# Beneficial Metabolic Effects of Prompt Surgical Treatment in Patients with an Adrenal Incidentaloma Causing Biochemical Hypercortisolism

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**Context:** In patients with adrenal incidentalomas, subclinical hypercortisolism (SH) is associated with an increased prevalence of the metabolic syndrome. The effect of surgical/conservative approach is debated.

**Objective:** The objective of the study was to determine the effect of the surgical and conservative approaches on the metabolic syndrome in patients with adrenal incidentalomas.

**Design:** This was a retrospective longitudinal study (18–48 months follow-up).

**Setting:** The study was conducted on an in- and outpatient basis.

**Patients:** One hundred eight patients with adrenal incidentalomas were studied for the presence of SH, which was diagnosed in the presence of more than two of the following: urinary free cortisol greater than 70 $\mu$g per 24 h (193 nmol per 24 h), cortisol after 1 mg dexamethasone suppression test greater than 3.0 $\mu$g/dl (83 nmol/liter), ACTH less than 10 pg/ml (2.2 pmol/liter).

**Interventions:** Surgery was performed in 25 patients with SH (group TrSH+) and 30 without SH (group TrSH−), whereas the conservative approach was chosen by 16 patients with SH (group UntrSH+) and 37 without SH (group UntrSH−).

**Main Outcome Measures:** During the follow-up, the improvement/worsening of body weight, blood pressure, or glucose and cholesterol levels was defined in the presence of a greater than 5% weight decrease/increase and following the European Society of Cardiology or the Adult Treatment Panel III criteria, respectively.

**Results:** In group TrSH+, weight, blood pressure, and glucose levels improved (32, 56, and 48%, respectively) more frequently than in group UntrSH+ (12.5%, $P = 0.05$; 0.0%, $P < 0.0001$; 0.0%, $P = 0.001$; and 0.0%, $P = 0.0014$, respectively). In group UntrSH+, blood pressure, glucose, and low-density lipoprotein levels worsened more frequently (50.0, 37.5, and 50.0%, respectively) than in group TrSH+ (0.0%, $P < 0.0001$; 0.0%, $P = 0.001$; and 20.0%, $P = 0.05$, respectively).

**Conclusions:** Regarding the various components of the metabolic syndrome, in patients with adrenal incidentalomas and SH, surgery is beneficial. (***J Clin Endocrinol Metab*** **95: 2736–2645, 2010)**

The term subclinical hypercortisolism (SH) is commonly used to define a condition characterized by presence of alterations of the hypothalamic-pituitary-adrenal function in keeping with a subtle cortisol hypersecretion but in the absence of signs or symptoms specific of overt hypercortisolism (1, 2). This subtle cortisol excess has been described in up to the 30% of patients with an incidentally discovered adrenal mass (adrenal incidenta-

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Abbreviations: DST, Dexamethasone suppression test; HPA, hypothalamic-pituitary-adrenal; LDL, low-density lipoprotein; SH, subclinical hypercortisolism; UFC, urinary free cortisol.

loma) (3, 4). Considering the increasing frequency of the diagnosis of these adrenal nodules in the population older than 60 yr of age (about 4%), SH is relatively common (5–9).

The clinical relevance of SH is still debated (5). Indeed, several observational studies suggested that this subtle hypercortisolism may be associated with some typical, although not specific, complications of overt hypercortisolism such as obesity, diabetes, hypertension, dyslipidemia, and osteoporosis (9–20). However, other observational studies did not show an association between SH and these metabolic disorders (21, 22). Most importantly, studies specifically designed to investigate the possible benefits of SH treatment are partially conflicting, although all suggested an improvement of hypertension (11, 23–29). Although some authors described an improvement of all features of metabolic syndrome in patients with SH after the removal of the adrenal mass (11, 24, 27, 29), others did not, particularly regarding the changes in obesity and diabetes (23, 25, 26, 28). These discrepancies may be due to the fact that different criteria have been adopted to define SH.

Indeed, the definition of SH is still debated and controversial, mainly due to the characteristics of the disease *per se*. In SH the cortisol secretion is probably a continuum between normal and clear-cut cortisol excess and may be intermittent. Therefore, this subtle cortisol hypersecretion may be not reliably revealed by the commonly employed biochemical markers (30–32). As a consequence, it is possible that a patient classified as unaffected with SH could by additional measures show a slight degree of cortisol hypersecretion. Additionally, scarce data are available regarding the beneficial effects of surgical treatment in patients without SH who undergo the excision of the adrenal adenoma (11, 23, 24).

To date, due to the lack of an evidence-based efficacy of the surgical treatment in patients with adrenal incidentalomas with and without SH, there is no consensus about the clinical management of this condition (30–32). The present study was designed to evaluate the effect of the surgical treatment and the conservative approach on the features of the metabolic syndrome in patients with adrenal incidentalomas. Therefore, patients with incidentally discovered adrenal masses with and without SH, who underwent surgical or conservative approach, were studied.

## Subjects and Methods

### Subjects

The study was performed in four referral Italian Endocrinology Units: Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Instituto di Ricovero e Cura a Carattere Scientifico in Milan; Casa Sollievo della Sofferenza, Instituto di Ricovero e Cura a Carattere Scientifico in San Giovanni Rotondo; San Giuseppe Hospital; and Instituto di Ricovero e Cura a Carattere Scientifico, Policlinico San Donato, in Milan. We included in this retrospective study 108 consecutive patients regularly followed up in our institutions from December 2002 to December 2007. Diagnosis of adrenal incidentalomas was based on the detection of a unilateral adrenal mass (size >1 cm) by cross-sectional imaging methods of the abdomen in the course of diagnostic testing or treatment for other clinical conditions that are not related to suspicion of adrenal disease.

Exclusion criteria were: 1) past or current history of hypogonadism [in men testosterone levels <300 ng/dl (10.4 nmol/liter) and in premenopausal women fewer than six menstrual cycles/year] and diseases known to affect glucose metabolism other than type 2 diabetes (*i.e.* thyrotoxicosis, bowel diseases, chronic renal failure, chronic hepatic disease, alcoholism, eating disorders, rheumatologic or hematological diseases); 2) administration of drugs influencing cortisol and dexamethasone metabolism or cortisol secretion; or 3) signs or symptoms specific of cortisol excess (moon facies, striae rubrae, skin atrophy, proximal muscle weakness) that best discriminate Cushing's syndrome, even if they do not have a high sensitivity (33).

No subject had evidence of metastatic diseases. At computed tomography all adrenal masses were homogeneous and hypodense and with well-shaped features, consistent with the diagnosis of an adrenocortical adenomas. In all patients, the diagnosis of pheochromocytoma and aldosteronoma was excluded by appropriate hormonal determinations (24 h urinary catecholamines and upright plasma renin activity and aldosterone). The contralateral adrenal gland was normal in all patients.

All patients were screened for the presence of SH, which was diagnosed on the basis of the presence of at least two of the following three alterations of hypothalamic-pituitary-adrenal (HPA) axis: 1) urinary free cortisol (UFC) levels greater than 70 $\mu$g per 24 h (193 nmol per 24 h; normal values 10–70 $\mu$g per 24 h, 28–193 nmol per 24 h), which is the cutoff of both our own and international normal reference values (34); 2) serum cortisol levels after 1 mg dexamethasone suppression test (DST) greater than 3.0 $\mu$g/dl (83 nmol/liter); and 3) morning (0800 h) ACTH levels less than 10 pg/ml (2.2 pmol/liter). The use of a 1-mg DST cutoff of 3.0 $\mu$g/dl (83 nmol/liter) rather than 5 $\mu$g/dl (138 nmol/liter) as recommended by the National Institutes of Health (30), was preferred to increase the test sensitivity (31). Moreover, this cutoff showed the best accuracy in predicting vertebral fractures, which are one of the deleterious effects of hypercortisolism (20). Currently the criteria for diagnosing SH are debated and no consensus is available (32). We decided to use these criteria be-

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cause they have been previously substantiated on a clinical basis (11, 15, 20). On the basis of these criteria, 41 patients were diagnosed as having SH (SH+) and 67 as not having it (SH−). In the eight patients who were diagnosed as affected with SH and with ACTH levels higher than 10 pg/ml (2.2 pmol/liter), the adrenal origin was confirmed by CRH test.

Because no widely accepted guidelines are available, surgery was suggested to all SH+ patients, explaining possible advantages and disadvantages of this option. Twenty-five SH+ patients therefore underwent surgery (group TrSH+), whereas 16 refused it and were followed up with a conservative approach for at least 18 months (group UntrSH+). Among the 67 patients without SH, in 30 the surgical option was mandatory, on the basis of the increasing dimensions (>1 cm increase during 12 months of follow-up) and/or to the size larger than 4 cm at the diagnosis (group TrSH−), whereas 37 were followed up with a conservative approach for at least 18 months (group UntrSH−). In this latter group, the size of adrenal mass was less than 4 cm and remained stable during the follow-up period.

Laparoscopic or laparotomic (open) adrenalectomy was performed, depending on the size of the adrenal adenoma and the clinical characteristics of the subjects. No patient had perioperative and/or postoperative complications. In all patients the histological findings were consistent with adrenal adenoma. After adrenalectomy, a precautionary steroid therapy with hydrocortisone 100 mg iv, during surgery, and cortisone acetate per os (at weight related doses ranging between 25 and 37.5 mg/d in three subdivided doses during the day), immediately after surgery, was administered. The commonly used cortisone acetate dose was 25 mg/d (49 patients), whereas higher doses of 31.3 and 37.5 mg/d were used in four and two obese patients, respectively. In all patients, cortisol secretion was reevaluated, after 2 months, by ACTH stimulation test. If inconclusive results were obtained, the insulin tolerance test was given. In patients with persistent adrenal insufficiency, steroid substitutive therapy was continued and HPA axis function reassessed every 6 months.

The duration of the steroid substitutive therapy was comparable between group TrSH+ and group TrSH− (12.3 ± 14.1 *vs.* 11.8 ± 13.8 months).

In patients who did not undergo surgery, the HPA axis activity was reevaluated at 12 and 18 months and subsequently every 12 months during the follow-up period, and in all, cortisol secretion did not change. In all patients operated on for SH, after discontinuation of the steroid substitutive therapy, the biochemical testing showed a normal cortisol secretion with a significant increase of ACTH (before surgery 7.8 ± 4.2, after surgery 21.2 ± 6.2, $P < 0.001$) and decrease of UFC levels (before surgery 66.2 ± 35.6, after surgery 29.6 ± 8.7, $P < 0.0001$). Postoperatively, at the end of follow-up, in patients operated on for the size of the adenoma, the biochemical testing showed a significant increase in ACTH values (before surgery 9.1 ± 5.5, after surgery 18.1 ± 7.7, $P = 0.001$), whereas UFC levels did not show a significant change in respect to the preoperative period (before surgery 64.7 ± 25.6, after surgery 52.5 ± 18.1, $P = 0.107$).

Patients gave informed consent to participate and the study was conducted in accordance with Helsinki Declaration II and approved by local ethical Committees.

## Methods

In all patients, clinical examination was performed at baseline, at 12 months, at 18 months, and afterward at 12-month intervals during the follow-up period, measuring weight, height, and waist circumference and recording the presence of obesity, hypertension, dyslipidemia, type 2 diabetes mellitus, and features of metabolic syndrome. Subjects with body mass index greater than 30 kg/m$^2$ were considered obese. Subjects with systolic blood pressure of 130 mm Hg or greater and/or diastolic blood pressure 85 mm Hg or greater and/or on antihypertensive treatment were defined as hypertensive. Diabetes mellitus was diagnosed using World Health Organization criteria (35), and patients were also considered diabetic if any hypoglycemic drug was given. Dyslipidemia was defined as serum triglyceride levels of at least 150 mg/dl (1.7 mmol/liter) or high-density lipoprotein cholesterol levels of less than 40 mg/dl (1.0 mmol/liter) in men and 50 mg/dl (1.3 mmol/liter) in women (36). Patients were also considered dyslipidemic if any antidyslipidemic treatment was given.

The improvement or worsening of body weight was defined by a greater than 5% decrease or increase of body weight (37), respectively, between baseline and the end of the follow-up period. The improvement or worsening of arterial blood pressure was defined if during the follow-up period the nonhypertensive patients passed from a prehypertension category to another or the hypertensive patients from a hypertension grade to another, following the Guidelines for the Management of Arterial Hypertension of the European Society of Cardiology (38). Fasting glucose and cholesterol levels were considered improved or worsened if they passed from a category to another in agreement with the Adult Treatment Panel III criteria (36). The improvement or worsening of body weight, arterial blood pressure, fasting glucose, and cholesterol levels were established at 18 months and at the last follow-up. Serum and urinary samples were collected and stored at −20 C until assayed.

In all patients serum ACTH levels (mean of three determinations at 20 min intervals) were measured by immunoradiometric assay (BRAHMS Diagnostica GmbH, Berlin, Germany), and serum cortisol and UFC levels (after dichloromethane extraction) were determined immunofluorimetrically by TDX-FLX Abbott, GmbH, Diagnostika kits (Wiesbaden-Delkenheim, Germany). The intra- and interassay coefficients of variation were less than 15% for ACTH and less than 10% for all other assays.

## Statistical analysis

Results are expressed as mean ± SD along with range for normally distributed continuous variables or as absolute frequencies and percentages for categorical variables.

Comparison of continuous variables among the different groups was performed using one-way ANOVA and Bonferroni correction for *post hoc* analysis. Categorical variables were compared by $\chi^2$ test or Fisher exact test, as appropriate.

Body weight, fasting glucose, blood pressure, and low-density lipoprotein (LDL) cholesterol levels at 18 months and at the end of follow-up were used as end points. For each single end point, the effect of surgical treatment was first assessed in the overall sample adjusting for age; duration of follow-up; SH group; and, separately, for the presence at baseline of obesity, type 2 diabetes mellitus, arterial hypertension, and dyslipidemia, according to the specific end point at issue. Furthermore, an adjusted subgroup analysis, respectively for SH+ and SH− groups was performed to assess the potential heterogeneous effect of treatment between the two SH groups. Treatment heterogeneity for each end point was tested in an overall model including the treatment-by-SH group interaction.

$P < 0.05$ was considered statistically significant. All analyses were performed using SAS Statistical Package Release 9.1 (SAS Institute, Cary, NC).

## Results

The clinical characteristics at baseline of all treated and untreated patients with and without SH are reported in Table 1. In group TrSH+, patients were younger than in groups UntrSH+ and UntrSH−. Cortisol secretion, as reflected by 1 mg DST and UFC levels, was comparable between groups TrSH+ and UntrSH+, whereas, as expected, it was higher in groups TrSH+ and UntrSH+ than groups TrSH− and UntrSH−. As expected, ACTH levels were lower in group TrSH+ than groups TrSH− and UnTrSH− and in group UnTrSH+ than group UnTrSH−. Unexpectedly, ACTH levels were lower in TrSH− than UntrSH− subjects.

Individual data of patients with SH are reported in Table 2. Looking at the 41 patients diagnosed as affected with SH, in 10 cases DST was 5 $\mu$g/d or greater. Seventeen of the remaining 31 patients with DST less than 5 $\mu$g/dl showed elevated UFC. In all the remaining 14 SH+ cases, DST was 3 $\mu$g/d or greater.

In all samples, body weight, blood pressure, fasting glucose, and LDL cholesterol levels were compared between baseline and the 18 month follow-up and the end of the follow-up.

The treatment or the conservative approach in SH+ patients showed that in group TrSH+, body weight, blood pressure, and fasting glucose levels improved more frequently than in groups UntrSH+ and TrSH− (Table 3). The prevalence of patients who lost weight was similar between subjects with and without improvement of blood pressure and fasting glucose levels (data not shown).

In group UntrSH+, blood pressure, fasting glucose, and LDL levels worsened more frequently than in groups TrSH+ and TrSH− (Table 3). Finally, in group UntrSH+, fasting glucose levels worsened more frequently than in group UntrSH− (Table 3).

The treatment or the conservative approach in SH− patients showed that in group TrSH−, blood pressure improved more frequently and LDL levels worsened less frequently than in group UntrSH− (Table 3).

In each group, the prevalence of patients who experienced improvement or the worsening of body weight and blood pressure at an 18-month standardized follow-up period and at the end of follow-up was the same.

Data expressed as absolute values at baseline, 18 months, and last follow-up regarding body weight, blood pressure, fasting glucose, and LDL cholesterol levels in the four groups (TrSH+, TrSH−, UnTrSH+,

**TABLE 1.** Clinical characteristics of surgically treated and untreated patients with and without subclinical hypercortisolism

| | SH+ treated (n = 25) | SH+ untreated (n = 16) | SH− treated (n = 30) | SH− untreated (n = 37) |
|---|---|---|---|---|
| Gender (female/male) | 20/5 | 13/3 | 23/7 | 24/13 |
| Age (yr) | 54.8 ± 11.6[a,b] (33–74) | 64.4 ± 10.1 (40–78) | 57.1 ± 10.9 (24–75) | 61.1 ± 9.8 (37–80) |
| BMI (kg/m$^2$) | 29.8 ± 6.1 (22.3–40.0) | 29.1 ± 4.8 (21.6–38.0) | 26.8 ± 5.0 (17.4–40.0) | 27.1 ± 5.0 (21.5–39.8) |
| Waist circumference (cm) | 96.3 ± 13.1 (74.0–120.0) | 93.9 ± 11.9 (78.0–115.0) | 88.6 ± 11.9 (64.0–120.0) | 90.8 ± 10.4 (76.0–115.0) |
| Diameter of the tumor (cm) | 3.2 ± 1.0 (1.2–5.0) | 2.4 ± 0.8 (1.0–3.8) | 3.5 ± 1.4 (1.5–9.0) | 2.4 ± 0.9 (1.0–4.3) |
| Follow-up (months) | 29.4 ± 13.8 (18–54) | 36.4 ± 11.6 (18–54) | 29.6 ± 14.0 (18–54) | 34.2 ± 10.2 (22–54) |
| Obese patients, n (%) | 12 (48.0) | 8 (50.0) | 8 (26.7) | 9 (24.3) |
| Hypertensive patients, n (%) | 14 (56.0) | 10 (62.5) | 16 (53.3) | 22 (59.5) |
| Diabetic patients, n (%) | 7 (28.0) | 4 (13.3) | 3 (14.3) | 3 (8.1) |
| Dyslipidemic patients, n (%) | 12 (48.0) | 5 (31.3) | 9 (30.0) | 14 (37.8) |
| ACTH (pg/ml) | 7.8 ± 4.2 (5.0–18.4)[c,d] | 9.1 ± 5.5 (5.0–28.2)[c] | 11.5 ± 5.3 (5.2–26.9) | 14.6 ± 7.5 (5.0–34.0)[d] |
| 1-mg DST (mg/dl) | 3.8 ± 1.1 (1.7–5.4)[c,e] | 3.7 ± 1.1 (1.8–5.9)[c,e] | 1.9 ± 0.6 (0.9–3.1) | 1.6 ± 0.5 (0.5–2.6) |
| UFC (mg per 24 h) | 66.2 ± 35.6 (14.1–135.5)[c,d] | 64.7 ± 25.6 (10.1–96.4)[c,d] | 40.9 ± 21.8 (10.0–112.0) | 29.1 ± 15.8 (10.0–86.0) |

Data are expressed as mean ± SD with range in *parentheses* or as absolute number with percentage in *parentheses*. ACTH SI conversion factor is 0.22; 1-mg DSTSI conversion factor is 27.58; UFC SI conversion factor is 2.758.

[a] $P < 0.01$ *vs.* untreated SH+ patients.
[b] $P < 0.05$ *vs.* untreated SH− patients.
[c] $P < 0.001$ *vs.* untreated SH− patients.
[d] $P < 0.05$ *vs.* treated SH− patients.
[e] $P < 0.001$ *vs.* treated SH− patients.

**TABLE 2.** Individual data of patients with subclinical hypercortisolism

| Patients, n | 1-mg DST (mg/dl) | UFC (mg per 24 h) | ACTH (pg/ml) | Surgery |
|---|---|---|---|---|
| 1 | 1.7 | 73.6 | 4.4 | Yes |
| 2 | 4.0 | 120.2 | 11.6 | Yes |
| 3 | 2.4 | 79.5 | 9.7 | Yes |
| 4 | 4.3 | 43.6 | 7.2 | Yes |
| 5 | 2.4 | 96.0 | 7.8 | Yes |
| 6 | 1.9 | 84.8 | 6.4 | Yes |
| 7 | 5.0 | 59.8 | 4.9 | Yes |
| 8 | 3.0 | 26.7 | 7.0 | Yes |
| 9 | 3.7 | 135.5 | 5.0 | Yes |
| 10 | 3.2 | 19.7 | 9.2 | Yes |
| 11 | 3.1 | 98.6 | 14.8 | Yes |
| 12 | 5.1 | 106.0 | 6.2 | Yes |
| 13 | 5.0 | 18.8 | 5.0 | Yes |
| 14 | 5.1 | 27.7 | 2.7 | Yes |
| 15 | 3.2 | 43.9 | 5.8 | Yes |
| 16 | 4.8 | 115.5 | 8.0 | Yes |
| 17 | 5.0 | 14.1 | 8.9 | Yes |
| 18 | 3.6 | 65.0 | 13.3 | Yes |
| 19 | 5.4 | 107.6 | 6.4 | Yes |
| 20 | 3.5 | 70.0 | 18.4 | Yes |
| 21 | 4.1 | 65.2 | 16.2 | Yes |
| 22 | 5.0 | 41.9 | 5.0 | Yes |
| 23 | 4.9 | 82.0 | 5.0 | Yes |
| 24 | 3.5 | 22.1 | 1.0 | Yes |
| 25 | 3.0 | 44.0 | 5.0 | Yes |
| 26 | 3.2 | 42.0 | 9.0 | No |
| 27 | 3.0 | 74.9 | 28.2 | No |
| 28 | 3.1 | 52.0 | 8.0 | No |
| 29 | 3.1 | 50.0 | 5.4 | No |
| 30 | 4.6 | 95.0 | 9.0 | No |
| 31 | 5.0 | 75.0 | 5.0 | No |
| 32 | 2.9 | 96.4 | 9.3 | No |
| 33 | 1.9 | 71.0 | 7.0 | No |
| 34 | 4.1 | 39.0 | 5.0 | No |
| 35 | 3.5 | 80.0 | 9.6 | No |
| 36 | 5.9 | 42.0 | 7.5 | No |
| 37 | 5.5 | 79.0 | 11.0 | No |
| 38 | 3.1 | 10.1 | 8.3 | No |
| 39 | 3.4 | 74.0 | 6.0 | No |
| 40 | 3.4 | 78.7 | 6.1 | No |
| 41 | 3.7 | 76.5 | 11.9 | No |

ACTH SI conversion factor is 0.22; 1-mg DST SI conversion factor is 27.58; UFC SI conversion factor is 2.758.

UnTrSH−) are reported in Table 4. Comparing data at baseline with those at 18 months and at the end of the follow-up, we found that in group TrSH+ blood pressure and fasting glucose levels improved after surgery, whereas in group UntrSH+ these worsened during the follow-up period; in TrSH− patients, blood pressure improved significantly after surgery, whereas in UnTrSH− subjects, LDL levels worsened during the follow-up period (Table 4).

Similar results were obtained when analyzing data from TrSH+ patients (n = 15) and TrSH− patients (n = 25), who were no longer on steroid substitutive therapy for at least 1 yr (data not shown). In addition, no differences were found between patients with and without postsurgical hypocortisolism in terms of mass size or baseline biochemistry (data not shown).

The adjusted subgroups analysis showed that in the overall sample, the surgical treatment of adrenal incidentalomas was associated with weight loss, improvement of blood pressure, and fasting glucose levels, regardless of age and duration of follow-up, and for the presence of obesity, arterial hypertension, and diabetes mellitus at baseline, the latter three covariates were separately considered (Table 5). The same analysis showed that this effect was present in SH+ but not in SH− patients. Finally, for fasting glucose and blood pressure levels, a treatment-by-SH group interaction was present, even without reaching the statistical significance for this latter end point ($P = 0.073$) (Table 5).

Overall, these data suggest that surgical management of SH improves body weight, blood pressure, and fasting glucose levels over conservative management and that the benefit is evident also in SH− patients but much greater in the SH+ than the SH− patients (Table 3). Moreover, an interaction between the surgical approach and the presence of SH for improving fasting glucose levels is present, even after adjusting for possible confounding factors (Table 5).

## Discussion

Our study suggests that surgical treatment of SH in patients with incidentally discovered adrenal mass is associated with a significantly higher probability of improving body weight, blood pressure, and fasting glucose levels. In addition, this treatment significantly protects from worsening of blood pressure, fasting glucose, and LDL cholesterol levels.

Previous data regarding the outcome of the several components of the metabolic syndrome after recovery from SH are conflicting. Indeed, some studies described an improvement of some features of metabolic syndrome in patients with SH and adrenal incidentalomas after surgical removal of the adrenal mass (11, 24, 25, 27, 29), whereas others gave more conflicting results (23, 26, 28). This discordance is possibly due to the small sample size (11, 23–28) and the lack of a control group in most studies (23, 24, 26, 27) and to the different design (*i.e.* retrospective or prospective). Of utmost importance, the criteria for diagnosing SH were largely different, thus rendering the results of previous studies hardly comparable.

Our finding of an improvement of the several components of the metabolic syndrome after recovery from SH is in keeping with a recent prospective, randomized study of Toniato *et al.* (29). In this study, however, the control

**TABLE 3.** Change of body weight, blood pressure, fasting glucose, and LDL cholesterol in treated and untreated patients with and without subclinical hypercortisolism

| | SH+ treated (n = 25) | SH+ untreated (n = 16) | SH− treated (n = 30) | SH− untreated (n = 37) |
|---|---|---|---|---|
| Steady body weight, n (%) | 15 (60.0) | 10 (62.5) | 21 (70) | 25 (67.6) |
| Decreased body weight, n (%) | 8 (32.0)[a,b] | 2 (12.5) | 3 (10.0) | 2 (5.4) |
| Increased body weight, n (%) | 2 (8.0) | 4 (25.0) | 6 (20.0) | 10 (27.0) |
| Steady blood pressure, n (%) | 11 (44.0) | 8 (50.0) | 17 (56.7) | 21 (56.8) |
| Improved blood pressure, n (%) | 14 (56.0)[b,c] | 0 (0.0) | 9 (30.0)[d] | 5 (13.5) |
| Worsened blood pressure, n (%) | 0 (0.0)[c] | 8 (50.0)[e] | 4 (13.3) | 11 (29.7) |
| Steady fasting glucose, n (%) | 13 (52.0) | 10 (62.5) | 26 (86.7) | 30 (81.1) |
| Improved fasting glucose, n (%) | 12 (48.0)[b,c] | 0 (0.0) | 3 (10.0) | 3 (8.1) |
| Worsened fasting glucose, n (%) | 0 (0.0)[c] | 6 (37.5)[b,d] | 1 (3.3) | 4 (10.8) |
| Steady LDL cholesterol, n (%) | 10 (40.0) | 5 (31.2) | 19 (63.3) | 11 (29.8) |
| Improved LDL cholesterol, n (%) | 9 (36.0) | 3 (18.8) | 8 (26.7) | 9 (24.3) |
| Worsened LDL cholesterol, n (%) | 6 (24.0)[a] | 8 (50.0)[b] | 3 (10.0)[f] | 17 (45.9) |

Data are absolute number of patients with percentage in *parentheses* comparing data at baseline with those at the end of the follow-up. The same results were obtained comparing data at baseline with those at 18 months of follow-up. LDL, Low density lipoprotein.

[a] $P = 0.05$ *vs.* untreated SH+ patients.

[b] $P < 0.01$ *vs.* treated SH− patients.

[c] $P < 0.001$ *vs.* untreated SH+ patients.

[d] $P = 0.05$ *vs.* untreated SH− patients.

[e] $P < 0.05$ *vs.* treated SH− patients.

[f] $P < 0.001$ *vs.* untreated SH− patients.

groups of treated and untreated SH− subjects were lacking, and, therefore, the effect of the surgical treatment and the usefulness of the diagnosis of SH could not have been fully elucidated. Indeed, the difference between the frequency of the improvement/worsening of the features of the metabolic syndrome in treated SH+ patients compared with SH− patients treated for the tumor size or growth and in untreated SH+ subjects compared with untreated SH− ones suggests that in patients with adrenal incidentalomas, the diagnosis of SH is useful in identifying patients who may benefit from the surgical treatment.

However, we found that in SH− patients treated for tumor size or growth, LDL worsened less frequently and blood pressure levels improved more frequently than in untreated SH− subjects (Table 2). These data are in agreement with previous studies suggesting a possible improvement of blood pressure (11, 23) and fasting glucose levels (11, 23, 24) after surgery for adrenal incidentalomas, even in patients without a diagnosis of SH before operation. Because the diagnosis of SH is defined by using arbitrary cutoffs of indexes of cortisol secretion, it is possible to hypothesize that some patients classified as not having SH might have, in fact, a mild degree of cortisol hypersecretion. The finding that ACTH levels were lower in SH− patients treated for tumor size or growth than in untreated SH− patients and that the duration of postoperative hypoadrenalism did not differ between patients with or without SH supports this view. In patients with adrenal incidentalomas, indeed, the currently used criteria for diagnosing SH are probably not sufficiently sensitive because cortisol secretion is a continuum, and it is highly variable (31, 33, 39–41). Consequently, one could hypothesize that in patients with incidentally discovered adrenal masses, the surgical treatment could be indicated, regardless of the presence of SH. It is also important to underline that the criteria for defining SH are still debated (32), mainly for the lack of a clearly demonstrated association between the indexes of cortisol secretion and the clinical features of subtle cortisol excess. However, the criteria used in the present study have been previously somewhat substantiated on clinical basis (11, 15, 20) and recently by a paper specifically designed to investigate this topic (41). Regarding the best cutoff of 1-mg DST in diagnosing SH, no consensus is available (33). The use of a 1-mg DST cutoff of 3.0 $\mu$g/dl (83 nmol/liter) rather than 5 $\mu$g/dl (138 nmol/liter) as recommended by the National Institutes of Health (30) was preferred to increase the test sensitivity (31) and because this cutoff showed the best accuracy in predicting vertebral fractures, which are one among the deleterious effects of hypercortisolism (20). Finally, as reported in the recent Endocrine Society Guidelines (33), even if in patients with overt hypercortisolism, the determination of the ACTH levels has to be used for the differential diagnosis of the origin of cortisol hypersecretion, in patients with adrenal incidentalomas without the classic signs or symptoms of overt cortisol excess, this test may be considered among the criteria for diagnosing adrenal autonomy. For this reason, several authors have proposed a low

**TABLE 4.** Body weight, blood pressure, fasting glucose, and LDL cholesterol levels as absolute values at baseline, 18 months, and last follow-up in treated and untreated patients with and without subclinical hypercortisolism

| | SH+ treated (n = 25) | SH+ untreated (n = 16) | SH− treated (n = 30) | SH− untreated (n = 37) |
|---|---|---|---|---|
| Baseline BW (kg) | 77.3 ± 20.4 (52–129) | 75.0 ± 14.8 (53.7–97.5) | 69.9 ± 16.4 (48.0–130.0) | 70.8 ± 13.7 (50.0–103.0) |
| 18-months BW (kg) | 76.3 ± 21.2 (51–140) | 75.6 ± 14.8 (55–102) | 70.0 ± 15.6 (4–125) | 72.6 ± 13.6 (51.3–115.0) |
| Last follow-up BW (kg) | 75.1 ± 19.1 (49–123) | 76.1 ± 14.9 (55–103) | 70.1 ± 16.5 (47–130) | 72.0 ± 13.6 (51.3–111.0) |
| Baseline SBP (mm Hg) | 134.9 ± 16.4 (105–170) | 129.9 ± 9.4 (125–135) | 127.8 ± 14.1 (100–150) | 128.2 ± 15.7 (100–160) |
| 18-months SBP (mm Hg) | 122.8 ± 11.6 (105–155)[a] | 140.6 ± 17.4 (110–170)[b] | 120.0 ± 16.4 (90–165)[c] | 132.3 ± 18.7 (105–180) |
| Last follow-up SBP (mm Hg) | 123.9 ± 11.5 (110–155)[a] | 139.4 ± 14.2 (132–147)[b] | 119.8 ± 15.8 (90–160)[c] | 130.5 ± 15.8 (110–170) |
| Baseline DBP (mm Hg) | 81.8 ± 10.55 (60–115) | 77.0 ± 6.5 (74–80) | 80.5 ± 7.1 (70–95) | 77.3 ± 8.2 (60–90) |
| 18-months DBP (mm Hg) | 74.3 ± 7.9 (60–89)[d] | 84.4 ± 12.1 (110–170)[e] | 73.8 ± 8.3 (60–90)[f] | 80.2 ± 9.9 (60–100) |
| Last follow-up DBP (mm Hg) | 75.5 ± 7.3 (65–85)[d] | 83.1 ± 10.0 (78–88)[e] | 77.6 ± 8.5 (860–95)[f] | 78.6 ± 7.9 (60–95) |
| Baseline FG (mg/dL) | 98.9 ± 18.9 (72–137) | 92.6 ± 12.6 (74–129) | 99.0 ± 32.3 (66–235) | 90.5 ± 12.3 (73–130) |
| 18-month FG (mg/dl) | 89.3 ± 12.0 (74–130)[g] | 114.6 ± 37.3 (73–195) | 90.0 ± 17.8 (67–150) | 95.7 ± 20.0 (75–180) |
| Last follow-up FG (mg/dl) | 90.0 ± 14.6 (74–138)[g] | 113.6 ± 37.8 (73–190)[h] | 90.3 ± 17.3 (67–144) | 94.8 ± 20.1 (75–180) |
| Baseline LDL (mg/dl) | 141.1 ± 38.3 (65–223) | 124.5 ± 38.6 (77–200) | 122.1 ± 35.0 (61–233) | 124.0 ± 34.9 (55–230) |
| 18-months LDL (mg/dl) | 124.1 ± 37.8 (52–201) | 125.2 ± 19.8 (102–169) | 123.0 ± 35.0 (60–204) | 138.2 ± 26.5 (93–195)[i] |
| Last follow-up LDL (mg/dl) | 124.9 ± 39.7 (52–201) | 125.5 ± 19.5 (102–169) | 123.2 ± 35.8 (50–204) | 138.7 ± 27.2 (93–205)[i] |

BW, Body weight; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting glucose; LDL, low density lipoprotein.

[a] $P < 0.01$ *vs.* baseline SBP in SH+ treated group.

[b] $P < 0.05$ *vs.* baseline SBP. in SH+ untreated group.

[c] $P < 0.05$ *vs.* baseline SBP. in SH− treated group.

[d] $P < 0.01$ *vs.* baseline DBP in SH+ treated group.

[e] $P < 0.05$ *vs.* baseline DBP in SH+ untreated group.

[f] $P < 0.01$ *vs.* baseline DBP in SH−-treated group.

[g] $P < 0.05$ *vs.* baseline FG in SH+-treated group.

[h] $P < 0.05$ *vs.* baseline FG in SH+-untreated group.

[i] $P < 0.01$ *vs.* baseline LDL in SH−-untreated group.

**TABLE 5.** Effect of intervention on body weight, blood pressure, fasting glucose, and LDL cholesterol in the overall sample and by SH group

| | Overall sample | | SH | | | | Interaction |
|---|---|---|---|---|---|---|---|
| | | | SH+ | | SH− | | |
| Outcome | OR (95% CI)[a] | *P* | OR (95% CI)[b] | *P* | OR (95% CI)[b] | *P* | *P*[c] |
| Body weight | 6.48 (1.15–36.52) | 0.034 | 12.11 (0.94–156.64) | 0.056 | 3.19 (0.25–40.62) | 0.371 | 0.818 |
| Blood pressure | 5.86 (1.91–17.98) | 0.002 | 26.46 (2.34–299.10) | 0.008 | 3.12 (0.77–12.64) | 0.111 | 0.073 |
| Fasting glucose | 4.411 (1.15–16.94) | 0.031 | 26.14 (2.13–21.05) | 0.011 | 1.20 (0.19–7.69) | 0.851 | 0.036 |
| LDL cholesterol | 2.49 (0.75–8.22) | 0.135 | 3.33 (0.28–39.47) | 0.341 | 1.42 (0.32–6.36) | 0.650 | 0.622 |

OR, Odds ratio; CI, confidence interval; LDL, low density lipoprotein.

[a] ORs are adjusted for age, follow-up time, SH, and presence at baseline of obesity (for body weight), arterial hypertension (for blood pressure), diabetes mellitus (for fasting glucose), and dyslipidemia (for LDL cholesterol).

[b] ORs are adjusted for age, follow-up time, and presence at baseline of obesity (for body weight), arterial hypertension (for blood pressure), diabetes mellitus (for fasting glucose), and dyslipidemia (for LDL cholesterol).

[c] SH group by intervention interaction *P* values represent the by-group heterogeneity of the adjusted ORs.

ACTH level as a parameter for diagnosing SH in patients with adrenal incidentalomas (1).

On the other hand, in our data set, patients with SH convincingly improved more with surgery than patients without SH. Indeed, the adjusted subgroup analysis showed that the effect of the surgical treatment is evident only in patients with SH and that an interaction between surgical intervention and SH is present, suggesting that the biochemical diagnosis of SH is useful in identifying those individuals who may better benefit from the surgical approach.

Although the surgical approach was suggested to all patients with a diagnosis of SH, 16 patients preferred not to be operated on. These patients were older than the SH patients who underwent surgery. Therefore, we cannot exclude that this could have partially biased our results because older patients are more likely to experience the worsening of the metabolic parameters. However, the fact that the surgical approach was found to be associated with a beneficial effect on the features of the metabolic syndrome, regardless of age, argues against this hypothesis.

Another possible confounding factor may be related to the steroid substitutive therapy. Indeed, even if its duration was comparable between group TrSH+ and TrSH−, it is not possible to exclude that treatment with cortisone acetate may have mitigated part of the improvement in metabolic parameters experienced postoperatively. On the other hand, a blood pressure-lowering effect may be attributed to surgery *per se*, regardless for the hormonal status. However, the fact that improvement is better in the SH+ than SH− groups argues against this possibility.

Finally, this study was not designed to investigate which parameter or combination of parameters are the best for diagnosing SH and reliably identifying surgical candidates. Further studies are needed to clarify this issue.

Overall, although the study is not randomized and has some limitations, such as the small sample size and its retrospective nature, the present findings suggest that the biochemical diagnosis of hypercortisolism, even in the absence of the specific clinical features, is important. In the presence of a consistent evidence of a biochemical cortisol overproduction, the diagnosis of hypercortisolism should be assumed, despite the degree of clinical features that is always a spectrum of clinical findings; in patients with an adrenal incidentaloma causing biochemical hypercortisolism, a prompt treatment is beneficial, and it is not appropriate to follow them until they develop classical features or more complications of excessive cortisol production.

In conclusion, the present study has two important clinical applications: 1) in patients with adrenal incidentalomas, particularly if potential comorbidities are present, the surgical treatment appears to be useful, whereas the conservative approach deleterious regarding blood pressure and fasting glucose levels and 2) the biochemical diagnosis of SH is useful in detecting patients who better take advantage of the surgical treatment. To confirm the present findings, a prospective randomized clinical trial on a larger sample of patients with adrenal incidentalomas with and without SH, treated with surgery or with a conservative approach, is needed.

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