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

M. O. van Aken, A. M. Pereira, N. R. Biermasz, S. W. van Thiel, H. C. Hoftijzer, J. W. A. Smit, F. Roelofsema, S. W. J. Lamberts, and J. A. Romijn

Department of Endocrinology (M.O.v.A., A.M.P., N.R.B., S.W.v.T., H.C.H., J.W.A.S., F.R., J.A.R.), Leiden University Medical Center, 2300 RC Leiden, The Netherlands; and Erasmus Medical Center (S.W.J.L.), 3000 DR Rotterdam, The Netherlands

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)
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 T4 and testosterone (male patients). If results informed consent before enrollment in the study.

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 to recruit a healthy relative with the same sex and a similar age to participate in this study. Second, Dutch or West European medical center of the Department of Endocrinology of the Leiden University Medical Center to recruit a healthy relative with the same sex and age-adjusted mean reference values were collected from the literature for all four questionnaires.

Statistical analyses were performed by using commercially available software (SPSS, Chicago, IL). The significance level was set at 0.05. Descriptive statistics were used to determine means, SDs, and ranges. Differences in characterisitcs between patients treated for Cushing’s disease and 98 healthy controls were evaluated by Student’s t-test for independent samples. The Pearson χ2-test was used to test for differences in frequencies of categorical variables. The differences between the groups were considered statistically significant if the two-tailed probability of the χ2-test was less than 0.05.

### Results

**Patients 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

| 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* |
| Sex (M/F) (n) | 10/48 | 23/75* |
| Preoperative urinary 24-h cortisol excretion (μg/24 h)b | 518 (58–2542 μg/24 h) | NA |
| Radiotherapy (%) | 11 (19) | NA |
| Bilateral adrenalecotomy (%) | 3 (5) | NA |
| Hypopituitarism (%) | 30 (52) | NA |
| Follow-up (yr) (mean ± SD) | 13.4 ± 6.7 | NA |
| **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.** | | |

### Table 1. Characteristics of 58 patients treated for Cushing’s disease and 98 healthy controls

- **Age (yr)**: Mean age of patients was 51.7 years with a standard deviation of 15.2 years. Controls had a mean age of 52.5 years with a standard deviation of 13.3 years.
- **Sex (M/F)**: There were 10 males and 48 females in the patient group, compared to 23 males and 75 females in the control group.
- **Preoperative Urinary 24-h Cortisol Excretion**: Mean cortisol excretion was 518 μg/24 h in patients, whereas controls had values not provided.
- **Radiotherapy**: 11% of patients received radiotherapy.
- **Bilateral Adrenalecotomy**: 3% of patients underwent bilateral adrenalecotomy.
- **Hypopituitarism**: 30% of patients had hypopituitarism.
- **Follow-up**: Average follow-up time was 13.4 years.

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### Statistics

SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL) was used to conduct data analysis. Data were expressed as mean ± SD unless otherwise mentioned. We used unpaired t tests and χ2 tests to compare patient and control data and different patient 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
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...
European reference data were retrieved from the literature (n, number of subjects). SF-36, van der Zee reduced activity (11.2 worse compared with male patients on several fatigue scales: Gender. Female patients treated for Cushing’s disease scored Cushing’s disease according to all questionnaires and all factors affecting quality of life in patients treated for Cushing’s disease with Dutch or West European age-higher compared with controls. HADS, both anxiety and depression scores were significantly 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, pain, 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
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 be 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 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 Cush-
ing’s syndrome. Forget et al. (37) studied several aspects of
cognitive function in patients 1 yr after treatment for Cush-
ing’s syndrome. The results showed little change in perfor-
tion tests of attention, visuospatial processing, memory,
reasoning, and verbal fluency, suggesting that hypercorti-
solism can cause long-lasting and possibly irreversible del-
eterious effects on cognitive function and subsequently qual-
ity of life.

The observed long-term effect of hypercortisolism on
physical and psychological aspects of quality of life has sev-
eral possible explanations. The brain is a well-recognized
healthy cell that can undergo harm due to glucocorticoids.
For instance, Lupien et al. (38) dem-
strated that aged humans with significant prolonged cor-
tisol elevations, but without clinical signs of hypercorti-
solism, showed reduced hippocampal volume and deficits in
hippocampus-dependent memory tasks compared with con-
trols with normal cortisol levels. In addition, early postnatal
dexamethasone therapy has been shown to induce substan-
tial 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. Alterna-
tively, persisting physical impairments or psychological dis-
tress 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 re-
mission after treatment for Cushing’s disease is reduced
compared with controls and literature reference values,
assessed by four health-related questionnaires, with both phys-
ical and psychological impairments. Especially patients with
hypopituitarism had worse quality of life scores, despite
conventional hormone replacement therapy.

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Address all correspondence and requests for reprints to:
J. A. Romijn, M.D., Department of Endocrinology, Leiden
University Medical Center, P.O. Box 9600, 2300 RC Leiden, The
Netherlands. E-mail: j.a.romijn@lumc.nl.

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