Exercise Can Alter Cortisol Responses in Obese Subjects

Brynjar Foss¹, Lars Rune Sæterdal¹, Oddmund Nordgård², Sindre Mikal Dyrstad³

¹Department of Health Studies, University of Stavanger, Stavanger, Norway, ²Department of Hematology and Oncology, Stavanger University Hospital, Stavanger, Norway, ³Department of Education and Sport Science, University of Stavanger, Stavanger, Norway

ABSTRACT

Foss B, Sæterdal LR, Nordgård O, Dyrstad SM. Exercise Can Alter Cortisol Responses in Obese Subjects. JEPonline 2014;17(1):67-77. The aim of this study was to examine the influence of a 22-wk lifestyle intervention program on the cortisol response in 35 inactive, obese subjects with a body mass index >35. The subjects were randomized into a Test Group and a Control Group. The intervention program consisted of physical activity supplemented with diet and cognitive therapy seminars. Saliva was collected 3 times a day, before and after the intervention program, and 6 months later. The morning awakening and peak cortisol levels (30 min after awakening) were 67% higher in the Test Group (n = 12) than the Control Group (n = 10; P<0.05). Whereas 6 months after the intervention the cortisol awakening levels had decreased by 33% in the Test Group, the peak level was 125% higher compared with the Control Group (P<0.05). The morning cortisol increase was 90% higher 6 months after the intervention compared with the post-intervention samples in the Test Group (P<0.05). The results indicate that the 22-wk lifestyle intervention program altered cortisol levels in the inactive, obese subjects. The increased cortisol reaction may hinder efforts at weight reduction and may explain why losing weight through physical activity is difficult for obese people.

Key Words: Obesity, Cortisol, Exercise, Lifestyle
INTRODUCTION

Obesity is a global health challenge because of the increased risk of contracting chronic diseases that include hypertension and type 2 diabetes, and the projected increase in rates of chronic diseases (12). The diverse biological mechanisms behind obesity seem to include the stress system and cortisol, which is released by the adrenal cortex through physiological stress activation (2,7,10,17). Some studies suggest that altered cortisol secretion is associated with obesity (2,7,17). Wallerius et al. (25) indicate that the morning rise in cortisol seems to be associated with the increase in body mass index (BMI), which is in agreement with Gluck and colleagues (9) who reported that obese women with a binge eating disorder have higher morning cortisol levels than women without this disorder. Then, too, a lower morning cortisol level with an increase in salivary cortisol responsiveness to lunch has been found in overweight women with abdominal fat distribution compared with overweight women with peripheral fat distribution (5). Healthy adults given corticotrophin-releasing hormone, a cortisol release trigger, showed increased calorie intake compared with controls (8). Interestingly, a recent hypothesis links the stress system and weight gain via a positive feedback mechanism (7). Thus, there seems to be a clear, but not well-articulated association between cortisol and obesity.

Physical activity and diet have been the prime targets of preventative and therapeutic approaches to obesity. However, physical activity is also known to activate the stress system and to trigger cortisol release in healthy subjects (13,15). These effects seem to be dependent on both exercise intensity and duration (1,3,11,24). Yet, most studies of physical activity on cortisol secretion are done on bouts of exercise. The long-term effects of physical activity are not well studied. In effort to further clarify the role of cortisol and the stress system in obesity, we aimed to elucidate how a 22-wk lifestyle intervention program dominated by physical activity influences salivary cortisol levels in obese and inactive subjects.

METHODS

Subjects
A total number of 35 subjects matched the inclusion criteria of the study, which were: age 18 to 65, preferred BMI >35, inactive but still able to move without help, and holding a referral by their general practitioners. The subjects were randomized into two groups: the Test Group (TG, n = 18) and the Control Group (CG, n = 17). Only the TG attended the lifestyle intervention program. The CG was invited to join the intervention program after 12 months. A total of 22 subjects (6 men) with a mean age of 45.2 ± 9.6 yrs completed all or most of the initial saliva cortisol samples and were therefore included in the study. Of these, 15 subjects completed the 6-month follow-up test. The drop-out reasons were mainly due to injury, illness or surgery, and were equally divided between the 2 groups. Written informed consent was obtained from the subjects, and the study was approved by the Regional Ethics Committee for Medical Research (ref #: 2010/1270).

Lifestyle Intervention Program
The 22-wk lifestyle intervention program (22LIP) consisted of an organized group-based exercise program of 60 min, 3 days·wk⁻¹. The intervention program consisted of 3 types of activities: (a) gym activities including circuit training, strength training, high-intensity running, ball games, and aerobics; (b) outdoor walks; and (c) pool activities that included endurance and strength training. The intensity level was moderate to vigorous. Once a week prior to exercise the subjects joined a group seminar concerning four diet sessions with two additional food preparation lectures, four cognitive therapy sessions, and different sessions like “Activity and health,” “How to sustain the new lifestyle,” and “Peer exchanges.”
Saliva Samples
Saliva sampling was performed based on previous work (18,19,25,26) with modifications. Saliva was collected by Salivette® Cortisol swabs (Sarstedt AG & Co., Nümbrecht, Germany) that were carefully chewed for 45 sec. Three samples were collected per day: (a) in the morning immediately on awakening (C₀); (b) 30 min after awakening (C₃₀); and (c) immediately before going to bed in the evening (Cₑ). This was done on two consecutive days before the 22LIP (preC₀, preC₃₀, preCₑ), after the 22LIP (postC₀, postC₃₀, postCₑ) and 6 months after the post-tests (6mC₀, 6mC₃₀, 6mCₑ) for both the TG and the CG (i.e., the CG followed the same sample schedule as the TG).

The morning rise in cortisol level in response to awakening is an established method to assess the stress response of the hypothalamic–pituitary–adrenal axis to different conditions (18,19) including obesity (14,25). The morning cortisol rise was measured as previously described by Wallerius et al. (25), which consisted of calculating the difference between the morning peak (C₃₀) and awakening levels (C₀) (i.e., the C₃₀–₀ slope of average values of consecutive days). Similarly, the daily cortisol decrease was measured by calculating the differences between Cₑ and C₃₀ (i.e., the Cₑ–₃₀ slope of average values of consecutive days). One subject in the TG had an estimated negative Cₑ value and was excluded from the cortisol increase and decrease analysis. The subjects were instructed not to eat, drink, brush their teeth or smoke for 30 min prior to sampling. They were also instructed not to touch the swab before or after saliva collection. The Salivette® Cortisol swab tubes were stored at 4°C until the day of transfer to the laboratory that was generally within 3 days. The samples were then centrifuged and stored at -80°C until analysis.

Cortisol Analysis
Quantitative determination of saliva cortisol was analyzed using the enzyme immunoassay kit Parameter™ Cortisol assay (R&D Systems, Abingdon, UK). The analysis was performed strictly in accordance with the manufacturer’s instructions with the exception that absorbance was read with no wavelength correction, which was in accordance with R&D Systems. Standards and sample dilutions were always diluted and prepared in the supplied diluents. Standard curves were determined using the mean of duplicates analysis and generated by using a four-parameter logistic curve-fit. Minimal detectable levels of saliva cortisol were 156 pg·mL⁻¹. All saliva samples were analyzed in duplicate. Average cortisol values of parallel samples on consecutive days and parallel immunoassay samples were generally used for statistical analysis.

Statistical Analyses
Statistical analysis was performed using PASW Statistics 18 (SPSS Inc., Chicago, IL). Because the samples were not normally distributed, the comparisons between the TG and the CG were done by Mann–Whitney U Test. Comparisons within the groups were done by Wilcoxon Signed Rank Test. Statistical differences were considered to be significant for P<0.05. A P value between 0.05 and 0.1 indicated a tendency.

RESULTS
There were no significant differences in body weight and waist circumference between the TG and the CG at the start. Whereas body weight and waist circumference did not change during the 22LIP in the CG, body weight tended to decrease by 3.6%, and waist circumference decreased by 3.4% in the TG (Table 1, P = 0.081 and 0.029, respectively).
Table 1. Mean ± SD for Body Mass and Waist Circumference at Baseline and After 22 wks for Test Group (TG) and Control Group (CG).

<table>
<thead>
<tr>
<th></th>
<th>TG</th>
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<th>CG</th>
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<tr>
<td></td>
<td>n Baseline</td>
<td>22 wks</td>
<td>P</td>
<td></td>
<td>n Baseline</td>
<td>22 wks</td>
<td>P</td>
</tr>
<tr>
<td>BM (kg)</td>
<td>12 118.5 ± 16.9</td>
<td>115.5 ± 16.9</td>
<td>0.081§</td>
<td>10</td>
<td>114.4 ± 27.5</td>
<td>115.8 ± 25.3</td>
<td>0.40</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>12 120.7 ± 14.1</td>
<td>116.6 ± 14.8</td>
<td>0.029*</td>
<td>10</td>
<td>123.0 ± 17.7</td>
<td>123.6 ± 16.1</td>
<td>0.81</td>
</tr>
</tbody>
</table>

BM = body mass; WC = waist circumference; CG pre and post-test; n = 10 (six females, four males), CG 6-month test; n = 6 (4 females, 2 males), TG pre and post-test; n = 12 (10 females, 2 males), TG 6-month test; n = 9 (8 females, 1 male). § = tended to be different from baseline. * = significantly different from baseline.

Morning Cortisol Levels

The morning cortisol levels of TG (n = 12) and CG (n = 10) pre and post 22LIP and 6 months after 22LIP are presented in Figure 1 (raw data) and Table 2 (means ± SD). There were no significant differences between the awakening levels (preC0) and the levels 30 min after awakening (preC30) in the two groups. Nor were there significant differences between preC0 and postC0 as well as preC30 and postC30 in the CG and the TG. However, the TG postC0 was 67% higher than the CG postC0 (Table 2, P = 0.021). Similarly, the postC30 was 67% higher in the TG compared with the CG (Table 2, P = 0.011).

The morning awakening cortisol level 6 months after the 22LIP (6mC0) in the TG was 33% lower compared with postC0 (Table 2, P = 0.011, n = 9). A similar decrease was not detected in the CG (n = 6). The 6mC0 of the TG and the CG were not significantly different, but the TG 6mC30 was 125% higher than the CG 6mC30 (Table 2, P = 0.026).

Table 2. Mean ± SD for Cortisol Levels at Baseline and After 22 wks and 6 months for Rest Group (TG) and Control Group (CG).

<table>
<thead>
<tr>
<th></th>
<th>preC0</th>
<th>preC30</th>
<th>preCe</th>
<th>postC0</th>
<th>postC30</th>
<th>postCe</th>
<th>6mC0</th>
<th>6mC30</th>
<th>6mCe</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>3.9 ± 1.8</td>
<td>4.7 ± 2.7</td>
<td>0.6 ± 0.3</td>
<td>3.3 ± 1.5</td>
<td>4.6 ± 1.6</td>
<td>0.8 ± 0.8</td>
<td>2.7 ± 0.5</td>
<td>3.6 ± 1.2</td>
<td>0.5 ± 0.4</td>
</tr>
<tr>
<td>TG</td>
<td>5.2 ± 3.9</td>
<td>8.3 ± 5.7</td>
<td>1.0 ± 1.0</td>
<td>5.5 ± 2.2*</td>
<td>7.7 ± 3.4*</td>
<td>0.9 ± 0.9</td>
<td>3.7 ± 2.0**</td>
<td>8.1 ± 5.6*</td>
<td>1.0 ± 1.5</td>
</tr>
</tbody>
</table>

CG pre and post-test; n = 10 (6 females, 4 males), CG 6-month test; n = 6 (4 females, 2 males), TG pre and post-test; n = 12 (10 females, 2 males), TG 6-month test; n = 9 (8 females, 1 male). * = significantly different from CG. ** = significantly different from TG postC0.
Figure 1 a, b, c, d. The graphs present the morning rise of cortisol \((C_0 \text{ and } C_{30})\) for all subjects before (pre), after (post) and 6 months after the lifestyle intervention programme. CG, Control Group; TG, Test Group. (a) CG morning cortisol levels before intervention \((n = 10)\), (b) CG morning cortisol levels after intervention \((n = 10)\), (c) CG morning cortisol levels 6 months after intervention \((n = 6)\), and (d) TG morning cortisol levels before intervention \((n = 12)\).
Morning Cortisol Increase
The morning cortisol increase (i.e., preC$_{30-0}$, postC$_{30-0}$ and 6mC$_{30-0}$) did not differ significantly between the CG and TG (Table 3). However, in the TG only, the 6mC$_{30-0}$ mean morning cortisol increase was 90% higher than postC$_{30-0}$ (P = 0.036).

Table 3: Mean ± SD for Cortisol Levels at Baseline and After 22 wks and 6 months for Test Group (TG) and Control Group (CG).

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<thead>
<tr>
<th></th>
<th>Morning increase</th>
<th>Daily decrease</th>
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<tbody>
<tr>
<td></td>
<td>preC$_{30-0}$</td>
<td>postC$_{30-0}$</td>
</tr>
<tr>
<td>CG</td>
<td>0.88 ± 2.21</td>
<td>1.23 ± 1.43</td>
</tr>
<tr>
<td>TG</td>
<td>2.12 ± 2.95</td>
<td>2.32 ± 3.26</td>
</tr>
<tr>
<td></td>
<td>-4.19 ± 2.61</td>
<td>-3.78 ± 1.65</td>
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<tr>
<td></td>
<td>-6.72(± 4.72)</td>
<td>-7.06 ± 8.85**</td>
</tr>
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</table>

CG pre and post samples, n = 10. CG 6m samples, n = 6. TG pre and post samples, n = 11. TG 6m samples, n = 8. * = significantly different from postC$_{30-0}$; ** = significantly different from CG. $^\S$ = tended to be different from CG (P = 0.081).

Daily Cortisol Decrease
The daily cortisol decrease, expressed as the difference between evening levels (C$_{e}$) and the morning cortisol peak (C$_{30}$), was 87% higher in the TG compared with the CG in the postC$_{e-30}$ (Table 3, P =
DISCUSSION

The purpose of this study was to measure the influence of a 22-wk lifestyle intervention program dominated by physical activity on the stress system in obese subjects. We found that while there was no significant cortisol difference between the TG and the CG before the 22LIP and no significant cortisol change in the 2 groups over the 22-wk period, the morning cortisol after the 22 wks (postC0) was significantly higher in the TG compared with that in the CG (Table 2). Findings were identical at 30 min after awakening (postC30, Table 2). However, no differences in morning cortisol increase were found between the TG and the CG, although the increase was higher in the TG 6 months after the 22LIP compared with the TG post samples (Table 3). All together these results suggest that whereas the morning cortisol increase did not differ between the two groups, the exercising obese subjects may still have experienced higher morning cortisol levels after the 22LIP compared with controls. This suggests that the 22LIP may alter the cortisol release in exercising obese subjects. Importantly, this observation must be carefully interpreted, as we did not detect significant differences in the TG before and after the 22LIP.

Our observation that the morning cortisol increase was altered 6 months after the 22LIP in the TG but not in the CG (Table 3) supports the hypothesis of altered cortisol response in the TG. However, as indicated in Table 2, it is important to take into account that the great variation seen in the subjects may influence our results and conclusion. The SD in the TG mean preC30 is large, which may explain why we did not find significant differences in cortisol levels between the TG and the CG prior to the 22LIP. Thus, the observed difference in cortisol level between the TG and the CG after the 22LIP may have been influenced by factors other than physical activity alone. We assume that the low number of subjects (see below) and the great heterogeneity of cortisol levels across the two groups are relevant factors. As presented in Figures 1 d–e, one of the TG subjects had clearly higher cortisol levels than the CG (it was the same subject on all occasions who had the highest levels in Figures 1 d–f). Because of the lack of clear exclusion criteria, this subject was included in the study. However, when excluded in an alternative statistical analysis, none of the significant cortisol level differences (Table 2) was changed. In fact, by excluding this single subject, the statistical analysis also showed a tendency of TG postC0 levels to be higher than preC0 (P = 0.062), suggesting that the 22LIP may increase awakening cortisol levels. Thus, we argue that our conclusion of the 22LIP as a potential trigger of the cortisol and stress response among obese subjects is not an overstatement but rather a more conservative conclusion. Obviously, further studies are needed to fully characterize these effects.

Six months after the 22LIP, it was observed that the morning cortisol level (6mC0) in the TG was significantly lowered compared with the postC0. In addition, it was found that the TG had significantly higher 6mC30 levels compared with the CG (Table 2), and that the TG morning cortisol increase was higher than in post samples (Table 3), as already described above. These observations are interesting because on the one hand, the lower awakening cortisol levels may suggest reduced stress among the TG, while the higher 6mC30 compared with the CG (Table 2), together with the higher morning cortisol increase compared with the post test (Table 3), suggests that the TG exhibited an altered cortisol and stress reaction.

Generally, the morning rise of cortisol in response to awakening is used to assess the stress response (14,18,19,25). However, our study does not show a higher morning rise of cortisol levels in
response to awakening in the TG compared with the CG. Yet, based on the combination of: (a) decreased 6mC₀ compared with postC₀, which was not seen in the CG; (b) the higher 6mC₃₀ in the TG compared with the CG; and (c) the higher 6mC₃₀₋₀ compared with postC₃₀₋₀ in the TG only, we argue that the cortisol and the stress reaction in the TG was altered compared with the CG even 6 months after the 22LIP. This obviously leads us to ask: What happened with the TG during the 6-month interval? We are unable to answer this question, but it is reasonable to suggest that the 22LIP may have altered the subjects’ lifestyle in a way that altered the stress response. Further studies are required to clarify this issue.

It was also important to show whether the 22LIP influenced the daily cortisol decrease characterized by calculating the difference between C₃₀ and Cₑ. As presented in Table 3, the daily decrease was higher in the TG compared with the CG after the 22LIP and tended to be higher 6 months later. These observations are most likely explained by the fact that the C₃₀ levels on both occasions were significantly higher in the TG than the CG, given that in vivo cortisol reduction through the day is regulated by cortisol half-life in a way that makes the Cₑ levels similar.

Altered stress load, judged by cortisol morning levels and cortisol increase, is repeatedly described in obesity (2,7,17). However, the mechanism behind altered cortisol secretion in obesity is not fully understood. This is partly at least because of a discrepancy between previous reports characterizing cortisol regulation in obesity. In some studies, cortisol levels are found to be lower among obese compared with non-obese subjects (6,22); whereas, other observations show that obese subjects or those with stress-induced obesity have higher cortisol levels than controls (20,23). Then, too, it is reasonably clear that the morning cortisol level increase is linked to elevated BMI (25), which provides a link between depression and increased BMI in girls (4).

Based on these and several other observations, we recently hypothesized that the stress system and weight gain in obesity may be linked via a positive feedback system (7). A consequence of this hypothesis is that dealing with weight reduction in obesity requires dealing with the body’s stress system as well. Together with our results presented here, losing weight by physical activity, which seems to be a difficult task (21), might be further challenged because the stress system may oppose weight loss mechanisms. In spite of an increased cortisol level in the TG, which theoretically could result in an increased body weight, they tended to reduce their body weight (Table 1). However, for many subjects, this reduction in body weight was far less than expected according to their nutrition and activity levels during this period. Therefore, it is possible that the change in cortisol level described in the present study prevented weight reduction in some obese people. Possible explanations for how the stress system can oppose weight loss are suggested in studies showing that cortisol seems to increase the intake of high-energy food (8,16) and that cortisol can influence the role of leptin and neuropeptide Y (17) thereby altering the energy balance.

An important previous study of physical activity, assessed by questionnaire, did not affect cortisol reactivity, assessed by the Trier Social Stress Test for children, or BMI among girls or boys (4). In contrast, our study of in vivo cortisol levels still shows that a 22-wk lifestyle intervention program, dominated by exercise, can alter cortisol secretion among obese subjects. The discrepancy between the two studies may be explained by differences in both methods and study cohorts. Nevertheless, it underlines the complexity of the interplay between physical activity, cortisol reaction, and obesity.

An important observation made in the present study is that not all the subjects in the TG or the CG had increased cortisol secretion during the first 30 min after awakening (Figure 1). This observation has been described elsewhere (25) and should be further studied to understand better why different
persons show different morning cortisol patterns and the consequences that this may have for weight reduction.

Limitations of the Study
The total number of subjects was low, which was partly due to a high drop-out rate. This study was also limited by the high heterogeneity of the subjects, particularly in relation to supplemental diagnosis and medication. Various biological and medical conditions, as well as habits that may influenced cortisol secretion, should be taken into account when characterizing stress responses (13). A number of these potentially relevant factors, including nicotine, coffee and alcohol habits, social support, menstrual cycle phase, and the use of oral contraceptives, were not controlled for in our study. Nevertheless, the significant differences that we found between the TG and the CG suggest that in spite of the low number of subjects and the potentially great heterogeneity, the 22LIP appeared to affect cortisol responses among obese subjects.

Another limitation of our study design is that the awakening and sleeping times of the subjects that were likely to differ widely were not predefined or identified. However, our design and methods were conducted in accordance with a previous report (25). We therefore assume that the timing of saliva sampling did not influence our results significantly.

CONCLUSIONS
Our study showed that a 22-wk lifestyle intervention program for obese subjects increased the cortisol levels and, in particular, the morning cortisol peak that was found to be high also 6 months after the intervention ended. Thus, exercise can alter the cortisol reaction among obese people, and the change in cortisol level may resist weight reduction. This finding might be an explanatory factor to why the reduction in body weight was far less than expected according to their nutrition and activity levels during this period.

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Address for correspondence: Brynj Foss, PhD, Department of Health Studies, Kjell Arholms hus, University of Stavanger, 4036 Stavanger, Norway. Email: brynj.foss@uis.no

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