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ORIGINAL ARTICLE

Effects of dynamic exercise on circulating IGF-1 and IGFBP-3 levels in patients with rheumatoid arthritis or ankylosing spondylitis

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Abstract This study was performed to determine the effects of short-term dynamic exercise on serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) levels in the patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Patients with RA or AS and healthy controls were recruited. Dynamic treadmill exercise therapy was accomplished for 20 min/session with all of the participants. There were five sessions per week for 2 weeks. Morning stiffness duration, body pain, Stanford health assessment questionnaire, Ritchie articular index, Bath ankylosing spondylitis disease activity index (BASDAI), and Bath ankylosing spondylitis functional index (BASFI) were evaluated in the RA and AS patients. Laboratory assessments included: erythrocyte sedimentation rate, serum C-reactive protein, IGF-1, and IGFBP-3. Clinical and laboratory assessments were recorded at baseline and during exercise treatment on days 7 and 15. Twenty patients with RA, 15 with AS, and 14 healthy controls were included in this study. The pain evaluation, Ritchie, BASDAI, and BASFI scores were significantly improved by the exercise treatment in both patient groups. The important increases were found in circulating IGF-1 in RA ($p<0.001$) and AS ($p=0.001$) at the end of 2 weeks. In control individuals, serum IGF-1 levels showed a significant decline in the first week ($p<0.05$). No significant changes were observed on serum IGFBP-3 levels. Our data suggest that serum IGF-1 levels are increased by the dynamic exercise program in RA and AS patients. The increased IGF-1 may play an important role in the beneficial effects of dynamic exercise therapy in these patients.

Keywords Ankylosing spondylitis · Dynamic exercise · IGF-1 · IGFBP-3 · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are inflammatory rheumatic diseases that lead to high levels of pain, stiffness, and disability. Reduced function, difficulty in daily living activities, and psychosocial impairment are often seen in these disorders. However, among patients with functional class II RA, muscular strength and aerobic capacity were reduced by 25–50% and 20–30%, respectively [1]. The impaired physical capacities may be attributed to inadequate levels of physical activity. Therefore, exercise regimens are recommended for the rehabilitation of RA and AS patients. It is well documented that dynamic exercises such as swimming, walking, and bicycling are more effective in improving muscle strength and cardiorespiratory function than conventional exercise programs such as range of motion and isometric exercises in RA patients [2, 3]. In addition, it is known that exercise therapy has beneficial effects on the Bath ankylosing spondylitis metrology index (BASMI), Bath ankylosing spondylitis disease activity index (BASDAI), and Bath ankylosing spondylitis functional index (BASFI) of AS patients [4, 5]. Although the benefits of exercise are well known to improve the disease activity and physical capacity, the molecular and cellular effects of exercise are less clear.

Insulin-like growth factor-1 (IGF-1) plays an important role in the cell growth and differentiation. Most of the IGF-1 found in serum is produced in the liver, but most somatic cells can also synthesize it [6]. A dynamic equilibrium is present between circulating concentrations of IGF-1 and tissue production of this peptide [7]. A number of studies have been performed to measure IGF-1 levels during exercise in healthy individuals, but the results have been controversial [8, 9]. Whether exercise has an important role in the serum IGF levels of patients with inflammatory disorders is not yet known. This study was performed to determine the effect of short-term dynamic exercise on the serum IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3) levels in the patients with RA and AS.

Materials and methods

Twenty patients with RA and 15 patients with AS were recruited along with 14 healthy controls. The diagnosis of RA was made according to the criteria of the American College of Rheumatology [10]. The diagnosis of AS was made according to the modified New York criteria [11]. Excluded from the trial were individuals using oral contraceptive drugs, subjects with co-morbid medical conditions known to affect IGF status, and individuals whose disease made it impossible for them to tolerate walking on the treadmill.

In RA patients, morning stiffness duration, patient's pain evaluation (by visual analogue scale [VAS]), Stanford health assessment questionnaire (HAQ) [12], and Ritchie articular index [13] were documented by clinical examination. The clinical variables were morning stiffness duration, patient's pain evaluation, BASDAI [14], and BASFI [15] in the patients with AS. Sedentary healthy controls were selected according to a questionnaire that quantifies physical activity undertaken during a normal week on an 8-point scale [16]. The habitual exercise level of participants was determined using this questionnaire.

Body weight and height were measured in all of participants. The body mass index (BMI) scores were recorded as body weight divided by height squared (kg/m^2). For the laboratory assessment, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IGF-1, and IGFBP-3 levels were defined. The ESR level was determined by the Westergren method. A nephelometric method was used for measuring CRP levels (Beckman Array Protein System, USA). The IGF-1 and IGFBP-3 levels were measured by radioimmunoassay method (BioSource Europe S. A., Belgium).

All of the patients were hospitalized in Department of Physical Medicine and Rehabilitation to prevent disease aggravation due to environmental effects for 2 weeks during the treatment period. Dynamic exercise therapy on a treadmill was accomplished with all of the participants as follows: (a) intensity level such that heart rates exceeded 60% of maximal heart rate for 20 min; (b) the exercise frequency was five sessions per week for 2 weeks. Clinical and laboratory assessments of subjects were recorded before therapy at baseline, and then on treatment on the 7th and 15th days of treatment.

The statistical analysis was performed by means of SPSS 10.0 for Windows. A paired samples t test was used for comparison of data within groups at the baseline and at prescribed follow-ups. The mean changes in IGF-1 and IGFBP-3 variables (Δ), calculated as the difference between two time points (Δ_{0-7}, Δ_{7-15}, and Δ_{0-15}), were analyzed between the three groups by multiple factor variance analysis. Age and BMI scores were used as covariates. The differences on mean changes in the other variables were determined between patient groups and controls by the one-way analysis of variance (ANOVA). Post hoc evaluations were made using the least significant difference test in multiple factor variance analysis and one-way ANOVA. Values with $p<0.05$ were accepted as statistically significant.

Results

Twenty patients with RA, 15 patients with AS, and 14 healthy controls were included in this study. All of the patients were clinically non-active because the disease activity can affect IGF-1 and IGFBP-3 levels, and on stable medication. None of RA patients had clinically active disease, which is defined by the presence of at least two of the following criteria: (a) morning stiffness duration >30 min, (b) six or more tender joints, (c) three or more swollen joints, and (d) ESR >28 mm/h. In AS patients, non-activity was defined according to CRP, ESR levels, and BASDAI scores. The participants were all females because IGF-1 and IGFBP-3 levels are affected by gender [17]. One RA patient was excluded from the study on the third day because of poor tolerance of the exercise. Thirteen of the RA patients were being treated with methotrexate (MTX), and seven were receiving sulphasalazine. The patients with RA were deemed to be functional status class I–II, as defined by the American College of Rheumatology [18]. In the AS group, 13 patients were being treated with sulphasalazine and two with MTX.

The patients with RA and the healthy controls were similar in age distribution (mean 46.4±8.3 and 43.2±6.9 years, respectively). The AS patients were younger than other participants (mean 37.7±5.9; $p<0.05$). The BMI scores of control subjects were lower than those of the RA and AS groups (mean 26.4±3.8, 30.6±7.5, and 30.6±

3.6, respectively; $p<0.05$). The RA patients exhibited a long duration of symptoms (mean 80.7±75.8 months in RA and 8.1±6.3 months in AS; $p=0.001$) and high pain scores (mean 5.2±1.7 in RA and 3.7±1.9 in AS; $p<0.05$) in comparison to AS patients.

The pain evaluation and Ritchie scores were significantly improved after the exercise treatment in the RA patients. In the AS group, the pain scores were significantly decreased at the end of 2 weeks ($p<0.01$), whereas BASDAI and BASFI scores were statistically significantly changed only in the first week ($p<0.05$). There was not a significant difference between healthy controls and patient subjects with regard to baseline IGF-1 levels. The important increases were found in circulating IGF-1 in RA ($p<0.001$) and AS ($p=0.001$) patients at the end of 2 weeks. However, the increase in IGF-1 levels was higher in the first week than in the second week in RA group (Table 1).

In the control group, serum IGF-1 levels showed a decline after exercise; however, these changes were not statistically significant, except in the first week ($p<0.05$; Table 2). No significant changes were observed in serum IGFBP-3 levels in three groups.

There were no significant differences on mean changes in circulating IGF-1 between both patient groups at the end of 2 weeks. The mean changes in IGF-1 levels were greater in patient groups than in healthy controls after exercise (Table 3).

Discussion

A number of studies have investigated the association of exercise and IGF status in the healthy subjects [8, 9]. As far as we know, this study is the first study investigating the effect of dynamic exercise on IGF-1 and IGFBP-3 concentrations in RA and AS patients. Our observations revealed that serum IGF-1 levels were gradually increased by dynamic exercise during 2 weeks in both patient groups, but reduced in healthy controls.

It is known that dynamic exercise therapy has beneficial effects in RA and AS patients [19, 20]. Most of the studies reported improvements on aerobic capacity, muscle strength, and disease activity with dynamic exercise in RA patients [21]. In our study, measurements of disease activity such as pain scores, Ritchie articular index, BASDAI, and BASFI scores showed a decline with exercise, and dynamic exercise was well tolerated by both patient groups during 2 weeks of therapy. No disease aggravation occurred in any of the cases.

Increasing IGF-1 concentrations may improve aerobic capacity. Indeed, some studies have reported that serum IGF-1 levels are positively associated with physical fitness and aerobic capacity in healthy individuals [22]. On the other hand, studies investigating IGF-1 status reported controversial results in RA and AS. Some studies have determined the reduced levels of serum IGF-1 in these patients compared with controls [23], whereas others could not demonstrate any change [24, 25]. In this study, baseline circulating IGF-1 and IGFBP-3 levels were not different in patients and healthy controls.

In RA and AS, the increased IGF-1 may provide beneficial effects. *Firstly*, the importance of IGF-1 during exercise may involve skeletal muscle glucose uptake and beneficial cardiovascular effects [26]. It has been shown that IGF-1 can stimulate glucose uptake in human muscle during exercise [27]. Therefore, the increasing IGF-1

Table 1 Comparison of clinical and laboratory data on 7th and 15th days vs before exercise in both patient groups (mean±SD)

	RA group			AS group		
	Baseline	7th day	15th day	Baseline	7th day	15th day
Stiffness (min)	38.68±32.65	34.47±27.12	30.52±19.21	23.33±8.79	22.33±8.20	22.00±9.21
Pain (VAS)	5.15±1.67	4.42±1.42****	4.26±1.24***	3.73±1.94	3.26±1.62**	3.06±1.83**
HAQ	5.63±5.33	4.68±4.72	4.68±4.72	–	–	–
Ritchie	15.26±10.08	11.57±7.25*	11.10±6.91*	–	–	–
BASDAI	–	–	–	25.60±10.37	25.00±9.97*	24.73±10.15
BASFI	–	–	–	39.13±23.53	39.46±23.43*	39.66±23.83
ESR (mm/h)	23.21±5.11	23.42±7.32	24.31±6.21	23.40±6.36	24.00±7.26	25.53±8.00
CRP (mg/l)	0.41±0.07	0.43±0.11	0.41±0.09	0.46±0.15	0.45±0.14	0.45±0.14
IGF-1 (ng/ml)	397.57±199.19	460.42±225.25**	496.89±252.61****	373.06±104.21	422.60±108.92***	428.46±106.14***
IGFBP-3 (ng/ml)	3,470.84±1,318.36	3,721.32±1,229.15	3,735.36±1,371.45	2,854.13±9,51.99	3,687.60±1,733.46	2,994.00±1,019.65

p values were compared with baseline values.
*$p<0.05$
**$p<0.01$
***$p=0.001$
****$p<0.001$

Table 2 Comparison of laboratory data on 7th and 15th days vs before exercise in healthy individuals (mean±SD)

	Control group		
	Baseline	7th day	15th day
ESR (mm/h)	13.78±5.07	12.71±5.31	12.85±5.02
CRP (mg/l)	0.39±0.05	0.41±0.06	0.40±0.05
IGF-1 (ng/ml)	504.85±248.33	479.28±239.48*	457.92±216.33
IGFBP-3 (ng/ml)	3,619.64±1,126.33	3,478.92±995.73	3,767.00±1,064.61

p value was compared with baseline values.
*$p<0.05$

during exercise may contribute to reduced muscle function in RA patients. *Secondly*, RA and AS are connected with increased risk for cardiovascular disease and premature death [21]. However, it has been reported that IGF-1 decreases circulating levels of triglycerides and free fatty acids and leads to vasodilatation by increasing nitric oxide levels in endothelial cells [28, 29]. These effects may provide marked improvements on cardiovascular functions and atherosclerosis in inflammatory disorders, like RA and AS. *Thirdly*, systemic osteoporosis is often described in patients with RA and AS. It is due to various factors such as physical disability, increased bone-resorbing cytokines, disease activity, local inflammation around joints, and glucocorticoid treatment. On the other hand, IGF-1 is a bone-promoting peptide that reflects osteoblast function [7]. It was reported that osteoporotic patients had reduced circulating IGF-1 and IGFBP-3 levels [30]. The increased IGF-1 concentrations by exercise may decrease the severity of osteoporosis in RA and AS patients.

Many studies have investigated the relationship between circulating IGF-1 levels and exercise in healthy individuals but reported controversial results [8, 9, 22]. In this study, circulating IGF-1 levels were reduced in healthy subjects by dynamic exercise, whereas it was increased in rheumatic patients. This may be attributed to inflammation. Many pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α) are produced by the inflammatory process in RA and AS. In addition, it is well known that serum levels of these cytokines are increased by exercise in healthy controls [31]. On the other hand, several studies reported that IGF-1 synthesis and activity were inhibited by IL-1 and TNF-α [32]. However, the increased IL-1 and TNF-α levels may prevent the rise in IGF-1 concentrations during exercise in healthy cases. This hypothesis may explain the decrease in serum IGF-1 levels of healthy controls in our study. On the other hand, the levels of IL-1 and TNF-α in inflammatory disorders, such as RA and AS, are already higher than the healthy individuals. Therefore, the increase in these cytokines may be less pronounced in RA and AS patients during exercise. This limited increase should not have suppressed the anticipated rise in the levels of serum IGF-1. However, Evans et al. [33] studied the effects of 45-min-bicycle exercise on IL-1 activity in the plasma of male runners and untrained men. Plasma IL-1 levels in the trained men were higher than in the untrained men before exercise. **T**here was no increase in the trained individuals, whereas IL-1 activities increased after exercise in all of the untrained men.

In this study, we assessed the short-term effects of dynamic exercise on serum IGF-1 and IGFBP-3 levels in RA and AS patients. Our results indicated that levels of serum IGF-1 were increased by the dynamic exercise program without apparent aggravation on disease activity

Table 3 Comparison of mean changes on 7th and 15th days among groups

	RA group	AS group	Control group
IGF-1 (ng/ml)			
Δ_{0-7}	62.84±94.25**,b	49.53±44.89**,a	−25.57±34.34
Δ_{7-15}	36.47±75.11*,b	5.86±36.52	−21.35±65.42
Δ_{0-15}	99.31±82.10**,b	55.40±51.49***,a	−46.92±82.59
IGFBP-3 (ng/ml)			
Δ_{0-7}	250.47±1,482.45	833.46±1,571.55	−140.71±1,036.92
Δ_{7-15}	14.05±1,064.03	−693.60±1,648.16	288.07±691.50
Δ_{0-15}	264.52±1,514.15	139.86±1,047.30	147.35±1,324.19

Δ_{0-7} $\Delta_7-\Delta_0$ mean changes, Δ_{7-15} $\Delta_{15}-\Delta_7$ mean changes, Δ_{0-15} $\Delta_{15}-\Delta_0$ mean changes
[a] Significance level of changes, between AS and control groups
[b] Significance level of changes, between RA and control groups
*$p<0.05$
**$p<0.01$
***$p=0.001$

in these patients. The increase in circulating IGF-1 concentrations may play an important role in beneficial effects of dynamic exercise therapy in RA and AS. Further research is needed to establish the best intensity and duration of exercise training to induce these changes.

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