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Title: Health-related quality of life and fatigue in patients with adrenal incidentaloma

Running title: QoL in adrenal incidentaloma patients

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Abstract

Objective: The objective of the present study was to examine several dimensions of quality of life (QoL) and fatigue in patients with adrenal incidentaloma. *Research methods and procedures:* This was a case-control study designed to analyze patient outcomes using three validated generic QoL questionnaires, EQ-5D, SF-36 and MFI-20, the results of which were compared to those obtained for age- and sex-matched controls. The study population comprised 139 consecutive patients with nonfunctioning adrenal masses (104 females, 35 males; age 59.1±10.8) and 139 age- and sex-matched controls. *Results:* Reduced QoL was found in patients with adrenal incidentaloma as compared to controls. Dimensions of QoL that were notably affected included mobility (p=0.03), performance of usual activities (p=0.002) and anxiety/depression (p=0.04) as evaluated using the EQ-5D; physical functioning (p<0.001), physical role (p<0.001), general health (p<0.001), vitality (p=0.001), social functioning (p=0.001) and emotional role (p<0.001) as evaluated using the SF-36; and physical fatigue (p=0.04) as assessed using the MFI-20 questionnaire. In addition, perceived health on a visual analogue scale was also significantly lower in patients than in controls (64.8±19.2 vs. 77.1±15.1; p<0.001). *Conclusion:* Patients with adrenal incidentaloma reported reduced QoL and a higher level of physical fatigue compared to age- and sex-matched controls. This subject will benefit from further studies comparing QoL outcomes of laparoscopic adrenalectomy vs. no treatment in patients with adrenal incidentaloma.

Key words: adrenal incidentaloma, quality of life, subclinical Cushing's syndrome, EQ-5D, SF-36, MFI-20

Introduction

Adrenal incidentalomas are clinically inapparent adrenal masses discovered incidentally during diagnostic management for other clinical conditions. In the last few decades, improvements in imaging techniques and advances in their availability have increased the detection of these tumors among the population, making the management of these tumors an important aspect of health care. Adrenal tumors are found in 3% of persons older than the age of 50, as determined in autopsy studies (1). Another study reported that adrenal adenomas were found in up to 10% of patients who died without any premortem suspicion of adrenal disease (2).

Although adrenal incidentalomas are usually benign tumors, several studies have demonstrated that they can be associated with poor health outcomes. A study by Terzolo et al. (3) showed that subclinical Cushing's syndrome in patients with adrenal incidentaloma was associated with an increased risk of metabolic syndrome. Another study reported increased cardiovascular risk profiles as well as an increased frequency of atherosclerotic plaques in these patients (4). Finally, a few studies have demonstrated lower bone mineral densities in patients with adrenal incidentaloma as compared with healthy controls (5, 6).

In view of these data, the effect of adrenal incidentaloma on subjective well-being is of great interest. The present study, therefore, examined patient outcomes using three generic, validated, quality-of-life (QoL) questionnaires: EuroQol (EQ-5D), Short Form 36 (SF-36) and Multidimensional Fatigue Index (MFI-20). The patients' answers were compared with those of age- and sex-matched controls.

Current recommendation consider adrenalectomy if the adrenal mass is 4 cm or greater in diameter, if the mass enlarges significantly during the period of observation, or if there is evidence of autonomous hormonal secretion (7). However, with this study we propose that the treatment decision should not be based solely on tumor size and hormone status but also on patients' QoL.

Materials and Methods

Patients

The study population comprised 139 consecutive patients in whom adrenal masses were discovered incidentally (104 females, 35 males; age: 59.1±10.8 years). Patients were recruited in the period between September 2008 and November 2009 from the outpatient clinic of the Department of Endocrinology, University Hospital of Zagreb, which is the Croatian referral center for adrenal gland disorders. All patients have been examined and interviewed by a single endocrinologist (DK). Patients diagnosed with pheochromocytoma, aldosteronoma, overt Cushing's syndrome, adrenal carcinoma and adrenal gland metastases were excluded. Before entering the study, each patient signed an informed consent form. The Local Ethics Committee approved the study.

Among the patients examined, 111 (79.9%) had unilateral adrenal masses, whereas both glands were affected in 28 (20.1%) patients. Tumors smaller than 4 cm in diameter were found in 118 (84.9%) patients, and tumors larger than 4 cm were found in 21 (15.1%) patients. In 46 (33.1%) patients adrenal incidentaloma was found by abdominal ultrasound during routine annual checkup whereas in 93 (66.9%) patients indication for CT was nonspecific abdominal pain. However, at the time of examination

all patients were free of any symptoms or disease other than hypertension, diabetes and dyslipidemia.

Hypertension, defined as a diastolic blood pressure more than 90 mm Hg or a systolic blood pressure more than 140 mm Hg, was present in 95 (68.3%) patients. Dyslipidemia, defined as an abnormal plasma lipid status, was present in 60 (56.8) patients. Type 2 diabetes mellitus diagnosed using the criteria recommended by the American Diabetes Association (8) was present in 18 (12.9%) patients, and 56 (40.3%) patients had a body mass index (BMI) above 30 kg/m². Eighteen of 139 patients (12.9%) had subclinical Cushing's syndrome (SCS), defined by the presence of two of the following: elevated urinary free cortisol (>379 nmol/24 h), low ACTH level (<2.2 pmol/l) and plasma cortisol level >82.8 nmol/l following 1 mg overnight dexamethasone suppression (9). There were no differences in age, BMI, prevalence of hypertension, dyslipidemia or type 2 diabetes between patients with and without SCS.

For this study, 139 age- and sex-matched control subjects (104 females and 35 males) were recruited among the friends and neighbors of the study personnel. Patients had significantly higher average body mass index (29.2±5.8 vs. 26.4±4.0; p<0.001) and a higher prevalence of hypertension (68.3% vs. 46.0%; p=0.002) than controls, while there was no difference in the prevalence of dyslipidemia (56.8% vs. 46.0%; p=0,072) type 2 diabetes (12.9% vs. 14.4%; p=0,727) or other comorbidities. The clinical and demographic characteristics of patients with adrenal incidentaloma and controls are shown in Table 1.

Serum ACTH, serum cortisol and urine cortisol were measured using an electrochemiluminescence immunoassay on a Cobas E601 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

Questionnaires

Health-related QoL and fatigue were assessed using the EQ-5D, SF-36 and MFI-20 questionnaires. All patients were asked to fill out the questionnaires during their first visit to the endocrinologist. The return rate of questionnaires was 100% (no patient refused to participate).

The EQ-5D is a well-known, generic QoL instrument that has been used in the context of many different diseases. It is a two-part questionnaire comprising five questions that cover five dimensions of health: mobility, self-care, pain/discomfort, usual activity and anxiety/depression. Three possible answers are offered for each item: no problems, some problems or severe problems. The end of the questionnaire includes a self-related global valuation of perceived health using a visual analogue scale graded 0 to 100 (0=worst possible health; 100=perfect health) (10).

The SF-36 consists of 36 items assessing eight domains of QoL: physical functioning (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (RE) and mental health (MH). Scores range from 0 to 100, with higher values representing better QoL (11).

The MFI-20 is a 20-item self-report instrument designed to measure five different dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue (12). General fatigue is an overall indicator of fatigue.

Physical fatigue indicates the physical sensations related to the feelings of tiredness. Reduced motivation and reduced activity concern possible consequences of fatigue, namely, a lack of motivation to start an activity and a decreased level of activity. Mental fatigue relates to cognitive functions such as ability to focus and concentrate. Each dimension of fatigue contains four items that are rated on a five-point Likert scale (range between 4 and 20), where higher scores indicate a higher level of fatigue.

Statistics

The normality of the distributions was tested using Shapiro-Wilk W-test, and the variance homogeneity was tested using Lindman's test prior to the analysis of correlation and between-group differences. Differences between groups with respect to the dependent variables were analyzed using the Wilcoxon matched-pairs test. Differences in the prevalence of individual conditions were compared using the χ^2 test. The differences between groups and the impact of categorical variables were estimated by MANOVA, and continuous variables were controlled for by using MANCOVA. The significance of the correlation between variables and the correlation trend were analyzed by Spearman's rank order correlations test. Statistical significance was defined as $p < 0.05$ in all analyses, which were carried out using SAS (version 9.1.3.).

Results

Patients with adrenal incidentaloma reported reduced QoL and a higher level of physical fatigue compared to age- and sex-matched controls.

Figure 1 summarizes the comparison of the EQ-5D domains between patients with adrenal incidentaloma and controls. Three of the five dimensions of EQ-5D were affected by the presence of an adrenal gland tumor. Significantly more patients than controls reported moderate or extreme problems in mobility (40.3% vs. 28.1%; $p=0.03$), usual activity (41.7% vs. 20.9%; $p=0.002$) and anxiety/depression (60.4% vs. 48.2%; $p=0.04$). There was no significant difference between patients and controls in items related to self-care and pain/discomfort. In addition, perceived health on a visual analogue scale was significantly lower for patients than for controls (64.8 ± 19.2 vs. 77.1 ± 15.1 ; $p<0.001$).

The SF-36 scores in the patients with adrenal incidentaloma and the control group is shown in Table 2. Patients reported reduced QoL, as evaluated using the SF-36 dimensions ($p<0.001$). The difference was significant for physical functioning ($p<0.001$), physical role ($p<0.001$), general health ($p<0.001$), vitality ($p=0.001$), social functioning ($p=0.001$) and emotional role ($p<0.001$). The differences remain significant even after controlling for BMI and the prevalence of hypertension (physical functioning $p=0.008$; physical role $p=0.005$; general health $p<0.001$; social functioning $p=0.04$; emotional role $p<0.001$) except for the difference in vitality which was of borderline significance ($p=0.05$).

No difference in MFI-20 dimensions was found between patients and controls, except for physical fatigue, which was significantly higher in patients ($p=0.04$; Table 3).

The difference remain significant after controlling for BMI and the prevalence of hypertension ($p=0.01$).

In a group of patients with SCS ($n=18$), QoL scores were not different from those reported by other patients with adrenal incidentaloma in any dimension of the EQ-5D, SF-36 or MFI-20 questionnaire (all p 's >0.05).

Discussion

In the last few decades, the management of adrenal incidentaloma has become an important aspect of health care. The treatment decision has been based on hormonal status and the size of the tumor rather than on patients' emotional and functional well-being. Adrenalectomy was considered in patients with functional tumors and in those with nonfunctioning adrenal masses larger than 4 cm (7). Although the clinical and biochemical characteristics of inapparent adrenal masses have been explored in a number of studies (13–16), data related to QoL in these patients are scant. This lack of data seems to be an important issue, as it may be argued that the patient's quality of life should also be taken into account when considering treatment options. The present study clearly demonstrated reduced QoL in the patients with adrenal incidentaloma. Dimensions that were notably affected included mobility, performance of usual activities and anxiety/depression, as assessed by EQ-5D; physical functioning, physical role, general health, vitality, social functioning and emotional role, as assessed by SF-36, and physical fatigue as assessed by the (MFI-20).

The causal relationship between adrenal incidentaloma and reduced QoL needs to be clarified. The psychological aspects of the disease, such as patients' worries about their condition, fear of having a tumor and anxiety about the future, probably impair QoL. Furthermore, the fact that even subtle endocrine abnormalities could be associated with poor health outcomes is well documented (3–6). Eighteen patients in our study group had SCS. Their QoL scores were not found to be significantly different from those of other patients with adrenal incidentaloma. However, the use of disease specific

CushingQoL questionnaire in the group of patients with SCS would probably be more reliable than the use of generic questionnaires (17).

To our knowledge, this is the first study exploring the QoL in patients with adrenal incidentaloma. The most recent study, by Sukor et al., reported impaired QoL in patients with unilateral primary aldosteronism that significantly improved by 3 months after laparoscopic adrenalectomy (18). Studies on pituitary adenomas, another relevant group of endocrine tumors, indicated the impairment of multiple aspects of life quality and fatigue in patients as compared to controls (19, 20). Study by Johnson et al. analyzed QoL in 51 patients with non-functioning pituitary adenoma prior to treatment and demonstrated impairment in both physical and mental measures compared with the control population (19). However, some important factors that influence QoL in pituitary adenoma are not relevant in adrenal incidentaloma, such as mass effects of the tumor and partial or complete hormone deficiency.

Although our results undoubtedly suggest reduced QoL in patients with adrenal incidentaloma, it remains to be determined by further studies whether unilateral laparoscopic adrenalectomy can improve QoL in these patients. Studies on pituitary tumors demonstrated reduced QoL even after successful removal of the tumor and despite optimal hormone substitution (21, 22).

The present study had several limitations. Three generic questionnaires, EQ-5D, SF-36 and MFI-20, were used to analyze different dimensions of QoL and fatigue in patients with adrenal incidentaloma. The main advantage of such generic instruments is that their scores can be compared with those related to other conditions in different populations. However, these questionnaires do not cover more specific aspects of a

disease. Therefore, further studies using disease-specific questionnaires are needed to confirm our findings. Another shortcoming of the study is the fact that the patients had a higher average body mass index and a higher prevalence of hypertension than did the control group members, a discrepancy that potentially could have influenced the results. However, differences between the patients and controls in a certain domains of SF-36 and MFI-20 questionnaires remain significant even after controlling for BMI and the prevalence of hypertension. Nevertheless, the fact that the controls did not share the same clinical condition that led to the discovery of adrenal incidentalomas in patients could bias the results. Finally, we did not have any information about the socioeconomic status of the study participants in either group.

In conclusion, our study demonstrated impaired QoL in patients with adrenal incidentaloma as compared to age- and sex-matched controls. However, since the clinical relevance of the results is less obvious, this subject will benefit from further investigation that compare the QoL outcomes of laparoscopic adrenalectomy vs. no treatment.

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Figure 1. Percentage of patients and controls reporting no problems, some problems or severe problems in each domain of the EQ-5D.

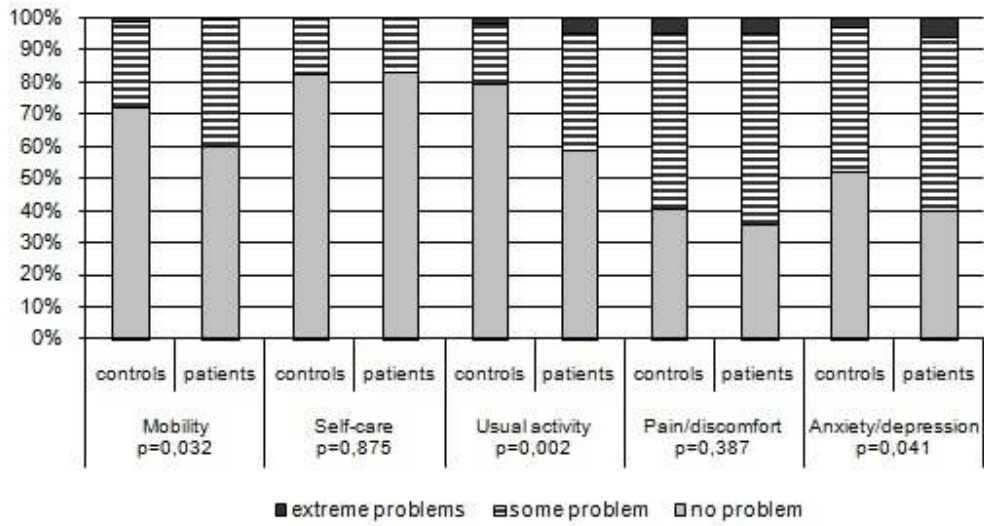


Table 1. Clinical and demographic characteristics of the patients with adrenal incidentaloma and controls

	Adrenal incidentaloma (n=139)	Controls (n=139)	<i>P</i> value
Age (years)	59.1±10.8	59.1±10.8	NS
Male/female	35/104	35/104	NS
BMI (kg/m ²)	29.2±5.8	26.4±4.0	<0.001
Hypertension (%)	68.3	46.0	0.002
Diabetes (%)	12.9	14.4	NS
Dyslipidemia (%)	56.8	46.0	NS

Results are mean ± SD

Table 2. SF-36 scores for the patients with adrenal incidentaloma and for the control group.

	Adrenal incidentaloma (n=139)	Controls (n=139)	<i>P</i> value
Physical functioning	62.0±28.3	75.2±28.3	<0.001
Physical role	55.0±40.8	73.2±37.8	<0.001
Bodily pain	63.4±24.7	65.9±22.4	NS
General health	48.6±20.5	58.3±17.6	<0.001
Vitality	49.5±20.5	55.0±15.0	0.001
Social functioning	59.7±25.0	66.5±22.7	0.001
Emotional role	52.0±40.5	77.2±35.9	<0.001
Mental health	58.7±19.7	60.6±14.2	NS

Results are mean ± SD

Table 3. MFI-20 scores for the patients with adrenal incidentaloma and for the control group.

	Adrenal incidentaloma (n=139)	Controls (n=139)	<i>P</i> value
General fatigue	11.2±1.9	11.4±1.9	NS
Physical fatigue	12.0±2.1	11.5±1.9	0.04
Reduced activity	12.2±2.1	12.0±2.2	NS
Reduced motivation	12.1±2.6	12.3±2.1	NS
Mental fatigue	10.7±1.9	11.0±2.0	NS

Results are mean ± SD