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Research report

Growth hormone, prolactin and cortisol response to exercise in patients with depression

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ABSTRACT

Background: A blunted growth hormone and prolactin response to pharmacological stress test have previously been found in depressed patients, as well as an increased cortisol response to psychosocial stress. This study investigated these hormones in response to acute exercise using an incremental bicycle test.
Method: A cross-sectional comparison of cortisol, growth hormone, and prolactin in depressed ($n=137$) and healthy ($n=44$) subjects during rest and in response to an incremental bicycle test. Secondly, we tested the depressed patients again after a 4-month randomized naturalistic exercise intervention.
Results: Resting plasma levels of growth hormone (GH), cortisol, or prolactin (PRL) did not differ between depressed and healthy subjects (all p-values $>.12$). In response to an incremental bicycle test the GH ($p=.02$) and cortisol ($p=.05$) response in depressed was different compared to healthy controls. The effect of acute exercise stress on PRL ($p=.56$) did not differ between depressed and healthy subjects. Apart from a decrease in GH response in the strength-training group ($p=.03$) the pragmatic exercise intervention did not affect resting hormonal levels, or the response to acute exercise.
Conclusions: Patients with mild to moderate depression had a different growth hormone and cortisol response to acute exercise stress compared to healthy controls. Strength training was able to reduce the growth hormone response to acute exercise stress in this patient population. Studies with more rigorous inclusion criteria and higher exercise frequencies are needed to evaluate and confirm the possible effect of exercise in depressed subjects.

1. Introduction

Exercise is a known and potent stimulator of growth hormone, prolactin, and cortisol release (Karkoulias et al., 2008;Weltman et al., 2003), and exercise training have been shown to modulate neuroendocrine response to challenge test in human subjects (Broocks et al., 2001, 2003;Weicker and Struder, 2001). Furthermore, there are indications that exercise potentially has an antidepressant effect (Mead et al., 2008).

One of the hallmarks of biological psychiatry is the hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis that has been demonstrated in patients with major depressive disorder (MDD). It has been proposed that the effect of antidepressants partly relies on their capability to normalize it (Barden, 2004). Disturbances in the HPA axis have been demonstrated especially during high levels of psychosocial stress (Burke et al., 2005). The HPA axis response to psychosocial stress and acute exercise is similar, though a stronger response is seen during exercise (Negrao et al., 2000).

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The pituitary release of growth hormone and prolactin is centrally regulated, and an abnormal hormone response to pharmacological challenge tests has been observed. Compared to healthy controls patients with depression have a blunted growth hormone response to the growth hormone stimulator clonidine (Mokrani et al., 2000;Valdivieso et al., 1996), as well as a blunted prolactin response to challenge agents that stimulates 5-HT neurotransmission (Cleare et al., 1996;Lerer et al., 1996).

One smaller study including 24 patients and 22 healthy volunteers (Kiive et al., 2004) previously measured the effect of acute exercise to plasma growth hormone, cortisol, and prolactin in male subjects exclusively. The study concluded that the prolactin response was higher in depressed patients. However, given the large individual variation in hormone levels a larger sample size might be required to detect any differences reducing the risk of spurious findings. Furthermore, in the study by Kiive et al. 22 of the 24 included patients used antidepressant medication and thus any effect of antidepressant medication on hormonal response to acute exercise would be difficult to adjust for.

The main objective of this study was to compare the plasma response of growth hormone (GH), cortisol, and prolactin (PRL) to acute exercise in depressed patients and healthy volunteers (Part 1). We hypothesized, in the following order, that patients would have a lower GH response, a higher cortisol response, and a lower prolactin response to an incremental bicycle test compared to healthy controls. Secondly, we hypothesized that a strength, or an aerobic training intervention would be able to change the hormonal response to acute exercise in depressed patients (Part 2).

2. Methods

The protocol was accepted by the local ethics committee (KF 01-213), and registered at ClinicalTrials.gov (NCT 00103415) and the Danish Data Protection Agency (J.nr. 2004-54-1587).

2.1. Part 1

2.1.1. Subjects

We recruited 46 healthy controls through advertisements, who had no self-reported physical or mental disorders, no actual or previous psychiatric treatment, nor did they engage in any exercising activities for more than 1 h/week. The healthy controls were group-matched to patients for age, sex, and body mass index.

We included 137 patients from the DEMO trial (Krogh et al., 2009) for hormonal assessment. The DEMO trial is a three-armed, parallel-group, observer-blinded randomized clinical trial investigating the effect of exercise on depression. Participants had clinical depression according to ICD-10 diagnostic criteria (F32.0, F32.1, F33.0 and F33.1), aged 18–55, and were living in the vicinity of Copenhagen, Denmark. The diagnosis was based on the Medical Depression Inventory (MDI) (Bech et al., 2001) by trained research staff (psychiatric nurse and psychologist). Exclusion criteria were current substance abuse, contraindications to physical exercise, exercising more than 1 h/week, sick leave for more than 24 months, early-retirement or having a high risk of suicidal behaviour. All patients were referred from a clinical setting.

2.2. Incremental bicycle test

To assess hormonal response to acute exercise we used an incremental bicycle test. The test and calculation of maximal oxygen uptake (VO_{2max}) is based on L. B. Andersens bicycle exercise protocol (Andersen, 1995). Subjects were instructed to fast from midnight prior to exercise testing, and they were examined between 8:30 and 10:00 a.m. the following morning. Prior to the exercise test all subjects were instructed in the ergometer test procedure. It was emphasized that the subjects had to continue until exhaustion. In the initial 5 min of the cycle test (Monark) the workload was 75 W for women, and 100 W for men. We aimed at a pulse rate of 120 (+/−10) at the end of the 5 min, and workload was adjusted accordingly. After the initial 5 min the workload was increased by 25 W per 2 min till exhaustion. All subjects were moderately verbally encouraged. A venous catheter was inserted in the antecubital vein and blood samples were collected 15 min prior to exercise testing (after 5 min rest), and at the peak of exercise (at VO_{2max}), 15, 30 and 60 min after the exercise test. Pre-test samples were collected with the subject lying down, and the remaining with the subject in a sitting position. Blood samples were collected in vacutainers and immediately sent to the laboratory and analyzed.

2.3. Outcomes

A laboratory technician blind to subject status immediately analyzed the blood samples. Growth hormone was analysed using an immunflourometric assay (IFMA), CV_{max} = 6%, having a detection limit at 0.03 miu/l. Cortisol was analysed using an automated electrochemiluminescense immunoassay (ECLICA), CV_{max} = 8%, having a detection limit at 0.5 nmol/l. Prolactin was analyzed using an automated (BRAMHMS Kryptor) IFMA, CV_{max} = 7%, having a detection limit at 5 miu/l.

Repetition maximum (1 RM) was defined as the maximum amount of weight the subject could lift/push doing one repetition. This was measured using machines and standardized procedures. Participants' weight in kg was measured using an electronic weight (Bisco, Denmark). We used the Hamilton Depression Scale (HAM-D_{17}) (Hamilton, 1960) to assess severity of depression.

2.4. Part 2 — randomized clinical trial

2.4.1. Subjects and design

The objective was to investigate if a 4-month exercise intervention could change the hormonal response to acute exercise. The incremental bicycle test was performed before and after the intervention. The test and other outcomes are described above. After the initial cycle test the 137 patients were randomized to an exercise intervention: 42 to a strength training program, 47 to an aerobic training program, and 48 to a relaxation program. Randomization was centralized and stratified according to an antidepressant medication: 1) not receiving an antidepressant medication; 2) having received an antidepressant medication for less than six weeks; or 3) having received an antidepressant medication for more than six weeks. DEMO trial staff contacted the Copenhagen Trial Unit (CTU) by phone. Randomization was carried out by CTU using

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computerized restricted randomization with a block size of 6. The block size and thus allocation sequence were unknown to the DEMO trial staff. Only 88 patients completed hormonal analysis after the intervention.

2.5. Interventions

All three patient groups met twice a week in the afternoon for four months. The patients in the relaxation and aerobic training group carried pulse monitors (Polar m-31 and m-61); In the relaxation group the pulse monitors were used during some of the sessions to secure a low pulse (maximum 120; Borg 12) and in the aerobic exercise group they were used in each session to secure exercise in the prescribed pulse interval.

2.5.1. Strength training group

The strength training was designed to increase muscular strength as measured by one repetition maximum (1 RM). The training was a circuit-training program involving large muscle groups, including both machines and free weights. Six exercises were made on machines training large muscle groups: leg extension, leg press, total abdominal, lower back, chest press, vertical traction. Additionally free weights and sandbags were used for training of the calf muscle, the arm-abductors, the triceps brachi and the hip abductors. Initially each exercise was done 2 times with 12 repetitions at a workload equivalent to 50% of RM. As the participants progressed each exercise was done 4 times with the number of repetitions reduced to 10 and 8 and workload increased to 75% of RM.

2.5.2. Aerobic training group

The aerobic training involved ten different exercises using large muscle groups. Machines were used for cycling, running, stepping, abdominal exercises and rowing. Additional exercises were sliding movements on small carpets, trampoline, step bench, jump rope and exercises on a Ski Fitter (Fitter International; Calgary, Alberta, Canada). Initially each exercise lasted 2 min, followed by 2 min rest, and repeated twice which amounted to a total exercise time of 40 min. This gradually increased to 3 min exercise and one-minute rest, and each exercise repeated twice amounting to a total exercise time of 60 min. When patients became acclimated to the training, the intensity defined as $\%HR_{max}$ rose from initially 70% to 90%.

2.5.3. Relaxation exercise group

The purpose of the relaxation training was to secure the same level of social interaction as in the other groups, while avoiding muscular contractions or stimulation of the cardiovascular system, thus working as a control group. The patients did not engage in activity perceived higher than 12 on the Borg scale, and the main exercises were done at an intensity level at 6–10 on the Borg scale. The first 20–30 min the patients performed different movements on mattresses or Bobath balls (Ledregomma; Udine, Italy). They were also given massage on the back using a Ball Stick Ball (Select; Glostrup, Denmark) for 10 min by another patient. This was followed by balance- and light exercises with tubes in a 10–20 min program. The sessions ended with relaxation exercises for 20–30 min were the patients alternately contracted and relaxed different muscle groups.

2.6. Statistical analysis for Part 1 and Part 2

Our analytical strategy was to compare the hormonal response of depressed and healthy controls in a repeated measurement analysis (group × time). Simply comparing hormonal levels at different time points would not sufficiently describe differences in response to acute physical stress, but possibly reflect baseline differences. In case the groups differed on distribution of important variables we would adjust for these in our analysis. A crucial point in this method is to ensure that our analysis reflected comparable maximum physical stress. To ensure this we a priori decided to adjust for VO_{2max}. This variable reflects the subjects' maximal physical performance obtained during standardized conditions. While the repeated measurement analysis do not pinpoint where possible differences are, we investigated the hormonal response from rest to maximum levels — Δ_{max}.

Group comparison was done with Student's *t* or chi-square tests for cross-tables. Due to non-parametric distribution of hormonal values, comparison of healthy individuals and depressed patients at rest was done with Mann–Whitney *U* and presented with median and interquartile range (25th and 75th percentile).

We used a repeated measurement analysis with a mixed model approach to analyze the hormonal response to the incremental bicycle test. This was done by the 'Mixed' command in SPSS version 11.0. Based on Akaike's information criterion we chose an unstructured variance model for covariance matrix, adjusted for relevant covariates. Data was log-transformed prior to analysis. The assay for cortisol measurement has a known cross-reactivity with oral contraception causing artificial elevated cortisol levels (Klose et al., 2007). Based on this we chose to exclude individuals using either oral contraception (OC) or hormone replacement therapy (HRT) from our cortisol analysis. In analysis of GH or PRL response we used 'hormonal therapy' as a dichotomous covariate. This variable included both the use of OC or HRT.

Data and analysis from the randomized trial only included completers. Completers are defined as patients that had blood samples taken both at baseline and at follow-up. Group comparisons for demographical distribution were done with ANOVA, and for hormonal data with Kruskal–Wallis test.

3. Results

3.1. Characteristics and background

For technical reasons (primarily inability to insert the venous catheter) we were only able to get blood samples from 137 of the 165 (83%) patients included in the DEMO trial. Please see Fig. 1 for subject flow. Except for BMI, we found no differences on key variables between patients that we were able to get blood samples from and those we did not (sex, age, HAM-D_{17}, antidepressant medication, melancholiform depression, and VO_{2max}). The patients we did not get samples from, had on average a BMI that was 3.6 kg/m^2 higher (95% CI: 1.2 to 6.0; $p = .003$). We were able to get blood analysis from 44/46 (95.7%) of the healthy volunteers.

Demographic and other background characteristics of patients and controls are presented in Table 1. The majority of patients were female and 69.3% used an antidepressant

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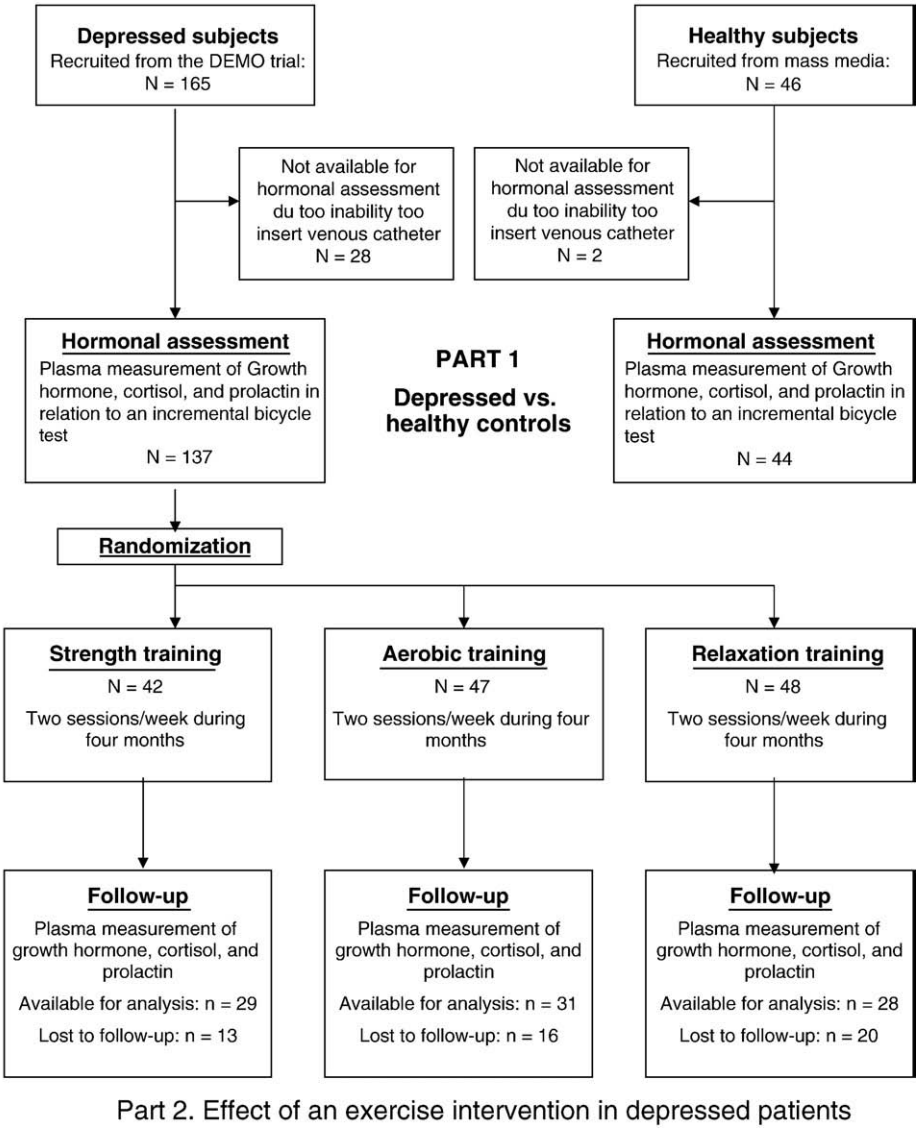

Fig. 1. Flowchart of patient flow. Part 1 refers to the comparison of patients with depression on hormonal response to acute exercise. Part 2 refers to the comparison of the effect of an exercise intervention on the hormonal response to acute exercise in patients with depression.

medication. The healthy controls were well matched to the patient group, except for the use of oral contraceptives or hormonal replacement therapy. This was unevenly distributed in the two groups with 10.9% using this in the patient group vs. 25% in the group of healthy controls ($\chi^2_1 = 5.35$; $p = .02$).

3.1.1. Incremental bicycle test

VO_{2max} (ml/kg/min) for patients were 27.7 (SD = 6.7) vs. 30.3 (SD = 7.1) for healthy controls (mean diff. 2.6, 95% CI: 0.09 to 4.8; $p = .03$). It could be assumed that depressed patients would not be able to reach their physical limits as well as healthy controls. However, the ratio between predicted maximal heart rate ($208 - 0.7 \times$ age) (Tanaka et al., 2001) and observed maximal heart rate was 1.069 (SD = 0.014) and 1.069 (SD = 0.093) for healthy and patients respectively (mean dif. 0.0005; 95% CI: −0.036 to 0.037, $p = .98$). The relative physical performance was therefore equal in the two groups.

3.2. Part 1 — healthy subjects compared to depressed patients

3.2.1. Growth hormone

GH in depressed patients at rest was 1.2 miu/l (IQR 0.3 to 5.0 miu/l) compared to 3.5 miu/l (IQR 0.6 to 7.8 miu/l) in healthy controls ($U = 2447.5$, $p = .16$).

The growth hormone response to acute exercise (Fig. 2) was significantly different in the depressed patients compared to healthy controls (depression status × time; $F_{4,\ 168} = 2.916$; $p = .02$), in a model adjusted for VO_{2max} ($p < 0.001$), antidepressant medication ($p = .01$), and hormonal therapy ($p < .001$).

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Table 1
Baseline data for patients with mild to moderate depression and a group-matched healthy control group.

	Depressed patients N = 137	Controls N = 44	P-value
Female	101 (73.7%)	35 (79.5%)	0.29
Age in years, mean (SD)	38.9 (9.6)	38.2 (10.2)	0.76
Hormonal therapy [a]	15 (10.9%)	11 (25%)	0.02
Caucasian	125 (91.2%)	42 (95.5%)	0.34
Other	12 (8.8%)	2 (4.5%)	–
Depression			
Hamilton depression scale (17 items), mean (SD)	17.8 (3.8)	3.0 (2.3)	<0.001
Hamilton anxiety scale, mean (SD)	14.9 (5.4)	2.0 (1.7)	<0.001
Alcohol, weekly consumption > rec.	6 (4.4%)	5 (11.4%)	0.10
Antidepressant medication	95 (69.3%)	–	–
Started medication > 6 weeks ago	85 (62.0%)	–	–
>2 previous episodes [b]	43 (31.4%)	–	–
Physical			
Body mass index, mean (SD)	26.0 (4.8)	25.6 (4.3)	0.57
Maximal oxygen uptake (ml/kg/min), mean (SD)	27.7 (6.7)	30.3 (7.1)	0.03

Continuous variables are analyzed by Student's *t* and dichotomous outcomes are analyzed by chi-square test for cross-tables.

[a] Hormonal therapy refers to the use of either oral contraceptives or hormonal replacement therapy.

[b] More than 2 previously diagnosed episodes of depression.

The interaction terms hormonal therapy × time ($p = .26$) and time × antidepressant medication ($p = .21$) were insignificant.

The median $GH\Delta_{max}$ was 4.17 miu/l (IQR 0.52 to 18.97 miu/l) in depressed patients and 1.88 miu/l (IQR −0.68 to 10.49 miu/l) in healthy controls ($U = 2235.0$, $p = .06$).

3.2.2. Cortisol

Cortisol levels in depressed patients at rest were 313.0 nmol/l (IQR 237 to 425 nmol/l), and 367.0 nmol/l (IQR 263 to 458 nmol/l) in healthy controls ($U = 1655.0$, $p = .12$).

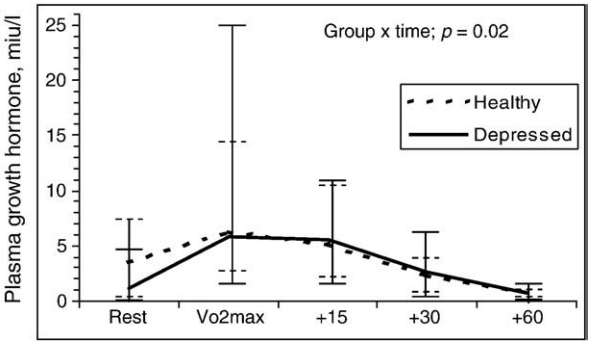

Fig. 2. Median plasma growth hormone in response to an incremental bicycle test in healthy controls and patients with depression, (a) repeated measurement analysis using a mixed model approach. Adjusted for VO_{2max}, antidepressant medication, and the use of hormonal therapy. Error bars represent interquartile range.

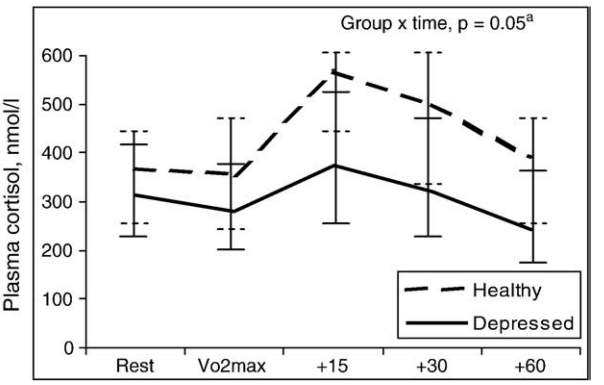

Fig. 3. Median plasma cortisol in response to an incremental bicycle test in healthy controls and patients with depression (a) repeated measurements analysis using a mixed model approach. Adjusted for VO_{2max} and antidepressant medication. Error bars represent interquartile range.

The cortisol response to the incremental exercise test (Fig. 3) did differ between depressed and healthy subjects (depression status × time; $F_{4,\ 149} = 2.399$; $p = .05$) adjusted for VO_{2max} and antidepressant medication ($p = .42$). Antidepressant medication × time ($p = .09$) did not influence the model.

The median $Cortisol\Delta_{max}$ was 22 miu/l (IQR −42 to 180 miu/l) for depressed and 130.0 miu/l (IQR 36 to 202 miu/l) in healthy individuals ($U = 2022$, $p = .002$). The effect of depression was still significant ($p = .04$) in a linear regression adjusted for VO_{2max}. The residuals had a normal distribution in this model.

3.2.3. Prolactin

At rest prolactin in depressed patients was 186.0 miu/l (IQR 145.0 to 267 miu/l) and 188.0 miu/l (IQR 128 to 262 miu/l) in healthy controls ($U = 763.5$, $p = .76$).

The prolactin response to acute exercise (Fig. 4) did not significantly differ (depression status × time; $F_{4,\ 155} = 0.74$; $p = .56$) in a model adjusted for VO_{2max} ($p = .12$), antidepressant medication ($p = .06$), and hormonal therapy ($p = .86$). Hormonal

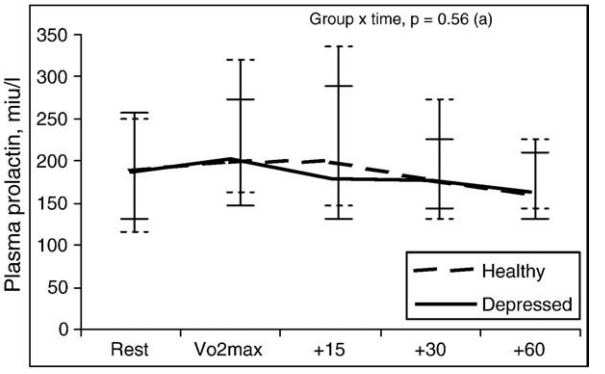

Fig. 4. Median plasma prolactin in response to an incremental bicycle test in healthy controls and patients with depression (a) repeated measurements analysis using a mixed model approach. Adjusted for VO_{2max}, antidepressant medication, and the use of hormonal therapy. Error bars represent interquartile range.

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therapy × time ($p = .99$), and antidepressant medication × time ($p = .70$) were all statistically insignificant.

The median PRLΔ_{max} was 6 miu/l (IQR −18 to 34.5 miu/l) for depressed patients and 18 miu/l (IQR 3 to 34 miu/l) for healthy controls ($U = 2534.0$, $p = .24$).

3.3. Part 2 — the effect of an exercise intervention in depressed patients

3.3.1. The randomized controlled trial

Of the 137 patients included for hormonal assessment, data from 88 patients (completers) were available for post-intervention analysis. At baseline (prior to exercise intervention) the 88 patients did not significantly differ from the non-completers on distribution of age, sex, use of antidepressant medication, melancholiform depression, >2 previous episodes of depression, or resting levels of GH, cortisol or PRL. However, the completers did on average have a lower HAM-D_{17} score at baseline (17.3 vs. 18.9, $p < .04$), and the average participation was higher in the completer group (60.4% vs. 28.9%, $p < .001$). Only data from completers are presented in the following. The demographic distribution in the three patient groups is presented in Table 2. The percentage of female patients in the three groups was 89.7%, 83.4%, and 42.9% in the strength, aerobic, and relaxation groups respectively ($\chi^2_2 = 12.65$query; $p < .001$). Furthermore, the HAM-D scores differed significantly with the mean being 17.6 (SD = 3.5), 18.4 (SD = 4.2), and 15.6 (SD = 3.4) in the strength, aerobic, relaxation groups respectively ($F = 6.033$; $p = .02$).

The average participation in the training sessions was 66.3%, 61.6%, and 52.3% for the strength, aerobic, and relaxation groups respectively ($F = 0.703$; $p = .50$). The increase in 1 RM for knee press was on average 10.3 kg higher (95% CI: 3.6 to 17.0, $t = 3.10$, $df. = 51$, $p = .003$) in the strength group compared to the relaxation group. The increase in maximal oxygen uptake in the aerobic group compared to the relaxation group was 2.9 ml/kg/min (95% CI: 1.0 to 4.8; $t = 3.05$, $df. = 61$, $p = .003$). This indicates that the intervention was conducted as designed. The average increase in 1 RM for knee press was 10.8 kg (95% CI: 4.8 to 16,7; $t = 3.00$, $df. = 48$, $p = .001$) in the strength group compared to the aerobic training group. The mean increase in maximal oxygen uptake was 1.5 ml/kg/min (95% CI: 0.1 to 3.0; $t = 2.12$, $df.$ 56, $p = 0.038$) in the aerobic compared to the strength group. The number of patients in treatment with antidepressants post intervention was 18/25, 17/28, and 12/25 in the strength, aerobic, and relaxation groups respectively ($\chi^2_2 = 3.01$query, $p = .22$). The reduction in HAM-D_{17} score from baseline to post-intervention was −7.9 (SD 5.4), −7.0 (SD 7.1), and −6.0 (SD 5.7) in the strength, aerobic, and relaxation groups respectively ($F = 0.592$, $p = .56$).

3.3.2. Growth hormone

Resting values of growth hormone did not differ between the groups at baseline ($\chi^2_2 = 1.18$, $p = .55$). Post-intervention the resting values were 1.0 miu/l (IQR 0.51 to 5.8 miu/l), 2.1 miu/l (IQR 0.4 to 6.1 miu/l), and 0.53 miu/l (IQR 0.1 to 10.2 miu/l) in the strength, aerobic, and relaxation-groups respectively ($\chi^2_2 = 0.46$, $p = .80$).

GH response to acute exercise was independent of group allocation at baseline as a main effect ($p = .85$) as well as group × time ($p = .99$). Post-intervention the response to exercise was significant for group as a main effect ($F = 4.8$, $p = .01$) but not as group × time ($F_{8, 70} = 1.5$, $p = .18$) adjusted for VO_{2max} ($p = .001$), antidepressant medication ($p = .91$), HAM-D_{17} score ($p = .75$), sex ($p = .02$), and hormonal therapy ($p = .01$). The interaction term time × antidepressant medication ($p = .98$) and time × hormonal therapy ($p = .18$) were statistically insignificant.

The GHΔ_{max} was similar at baseline in the three groups (Kruskal–Wallis: $\chi^2_2 = 2.641$, $p = .28$). Post-intervention the increase was 0.8 miu/l (IQR 0.3 to 9.0), 5.0 miu/l (IQR 1.4 to 20.6), and 10.5 miu/l (IQR 1.8 to 22.7) in the strength, aerobic, and relaxation groups respectively (Kruskal-Wallis: $\chi^2_2 = 7.1$, $p = .03$).

Table 2
Baseline data for patients with clinical depression randomized to either strength, aerobic, or relaxation-training.

	Strength N = 29	Aerobic N = 31	Relaxation N = 28	P-value
Female	26 (89.7%)	26 (83.4%)	12 (42.9%)	<0.001
Age in years, mean (SD)	42.4 (9.5)	39.3 (9.8)	36.0 (9.8)	0.05
Hormonal therapy	3 (10.3%)	2 (6.5%)	4 (14.3%)	0.52
Depression				
Hamilton depression scale (17 items), mean (SD)	17.6 (3.5)	18.4 (4.2)	15.6 (3.4)	0.02
Antidepressant medication	18 (62.1%)	20 (64.5%)	19 (67.9%)	0.90
Started medication > 6 weeks ago	15 (51.7%)	18 (58.1%)	15 (53.6%)	0.75
Melancholiform depression	7 (24.1%)	2 (6.5%)	4 (14.3%)	0.17
> 2 previous episodes of depression	8 (27.6%)	13 (41.9%)	7 (25.0%)	0.32
Alcohol, weekly consumption > rec	0 (0.0%)	1 (3.2%)	0 (0.0%)	0.40
Physical assessment				
Body mass index (kg/m^2), mean (SD)	24.8 (4.0)	26.5 (5.3)	25.7 (4.3)	0.34
$V \cdot O_{2max}$ (ml/kg/min), mean (SD)	28.5 (5.2)	26.6 (5.6)	30.5 (6.0)	0.03
1 Rep. maximum				
Knee press kg, mean (SD)	44.0 (17.6)	54.6 (21.3)	62.9 (21.4)	0.01
Leg press kg	88.6 (34.0)	103.3 (39.2)	118.0 (45.5)	0.03
Chest press kg	32.4 (13.0)	36.0 (14.0)	50.7 (23.8)	0.01

Continuous variables are analyzed by Student's *t* and dichotomous outcomes are analyzed by chi-square test for cross-tables.

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3.3.3. Cortisol

At baseline the resting levels of cortisol did not differ between the groups ($\chi^2_2 = 1.59$, $p = .45$). Post-intervention the median cortisol values were 346.5 nmol/l (IQR 248.3 to 469 nmol/l), 338.0 nmol/l (IQR 294 to 513 nmol/l), and 349.0 (IQR 259 to 460 nmol/l) in the strength, aerobic, and relaxation groups respectively ($\chi^2_2 = 0.239$, $p = .89$).

At baseline the cortisol response to acute exercise stress was similar in all three groups (group × time, $p = .69$). Post-intervention the effect of group allocation ($F = 0.486$, $p = .89$) and group × time was insignificant ($F_{10,\ 73} = 0.758$, $p = .64$). This model was adjusted for VO_{2max} ($p = 0.20$), antidepressant medication ($p = .16$), HAM-D_{17} ($p = .21$), and sex ($p = .45$).

3.3.4. Prolactin

At baseline the resting levels of prolactin did not differ between the groups ($\chi^2 = 0.162$, *df.* 2, $p = 0.9$). Post-intervention the median prolactin values were 157.5 miu/l (IQR 135 to 204 miu/l), 144.5 nmol/l (IQR 128 to 186 nmol/l), and 123.0 miu/l (IQR 103 to 157 nmol/l) in the strength, aerobic, and relaxation groups respectively ($\chi^2_2 = 4.694$, $p = .10$).

At baseline the prolactin response to acute exercise was similar in all three groups with group as a main effect ($p = .76$) or as group × time ($p = .19$). Post-intervention the effect of group allocation ($F = 0.486$, $p = .89$) and group × time was insignificant ($F_{8,\ 70} = 0.680$, $p = .71$). This model was adjusted for VO_{2max} ($p = .41$), antidepressant medication ($p = .46$), HAM-D_{17} ($p = .39$), sex ($p = .75$), and hormones ($p = 0.16$).

4. Discussion

This is the first study to observe that depressed patients have a significantly different growth hormone and cortisol response to acute exercise compared to healthy controls. A naturalistic exercise intervention did not significantly change the growth hormone, cortisol or prolactin response measured in a repeated measurement analysis.

4.1. Growth hormone

Exercise is a well-known and powerful stimulator for GH release and the GH response is within the range of pharmacological GHRH or clonidine stress test (Gann et al., 1995). The mechanisms which leads to an exercise induced increase in GH involves several neurotransmitting systems (adrenergic, cholinergic, and opioid pathways) (Giustina and Veldhuis, 1998), making the interpretation of any findings complex. However, the GH levels observed in plasma are ultimately reflecting a ratio between GHRH and ghrelin and the GH inhibitor somatostatin (somatotropin release-inhibiting hormone — SRIH). Our study suggests, a higher GH response to acute exercise in depressed patients compared to healthy controls. The increase in hormone secretion in response to physical exercise was higher in depressed patients in the Kiive study (Kiive et al., 2004) as well, but failed to reach significance. This finding is in contrast with the blunted or normal GH response observed in pharmacological GHRH or clonidine stimulation in healthy and depressed subjects. Whereas the pharmacological stress tests are highly specific, the GH response to exercise is the synthesis of a highly complex response. While the interpretation of these results is more difficult, they reflect real-life response to exercise stress.

Previous studies have found enhanced GH response in depressed patients to the acetylcholinesterase inhibitor pyridostigmine (PYD) (Cooney et al., 1997). Furthermore, blocking of cholinergic muscarinic receptors by atropine in one study completely inhibited exercise-induced GH secretion, suggesting a major role of the cholinergic system in GH response to exercise (Casanueva et al., 1984). The current findings could be the result of reduced SRIH tonus due to cholinergic hypersensitivity in depressed patients. In post-hoc analysis we found that the exercise intervention had reduced the exercise-induced increase in GH at VO_{2max} in the strength-training group compared to the relaxation group. This finding should be interpreted with caution since it is based on a relatively low number of patients and could thus be the result of random error.

4.2. Cortisol

We expected the response to acute exercise would be increased in the depressed patients as it has been shown in psychosocial stress test (Burke et al., 2005), but this study suggests that the opposite is the case during physical stress. However, the majority of patients in the current study had received antidepressant medication in more than six weeks and still fulfilled the ICD-10 criteria for depression suggesting a treatment resistant group, and thus the external validity in terms of depressed patients in general is limited.

We observed no effect of either strength or aerobic training on resting cortisol levels, which is in accordance with the majority of available literature (Duclos et al., 2003; Filaire et al., 1998;Fry et al., 1994;Hakkinen et al., 1998; Kargotich et al., 2007). Furthermore, we found no effect of exercise training to cortisol response to acute exercise stress. In a cross sectional study one research group found that physical conditioning was associated with an attenuated pituitary–adrenal activation only in highly trained runners (>75 km per week) and similar response for untrained and moderately trained individuals (24–40 km/week) (Luger et al., 1987). The lack of response to training could be related to the relatively low training impact in our study.

It could be argued that our analysis of cortisol is insufficient in terms of included covariates. Especially wake-up time and menstrual-cycle is known to influence cortisol levels. Our participants were recruited from a large age span regarding menstrual cycle and reproductive hormones in general. Including only male subject the tendencies from the full sample was replicated, albeit insignificant (data not shown).

4.3. Prolactin

We did not observe any effect of depression on prolactin levels during rest or in response to exercise, which is in contrast to findings by Kiive et al. (2004) who found an increased prolactin response to exercise in depressed individuals. We have no explanation for these discrepancies, except that the current findings possibly reflect a partly treatment resistant group of patients. A recent exercise trial randomizing healthy males to either a high or medium intensity

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exercise program lasting for 60 weeks observed higher plasma prolactin levels post-intervention in the high intensity program (Safarinejad et al., 2009), which might suggest that program in this trial was too short to induce any effect on resting prolactin levels.

4.4. Strengths and limitations

The strength of this study is the number of patients, and that laboratory staff was blinded to patient status and allocation. The staff conducting the bicycle test, were not blinded to subject status, which could introduce bias in either direction. Though we found no statistical evidence for increased variation due to antidepressant medication this could be considered a limitation of the study since these products are known to have a chronic effect on the monoamines and the HPA axis. The number of participants using hormonal medication was different between healthy and patients. Oestrogen is known to interfere with cortisol measurements in the chosen method of analysis, thus hormonal therapy was a well known confounder (Klose et al., 2007). Another limitation was that we did not use Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 2008) or similar instruments to diagnose this patient group, but the much shorter MDI (Bech et al., 2001). Since all patients were referred from other professional staff it seems fairly reasonable to assume that the diagnosis of depression is correct, but it could be argued that important knowledge of co-existing psychiatric diagnosis is limited. The current study included both sexes, a reasonable wide age group, medicated and unmedicated patients, and all patients were recruited from a clinical setting providing a high level of external validity. However, the results could not be inferred to severely depressed or patients with a high body mass index.

The strength of the trial part of study was a centralized and computerized randomization process providing adequate allocation concealment. A limitation was the large number of patients that we could not get samples from at the follow-up. This is a potential bias, which compromises the validity of trial, and restrict our findings to patients with lower BMI scores (<27). Also the attrition to the exercise protocol was low in all groups. On average the participants came to half the scheduled sessions. Therefore a conclusion stating that exercise does not induce changes in CNS would be erroneous. However, our results do not support that a naturalistic exercise intervention capable of changes in any of the observed hormonal systems. Furthermore, the analysis of the psychometrical data did not suggest that the exercise interventions had any significant effects on depression scores compared to the relaxation group. Since other trials have shown a positive effect of exercise on depression symptoms, it could be argued that our patient sample received too little exercise. Furthermore, randomization by chance distributed sex, Hamilton ratings, maximal oxygen uptake, and 1 RM unevenly in the three groups. In our repeated measurement analysis we adjusted for these variables limiting the potential bias.

5. Conclusion

We did observe differences in growth hormone and cortisol response in healthy volunteers and depressed subjects. However, the observations were somewhat the opposite of expected and the results should thus be interpreted with caution. Our data also suggest that an exercise intervention can change the response of growth hormone to acute exercise. However, no effect of a naturalistic exercise intervention on the neuroendocrine response of cortisol or prolactin. Further studies with a less heterogeneous (e.g. medicated/non-medicated) population, higher exercise levels, and possibly pharmacological challenge test are needed to evaluate the effect of exercise on the neuroendocrine response in patients with depression.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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