Effects of prolonged combined strength and endurance training on physical fitness, body composition and serum hormones in women with rheumatoid arthritis and in healthy controls

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Abstract

Objective

The effects of a 21-week combined strength and endurance training period on physical fitness, serum hormone concentrations, and subcutaneous fat in 23 women with rheumatoid arthritis (RA) and in 12 matched healthy subjects was studied.

Methods

The measurements included leg extension forces and EMG activity, muscle and fat thickness on thigh, maximal oxygen uptake (VO_2max) and serum concentrations of testosterone, free testosterone, growth hormone, insulin-like growth factor-I (IGF-I), dehydroepiandrosterone sulphate (DHEAS), and cortisol.

Results

During the training period significant increases took place in VO2max, muscle strength and EMG activity in both groups. The increases of the quadriceps femoris thickness were 6.5% ($p < 0.001$) in the healthy controls and 7.4% ($p < 0.001$) in the RA cases. The decreases in subcutaneous fat thicknesses were 9.9% ($p < 0.001$) and 12.3% ($p < 0.001$), respectively. No significant changes were found in serum hormone concentrations, but RA women showed lower levels of IGF-I during the whole follow-up.

Conclusions

In RA women with stable disease the combined strength and endurance training increases physical fitness. Further, the training increases muscle mass and decreases subcutaneous fat. It may decrease risks of cardiovascular diseases in RA patients. The intensive training had minor effects on serum hormone concentrations.

Key words

Muscle strength, muscle hypertrophy, body fat, serum hormone, rheumatoid arthritis.

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This study was supported in part by a grant from Central Finland Health Care District.

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Received on November 29, 2004; accepted in revised form on April 1, 2005.

Introduction

Strength training in addition to endurance training has become an important exercise component in enhancing health outcomes in healthy middle-aged and older people (1-3). The physiological stimuli directed to skeletal muscle as results of strength or endurance training are divergent in nature (4-6). Prolonged endurance training enhances aerobic performance by improving oxidative capacity and increasing glycogen stores of the muscle cells (7). On the other hand, systematic heavy resistance strength training results in neural and muscular hypertrophic adaptations (8).

Growth hormone (GH) and insulin like growth factor I (IGF-I) impose important influences on muscle growth and strength, and consequently, on the trainability capacity of an individual (9, 10). IGF-I may also play a role in the regulation of immunity and inflammation. Reportedly, IGF-I levels in sera of patients with RA are significantly lower than those in healthy controls (11, 12), while the GH kinetics, however, has been reported to be unaltered in RA patients in comparison to healthy controls (12). Androgens are biologically diverse and targeting not only reproductive but also other tissues, such as muscle. Similar to men, also in healthy women, levels of circulating testosterone, dehydroepiandrosterone (DHEA) and its sulphate ester, DHEAS, decrease considerably with aging and in line with muscle mass (13, 14). Lowered serum DHEAS levels as well as reduced androgens/estrogen ratio have also been detected both in male and in female RApatients (15).

The effects of glucocorticoids in human body are pervasive. Cortisol contributes e.g. to the maintenance of resting and stress-related homeostasis (16, 17). RA patients, however, have inappropriately low spontaneous as well as stimulated cortisol secretion in relation to systemic inflammation (18-20). The pervasiveness of cortisol should not be underscored. Up to 20% of the expressed genome of a human leucocyte is responsive to this hormone in either a stimulatory or inhibitory fashion (21). Thus, human body has a sophisticated homeostatic regulatory system to maintain cortisol production within narrow daily range (22).

Recent studies have shown that high-intensity strength training is a safe and important component of non-pharmacological treatment in well-controlled RA patients including the effect of training-induced increase in muscle mass (23-25). As the training for physical fitness in both healthy subjects and RA patients calls for the development of both muscle strength and endurance, the construction of maximal strength and endurance exercises is important for overall fitness training. However, the effects of combined strength and endurance training in RAhave not been studied. The purpose of this study was to investigate the effects of combined strength and endurance training on physical fitness, muscle and fat composition and on serum hormones in women with RA and in healthy control subjects.

Methods

Participants

Twenty-three women with established RA (26) in ARA functional classes I and II, with low disease activity and no present involvement of major weight bearing joints were recruited for the study. Before inclusion the patients were examined by a rheumatologist (PH) to assess the clinical status and to exclude contraindications to perform maximal physical fitness tests. The mean (SD) duration of disease was 8 (6) years. During the study all the women with RA with the exception of 2 cases using non-steroidal anti-inflammatory drugs only, were on DMARDs [11 patients were on a single DMARD (3 on aurothiomalate, 3 on sulphasalazine, 4 on methotrexate, 1 on hydroxychloroquine) and the other used a combination of 2-3 DMARDs including a patient on a combination of methotrexate and infliximab]. Seven patients had been earlier treated and 5 cases were on a low dose oral glucocorticoids (2.5-7.5 mg prednisolone/day) during the trial. In these cases the mean (SD) total duration of prednisolone treatment was 18 (16) months.

Twelve healthy matched women recruited (by the distribution of flyers) from the city of Jyväskylä served as controls. Physical characteristics and clinical data of the patients and controls are given in Table I. The local ethics committee approved the study.

Muscle strength measurements
A David 210 dynamometer (David Fitness and Medical Ltd., Outokumpu, Finland) was used to measure maximal bilateral concentric force production of the leg extensors (1 RM, repetition maximum) (27). After each repetition the load was increased until the subject was unable to extend the legs to full extension). The last acceptable extension with the highest possible load was determined as 1 RM. Maximal isometric force of the bilateral leg extension was measured on a special dynamometer (27).

EMG: Electromyography (EMG)
Bipolar (20 mm interelectrode distance) surface EMG recording (miniature-size skin electrodes 650437, Beckman, Chicago, IL, USA) was used to register the EMG activity of the right vastus lateralis (VL) and vastus medialis (VM) muscles during the maximal bilateral isometric leg extension (Glonner, Biomes 2000, München, Germany (28). The EMG signal was amplified (by a multiplication factor of 200, lowpass cut-off frequency of 360 Hz per 3 dB) and digitized at a sampling frequency of 1000 Hz. EMG was integrated (IEMG) and expressed for 1 sec (μVxs). The maximal IEMG was calculated in the maximal peak force phase of the isometric extension and averaged for the VL and VM (28).

Muscle mass and subcutaneous fat thickness
The muscle mass thickness of the right quadriceps femoris muscle group (for the rectus femoris, vastus lateralis, vastus medialis) was measured with a compound ultra-sonic scanner (Aloka FANSONIC, SSD-190) and a 5 Mhz convex transducer at the mid portion between the greater trochanter and lateral joint line of the knee.

Aerobic performance
Maximal oxygen uptake ($VO_{2\,max}$) test was carried out using the Tunturi® E980 bicycle ergometer. The intensity was 50 W in the beginning of the test and was increased by 25 W every 2nd min until exhaustion. Heart rate and blood pressure were monitored during the test. The VO_{2max} was measured breath-by-breath continuously (SensorMedics® Vmax229). Blood samples were taken from fingertip every 2nd min to measure blood lactate concentrations and determine aerobic and anaerobic thresholds (29). Blood lactate was determined using a Roche-640 lactate analyzer. A physician supervised the maximal tests.

Serum hormones
Concentrations of testosterone, free testosterone, growth hormone, insulin-like growth factor-I (IGF-I), dehydroepiandrosterone sulphate (DHEAS), and cortisol were collected before, at seven week intervals and after the 21-week training period. At the baseline blood samples were taken after 10 h of fasting and about 8 h of sleep in the morning (between 7:30 and 8:30 AM) of the force measurement day. The final samples were drawn after a 24 hour rest from the last training session. Serum samples for hormonal analyses were kept frozen at -20ºC until assayed. The detailed description of hormonal analyses is in our earlier report (30).

Subjective outcome and clinical status
Pain and general health were assessed using visual analog scale (VAS, 0-100 mm). The patient self-report Health Assessment Questionnaire (HAQ, scale 0-3 points) was used for the assessment of physical function (31). The number of tender and swollen joints of RA patients was recorded by the 66/68 joint count (32). The joint index was determined by adding together the scores of the numbers of tender and swollen joints of each assessment. Erythrocyte sedimentation rate (ESR) was used to evaluate clinical disease activity. In addition, the Modified 28-joint Disease Activity Score (DAS 28), including 28 tender and swollen joint counts, patient's self-report global status (on a 100 mm visual analog scale, VAS) and erythrocyte sedimentation rate (ESR), was used to evaluate clinical disease activity (33).

Experimental design
The experimental period consisted of a 21-week concurrent strength and endurance training period. The measurements were repeated at 7-week intervals (i.e. weeks 0, 7, 14 and 21) (34).
Strength training: The supervised 21-week strength training was carried out 3 times per a 2-week time period. Each training session included two exercises for the leg extensor muscles and four to five exercises for the other main muscle groups of the body (the bench press and/or the triceps pushdown and/or lateral pull down exercise for the upper body; the sit-up exercise for the trunk flexors and/or another exercise for the trunk extensors; and the bilateral/unilateral elbow and/or knee flexion exercise and/or leg adduction/abduction exercise). During the first seven weeks of the training the subjects trained with loads of 50 to 70% of the 1RM, 10-15 repetitions per set and 3-4 sets of each exercise. The loads were 50 to 60% and 60 to 80% of the maximum during the second seven-week period. In the two exercises for the leg extensor muscles the subjects now performed either 8-12 repetitions per set (at lower loads) or 5-6 repetitions per set (higher loads) and performed 3-5 sets. In the other four exercises the subjects performed 10-12 repetitions per set and performed 3-5 sets. During the last seven weeks of the training (weeks 15-21) two different load ranges were used in the two exercises for the leg extensors so that the subjects completed 3-6 repetitions per set with the loads of 70 to 80% of the maximum and 8-12 repetitions per set with the loads of 50 to 60%. The number of sets varied between 4 and 6. In the other four exercises the subjects performed 8-12 repetitions per set and performed 3 to 5 sets altogether. A part of the knee extension exercises (20%) were performed with light loads (50 to 60% of the maximum) as "explosively" as possible. The loads were individually determined during the training sessions throughout the training period.
Endurance training was also carried

Table I. Characteristics of women with rheumatoid arthritis and healthy controls.

	RAwomen (n = 21)	Healthy women (n=12)	P-value between the groups
Age (yrs), mean (SD)	44 (9)	42 (9)	0.60
min -max	32 -56	32-56	
Height (cm), mean (SD)	165 (6)	163 (5)	0.17
Weight (kg), mean (SD)			
- before	63.7 (13.4)	62.6 (6.8)	0.77
- change during 21 weeks	-0.2 (-0.9 to 0.6)	0.0 (-1.3 to 1.3)	

Table II. Clinical parameters in RAwomen.

	RAwomen Mean (SD)	Change from baseline to week 21 Mean (95% CI)
HAQ, scale 0-3	0.22 (0.32)	0.05 (-0.11 to 0.22)
Pain, VAS, 0-100 mm	13 (14)	0 (-9 to 9)
General health, VAS, 0-100 mm	16 (15)	-1 (-12 to 9)
Joint index, Score 66/68	3.3 (3.4)	-0.2 (-2 to 1)
ESR, mm/hour	9 (7)	-1 (-3 to 1)

out 3 times per a 2-week time period. During the first 7 weeks the subjects trained 30 min by bicycle ergometer or by walking to train basic endurance (under the level of aerobic threshold), determined during the aerobic performance test before the intervention. All subjects applied pulse meters during their training in order to maintain the intensity of exercise at the required level. On weeks 8-14 the duration of training session of 45 minutes was divided into 4 loading levels: 15 min under the level of aerobic threshold, 10 min between the aerobic-anaerobic thresholds, 5 min above the anaerobic threshold and 15 min again under the aerobic threshold. The focus of the last 7 weeks of training was to improve cycling speed and maximal endurance carried out in a 60 min session as follows: 15 min under the aerobic threshold, 2 x 10 min between the aerobic-anaerobic thresholds, 2 x 5 min above the anaerobic threshold and 15 min in the end under the aerobic threshold.

Statistics

The results are expressed as mean, standard deviation (SD), range, and 95 percent confidence intervals (95% CI). However, as variables were skewed, 95% confidence intervals for the means and time weighted area under the curve (AUC) were obtained by bias corrected and accelerated bootstrapping (5000 replications) (35). Statistical comparison was performed by using analysis of covariance (ANCOVA) or by permutation test with Hommel's approach for multiple comparisons (36).

Results

One patient dropped out after baseline measurements due to lack of motivation and one discontinued to exercise due to tenderness in small joints of the feet (they are not included in the analyses). One RA patient became pregnant and did not attend to VO_{2max} test at week 21. Otherwise the compliance of the participants in the supervised training program was perfect. If the subjects were unable to perform the planned workout in a certain day (e.g. due to flu, traveling), they performed an extra training session in advance or compensated the missing session later.

The changes in all clinical parameters were minor and statistically not significant in females wit RA (Table II). At the baseline there was no difference in the aerobic performance or muscle strength between the groups. During the 21-week training period significant increases took place in the $VO_{2\,max}$ as well as in maximal concentric and isometric bilateral leg extension forces in both groups (Table III). The increase in maximal isometric force was accompanied by a significant increase in the maximal IEMG-activity both in heal-

Table III. Changes in physical fitness parameters during 21-week combined strength and endurance training in women with rheumatoid arthritis and healthy controls.

	Baseline		Change to weeks 21		P-value between groups†
	Healthy women Mean (SD)	RAwomen Mean (SD)	Healthy women Mean (95% CI)	RAwomen Mean (95% CI)	
Bilateral isometric leg extension force (N)	1493 (405)	1357 (334)	293 (191 to 394)	348 (227 to 468)	0.46
- Maximal iEMG (VL+VM/2)	285 (130)	324 (138)	58 (19 to 100)	69 (31 to 108)	0.75
Bilateral dynamic 1-RM leg extension (kg)	94 (19)	90 (15	22 (16 to 28)	22 (18 to 24)	0.97
Muscle thickness, cm	5.07 (0.51)	4.75 (0.65)	0.33 (0.21 to 0.46)	0.35 (0.27 to 0.42)	0.81
Fat thickness, cm	2.94 (1.08)	3.08 (1.41)	- 0.29 (-0.39 to -0.20)	-0.38 (-0.44 to -0.32)	0.10
Maximal oxygen uptake (mm/kg/min)	24.8 (2.3)	25.0 (6.9)	1.8 (0.7 to 2.9)	3.8 (2.3 to 5.3)	0.066
Blood pressure					
- systolic	132 (20)	127 (12)	- 8 (- 13 to - 3)	- 7 (- 14 to 0)	0.66
- diastolic	81 (11)	78 (9)	- 4 (- 8 to - 1)	- 3 (-7 to 1)	0.38

† Analysis of covariance (ANCOVA), baseline values as covariate.

thy subjects and in RApatients.

During the 21-week training period no change took place in total body weight (Table I). The mean (SD) relative increases in the muscle mass thickness of the quadriceps femoris were 6.5% and 7.4% in the healthy and RAgroups, respectively (Table III). On the other hand, the decreases in subcutaneous fat thicknesses were 9.9% in the healthy and 12.3% in the RAgroup. Both groups showed a tendency towards decreased blood pressure.

Neither of the groups showed statistically significant changes in basal serum hormone concentrations during the course of the 21-week strength training period (Fig. 1). In the univariate testing the decrease in IGF-I in RA women was statistically significant ($p = 0.012$), but in the multivariate testing the significance disappeared. Area under the curve analysis including measures of serum hormones at weeks 0, 7, 14 and 21 shows low level of IGF-I in RAwomen (Table IV). Serum IGF-I concentration at the baseline correlated negatively with age in healthy women (r= -0.59, 95% Cl 0.01 to 0.89), while in RA women no significant correlation existed.

Despite its high intensity, volume and frequency, the applied combined strength and endurance training program did not affect on disease activity in RA women. Mean (SD) DAS 28 even slightly decreased from 1.51 (1.01) to 1.34 (1.07) during the training.

Discussion

The present findings show that the 21-week combined strength and endurance training remarkably improved the aerobic performance capacity in both healthy women and women with RA. Likewise, the present combined training led to significant increases in maximal strength of the lower extremities in both groups. The IEMG-activity increased throughout the training period suggesting that the nervous system has an important role in strength development. Further, the RA women were able to increase their knee extensor muscle thickness comparably to the healthy controls. The finding suggests that intensive training may be able to

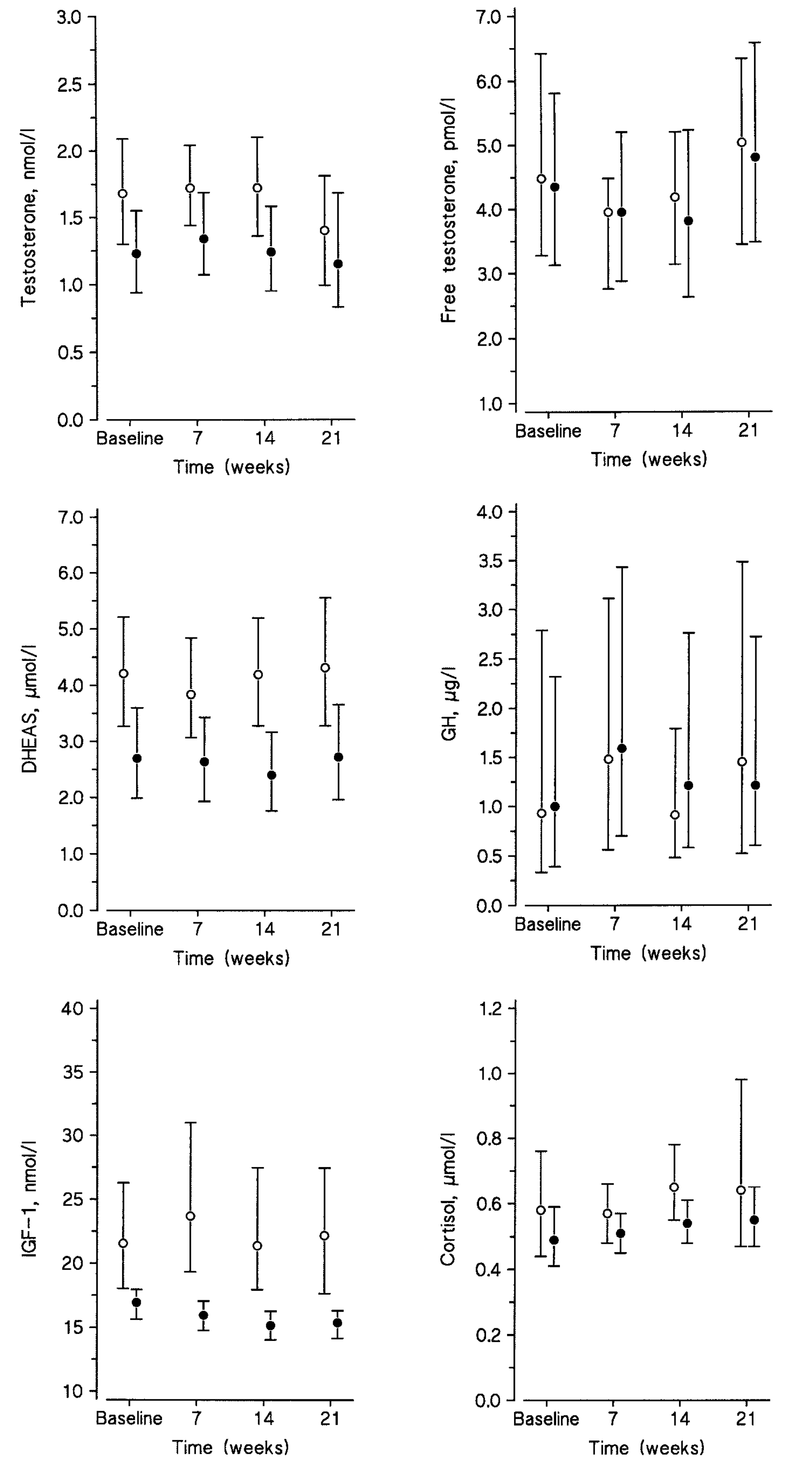

Fig. 1. Basal serum hormone concentrations in healthy women (open circle) and in women with RA during the 21-week combined strength and endurance training period.

reverse protein catabolism and even stimulate muscle hypertrophy in RA. The frequencies both in strength and aerobic training could be only 1.5 times a week providing that the loading intensity of training is sufficient and that it is increased progressively. In addition to significant increases in maximal strength of the lower extremities the present whole body strength training

Table IV. Area under the curve (AUC) of basal serum hormones (AUC counted from measurements taken at weeks 0,7,14 and 21).

	Health Mean (95%Cl)[†]	RA Mean (95%Cl)[†]	P-value between groups[††]
Testosterone AUC , nmol/l	1.66 (1.34 to 2.01)	1.25 (0.98 to 1.57)	0.32
Free testosterone AUC, pmol/l	4.29 (3.22 to 5.11)	4.11 (2.90 to 5.32)	0.88
DHEAS AUC, μmol/l	4.10 (3.21 to 5.08)	2.58 (1.84 to 3.34)	0.11
GH AUC, μg/l	1.19 (0.57 to 2.07)	1.30 (0.67 to 2.36)	0.88
IGF -1 AUC nmol/l	22.3 (18.34 to 27.47)	15.5 (14.8 to 16.7)	0.003
Cortisol AUC, μmol/l	0.61 (0.50 to 0.72)	0.52 (0.46 to 0.59)	0.48

[†] 95% confidence interval obtained by bias corrected and accelerated bootstrapping (5000 replications)
[††] Permutation test with Hommel's adjustment.

program led to large strength gains also in the upper extremities and trunk as reported earlier (34).

RA patients are in a higher risk to develop cardiovascular diseases (37-40). Accelerated atherosclerosis is a major cause of increased morbidity and mortality in RA patients (39). The loss of fat-free mass (i.e., primarily skeletal muscle) is undesirable due to the important functional and metabolic roles the muscles play not only in force production but also in energy metabolism. In healthy subjects, in addition to neuromuscular adaptation, strength training has favourable effects on lipid metabolism, insulin excretion and blood pressure (41-43). Effects of aerobic type endurance training alone are mainly transmitted through the enhancement of the cardiovascular system and oxidative capacity with only minor changes in the muscle mass or force production capacity of the neuromuscular system. In contrast, as a result of neuromuscular adaptations, high-load strength training increases maximal strength and size of muscles trained (5). The combination of both training methods seems desirable, since in the present study both groups showed a significant loss of subcutaneous fat thickness. As the whole body weight in both groups remained unchanged, we conclude that the relative proportion of active muscle mass increased and the proportion of fat mass decreased both in RA and healthy women. Also a slight decrease in blood pressure was detected. Consequently, the combined strength and endurance training not only reverses the loss of physical fitness and muscle tissue in RA, but it may decrease cardiovascular risks in this devastating disease.

Chronic, relative deficiency of steroid hormones of adrenal origin is believed to contribute to development of inflammatory manifestations in RA (44). Further, the observed sarcopenia in RA, in analogy to normal aging process, could be in part due to decreased production of GH and testosterone. Strength-training induced gains in muscle strength as well as muscle hypertrophy are due to anabolic processes, which at least partially may be mediated by anabolic hormones like GH, testosterone, and DHEAS. Strength training studies, however, have not shown systematic increases in basal androgen levels during intensive training neither in healthy men or women (45, 46). On the other hand, Häkkinen *et al*. (2000) have shown that mean levels of serum testosterone and free testosterone correlate statistically significantly with the individual changes in maximal strength, especially in elderly women (47). In the present study neither the basal serum concentrations of adrenal androgens, cortisol or GH changed during the training period. A part of this finding may be explained by the known diurnal variation in GH secretion; the 24-hour serum GH measurements to capture the acute response of GH secretion to loading were not performed. However, we have earlier reported that a significant acute increase of GH concentration takes place during a single strength training session in healthy women and in women with fibromyalgia (30). The GH concentration elevates immediately after the loading, and remains elevated for 15-30 minutes. The finding may reflect the adaptation of the endocrine system to training contributing to the changes in the function and structure of the neuromuscular system.

Serum IGF-I reportedly plays an important role in muscle growth and improvement of muscle strength (9,10). In the present study the women with RA had lower mean serum IGF-I concentrations than healthy women at baseline. Further, this difference sustained throughout the training period. Interestingly, Matsumoto and coworkers have reported elevated IGF-I levels in synovial fluid of RA patients (11). In fact, serum measurements of chemical mediators including hormones may mirror poorly the intracellular, often receptor mediated regulatory or metabolic cascades in various compartments of the body.

Straub with coworkers recently demonstrated that decreased adrenal production or increased conversion to downstream hormones (rather than increased urinary excretion) are the most likely causes of inadequately low serum levels of adrenal hormones in RA (48). Both acute exercise bouts of varying severity as well as long term physical training have been found to affect the immune response cascade. Presumably light to moderate exercise increases immune responsiveness but high-level training leads to immunosuppression. Serum DHEAS concentrations were slightly, but not statistically significantly inferior in our RApatients when compared to those of healthy controls. However, the DHEAS levels remained unchanged during the training period permitting us to conclude that physical training was not the reason for the lowered concentration.

Chronic relative glucocorticoid insufficiency is believed to contribute to development of inflammatory manifestations in RA. Further, regulation of serum cortisol levels, in addition to that of testosterone, most probably is of central importance in the process of recovery from both psychological and physical stress e.g. from physical exercise sessions (49). The baseline level of serum cortisol in our RA patients was within reference values and the concentrations did not change systematically during the intensive training period. The data indicate that the total loading of the present combined strength and endurance training sessions was not too strenuous for our women with RA and healthy controls. The length of the recovery periods between the training sessions plays an important role as well.

In summary, the present combined endurance and strength training regimen for 21 weeks resulted in considerable improvements in physical fitness, not only in healthy subjects, but also in women with RA. The improvements in fitness were accompanied by positive changes in body composition. Further, intensive physical training induced no significant changes in serum levels of anabolic hormones or that of cortisol. However, in comparison to healthy subjects, women with RA showed lower serum IGF-I throughout the entire experimental period. We conclude that the combined strength and endurance training was tolerated by RA patients comparably to healthy persons.

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