Exercise and Inflammation in Pediatric Crohn's Disease

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Key words
- children
- cycle ergometry
- cytokines
- growth factors
- inflammatory bowel disease

Abstract

We examined inflammatory cells, cytokines and growth factors in response to acute bouts of moderate intensity continuous exercise and high intensity intermittent exercise in youth with Crohn's disease and in healthy matched-controls. 15 patients and 15 controls performed 30 min of cycling at 50 % of peak mechanical power (PMP) and 6 bouts of 4 × 15-s of cycling at 100 % PMP. Blood was collected at rest, at the mid-point, at the end of exercise and at 30 and 60 min into recovery. In patients with CD, both types of exercise increased immune cells and GH and decreased IGF-I. Moderate intensity exercise induced a greater increase in leukocytes ($p < 0.05$), neutrophils ($p < 0.05$), lymphocytes ($p < 0.001$), monocytes ($p < 0.05$), IL-6 ($p < 0.05$), IL-17 ($p < 0.05$) and GH ($p < 0.05$) and a similar decrease in IGF-I, compared with high intensity exercise. TNF-α did not change significantly with either exercise. Responses in patients were similar compared with controls; however, in patients monocytes remained elevated significantly longer in response to MICE. Youth with Crohn's disease can engage in distinctly different types of exercise without a significant acute exacerbation of inflammation.

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect both the small and large intestines. In North America and Europe the incidence and prevalence of CD is high compared to other parts of the world [16]. Canada is the leading country in CD incidence, with an estimated prevalence at 338 per 100 000 people for CD [3] and recently published data on pediatric inflammatory bowel disease in southwestern Ontario (the largest province in Canada) showed that the incidence of CD in children nearly doubled from 3.5 to 6.1 per 100 000 children between 2002 and 2006 [12].

CD is characterized by inflammation both at the site of the mucosa and in the periphery [27] and low levels of the anabolic hormone insulin-like growth factor-I (IGF-I) in the circulation [30]. The altered immune function is primarily associated with a T-helper 1 mediated cell response and a chronic dysregulation of the innate immune system resulting in increased cytokine secretion. Tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6 are thought to play key roles in growth failure of children with CD [29] and recently the role of IL-17 has been recognized [1]; IL-17 is believed to contribute to the pathogenesis of CD and it can enhance the secretion of other pro-inflammatory cytokines such as IL-6 [1]. TNF-α is associated with muscle cachexia [26] and may, together with other altered cytokines in CD pathology, impact exercise capacity. In fact, low levels of both aerobic and anaerobic capacity have been reported in youth with CD [25].

Regular exercise may be beneficial for children with CD, not only to improve exercise capacity, but because this type of exercise is considered anti-inflammatory [24] and has the potential to exert anabolic properties that may stimulate growth and development [15]. However, single bouts of exercise in healthy persons are known to activate the very same inflammatory markers (e.g., IL-6) involved in the pathology of CD [31], although we do not know if a single bout of exercise will have the same effects in children with CD. It is possible that single sessions of exercise in patients with CD might elicit an exacerbated inflammatory response, as has been demonstrated in children with cystic fibrosis [34]. This apparent paradox between acute changes to sin-

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Bibliography
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gle bouts of exercise vs. chronic adaptations to regular exercise demands further study.

Understanding the impact of acute bouts of exercise on inflammatory markers and growth factors is important when designing safe and effective exercise programs. For youth with CD, safe exercise should be that which does not exacerbate the underlying pathology while promoting the growth factors involved in positive adaptations to exercise. Current exercise programs for children are often based on continuous exercise of moderate intensity reflecting the traditional adult-based approach to exercise prescription to improve endurance. However, shorter bouts of intense intermittent exercise can elicit similar metabolic adaptations compared to more lengthy, continuous exercise [6] and are associated with smaller cytokine changes [5]. Moreover, intermittent exercise also reflects children's natural physical activity patterns [2], which may improve exercise adherence. Consequently, a clearer understanding of the effects of different types of exercise on inflammatory cytokines and growth factors in youth with CD is needed.

The aims of this study were 1) to investigate the effects of moderate intensity continuous exercise (MICE) and high intensity intermittent exercise (HIIE) on key markers of inflammation and growth relevant to children with CD, and 2) to compare these responses with healthy matched-controls. MICE reflects the traditional adult-based exercise bout whereas HIIE reflects the natural physical activity patterns seen in children [2]. It was hypothesized that, 1) compared with MICE, HIIE will induce smaller inflammatory changes, but similar or greater growth factor responses given its relevance to children's natural physical activity behavior, and 2) children with CD would have greater inflammatory response and similar growth factor response compared to healthy matched-controls.

Material and Methods

Patients

20 patients with CD volunteered to participate in this study, which was approved by our local Research Ethics Board and performed in accordance with the ethical standards of the International Journal of Sports Medicine [13]. Healthy control participants were recruited from the local community by advertisement. Patients and controls were matched by gender and biological age, as determined by the estimated years from the age of peak height velocity [19]. All participants and their legally authorized representative gave written consent after the study purpose and procedures were explained. Patients included in this study were those who were in remission as determined by a score <10 on the Pediatric Crohn's Disease Activity Index (PCDAI). Exclusion criteria were active disease as determined by PCDAI within the previous 2 weeks, and in females, the use of any form of contraceptives. Of the 20 patients who volunteered to participate, 16 completed all aspects of the study and 15 were included in the data analysis. 1 patient was excluded due to illness (seasonal flu) at the time of testing. 4 patients dropped out after the first visit, 2 due to personal reasons unrelated to the study procedures and 2 due to problems related to their disease (although not caused or triggered by the exercise sessions). Characteristics of the 15 patients and 15 healthy matched-controls are presented in **Table 1**, missing data is due to soft- or hardware malfunction. Patients' mean PCDAI scores were 0.6±2.1 (range 0–7.5) and mean disease duration was 3.1±1.9 years. 2 patients had undergone ileocecal restriction in the past. As is common in this population, the majority of patients were receiving medication (5-ASA n=13, azathioprine n=4, methotrexate n=2, infliximab n=1).

Table 1 Participants anthropometric and fitness characteristics.

	Patients (n=15) Mean±SD	Healthy matched-controls (n=15) Mean±SD
age (years)	14.5±2.4	13.9±2.2
gender (f/m)	2/13	2/13
pubertal status (tanner stage)	4.0 [2/5] (1–5)[a]	4.0 [3/5] (1–5)[a]
years from peak height velocity	1.0±2.2	0.8±2.1
height (cm)	163.4±12.9	167.7±14.8
sitting height (cm)	86.4±7.4	87.1±7.3
weight (kg)	51.7±11.6	55.4±13.8
BMI (kg/m^2)	19.1±2.3	19.3±2.3
BMI percentile	35.0±22.2	48.2±20.6
FFM (kg)	44.3±10.6	48.0±12.1[b]
% Body fat	14.5±5.14	13.4±6.4
WC (cm)	70.2±5.1	70.2±6.3
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})*	43.9±9.9[b]	53.6±7.9
W_{peak} (Watts·kg^{-1})	3.6±0.7	3.9±0.6
HR_{peak} (beats·min^{-1})	191±7	186±8[b]
RER_{peak}	1.29±0.14[b]	1.22±0.10[b]

f: females, m: male, [a]: median [25th/75th percentile] (range), BMI: body mass index, FFM: fat free mass, [b]: n=14, WC: waist circumference, $\dot{V}O_{2peak}$: peak oxygen uptake, *: significant difference between groups $p<0.05$, W_{peak}: peak aerobic mechanical power, HR_{peak}: peak heart rate, RER_{peak}: peak respiratory exchange ratio

Preliminary session

Each participant underwent assessments of anthropometry, including height, sitting height (Harpender wall-mounted Stadiometer 2109, CMS Weighing Equipment, Ltd, London, UK), waist circumference (WC, measured 4 cm above the navel using a standard anthropometry tape), body mass (Digital Electronic Professional Personal Scale, model BWB-800, Tanita Corporation, Tokyo, Japan), and percentage body fat estimated by bioelectrical impedance analysis (RJL model BIA-101 A; RJL Systems Inc, Clinton Township, MI). Pubertal development was self-assessed using the criteria of Tanner (pubic hair for boys; breast development for girls). Body mass index (BMI) was calculated as weight (kg)÷height^2 (m), height-for-age and BMI percentiles were calculated using CDC growth charts. Peak aerobic power (VO_{2peak}) was then assessed on a cycle ergometer (Metabo-Fleisch, Basel, Switzerland) using the McMaster All-Out Progressive Continuous Cycling test, as previously described [25]. Peak aerobic mechanical power (W_{peak}) was taken as the highest achieved workload during the exercise test, prorated according to the time point of termination in an exercise test stage. The test duration ranged between 8–13 min for patients and 9–16 min for controls, and was terminated when pedaling rate dropped below 60 rpm for more than 30 s and the participant could not keep up despite strong verbal encouragement.

Experimental sessions

A time interval of approximately 1 week was set between 2 experimental sessions. Prior to the first experimental session, participants recorded their food intake the day before and the day of the visit and they were asked to refrain from consuming any fast food. A copy of the food log was made at the first exper-

imental visit and returned to the participants so they could duplicate their diet as best as possible before the next experimental visit. 3 h prior to both experimental visits, participants were asked to refrain from eating or drinking with the exception of water. Participants were permitted to maintain their normal exercise activity over the course of the study, but to refrain from strenuous exercise 24 h prior to each experimental visit. Female participants completed the experimental visits between the first and tenth day of their menstrual cycle.

Participants visited the laboratory at the same time of the day for their experimental visits. After a 10-min supine rest, a 22- or 24-gauge plastic catheter (Becton Dickinson Infusion Therapy Systems Inc., Sandy, UT) was placed into the antecubital vein of either the right or left arm for ease of blood collection and a pre-exercise blood sample (REST) was taken. Following the resting blood sample, the participant began one of the exercise protocols (MICE or HIIE). For MICE, participants cycled at 50 % of their W_{peak}, as determined in the preliminary session. The exercise task consisted of 2 bouts of 30 min each performed at 60 rpm with a 6-min rest between bouts. The total exercise duration was 60 min. For HIIE, participants cycled at 100 % of their W_{peak}. The exercise task consisted of a set of 4 bouts of 15-s each performed at 60 rpm with a 1-min rest between bouts. This set was repeated 6 times with a 6-min rest between each set. The total exercise duration was 6 min.

Upon completing each exercise, participants remained seated on a chair, in the same room where the exercise was performed, for a 1-h recovery period. Participants were only allowed to move about when they had to use the washroom. During and after the exercise, participants could drink water ad libitum and they watched a DVD of their choice. In addition to the REST blood sample, blood samples were taken at the mid-point of exercise (EX-MID), at the end of exercise (EX-END), and at 30 min (REC-MID) and 60 min (REC-END) after the end of the exercise. The catheter was flushed after every blood sample with approximately 3 mL of sterile saline (0.9 % NaCl). Consequently, the first few mL of blood at each sampling time were discarded.

Measurements

Blood was collected in EDTA containing vacutainers (2 mL) for complete blood counts analysis at the McMaster University Medical Centre Core Laboratory. Blood was analyzed for total leukocytes, neutrophils, lymphocytes, monocytes, hemoglobin and hematocrit using an automated Coulter counter. Hemoglobin and hematocrit were used to calculate changes in blood and plasma volume to correct both inflammatory cytokine and growth factor concentrations for exercise-induced changes in plasma volume [8].

Inflammatory cytokines and growth factors

Blood was collected in pre-cooled EDTA containing vacutainers (10 mL) and kept on ice for 30 min. Samples were then centrifuged for 20 min at 2 000 g and 4 °C, then directly aliquotted and stored at −20 °C until further analysis. For each sampling time point, plasma samples were assayed in duplicate for TNF-α, IL-6, IL-17, total IGF-I and GH by enzyme-linked immunosorbent assay (ELISA). All kits were purchased from R&D Systems (Minneapolis, MN) except for IL-17 (BioSource International, Inc., Cammarillo, CA). All assays were performed in accordance with the manufacturer's instructions. The lowest sensitivities of these kits, as reported by the manufacturer, are 0.0038 $pg \cdot mL^{-1}$ (TNF-α), 0.016 $pg \cdot mL^{-1}$ (IL-6), 2 $pg \cdot mL^{-1}$ (IL-17), 0.007 $ng \cdot mL^{-1}$ (IGF-I) and 0.64 $ng \cdot mL^{-1}$ (GH). In patients, 8 out of 160 samples (REST or REC) were below the minimum detection level and were therefore set to the lowest value detectable in the assay. In patients, intra-assay coefficients of variation (CV) for the 160 samples assayed averaged 6.5 % for TNF-α, 3.4 % for IL-6, 4.6 % for IL-17, 2.2 % for IGF-I and 3.1 % for GH. Inter-assay CVs averaged 4.0 % for all inflammatory cytokines and growth factors. In controls intra-assay CVs were 4.21 % for TNF-α, 4.1 % for IL-6, 2.6 % for IGF-1, 2.7 % for GH and inter-assay CVs averaged 4.8 % for all inflammatory cytokines and growth factors.

Statistical analysis

The data were analyzed using SPSS 13.0. Differences in baseline variables between patients with CD and healthy matched-control were tested using independent-samples t tests. To determine the effects of exercise on immune cell measures, inflammatory cytokines and growth factors, we used 1-way repeated measures analysis of variance (ANOVA) separately in patients and controls for both MICE and HIIE, with the 5 time points as the within subject factor (main effect of time). A manual Tukey's post-hoc test was used to determine significant differences from resting values when the main effect of time revealed significance. The difference scores from rest were then analyzed by a 2-way repeated-measures ANOVA with time (4 levels) and exercise type (2 levels) as within-subject factors. Differences between patients and controls were analyzed by a 2-way repeated-measures ANOVA with time (4 levels) as within-subject factor and group (2 levels) as between-subject factors. We used the difference scores to eliminate variance found in resting levels of cytokines and growth factors between the participants and to highlight the magnitude of the effect of exercise. When the exercise × time interaction revealed significance comparisons between the 2 types of exercise at the different time points were made with Bonferroni corrected paired t-tests. Due to the small number of patients with detectable IL-17 levels, a Friedman test was used only to explore the main effect of exercise on this cytokine. Data are presented as means ± SD. The statistical significance was set at $p < 0.05$.

Results

Participants

Maximal effort on the $\dot{V}O_{2peak}$ test during the first visit was confirmed by the HR_{peak} and RER_{peak} values. Resting levels of immune cells, inflammatory cytokines, and growth factors are provided in **Table 2**. There were no significant differences in resting values between the 2 experimental visits for both groups; therefore the mean of the 2 visits was taken when comparisons for baseline values between groups were made. 8 patients were lymphopenic according to reference values for age and gender provided by the core laboratory.

Immune cell responses to exercise

All immune cell responses are presented in **Fig. 1**.

Leukocytes: There was no significant difference in leukocyte response between patients and controls for both MICE and HIIE (time × group, both $p > 0.05$). Total circulating leukocytes increased significantly in both patients and controls with MICE (time, both $p < 0.001$) and HIIE (time, both $p < 0.05$); however, the degree of change was greater with MICE in patients and controls (time × exercise, both $p < 0.05$).

Table 2 Resting levels of immune cells, inflammatory cytokines, and growth factors.

	Patients (n = 15)		Healthy matched-controls (n = 15)	
	MICE	HIIE	MICE	HIIE
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
leukocytes ($10^9 \cdot L^{-1}$)	6.9 ± 2.0	7.4 ± 1.8	6.0 ± 1.4	6.4 ± 1.7
neutrophils ($10^9 \cdot L^{-1}$)*	4.4 ± 1.9	4.9 ± 1.8	2.9 ± 0.9	3.4 ± 1.4
lymphocytes ($10^9 \cdot L^{-1}$)*	1.6 ± 0.6	1.5 ± 0.6	2.4 ± 0.6	2.2 ± 0.6
monocytes ($10^9 \cdot L^{-1}$)*	0.6 ± 0.2	0.6 ± 0.3	0.5 ± 0.1	0.5 ± 0.2
TNF-α ($pg \cdot mL^{-1}$)	1.6 ± 1.5	2.4 ± 3.9	0.9 ± 0.3	1.0 ± 0.4
IL-6 ($pg \cdot mL^{-1}$)*	5.9 ± 5.5	6.3 ± 4.9	1.0 ± 0.8	1.3 ± 1.5
IL-17 ($pg \cdot mL^{-1}$)	32.4 ± 48.4[a]	25.1 ± 35.0[a]	N/A ± N/A	N/A ± N/A
IGF-I ($ng \cdot mL^{-1}$)*	133.9 ± 69.9	131.3 ± 65.7	182.4 ± 72.2	184.2 ± 68.9
GH ($ng \cdot mL^{-1}$)	2.2 ± 2.8	5.4 ± 6.5	3.8 ± 4.7	1.4 ± 2.0

*significant difference between groups $p \leq 0.05$, TNF: tumor necrosis factor, IL: interleukin, [a]: n = 6, N/A: Not Applicable, IGF: insulin-like growth factor, GH: growth hormone

Neutrophils: There was no significant difference in neutrophil response between patients and controls for MICE and HIIE (time × group, both $p > 0.05$). Total circulating neutrophils increased significantly in MICE for patients and controls (time, both $p < 0.001$). For HIIE a significant increase was seen in patients (time, $p < 0.05$), but not for controls (time, $p > 0.05$). The degree of change was greater with MICE for both patients and controls (time x exercise, both $p < 0.05$). With MICE, leukocytes and neutrophils continued to increase into the recovery period and remained significantly elevated compared to resting values.

Lymphocytes: There was no significant difference in lymphocyte response between patients and controls for both MICE and HIIE (time × group, both $p > 0.05$). In both groups a significant effect over time was seen for MICE and HIIE (time, $p < 0.001$ and $p < 0.05$ respectively). For both patients and controls, levels increased significantly more during and at the end of MICE compared with HIIE (time × exercise, $p < 0.001$), but returned to baseline levels by REC-MID.

Monocytes: For monocytes a significant difference between patients and controls was seen for MICE (time × group, $p < 0.05$). In patients a significant effect of both exercise types was seen (time, both $p < 0.001$). With MICE, monocytes increased significantly at EX-END and remained elevated into the recovery period. With HIIE, levels tended towards an increase but decreased in recovery (time × exercise, $p < 0.05$). In controls a significant effect of MICE was seen (time, $p < 0.001$), but not for HIIE (time, $p > 0.05$), there was no significant difference between MICE and HIIE (time x exercise, $p > 0.05$).

Inflammatory cytokine responses to exercise

All cytokine responses are presented in **Fig. 2**.

TNF-α: There was no significant difference in TNF-α response between patients and controls for both MICE and HIIE (time × group, both $p > 0.05$). In patients TNF-α did not change with either exercise protocol (time and time × exercise, $p > 0.05$). In controls TNF-α changed significantly with MICE (time, $p < 0.05$), but not with HIIE (time, $p > 0.05$), there was no significant interaction effect between MICE and HIIE (time × exercise, $p > 0.05$).

IL-6: A significant difference between patients and controls was found for MICE (time × group, $p < 0.05$). In patients IL-6 significantly increased at EX-END in MICE but then returned to baseline levels by REC-END (time, $p < 0.001$). In controls a similar response was seen, however levels remained elevated until the end of the recovery period (time, $p < 0.001$). Values did not change significantly with HIIE in patients or controls (time, both $p > 0.05$). A significant interaction effect between MICE and HIIE was seen for patients and controls (time × exercise, $p < 0.05$ and $p < 0.001$, respectively).

IL-17 was detectable in 6 patients, a significant time effect was only seen for MICE ($p < 0.05$). Since IL-17 is not expected to be detectable in healthy persons, we did not perform analyses on samples from the healthy matched-controls.

Growth factor responses to exercise

All growth factor responses are presented in **Fig. 3**.

IGF-I: There was no significant difference in IGF-I response between patients and controls for both MICE and HIIE (time × group, both $p > 0.05$). In patients IGF-I showed the same pattern (time × exercise, $p > 0.05$) with both MICE and HIIE (time, $p < 0.001$ and $p < 0.05$, respectively). During and at the end of exercise levels decreased but returned back to baseline levels by REC-MID. In controls no significant change was seen in MICE and HIIE (time, both $p > 0.05$ and time x exercise, $p > 0.05$)

GH: There was no significant difference in GH response between patients and controls for both MICE and HIIE (time × group, both $p > 0.05$). In patients GH changed with both MICE and HIIE (time, $p < 0.001$ and 0.05, respectively), however only the MICE levels at EX-MID and EX-END were significantly greater than baseline levels (time × exercise, $p < 0.05$). In controls, GH increased with both MICE and HIIE (time, both $p < 0.001$) and a significant interaction effect was found (time × exercise, $p < 0.05$).

Discussion

This study investigated the effects of 2 different types of exercise on immune cells, inflammatory cytokines and growth factors in youth with CD, and compared these with healthy matched-controls. Studying exercise and inflammation in patients with CD is important to help inform safe and effective exercise prescription. In patients with CD we found that MICE induced a greater increase in leukocytes, neutrophils, lymphocytes, monocytes, IL-6 and GH and a similar decrease in IGF-I compared with HIIE. Similar responses were found in the control group, with only a significant difference between patients and controls for monocytes and IL-6 following the MICE exercise.

For MICE compared to HIIE, leukocytes and neutrophils continued to increase into the recovery period, lymphocytes increased during and directly after the exercise and returned to baseline

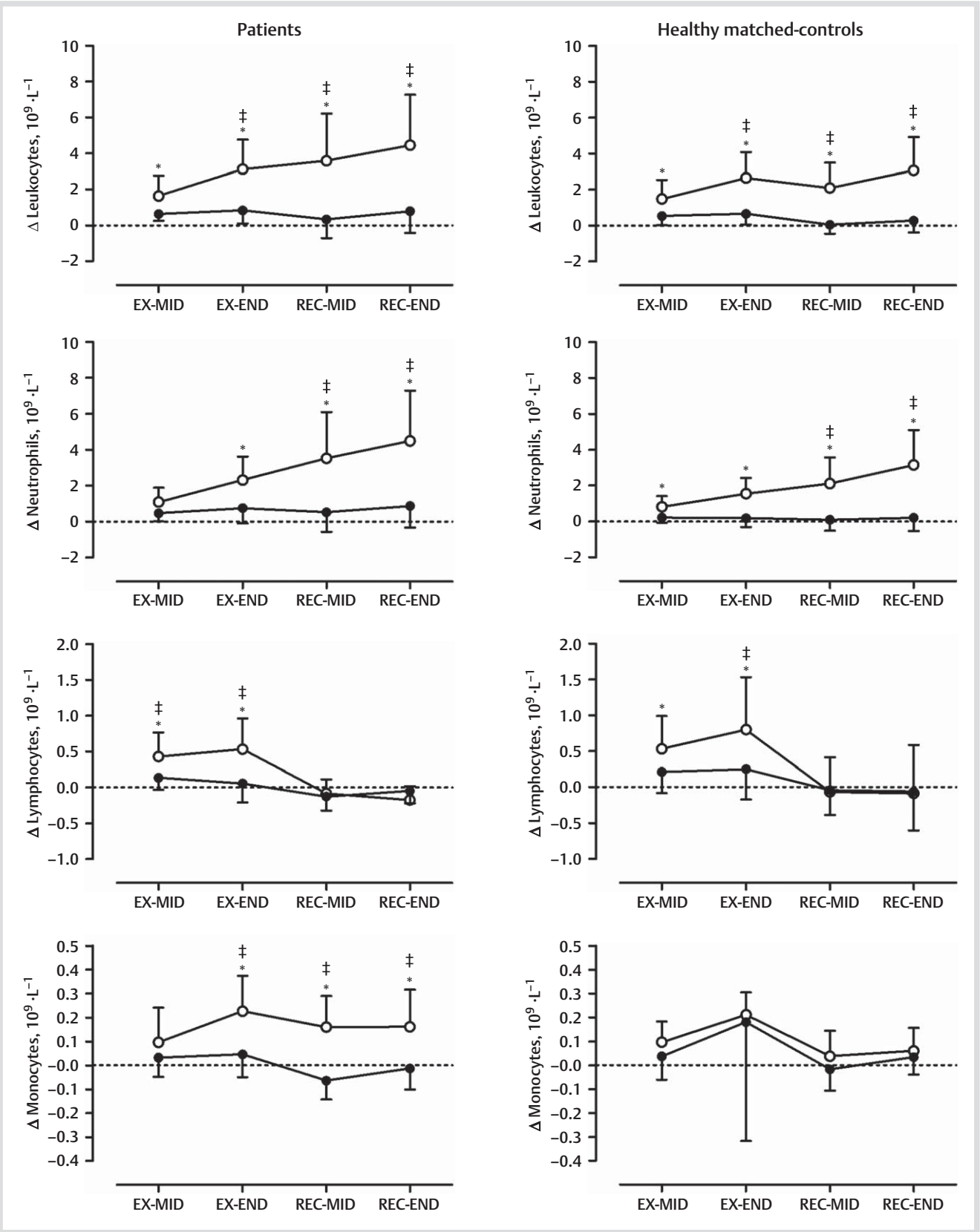

Fig. 1 Immune cell responses to MICE and HIIE in patients with CD (left column) and healthy matched-controls (right column). Data are expressed as means ± SD. MICE: open circles, HIIE: closed circles. *: significant difference at $p < 0.05$ between MICE and HIIE, ‡: significant difference at $p < 0.05$ from rest.

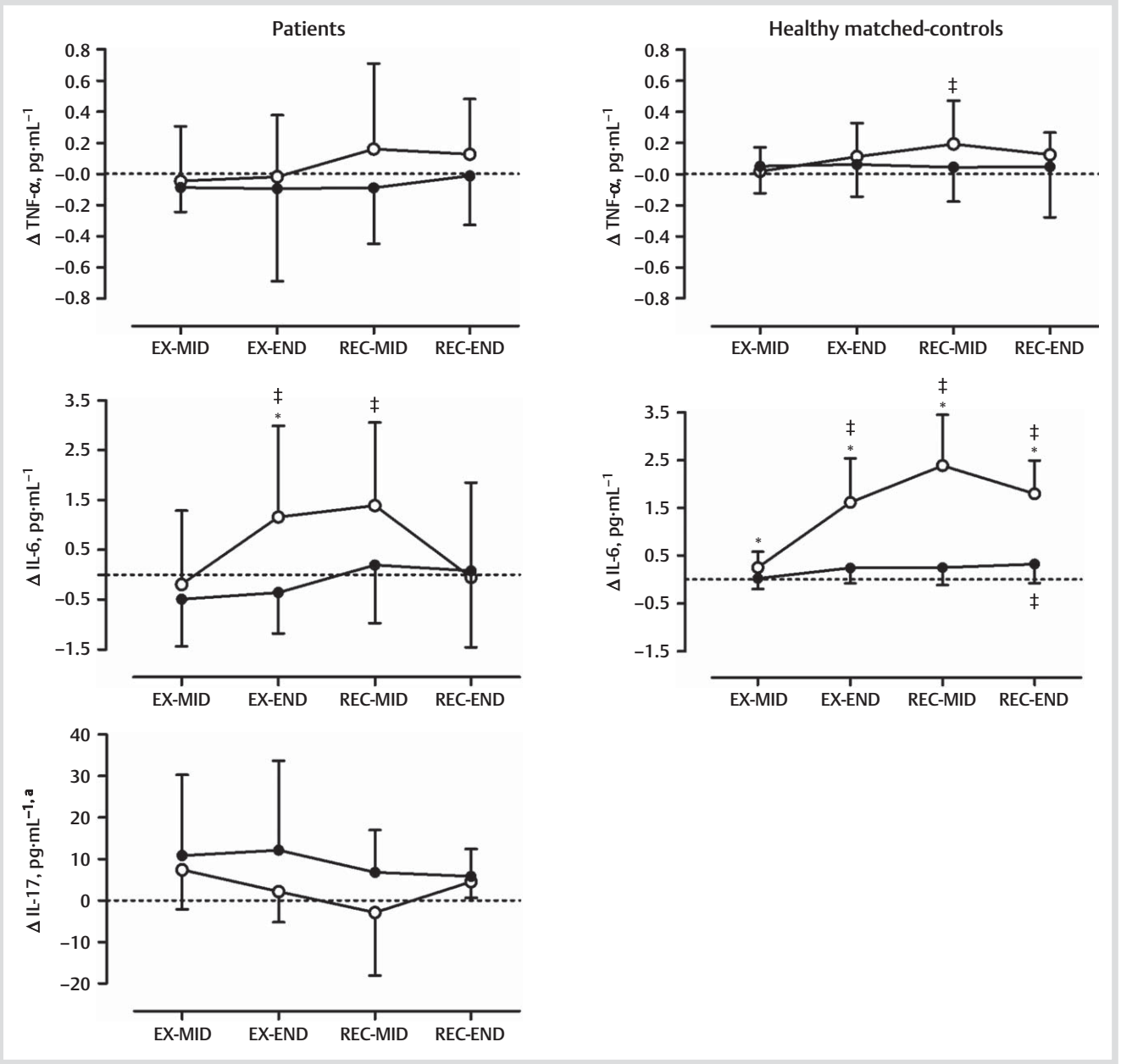

Fig. 2 Inflammatory cytokine responses to MICE and HIIE in patients with CD (left column) and healthy matched-controls (right column). Data are expressed as means ± SD. MICE: open circles, HIIE: closed circles. *: significant difference at $p < 0.05$ between MICE and HIIE, ‡: significant difference at $p < 0.05$ from rest, [a]: n = 6.

levels by 30 min of recovery. These findings are in line with other pediatrics studies [21,33]. Monocytes increased at the end of exercise and remained elevated until the end of the recovery period, which differed from the response in healthy controls. Also in other pediatric exercise studies monocytes are known to return back to resting levels in the recovery period, often within 30 min [4,22,32,33]. The reason for the maintained moncytosis in the patients is unknown, but future work may want to examine the characteristics of monocytes that remain elevated during the recovery period.

Exercise had only a significant effect on measured TNF-α in healthy controls following MICE. However levels had returned back within the hour of recovery. Although a similar pattern was seen in patients, changes did not reach significance. This is consistent with the literature in healthy children where increases are most likely to be seen after strenuous exercise (e.g. 1.5 h of wrestling practice or soccer practice) [20,28]. IL-6 increased throughout the MICE exercise only, with a significant increase at EX-END. In patients IL-6 stayed elevated into the recovery and returned to baseline levels by REC-END, whereas levels in controls remained significantly elevated at REC-END. The exercise effects on IL-6 are well described in the literature [23]. Whereas IL-6 seen in the pathology of CD is considered a pro-inflammatory cytokine, the increase in IL-6 seen after the exercise is likely to be mainly muscle derived and serve an anti-inflammatory function [23]. Exercise induced IL-6 may act to inhibit TNF-α [23], however whether or not this mechanism applies in autoimmune diseases remains unknown.

This study is the first to investigate the effect of exercise on the pro-inflammatory cytokine IL-17 in CD. IL-17 is thought to play

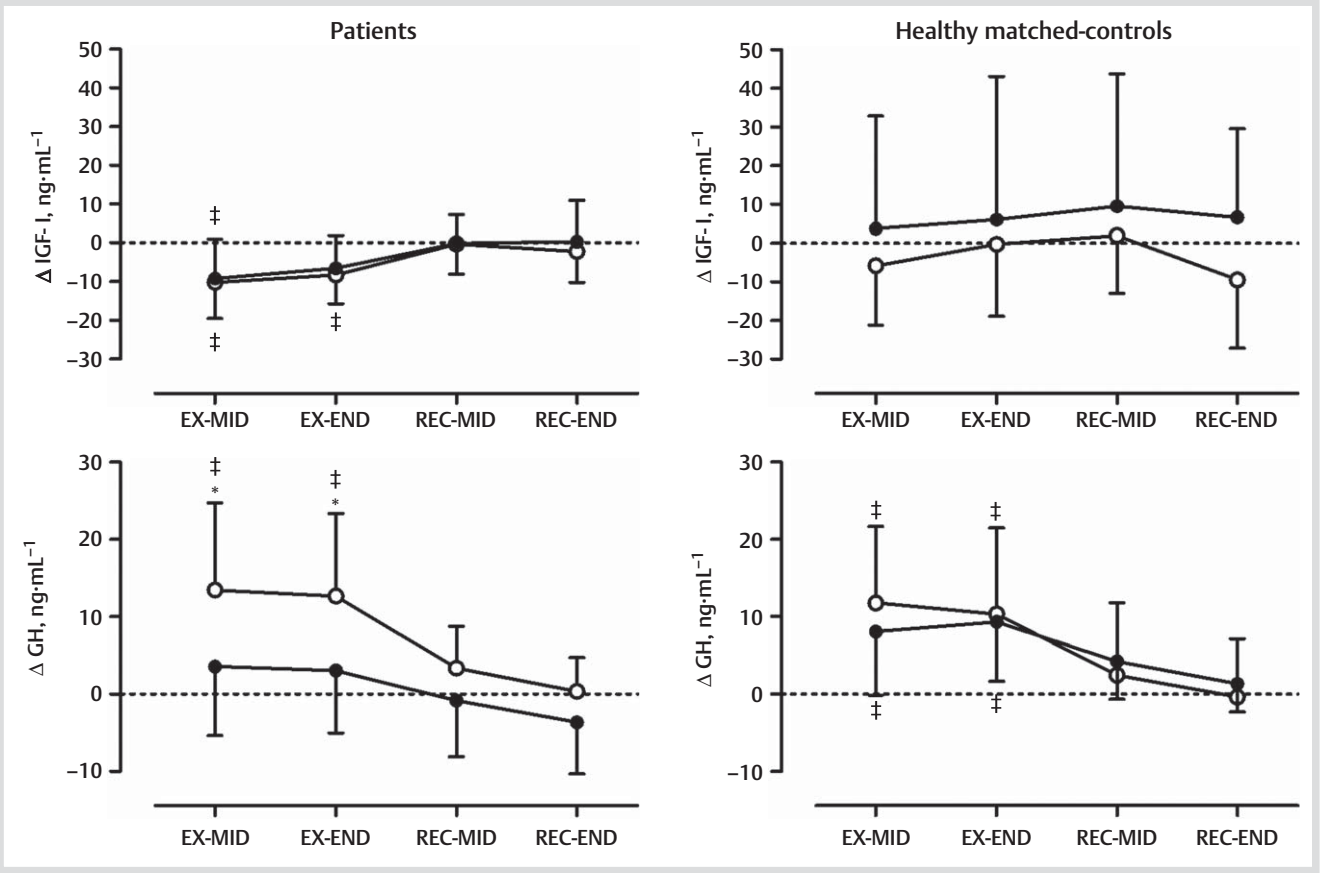

Fig. 3 Growth factor responses to MICE and HIIE in patients with CD (left column) and healthy matched-controls (right column). Data are expressed as means ± SD. MICE: open circles, HIIE: closed circles. *: significant difference at $p<0.05$ between MICE and HIIE, ‡: significant difference at $p<0.05$ from rest.

a major role in the destructive inflammation in a variety of chronic inflammatory diseases including CD [17,18] and is currently being investigated as a cytokine to target for the treatment of CD [18]. IL-17 is produced by the recently discovered Th17 cells, a new T-cell subset [18] and has been found elevated in the gut mucosa [14] and the serum of CD patients both in remission and with active disease [11]. Even though we used a sensitive ELISA method to assess IL-17, it was only detectable in 6 of the 15 patients with CD; we therefore only explored the exercise effect on IL-17 descriptively in patients and not in controls since IL-17 is not expected to be detectable in this group. It seems that IL-17 is responsive to both MICE and HIIE in children with CD who had detectable IL-17 levels. Although the exact contribution of IL-17 to the inflammation in CD is conflicting, IL-17-responsiveness to exercise may provide novel information that could help inform clinical management of CD.

IGF-I was only responsive in patients and showed a similar pattern for both types of exercise, a decrease during and directly at the end of exercise with levels returning to baseline by REC-MID, opposing our hypothesis. This exercise-associated fall in IGF-I has been observed in other studies [20,28] and generally occurs after a short initial increase in IGF-I. It might be possible that levels initially increased but were not detected due to the timing of our blood samples after the onset of exercise. Furthermore, IL-6 in chronic inflammatory disease plays a major role as an inhibitor of IGF-I [7] and exercise induced IL-6 might also prevent IGF-I increases following exercise as recently discussed [9]. However, IL-6 only increased with MICE and not with HIIE, while both exercises showed a decrease in IGF-I. We observed that IL-6 returned to resting levels by 1 h. This transient change suggests that exercise probably does not exacerbate inflammation in these patients.

GH increased significantly in MICE in both groups. In response to HIIE, GH only significantly increased in controls and not in patients with CD opposing our hypothesis. It is possible that the 6 min of exercise at this intensity were not enough to stimulate GH secretion [10]. Although MICE induced a greater GH response it is important to consider that the total work performed and thus the total energy expenditure with MICE was higher than the HIIE.

Limitations

While this study provides novel information on the effects of exercise on inflammatory cytokine and growth factors in youth with CD, we acknowledge limitations with this study. Firstly, we are aware of the effect of gender and pubertal status on immune status in response to exercise. However, each participant served as his or her own control for comparisons between exercise type, and controls were matched to patients by gender and biological age. Secondly, drug intake has been shown to have an effect on the exercise response of immune cells and inflammatory cytokines [34]. In our study, it was difficult to control for the possible influence of medication on exercise responses of the markers measured. 7 patients were on anti-inflammatory

medication (5-ASA), 5 were on both 5-ASA and immunosuppressive medication, 1 was on 5-ASA and infliximab, 1 was on immunosuppressive medication alone; only 1 patient was not on any kind of medication. The patient that was not on any kind of medication had the highest total leukocytes count and one of the highest levels of TNF-α and IL-6 at rest. Moreover, despite the fact that so many children were using anti-inflammatory medication, inflammatory responses to exercise were still seen. Therefore, the exercise responses seen in this study might not reflect the exercise response in patients who are not taking any medication (which would be rare for this patient population) or those on different types of medication.

Conclusion

This study provides novel information about the effects of 2 different types of exercise on inflammatory cytokines and growth factors in youth with CD, which is increasing in prevalence among Canadian children. We can conclude from this study that neither exercise type increased circulating TNF-α in the patients, an inflammatory cytokine that is often elevated in CD. IL-6 increased during exercise but returned back to resting values and in this exercise context, not considered to be pro-inflammatory. The exercise induced patterns of measured inflammatory makers were in general similar to healthy matched-controls. Except for monocytes in response to MICE, all markers showed normal exercise induced responses and are not thought to enhance inflammation. However caution must be taken since baseline levels for most markers and thus absolute peak concentration in response to exercise where significantly higher in patients compared to controls. HIIE did not significantly increase immune makers and is therefore considered safe exercise, nor did MICE exacerbate the cytokine response. Future studies should look at the effects of regular exercise on inflammation in patients with CD. This study is the first step in developing evidence-based physical activity recommendations for youth growing up with an inflammatory bowel disease.

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