Adrenalectomy may improve cardiovascular and metabolic impairment and ameliorate quality of life in patients with adrenal incidentalomas and subclinical Cushing's syndrome

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Background. *Adrenalectomy represents the definitive treatment in clinically evident Cushing's syndrome; however, the most appropriate treatment for patients with subclinical Cushing's syndrome (SCS) with an adrenal incidentaloma remains controversial. This study was aimed to assess whether adrenalectomy may improve cardiovascular and metabolic impairment and quality of life compared with conservative management.*

Methods. *Twenty patients with adrenal incidentaloma underwent laparoscopic adrenalectomy for SCS, whereas 15 were managed conservatively. Hormonal laboratory parameters of corticosteroid secretion, arterial blood pressure (BP), glycometabolic profile, and quality of life (by the SF-36 questionnaire) were compared at baseline and the end of follow-up.*

Results. *The 2 groups were equivalent concerning all the examined parameters at baseline. In the operative group, laboratory corticosteroid parameters normalized in all patients but not in the conservative-management group (*$P < .001$*). In operated patients, a decrease in BP occurred in 53% of patients, glycometabolic control improved in 50%, and body mass index decreased; in contrast, no improvement or some worsening occurred in the conservative-management group (*$P < .01$*). SF-36 evaluation improved in the operative group (*$P < .05$*).*

Conclusion. *Adrenalectomy can be more beneficial than conservative management in SCS and may achieve remission of laboratory hormonal abnormalities and improve BP, glycemic control, body mass index, and quality of life. (Surgery 2012;152:991-7.)*

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An increasing number of patients are being diagnosed with adrenal incidentaloma (approximately 4% in the population older than 60 years of age), with the widespread use of cross-sectional imaging tools[1,2]; most of these masses are nonfunctional, but an autonomous, ACTH-independent cortisol hypersecretion altering the normal hypothalamic-pituitary-adrenal axis may be present in up to 30% of patients.[3,4] This subtle hypersecretion of cortisol may be insufficient to achieve the classic signs and symptoms of the clinically manifest Cushing's syndrome and has been defined as subclinical Cushing's syndrome (SCS).[2-4]

Although SCS by definition is not associated with signs and/or symptoms specific to overt cortisol excess,[5] some evidence suggests that this condition may lead to the same long-term consequences of cortisol excess, including diabetes, hypertension, dyslipidemia, obesity, and osteoporosis.[6-11] Adrenalectomy represents the definitive treatment in clinically evident Cushing's syndrome, whereas the most appropriate treatment for patients with adrenal incidentalomas and SCS remains controversial.[12]

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Several studies have reported conflicting results concerning the impact of adrenalectomy on this metabolic syndrome, both improvement and no change being reported.[2,6,7,10-14]

This study was aimed to compare the outcome of adrenalectomy or conservative management in patients with benign adrenocortical incidentalomas with SCS to verify whether adrenalectomy might improve the laboratory parameters of corticosteroidal secretion, arterial blood pressure (BP), glycometabolic control, lipid profile, body mass index (BMI), bone mass density (BMD), and health-related quality of life.

MATERIALS AND METHODS

The present study included 35 consecutive patients with adrenal incidentalomas and SCS, enrolled prospectively between 2000 and 2009 at the Endocrine Surgery Unit of the Padua University, Padua, Italy. Diagnosis of adrenal incidentaloma was determined by the detection of an unilateral adrenal mass greater than 1 cm by cross-sectional abdominal imaging in the course of diagnostic testing for other clinical conditions.

SCS was defined on the basis of the absence of clinical features specific for overt Cushing's syndrome (facial plethora, striae rubrae, easy bruising, and proximal muscle weakness, assessed on clinical basis, that best discriminate Cushing's syndrome)[5] and the presence of laboratory abnormalities suggestive of ACTH-independent hypercortisolism[12,15,16]: morning serum cortisol levels greater than 5 μg/dL after the administration of 1 mg of dexamethasone in the evening the day before; morning ACTH levels less than 10 pg/mL, and daily urinary-free cortisol (UFC) greater than 76 μg/day.[2-4,17]

Patients with concomitant mineral corticoid or catecholamine hypersecretion (as assessed by 24-hour urinary catecholamines or metanephrines and plasma renin activity and aldosterone), patients presenting signs or symptoms specific for cortisol excess, and patients with adrenal or extra-adrenal malignancies were not included in the study.

Adrenalectomy was suggested to all patients, and we explained the possible advantages and disadvantages of this option. Patients accepting adrenalectomy underwent a laparoscopic adrenalectomy by a transperitoneal approach with the patients in the flank position (Operative Group) as described previously,[18,19] whereas patients refusing surgery were followed with a conservative approach (Control Group). All patients gave informed consent.

In the operative group, to avoid the risk for hypoadrenalism, precautionary steroid therapy with hydrocortisone (100 mg intravenous bolus) during surgery, and cortisone acetate orally (25–37.5 mg/day) during the postoperative period was administered; the treatment was decreased gradually and discontinued in 3–6 weeks in all patients.

Demographic, clinical, and laboratory details (including age, sex, size of adrenal mass as assed by imaging techniques) were recorded; clinical and laboratory assessment was performed in all patients at baseline, at 6 months, and yearly during the follow-up period; at the end of the follow-up all patients underwent extensive re-examination, and data were reviewed retrospectively.

Examined data in all patients included the following: laboratory hormonal parameters of corticosteroid secretion (morning ACTH levels, normal values, 10–50 ng/L; daily UFC, normal values, 10–76 μg/day; responsiveness to overnight 1 mg of dexamethasone suppression test); arterial systolic and diastolic BP; glycometabolic control parameters (serum fasting glucose concentrations, normal value 70–110 mg/dL, and glycosylated hemoglobin [HbA1c], normal value 4.3–5.9%); lipid profile (serum triglyceride, normal value 40–150 mg/dL; total, high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterol levels, normal value 130–200 mg/dL, $>$50 mg/dL and $<$100 mg/dL, respectively); BMI; BMD; and subjective perception of health-related quality of life.

Subjects with systolic blood pressure of 140 mmHg or greater and/or diastolic blood pressure 90 mmHg or greater and/or on antihypertensive treatment were defined as hypertensive. Arterial BP was considered improved when a hypertensive patient passed from a hypertension category to a less severe one or when the antihypertensive drugs were able to be decreased or stopped; BP was considered to have worsened when a non-hypertensive patient became hypertensive or when he or she moved from a hypertension grade to a more severe grade, or if the antihypertensive treatment was increased to maintain the therapeutic target.[12]

Patients with fasting glucose concentrations exceeding 110 mg/dL were considered as having impaired glucose tolerance (IGT), and those with fasting glucose concentrations greater than 126 mg/dL or who were taking antidiabetic medication were regarded as diabetic. The improvement/worsening of the glycometabolic control was defined by the decrease/increase of at least a percentage point of HbA1c and/or by the achievement/loss of the usually recommended targets, or if the

Table I. Hormonal, laboratory, and clinical parameters in 35 patients with an adrenal incidentaloma and subclinical hypercortisolism

	Operative group			*Control group*		
	Before adrenalectomy	*After adrenalectomy*	P *value*	*At baseline*	*At the end of follow up*	P *value*
ACTH, pg/mL	7.1 ± 1.4	33.2 ± 7.9*	<.0001	7.1 ± 1.5	6.9 ± 1.4	.58
UFC, μg/day	120 ± 26	58 ± 14*	<.0001	122 ± 25	136 ± 26	.045
Systolic BP, mmHg	142 ± 22	136 ± 20*	.011	146 ± 20	152 ± 20	.005
Diastolic BP, mmHg	86 ± 9	83 ± 8*	.02	87 ± 9	92 ± 7	.04
Fasting glucose, mg/dL	117 ± 34	98 ± 28*	<.0001	110 ± 30	117 ± 4	.11
HbA1c, %	6.2 ± 1.1	5.7 ± 0.6*	.017	6.1 ± 0.9	6.33 ± 1.2	.56
Triglyceride, mg/dL	167 ± 30	145 ± 19*	.0001	162 ± 32	160 ± 25	.52
Total cholesterol, mg/dL	226 ± 54	208 ± 44	.043	221 ± 66	232 ± 47	.15
HDL cholesterol, mg/dL	42.5 ± 6	41 ± 8	.92	43 ± 8	45 ± 9	.83
LDL cholesterol, mg/dL	141.3 ± 37	155 ± 29	.47	149 ± 25	151 ± 36	.33
BMI, kg/m^2	27.9 ± 3.7	26.1 ± 3.6*	.02	28.6 ± 3.8	29 ± 2.8	.44
T-score	−1.23 ± 0.74	−1.29 ± 0.77	.11	−1.19 ± 0.74	−1.27 ± 0.82	.1
SF-36 MCS	43.8 ± 11.8	54.1 ± 10.1*	.003	44.5 ± 10.8	44.9 ± 12.4	.78
SF-36 PCS	50.9 ± 7.3	56.7 ± 7.3*	.0016	51.7 ± 9.7	50.5 ± 9.4	.45

*$P < .05$ versus the control group.
Data are expressed as mean ± SD.
BMI, Body mass index; *BP*, blood pressure; *HbA1c*, glycosylate hemoglobin; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *MCS*, Mental Component Summary measure; *PCS*, Physical Component Summary measure; *UFC*, urinary free cortisol.

antidiabetic drugs were decreased/stopped or increased.[12]

Dyslipidemia was defined as serum triglyceride levels of at least 150 mg/dL or HDL cholesterol levels of less than 40 mg/dL in men and 50 mg/dL in women or if any antidyslipidemic treatment was given.[12] The BMI was calculated as body weight (kg) / height (m^2) (normal values from 20 to 24.9). "Overweight" was defined by BMI values between 25 and 29.9, whereas "obesity" was defined as BMI greater or equal to 30. The BMD measurement was obtained by dual-energy x-ray absorptiometry from the lumbar spine with the values standardized as T-scores expressed in standard deviations (SD); "osteoporosis" was defined by a T-score less than −2.5 SD, whereas "osteopenia" by a T-score between −1 and −2.5 SD.

Patient's subjective perception of health-related quality of life was scored according to the SF-36 Health Survey. The SF-36 is a self-administered and validated questionnaire[20] consisting of 36 questions evaluating various discrete dimensions, which may be aggregated into 2 summary measures: the Physical Component Summary (PCS), and the Mental Component Summary (MCS). The PCS and MCS correlate with the patient's physical and mental subjective perception of quality of life, respectively. Scores may range from 0 (poorest health status) to 100 (best health status).

Statistical evaluation included χ^2 for trend or the Fisher's exact test for categorical variables, Student's *t* test, and the Wilcoxon matched-paired test for continuous variables, and Spearman or Pearson correlation test, as appropriate. $P < .05$ was considered statistically significant.

RESULTS

The results are summarized by the Tables I and II. Twenty patients were included in the operative group and 15 in the control group. No significant differences were found at baseline between the operative and control groups concerning all the examined parameters, including age (median 57 years, range 36–78 vs 58, range 39–75, respectively), male/female ratio (12/8 vs 8/7), size of adrenal mass (median 39 mm, range 30–54 vs 38, range 29–52), duration of follow-up to retesting (mean 54 ± 34 months vs 56 ± 37 months), ACTH and daily UFC levels, responsiveness to 1 mg of dexamethasone, arterial BP, hypertensive patients (75% vs 80%), glycometabolic control parameters, diabetic or IGT patients (50% vs 40%), lipid profile, BMI, rate of obese or overweight patients (75% vs 80%), BMD, rate of osteoporotic or osteopenic patients (30% vs 26.7%), and SF-36 related MCS and PCS (P = NS).

In the operative group, no postoperative morbidity or mortality occurred, and no conversion to laparotomy was needed; a benign adrenocortical adenoma was confirmed at pathology in all patients. Biochemical cure of SCS was achieved within 6 months after adrenalectomy in all patients

Table II. Clinical features in 35 patients with adrenal incidentaloma and subclinical hypercortisolism

	Operative group						*Control group*				
		After adrenalectomy					*At the end of follow up*				
	Before adrenalectomy	*Cure or normalization*	*Improvement*	*No changes*	*Worsening*	P *value*	*At baseline*	*Cure or normalization*	*Improvement*	*No changes*	*Worsening*	P *value*
Hypertensive patients	15 (75%)	2/15 (13%)*	6/15 (40%)	7/15 (47%)	—	.002	12 (80%)	—	—	9/12 (75%)	3/12 (25%)	—
Diabetic and IGT patients	10 (50%)	1/10 (10%)*	4/10 (40%)	5/10 (50%)	—	.032	6 (40%)	—	—	4/6 (67%)	2/6 (33%)	—
Dyslipidemic patients	10 (50%)	2/10 (20%)	—	8/10 (80%)	—	.47	7 (46.7%)	—	—	7/7 (100%)	—	—
Abnormal BMI patients	15 (75%)	4/15 (27%)*	2/15 (13%)	9/15 (60%)	—	.19	12 (80%)	—	—	9/12 (75%)	3/12 (25%)	—
Abnormal T-score patients	6 (30%)	—	—	5/6 (83%)	1/6 (17%)	—	4 (26.7%)	—	—	3/4 (75%)	1/4 (25%)	—

*$P < .05$ versus the control group.

Data are expressed as absolute numbers with percentage in parentheses. Abnormal BMI: >25 (ie, obese and overweight patients); abnormal T-score: <−1 (ie, osteoporotic and osteopenic patients).

BMI, Body mass index; *IGT*, impaired glucose tolerance.

and persisted up to the end of the study at a median of 38.5 months (range 24–120). In fact, the normalization of 24-hour UFC, morning ACTH levels, and postdexamethasone cortisol suppressibility occurred in all operated patients; in addition, ACTH levels increased and daily UFC decreased ($P < .0001$) (Table I).

In the control group at the end of the follow-up (median 36 months, range 24–120), persistent laboratory alterations of ACTH-independent hypercortisolism (unresponsiveness to overnight 1 mg dexamethasone administration, low serum ACTH and high daily UFC levels) were observed in all patients; daily UFC levels also increased ($P = .045$). There was no enlargement of the adrenal mass (P = NS) nor evident signs or symptoms of clinically overt Cushing's syndrome (Table I).

In the operative group, both systolic and diastolic BP decreased after adrenalectomy ($P = .011$ and $P = .02$, respectively); BP of hypertensive patients improved or normalized (8 of 15); 40% ($n = 6$) had a decrease in the number or doses of antihypertensive medications, and 2 became normotensive without medication ($P = .002$). Fasting glucose levels and HbA1c decreased ($P < .0001$ and $P = .017$, respectively); cure or improvement of diabetes or glucose intolerance was achieved in 50% of patients ($P = .032$). Serum triglyceride and total cholesterol levels decreased ($P = .0001$ and $P = .043$, respectively); BMI decreased after adrenalectomy ($P = .02$); in the population with an abnormal BMI (ie, >25), 4 "overweight" patients normalized their BMI, and 2 "obese" patients improved but remained "overweight" (P = NS). There were no changes in the mean T-score nor the number of patients with an abnormal T-score (ie, <−1), although one "osteopenic" patient became "osteoporotic" (P = NS). The SF-36 evaluation of subjective health-related quality of life revealed a significant amelioration regarding both MCS and PCS ($P = .003$ and $P = .0016$, respectively) (Tables I and II).

To the contrary, in the control group, both systolic and diastolic BP worsened ($P = .005$ and $P = .04$, respectively); with 3 hypertensive patients needing to increase the daily dose or the number of drugs. No changes were observed in fasting glucose levels and HbA1c; cure or improvement was never achieved among the patients with preoperative diabetes or glucose intolerance ($n = 6$), whereas a worsening was observed in 2 patients (P = NS). No changes occurred in the number of dyslipidemic patients nor in serum triglyceride, and total, HDL, and LDL cholesterol levels. The mean BMI and the number of patients with abnormal BMI remained unchanged, but 3 "overweight"

patients became "obese." No changes in the mean T-score and the number of patients with an abnormal T-score occurred, although one "osteopenic" patient became "osteoporotic." The SF-36 evaluation of subjective health-related quality of life revealed no changes in MCS and PCS (P = NS) (Tables I and II). In both groups no mortality, major cardiovascular events, or vertebral fractures occurred.

No significant correlations were found between age, sex, size of the adrenal mass, and duration of follow-up, with changes in BP, glycometabolic parameters, lipid profile, BMI, BMD, and SF-36 MCS and PCS evaluation in both groups (P = NS).

When we compared the outcome in the 2 groups at the end of the follow-up, a beneficial effect of adrenalectomy became evident for several variables: significantly greater ACTH and lesser daily UFC levels were found in the operative group ($P < .0001$); systolic and diastolic BP were less, as were the number of hypertensive patients (P = .02, P = .01, and P = .0016, respectively); fasting glucose, HbA1c levels, and the number of patients with diabetes or glucose intolerance were less (P = .049, P = .033, and P = .025, respectively); BMI values and the rate of "obese" or "overweight" patients were less (P = .013 and P = .016, respectively); serum triglyceride levels were less (P = .049), but no differences were detected concerning the total, HDL, and LDL cholesterol levels; number of dyslipidemic patients; number of osteoporotic or osteopenic patients; and the T-score values (P = NS). Finally, SF-36 MCS and PCS values were greater in the operative than control group (P = .016 and P = .039, respectively).

DISCUSSION

Patients with an adrenal incidentaloma and SCS represent a relatively frequent finding, with an estimated prevalence between 0.2% and 2% in the general adult population.[1,2] This association has been noticed to share some features of the metabolic syndrome and osteoporosis, with an increased risk of cardiovascular morbidity and fractures.[1,6-11,21] The present study confirmed this finding; hypertension was present in approximately 80% of patients, glucose and lipid metabolism was impaired in approximately in 50%, and osteoporosis evident in one third of patients.

Nevertheless, the optimal treatment of adrenal incidentaloma with SCS is still debated; a marked improvement in hypertension and diabetes has been reported recently.[7,10,22] A prospective, randomized trial found a normalization or improvement of BP in 67% of patients[14]; Chiodini et al[2] found improvement in BP in 56% and amelioration of glycometabolic dysfunction in 48% of patients. In contrast, other studies have found more conflicting results, especially concerning obesity, osteoporosis, and dyslipidemia.[6,23] These discrepancies might be attributable to methodologic reasons (small sample sizes, retrospective design, lack of control group, analysis bias)[6,10,22]; an accepted definition of SCS is still controversial because overlap between SCS and mild hypercortisolism may exist.[12]

Furthermore, patients with clinically manifest Cushing's syndrome or with debatable biochemical diagnosis of hypercortisolism have been included in some papers focusing on SCS.[2,7,12]

In the present study we included only truly subclinical patients, without any specific features of Cushing's syndrome,[5] with cortisol levels after 1 mg dexamethasone suppression test greater than 5 μg/dL, which is considered the most specific cut-off for making the diagnosis of hypercortisolism,[3,17] to avoid the inclusion of false-positive cases.

We confirmed that adrenalectomy was effective in correcting the hormonal abnormalities because daily UFC and ACTH normalized and responsiveness to dexamethasone suppression test was restored in all patients. In contrast, a worsening was observed in conservatively treated patients, who had increased UFC levels despite the observation that none developed overt Cushing's syndrome and the size of the adrenal mass size remained stable at a median follow-up of 3 years, concordantly with previous reports.[1,4,10,21] Some reports, however, have documented a worsening of symptoms or enlargement of the adrenal mass during a longer follow up.[14,24] Thus, there appears to be a need for a careful long-term monitoring in patients receiving conservative management.

As in previous reports,[2,7,10,13,14] in our experience, adrenalectomy had beneficial effects in reducing both systolic and diastolic BP in the hypertensive patients; in the control group, however, a worsening of BP levels occurred.

Adrenalectomy was effective also in improving the glycometabolic control, with amelioration of fasting glucose and HbA1c levels, whereas in the control group, worsening occurred in 20% of patients. These findings correlate well with previous studies.[6,7,9,12,13] Concerning the lipid profile, the beneficial effects were less evident.

The beneficial effects of operation on body weight were evident, with a decrease in BMI in 40% of patients whereas weight gain occurred in 25% of patients in the control group. No changes of BMD were found in either group.

Finally, adrenalectomy led to an improvement in the patient's subjective perception of the health-related quality of life, according to SF-36 survey, both for the physical and mental component, whereas no changes were evident in the control population. SF-36 is a generic and nonspecific questionnaire, but it has been previously demonstrated to be effective in evaluating the outcome after adrenalectomy for clinically manifest Cushing's syndrome.[15,16]

Our study has some limitations. The patients were not randomized, although patients were enrolled prospectively and no differences were evident between the 2 groups concerning demographics and the hormonal, cardiovascular, and metabolic parameters at baseline. The need for a randomized trial eventually designed to evaluate the surrogate end points (hypertension, diabetes, dyslipidemia, obesity, and osteoporosis) as well as some "hard" end points (such as the incidence of major cardiovascular events, progression of diabetic complications, vertebral fractures, and mortality) has been advocated previously to compare the effects of operative and conservative approaches,[12] but such a study would require a large number of patients followed for a period of time more than 10 years.

Furthermore, in the present study, the beneficial effects of a laparoscopic approach, without any complications, or conversions to open surgery should be acknowledged[18,19]; the occurrence of complications may theoretically alter the reported beneficial effects of the procedure.[21]

It should be acknowledged that one-half of our patients had an adrenal mass greater than 4 cm, which represents an usual criteria for suggesting surgery for adrenal incidentaloma[1]; however, no correlations were found between the size of the mass and the outcome in both groups, suggesting that biochemical ACTH-independent hypercortisolism could represent an indication to adrenalectomy, even in the absence of the classic signs and symptoms of Cushing's syndrome, independently from the size of the adrenal mass.

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DISCUSSION

Dr James Broome (Nashville, TN): It is interesting that we don't see nearly as many of these as you do. My question is: had all these patients a single radiographic abnormality in the adrenal gland? Do you ever see anybody with bilateral abnormalities? If so, how do you deal with those people who have had bilateral adrenal abnormalities on imaging and subclinical Cushing's syndrome?

Dr Maurizio Iacobone: In the present study every patient had only a single side adrenal gland affected; no bilateral disease was included. However, in my opinion, in these cases, a noriodocholesterol scintigraphy may be useful for planning the therapeutic strategy.

Dr Eren Berber (Cleveland, OH): How did you control for the difference that might be present in the patients' lifestyles? How would you know the patients in the operative group were not more active or had some dietary modifications compared with the other group?

Dr Maurizio Iacobone: No, we had no data concerning this issue.

Dr Brian Saunders (Hershey, PA): A question about your conservatively managed group. Were any of them treated with steroidogenesis inhibitors, such as ketoconazole or anything like that?

Dr Maurizio Iacobone: All patients in the control group were medically treated, and they were managed by several endocrinologists. Instead of the medical treatment, as you can see in this series, there was a slight worsening of some parameters. However, no specific medical treatment against hypercortisolism was used.

Dr Douglas Evans (Milwaukee, WI): You used a very conservative definition of subclinical Cushing's, with a morning administration of cortisol greater than 5 μg/dL. How do you manage the patients ranging between 3 and 5 μg/dL? Do you use salivary cortisols? What do you do with that patient population?

Dr Maurizio Iacobone: According to the previous literature, most European studies used the cut-off of 3 μg/dL, and they obtained similar results, with some controversies. However, the cut-off of 5 μg/dL is more specific, according to the NIH's suggestion. I think that if you use a lower cut-off level, you may have more patients included in the sample because it is more sensitive, but you are never assured that these patients really have hypercortisolism. For these reasons, in the present study, we decided to use this more specific cut off to include only patients who had an unequivocal hypercortisolism. Salivary cortisol may be a further criterion to assess that they have a cortisol hypersecretion.