0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(6):3279–3286

doi: 10.1210/jc.2004-1375

Quality of Life in Patients after Long-Term Biochemical Cure of Cushing's Disease

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To evaluate the long-term impact of cured Cushing's disease on subjective well-being, we assessed quality of life by validated health-related questionnaires in 58 patients cured from Cushing's disease by transsphenoidal surgery (n = 58), some of whom received additional radiotherapy (n = 11) and/or bilateral adrenalectomy (n = 3). The mean duration of remission was 13.4 ± 6.7 yr (range of 2–25 yr). Patient data were compared with a control group of 98 healthy subjects with the same age and sex distribution and with age-adjusted reference values available from the literature.

General perceived well-being, measured by the Nottingham Health Profile and the Short Form, was reduced compared with controls for all subscales ($P < 0.001$). Patients with Cushing's disease had worse scores on subscales of fatigue Multidimensional Fatigue Index and anxiety and depression (Hospital Anxiety and Depression Scale). Compared with reference values from the literature, quality of life was also reduced in the patients according to all questionnaires and all items, except pain (Short Form), sleep (Nottingham Health Profile), and reduced activity (Multidimensional Fatigue Index). Despite conventional hormone replacement therapy, hypopituitarism was an important independent predictor of reduced quality of life. Patients without hypopituitarism (n = 28) showed reduced scores on physical items but normal scores on mental items compared with controls.

In conclusion, despite long-term cure of Cushing's disease, patients experience a considerable decrease in quality of life, with physical and psychosocial impairments, especially in the presence of hypopituitarism. **(*J Clin Endocrinol Metab* 90: 3279–3286, 2005)**

CHRONIC EXPOSURE TO endogenous glucocorticoid excess in patients with Cushing's disease has an array of effects on many tissues in the body, such as truncal obesity, facial fullness, gonadal dysfunction, hirsutism (in females), muscle weakness, and osteoporosis (1). The brain is another well-recognized target of glucocorticoids. Mood disorders and cognitive impairment occur in 50–80% of patients with active Cushing's disease (2, 3). Transsphenoidal selective adenomectomy is the most widely accepted primary therapy for pituitary-dependent Cushing's disease (4). When performed by a specialist neurosurgeon, long-term remission rates up to 70% can be achieved (5–7). In patients not cured by transsphenoidal surgery, pituitary irradiation and/or bilateral adrenalectomy can eventually normalize cortisol levels (8, 9). However, despite successful treatment of cortisol excess, physical recovery is slow and often incomplete, with residual impairments including osteoporosis, hypertension, and pituitary deficiencies. Similarly, disappearance of psychological distress does not always occur upon proper endocrine treatment (2). These persisting physical and psychological impairments may affect quality of life in patients with Cushing's disease despite long-term biochemical cure. However, with a few exceptions, most studies on treatment of Cushing's disease have focused on hard biochemical outcome rather than functional recovery, and the long-term impact of Cushing's disease on subjective well-being after successful treatment of cortisol excess is unclear.

The purpose of the study was to evaluate various physical and psychological aspects of quality of life in patients with long-term cure of Cushing's disease. Therefore, we assessed in the present study quality of life in patients with Cushing's disease treated previously in our center by transsphenoidal surgery and, if necessary, by additional treatment consisting of pituitary irradiation and/or bilateral adrenalectomy. We used four validated health-related quality of life questionnaires and compared the results with a healthy control group with similar age and sex distribution and with literature reference ranges.

Patients and Methods

Protocol

To assess quality of life after treatment for Cushing's disease, we identified all living patients diagnosed with Cushing's disease who have been treated in our center between 1978 and 2002 by transsphenoidal surgery and, if necessary, by additional treatment. The effect of treatment on biochemical control of Cushing's disease in these patients have been extensively described previously (5). From a total of 81 patients treated by transsphenoidal surgery, 63 patients were identified who were considered cured according to normal 24-h urinary cortisol excretion of less than 80 μg/24 h (<220 nmol/24 h) and normal overnight suppression of serum cortisol less than 3.6 μg/dl (<0.1 μmol/liter) after 1 mg dexamethasone. With these stringent criteria for cure, persistence of (subclinical) Cushing's disease in these patients seems unlikely. Moreover, these tests were performed regularly during follow-up to detect possible recurrence of Cushing's disease, which was not found in the present series of patients. Of the 81 patients, 15 patients had died during follow-up, and three patients were lost to follow-up.

First Published Online March 1, 2005

Abbreviations: HADS, Hospital Anxiety and Depression Scale; MFI-20, Multidimensional Fatigue Index; NHP, Nottingham Health Profile; SF-36, Short Form.

All patients were seen at least twice yearly by an endocrinologist, with adequate evaluation and treatment of possible deficits of pituitary hormones. In patients who were glucocorticoid-dependent after treatment for Cushing's disease, recovery of the pituitary-adrenal axis was tested twice a year. The hydrocortisone dose was on average 20 mg/d divided into two to three dosages. After withdrawal of hydrocortisone replacement for 24 h, a fasting morning blood sample was taken for the measurement of serum cortisol concentration. Patients with a serum cortisol concentration less than 120 nmol/liter were considered glucocorticoid dependent, and hydrocortisone treatment was restarted. Patients with a serum cortisol level between 120 and 500 nmol/liter were tested by a 30-min ACTH stimulation test (250 μg). Normalization of cortisol production was defined as a stimulated cortisol more than 500 nmol/liter. Evaluation of GH deficiency was performed by insulin-tolerance test and/or arginine-GHRH test only in patients under the age of 70 yr and only after at least 2 yr of remission of Cushing's syndrome. Patients with an inadequate stimulation of GH by one of these tests was started on treatment with recombinant human GH, aiming at IGF-1 levels between 0 and +2 SD values. In addition, the twice yearly evaluation consisted of measurement of free T_4 and testosterone (male patients). If results were below the lower limit of the respective reference ranges, substitution with thyroxine or testosterone was started. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.

The patients were asked to participate by letter, and questionnaires were sent to their homes in prepaid envelopes. After 6 wk, nonresponders received a reminder letter, and thereafter they were contacted by telephone to encourage completion and return of the questionnaires.

The data obtained from the patients were compared with two different control populations. First, a control population with the same sex and age distribution and from the same geographical area as our patients was recruited. This was done by asking patients visiting the outpatient clinic of the Department of Endocrinology of the Leiden University Medical Center to recruit a healthy relative with the same sex and a similar age to participate in this study. Second, Dutch or West European age-adjusted mean reference values were collected from the literature for all four questionnaires.

Primary study parameters were the results of four health-related quality of life questionnaires. The outcomes were related to patients characteristics (age and sex), applied treatments (transsphenoidal surgery and radiotherapy), severity of cortisol excess, presence of hypopituitarism defined as the need for replacement therapy, and duration of cure.

The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center, and all subjects had given informed consent before enrollment in the study.

Patients and controls

A very high percentage of patients responded to the study. Fifty-nine patients returned the questionnaires (response rate of 95%), from which one patient preferred not to participate in the study, resulting in a study population of 58 patients. The patient group consisted of 10 male and 48 female patients, with a mean age of 51.7 ± 15.2 yr (range of 31–84 yr). A microadenoma was originally present in 51 cases, and a macro adenoma was present in seven cases. Patient characteristics are detailed in Table 1. The mean age of the control group was 52.5 ± 13.3 yr, and there were 23 male and 75 female controls. The age and sex were not different between patients and controls ($P = 0.72$ and $P = 0.42$, respectively).

Questionnaires

Short form. The Short Form-36 (SF-36) questionnaire comprises 36 items and records general well-being during the previous 30 d (11, 12). The items are formulated as statements or questions to assess eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions and change in health. Because the Hospital Anxiety and Depression Scale (HADS) and the Multidimensional Fatigue Index (MFI-20) (see below) are more specific questionnaires for mental health, vitality and general mental health were left out in this evaluation. Scores are expressed on a 0–100 scale, and higher scores are associated with a better quality of life. Age-related Dutch reference values were derived from the Dutch manual (13).

TABLE 1. Characteristics of 58 patients treated for Cushing's disease and 98 healthy controls

	Patients treated for Cushing's disease (n = 58)	Controls (n = 98)
Age (yr) (mean ± SD)	51.7 ± 15.2	52.5 ± 13.3[a]
Sex (M/F) (n)	10/48	23/75[a]
Preoperative urinary 24-h cortisol excretion (μg/24 h)[b]	518 (58–2542 μg/24 h)	NA
Radiotherapy (%)	11 (19)	NA
Bilateral adrenalectomy (%)	3 (5)	NA
Hypopituitarism (%)	30 (52)	NA
Follow-up (yr) (mean ± SD)	13.4 ± 6.7	NA

NA, Not applicable; M, male; F, female.

[a] Not significantly different from patients treated for Cushing's disease.

[b] Reference range less than 80 μg/24 h. To convert to SI units (nmol/24 h), multiply by 2.75.

Nottingham Health Profile. The Nottingham Health Profile (NHP) is frequently used in patients with pituitary disease to assess general well-being and consists of 38 yes/no questions, which are subdivided in six scales assessing impairments, *i.e.* pain (eight items), energy level (three items), sleep (five items), emotional reactions (nine items), social isolation (five items), and disability/ functioning, *i.e.* physical mobility (eight items) (14, 15). Subscale scores are calculated as a weight mean of the associated items and are expressed as a value between 0 and 100. The total score is the mean of the six subscales. A higher score is associated with a worse quality of life. Age-related West European reference values were derived from the paper by Hinz *et al.* (16).

MFI-20. The MFI-20 comprises 20 statements to assess fatigue, which are measured on a five-point scale (17). Five different dimensions of fatigue (four items each) are calculated from these statements: 1) general fatigue; 2) physical fatigue; 3) reduced activity; 4) reduced motivation; and 5) mental fatigue. Scores vary from 0–20, a high score indicating higher experienced fatigue. Age-related Dutch reference values were derived from the study by Smets *et al.* (18).

HADS. The HADS consists of 14 items pertaining to anxiety and depression, which are measured on a four-point scale. Scores for the anxiety and depression subscale range from 0–21 and for the total score from 0–42. Higher scores indicate more severe anxiety or depressive symptoms, with a total score more than 13 indicating major depression (19). Dutch reference values of the general population were derived from the paper by Spinhoven *et al.* (20).

Statistics

SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL) was used to perform data analysis. Data were expressed as mean ± SD unless otherwise mentioned. We used unpaired *t* tests and χ^2 tests to compare patient and control data and different patients groups. Independent variables affecting quality of life were explored by stepwise linear regression analysis. Literature reference data used were weighted means according to the age distribution in our patient cohort.

Results

Patient characteristics (Table 1)

Clinical characteristics of the patients are detailed in Table 1. Transsphenoidal surgery was performed as an initial treatment in all 58 patients by a single neurosurgeon. Because of

persistent postoperative Cushing's disease, additional treatment was given in the form of radiotherapy in 11 patients and bilateral adrenalectomy in three patients. In the present evaluation, all 58 patients were considered cured according to persistently normal 24-h urinary cortisol excretion and normal overnight suppression of serum cortisol after 1 mg dexamethasone. The mean duration of remission was 13.4 ± 6.7 yr (range of 2–25 yr).

After treatment for Cushing's disease, hypopituitarism, defined as one or more pituitary hormone deficiencies requiring replacement therapy, occurred in 30 (52%) patients [replacement of glucocorticoids in 28 (48%) patients, GH in 13 (22%) patients, thyroxine in 21 (36%) patients, testosterone in 1 (10%) of 10 male patients, estrogen in 7 (25%) of 28 premenopausal women, 1-disamino-β-D-arginine vasopressin in 11 (19%) patients, and fludrocortisone in the 3 (5%) patients after bilateral adrenalectomy]. Twenty-two (38%) patients had multiple hormone deficiencies, from which 16 (27%) patients had panhypopituitarism. From 11 patients who underwent radiation therapy, five (45%) had deficiency of one or more pituitary hormones, and six (55%) had normal pituitary function.

General perceived health in patients treated for Cushing's disease and controls (Fig. 1 and Table 2)

Compared with our own controls, patients treated for Cushing's disease had a reduced quality of life as judged by all questionnaires and all assessed items (Fig. 1). This finding was consistent between the comparable items of different questionnaires, reflected in highly significant correlations between those items (data not shown). According to the SF-36, we observed reduced physical and social functioning, limitations in role functioning due to both emotional and physical problems, increased pain, and a decreased general well-being. The corresponding items of the NHP supported these findings, and also the sleep score was significantly worse in patients treated for Cushing's disease compared with controls. All subscales of fatigue as assessed using the MFI-20 were affected, especially general fatigue, physical

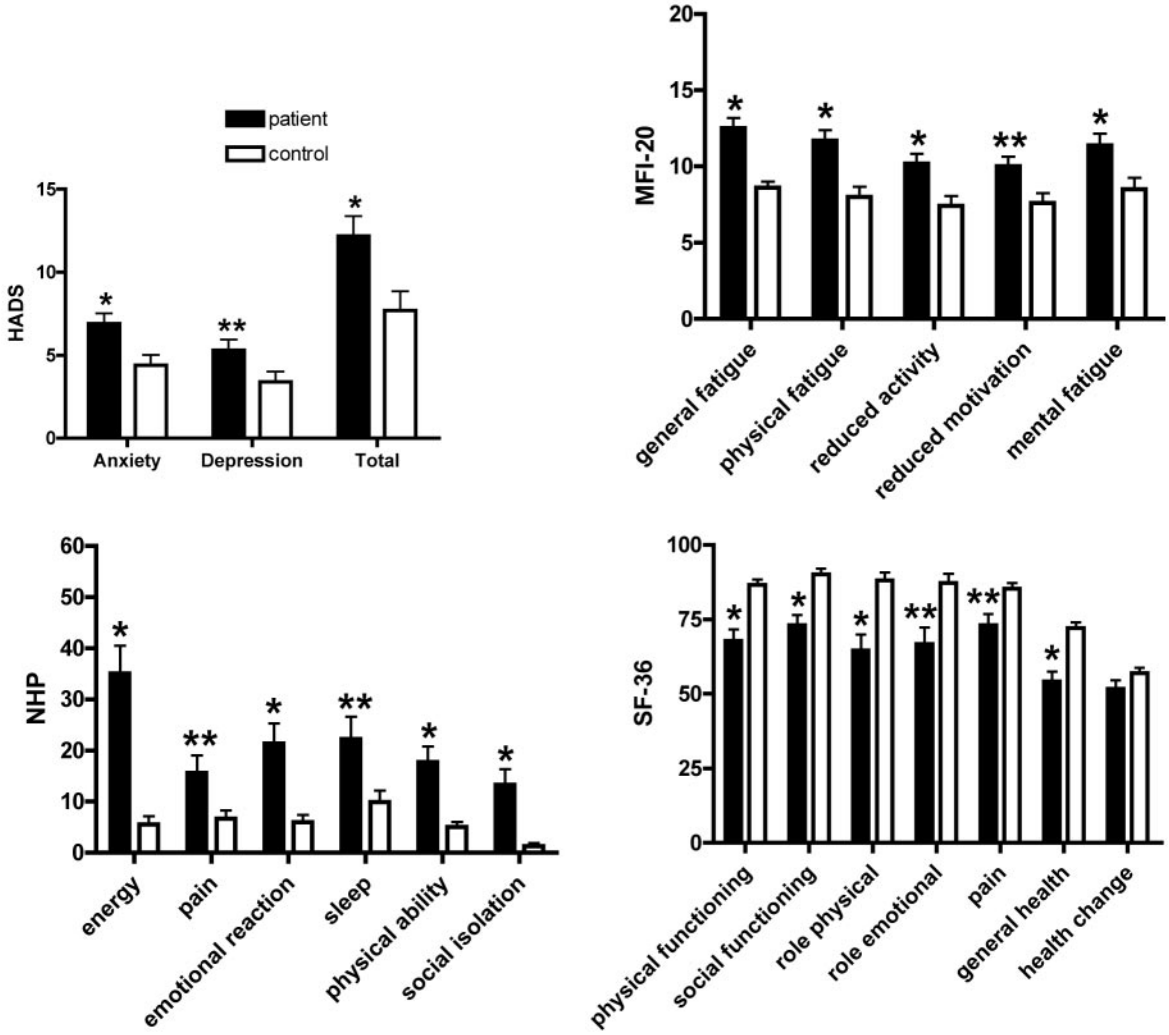

FIG. 1. Quality of life in patients cured from Cushing's disease (n = 58; *black bars*) and healthy controls with the same age and sex distribution (n = 98; *white bars*), according to HADS, MFI-20, NHP, and SF-36. Comparisons showing significant differences between patients and controls are shown by *asterisks*: *, $P < 0.001$ patients *vs.* controls; **, $P < 0.01$ patients *vs.* controls.

TABLE 2. Summary of quality of life assessments between patients treated for Cushing's disease and age-adjusted reference values from the literature

Questionnaire	Patients treated for Cushing's disease (n = 58)	Age-adjusted reference values from literature	*P* value Cushing *vs.* literature reference
SE-36			
Physical functioning	68 ± 29	79 ± 22	<0.05
Social functioning	73 ± 26	87 ± 21	<0.001
Role limitations due to physical problems	65 ± 41	77 ± 37	<0.05
Role limitations due to emotional problems	67 ± 42	84 ± 32	<0.01
Bodily pain	73 ± 28	80 ± 25	NS
General health perception	54 ± 25	69 ± 22	<0.001
Change in health	52 ± 22	51 ± 19	NS
NHP			
Energy	35 ± 40	14 ± 26	<0.001
Pain	16 ± 26	8 ± 18	<0.05
Emotional reaction	21 ± 30	9 ± 16	<0.01
Sleep	22 ± 32	16 ± 25	NS
Physical ability	18 ± 22	7 ± 14	<0.001
Social isolation	13 ± 24	6 ± 16	<0.05
MFI-20			
General fatigue	13 ± 5	10 ± 5	<0.01
Physical fatigue	12 ± 5	9 ± 5	<0.01
Reduced activity	10 ± 5	9 ± 5	NS
Reduced motivation	10 ± 5	8 ± 4	<0.02
Mental fatigue	11 ± 6	8 ± 5	<0.001
HADS			
Anxiety	7 ± 5	5 ± 4	<0.01
Depression	5 ± 5	4 ± 3	<0.02
Total	12 ± 9	8 ± 4	<0.01

Data shown are mean ± SD. Reference values are weighted means according to the age distribution in our patient cohort. Dutch or West European reference data were retrieved from the literature (n, number of subjects). SF-36, van der Zee *et al.* (13) (n = 1063); NHP, Hinz *et al.* (16) (n = 1996); MFI-20, Smets *et al.* (18) (n = 139); HADS, Spinhoven *et al.* (20) (n = 2100). NS, Not significant.

and mental fatigue, and activity level. According to the HADS, both anxiety and depression scores were significantly higher compared with controls.

Comparing the data obtained in our patients cured for Cushing's disease with Dutch or West European age-adjusted mean reference values available from the literature (Table 2), quality of life was reduced in patients treated for Cushing's disease according to all questionnaires and all items, except pain (SF-36), sleep (NHP), and reduced activity (MFI-20).

Factors affecting quality of life in patients treated for Cushing's disease

Gender. Female patients treated for Cushing's disease scored worse compared with male patients on several fatigue scales: reduced activity (11.2 ± 4.8 *vs.* 5.5 ± 1.4; $P = 0.001$), reduced motivation (10.9 ± 4.8 *vs.* 5.5 ± 2.0; $P = 0.001$), and mental fatigue (12.4 ± 5.6 *vs.* 6.8 ± 3.8; $P = 0.004$). Accordingly, in the NHP, energy was reduced in female patients (40.0 ± 41 *vs.* 12.4 ± 21.7; $P = 0.006$).

Age. In patients treated for Cushing's disease, there was an association of increasing NHP scores (and thus decreased quality of life) with increasing age for sleep (NHP, R = 0.396; $P = 0.002$) and physical ability (NHP, R = 0.471; $P < 0.001$). In the SF-36, a decreasing score (and thus impaired quality of life) with advancing age was seen for physical functioning (SF-36, R = −0.367; $P = 0.001$). In the other questionnaires, no age trends were observed.

In our control subjects, age was also associated with decreased quality of life for several items, including in the NHP for pain, sleep, and physical mobility and in the SF-36 for physical functioning.

Severity of disease (24-h urinary cortisol excretion). Severity of hypercortisolism, assessed by 24-h urinary cortisol excretion before treatment, did not correlate to any of the quality of life scales. In addition, we did not find a relationship between the interval since cure of Cushing's disease and any item of quality of life.

Radiotherapy

Patients who underwent radiotherapy as a part of treatment of Cushing's disease did not report worse quality of life scores compared with patients who had no irradiation.

Hypopituitarism. The presence of any degree of hypopituitarism, defined as one or more pituitary hormone deficiencies requiring replacement therapy, did affect quality of life in this cohort, as evidenced by significant differences in several assessed questionnaires (Fig. 2). In the HADS, patients with hypopituitarism showed worse scores for anxiety, depression, and total scores, whereas patients without hypopituitarism had similar scores compared with controls. Similarly, in the MFI-20, patients with hypopituitarism had impaired quality of life for all items, whereas patients without hypopituitarism only scored worse for general fatigue. In the NHP, however, the influence of hypopituitarism was less pronounced. Patients with normal pituitary function scored worse on all items except pain and sleep compared with controls. The same was also true for the SF-36, in which the presence of hypopituitarism only influenced scores for emotional role, pain, and general health. Patients with multiple

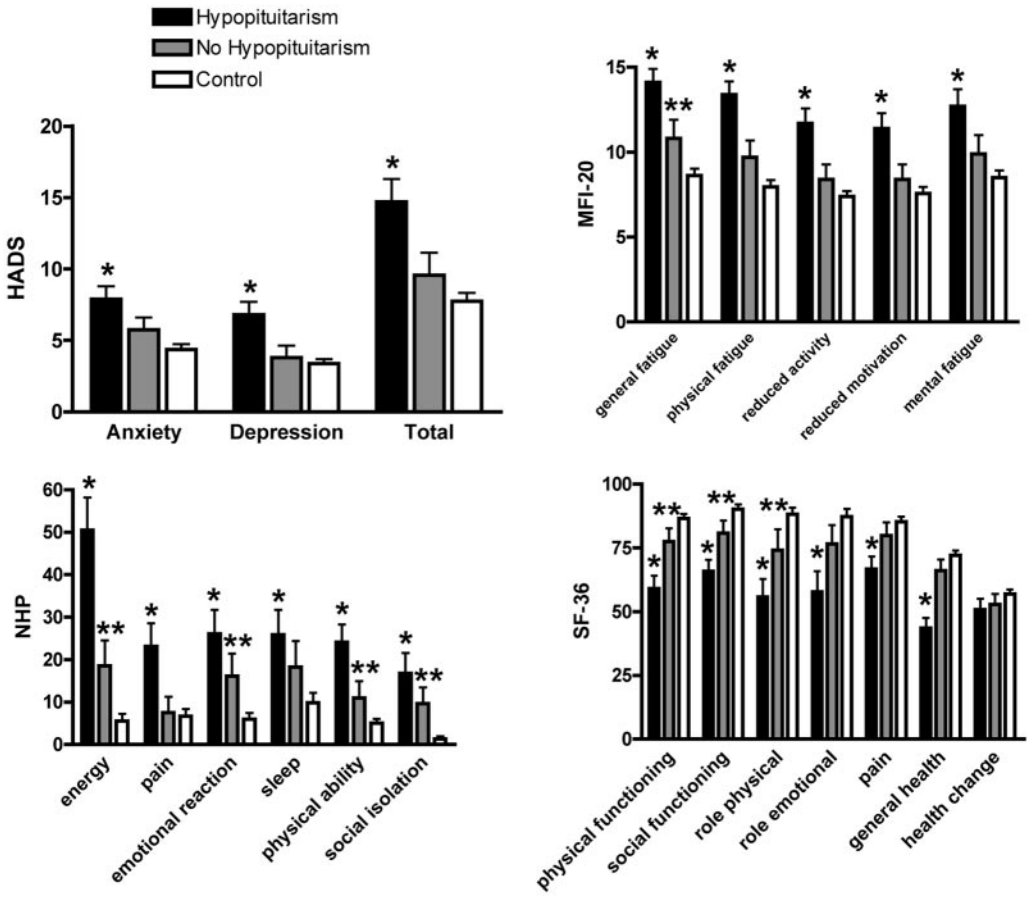

FIG. 2. Quality of life in patients cured from Cushing's disease with hypopituitarism (n = 28; *black bars*) and without hypopituitarism (n = 30; *gray bars*) and healthy controls with the same age and sex distribution (n = 98; *white bars*), according to HADS, MFI-20, NHP, and SF-36. Comparisons showing significant differences between patients and controls are shown by *asterisks*: *, $P < 0.05$ patients with hypopituitarism *vs.* controls; **, $P < 0.05$ patients without hypopituitarism compared with controls.

hormone deficiencies or panhypopituitarism did not have worse quality of life scores compared with patients with one hormone deficiency.

Linear regression analysis. Stepwise univariate linear regression analysis was performed in a model including age, age at time of diagnosis, gender, severity of hypercortisolism (reflected by 24-h urinary cortisol excretion before treatment), applied radiotherapy, treatment for hypopituitarism, duration of cure, and presence of depression/anxiety symptoms as independent variables and the questionnaire items as dependent variable. Age was a significant independent predictor of change in health (SF-36) and of sleep, physical mobility, and total score of the NHP. Age at diagnosis negatively influenced physical functioning and physical role limitations (SF-36), with a positive effect on change in health (SF-36). Male patients showed a better score on motivation and activation compared with female patients (MFI-20). Patients with hypopituitarism had worse scores on physical function and general health scales (SF-36), physical fatigue and reduced activation scales (MFI-20), and energy and pain scales of the NHP. Remarkably, duration of cure did not affect any of the quality of life parameters. Anxiety and depression scores according to the HADS significantly influenced the scores on the other quality of life questionnaires. Thus, age, age at diagnosis, gender, HADS score, and especially hypopituitarism are independent determinants of quality of life after successful treatment of Cushing's disease.

Discussion

The results of the present study demonstrate that, in patients successfully treated for Cushing's disease, several aspects of quality of life are reduced, especially items concerning fatigue and physical ability. Despite conventional hormone replacement therapy, the presence of hypopituitarism in these patients has a strong negative influence on quality of life, whereas patients with intact pituitary function have a relatively preserved quality of life compared with the normal population. The decreased quality of life perception of various health-related aspects contrasts with the successful and long-term elimination of hypercortisolism in all patients in this study.

The response rate of this study was very high, because 92% of patients chose to participate. Therefore, selection bias is not involved in this study, also because the clinical characteristics of few patients, which could not be included, were not different from the participating patients. The use of a control population of relatives of patients from the outpatient clinic of the department of endocrinology, but chosen by

these patients, may have introduced a bias because controls with a good quality of life are more likely to being asked. Conversely, the health status of the control population was only checked by asking these subjects about any (recent) diseases. Because of this potential bias, we also report age-adjusted reference data from the literature. The scores reported by our own controls were significantly better than those reported in the literature for age-matched subjects. However, compared with the literature reference populations, patients treated for Cushing's disease still scored worse on all items, except pain (SF-36), sleep (NHP), and reduced activity (MFI-20).

A control population of patients who underwent transsphenoidal surgery for nonfunctioning pituitary tumors could add valuable information, offering the opportunity to further explore the separate effects of hypercortisolism and the effect of transsphenoidal surgery *per se*. However, such a control group would not necessarily have the same pituitary hormone deficits, hindering direct comparisons.

One might argue that a limitation of our study is the use of questionnaires that have not specifically been developed for the measurement of quality of life in patients with (cured) Cushing's disease. In contrast to acromegaly, for which recently a disease-specific questionnaire has been developed (Acromegaly-Quality of Life) (21), there is no disease-specific questionnaire available for Cushing's syndrome. We used questionnaires regarding different aspects of quality of life (physical and mental), validated for West European subjects, with West European reference ranges. Comparable items of different questionnaires showed consistent results, with highly significant correlations between those items. We therefore believe that our study provides a valid assessment of quality of life in our patients treated for Cushing's disease.

Structured quality of life research in patients with active Cushing's disease has been subject to study in only few reports up to now, although this important clinical topic receives increasing attention. Hypercortisolism has been reported to seriously compromise health-related quality of life (22). Compared with patients with other pituitary adenomas, quality of life in patients with active Cushing's disease was most severely affected (23).

Most studies, with a few exceptions, on successful treatment of Cushing's disease have focused on normalization of cortisol secretion and/or clinical outcome parameters rather than on functional recovery. Recently, Lindholm *et al.* (24) evaluated quality of life in 45 patients cured for Cushing's disease using the SF-36 questionnaire. Their results showed significantly impaired quality of health for all items, except for bodily pain and mental health. Similarly, two other studies have shown lower SF-36 scores in patients treated for Cushing's disease by bilateral adrenalectomy (25, 26). In another survey on 74 patients treated for Cushing's syndrome, including 43 patients with Cushing's disease, only 46% reported to feel fully recovered, with 31% not feeling recovered, and 23% to be unsure (27). The present study is the first cross-sectional study to evaluate various physical and psychological aspects of quality of life in patients after long-term biochemical cure of Cushing's disease. Collectively, the data point to the notion that Cushing's disease induces persistent, most likely irreversible, limitations in both physical and mental functioning.

The observation that patients without hypopituitarism were not significantly different from controls on many scores suggests that hypopituitarism plays an important role in the quality of life after treatment of Cushing's disease. However, patients without hypopituitarism showed reduced quality of life on items concerning fatigue and physical functioning, indicating that hypopituitarism does not explain all of the findings of reduced quality of life. Previous studies of patients with pituitary insufficiency have indicated that these patients suffer from suboptimal well-being and impaired psychological functions, despite replacement with adequate doses of conventional hormones, including GH (28–31). Recently, Malik *et al.* (32) confirmed significant impairments in multiple aspects of quality of life, despite replacement with GH and other pituitary hormones for at least 1 yr (mean, 3 yr). Another recent study focused on the effect of GH replacement in 135 hypopituitary patients treated previously for Cushing's disease, showing a modest, nonsignificant increase in quality of life (33). These observations are in agreement with the results in our cohort of patients treated for Cushing's disease, in which the presence of coexistent hypopituitarism had a negative effect on quality of life. This finding might be explained by intrinsic shortcomings of hormone replacement therapy (34) and/or by long-term endocrine withdrawal effects after correction of longstanding hypercortisolism (35).

In the present study, a relatively high percentage of patients had one or more pituitary hormone deficiencies, with almost half of the patients showing long-term glucocorticoid deficiency. According to our protocol, glucocorticoids were tapered off and stopped twice yearly, with subsequent ACTH testing, to detect recovery of the hypothalamic-pituitary-adrenal axis. Although protracted hypothalamic-pituitary-adrenal axis recovery is a well-known phenomenon, the cause of the observed persistent glucocorticoid dependency in a relatively large proportion of our patients is unclear. In view of the general predictable order of pituitary hormone deficiency, the incidence of TSH deficiency in this population is surprisingly high, for which we have no straightforward explanation.

Cushing's syndrome is associated with significant psychopathology during the course of the disease, as shown by a longitudinal study by Dorn *et al.* (2). In active Cushing's disease, 67% of the patients had significant psychopathology. After cure, overall psychopathology decreased significantly to 54% at 3 months, 36% at 6 months, and 24% at 12 months. In our cohort, 26 (45%) patients had a total HADS score larger than 13, indicating depression (19). The discrepancy between patient and physician assessments of medical comorbidity in chronic depression is of note and may relate to the depressed mood (36). This can explain our finding of a significant association between the anxiety and depression scores as assessed with the HADS and all other quality of life scores and reflects the important influence of depression and anxiety symptoms on the experience of all other complaints. Alternatively, but less likely, the HADS could be a sensitive measure of quality of life.

Deficits in cognitive function are another consequence of

chronic exposure to elevated glucocorticoid levels in Cushing's syndrome. Forget *et al.* (37) studied several aspects of cognitive function in patients 1 yr after treatment for Cushing's syndrome. The results showed little change in performance in tests of attention, visuospatial processing, memory, reasoning, and verbal fluency, suggesting that hypercortisolism can cause long-lasting and possibly irreversible deleterious effects on cognitive function and subsequently quality of life.

The observed long-term effect of hypercortisolism on physical and psychological aspects of quality of life has several possible explanations. The brain is a well-recognized target of glucocorticoids. For instance, Lupien *et al.* (38) demonstrated that aged humans with significant prolonged cortisol elevations, but without clinical signs of hypercortisolism, showed reduced hippocampal volume and deficits in hippocampus-dependent memory tasks compared with controls with normal cortisol levels. In addition, early postnatal dexamethasone therapy has been shown to induce substantial adverse effects on neuromotor and cognitive function at school age (39). A recent study in patients with Cushing's syndrome showed that brain volume loss is highly prevalent in Cushing's syndrome and is at least partially reversible after correction of hypercortisolism (40). Therefore, the impaired quality of life after long-term remission of Cushing's disease may be explained by irreversible glucocorticoid-induced changes in the central nervous system. Alternatively, persisting physical impairments or psychological distress of living with a previous disease and treatment might play a role. Finally, long-term endocrine withdrawal effects may have led to irreversible alterations in perceived quality of life (35).

In conclusion, quality of life in patients in long-term remission after treatment for Cushing's disease is reduced compared with controls and literature reference values, assessed by four health-related questionnaires, with both physical and psychological impairments. Especially patients with hypopituitarism had worse quality of life scores, despite conventional hormone replacement therapy.

Acknowledgments

Received July 15, 2004. Accepted February 22, 2005.

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