Hypothalamic-Pituitary-Adrenal Hormonal Responses to Exercise Stress Test in Patients with Rheumatoid Arthritis Compared to Healthy Controls

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ABSTRACT. ***Objective.*** There is controversy about hormonal dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis that is supposed to contribute to the development or persistence of rheumatoid arthritis (RA). We investigated whether there is an altered and blunted response of the HPA axis when stimulated by exercise stress in patients with RA.

Methods. Twenty women with RA and 15 matched healthy controls were included in the study. All subjects took an ergospirometric exercise test on the treadmill to determine anaerobic threshold (AT). On another day, blood was collected for basal plasma levels of growth hormone (GH), insulin-like growth factor-I, cortisol, and adrenocorticotrophic hormone (ACTH); and subjects exercised on treadmill at an intensity above their AT. Blood was collected again to measure hormone levels just after the exercise stopped and 60 minutes later.

Results. Two subjects left the study, so 19 patients and 14 controls were evaluated. Peak oxygen consumption (VO_2), VO_2 at AT, exercise test duration, and basal hormone levels were similar in groups. In both groups, GH slightly increased just after the exercise (0 min), and decreased at 60 min compared to baseline, but the change was not different between groups. Cortisol levels decreased significantly at 0 and 60 min in both groups, ACTH levels did not change in time, and there was no difference between groups.

Conclusion. There was no perturbation in HPA axis stimulated by exercise stress test in patients with RA and all the variables measured were similar to those of the control group. (J Rheumatol 2006;33:1530–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS HYPOTHALAMIC-PITUITARY-ADRENAL AXIS EXERCISE

The close relationship between the immune system and the neuroendocrine system in inflammatory and stress conditions is well known[1,2]. Immune cell products, predominantly cytokines such as tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), and IL-6 stimulate corticotropin-releasing hormone (CRH) secretion, thereby activating both the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system during inflammatory stress[3-7]. It was also shown that growth hormone (GH) is stress related, because hypoglycemia, exercise, and surgery increase its release[8-10]. Certain autoimmune diseases including rheumatoid arthritis (RA) tend to increase in incidence and severity in states associated with a hyporesponsive HPA axis, for example, during the postpartum period when the HPA axis is suppressed[1]. Conversely, these diseases rarely develop and are infrequently active in states associated with hypercortisolism, such as active Cushing's syndrome or pregnancy in the last trimester[11-13]. Hormonal dysfunction in the HPA axis was suggested to contribute to or exist with RA, and this has been the subject of numerous studies, with contradictory results[14-19]. Patients with RA experience physical stress caused by inflammatory pain, deformity of joints, and various other complications, in addition to mental stress due to their situation. Normally, homeostasis is maintained by the neuroendocrine-immune system network. However, it was hypothesized that longterm mental and psychological stress in RA may primarily affect the HPA axis and immune system[20]. The results of some studies on patients with RA have indirectly indicated the impairment to be at the hypothalamic level[21,22]. In some studies HPA axis was stimulated to observe the response in patients with RA, but results of these studies have also been inconclusive[14,23-25]. Subtle abnormalities have also been reported in cortisol response to many stimuli[22,26]. In general, a cortisol level lower than expected is increasingly being accepted as a feature of RA[27].

Stimulation of the HPA axis has generally resulted in a blunted response in RA patients in many studies[28-30]. HPA axis is also perturbed in patients with other chronic pain conditions, such as fibromyalgia syndrome and chronic fatigue syndrome; moreover, as an external stressor, exercise stimula-

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tion led to an exaggerated response in GH levels in these patients[31,32]. There are a number of reviews on the effects of exercise in patients with RA, all of which conclude that there is no adverse effect on disease activity[33-35]. Further, exercise has favorable effects on patient general health, well-being, and the ability to perform activities of daily living[36]. Yet there appears to be no satisfactory study on the hormonal responses to exercise in patients with RA compared to healthy individuals.

As is well known, acute exercise is a potent modulator of the release of HPA hormones[37,38]. Therefore, exercise has been used as a stressor in research because of its reliability, reproducibility, and safety. We investigated the hormonal responses to exercise in patients with RA, and whether exercise might be a tool for HPA axis regulation in RA in addition to its many favorable effects.

MATERIALS AND METHODS

Patients and controls. Twenty women with RA (mean age 48.3 ± 8.4 yrs) were recruited from patients admitted to the inpatient and outpatient clinics of the Physical Medicine and Rehabilitation Department of our institution. Inclusion criteria for the patient group were as follows: diagnosis of RA according to 1987 American College of Rheumatology (ACR) criteria[39], functional classification of I–II according to ACR criteria[40], and ability to perform submaximal graded exercise testing on a treadmill.

Exclusion criteria. Exclusion criteria were severe arthritis in one or more of the lower extremity joints, concomitant severe illness other than RA, or other general contraindications for a graded exercise test[41].

Fifteen age and sex matched sedentary healthy subjects (mean age 48.4 ± 7.9 yrs) were recruited as controls. In particular, control subjects with a low level of activity were chosen, since hormonal levels and hormonal responses to exercise differ according to the fitness level of the individual. Exclusion criteria for healthy control subjects were the presence of a chronic systemic disease, chronic pain, or any condition that might put the subject at risk during the exercise test. Both patients and controls gave informed consent for the study.

Clinical assessment. Patients were evaluated first by routine clinical and laboratory measures, and then by the following: Duration of morning stiffness in minutes; pain during the preceding week recorded on 100 mm visual analog scale (VAS, 0 = no pain, 100 = worst pain); fatigue assessed by a 5-point scale (1 = none, 5 = very severe); patient and physician general health assessment recorded using 100 mm VAS (0 = best possible, 100 = worst possible), and disease activity assessment based on number of tender and swollen joints (total 28 joints)[42]. For each patient, Disease Activity Score 28 (DAS28) was also calculated from the number of tender and swollen joints, erythrocyte sedimentation rate (ESR), and patient general health assessment using a VAS[43].

Laboratory assessment. ESR was measured by Westergren method (mm/h) and CRP level was measured by nephelometric method (mg/l).

Exercise tests. Patients and controls performed 2 exercise tests. The aim of the first test was to evaluate and compare peak oxygen consumption (VO_2peak) of the 2 groups and establish an anaerobic threshold (AT); this allowed determination of the intensity of the second test, which was set at a higher level than AT to provoke hormonal responses. Each subject had ergospirometric exercise testing to volitional exhaustion (symptom-limited termination) on a treadmill using Bruce protocol at 8:30 AM. 12-Lead electrocardiography (Marquette Case I; Marquette, Milwaukee, WI, USA) was recorded, and breath-by-breath analysis of respiratory gases (V_{max}29, SensorMedics, Yorba Linda, CA, USA) was performed during the exercise. AT was determined by V-slope technique on VO_2 versus VCO_2 graphic[44]. Each subject's oxygen consumption (ml/kg/min) and heart rate at AT point were determined.

The second exercise test was performed at the same time on another day within the same week. Prior to the test, blood samples were drawn to measure fasting basal levels of GH, insulin-like growth factor-I (IGF-I), adrenocorticotrophic hormone (ACTH), and cortisol. Exercise testing was performed on a treadmill with 12-lead electrocardiography; breath-by-breath analysis of respiratory gases was conducted throughout the test. Each subject's exercise intensity was set above her AT, as guided by heart rate and oxygen consumption. The duration of exercise was 10 minutes after reaching the AT, and this was standard for all subjects. Postexercise blood samples were drawn to measure the levels of GH, ACTH, and cortisol, at 0, 30, and 60 minutes. Since IGF-I is not secreted acutely after a stimulation, it was only measured at 60 minutes.

Hormonal analysis. Blood samples for basal and exercise-induced plasma ACTH, cortisol, GH, and IGF-I levels were collected through an indwelling catheter applied 1 hour before the test. The serum samples were stored at –20°C until assayed. Plasma ACTH levels were measured by immunometric assay system, using Immulite 2000® apparatus and DPC® kits. Serum cortisol levels were measured by an immunoenzymatic assay method using a Beckman Coulter® apparatus. Serum GH levels were measured by radioimmunoassay method using DSL® kits, and serum IGF-I levels were also measured by radiommunassay method using Shering CIS® kits.

Sample size. The sample size required for the study was calculated based on the primary outcome variable, ACTH. Group sample sizes of 20 and 15 achieve 80% power to detect a difference of 4 in ACTH between RA and control groups; the estimated group standard deviations of 4 for both groups was set at 5% significance level (alpha), using a 2-sided Mann-Whitney test assuming the actual distribution as normal.

Statistical analysis. Statistical comparison of the demographic and test variables of patients and controls, including VO_2peak, maximal heart rate at the first exercise test, and basal values of GH, IGF-I, ACTH and cortisol was performed by Student's t test or Mann-Whitney U test, where applicable. The response of GH, ACTH, and cortisol following exercise was evaluated by Friedman 2-way analysis of variance. For pairwise comparisons, Bonferroni-corrected Wilcoxon signed-ranks test was used. The level of significance was $p < 0.05$ for all tests.

RESULTS

One subject from each group did not attend for the second exercise test and blood sampling, with no reason given, so 19 patients in the RA group and 14 subjects in the control group were tested. There were no adverse events after exercise testing in either group. Clinical characteristics of the patients are shown in Table 1. Fifteen patients were taking disease modifying antirheumatic drugs; 13 of them were also taking nonsteroidal antiinflammatory drugs (NSAID); 1 patient was taking only NSAID; and 4 patients were taking prednisolone (7.5–15 mg). Exercise test variables of the subjects are shown in Table 2. There were no significant differences between groups in variables related to fitness levels.

GH, IGF-I, ACTH, and cortisol levels measured prior to the exercise test and after the test at intervals are shown in Tables 3 to 5. Basal hormone levels did not differ between groups. GH levels increased shortly after exercise and then returned to the levels below baseline. This was significant within groups, except for the difference between baseline and 1 hour after exercise in the control group ($p_{GH\ 0–1} = 0.033$, $p_{GH\ 0–2} = 0.047$; $p_{GH\ 0–1} = 0.001$, $p_{GH\ 0–2} = 0.147$, for RA and control groups, respectively). ACTH levels also showed an increase after the exercise, which was not significant for the control group ($p_{ACTH\ 0–1} = 0.023$; $p_{ACTH\ 0–1} = 0.814$, for RA

Table 1. Clinical characteristics of patients with RA.

	Mean ± SD	Median (min-max)
Disease duration, mo	128.8 ± 85.6	108 (6–336)
No. of swollen joints	1.2 ± 2.2	0 (0–6)
No. of tender joints	5.5 ± 6.0	2 (0–21)
DAS28	3.9 ± 1.5	3.7 (1.2–6.5)
Duration of morning stiffness, min	34.2 ± 44.7	10 (0–120)
Patient's global assessment, VAS	36.6 ± 20.8	40 (0–78)
Physician's global assessment, VAS	30.2 ± 18.0	31 (0–72)
Pain, VAS	43.9 ± 22.0	49 (0–86)
Fatigue, 0–5	1.4 ± 0.9	1 (0–3)
ESR, mm/h	26.0 ± 15.8	23 (4–65)
CRP, mg/l	12.0 ± 12.6	8.5 (1.0–49.2)

VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. DAS28: Disease Activity Score 28.

Table 2. Dynamic lung functions and exercise test variables of the patient and control groups.

	RA, n = 19		Control, n = 14		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p
FVC, l	2.78 ± 0.56	2.65 (1.87–3.85)	2.76 ± 0.34	2.72 (2.09–3.38)	0.89
FEV_1, l	2.35 ± 0.48	2.50 (1.37–3.17)	2.39 ± 0.26	2.41 (1.73–2.74)	0.80
FEV_1/FVC, %	84.6 ± 7.9	86.0 (63–96)	84.3 ± 9.0	83.5 (63–98)	0.92
VC, l	2.90 ± 0.49	2.76 (2.14–3.85)	2.89 ± 0.40	2.90 (2.09–3.71)	0.94
MVV, l/min	94.9 ± 22.3	94 (51–133)	83.9 ± 19.7	88.5 (34–108)	0.15
VO_2-AT, ml/kg/min	14.2 ± 2.6	13.6 (10.8–20.5)	15.7 ± 3.5	15.3 (10.1–21.7)	0.17
VO_2-peak, ml/kg/min	23.7 ± 4.9	24 (14.6–30.5)	26.6 ± 6.0	26.1 (17.8–36.2)	0.14
Exercise test duration, s	709.7 ± 141.8	730 (333–995)	663.1 ± 185.6	706 (255–927)	0.42
Max HR, beat/min	154.1 ± 21.2	154 (115–188)	163.1 ± 24.8	171.5 (106–189)	0.19
Max systolic BP, mmHg	160.0 ± 26.6	150 (120–200)	158.9 ± 27.6	160 (120–200)	0.99
Max diastolic BP, mmHg	76.3 ± 8.5	80 (60–90)	74.6 (8.0)	80 (60–85)	0.65
MET	7.43 ± 2.11	7.2 (3.3–12.7)	8.84 ± 2.79	8.25 (4.5–14.4)	0.11

FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 s, VC: Vital capacity, MVV: Maximal voluntary ventilation, VO_2-AT: oxygen consumption at anaerobic threshold VO_2-peak: peak oxygen consumption, BP: Blood pressure.

Table 3. Basal insulin-like growth factor-I (IGF-I) basal and postexercise levels of growth hormone (GH) in groups.

	RA, n = 19		Control, n = 14	
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)
GH (0)	2.46 ± 3.99	1.50 (0.15–17.5)	2.09 ± 3.53	0.76 (0.07–13.4)
GH (1)	5.34 ± 7.78	2.70 (0.25–31.4)	7.66 ± 15.07	2.05 (0.06–56.6)
GH (2)	1.13 ± 1.29	0.76 (0.07–5.5)	1.14 ± 1.98	0.39 (0.05–6.5)
IGF-I	49.48 ± 46.66	35.15 (6.5–192)	82.97 ± 89.68	36 (1.1–278.2)

Table 4. Basal and postexercise levels of adrenocorticotrophic hormone (ACTH) in groups.

	RA, n = 19		Control, n = 14	
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)
ACTH (0)	10.37 ± 5.73	7.53 (4.9–21.8)	12.10 ± 6.13	10.1 (4.9–25.0)
ACTH (1)	15.91 ± 13.31	8.62 (4.9–46.2)	12.37 ± 6.77	12.4 (1.0–25.5)
ACTH (2)	9.97 ± 7.00	7.59 (4.9–32.2)	8.84 ± 2.80	9.5 (5.3–15.7)

and control groups, respectively), and returned to the levels below baseline 1 hour after the exercise ($p_{ACTH\ 0–2} = 0.100$; $p_{ACTH\ 0–2} = 0.026$, for RA and control groups, respectively). Cortisol (CORT) levels progressively and significantly decreased after the exercise in both groups ($p_{CORT\ 0–1} = 0.528$, $p_{CORT\ 0–2} = 0.001$, $p_{CORT\ 1–2} = 0.001$; $p_{CORT\ 0–1} = 0.363$, $p_{CORT\ 0–2}$

Table 5. Basal and postexercise levels of cortisol in groups.

	RA, n = 19		Control, n = 14	
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)
Cortisol (0)	10.06 ± 4.57	10.4 (0.96–16.40)	11.12 ± 3.36	10.55 (6.44–17.80)
Cortisol (1)	9.61 ± 4.43	9.85 (1.50–17.33)	10.70 ± 3.73	10.20 (5.76–19.18)
Cortisol (2)	7.82 ± 4.03	7.04 (0.85–15.37)	7.51 ± 1.64	7.83 (5.02–10.74)

= 0.004, $p_{CORT\ 1–2}$ = 0.003, for RA and control groups, respectively).

The change in hormone levels over time showed no significant difference between groups (Figures 1 to 3).

DISCUSSION

Different psychosocial stressors may have differing effects on the neuroendocrine and immune systems in individuals with RA, as well as those with other rheumatic conditions. Chronic and acute stressors appear to have different actions on immune mechanisms[29,45]. Intrinsic defects of the HPA axis are also suspected to be responsible for the susceptibility to inflammatory diseases. However, evidence is insufficient to indicate whether inflammatory diseases cause impairment in HPA axis or vice versa. Studies on arthritis-susceptible Lewis rats showed deficient HPA responses that were believed to be due to impaired regulation of CRH at the hypothalamic level[46]. In many human studies, HPA axis disturbance has been shown at different levels, but the results are still inconsistent[14,16,22,26,27,47].

In our study, the primary aim was to investigate whether exercise-stimulated hormonal responses were affected by a suggested HPA axis disturbance. As a secondary aim, we also investigated whether exercise might be a tool to stimulate the perturbed HPA axis. Our findings showed that basal cortisol, ACTH, IGF-I, and GH levels were not different between the RA and the control groups. Further, hormonal responses to exercise stimulus were as reported[37,38] and were similar in both groups. So, both hypotheses were not proved in our study.

Studies on basal hormone levels in patients with RA have displayed different results. Mukai, *et al* found lower ACTH activity in RA subjects versus controls; on the other hand, serum cortisol levels were not significantly different between groups[20]. In another study, plasma ACTH and CRH levels were found to be significantly lower in RA patients versus patients with osteoarthritis[48]. Allen, *et al* found low IGF-I concentrations in patients with juvenile chronic arthritis, probably due to varying factors, including nutrition, but they thought that this result did not reflect marked endocrinological abnormalities in most patients[49]. In another study, Butenandt, *et al* observed increased levels of IGF binding pro-

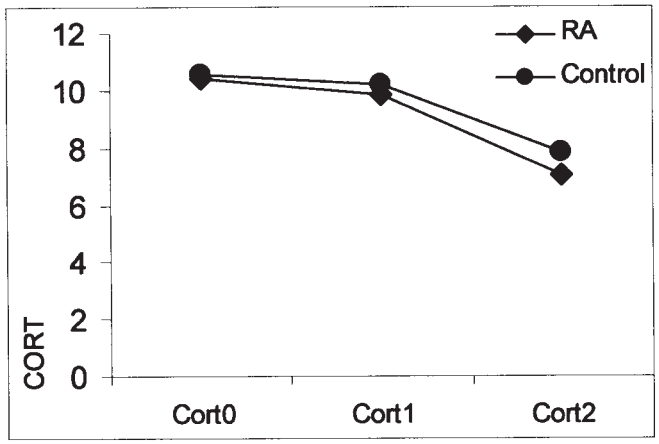

Figure 1. Baseline level of cortisol and its change within time in both groups.

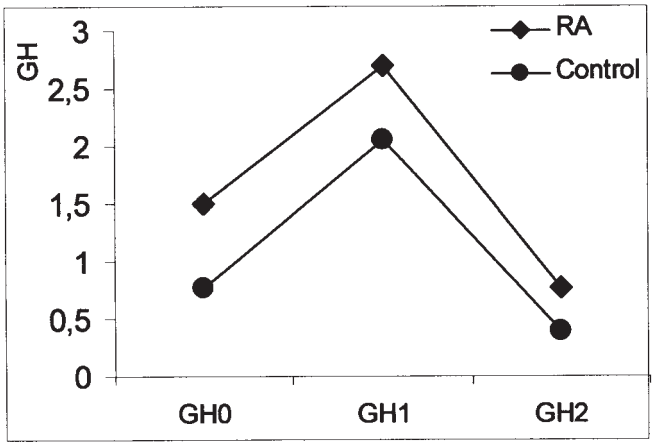

Figure 2. Baseline level of growth hormone and its change within time in both groups.

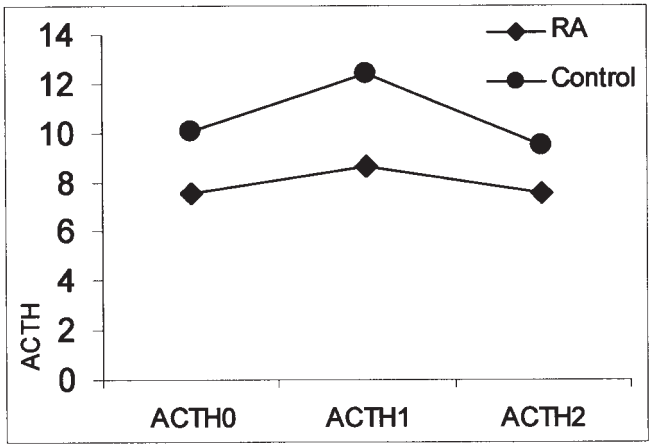

Figure 3. Baseline level of ACTH and its change within time in both groups.

teins in RA patients and suggested that this may result in the reduced availability of free IGF that can bind to IGF receptors. Yet the observed changes in the IGF system may thus participate in the catabolic processes in RA[50]. Lemmey, *et al* also found a reduction in the circulating IGF proteins in patients with RA, which was thought to be related to their sedentary lifestyle rather than to the inflammatory process[51]. No difference in hormone levels between groups was detected in that study. In our study, control subjects were chosen specifically from a population with low activity level and a sedentary lifestyle to exclude a possible bias caused by immobility or sedentary lifestyle of patients with RA.

Endogenous secretion of glucocorticoids appears to have an antiinflammatory effect[52], and disease activity throughout a 24-h cycle appears to correlate closely with serum cortisol level[53]. It has been suggested that cytokines may activate the HPA axis via the prostaglandin pathway[54], with the consequence that NSAID therapy may have an inhibitory effect on CRH release. In Denko, *et al*'s study, RA patients treated with prednisone did not exhibit changes in either GH or IGF-I levels compared to RA patients treated principally with NSAID and methotrexate[55]. Dekkers, *et al* assessed HPA axis responses to experimental stressors mimicking daily life challenges in patients with RA to determine whether HPA axis activity is associated with Th1 and Th2 activity[29]. Patients tended to have a less pronounced ACTH response and a significantly smaller cortisol response than healthy controls in reaction to the stressors. They concluded that HPA axis responsiveness was reduced in RA patients with recent diagnosis receiving longterm medication[29].

In our study, most patients were taking NSAID and only 4 patients were taking steroids; it seems that drugs did not affect serum cortisol and ACTH levels. One characteristic of our patient group, however, was low disease activity, which might mean there was no influence on disturbance of the HPA axis. Studies supporting this idea showed that symptomatic RA was associated with elevated serum growth hormone[55], and there were no differences in hypothalamic hormones in patients with newly diagnosed RA[28]. In contrast, in the latter study, Templ, *et al* showed that the GH response to GH-releasing hormone was blunted. The hypothalamic-pituitary-thyroid/gonadal and adrenal axes seemed to be unaltered in the same study. However, in the presence of chronic inflammation, normal plasma ACTH and cortisol concentrations must be considered as inappropriately low. So Templ, *et al* concluded that the observed blunted GH release might be mediated by cytokines (e.g., IL-1), which are known to be elevated in RA.

The correlation of disease activity and cytokine levels was shown by Mukai, *et al*[20]. Since cytokine levels were not in the scope of our study, they were not measured; however, it may be predicted that cytokine levels were probably not very elevated, reflecting low disease activity. This may explain why we did not observe any abnormality in the HPA axis. Gutierrez, *et al* showed that disease activity level in patients with RA was related to the degree of disturbance in the HPA axis, and their findings suggest that active RA is associated with subtle dysfunction of the HPA glucocorticoid function and normal PRL secretion[26].

Neuroendocrine responses to stress, particularly those mediated by the HPA axis, can differ significantly between males and females in many species[56-59]. Testosterone and estrogen appear to have opposing actions on the HPA axis, and this may provide a cellular basis for the sexual differentiation of HPA axis activity[60-62]. The implications of sex hormones in autoimmune diseases are well known[63-65]. Further, it is known that women during periods of estrogen and/or progesterone deficiency (e.g., in the postpartum period or menopause) have increased likelihood of RA[66,67]. It is also known that the reserve of HPA axis changes with aging. In our study, the hypothalamic-pituitary-gonadal axis was not tested, since exercise intensity achieved in this study was insufficient to provoke sex hormones, so the hormonal status of the patients was not determined, although study groups included both pre and postmenopausal subjects. This may be a weakness of our study. Yet there are not sufficient data implying an effect of sex hormones on response of the HPA to different stimuli, including exercise.

Another hypothesis regarding disturbance in the HPA axis in patients with RA suggests the HPA axis may be affected by chronic pain stress[14,48], as suggested for fibromyalgia and CFS[31,32]. In our patient group, disease duration was variable, and there were patients with early RA as well as those with a long disease duration; the mean pain level was moderate. Because duration of a painful condition and intensity of pain, which cause chronic stress, are not well defined, it is not easy to determine whether our patients with low disease activity and low to moderate pain are affected by chronic stress.

In healthy subjects plasma levels of pituitary hormones and GH increase in response to exercise, with both exercise duration and intensity[68,69]. GH response is related more closely to peak exercise intensity than to the duration of exercise or total work output[38]. It has been shown that GH release is observed at an exercise intensity of 30–40% VO_{2max}, or above AT[37]. Concentration of ACTH increases with duration of exercise if intensity is above 25% VO_{2max}, and plasma cortisol also increases during exercise with a delay of about 10 minutes[38]. Exercise increases the production and catabolism of cortisol. The level rises transiently during exercise of both moderate and severe intensity, and falls rapidly to the basal level or below within a few hours of completion of exercise, so the first exercise test done in our study should not affect hormonal responses observed on the second testing day. The critical level of exercise intensity to provoke release of cortisol is about 60% of VO_{2max}, and further increase is possible with more severe exercise[37]. There is an increase of similar proportions in both fit and unfit individuals when exercising to exhaustion[70]. In our study exercise was used as the stressor;

exercise causes stress to varying levels depending on exercise type and duration. Exercise intensity was set to a level above AT, which is sufficient to provoke hormonal responses[38]. Perhaps the level of exercise was a little too low for a sufficient cortisol response; however, RA patients, most of whom are sedentary in their daily life, sometimes were barely able to complete an exercise of 10 minutes. So it did not seem possible to increase duration or intensity of the exercises since this might cause a musculoskeletal injury.

Results of our study showed expected changes in hormone levels, and these did not differ between groups. One important issue that should be discussed is the time of the test. In such studies, it is suggested that administration of CRH in the afternoon could unmask a potential difference in cortisol increase more easily, and in some studies HPA axis was tested in the afternoon or later[10,28,71]. On the other hand, it is generally recommended to test HPA axis and related hormones in the morning: in most studies morning testing was preferred, and differences were detected in some of the studies[20,26,29-31,47,72,73]. In our study, since baseline levels of HPA hormones were also important for the suggested hypothesis, it was preferred to perform the tests in the morning.

There have been a number of reviews on the therapeutic effects of exercise in patients with RA[33-35], but there appears to be no study on hormonal responses of patients with RA to exercise and how they compare to those of healthy individuals. To our knowledge, this is the first study comparing effects of aerobic exercise on the HPA axis in patients with RA versus healthy controls. Although small sample size is a weakness of our study, special attention was paid to restrict inclusion criteria in order to make our study group as homogeneous as possible. Further, it was not easy to find eligible and willing patients because of the interventions implemented in our study.

In conclusion, moderate exercise at above the anaerobic threshold provoked similar hormonal responses in the HPA axis in RA patients with low disease activity compared to healthy controls. No disturbance in the HPA axis was noted under the stress of moderate intensity exercise in this RA patient group. Our second hypothesis was also not supported, since exercise did not stimulate the HPA axis more than expected. This hypothesis can be tested in patients with more severe disease involvement if their condition allows exercise testing.

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