Urologia Internationalis

Original Paper

Urol Int 2020;104:789–796
DOI: 10.1159/000508765

Received: March 9, 2020
Accepted: May 16, 2020
Published online: July 9, 2020

Impact of Adrenalectomy on Cortisol-Producing Adenoma: Longitudinal Evaluation of Health-Related Quality of Life following Laparoscopic Adrenalectomy

Shogo Inoue Tetsutaro Hayashi Jun Teishima Akio Matsubara

Department of Urology, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan

Keywords
Cortisol · Adrenalectomy · Health-related quality of life · Longitudinal evaluation · Cushing's syndrome

Abstract
Introduction: There is increasing interest in evaluating the quality of life of patients with cortisol-producing adrenocortical adenoma (CPA). Our objective was to assess patient-reported health-related quality of life (HRQOL) in patients with CPA compared to non-CPA. ***Methods:*** Between January 2012 and September 2015, a total of 24 and 62 patients who had laparoscopic adrenalectomy with CPA and non-CPA, respectively, were included in the study. General HRQOL was evaluated on Short Form 8 (SF-8) questionnaire. The SF-8 questionnaire was administered at preoperative baseline and at 3, 6, 9, 12, 18, and 24 months after adrenalectomy. The impact of changing 2 measures of the summary score on the physical component summary (PCS) and mental component summary (MCS) score of SF-8 was evaluated in prospective and longitudinal studies. ***Results:*** The baseline PCS score was significantly lower in the CPA than in the non-CPA group (43.6 vs. 49.0; $p = 0.0075$). Thereafter, the PCS score was significantly lower in the CPA group at 3, 6, 9, and 12 months postoperatively. The PCS score increased in the CPA group with no significant difference between both groups at 18 months (48.1 vs. 50.2; $p = 0.1202$) and 24 months (48.0 vs. 50.8; $p = 0.3625$) postoperatively. However, the baseline MCS score was not significantly different between the CPA and non-CPA group. The MCS score in both groups gradually increased with no significant differences between the groups at any time points after surgery. The PCS score was not significantly improved at all postoperative points than the baseline score in the CPA and non-CPA group. The MCS score was significantly improved than the baseline score from 6 months postoperatively only in the CPA group. ***Conclusion:*** Our research suggests that laparoscopic adrenalectomy may contribute to improving the physical and mental function in HRQOL.

Introduction

Hypercortisolism, which is a characteristic of active Cushing's syndrome (CS), has a negative impact on the health-related quality of life (HRQOL) of the patients [1]. These include not only physical impairments, such as central obesity, muscle weakness and fatigue, bone fractures, and skin abnormalities (including red striae, easy

karger@karger.com
www.karger.com/uin

Shogo Inoue
Hiroshima University Graduate School of Biomedical Sciences
1-2-3 Kasumi, Minami-ku
Hiroshima 7348551 (Japan)
inosyogo@hiroshima-u.ac.jp

bruising, thinning, and ulcerations) but also psychological problems, such as depression, emotional distress, anxiety, and bad memory. Surgical treatment with or without additional medications can help control hypercortisolism; however, often the signs and symptoms of active hypercortisolism are not completely eliminated. This applies to CS of any etiology and determines the persistent impairment of HRQOL despite endocrinological "cure" [2].

Quality of life (QOL) is a patient-reported outcome measure that can be assessed on a general, disease-generated, or specific questionnaire. It provides the assessment of an individual patient's health, including awareness of physical, emotional, psychological, and social health problems. Disease-generated questionnaires tend to be more sensitive in identifying posttreatment changes, but cannot be used with normal subjects or other diseases. However, general questionnaires are also effective for investigating the QOL of populations for various diseases or normal subjects [3].

Suffering from CS has been shown to adversely affect physical and psychological health aspects, even after endocrine "cure" and, thus, adversely affects HRQOL [1, 4, 5]. For patients with CS to improve long-term prognosis and QOL, early detection of hypercortisolism to reduce long-term diagnosis and effective treatment is essential [2]. To properly manage comorbidities such as diabetes, hypertension, and dyslipidemia, the current guidelines are also strongly recommended life-long evaluation with periodic tests and clinical evaluations, even in the long term after remission [3].

There is increasing interest in evaluating the QOL of patients with cortisol-producing adrenocortical adenoma (CPA). However, the lack of well-defined QOL concepts and potential confounders poses challenges to the interpretation and validity of the data. To our knowledge, this is the first study of a longitudinal analysis of HRQOL comparing CPA and non-CPA. Therefore, the primary objective of this study was to evaluate the patient-reported HRQOL of CPA compared to non-CPA. The purpose of this study was to compare the results of adrenalectomy in patients with CPA or non-CPA to determine whether adrenalectomy improves HRQOL.

Patients and Methods

Patients

Between January 2012 and September 2015, a total of 24 and 62 patients who had laparoscopic adrenalectomy for CPA and non-CPA, respectively, were included in this study. Indication for laparoscopic adrenalectomy included hormone secreting tumors and nonfunctioning tumors larger than 4 cm. We excluded from this study patients with malignant (i.e., adrenocortical carcinoma and metastatic adrenal carcinoma) and bilateral adrenal diseases.

Before surgery, all patients underwent a complete preoperative checkup including anesthesiological counseling for evaluating general performance status and endocrine study with complete hormonal tests to identify functioning adrenal tumors by the endocrine specialists team. For the diagnosis of CPA, hormonal tests including reduced cortisol suppression after 1-mg overnight dexamethasone suppression test (1-mg DST), low morning ACTH levels, high 24-h urinary-free cortisol, and high midnight serum cortisol levels were carried out in all patients for biological diagnosis of CPA by the endocrine specialists team. In addition, imaging examinations such as computed tomography or magnetic resonance imaging scanning and ^{131}I-19-norcholesterol adrenocortical scintigraphy were performed for radiological diagnosis of CPA.

All the included patients underwent postoperative hydrocortisone supplementation treatment following the institutional supplementation protocol by the endocrine specialists team: starting in the operating room just before gland removal operation, 100 mg intravenously (IV) on operation day and postoperative day 1, 50 mg IV 3 times every 6 h from first injection and postoperative day 2, and hydrocortisone 20 + 10 mg/day. Additional IV doses were administered if needed. Postoperative supplementation was then tapered progressively by the endocrinology specialist team on the basis of clinical and laboratory findings.

General HRQOL was evaluated on a Short Form 8 (SF-8) questionnaire. The SF-8 questionnaire was administered at preoperative baseline and at 3, 6, 9, 12, 18, and 24 months after adrenalectomy. The impact of changing 2 measures of the physical component summary (PCS) and mental component summary (MCS) scores of SF-8 were assessed in prospective and longitudinal studies.

Measures

We used validated HRQOL instruments to assess recovery. The SF-8 has been widely accepted as a useful tool in monitoring the health status of large patient populations. We selected the SF-8 for this study because of its relative simplicity and minimal time burden on the participant [6]. The physical component score of SF-8 assessed subjects' limitations in physical function. The mental component score was evaluated through 4 questions that estimate mental health [7].

HRQOL was evaluated using the SF-8 questionnaire. The survey consists of 8 domains that measure health status with each item being scored on a 5- or 6-point scale. SF-8 is composed of 8 subscales: PF (physical functioning), RP (role limitation due to physical problems), BP (body pain), GH (general health), VT (vitality), SF (social functioning), RE (role limitation due to emotional problems), and MH (mental health). In addition, there are 2 summary scores: PCS score and MCS score. The reliability and validity of this scale have been previously confirmed [8].

The research protocol was approved by the Institutional Review Board of Hiroshima University Hospital (IRB No. 434-1). Informed consent has been confirmed by the IRB.

Surgery

Under general and epidural anesthesia, the patient was placed in a modified 60° flank position, and the surgeons were standing facing the abdomen. Open laparotomy was performed, and insufflation

Table 1. Patient characteristics

	CPA (n = 24)	Non-CPA (n = 62)	p value
Mean age (range), years	55.8 (27–78)	49.6 (32–76)	0.054
Gender (male:female), n	12:12	28:34	0.687
Laterality (right:left), n	11:13	27:35	0.848
Mean BMI (range)	23.6 (15.4–39.7)	24.3 (19.1–29.7)	0.542
Procedure (LESS:conventional), n	20:4	47:15	0.441
Mean operative time (range), min	111.0 (61–234)	113.8 (65–181)	0.722
Mean estimated blood loss (range), mL	27.6 (0–100)	54.5 (5–1,090)	0.402
Mean period of steroid hormone replacement (range), months	11.1 (4–18)		
Preoperative diagnosis			
CS	11	–	
SCS	13	–	
Primary aldosteronism	–	39	
Pheochromocytoma	–	12	
Nonfunctional adenoma	–	11	

CPA, cortisol-producing adrenocortical adenoma; LESS, laparoendoscopic single-site surgery; CS, Cushing's syndrome; SCS, subclinical CS.

Table 2. Mean SF-8 score between CPA and non-CPA

Category	Baseline	3 months	6 months	9 months	12 months	18 months	24 months
PCS score							
CPA	43.6±1.6	43.3±1.3	42.4±1.9	43.8±1.7	46.2±1.8	48.1±2.0	48.0±2.7
p value	–	0.911	0.644	0.944	0.344	0.151	0.197
Non-CPA	49.0±1.1	49.6±0.9	50.5±1.2	51.1±1.2	51.3±1.1	50.2±1.2	50.8±1.5
p value	–	0.835	0.383	0.197	0.165	0.12	0.367
MCS score							
CPA	43.7±1.8	46.2±1.8	49.6±2.0	50.4±1.6	49.9±2.0	49.4±2.7	50.7±2.9
p value	–	0.272	0.016	0.004	0.015	0.044	0.023
Non-CPA	45.6±1.3	47.4±1.2	48.0±1.3	46.8±1.1	47.1±1.2	48.2±1.7	48.5±1.6
p value	–	0.364	0.212	0.619	0.526	0.261	0.214

SF-8, Short Form 8; PCS, physical component summary; CPA, cortisol-producing adrenocortical adenoma; MCS, mental component summary.

was achieved by CO_2. The Toldt line and typical vascular landmarks (inferior vena cava in right adrenal tumor and renal vein in left adrenal tumor) were dissected and exposed with laparoscopic instruments. In the right adrenal tumor, the right liver lobe was contracted using a snake retractor. The adrenal vein was exposed, clipped with two 5-mm polymer lock clips, and cut. A sealing device was used to complete the adrenal tissue removal. After hemostasis was assured, the entire adrenal tissue was released in the peritoneal cavity. A surgical suction drain had been placed in the surgical port.

Statistical Analysis

The research data were analyzed according to each approach using the χ^2 test and the Mann-Whitney U test. Each analysis performed had 2 tails. For all tests, a p value <0.05 was considered statistically significant. All values were shown as means ± SE (standard error), and the outcome at each interval after surgery was compared with the baseline level using paired t test. The survey data were analyzed using the Mann-Whitney U test in the comparison between CPA and non-CPA groups. The survey data were analyzed by JMP version 10 (SAS Institute, Cary, NC, USA).

Results

Demographic Characteristics

There were no significant intergroup differences in patient characteristics between the CPA and non-CPA groups. The patient's age was higher in the CPA group than in the non-CPA group (55.8 vs. 49.6; p = 0.054). The mean period of steroid replacement was 11.1 (4–18)

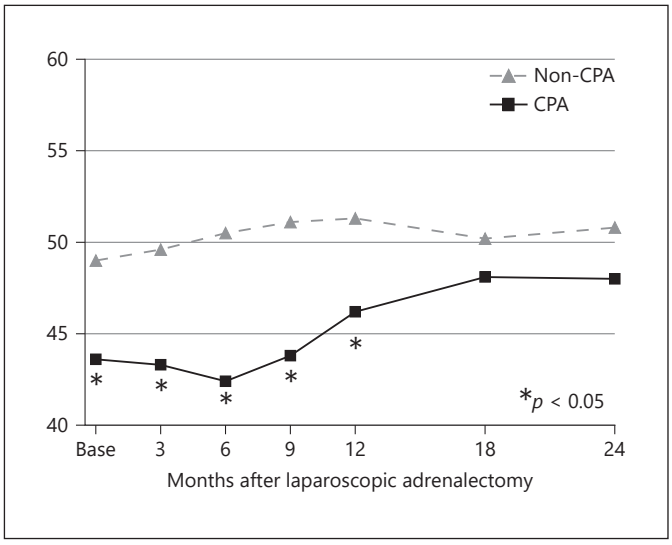


Fig. 1. Change in mean PCS score of SF-8. SF-8, Short Form 8; PCS, physical component summary; CPA, cortisol-producing adrenocortical adenoma. * $p < 0.05$.

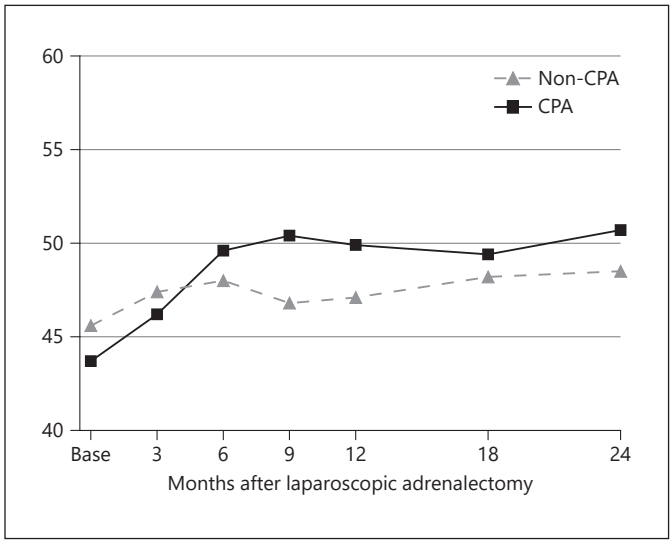


Fig. 2. Change in mean MCS score of SF-8. MCS, mental component summary; CPA, cortisol-producing adrenocortical adenoma; SF-8, Short Form 8.

months in the CPA group (Table 1). According to the CPA disease, the mean period of steroid replacement was 16.2 months in CS and 9.3 months in subclinical CS (SCS); the replacement period tended to be longer in CS than in SCS in our demographic characteristics.

HRQOL (SF-8 Scores)

As shown in Table 2, we compared the PCS and MCS scores at each interval after surgery with the baseline level. The PCS score was not significantly improved at all postoperative points than the baseline score in the CPA and non-CPA groups. By contrast, with the above results, the MCS score was significantly improved from 6 months postoperatively only in the CPA group. On the other hand, the MCS score was not was not significantly improved at all postoperative points than the baseline score in the non-CPA group.

The baseline PCS score was significantly lower in the CPA than in the non-CPA group (43.6 vs. 49.0; $p = 0.0075$). Thereafter, the PCS score was significantly lower in the CPA group at 3 (43.3 vs. 49.6; $p = 0.0002$), 6 (42.4 vs. 50.5; $p = 0.0006$), 9 (43.8 vs. 51.1; $p = 0.0080$), and 12 (46.2 vs. 51.3; $p = 0.0207$) months postoperatively. The PCS score increased in the CPA group with no significant differences between both groups at 18 (48.1 vs. 50.2; $p = 0.1202$) and 24 (48.0 vs. 50.8; $p = 0.3625$) months postoperatively (Fig. 1).

The period of delayed improvement of PCS in the CPA group was assumed to be caused by the period of steroid hormone replacement. After the finish of steroid hormone replacement, the PCS score improved immediately in the CPA group. However, the baseline MCS score was not significantly different between the CPA and non-CPA groups (43.7 vs. 45.6; $p = 0.3957$). The MCS score in both groups gradually increased with no significant differences between both groups at any time points after surgery (Fig. 2).

In the analysis according to each domain, longitudinal analysis revealed that the PF score in the CPA group was significantly lower at baseline (43.4 vs. 48.3; $p = 0.0037$), 3 (44.0 vs. 48.4; $p = 0.0045$), 6 (43.6 vs. 49.8; $p = 0.0028$), and 9 (44.1 vs. 49.8; $p = 0.0055$) months. The RP score in the CPA group was significantly lower at baseline (40.9 vs. 46.7; $p = 0.0187$), 3 (43.0 vs. 48.2; $p = 0.0032$), 6 (42.7 vs. 49.5; $p = 0.0067$), and 9 (42.7 vs. 49.6; $p = 0.0088$) months, which was the same for the PF scores, and these scores were significantly delayed for improvement than the other domains. On the other hand, there was no significant difference between CPA and non-CPA groups in the RE and MH scores at all time points (Fig. 3).

Discussion

CS is caused by prolonged overexposure to cortisol. Chronic cortisol exposure affects almost all tissues of the human body, causing a wide range of symptoms, including hypertension, central obesity, gonadal dysfunction,

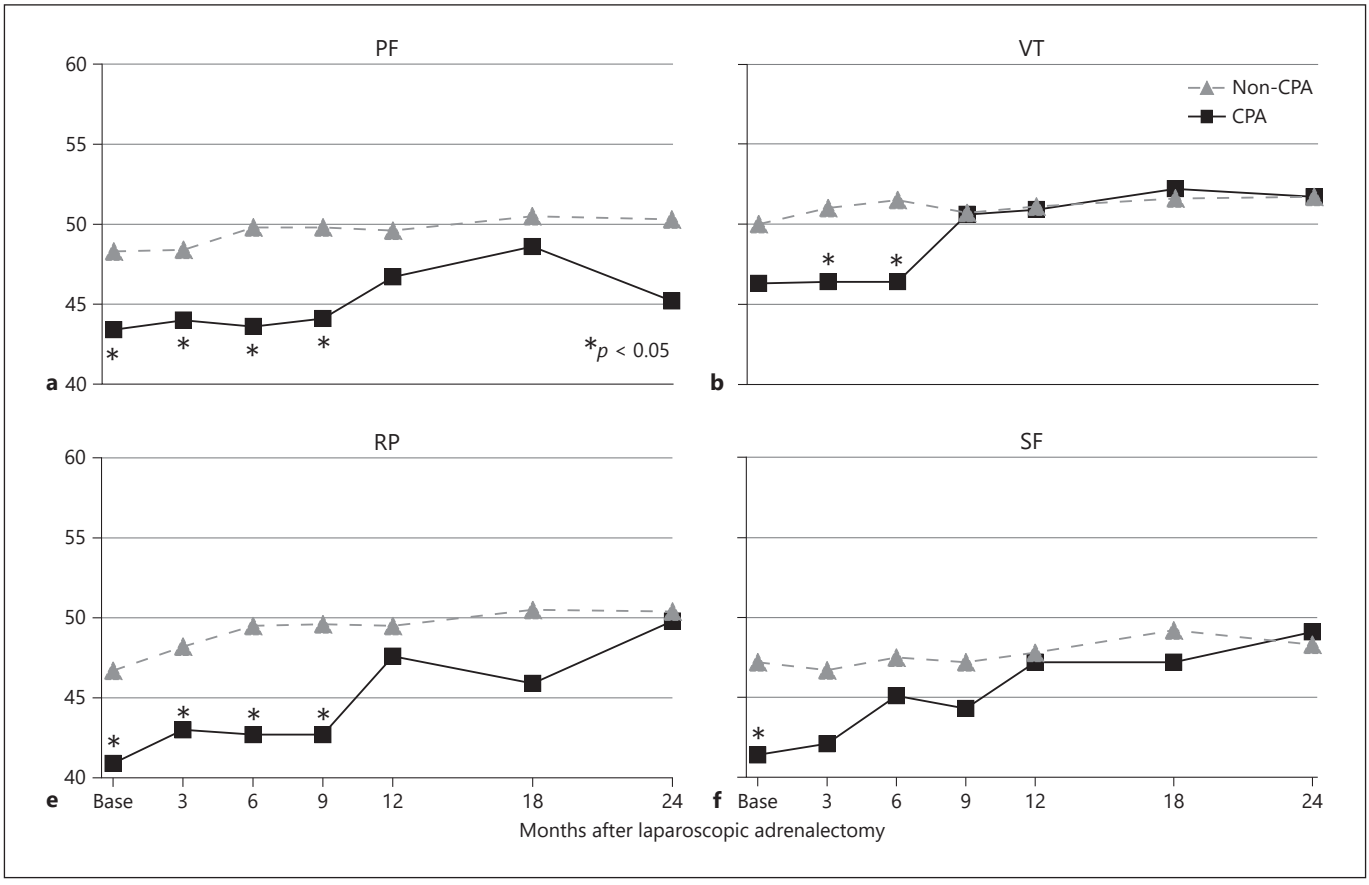


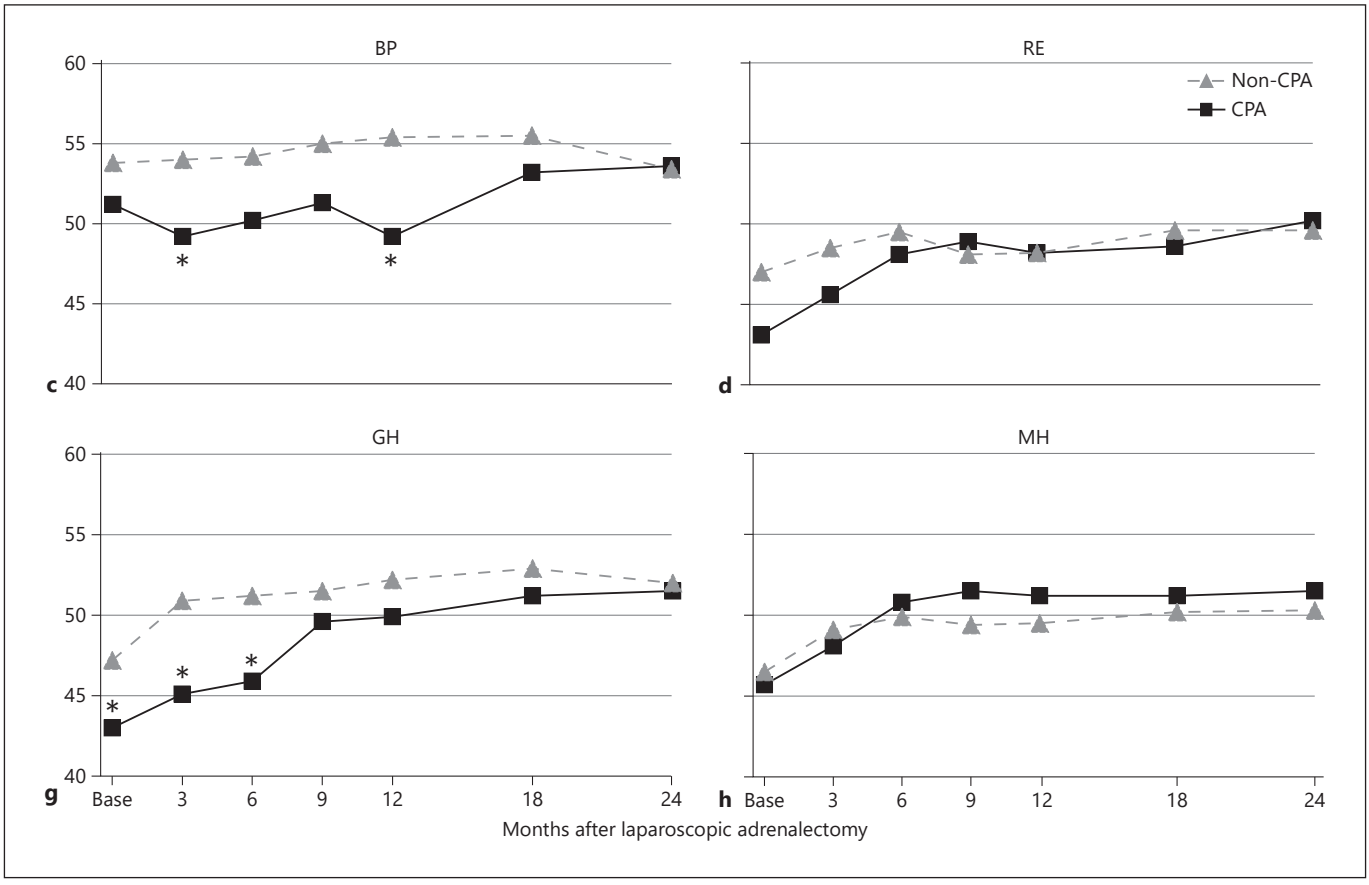
Fig. 3. a–h Change in mean subscale score of SF-8. CPA, cortisol-producing adrenocortical adenoma; SF-8, Short Form 8; PF, physical functioning; VT, vitality; BP, body pain; RE, role limitation due to emotional problems; RP, role limitation due to physical problems; SF, social functioning; GH, general health; MH, mental health. * $p < 0.05$.

(Figure continued on next page.)

muscle weakness, and osteoporosis [9]. Suffering from CS has been shown to negatively affect physical and psychological health aspects, and thus HRQOL, in affected patients, even after endocrine "cure" [3–5]. This evidence was initially evaluated on general questionnaires, such as SF-36 and derived SF-8, and recently on 2 disease-specific measures: the CushingQoL [10, 11] and the Tuebingen CD-25 questionnaires [7]. Because these latter approaches are particularly relevant to CS, the disease-specific measures of QOL are more informative for the dimensions that are particularly relevant to these patients. While these tools and other popular QOL tools reveal the determinants of disease-specific QOL in CS patients and the impact of treatment primarily in observational studies [6, 11], one randomized clinical trial has been performed [12].

Previous chronic exposure to endogenous glucocorticoid (GC) excess due to CS results in the morbidity and mortality associated with complications such as metabolic syndrome, cardiovascular events, bone fractures, muscle weakness, neurocognitive dysfunction, and mental disorders. This chronic exposure has been linked to comorbidities and has been suggested to contribute to poor QOL. Therefore, patients often complain of physical and psychological impairments, such as cognitive changes, depression, loss of self-confidence, and altered cognition of the disease, even after resolution of cortisol excess [13]. All of this leads to incomplete recovery and has a profound effect on QOL over the long term, even after control of cortisol excess [2].

QOL is significantly decreased in active CS and improves with treatment but remains significantly impaired compared to the QOL of the general population despite long-term remission. QOL improves after adrenal or pituitary surgery [1, 4, 5, 7, 10], but this improvement often takes several months or more than a year, and long-term



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disability remains higher when compared to normal healthy people [3]. "Cured" patients have a lower general health status, longer period of depression and anxiety, and lower QOL than healthy controls [1, 4, 5]. This impairment was consistent in all the studies, regardless of etiology, presence of synchronous hormone deficiency, treatment strategy, severity of high cortisol exposure, and time since treatment [14]. QOL was reduced in all forms of hypothalamic-pituitary-adrenal dysregulation but was greatest in CS patients with active hypercortisolemia [14, 15]. Clinical recovery is slower than biochemical recovery, patient-defined recovery takes longer than physician-defined recovery, and there are psychological features that are less likely to improve compared to other CS-related comorbidities [16]. Recognition of psychological problems, cognitive impairments, and negative perception of disease were associated with poor QOL in patients with CS. Mood disorders and cognitive dysfunction occur in 50–80% of patients with active Cushing disease (CD) [17]. Despite remissions defined by biochemical control of the disease after treatment, many patients suffer from poor QOL, fatigue, and cognitive impairment [18].

Mental fatigue is in particular characterized by the mental exhaustion experienced during sensory stimulation or after mentally intensive work [19]. Mental fatigue is common in CS patients in remission. The reason for the irreversibility of posttreatment mental fatigue and cognitive dysfunction in CS patients are still unknown to date [9]. Compared to patients treated for nonfunctioning pituitary tumors, patients who remit with CD worsened in terms of specific executive functions and memory and reported higher psychopathological prevalence [20]. This indicates that the effects of previous hypercortisol on cognitive function and on the central nervous system generally are irreversible. Interestingly, our results indicated that the MCS score was significantly improved from 6 months postoperatively in the only CPA group. These findings may induce the significance of laparoscopic adrenalectomy in the patients with CPA.

Obesity is a characteristic of CS, but the SF-36 survey and symptom questionnaires have confirmed differences

in QOL between both diseases [14]. Obese patients, mainly women with a mean age of 40–50 years, have a higher mean PCS score and worse mean MCS score than normal patients with CS. Although the presence of CS symptoms worsened the PCS and MCS scores, obese patients showed a surprisingly worse mental health score than the normal CS patients. Obesity was associated with PCS, but not CS, and no group was associated with MCS. The predictors of worse QOL in CS include delayed diagnosis of CS [21], pessimism, neurosis, and low extraversion [22]. In contrast, lower age, lower baseline QOL score, and treatment by specialists with CS knowledge are expected to improve postoperative QOL [19].

After successful treatment, some improvement is usually observed, but it often takes several months or more than a year. Physical appearance, partner or family problems, poor work or school performance, and helplessness often lead to depression and a poor perception of QOL [13]. In addition, it may be difficult to find the lowest possible GC replacement dose to maintain satisfactory health after successful surgery and promote endogenous recovery of adrenal axis inhibition. Sustained adrenal insufficiency requiring replacement therapy has been found to be associated with cognitive deterioration [23]. CS patients in remission experience mental fatigue and impaired executive function, independent of the etiology of CS, radiation therapy, and GC replacement therapy. In our study, the PCS score was not significantly improved at all postoperative points than the baseline score in both CPA and non-CPA groups. On the other hand, the PCS score increased from 18 months postoperatively in the CPA group compared with the non-CPA group. It was hypothesized that the period of delay in PCS improvement in the CPA group was reflected by the period of steroid hormone replacement.

Increasing numbers of patients have been diagnosed with adrenal incidentaloma due to the prevalence of CT imaging (about 4% of the population over 60 years) [24]. Although most of these adenomas are nonfunctioning, autonomic ACTH-independent cortisol hypersecretion that alters the normal hypothalamic-pituitary-adrenal axis can be present in up to 30% of patients [25]. This subtle hypercortisolism may clearly be insufficient to achieve the classic clinical signs and symptoms of CS and has been defined as SCS [13]. SCS is, by definition, not associated with signs and symptoms characteristic of overt cortisol excess [26], but this condition may be associated with the same long-term effects of cortisol excess such as obesity, diabetes, hypertension, dyslipidemia, and osteoporosis [17, 27]. Although surgery is the determinative treatment for clinically active CS, the most relevant treatment for patients with adrenal incidentaloma is controversial [18].

Our study has some limitations. Although the patients were enrolled prospectively, there were no significant differences between both groups in patient characteristics. Randomized trials are needed to evaluate the longitudinal analysis of HRQOL over a period of 10 years or more. Second, we longitudinally investigated HRQOL using SF-8. This has the advantage of being a simple questionnaire but has the disadvantage of being unreliable. Although SF-36 is a general questionnaire, it has previously been shown to be useful in assessing post-adrenalectomy outcomes for clinically apparent CS [28]. Third, the cohort of the non-CPA group consists of various diseases including primary aldosteronism and pheochromocytoma. There were only 11 cases (18%) of nonfunctional adenoma in the non-CPA group. Fourth, the patient's age tended to be higher in the CPA group than in the non-CPA group; there is no significant difference between both groups (55.8 vs. 49.6; $p = 0.054$). Netuveli et al. [29] investigated the impact of aging on QOL. They found a QOL increase from 50 to 68 years, followed by a progressive decline. It may be difficult to determine the precise evaluation of QOL score between the groups that were not matched in patient's age.

Finally, we found that for adrenalectomy, according to the longitudinal SF-8 study, physical factors led to a significant improvement in the patient's subjective perception of HRQOL in the patient with CPA than non-CPA. Besides, our results indicated that there was no significant difference in the mental factors between the patients with CPA and non-CPA. However, in the patients with CPA, mental factors were significantly improved than the baseline score from postoperative 6 months.

Conclusion

This study is the first comprehensive longitudinal analysis of patient-reported HRQOL before and after adrenalectomy in the patients between CPA and non-CPA. We discussed and focused on the impact of laparoscopic adrenalectomy on the improvement of HRQOL. In longitudinal analysis of postoperative change of HRQOL between CPA and non-CPA groups, patients with CPA had an improved physical and mental component score postoperatively in the different tendency. Our study suggests that laparoscopic adrenalectomy may contribute to improve HRQOL in both physical and mental function.

Statement of Ethics

This study complies with the guidelines for human studies and is in accordance with the World Medical Association Declaration of Helsinki. Subjects gave their written informed consent. The study protocol was approved by the institute's committee on human research. The research protocol was approved by the Institutional Review Board of Hiroshima University Hospital (IRB No. 434-1). Informed consent has been confirmed by the IRB. Ethical approval was not required, as the evaluation was made by questionnaires. Informed consent was obtained from all individuals participating in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Shogo Inoue: author, project development, data collection, and data analysis. Tetsutaro Hayashi: data management. Jun Teishima: data analysis and project development. Akio Matsubara: project development.

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