**CLINICAL STUDY**

**Long-term morphological, hormonal, and clinical follow-up in a single unit on 118 patients with adrenal incidentalomas**

R Giordano1, E Marinazzo2, R Berardelli2, A Picu2, M Maccario2, E Ghigo2 and E Arvat2

1Department of Clinical and Biological Sciences and 2Division of Endocrinology, Diabetology and Metabolism, Department of Internal Medicine, University of Turin, Azienda Ospedaliero-Universitaria San Giovanni Battista, Corso Dogliotti 14, 10126 Turin, Italy

(Correspondence should be addressed to E Arvat; Email: emanuela.arvat@unito.it)

**Abstract**

**Objective:** To evaluate long-term morphological, functional, and clinical outcome in adrenal incidentalomas.

**Design and methods:** A total of 118 patients (77 F and 47 M; age 62.3 ± 1.0 years) with adrenal incidentalomas were evaluated at baseline and followed-up for median 3 years (range 1–10 years) by clinical, biochemical, hormonal, and morphological evaluation. Among them, six patients with diagnosis of subclinical Cushing’s syndrome (SCS) underwent surgery.

**Results:** At entry, 86% (n = 102) of tumors were nonfunctioning (NF) and 14% (n = 16) showed SCS. Comparing NF with SCS patients, a significantly higher percentage of dyslipidemia was found in the group of SCS patients (50 vs 23%, P = 0.033). During follow-up, adrenal function remained normal in all NF patients, none of them developed subclinical or overt endocrine disease. The cumulative risk of mass enlargement was globally low (25%), but progressive up to 8 years. SCS was confirmed in all patients, and none of them shifted to overt Cushing’s syndrome. The cumulative risk of developing metabolic–cardiovascular abnormalities was globally low (22%), but progressive up to 8 years and new diseases were recorded in the group of NF patients only (three patients with dyslipidemia, four with impaired fasting glucose/impaired glucose tolerance, and three with diabetes mellitus). SCS patients who underwent surgery did not show any significant clinical improvement.

**Conclusions:** The risk of mass enlargement, hormonal, and metabolic impairment over time is globally low. Conservative management seems to be appropriate, but further prospective studies are needed to establish the long-term outcome of such patients, especially for metabolic status, cardiovascular risk profile and their relationship with endocrine function.

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**Introduction**

Adrenal incidentalomas, clinically unapparent adrenal masses discovered by abdominal imaging procedures for unrelated reasons, have become a common finding in clinical practice. In fact, the widespread use of abdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) have led to an increase in the detection of adrenal incidentalomas in recent years, ranging between 1 and 6% in different series (1–4). Although the majority of adrenal lesions are benign non-hypersecreting cortical adenomas, they represent a clinical concern because of the risk not only of malignancy but also of subclinical hormonal hypersecretion, mainly cortisol secretion (5, 6). The latter condition, the so called subclinical Cushing’s syndrome (SCS), is characterized by subtle alterations of the hypothalamus–pituitary–adrenal (HPA) axis due to autonomous cortisol-secreting adenomas without signs or symptoms of overt hypercortisolism (6). Data concerning the prevalence of SCS in patients with adrenal incidentalomas are controversial, due to different diagnostic criteria used, as no defined consensus for the biochemical diagnosis is available (6–9). The initial evaluation of a patient with an adrenal incidentaloma aims at defining the functional status and the possibility of malignant disease (3, 5, 10, 11). Except for masses suspected for malignancy and/or clearly hyperfunctioning, the majority of authors recommend a conservative approach (5, 10–20). However, no comprehensive guidelines exist concerning the frequency and duration of follow-up of patients with adrenal incidentalomas, due to limited data on the natural history and, namely, on possible changes in adrenal size and/or hormonal pattern. Moreover, although subclinical glucocorticoid excess of SCS patients has been supposed to induce metabolic derangement, it is controversial whether this pathological condition is or is not associated with long-term morbidity, may progress to overt Cushing’s syndrome (CS), and whether treatment to reverse subtle glucocorticoid excess can influence the outcome of the disease (21, 22).
Based on this background, in the present prospective study, we evaluated the long-term morphological, hormonal, and clinical outcome of 118 patients with adrenal incidentalomas.

Patients and methods

Experimental design

A total of 128 consecutive patients (77 F and 51 M; mean ± s.e.m. age: 62.4 ± 0.9 years, range age: 30–87 years) with diagnosed adrenal incidentalomas by abdominal CT or MRI were selected for this study.

All the patients gave their informed consent to participate in the study, which had been approved by the local ethical committee, in agreement with the Declaration of Helsinki.

Hormonal evaluation included morning serum cortisol, plasma ACTH, serum DHEA-sulfate (DHEA-S), 17-hydroxyprogesterone (17OHP), aldosterone, plasma renin activity (PRA), 24-h urinary free cortisol (UFC), 24-h urinary metanephrines, 1 mg dexamethasone suppression test (Nugent test, dose synacthen test (DST), dexamethasone 1 mg p.o. at midnight), and 48-h–2 mg/day dexamethasone suppression test (Liddle I test, low dose dexamethasone suppression test (LDDST), dexamethasone 0.5 mg p.o. every 6 h for 2 days). When endocrine abnormalities were found, confirmatory tests were always performed, namely cortisol rhythm for suspected SCS, high DST for suspicion of late onset congenital adrenal hyperplasia, saline loading test for suspicion of primary hyperaldosteronism, and iodine-123-metaiodobenzylguanidine (MIBG) scintigraphy for suspected pheochromocytoma.

The diagnosis of SCS was based on a post-DST cortisol level ≥ 1.8 μg/dl (50 nmol/l) combined with an abnormal result in at least one of the following tests to evaluate HPA axis: i) post-LDDST cortisol levels ≥ 1.8 μg/dl (50 nmol/l); ii) absence of cortisol rhythm (midnight serum cortisol ≥ 7.5 μg/dl (220 nmol/l)); iii) low ACTH levels (< 5 pg/ml (1.1 pmol/l)); and iv) high UFC (≥ 100 μg/24 h (275 mmol/24 h)), in the absence of clinical signs or symptoms of cortisol excess.

Using this diagnostic work-up, patients with overt endocrine disease (four patients: one with primary hyperaldosteronism and three with suspected pheochromocytoma) or CT/MRI malignant features (six patients) underwent surgery, and were excluded from the follow-up study (Fig. 1).

The resulting group was composed of 118 patients (71 F and 47 M; aged 62.3 ± 1.0 years, range 30–87 years). Among them, six patients with diagnosis of SCS underwent surgery (four patients with mass size > 40 mm and two patients with severe metabolic syndrome), and afterwards, they remained in the follow-up protocol as a different group (Fig. 1).
Statistical analysis

Results are expressed as mean ± S.E.M. or median. The statistical analysis was carried out using Mann–Whitney \( U \) test and Pearson’s \( \chi^2 \) test for comparison between NF and SCS patients; logistic regression analysis was performed to predict the risk of metabolic–cardiovascular diseases in SCS versus NF.

Kaplan–Meier curves were generated to estimate the cumulative risk of mass variation or metabolic–cardiovascular abnormalities occurrence during the follow-up. To evaluate the factors predictive of progressive disease, we selected the following parameters: age, sex, mass size and side, overweight/obesity (BMI cutoff: 25 kg/m\(^2\)) (27), arterial hypertension (blood pressure values cutoff: 125/80 mmHg) (28), impaired glucose tolerance (IGT; 2 h post OGTT glycemia value cutoff: 140–200 mg/dl) (29), diabetes (glycemia value cutoff: 126 mg/dl) (29), and dyslipidemia (triglyceride value cutoff: 150 mg/dl; total cholesterol values cutoff: 240 mg/dl) (30).

Statistical significance was set at \( P<0.05 \); Statistical Package for the Social Science (SPSS 17.0 for Windows; SPSS Inc., 1989–2005, Chicago, IL, USA) was used for the analysis (31).

Results

Data at baseline

At entry, 86% of cases (102 out of 118) were NF, while 14% of cases (16 out of 118) showed SCS (Fig. 1).

A total of 102 patients (86%) had unilateral (57 right side and 45 left side) and 16 (14%) bilateral lesions. The mean lesion diameter was of 22.2 ± 0.8 mm (range 9–48 mm); in 110 patients (93%), adrenal masses were smaller than 40 mm (two patients, 9 mm; ten patients, 10 mm; 50 patients, > 10 and ≤ 20 mm; and 48 patients, > 20 and < 40 mm), while in the remaining eight cases (7%) mass size was > 40 mm, including four NF (with CT features suggestive for myelolipomas) and four SCS (with unilateral lesion who underwent surgery) patients.

In total, 64 patients were obese or overweight (54%), 73 were hypertensive (61%), 32 were dyslipidemic (27%), while impaired fasting glucose (IFG)/IGT or DM was present in 18 patients (15%).

Comparing NF with SCS patients, no significant differences were found for age (61.9 ± 1.0 vs 65.0 ± 2.6 years), sex (in NF: 61 F and 41 M; in SCS: 10 F and 6 M), or mass size (mean ± S.E.M.: 21.5 ± 0.8 vs 26.5 ± 2.6 mm; Table 1). In both groups, the cumulative risk of mass variation or metabolic–cardiovascular diseases in SCS versus NF was significantly higher (81 vs 58%, OR 3.0, 95% confidence interval (CI) 1.1–9.6, \( P=0.033 \)). However, two of the SCS patients showed low density lipoprotein (LDL) cholesterol ≥ 190 mg/dl and triglycerides ≥ 150 mg/dl, while in two of them LDL were ≥ 160 mg/dl; none of them showed a high density lipoprotein cholesterol < 40 mg/dl (Table 1).

No significant difference was found for obesity/overweight (SCS versus NF: 43 vs 55%, odds ratio (OR) 0.2), hypertension (81 vs 58%, OR 3.0), or glucose intolerance (19 vs 15%, OR 1.3), while a significantly higher percentage of dyslipidemia was found in the group of SCS patients (50 vs 23%, OR 3.2, 95% confidence interval (CI) 1.1–9.6, \( P=0.033 \)). However, two of the SCS patients showed low density lipoprotein (LDL) cholesterol ≥ 190 mg/dl and triglycerides ≥ 150 mg/dl, while in two of them LDL were ≥ 160 mg/dl; none of them showed a high density lipoprotein cholesterol < 40 mg/dl (Table 1).

No correlation between lipid profile and degree of cortisol hypersecretion, or time between the first and the last evaluation was recorded in SCS patients.

In a multiple regression model which considered also age, mass size, obesity/overweight, and hypertension as predictors, the condition of SCS was associated with a significantly higher prevalence of dyslipidemia (OR 5.0, 95% CI 1.3–19.5, \( P=0.02 \)).

Data at last follow-up

In all patients with NF lesions, adrenal function persisted as normal and none of them developed subclinical or overt endocrine disease, all of them

Table 1 Characteristics of patients at follow-up. Value for continuous variables are given as mean ± S.E.M.

<table>
<thead>
<tr>
<th></th>
<th>NF (n=102)</th>
<th>SCS (n=16)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.9 ± 1.0</td>
<td>65.0 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mass size (mm)</td>
<td>21.5 ± 0.8</td>
<td>26.5 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26.8 ± 0.5</td>
<td>24.9 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>18.9 ± 1.7</td>
<td>17.2 ± 3.4 (2 pts &lt; 5)</td>
<td>NS</td>
</tr>
<tr>
<td>Morning cortisol ((\mu g/dl))</td>
<td>17.8 ± 1.5</td>
<td>16.4 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Midnight cortisol ((\mu g/dl))</td>
<td>–</td>
<td>9.8 ± 0.8 (13 pts ≥ 7.5)</td>
<td>–</td>
</tr>
<tr>
<td>UFC ((\mu g/24 h))</td>
<td>54.7 ± 3.5</td>
<td>68.5 ± 9.9 (4 pts ≥ 100)</td>
<td>NS</td>
</tr>
<tr>
<td>DHEA-S ((\mu g/l))</td>
<td>631.2 ± 60.6</td>
<td>665.1 ± 116.3</td>
<td>NS</td>
</tr>
<tr>
<td>Post-Nugent test cortisol ((\mu g/dl))</td>
<td>1.7 ± 0.1</td>
<td>4.6 ± 0.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Post-Liddle I test cortisol ((\mu g/dl))</td>
<td>1.6 ± 0.4</td>
<td>4.6 ± 0.8</td>
<td>0.05</td>
</tr>
<tr>
<td>OB/overweight (%)</td>
<td>55</td>
<td>43</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>58</td>
<td>81</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>23</td>
<td>50</td>
<td>0.033</td>
</tr>
<tr>
<td>IFG–IGT–DM (%)</td>
<td>15</td>
<td>19</td>
<td>NS</td>
</tr>
</tbody>
</table>

OB/OVER, obesity or overweight; HYPERT, hypertension; DYSLIP, dyslipidemia; IGF/IGT/DM, impaired fasting glucose/impaired glucose tolerance/diabetes mellitus. Results for binary variables are expressed as percentages (%). ACTH (pg/ml; 1 pg/ml × 0.22 = 1 pmol/l); cortisol (\(\mu g/dl\); 1 \(\mu g/dl\) × 27.59 = 1 nmol/l); DHEA-S (\(\mu g/l\); 1 \(\mu g/l\) × 0.0027 = 1 \(\mu mol/l\)), and UFC (\(\mu g/24 h\); 1 \(\mu g/24 h\) × 2.75 = 1 nmol/dl).
showing a cortisol level < 1.8 μg/dl after Nugent test. Considering individual cases, a change in mass size of at least 5 mm was observed in nine cases: an increase, with no signs of malignancy, in seven cases, while a decrease was seen in two cases.

In all SCS patients who did not undergo surgery, a condition of subclinical hypercortisolism was confirmed and none of them shifted to overt CS; moreover, none of them showed a tumor enlargement or reduction over time (Table 2).

At the end of follow-up, there were no significant changes in BMI in either NF or SCS, while new cardiovascular and metabolic diseases were recorded in the group of NF patients only: three patients developed dyslipidemia, four patients IFG/IGT, and three patients diabetes mellitus.

The six SCS patients who underwent surgery neither experienced corticotroph insufficiency nor showed any significant improvement in either BMI or any clinical and metabolic parameters.

During follow-up, no new cases of hypertension occurred and none of the known hypertensive patients needed an increase in the number or dosage of drug treatment, without any significant difference between SCS and NF.

**Survival analysis**

The cumulative risk of mass enlargement was globally low (about 25%) but progressive up to 8 years, independently of mass size and side at entry, gender, age, BMI, blood pressure, glucose tolerance, and dyslipidemia (Fig. 3).

The risk of mass reduction was very low (<10%), independently of mass size and side at entry, gender, age, BMI, blood pressure, glucose tolerance, and dyslipidemia (data not shown).

Also the estimated cumulative risk of developing metabolic–cardiovascular abnormalities over time was globally low (about 22%) but progressive up to 8 years. The occurrence of new diseases was not significantly associated with mass size change and side, gender, age, BMI, and duration of follow-up (Fig. 4).

![Figure 2](image.jpg)

**Figure 2** Metabolic and cardiovascular diseases in patients with nonfunctioning adrenal incidentalomas (NF) and with subclinical Cushing’s syndrome (SCS) at entry of follow-up. OB/OVER, obesity or overweight; HYPERT, hypertension; DYSLIP, dyslipidemia; IFG/IGT/DM, impaired fasting glucose/impaired glucose tolerance/diabetes mellitus. *P=0.033.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics of subclinical Cushing’s syndrome patients who did not undergo surgery, at entry and at last follow-up. Values for continuous variables are given as mean ± S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.1 ± 1.9</td>
</tr>
<tr>
<td>Mass size (mm)</td>
<td>24.9 ± 3.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 0.7</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>13.0 ± 2.4 (1 pt &lt; 5)</td>
</tr>
<tr>
<td>Morning cortisol (μg/dl)</td>
<td>15.9 ± 1.4</td>
</tr>
<tr>
<td>Midnight cortisol (μg/dl)</td>
<td>7.7 ± 0.6 (7 pt ≥ 7.5)</td>
</tr>
<tr>
<td>UFC (μg/24 h)</td>
<td>76.1 ± 15.2 (4 pts ≥ 100)</td>
</tr>
<tr>
<td>DHEA-S (μg/l)</td>
<td>649.0 ± 135.8</td>
</tr>
<tr>
<td>Post-Nugent test cortisol (μg/dl)</td>
<td>3.7 ± 0.5</td>
</tr>
<tr>
<td>Post-Liddle test cortisol (μg/dl)</td>
<td>3.8 ± 0.5</td>
</tr>
<tr>
<td>OB/OVER (%)</td>
<td>30</td>
</tr>
<tr>
<td>HYPERTEN (%)</td>
<td>70</td>
</tr>
<tr>
<td>DYSLIPID (%)</td>
<td>30</td>
</tr>
<tr>
<td>IFG–IGT–DM (%)</td>
<td>20</td>
</tr>
</tbody>
</table>

Results for binary variables are expressed as percentages (%).
Discussion

In the present study, we evaluated the risk of mass enlargement, endocrine, and metabolic–cardiovascular changes during a long-term follow-up of a group of patients with adrenal incidentalomas, which included both NF lesions and patients with SCS.

While several diagnostic and therapeutic algorithms have been proposed for management of patients with adrenal incidentalomas (3, 5, 10–20), follow-up studies are few and those reported in the literature are not univocal, probably on account of different durations of follow-up, numbers of patients studied, and methodological approach adopted (14–20).

The management of adrenal incidentalomas represents a clinical concern because of the risk not only of malignancy but also of subclinical hormonal hypersecretion, mainly cortisol secretion (5, 6). Data concerning the prevalence of SCS in patients with adrenal incidentalomas are controversial, due to different diagnostic criteria used, as no clear consensus for the biochemical diagnosis is available (6–9).

We found that SCS was the most frequent hormonal abnormality found at entry in our series of adrenal incidentalomas, in agreement with other authors (2, 6–9, 15). The criteria that we used for the diagnosis of SCS were a post-1 mg dexamethasone overnight test cortisol level \( \geq 1.8 \, \mu g/dl \) (50 nmol/l) and an abnormal result of at least one of the other tests for evaluating HPA axis, in the absence of clinical signs of cortisol excess. Although the National Institutes of Health state of the science conference panel on adrenal incidentaloma had recommended a cortisol cutoff of 5.0 \( \mu g/dl \) (140 nmol/l) (5), according to the Endocrine Society Clinical Practice Guidelines for CS and in order to reduce the number of false negative results in the screening for SCS (23), we used a cortisol cutoff of 1.8 \( \mu g/dl \) as first test for hormonal evaluation. Using these criteria, at baseline, we identified 16 patients with SCS, 13% of patients at entry of follow-up.

Although subclinical cortisol excess of SCS patients has been supposed to induce metabolic derangement (7, 9, 32–34), in our series of SCS patients, we did not find, at entry, any difference with NF patients in terms of obesity/overweight, hypertension, and glucose intolerance. This is in agreement with some (19, 20), but not with other previous reports (33, 34), which showed a higher prevalence of metabolic derangement in SCS patients. In agreement with these latter reports, we found, on the other hand, a higher prevalence of hypercholesterolemia and hypertriglyceridemia in SCS than NF patients: two out of SCS patients showed LDL cholesterol higher than 160 mg/dl, the cutoff for lifestyle intervention, while two of them displayed LDL cholesterol higher than 190 mg/dl, the cutoff for pharmacological intervention (30). Apparently, these data seem to be in agreement with the involvement of glucocorticoid hypersecretion in the occurrence of impaired lipid metabolism, although a random effect cannot be ruled out based on the small number of cases in our study.

In this context, our findings also showed that the six SCS patients who underwent adrenalectomy did not show any significant improvement in either BMI or any clinical and metabolic parameters, differently from other reports (7, 35). Our findings would not support a significant impact of subclinical glucocorticoid excess on metabolic status in patients with SCS, although only a case–control follow-up study in a large population of SCS patients undergoing surgery or not will clarify this crucial clinical point.

During the follow-up, tumor growth was detected in a low percentage of cases, all with NF tumors, with no evidence of malignant features at MRI or CT. The cumulative risk of mass enlargement was globally low (25%) but progressive up to 8 years, similarly to that reported by several authors (14, 17, 18), although lower percentages (3–4%) or even no mass enlargement was observed in other series (13). Moreover, mass reduction was also detected in few patients but no basal
predictor, either morphological (i.e. initial mass size) or functional (hormonal or metabolic status), has been found and mass changes were not associated with the development of either endocrine alterations or malignant transformation of the lesions, in agreement with previous reports (19).

Regarding the risk of developing new endocrine abnormalities over the time, we were unable to find any new overt or subtle endocrine alteration in patients with NF tumors, while the diagnosis of SCS was confirmed in all cases at each time of follow-up, without any fluctuation in cortisol secretion, and none of them showed a shift to overt clinical hypercortisolism. These findings, showing that the endocrine status of patients with adrenal incidentalomas is stable over time, independently of basal mass size and side, are in agreement with previous studies (19), although data in literature are controversial, mainly due to different study protocols and different diagnostic criteria adopted.

The third issue addressed in the present study concerned the risk of metabolic–cardiovascular abnormalities over time. Newly diagnosed metabolic diseases appeared in 10 out of 112 (9%) patients, all with NF lesions. This risk was globally low, about 22%, but progressive up to 8 years, and not associated with basal mass size, gender, age, BMI, duration of follow-up, and changes in mass volume. Differently from other reports (7, 14, 15), we did not find any new metabolic–cardiovascular disease overtime in the group of SCS patients, or any mass change. The absent progression of metabolic abnormalities over time in our patients with subclinical hypercortisolism, together with the lacking correlation between the lipid profile, more impaired in our SCS than in NF patients, and the degree of cortisol hypersecretion or the time between the first hormonal evaluation and the last follow-up are not supporting a significant impact of subclinical glucocorticoid excess on the metabolic outcome of patients with adrenal incidentaloma. However, as changes in the metabolic status of SCS overtime is likely to be subtle, a further anthropometric or metabolic evaluation, namely waist measure or HOMA index, would have better characterized the presence of some clinical changes in our population during the follow-up, so the lack of these parameters is a limitation of our study.

Once again, we cannot exclude that these data simply reflect the small number of SCS patients included in the present study; otherwise, it can also be suggested that some systemic or local factor, other than glucocorticoids, may be responsible for the progression of metabolic impairment in apparently NF tumors.

In conclusion, our results show that the majority of adrenal incidentalomas are apparently NF, and SCS is the most frequent hormonal abnormality. The risk of developing mass enlargement, hormonal, and metabolic impairment over the time seems to be globally low, thus suggesting conservative management. However, prospective multicentric case–control studies on large populations of patients with and without functioning or nonfunctioning incidentalomas are needed to establish the long-term outcome of such patients, especially for metabolic status, cardiovascular risk profile, and their relationship with endocrine function.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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