Effect of stress-dosed hydrocortisone on physical capacity in patients with Addison's disease (AD)

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Aim: To evaluate the effect of stress dose hydrocortisone (HC) on physical activity in female patients with AD.

Introduction: Many patients take stress doses during physical or psychological events and report benefit on performance and post-exertion fatigue. The effect of such dosing has not been demonstrated.

Results:

- V02max and duration of exercise were lower in AD than controls, and did not improve with stress dosing.
- The glucose response to exercise was attenuated in the patients compared with the controls
- The adrenaline response to exercise was flattened in patients compared with controls.

Design

Double blind, controlled, cross-over designed, randomized pilot trial to investigate the effects of **10 mg oral HC** on ergometer test to exhaustion.

Participants

- 10 female patients, age (mean SEM) 48 15,9 yr, BMI 22,9 4,6 kg. Regular treatment was cortisone acetate 30.1 7.6 mg (range 18.7-37.5 mg) and fludrocortisone 0.095 0.015 mg (0.05-0.1 mg).
- 10 age and BMI-matched healthy female controls.

Outcomes

- primary endpoint: oxygen uptake (O2 uptake) and maximal aerobic capacity (V_{O2} max)
- secondary endpoints: detailed cardiorespiratory parameters, duration of exercise, post-exercise hypoglycaemic events and glycaemic variability, endocrine and metabolic responses, and HRQoL evaluated by questionnaires.

Parameters	Treatment Observed Mean ± SE	Placebo Observed Mean ± SE	Placebo Predicted Mean Difference (95% CI)[a]	Healthy subjects Observed Mean ± SE	Healthy subjects Predicted Mean Difference (95% CI)[a]	P for interaction[b]
FFA[d] (mmol/L)						0.7[f]/0.002[g]
Before	0.4±0.05	0.4±0.07	0.03(-0.10,0.16)	0.4±0.08	0.03(-0.21,0.27)	
After	0.3±0.04	0.3±0.04	-0.01(-0.15,0.12)	0.4±0.06	0.03(-0.21,0.27)	
15 min	0.4±0.05	0.4±0.07	-0.01(-0.14,0.12)	0.3±0.06	-0.07(-0.31,0.17)	
30 min	0.4±0.05	0.4±0.06	-0.03(-0.16,0.09)	0.3±0.05	-0.12(-0.37,0.12)	
Glucose[c] (mmol/L)						0.06
Before	5.0±0.1	4.7±0.1	-0.29(-0.68,0.10)	5.4±0.2	0.36(-0.46,1.18)	
After	5.0±0.1	5.1±0.1	0.04(-0.37,0.46)	6.0±0.3	1.00(0.17,1.83)	
15 min	5.3±0.1	5.1±0.1	-0.17(-0.56,0.22)	5.9±0.3	0.69(-0.14,1.51)	
30 min	5.1±0.1	4.9±0.1	-0.18(-0.57,0.21)	5.7±0.3	0.48(-0.35,1.31)	
Insuline[c] (mIE/L)						0.34
Before	7.05±2.11	7.26±1.53	0.21(-3.67,4.09)	9.77±2.44	2.72(-4.89,10.33)	
After	7.14±2.13	8.92±1.95	0.70(-3.42,4.83)	14.51±1.56	6.60(-1.07,14.28)	
15 min	11.06±2.88	10.97±2.12	-0.09(-3.97,3.79)	14.01±1.34	2.59(-4.66,10.57)	
30 min	9.73±2.54	9.18±2.06	-0.55(-4.43,3.33)	11.97±1.60	2.29(-5.39,9.98)	
GH[e] (ug/L)						0.8[f]/0.3[g]
Before	-0.62±0.61	-0.79±0.57	-0.49(-2.62,1.64)	0.30±0.37	0.69(-2.15,3.53)	
After	-0.19±0.71	0.20±0.52	0.44(-1.83,2.70)	0.50±0.37	0.14(-2.74,3.03)	
15 min	0.47±0.47	0.43±0.40	-0.47(-2.60,1.66)	0.48±0.31	-0.86(-3.70,1.98)	
30 min	0.37±0.42	0.37±0.42	-0.13(-2.26,2.00)	0.05±0.37	-1.03(-3.92,1.85)	
Lactate (mmol/L)						0.81
Before	1.07±0.24	1.12±0.13	0.05(-1.71,1.82)	0.98±0.10	-0.09(-2.06,1.88)	
After	7.05±0.79	6.48±0.67	-0.57(-2.34,1.99)	6.51±0.51	-0.54(-2.51,1.43)	
15 min	4.40±0.63	4.06±0.61	-0.34(-2.11,1.43)	4.67±0.59	0.24(-1.70,2.24)	
30 min	2.19±0.34	2.09±0.47	-0.10(-1.87,1.67)	2.91±0.53	0.75(-1.27,2.22)	

Table 1. Comparison of selected parameters among patients and healthy subjects

a linear mixed effect models with random intercept; 95% CI for difference by post-hoc test for pairwise comparison (Sidak corrected).

b Overall P for interaction by likelihood ratio test.

c No statistically significant period or sequence effects.

d A statistically significant period effect for the cross-over of the treatment and placebo.

e A statistically significant sequence effect for the cross-over of the treatment and placebo.

f separate analysis for treatment and placebo.

g separate analyis for treatment and controls.

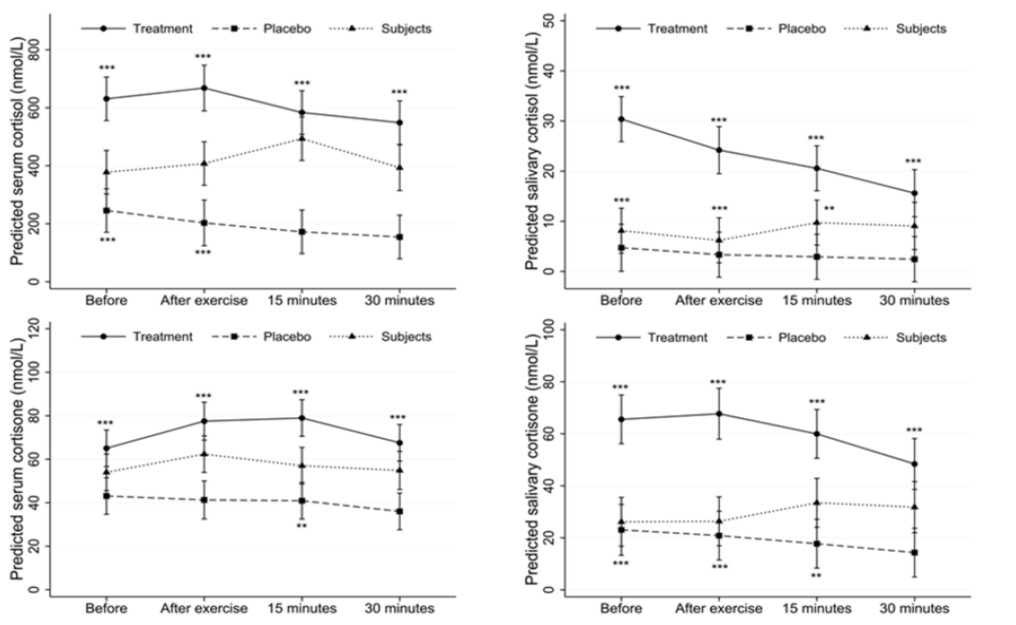

Figure 1. Serum or salivary cortisol, cortisone in patients and healthy subjects.

***P ≤ 0.001 for treatment vs placebo, ***P ≤ 0.001 for treatment vs subjects, **P ≤ 0.01 for treatment vs subjects

Parameters	Treatment Mean ± SE	Placebo Observed Mean ± SE	Placebo Predicted Mean Difference (95% CI)[a]	Healthy subjects Observed Mean ± SE	Healthy subjects Predicted Mean Difference (95% CI)[a]	P for difference[b]
$Load_{max}$ (W)	141±32.1	142± 33	0.8(-4.40, 5.96)	186 ± 35	44.7(12.51,76.87)	0.02
$Time_{max}$ (sec)	344 ±108	353± 99.7	9.0(9.82,27.82)	490± 98	146.0(50.05,241.95)	0.007
VO_{2max} (L/min)	1.56 ±0.43	17.5± 50.1	0.13(-0.063,0.33)	2.33± 0.55	0.77(0.31,1.23)	0.003
VO_2kg_{max}(ml/kg/min)	25.7 ±8.37	26.6 ± 8.11	0.91(-2.10,3.912)	34.1± 7.35	8.49(1.04,15.93)	0.06
VCO_{2max}(L/min)	1.9 ±0.489	2.03 ± 0.49	0.16(-0.08,0.35)	2.73± 0.66	0.83(0.28,1.38)	0.007
RER_{max}	1.2 ±0.046	1.21±0.046	0.01(-0.02,0.04)	1.17±0.054	-0.04(-0.08,0.01)	0.1
$BPdia_{max}$ (mmHg)	94.2 ±8.59	94.7± 11.8	0.5(-3.96,4.96)	95± 13.4	0.80(-10.44,12.04)	0.9
$BPsys_{max}$ (mmHg)	186 ±19.2	192± 18.9	6.0(-3.25,15.25)	195± 26	9.2(-12.05,30.45)	0.3
HR_{max} (beats/min)	160 ±20.3	159± 15.6	-0.9(-9.08,7.28)	172± 12	11.8(-3.13, 26.73)	0.2
O_2puls_{max} (ml)	9.82 ±1.84	10.7 ± 2.16	0.91(-0.37,2.19)	13.5± 3.22	3.71(1.24, 6.18)	0.007
Recovery (sec)	53 ±24.1	58 ± 22	5.0(-7.63,17.63)	107± 32.3	54.0(27.86, 80.14)	0.001

Table 2.Physical and cardiorespiratory parameters in response to a cycle test

a. By linear mixed effect models with random intercept; 95% CI for difference was obtained by post-hoc test for pairwise comparison (Sidak corrected). b. Overall P value for group difference obtained by likelihood ratio test.

Loadmax - Load max, timemax- duration of exercise, V02max -oxygen uptake, V02kgmax oxygen uptake per kg, VC02max- carbon dioxide production, RERmax- respiratory exchange rate, BPdiamax- Peak diastolic blood preassure, BPsysmax-Peak systolic blood preassure, HRmax- Peak heart rate , O2pulsmax-maximum peak of oxygen per pulse, Eemax- Energetic expenditure max, METSmax -Metabolic equivalents max, Recover-Time of recovery.

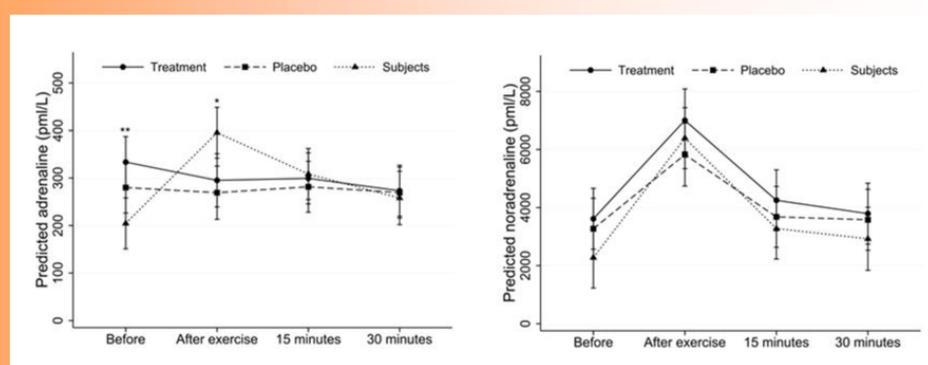

Figure 2. Levels of plasma adrenaline and noradrenaline in patients and healthy subjects **P ≤ 0.001 for treatment vs healthy subjects *P ≤ 0.01 for treatment vs healthy subjects

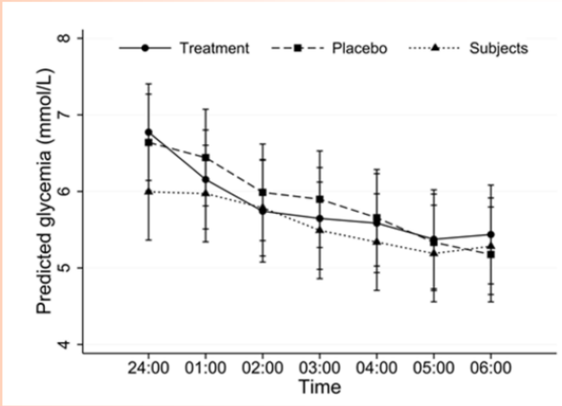

Figure 3. Post-exercise average levels of glycemia followed up from midnight to 0600 a.m. in patients and healthy subjects P for time-by-group interaction was 0.80

Conclusions

- **Stress dosing does not seem warranted for short-term exercise**
- **Dysfunction of the adrenal medulla and impaired glucose response to stress might lower performance and increase post-exertion fatigue in AD**

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