: 76-81, 2001.

41. Guyatt GH and Rennie D. Users' guides to the medical literature. JAMA 270: 2096-2097, 1993.

42. Heaney LG, Lindsay JT and McGarvey LPA. Inflammation in chronic obstructive pulmonary disease: Implications for new treatment strategies. Curr Med Chem 14: 787-796, 2007.

43. Heesen C, Gold SM, Hartmann S, Mladek M, Reer R, Braumann KM, Wiedemann K and Schulz KH. Endocrine and cytokine responses to standardized physical stress in multiple sclerosis. Brain Behav Immun 17: 473-481, 2003.

44. Higashimoto Y, Yamagata Y, Taya S, Iwata T, Okada M, Ishiguchi T, Sato H and Itoh H. Systemic inflammation in chronic obstructive pulmonary disease and asthma: Similarities and differences. Respirology 13: 128-133, 2008.

45. Hoebe K, Jiang Z, Georgel P, Tabeta K, Janssen E, Du X and Beutler B. TLR signaling pathways: opportunities for activation and blockade in pursuit of therapy. Curr Pharm Des 12: 4123-4134, 2006.

46. Hoffman I, Vermeire S, Van AG and Rutgeerts P. Infliximab for pediatric Crohn's disease. Drugs Today (Barc) 44: 615-628, 2008.

47. Hotamisligil GS. Inflammation and metabolic disorders. Nature 444: 860-867, 2006.

48. Ionescu AA, Mickleborough TD, Bolton CE, Lindley MR, Nixon LS, Dunseath G, Luzio S, Owens DR and Shale DJ. The systemic inflammatory response to exercise in adults with cystic fibrosis. J Cyst Fibros 5: 105-112, 2006.

49. Ischander M, Zaldivar F, Jr., Eliakim A, Nussbaum E, Dunton G, Leu SY, Cooper DM and Schneider M. Physical activity, growth, and inflammatory mediators in BMI-matched female adolescents. Med Sci Sports Exerc 39: 1131-1138, 2007.

50. King DE, Carek P, Mainous AG, III and Pearson WS. Inflammatory markers and exercise: differences related to exercise type. Med Sci Sports Exerc 35: 575-581, 2003.

51. Kinugawa T, Kato M, Ogino K, Osaki S, Tomikura Y, Igawa O, Hisatome I and Shigemasa C. Interleukin-6 and tumor necrosis factor-alpha levels increase in response to maximal exercise in patients with chronic heart failure. Int J Cardiol 87: 83-90, 2003.

52. Lancaster GI, Khan Q, Drysdale P, Wallace F, Jeukendrup AE, Drayson MT and Gleeson M. The physiological regulation of toll-like receptor expression and function in humans. J Physiol 563: 945-955, 2005.

53. Larsen AI, Aukrust P, Aarsland T and Dickstein K. Effect of aerobic exercise training on plasma levels of tumor necrosis factor alpha in patients with heart failure. Am J Cardiol 88: 805-808, 2001.

54. LeMaitre JP, Harris S, Fox KA and Denvir M. Change in circulating cytokines after 2 forms of exercise training in chronic stable heart failure. Am Heart J 147: 100-105, 2004.

55. Lucia A, Smith L, Naidoo M, Gonzalez-Freire M, Perez M, Rubio JC, Martin MA, Andreu AL and Arenas J. McArdle disease: Another systemic low-inflammation disorder? Neurosci Lett 431: 106-111, 2008.

56. Mackinnon LT. Chronic exercise training effects on immune function. Med Sci Sports Exerc 32: S369-S376, 2000.

57. Malm C. Exercise immunology: the current state of man and mouse. 2004.

58. Meckel Y, Eliakim A, Seraev M, Zaldivar F, Cooper DM, Sagiv M and Nemet D. The effect of a brief sprint interval exercise on growth factors and inflammatory mediators. J Strength Cond Res 23: 225-230, 2009.

59. Mohamed-Ali V, Armstrong L, Clarke D, Bolton CH and Pinkney JH. Evidence for the regulation of levels of plasma adhesion molecules by proinflammatory cytokines and their soluble receptors in type 1 diabetes. J Intern Med 250: 415-421, 2001.

60. Moldoveanu AI, Shephard RJ and Shek PN. Exercise elevates plasma levels but not gene expression of IL-1beta, IL-6, and TNF-alpha in blood mononuclear cells. J Appl Physiol 89: 1499-1504, 2000.

61. Nemet D, Oh Y, Kim HS, Hill M and Cooper DM. Effect of intense exercise on inflammatory cytokines and growth mediators in adolescent boys. Pediatrics 110: 681-689, 2002.

62. Nicklas BJ, Hsu FC, Brinkley TJ, Church T, Goodpaster BH, Kritchevsky SB and Pahor M. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. J Am Geriatr Soc 56: 2045-2052, 2008.

63. Niebauer J, Clark AL, Webb-Peploe KM and Coats AJ. Exercise training in chronic heart failure: effects on pro-inflammatory markers. Eur J Heart Fail 7: 189-193, 2005.

64. Nieman DC, Brendle D, Henson DA, Suttles J, Cook VD, Warren BJ, Butterworth DE, Fagoaga OR and Nehlsen-Cannarella SL. Immune function in athletes versus nonathletes. Int J Sports Med 16: 329-333, 1995.

65. Northoff H, Symons S, Zieker D, Schaible EV, Schafer K, Thoma S, Loffler M, Abbasi A, Simon P, Niess AM and Fehrenbach E. Gender- and menstrual phase

dependent regulation of inflammatory gene expression in response to aerobic exercise. Exerc Immunol Rev 14: 86-103, 2008.

66. Oudijk EJ, Lammers JW and Koenderman L. Systemic inflammation in chronic obstructive pulmonary disease. Eur Respir J Suppl 46: 5s-13s, 2003.

67. Pedersen BK and Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev 80: 1055-1081, 2000.

68. Pedersen BK and Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scandinavian Journal of Medicine Science in Sports 16: 2006.

69. Pedersen BK, Tvede N, Christensen LD, Klarlund K, Kragbak S and Halkjr-Kristensen J. Natural killer cell activity in peripheral blood of highly trained and untrained persons. Int J Sports Med 10: 129-131, 1989.

70. Pedersen BK, Tvede N, Halkjaer-Kristensen J, Baslund B and Steensberg J. Cellular Immunity in Highly Trained Elite Racing Cyclists During Periods of Training With High and Low Intensity. Scandinavian Journal of Medicine and Science in Sports 1: 163-166, 1991.

71. Petersen AM and Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol 98: 1154-1162, 2005.

72. Pullen PR, Nagamia SH, Mehta PK, Thompson WR, Benardot D, Hammoud R, Parrott JM, Sola S and Khan BV. Effects of yoga on inflammation and exercise capacity in patients with chronic heart failure. J Card Fail 14: 407-413, 2008.

73. Rabinovich RA, Figueras M, Ardite E, Carbo N, Troosters T, Filella X, Barbera JA, Fernandez-Checa JC, Argiles JM and Roca J. Increased tumour necrosis factor-alpha plasma levels during moderate-intensity exercise in COPD patients. Eur Respir J 21: 789-794, 2003.

74. Rall LC, Roubenoff R, Cannon JG, Abad LW, Dinarello CA and Meydani SN. Effects of progressive resistance training on immune response in aging and chronic inflammation. Med Sci Sports Exerc 28: 1356-1365, 1996.

75. Rosa JS, Oliver SR, Mitsuhashi M, Flores RL, Pontello AM, Zaldivar FP and Galassetti PR. Altered kinetics of interleukin-6 and other inflammatory mediators during exercise in children with type 1 diabetes. J Investig Med 56: 701-713, 2008.

76. Scheett TP, Mills PJ, Ziegler MG, Stoppani J and Cooper DM. Effect of exercise on cytokines and growth mediators in prepubertal children. Pediatr Res 46: 429-434, 1999.

77. Scheett TP, Nemet D, Stoppani J, Maresh CM, Newcomb R and Cooper DM. The effect of endurance-type exercise training on growth mediators and inflammatory cytokines in pre-pubertal and early pubertal males. Pediatr Res 52: 491-497, 2002.

78. Schulz KH, Gold SM, Witte J, Bartsch K, Lang UE, Hellweg R, Reer R, Braumann KM and Heesen C. Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. J Neurol Sci 225: 11-18, 2004.

79. Schwindt CD, Zaldivar F, Wilson L, Leu SY, Wang-Rodriguez J, Mills PJ and Cooper DM. Do circulating leucocytes and lymphocyte subtypes increase in response to brief exercise in children with and without asthma? Br J Sports Med 41: 34-40, 2007.

80. Sothern MS. The health benefits of physical activity in children and adolescents: implications for chronic disease prevention. 1999.

81. Spector SA, Lemmer JT, Koffman BM, Fleisher TA, Feuerstein IM, Hurley BF and Dalakas MC. Safety and efficacy of strength training in patients with sporadic inclusion body myositis. Muscle Nerve 20: 1242-1248, 1997.

82. Spruit MA, Troosters T, Gosselink R, Kasran A and Decramer M. Acute inflammatory and anabolic systemic responses to peak and constant-work-rate exercise bout in hospitalized patients with COPD. Int J Chron Obstruct Pulmon Dis 2: 575-583, 2007.

83. Stewart LK, Flynn MG, Campbell WW, Craig BA, Robinson JP, Timmerman KL, McFarlin BK, Coen PM and Talbert E. The influence of exercise training on inflammatory cytokines and C-reactive protein. Med Sci Sports Exerc 39: 1714-1719, 2007.

84. Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K and Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. Exerc Immunol Rev 8: 6-48, 2002.

85. Swain DP and Franklin BA. VO(2) reserve and the minimal intensity for improving cardiorespiratory fitness. Med Sci Sports Exerc 34: 152-157, 2002.

86. Tahan F, Karaaslan C, Aslan A, Kiper N and Kalayci O. The role of chemokines in exercise-induced bronchoconstriction in asthma. Ann Allergy Asthma Immunol 96: 819-825, 2006.

87. Timmerman KL, Flynn MG, Coen PM, Markofski MM and Pence BD. Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? J Leukoc Biol 84: 1271-1278, 2008.

88. Timmons BW. Immune responses to exercise in children: A brief review. Ped Exerc Sci 18: 290-299, 2005.

89. Timmons BW. Paediatric exercise immunology: health and clinical applications. Exerc Immunol Rev 11: 108-144, 2005.

90. Timmons BW and Bar-Or O. Lymphocyte expression of CD95 at rest and in response to acute exercise in healthy children and adolescents. Brain Behav Immun 21: 442-449, 2007.

91. Timmons BW, Hamadeh MJ, Devries MC and Tarnopolsky MA. Influence of gender, menstrual phase, and oral contraceptive use on immunological changes in response to prolonged cycling. J Appl Physiol 99: 979-985, 2005.

92. Timmons BW, Hamadeh MJ and Tarnopolsky MA. Two methods for determining plasma IL-6 in humans at rest and following exercise. Eur J Appl Physiol 105: 13-18, 2009.

93. Timmons BW and Raha S. A pediatric perspective on inflammation and oxidative stress in response to exercise. Appl Physiol Nutr Metab 33: 411-419, 2008.

94. Timmons BW, Tarnopolsky MA and Bar-Or O. Sex-based effects on the distribution of NK cell subsets in response to exercise and carbohydrate intake in adolescents. J Appl Physiol 100: 1513-1519, 2006.

95. Timmons BW, Tarnopolsky MA, Snider DP and Bar-Or O. Immunological changes in response to exercise: influence of age, puberty, and gender. Med Sci Sports Exerc 38: 293-304, 2006.

96. Timmons BW, Tarnopolsky MA, Snider DP and Bar-Or O. Puberty effects on NK cell responses to exercise and carbohydrate intake in boys. Med Sci Sports Exerc 38: 864-874, 2006.

97. Tirakitsoontorn P, Nussbaum E, Moser C, Hill M and Cooper DM. Fitness, acute exercise, and anabolic and catabolic mediators in cystic fibrosis. Am J Respir Crit Care Med 164: 1432-1437, 2001.

98. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T and McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 40: 181-188, 2008.

99. Van Helvoort HA, Heijdra YF, Thijs HM, Vina J, Wanten GJ and Dekhuijzen PN. Exercise-induced systemic effects in muscle-wasted patients with COPD. Med Sci Sports Exerc 38: 1543-1552, 2006.

100. Van Helvoort HA, van de Pol MH, Heijdra YF and Dekhuijzen PN. Systemic inflammatory response to exhaustive exercise in patients with chronic obstructive pulmonary disease. Respir Med 99: 1555-1567, 2005.

101. Vogiatzis I, Stratakos G, Simoes DC, Terzis G, Georgiadou O, Roussos C and Zakynthinos S. Effects of rehabilitative exercise on peripheral muscle TNFalpha, IL-6, IGF-I and MyoD expression in patients with COPD. Thorax 62: 950-956, 2007.

102. White LJ, Castellano V and Mc Coy SC. Cytokine responses to resistance training in people with multiple sclerosis. J Sports Sci 24: 911-914, 2006.

103. Wilmore JH and Costill DL. Physiology of Sport and Exercise. Human Kinetics, Champaign IL, 1994.

104. Wong SC, Macrae VE, McGrogan P and Ahmed SF. The role of pro-inflammatory cytokines in inflammatory bowel disease growth retardation. J Pediatr Gastroenterol Nutr 43: 144-155, 2006.

105. Woods J, Lu Q, Ceddia MA and Lowder T. Special feature for the Olympics: effects of exercise on the immune system: exercise-induced modulation of macrophage function. Immunol Cell Biol 78: 545-553, 2000.

106. Wouters EF. Management of severe COPD. Lancet 364: 883-895, 2004.

107. Zoico E and Roubenoff R. The role of cytokines in regulating protein metabolism and muscle function. Nutr Rev 60: 39-51, 2002.