0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(2):447–453

doi: 10.1210/jc.2005-1058

Long-Term Impaired Quality of Life in Cushing's Syndrome despite Initial Improvement after Surgical Remission

John R. Lindsay, Tonya Nansel, Smita Baid, Julie Gumowski, and Lynnette K. Nieman

Reproductive Biology and Medicine Branch (J.R.L., L.K.N., S.B.), Division of Epidemiology Statistics and Prevention Research (T.N.), National Institute of Child Health and Human Development, and National Institute of Allergy and Infectious Diseases (J.G.), National Institutes of Health, Bethesda, Maryland 20892

Context: Cushing's syndrome (CS) is associated with symptoms that may impair health-related quality of life (HRQL).

Methods: We used the short-form 36 survey to evaluate HRQL in 23 patients with Cushing's disease before and after transsphenoidal surgery (age, 42.7 ± 12.0 yr; 19 women and four men) and in a cross-section of 343 CS patients (age, 48.2 ± 14.1 yr; 265 women and 78 men) in remission for up to 25.8 yr after surgery (adrenal, 5%; ectopic, 6%). The z-scores were calculated for short-form 36 domains, and physical (PCS) and mental (MCS) summary scores were compared with those of age- and sex-matched controls (n = 6742).

Results: Active Cushing's disease was associated with low PCS and MCS scores ($P < 0.05$). Despite residual postoperative impairment, primarily of physical domains, all HRQL parameters improved after treatment with transsphenoidal surgery (3.2 ± 1.5 yr; $P < 0.05$). In the cross-section in remission at follow-up, there was a small, but significant ($P < 0.05$), impairment of both PCS and MCS. A longitudinal postoperative analysis confirmed stable, but impaired, HRQL over time. Logistic regression demonstrated that previous pituitary radiation and current glucocorticoid use had little effect on HRQL outcomes.

Conclusion: CS is associated with impaired HRQL, which partially resolves after treatment. At longer-term follow-up, however, there is residual impairment of HRQL. Determination of modifiable factors that contribute to impaired HRQL may help reduce the physical and psychosocial burden of this disease. **(*J Clin Endocrinol Metab* 91: 447–453, 2006)**

THE MAJORITY OF patients with Cushing's syndrome (CS) have physical and psychological symptoms that may lead to impaired health-related quality of life (HRQL) (1, 2). Important functional impairments arising from hypercortisolism include muscle weakness, fracture, and cardiovascular events, which can adversely affect the survival and well-being of these patients (3). Additional psychological consequences of hypercortisolism include depression (1), anxiety (4, 5), and cognitive decrements (6). Improved psychological functioning in CS has been observed after reversal of hypercortisolism (7, 8). Short-term series have shown significant improvements occurring within the first year of treatment (9). However, longer studies suggest that prolonged exposure to high levels of glucocorticoids may cause long-lasting deleterious effects (10–12).

Although the process of differential diagnosis and management of CS has been well validated (13), outcomes in relation to quality of life have received less attention. Impaired HRQL in CS has recently been demonstrated using the standard short-form 36 (SF-36) health survey, which is an integrated measure of physical and psychological well-being (3, 10, 14, 15). Previous studies were of relatively small groups of patients with Cushing's disease (CD) alone, with short duration of postoperative follow-up and in the absence of an age- and gender-matched control comparison.

We conducted a prospective study of HRQL using the SF-36 health survey in a cohort of patients with CD before and after transsphenoidal surgery (TSS). To characterize the impact on HRQL of successful treatment in CS, we also performed a cross-sectional analysis of HRQL in a cohort in long-term clinical remission, which included patients with ectopic, pituitary, and adrenal CS treated over a 25-yr period. The hypothesis was that we would observe improved HRQL after treatment and that HRQL would be greater with increasing duration of remission from hypercortisolism. We anticipated lower HRQL in patients with ectopic compared with adrenal- or pituitary-dependent CS due to associated comorbidity.

Patients and Methods

Patients

All patients were enrolled in a protocol approved by the institutional review board of the National Institute of Child Health and Human Development for investigation and management of CS. This study was carried out from 1999–2004 at the National Institutes of Health Warren Grant Magnuson Clinical Center (Bethesda, MD). In-patients with active CS were asked to complete the survey before and after treatment, and they comprise group 1. Twenty-five of 33 patients who completed a baseline pretreatment questionnaire also provided a follow-up questionnaire postoperatively. Twenty-three of these individuals who had been followed for at least 6 months postoperatively were included in the analysis. To assess longer-term outcomes in a cross-sectional sample, the

First Published Online November 8, 2005

Abbreviations: CD, Cushing's disease; CI, confidence interval; CS, Cushing's syndrome; HRQL, health-related quality of life; MCS, mental component scale; PCS, physical component scale; SF-36, short-form 36; TSS, transsphenoidal surgery; XRT, irradiation.

first author (J.R.L.) used an existing database of approximately 900 patients who had been enrolled in a range of protocols for investigation of CS. We identified 96 who had died since their inclusion in the protocol and excluded them from a mailing list sent to patients with confirmed CS. The survey was commenced in 1999, with two subsequent mailings in 2001 and 2004 to a total of 775 patients. Four hundred eighteen individuals returned 688 questionnaires; of these, 159 contributed two or more responses. Group 2 comprised a cross-sectional analysis of the most recent/latest questionnaire response from 343 subjects who were deemed to be in postoperative clinical remission. Seventy-five patients were excluded from this analysis, comprising eight patients who completed pretreatment responses alone, seven patients with insufficient follow-up data, and 60 individuals with possible/previously confirmed recurrence who are described below.

Quality of life

We used the SF-36R (version 2) for assessment of HRQL (16). The SF-36 is a generic health survey that has been widely validated and used in an international context to evaluate self-reported domains of health status (16). The SF-36 survey consists of a 36-item questionnaire that includes eight components of HRQL: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health. These eight domains formed two broader health dimension scales: a physical component scale (PCS) and a mental component scale (MCS).

SF-36 scoring algorithms produce a standardized score for each of the two health dimensions by setting the general population mean at 50 ± 10 (mean ± 1 SD). To control for any difference in age and gender between the population norms and our sample, we compared our sample with age- and sex-matched U.S. population norms from 6742 subjects studied by Ware *et al.* (16). To do this, we created a deviation score for each patient, calculated as the absolute difference between the individual's score and the appropriate age/gender norm. This score was then standardized to a z-score by dividing it by the SD for that age/gender norm. The resulting score, then, indicated for each individual how many SDs the patient deviated from his/her own age/gender population norm. In our analyses, we present data using both the SF-36 standardized score as well as this age/gender-controlled deviation score.

In addition to the SF-36 quality of life dimensions, cognitive function was assessed with the Medical Outcomes Study cognitive functioning scale (17). The Medical Outcomes Study quality of life assessment was the precursor to the SF-36; however, the cognitive functioning scale was omitted from the SF-36 in the interest of brevity. We elected to include the cognitive functioning scale, because this may be a particularly relevant dimension for this population.

Demographic variables and symptom checklist

The survey instrument included demographic data (age, gender, marital status, and highest grade of educational attainment), diagnosis, primary treatment, and subsequent treatments (surgery, medicine, or radiation) since discharge. The subjects were asked to indicate whether they had experienced a recurrence or were currently cured of CS and to indicate whether they were currently taking hydrocortisone, prednisone, dexamethasone, mitotane, or ketoconazole. All patients were requested to provide details of the most recent laboratory screening for objective assessment of remission status. Patients also were asked to indicate whether they were currently experiencing any of 42 items on a checklist containing signs and symptoms associated with CS.

Evaluation of long-term remission

The posttreatment cross-sectional analysis excluded patients with previously confirmed recurrence of CS as determined from our internal records (n = 34) and patients who indicated that they were not cured (n = 19). Patients with persistent hypercortisolism (n = 2) or who required ketoconazole (n = 4) or mitotane (n = 1) treatment were excluded. These responses were cross-checked with our records and with returned results of biochemical screening for examination of remission status.

Statistical analysis

Descriptive statistics were calculated for continuous variables. Frequencies were generated for other variables. Significance was assumed at $P < 0.05$. All data including the SF-36 domains are expressed as the mean ± SD, except where noted. χ^2 and Fisher's exact tests were used to examine differences in demographic variables. Only patients with both pre- and posttreatment responses were included in the intraindividual analysis for group 1. The mean and 95% confidence intervals (CIs) of z-scores for each group and domain were calculated. A mean z-score (effect size) less than 0.20 was considered clinically nonsignificant, a z-score in the range 0.2–0.5 was classified as small, a z-score in the range 0.5–0.8 as moderate, and a z-score greater than 0.8 as large (18, 19). Spearman's rank test was used to examine correlations between SF-36 outcomes and continuous demographic variables.

An analysis of the effect of time from treatment on HRQL was conducted within group 2, which included serial observations from individual respondents. However, if a subject contributed more than one observation during a single 5-yr period, only the most recent observation in that time period was used. Data were analyzed using mixed model analysis of repeated measures, followed by *post hoc* testing for pairwise comparisons among the times from treatment, using Statistical Analysis System (SAS) version 8 software (SAS Institute, Inc., Cary, NC).

Logistic regression analysis was used to evaluate the relationship of the physical symptom score, time from treatment, glucocorticoid use, previous pituitary irradiation (XRT) and deviation of greater than 0.5 SD in PCS and MCS domains below the normative mean. Testing was performed using the statistical package for social science (SPSS version 12 for Windows, release 09.04, 2003, SPSS, Inc., Chicago, IL) and GraphPad PRISM version 4.00 for Windows (GraphPad, San Diego, CA; www.graphpad.com).

Results

Group 1: HRQL in CD before and after TSS

Patients with active CD (Table 1) had low PCS, MCS, and low individual SF-36 domain z-scores compared with age- and sex-matched controls ($P < 0.05$; Fig. 1). Pretreatment PCS and MCS scores improved from 32.6 ± 10.5 and 38.8 ± 12.5 to 45.8 ± 12.7 and 50.5 ± 9.6, respectively ($P < 0.001$), at postoperative follow-up (mean, 3.2 ± 1.5; range, 0.7–5.4 yr; Table 2). All individual SF-36 domains improved after TSS ($P < 0.05$). We observed a significant improvement in cognitive function after treatment (56.2 ± 25.8 *vs.* 73.2 ± 29.4; $P = 0.02$)

Postoperatively, scores for bodily pain ($P = 0.5$), vitality ($P = 0.4$), social functioning ($P = 0.1$), role limitations due to emotional health ($P = 0.6$), general health ($P = 0.4$), mental health ($P = 0.5$), and the mental summary scores ($P = 0.8$), improved to levels similar to U.S. population norms. In contrast, physical functioning ($P = 0.04$), role limitations due to physical health ($P = 0.049$) and physical summary ($P = 0.04$) scores remained significantly below U.S. population norms.

Group 2: cross-sectional posttreatment survey of patients in clinical remission from CS

The characteristics of the 343 patients in remission from CS (CD, 89%; adrenal, 5%; ectopic, 6%) in the posttreatment cross-sectional sample were similar in terms of gender, education, and marital status to those in the posttreatment arm of group 1 (Table 1). Compared with group 1, the patients were older by approximately 6 yr ($P = 0.06$), a smaller proportion was treated by TSS alone ($P = 0.09$), and they had a longer period of remission ($P < 0.0001$). The SF-36 domain results from the cross-sectional group and posttreatment arm of group 1 were not statistically different.

In the cross-sectional group, PCS scores were higher in

TABLE 1. Characteristics of subjects treated for CS in the SF-36 analysis

	Group 1		Group 2 cross-sectional post-Rx (n = 343)
	pre-Rx (n = 23)	post-Rx (n = 23)	
Age (yr)	39.5 (11.5)	42.7 (12.0)	48.2 (14.1)
Age range (yr)	22–62	25–65	13–81
Gender (% female)	83		77
Marital status (%)			
Never married	26.1	26.1	19.0
Currently married	52.2	43.5	59.0
Separated		8.7	2.0
Divorced	21.7	21.7	14.3
Widowed			4.1
Unknown			1.7
Educational attainment (%)			
8th grade or less			2.9
Some high school; did not graduate			5.2
High school or GED	26.1	30.4	24.8
Some college or 2-yr degree	39.1	34.8	27.4
4-yr college degree	26.1	26.1	17.2
4+ college degree	8.7	8.7	21.3
Unknown			1.2
Time interval since treatment (yr)		3.2 (1.5)	11.8 (4.9)[a]
Diagnosis (%)			
CD		100	89
Adrenal CS			5
Ectopic CS			6
Glucocorticoid dependency (%)		26.1	27
Previous treatment (%)			
TSS		100	86.9
Unilateral ADX			4.7
Bilateral ADX			0.6
Pituitary XRT		4.3	0.6

Group 1: Before and after TSS in CD; group 2: cross-sectional posttreatment analysis of patients in apparent remission from CS. Results are means (SD). ADX, Adrenalectomy; GED, General Educational Development; Rx, treatment.

[a] $P < 0.0001$ for comparison of demographic data of patients in the posttreatment arm of group 1 and those in the cross-sectional series.

men ($P = 0.02$) and inversely associated with age ($r = -0.36$; $P < 0.001$). Both PCS and MCS scores were independent of diagnostic category and educational status.

Postoperatively at the longest follow-up point (11.8 ± 4.9 yr; range, 0.7–25.8 yr), z-scores for SF-36 domains were low ($P < 0.05$) compared with age- and sex-matched population controls (Fig. 2). Despite apparent clinical remission from CS, these patients had low PCS (45.7 ± 0.7) and MCS (47.0 ± 0.7) scores (mean ± SEM; $P < 0.0001$) compared with the general population controls (50 ± 0.1). Corresponding z-scores for PCS and MCS were −0.4 ± 1.2 and −0.3 ± 1.2.

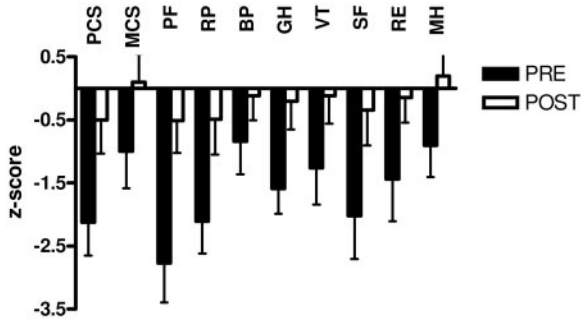

FIG. 1. Individual SF-36 domains before (Pre) and after (Post) treatment in 23 patients with CD treated with TSS. Results are expressed as the mean ± 95% CI for the pre- and posttreatment z-scores compared with age- and sex-matched controls from the U.S. population. SF-36 domains are PCS, MCS, physical functioning (PF), role limitations due to physical health (RP), body pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health (RE), and mental health (MH). $P < 0.0001$ for differences between all domains in the pre- and posttreatment arms, except for BP ($P = 0.03$).

Subjective health rating and satisfaction scale among cross-sectional analysis

Patients compared their current health to that before developing CS. Results from patients in the remission group were as follows: much better, 38%; somewhat better, 12%; about the same, 20%; somewhat worse, 20%; much worse, 7%; or missing, 3%. Similarly, when asked to rate their level of satisfaction with the outcome of treatment for CS, responses were: extremely satisfied, 57%; quite satisfied, 26%; moderately satisfied, 9%; slightly satisfied, 4%; not at all satisfied, 2%; or missing, 3%.

HRQL by time from treatment

We observed long-term higher PCS ($P < 0.0001$) and MCS ($P < 0.01$) scores in the cross-sectional analysis compared with the pretreatment arm of group 1 (Fig. 3). There were no significant changes in PCS or MCS scores in the posttreatment period with increasing time from treatment ($P > 0.05$).

Symptoms and relationship to SF-36 summary scores

Table 3 demonstrates the prevalence of active symptoms in the cross-sectional series at the most recent follow-up.

TABLE 2. SF-36 domains in patients treated for CS: before and after TSS in CD (n = 23) and in a cross-sectional posttreatment (post-Rx) analysis from those in apparent long-term remission from CS at latest follow-up (n = 343)

	Pre-Rx CD (n = 23)	Post-Rx CD (n = 23)	Post-Rx cross-sectional (n = 343)	Pre- *vs.* post-Rx CD (*P* value)	Pre-Rx CD *vs.* cross-sectional post-Rx (*P* value)	Post-Rx CD *vs.* cross-sectional post-Rx (*P* value)
PCS	32.6[a] (10.5)	45.8[b] (12.7)	45.7[a] (12.1)	<0.0001	<0.0001	0.95
MCS	38.8[a] (12.5)	50.5 (9.6)	47.0[a] (11.9)	<0.0001	0.0003	0.44
Physical functioning	28.3[a] (11.0)	45.9[b] (11.5)	45.5[a] (11.5)	<0.0001	<0.0001	0.96
Role physical	31.8[a] (10.4)	45.9[b] (12.9)	45.7[a] (12.1)	<0.0001	<0.0001	0.83
Bodily pain	41.9[a] (11.4)	48.6 (9.4)	47.4[a] (11.9)	0.03	0.03	0.63
General health	34.4[a] (8.4)	48.1 (9.9)	44.2[a] (12.7)	<0.0001	<0.0001	0.43
Vitality	36.4[a] (12.4)	48.3 (9.5)	46.5[a] (12.6)	<0.0001	<0.0001	0.75
Social functioning	29.8[a] (14.7)	46.7 (11.4)	47.2[a] (11.7)	<0.0001	<0.0001	0.72
Role emotional	36.6[a] (13.1)	49.0 (8.1)	45.6[a] (12.5)	<0.0001	<0.0001	0.81
Mental health	39.7[a] (11.1)	51.4 (9.5)	47.3[a] (11.4)	<0.0001	0.002	0.20

All statistical comparisons between groups are as indicated, and controls were derived from the 1998 U.S. general population (16). Results are means (SD).

[a] $P < 0.0001$ *vs.* population controls.

[b] $P < 0.05$ *vs.* population controls.

Fatigue (41%), forgetfulness (35.7%), and trouble sleeping (33.3%) were the most common symptoms. The presence of any symptom was associated with lower PCS/MCS in all cases in which a significant difference was observed. The presence of symptoms measured using the total numerical score of positive symptoms was inversely related to SF-36 summary domains: PCS: r = −0.5; $P < 0.0001$; and MCS: r = −0.6; $P < 0.0001$.

Effect of glucocorticoids

Although patients requiring glucocorticoids after remission of CS had marginally lower physical summary z-scores (−0.5 ± 1.3 *vs.* −0.3 ± 1.2; $P = 0.05$), the remainder of the SF-36 domains were similar ($P > 0.05$) compared with those who were glucocorticoid independent.

Predictors of HRQL

The use of glucocorticoids and previous pituitary XRT were not significantly associated with impaired PCS and/or MCS scores in a model that examined their relationship to z-score deviation of more than 0.5 SD below age- and sex-matched population means. Physical symptoms scores (defined in Table 3) were significantly associated with both impaired PCS and MCS. The odds ratio (95% CI) for impaired PCS was 14.4 (6.4–32.7) and for MCS was 6.1 (2.9–12.8) in those with six or more physical symptoms compared with those with none or one symptom. Increasing time from treatment was identified as a significant contributor to the observed variation in PCS scores, but not MCS scores. The odds ratios (95% CI) for impaired PCS was 0.4 (0.2–1.2), 0.36 (0.2–0.9), and 0.3 (0.1–0.6) for patients 0–5, 5–10, and 10–15 yr from treatment, respectively, compared with those who had been treated more than 15 yr previously.

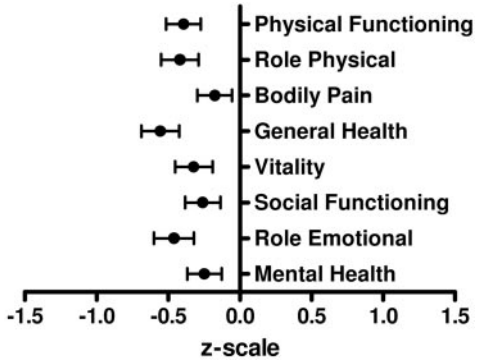

FIG. 2. Individual domains of SF-36 in 343 patients in long-term apparent remission after treatment for CS. Data are presented as the mean ± 95% CIs. All data crossing the zero line (U.S. population age- and sex-matched control values; n = 6742) are not significant.

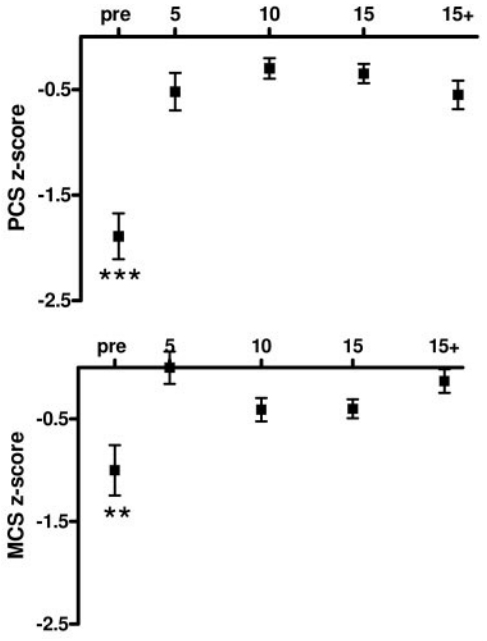

FIG. 3. PCS and MCS domains for the pretreatment arm of group 1 (pre) and the cross-sectional posttreatment responses, expressed as z-scores, compared with age- and sex-matched controls. The timing of each patient's posttreatment response was categorized according to time (years) from treatment: 0–4.9 (n = 44), 5–9.9 (n = 131), 10–14.9 (n = 171), and more than 15 (n = 94) yr. In the event of multiple responses within an individual 5-yr interval, the most recent response was selected for analysis. Results are expressed as the mean ± SEM. ***, $P < 0.0001$; **, $P < 0.01$ (for comparison with the posttreatment group).

TABLE 3. Prevalence of symptoms and relationship to SF-36 physical (PCS) and mental (MCS) component scores in patients comprising the posttreatment cross-sectional series

Active symptoms at follow-up	% of patients with symptoms	Mean norm-based PCS score (SD)		Mean norm-based MCS score (SD)	
		Symptom −ve	Symptom +ve	Symptom −ve	Symptom +ve
Fatigue[a]	41.3	50.5 (10.1)	39.0 (11.3)[b]	50.8 (9.5)	41.6 (12.7)[b]
Forgetfulness	35.7	49.0 (10.9)	39.8 (11.9)[b]	49.9 (10.8)	41.8 (12.0)[b]
Trouble sleeping	33.3	48.8 (10.6)	38.9 (12.5)[b]	49.9 (10.4)	40.6 (12.5)[b]
Depression	31.2	47.6 (11.7)	41.4 (12.0)[b]	51.8 (9.2)	36.4 (10.2)[b]
Weight gain[a]	30.4	47.5 (11.4)	41.2 (12.3)[b]	48.3 (11.7)	43.9 (11.7)[c]
Decreased muscle strength or weakness[a]	30.4	49.7 (10.5)	36.5 (10.4)[b]	49.8 (9.5)	40.4 (14.0)[b]
Bulging abdomen[a]	29.3	48.8 (10.9)	38.1 (11.4)[b]	49.3 (10.7)	41.3 (12.6)[b]
Anxiety	28.4	47.0 (11.8)	42.3 (12.2)[c]	50.5 (10.4)	38.1 (10.5)[b]
Facial hair	27.6	48.0 (11.2)	39.7 (12.3)[b]	48.1 (11.6)	44.0 (12.1)[c]
Feelings of sadness	27.6	48.0 (11.6)	39.5 (11.2)[b]	51.3 (9.1)	35.7 (10.9)[b]
Mood swings	27.4	47.0 (11.8)	42.6 (12.3)[c]	51.2 (9.1)	36.2 (11.2)[b]
Decreased ability to exercise[a]	27.0	49.9 (10.0)	34.3 (9.7)[b]	49.8 (10.1)	39.7 (13.0)[b]
High blood pressure[a]	25.2	48.4 (11.1)	37.7 (11.2)[b]	47.9 (11.5)	44.3 (12.5)[d]
Decreased attention span	24.6	47.6 (11.5)	39.7 (12.0)[b]	50.0 (10.5)	37.8 (11.1)[b]
Bruise easily[a]	24.3	47.7 (11.4)	39.5 (12.2)[b]	48.8 (10.8)	41.3 (13.2)[b]
Feelings of frustration	23.1	47.7 (11.3)	39.0 (12.3)[b]	50.2 (10.1)	36.1 (11.0)[b]
Feelings of being fat and ugly	21.6	47.8 (11.3)	38.0 (11.6)[b]	48.9 (11.2)	39.9 (11.8)[b]
Thin skin[a]	21.3	47.7 (11.1)	38.1 (12.6)[b]	48.2 (11.1)	42.6 (13.6)[c]
Increased irritability	21.3	47.0 (11.5)	40.8 (12.8)[b]	50.1 (10.0)	35.4 (10.9)[b]
Thinning or balding of hair[a]	21.0	47.3 (11.4)	39.3 (12.6)[b]	48.2 (11.3)	42.2 (12.7)[b]
Women and men: lack of sexual drive[a]	19.8	47.1 (11.9)	40.0 (11.0)[b]	48.2 (11.2)	42.0 (13.0)[b]
Unclear thinking	19.5	47.4 (11.5)	38.4 (11.7)[b]	49.5 (10.6)	36.6 (11.1)[b]
Weak bones[a]	18.0	47.6 (11.4)	37.0 (11.2)[b]	48.1 (11.2)	41.6 (13.4)[c]
Unable to work[a]	16.8	48.2 (10.8)	33.3 (10.2)[b]	49.1 (10.5)	36.6 (12.6)[b]
Temper outbursts	16.5	46.9 (11.5)	39.6 (13.2)[c]	49.5 (10.2)	33.9 (11.1)[b]
Crying spells	16.5	47.1 (11.6)	38.7 (12.4)[b]	49.3 (10.6)[b]	35.2 (11.0)[b]
Feelings of hopelessness	15.9	46.8 (11.7)	39.6 (12.3)[b]	49.9 (9.7)	31.5 (10.3)[b]
Indecision	15.6	46.9 (11.8)	39.0 (11.7)[b]	48.9 (10.7)	36.3 (12.0)[b]
Increased nervousness	15.6	46.5 (11.9)	41.3 (12.0)[c]	49.1 (10.8)	35.5 (11.0)[b]
Anger	15.6	46.6 (11.6)	40.9 (13.6)[c]	49.2 (10.5)	34.8 (11.2)[b]
Cuts/abrasions heal slowly[a]	15.3	46.9 (11.9)	38.8 (10.9)[b]	48.4 (10.9)	39.3 (14.1)[b]
Women: loss of menstrual periods[a]	14.7	45.7 (12.0)	39.8 (10.0)[c]	47.2 (11.7)	43.5 (12.3)
Purple stretch marks[a]	13.5	45.8 (12.2)	44.7 (11.7)	47.6 (11.7)	43.1 (12.2)[d]
Women: irregular menstrual periods[a]	11.3	44.8 (12.3)	45.8 (9.8)	47.0 (12.0)	42.9 (10.0)
Ruddy or red complexion[a]	10.5	46.5 (11.6)	38.3 (13.3)[b]	47.3 (11.8)	44.1 (12.7)
High blood sugar[a]	10.5	46.9 (11.6)	35.0 (10.9)[b]	47.3 (11.9)	44.2 (11.4)
Feelings of being left out of the family	9.3	46.5 (11.9)	37.2 (10.8)[b]	48.5 (10.7)	31.7 (11.8)[b]
Fat pads around neck and shoulders[a]	9.0	46.5 (11.8)	37.8 (11.9)[b]	47.5 (11.5)	41.2 (14.0)[c]
Round face[a]	8.1	46.4 (11.6)	37.1 (13.8)[b]	47.4 (11.7)	42.6 (13.0)[d]
Men: impotence[a]	8.0	49.4 (11.3)	38.5 (12.7)[d]	48.8 (11.3)	38.5 (15.5)[d]
Acne[a]	7.2	45.8 (12.0)	43.6 (13.6)	47.5 (11.5)	40.4 (13.9)[c]
Broken bones[a]	4.2	46.3 (11.7)	30.8 (11.2)[b]	47.1 (11.7)	44.2 (14.5)

Column 2 demonstrates the percentage of patients who indicated the presence of active symptoms.

[a] Symptoms that comprised physical symptoms score.

Mean (±SD) norm-based PCS and MCS scores were calculated for each group with (+ve) or without (−ve) symptoms and analyzed for significant differences using Student's unpaired *t* test; [b] $P < 0.0001$, [c] $P < 0.01$, [d] $P < 0.05$.

Differences between subjects in remission and those with a confirmed previous recurrence or persistent hypercortisolism at most recent mailing

We examined differences in SF-36 responses for those in apparent clinical remission compared with others who had been excluded from earlier analyses, as described above. PCS scores were lower among those who had a previous recurrence (37.6 ± 12.2), those with persistent hypercortisolism (38.3 ± 3.7), and those who believed they were not cured (34.2 ± 11.8) compared with the remission group detailed above (by ANOVA, $P < 0.0001$). Similarly, when we examined MCS scores, patients with a previous recurrence (41.9 ± 16.4), with persistent hypercortisolism (44.9 ± 3.7), or who believed they were not cured (39.6 ± 13.3) had lower scores than the remission group ($P < 0.0001$).

Discussion

The present series confirms that active CS is associated with impaired HRQL. The magnitude of difference compared with age- and sex-matched controls was large in all SF-36 domains, except for mental health and bodily pain, which were moderately impaired. The magnitude of these changes also was similar to previous reports that HRQL in active CS is significantly impaired compared with that in subjects with acromegaly, prolactinoma, or nonfunctioning tumors (14).

Postoperative HRQL values within the first 3 yr of follow-up improved compared with pretreatment values. However, despite apparent clinical remission, when compared with the U.S. population, there was residual impairment primarily of physical scores, comprised of physical function-

ing, role limitations due to physical health, and PCS domains. In the remaining domains, no other differences were apparent at early postoperative follow-up compared with the general U.S. population. However, when compared with age- and gender-matched controls, HRQL remained impaired (see below).

Our observations extend the early postoperative observations by Vance *et al.* (20) of HRQL in 20 patients with successfully treated CD. Although the baseline PCS scores in the present series were lower than those reported by that group at a mean of 13 months after surgery, the direction of change and postoperative values were similar. Lumachi *et al.* (21) also reported improved HRQL in 46 patients at 23 months after bilateral adrenalectomy for CD. All SF-36 components improved significantly, except for trends to improvement in the domain for emotional role and an increase in bodily pain, which were close to statistical significance (21).

Dorn *et al.* (9) reported the time course for improvements in psychopathology in 33 patients. From a baseline of 66% of affected adult patients before treatment, residual psychopathology was present in 53.6% at 3 months, 36% at 6 months, and 24.1% at 12 months of recovery from hypercortisolism (9). Thus, the timing of survey administration during the early postoperative period may have influenced our results.

The present cross-sectional series demonstrated no significant differences in HRQL relating to treatment modality or between diagnostic categories, consistent with previous series (22). However, the number of patients with nonpituitary disease was small, so that evaluation of a larger group might show a difference. It is also possible that the degree or duration of hypercortisolism influences HRQL. This study was not designed to answer that question.

Improved, but persistently impaired, HRQL may have significant social and economic consequences for the patient recovering from CS. In the current survey, although 57% of the patients were extremely satisfied with their treatment for CS, subjectively only 38% felt much better after treatment, 20% felt similar to before treatment, and 20% felt somewhat worse after treatment compared with before they developed CS. Hawn *et al.* (15) reported an objective decrease in HRQL in 11 patients, nine of whom reported that their health improved after adrenalectomy. Pikkarainen *et al.* (3) reported that despite improvements in HRQL after treatment in CS, the mean duration of postoperative sick leave was 3.8 months. After surgery, only about 81% were able to return to work, illustrating the potential socioeconomic burden during recovery from CS (3).

In the cross-sectional remission series, we observed moderate impairment of general health compared with age- and sex-matched controls over a mean time from treatment of almost 12 yr. All other domains, except for bodily pain, showed small residual impairments at long-term follow-up. Thus, as demonstrated by this and other reports, there is mounting evidence of persistent impairments in HRQL in subjects in long-term remission from CS (10, 12). Others have reported impairments in HRQL at a mean of 29 months, 7.7 yr, and 13 yr after treatment (10).

We do not know exactly which factors contribute to impaired HRQL despite clinical remission at long-term follow-up. van Aken *et al.* (10) showed that hypopituitarism, which occurred in approximately half of the 58 subjects treated for CS, was an independent predictor of HRQL. Although we do not have biochemical data on the presence of hypopituitarism or GH deficiency in our cross-sectional series (see below), we did find small differences in SF-36 PCS scores for glucocorticoid users compared with age- and sex-matched population controls. These differences were not apparent in the logistic regression, suggesting that other factors are involved. Similarly, the absence of menses was associated with impaired PCS scores in women, and impotence was associated with lower PCS and MCS scores in men, suggesting that hypogonadism contributed to impaired HRQL. Using a logistic regression model that was controlled for age and gender, we did not find that previous pituitary XRT was a significant contributor, consistent with one recent small series that found similar HRQL in those who had never been or were treated with XRT (12).

PCS scores were more likely to be below population norms in subjects 15 yr or more from treatment. These observations are in contrast to those of van Aken *et al.* (10), who found no difference in HRQL arising from time interval since remission. Although that report was similar in terms of age, gender, and duration of remission, it only included patients with CD. Our series comprised a larger group of patients with a wider range of diagnoses and a smaller proportion who were glucocorticoid dependent. However, the exact reason for the differences between these series is unknown.

Other factors that may have contributed to persistent long-term impaired HRQL are irreversible effects of hypercortisolism on neurological function or physical conditioning (11). Elevated cortisol levels in CS are associated with cognitive decrements and loss of brain volume (6). Furthermore, the apparent decrease in hippocampal volume associated with functional impairments in cognition appeared to be only partially reversible upon correction of hypercortisolism (23, 24). Similarly, deleterious effects on the cardiovascular system and metabolic parameters persist even after successful treatment of CS (25). Unfortunately, in this series we do not have data on these and other comorbid conditions that may have influenced HRQL. However, previous studies using the SF-36 survey showed impaired HRQL in patients with ischemic heart disease and markers of the metabolic syndrome (25, 26). It is possible that these and other factors may have contributed to the observed long-term impairment in HRQL in our series (25, 26).

As would be expected, the presence of physical and mental symptoms was inversely related to PCS and MCS scores. We detected significantly higher SF-36 PCS scores in patients in apparent clinical remission compared with those with a definite previous recurrence and in those who indicated possible recurrence. In this respect the SF-36 health survey or the 42-item symptom checklist might have utility for screening patients for disease recurrence at postoperative follow up. We believe that the utility of these methods and their relationship to biochemical screening in postoperative surveillance merit prospective study.

This study has several limitations and biases. First, the paired pre- and posttreatment surveys included only 23 patients. Although these numbers are small relative to our larger cross-sectional group, they are similar to other pub-

lished series (12, 20). Second, because the National Institutes of Health serves as a worldwide referral center for management of CS, many patients resume posttreatment care with local endocrinology services and have not been uniformly reevaluated at the National Institutes of Health. Our determination of remission status relied primarily on self-report and limited biochemical data, with variable laboratory reference ranges and methodologies. Although no patient with definite recurrent hypercortisolism was included from the posttreatment series based on this information, we cannot exclude unrecognized recurrence in all.

Similarly, we could not quantify the prevalence of other factors that might impair HRQL. These include diminished GH reserve, present in about 20% in a previous series of patients treated for CS (12, 27), as well as gonadal steroid deficiency or glucocorticoid-associated comorbidities leading to glucose intolerance, hypertension, and hyperlipidemia.

In conclusion, we have demonstrated impaired quality of life in CS that partially resolves after successful treatment. At long-term follow-up, despite apparent clinical remission, there is evidence of residual impairment of HRQL. Assessment of quality of life is an essential outcome measure in the postoperative period, which may have utility in the assessment of remission status at subsequent follow-up. Determination of modifiable factors that contribute to HRQL in this vulnerable population might help reduce the physical and psychosocial burden of disease.

Acknowledgments

We acknowledge other attending physicians who admitted some of these patients to the Clinical Center, including Drs. D. Lynn Loriaux, Gordon Cutler, Dimitris Papanaicolaou, and George Chrousos. We are grateful for the efforts of students, Stacey Spechler, Andrew Steele, and Vanessa Lopez, who assisted with data entry. We thank our neurosurgery colleagues, Dr. Edward Oldfield, Hetty DeVroom, and Rene Smith, for assistance with establishing long-term recurrence status. Finally, we thank the patients and families who responded to our survey.

Received May 12, 2005. Accepted October 28, 2005.

Address all correspondence and requests for reprints to: Dr. Lynnette K. Nieman, Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development, National Institutes of Health, Building 10, Clinical Research Center, Room 1-3140, 10 Center Drive, Bethesda, Maryland 20892-1109. E-mail: niemanl@mail.nih.gov.

References

1. **Sonino N, Fava GA, Raffi AR, Boscaro M, Fallo F** 1998 Clinical correlates of major depression in Cushing's disease. Psychopathology 31:302–306
2. **Kelly WF** 1996 Psychiatric aspects of Cushing's syndrome. Q J Med 89:543–551
3. **Pikkarainen L, Sane T, Reunanen A** 1999 The survival and well-being of patients treated for Cushing's syndrome. J Intern Med 245:463–468
4. **Loosen PT, Chambliss B, DeBold CR, Shelton R, Orth DN** 1992 Psychiatric phenomenology in Cushing's disease. Pharmacopsychiatry 25:192–198
5. **Starkman MN, Schteingart DE** 1981 Neuropsychiatric manifestations of patients with Cushing's syndrome. Relationship to cortisol and adrenocorticotropic hormone levels. Arch Intern Med 141:215–219
6. **Starkman MN, Giordani B, Berent S, Schork MA, Schteingart DE** 2001 Elevated cortisol levels in Cushing's disease are associated with cognitive decrements. Psychosom Med 63:985–993
7. **Kelly WF, Kelly MJ, Faragher B** 1996 A prospective study of psychiatric and psychological aspects of Cushing's syndrome. Clin Endocrinol (Oxf) 45:715–720
8. **Kelly WF, Checkley SA, Bender DA, Mashiter K** 1983 Cushing's syndrome and depression–a prospective study of 26 patients. Br J Psychiatry 142:16–19
9. **Dorn LD, Burgess ES, Friedman TC, Dubbert B, Gold PW, Chrousos GP** 1997 The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. J Clin Endocrinol Metab 82:912–919
10. **van Aken MO, Pereira AM, Biermasz NR, van Thiel SW, Hoftijzer HC, Smit JW, Roelfsema F, Lamberts SW, Romijn JA** 2005 Quality of life in patients after long-term biochemical cure of Cushing's disease. J Clin Endocrinol Metab 90:3279–3286
11. **Forget H, Lacroix A, Cohen H** 2002 Persistent cognitive impairment following surgical treatment of Cushing's syndrome. Psychoneuroendocrinology 27: 367–383
12. **Heald AH, Ghosh S, Bray S, Gibson C, Anderson SG, Buckler H, Fowler HL** 2004 Long-term negative impact on quality of life in patients with successfully treated Cushing's disease. Clin Endocrinol (Oxf) 61:458–465
13. **Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M** 2003 Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 88:5593–5602
14. **Johnson MD, Woodburn CJ, Vance ML** 2003 Quality of life in patients with a pituitary adenoma. Pituitary 6:81–87
15. **Hawn MT, Cook D, Deveney C, Sheppard BC** 2002 Quality of life after laparoscopic bilateral adrenalectomy for Cushing's disease. Surgery 132:1064–1068
16. **Ware J KM, Dewey JE** 2000 How to score version two of the SF-36® Health Survey, 3rd Ed. Lincoln, RI: QualityMetric
17. **Stewart AL Ware JE** 1992 Measuring functioning and well being: the medical outcomes study approach. Durham, NC: Duke University Press
18. **Kazis LE, Anderson JJ, Meenan RF** 1989 Effect sizes for interpreting changes in health status. Med Care 27:S178–S189
19. **Bianchi GP, Zaccheroni V, Solaroli E, Vescini F, Cerutti R, Zoli M, Marchesini G** 2004 Health-related quality of life in patients with thyroid disorders. Qual Life Res 13:45–54
20. **Vance ML, Chernawsky DR, Woodburn CJ,** Recovery from Cushing's disease: changes in quality of life. Program of the 86th Annual Meeting of The Endocrine Society, New Orleans, LA, 2004, p 419 (Abstract P2-456)
21. **Lumachi F, Basso SM, Lacobone M, Armanini D, Favio G,** Long-term outcome and quality of life after bilateral adrenalectomy in patients with Cushing's disease previously treated by transsphenoidal pituitary microsurgery. Program of the 86th Annual Meeting of The Endocrine Society, New Orleans, LA, 2004, p 412 (Abstract P3-565)
22. **Sonino N, Fava GA, Belluardo P, Girelli ME, Boscaro M** 1993 Course of depression in Cushing's syndrome: response to treatment and comparison with Graves' disease. Horm Res 39:202–206
23. **Bourdeau I, Bard C, Noel B, Leclerc I, Cordeau MP, Belair M, Lesage J, Lafontaine L, Lacroix A** 2002 Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. J Clin Endocrinol Metab 87:1949–1954
24. **Starkman MN, Giordani B, Gebarski SS, Schteingart DE** 2003 Improvement in learning associated with increase in hippocampal formation volume. Biol Psychiatry 53:233–238
25. **Faggiano A, Pivonello R, Spiezia S, De Martino MC, Filippella M, Di Somma C, Lombardi G, Colao A** 2003 Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 88:2527–2533
26. **Kiebzak GM, Pierson LM, Campbell M, Cook JW** 2002 Use of the SF36 general health status survey to document health-related quality of life in patients with coronary artery disease: effect of disease and response to coronary artery bypass graft surgery. Heart Lung J Acute Crit Care 31:213
27. **Malik IA, Foy P, Wallymahmed M, Wilding JP, MacFarlane IA** 2003 Assessment of quality of life in adults receiving long-term growth hormone replacement compared to control subjects. Clin Endocrinol (Oxf) 59:75–81

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.