A direct comparison of quality of life in obese and Cushing's syndrome patients

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Abstract

Objective: Obese (OB) individuals and patients with Cushing’s syndrome (CS) often have similar clinical presentations. While each group has reduced health-related quality of life (HRQL), it is not known whether the degree of impairment is different and might distinguish between them. The objective of this study was to compare HRQL in these two populations.

Design: Cross-sectional study.

Methods: Three hundred and twenty-seven OB patients (48.1 ± 11.7 years; 72.5% women) with weight gain and at least two features of CS were recruited from an outpatient weight management clinic. Sixty-six untreated patients with CS (41.6 ± 13.2 years; 78.8% women) presented to the NIH Clinical Center for evaluation. Subjects completed the SF-36 survey and a locally created symptom questionnaire.

Results: After adjusting for symptom count, OB patients had a significantly higher (better HRQL) mean physical component summary (PCS) score than CS patients (44.9 ± 0.6 vs 35.4 ± 1.5, P < 0.0001). However, the mean mental component summary (MCS) score was lower (worse HRQL) in the OB group (41.6 ± 0.6 vs 50.7 ± 1.6, P < 0.0001). Symptom count showed significant correlations with PCS and MCS scores. BMI correlated with PCS (r = 0.29) in OB but not in CS patients. BMI was not associated with MCS in either group.

Conclusion: HRQL is significantly different between OB and CS patients. Surprisingly, after adjusting for symptom count, OB patients showed worse mental health scores than the CS population. Significant differences in HRQL and symptom count may suggest which OB patients should be screened for CS.

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Introduction

Patients with obesity (OB) and with Cushing’s syndrome (CS) have clinical presentations that often overlap. Both groups suffer from weight gain and difficulty with weight loss, as well as physical and emotional symptoms such as fatigue and depression. Both groups are at increased risk for developing diabetes mellitus, dyslipidemia, and hypertension, all of which can increase the risk of cardiovascular disease (1, 2, 3). The increased incidence of obesity in the United States has led to an increased number of evaluations for medical causes of weight gain. These evaluations often include consideration of CS. However, CS is a rare disease and the false-positive rates among screening tests in OB patients can be as high as 16% (4). To avoid costly additional evaluation of false-positive results, physicians are challenged with the question of whom to screen for CS.

Both OB and CS patients are known to have impaired health-related quality of life (HRQL) (5, 6, 7, 8). However, no previous research has directly compared HRQL between the two. In OB patients, it has been reported that the extent of overweight, pain, and exercise tolerance determines quality of life (QOL) (9, 10, 11). In CS patients, it has been proposed that the presence and possibly severity of hypercortisolism contribute significantly to an impaired HRQL (7, 12, 13, 14).

Using the SF-36 survey, a tool used to compare QOL between groups of patients, this study investigated whether HRQL is markedly different between OB and untreated CS patients. We also evaluated what variables might affect HRQL in these two groups and considered whether or not assessment of HRQL could be used as a tool to suggest the need for CS screening in OB patients. In addition, we compared the number of CS-related signs and symptoms between the groups.
We proposed four hypotheses: i) OB patients would have better HRQL (physical component summary score (PCS) and mental component summary scores (MCS)) than CS patients; ii) BMI would have a negative association with PCS in both patient groups; iii) the number of symptoms would be negatively associated with HRQL (PCS and MCS) in both groups; and iv) HRQL would be associated with the degree of hypercortisolism in the CS group.

Materials and methods

The Institutional Review Board of the Eunice Kennedy Shriver National Institute of Child Health and Human Development approved the study protocols (NCT00 361777). All subjects provided written informed consent.

Overweight and OB subjects

From October 2003 to April 2008, 471 individuals from the immediate Washington DC area presenting for nonsurgical weight loss treatment at The George Washington University Weight Management Program were enrolled in a study evaluating the performance of screening tests for CS. This was a self-pay program, as insurance coverage was not accepted. Inclusion criteria were age 18–75 years, weight gain, and the presence of at least two other features of CS. Entry criteria were recorded by a study provider. Exclusion criteria included weight > 350 lbs (159 kg) (maximum weight allowed on imaging tables), serum creatinine > 2.6 mg/dl, pregnancy, serious medical conditions that might alter pituitary–adrenal function, and recent or anticipated use of medications affecting glucocorticoid physiology, including glucocorticoids, black licorice, chewing tobacco, phenytoin, barbiturates, loperamide, and opiates. At the first visit, staff performed a history and physical examination. Fasting blood sugar was also measured during this visit. Subjects without known diabetes underwent an oral glucose tolerance test. These subjects were asked to perform three screening tests for CS (4): i) 1 mg overnight dexamethasone suppression test with measurement of serum dexamethasone and cortisol; ii) measurement of bedtime salivary cortisol; and iii) measurements of 24-h urine free cortisol excretion (UFC) (tandem mass spectrometry (LC–MS/MS), Mayo Laboratories, (Mayo) Rochester, MN, USA; reference range 3–45 μg/24 h; 8–124 nmol/24 h; interassay coefficient of variation (CV) 5.6–8.3%). Creatinine excretion rate and/or the total sample volume were measured in the urine collection to ensure the quality of the specimen (true for CS group as well). Subjects with abnormal cortisol screening test results were asked to follow up at the NIH Clinical Center for further evaluation (4). Subjects completed the SF-36 survey at or shortly after their first visit and before starting a weight loss program.

CS subjects

From 1999 to 2012, 78 patients with laboratory data highly suggestive of CS were admitted for evaluation of the disease. These patients were from the USA and abroad; some have been previously described (15). UFC and midnight cortisol levels confirmed the diagnosis of CS. Among this group, patients with unconfirmed disease or who were receiving medical treatment were excluded from the analysis. During the admission, staff reviewed each patient’s history and performed a physical examination including measurements of weight and height to calculate BMI. Subjects performed a 24-h UFC measured by LC/MS–MS (Mayo), chemiluminescence immunometric assay (Nichols Advantage one site, NIH Clinical Center, Bethesda, MD USA; range 8–77 μg/24 h; 22–212 nmol/24 h; interassay CV 6.8–12.2%), or an IRMA (Mayo; range 24–108 μg/24 h: 66–298 nmol/24 h; interassay CV 3.8–5.3%) depending on the date that the sample was collected. Patients were not taking medications that were known to interfere with cortisol assays. Patients completed the SF-36 survey upon admission to the NIH Clinical Center.

HRQL evaluation

HRQL was assessed using the SF-36R, which has been previously validated and widely used across a variety of medical conditions (8, 16). Possible scores range from 0 to 100 points, with higher scores indicating better HRQL. The measure is normalized such that the general population is 50 ± 10 (mean ± 1S.D.). The questionnaire consists of eight subscales of HRQL: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. These eight subscales comprise two summary scores of HRQL: the PCS score and the MCS score.

Symptom questionnaire

All subjects were asked to complete a 39-item locally developed CS questionnaire indicating the presence of signs and symptoms of CS within the last month. Because some symptoms were sex specific, resulting in different numbers of possible symptoms for men and women, the percentage of positive symptoms reported was calculated (symptom cost).

Statistical analysis

Descriptive statistics were used to describe the study sample. Between-group differences in demographic variables were examined using t-tests for continuous variables and χ² analyses for categorical variables.
To correct for differences in the 24-h UFC normal range, the percentage above the upper limit of normal was calculated and used for all analyses. Bivariate associations in continuous variables were examined using Pearson correlations.

Differences between OB and CS patients in SF-36 subscale and component scores were examined using t-tests. T-tests were also used to compare each group’s component scores to US population means. Scores are presented as mean ± S.E.M. ANCOVA was used to test for differences between CS and OB patients in SF-36 component scores controlling for relevant covariates. Age, sex, BMI, UFC, percent symptom count (symptom count), and diabetes diagnosis were evaluated as potential covariates and included in the full model if significantly associated with PCS or MCS when tested individually. Age, BMI, symptom count, and diabetes were significantly associated with PCS and therefore included in the full model for PCS (UFC and gender were not associated with PCS). Age and symptom count were significantly associated with MCS and therefore included in the full model for MCS (BMI, UFC, gender, and diabetes diagnosis were not significantly associated with MCS) (Table 1).

Significance was assumed at $P < 0.05$ for all analyses except comparisons of the 39 individual symptoms; for these, $P < 0.001$ was used to account for multiple comparisons. Analyses were performed using SPSS version 17.0.

### Results

Of the 471 OB subjects, 111 (mean age 47 ± 12 years; mean BMI 39 ± 9; 76 F) did not complete the HRQL measure and/or dropped out of the study before being screened for CS. The majority of these patients did not return to the weight management center after the initial consult. Twenty-eight patients did complete the questionnaire but did not undergo screening for CS (mean age 50 ± 10 years; mean BMI 38 ± 6; 18 F). There was no significant difference in age or BMI between those that participated and those that did not. Of the 78 CS patients, nine had either confirmed disease or were undergoing treatment; one did not complete the survey. Five OB subjects and two CS patients were provided with questionnaires but did not complete sufficient items for calculation of PCS and MCS scores. Thus, SF-36 data from 327 OB subjects and 66 patients were available for analysis. A higher score represents better QOL. Demographic data are provided in Table 2 and obesity classifications are shown in Fig. 1. In addition, six CS patients were from the following countries: Israel, Bahamas, Uganda, Russia, Greece, and Slovenia. Nine OB subjects were > 350 lbs (159 kg); however, they were not excluded from this study as imaging

#### Table 2 Demographic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>OB (total n)</th>
<th>CS (total n)</th>
<th>Significant ($P$ value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years); (mean ± s.d.)</td>
<td>48.1 ± 11.7</td>
<td>41.6 ± 13.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Range</td>
<td>18–77 (n = 327)</td>
<td>18–73 (n = 66)</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>27.5</td>
<td>21.2</td>
<td>NS</td>
</tr>
<tr>
<td>Female (%)</td>
<td>72.5</td>
<td>78.8</td>
<td>NS</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>85.9</td>
<td>83.3</td>
<td>0.01</td>
</tr>
<tr>
<td>African American</td>
<td>6.1</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) (mean ± s.d.)</td>
<td>38.2 ± 7.6</td>
<td>34.9 ± 9.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Range</td>
<td>26.0–83.0 (n = 327)</td>
<td>20.6–80.6 (n = 66)</td>
<td></td>
</tr>
<tr>
<td>24-h UFC (% over ULN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median and IQR</td>
<td>40.0 (26.7, 60.0)</td>
<td>310.2 (194.3, 1092.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Range</td>
<td>3.7–175.6 (n = 310)</td>
<td>68.3–25 891.1 (n = 60)</td>
<td></td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>20.4 (n = 323)</td>
<td>45.0 (n = 60)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

OB, obese; CS, Cushing’s syndrome; NS, not significant; UFC, urine free cortisol; % over ULN, percent over upper limit normal; NA, not applicable.

*Test for continuous variables; $\chi^2$ for categorical variables.
procedures were not required. The OB group was significantly older and had higher mean BMI than the CS group, while the CS group included a significantly greater percentage of diabetic subjects. Three of the OB subjects completed only one screening test, which were normal; all had a low probability of CS based on the history and physical examination. All others completed two or more tests. Of the 324 OB subjects who completed two or more screening tests, 72 had at least one abnormal screening test result. PCS and MCS scores were not significantly different between those that had an abnormal screening test result and those that did not. None of the OB subjects were found to have CS on follow-up testing (4). Of the 66 CS patients, surgical pathology confirmed that 49 had Cushing’s disease, eight had ectopic ACTH secretion with a confirmed source (pulmonary neuroendocrine tumor (NET), \( n = 4 \); metastatic NET with likely pulmonary origin, \( n = 1 \); metastatic gastrinoma of liver, \( n = 1 \); thymic NET, \( n = 1 \); and small-cell lung carcinoma, \( n = 1 \)), and five have occult ectopic disease. In the remaining four, biochemical data and response to radiation treatment suggested Cushing’s disease.

In unadjusted analyses, PCS score were significantly higher in the OB than in the CS groups, 45.2 ± 0.6 vs 34.6 ± 1.4 (\( P < 0.0001 \)). MCS scores, however, were not significantly different between the groups, 43.2 ± 0.7 vs 40.9 ± 1.6 (\( P = 0.17 \)). HRQL subscale scores were significantly higher in the OB than in the CS groups for all subscales except mental health (Fig. 2). For all eight subscales and component scores, both groups had significantly lower scores compared with the US population mean of 50.0 (Fig. 2).

After controlling for age, BMI, symptom count, and diabetes diagnosis (full model for PCS), PCS scores remained significantly higher in the OB than in the CS groups, 44.9 ± 0.6 vs 35.4 ± 1.5 (\( P < 0.0001 \)). However, after controlling for age and symptom count (full model for MCS), the mean MCS score was significantly lower in the OB group compared with the CS group, 41.6 ± 0.6 vs 50.7 ± 1.6 (\( P < 0.0001 \)).

Of the 39 symptoms on the questionnaire, OB subjects (\( n = 326 \)) reported an average of 28 ± 18% (mean ± s.d.; range 0–84%) and CS patients (\( n = 53 \)) reported an average of 57 ± 18% (mean ± s.d.; range 16–89%; \( P < 0.0001 \)). In OB subjects, the symptom count had a weak negative correlation with PCS scores, \( r = -0.24 (P < 0.0001) \), and strong negative correlation with MCS scores, \( r = -0.56 (P < 0.0001) \). BMI had a negative correlation with PCS scores (\( r = -0.29, P = 0.0001 \)) and was not correlated with MCS scores. Twenty-four hour UFC was not correlated with symptom count, PCS scores, or MCS scores. In CS patients, the symptom count had a strong negative correlation with both PCS (\( r = -0.41; P = 0.0022 \)) and MCS (\( r = -0.47, P < 0.0001 \)) scores. BMI was not significantly correlated with either PCS or MCS scores. Twenty-four hour UFC was not correlated with symptom count, PCS scores, or MCS scores.

The percent of CS and OB patients reporting each symptom on the CS questionnaire is shown in Table 3. Significant differences in 22 of the 39 individual symptoms were seen between the OB and CS groups with all 22 being more common in the CS patients.

**Discussion**

In this study, CS patients had significantly poorer physical HRQL and a greater number of physical symptoms than OB subjects seeking treatment. This difference was seen across all subscales of the SF-36 except for mental health. Findings regarding mental HRQL were opposite to those hypothesized. In unadjusted analyses, there was no difference in MCS between CS and OB patients. After adjusting for age and symptom count, OB patients showed poorer MCS than CS patients. However, this may reflect a selection bias as the OB patients were seeking treatment and were also participating in a program requiring self-payment.

In interpreting these findings, it is important to consider the covariates included in the adjusted models.

![Figure 1](https://www.eje-online.org)  
**Figure 1** BMI (kg/m²) categories in obese subjects (white bars) vs Cushing’s syndrome patients (shaded bars). Not overweight (BMI < 25.0); overweight (BMI 25.0–29.99); obesity class I (30.0–34.99), obesity class II (35.0–39.99), and obesity class III (≥ 40.0).

![Figure 2](https://www.eje-online.org)  
**Figure 2** Mean unadjusted SF-36 subscale scores ± s.e.m. in obese subjects (white bars) vs Cushing’s syndrome (CS) patients (shaded bars). Domain scores can range from 0 to 100, with higher values indicating better QOL. For each subscale, each group had significantly lower scores than the US population mean of 50.0 (\( P < 0.0001 \)). *\( P < 0.05 \) for obese vs CS scores.
In evaluation of PCS, CS patients demonstrated lower scores independent of age, BMI, diabetes diagnosis, and symptom count. That is, holding these variables constant across groups, CS patients still demonstrated poorer PCS. Therefore, the poorer physical HRQL seen in these patients cannot be attributed only to the greater degree of symptoms they experience. In the adjusted model examining mental HRQL, findings opposite to those hypothesized were seen, with OB patients demonstrating lower MCS than CS patients when controlling for age and symptom count. In both OB and CS groups, symptom count was highly correlated with MCS. Despite a significantly higher symptom count, CS patients demonstrated an MCS equivalent to OB patients in unadjusted analyses. After adjusting for the effect of symptom count on MCS, CS patients demonstrated higher MCS than OB patients. That is, if symptom count was to be held constant across the two groups, the CS patients would have higher mental HRQL. CS patients therefore appear to be demonstrating a higher level of emotional coping with their symptom load than would be anticipated.

What might account for this difference between the OB and CS groups? A previous study in a large group of Dutch men and women showed a significant decrease in QOL scores as number of dieting attempts increased. Specifically, they found that a history of repeated weight loss independently contributed to reduced scores of emotional and mental dimensions of HRQL, especially in women (17). Although we did not collect data on dieting attempts, it is possible that for this OB group, largely comprised of women, the same is true.

One should consider that the OB group was self-selected in that they sought clinical help in a weight management program that required self-payment. In addition, they elected to participate in a research study to find a medical explanation for their weight. A greater sense of helplessness and stress regarding their weight may be inferred, resulting in a lower MCS. In this light, previous studies have shown that psychopathology, especially depression, is greater among OB patients seeking treatment (18).

In interpreting the MCS, strong consideration must also be given to the stigma associated with obesity. There is a large literature reporting on the discriminatory behaviors toward OB patients in educational, employment, and even health care settings. In a comprehensive review, Puhl & Heuer (19) describe multiple studies demonstrating that physicians, nurses, and medical students believe that their overweight and OB patients are lazy and lack self-discipline. These beliefs translate into negative behaviors in the practice setting that do not go unnoticed by patients. Patients with CS, a rare and serious medical disease, require prompt attention, management, and treatment by the health care community. Certainly, an OB patient who is assigned a diagnosis of CS is likely to start encountering positive attitudes such as sympathy and encouragement from family, friends, colleagues, and those in the health care community. This might contribute to better emotional health in the CS group (20).

High BMI is reported to impair HRQL. However, in the context of mental health, only a few reports show lower MCS in OB individuals (21); most HRQL studies describe a lesser effect of BMI on mental compared with physical health. Some studies show mental health functioning similar to normal-weight people, especially when generic measures such as the SF-36 are used (6, 22). These findings are consistent with those of the current study in which BMI was not associated with MCS in either population. However, there are data that show negative associations between BMI and worse emotional health when obesity-specific questionnaires are used (23).
It is curious that BMI was associated with PCS in the OB but not in the CS group. Previous studies in the OB show a dose–response relationship between BMI and the degree of HRQL impairment, especially in the physical domains (6). In this study, the OB group, compared with the CS group, contained a larger percentage of class III OB patients, who may experience worse physical symptoms allowing for a significant correlation. The lack of effect of BMI in the CS group may imply that other factors present in CS, e.g. hypercortisolism and symptom count, have a greater impact on HRQL.

Psychiatric co-morbidities are also associated with worse HRQL in both OB and CS patients (24, 25). In a large multicenter, collaborative study designed to investigate QOL in OB patients seeking treatment, Mannucci et al. (26), showed that psychopathology was a strong predictor of poor HRQL in both physical and psychosocial domains. Similarly, QOL analysis performed in The European Registry on CS project showed depression to be a negative predictor of HRQL in CS patients (25). On the symptom questionnaire used in this study, about 40% of the OB group reported depression and/or anxiety in the last month. While we do not have a formal psychiatric evaluation in these patients, the presence of these Axis I disorders might account for decreased HRQL compared with the general population. However, the similar rates of these disorders in CS patients (54%, Table 3) cannot account for the MCS score difference between the two patient groups.

We hypothesized that the presence of hypercortisolism in the CS group would be associated with poorer PCS, as previous studies have implicated hypercortisolism as a possible determinant of HRQL (5, 7, 8, 27). However, pretreatment 24-h UFC levels were not associated with PCS or MCS scores in this study. One possible reason for the lack of association is that UFC represents only a single day and is not a long-term integrated value. It is possible that cumulative exposure would be a more useful measurement: the association between symptom count and HRQL also suggests this possibility.

Diabetes diagnosis was associated with physical HRQL in bivariate analyses but did not show an independent effect of a diagnosis of diabetes on physical HRQL in the full model. Previous QOL studies in diabetic subjects (without CS) report lower HRQL compared with that in the general population (28, 29). This may be associated with many factors, in particular, the number of complications associated with the disease. In an analysis of 5145 overweight and OB patients with diabetes, Rejeski et al. (11) found that a lower PCS score was related to a greater number of physical symptoms and complaints. The current study also showed that the number of (CS) symptoms was negatively associated with HRQL scores in both CS and OB groups. Findings suggest that the effects of hypercortisolism in CS patients and diabetes in both groups are less important to HRQL than the number of symptoms a patient experiences, regardless of the diagnosis.

The significant association of PCS and MCS scores with symptom count is of clinical interest. As suggested earlier, symptom count may be the ‘representative’ of the disease in regard to QOL. The number of positive symptoms was significantly different between the OB and the CS groups. Despite some overlap in the ranges, it may be possible to use this as a foundation for the development of a diagnostic questionnaire. A survey designed to highlight differences in symptoms between groups might help to determine which OB patients should be screened for CS.

There are limitations to this study. As noted earlier, psychological impairment, especially depression, is a significant predictor of lower HRQL scores in both OB and CS patients (25, 26, 30). The lack of data regarding the prevalence of depression for both groups in this study is a limitation in the interpretation of HRQL scores. In addition, this OB group was treatment-seeking and thus may not be representative of all OB persons. Finally, the lack of detailed geographical and socioeconomic status information should also be considered while interpreting the scores.

The strength of this study is the comparison of HRQL between OB and CS patients, two groups with similar clinical presentations, but significantly different etiologies. Use of the SF-36 survey allowed us to compare these two populations with each other while also comparing their HRQL scores with US population means providing perspective on each group’s overall HRQL. The results highlight two interesting findings. First, we introduce the possibility that emotional tolerance of obesity and, thus, QOL may be improved by assignment of a treatable medical diagnosis. Secondly, we show that symptom count significantly contributes to determination of QOL and is significantly different between the groups. A new diagnostic questionnaire incorporating symptom count and HRQL data may help identify which OB patients should be screened for CS.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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