

Adrenal Incidentaloma: A New Cause of the Metabolic Syndrome?

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A number of patients with adrenal incidentaloma are exposed to a slight degree of cortisol excess resulting from functional autonomy of the adrenal mass (usually a cortical adenoma). At present, there are only scant data on the unwanted effects of this endocrine condition referred to as subclinical Cushing's syndrome. The aim of the present study was to look for some features of the metabolic syndrome in patients with incidental adrenal adenoma. Forty-one patients (9 men and 32 women) bearing adrenal incidentaloma with typical computed tomography features of cortical adenoma were studied. For both patients and controls, exclusion criteria were age equal to 70 yr or greater, previous history of fasting hyperglycemia, or impaired glucose tolerance (IGT), severe hypertension, current use of medication or concomitant relevant illnesses, and body mass index (BMI) equal to 30 kg/m² or greater. Forty-one patients with euthyroid multinodular goiter accurately matched for sex, age, and BMI served for a 1:1 case-control analysis. The study design included an oral glucose tolerance test (75 g) and an endocrine workup aimed at the study of the hypothalamic-pituitary-adrenal axis. Age and BMI were fully comparable between patients (54.0 ± 10.7 yr, 23.8 ± 2.4 kg/m²) and controls (52.2 ± 11.6 yr, 23.5 ± 2.8 kg/m²). Fasting glucose and fasting insulin levels were not different between the two groups (4.96 ± 0.61 mmol/liter vs. 4.88 ± 0.58 mmol/liter; 67 ± 34 pmol/liter vs. 59 ± 32 pmol/liter), but the 2-h postchallenge glucose was significantly higher in patients than in controls (7.43 ± 2.49 mmol/liter vs. 6.10 ± 1.44 mmol/liter, *P* = 0.01). Fifteen patients (36%) reached the World

Health Organization criteria for IGT and two other patients (5%) reached those for diabetes, and 14% of the controls qualified for IGT (*P* = 0.01). No difference in the lipid pattern was seen between the two groups, but either systolic or diastolic blood pressure were higher in patients (135.4 ± 15.5 mm Hg vs. 125.0 ± 15.6 mm Hg, *P* = 0.003; 82.9 ± 9.1 mm Hg vs. 75.3 ± 6.6 mm Hg, *P* < 0.0001). We calculated the whole-body insulin sensitivity index derived from the oral glucose tolerance test that was significantly reduced in the patients (4.3 ± 1.7 vs. 5.7 ± 2.5, *P* = 0.01). In a multiple regression analysis, 2-h glucose was associated with BMI and midnight cortisol values (*r*² = 0.36, *P* = 0.002). The comparison of the patients with nonfunctioning adenoma (*n* = 29) with those with subclinical Cushing's syndrome (*n* = 12) yielded significant differences as to 2-h glucose and triglyceride levels, which were significantly higher in the second group (7.02 ± 1.76 mmol/liter vs. 8.72 ± 3.17 mmol/liter, *P* = 0.03; 1.06 ± 0.4 mmol/liter vs. 1.73 ± 0.96 mmol/liter, *P* = 0.002), but the insulin sensitivity index was conversely reduced (5.2 ± 1.4 vs. 2.9 ± 1.2, *P* < 0.0001). In conclusion, many patients with incidental adrenal adenoma display altered glucose tolerance, that may be explained by reduced insulin sensitivity, and increased blood pressure levels in comparison with carefully age- and BMI-matched controls. The slight hypercortisolism observed in some such patients may significantly contribute to this state of insulin resistance. Midnight serum cortisol appears as a sensitive marker of the metabolic effects of subclinical Cushing's syndrome. (*J Clin Endocrinol Metab* 87: 998–1003, 2002)

THE MANAGEMENT OF adrenal incidentaloma is a highly controversial matter, and the dilemma is to choose between surgery and a conservative approach (1). The problem is not trivial because adrenal masses are frequent in the aged population, as demonstrated by autopsy studies (2, 3), and they are currently being found (serendipitously) in millions of people worldwide (4, 5).

Suggested algorithms and current practice vary widely across different centers (1, 5–11). These uncertainties reflect our limited knowledge on the morbidity associated with adrenal incidentalomas (5). It is conceivable that primary or secondary malignant adrenal tumors, as well as pheochromocytomas, can significantly affect patients' health, but the potential harm associated with cortical adenomas, the most

frequent type among adrenal incidentalomas (1, 12, 13) is presently unclear (14, 15). Incidental adrenal adenomas are detected in patients who do not present with a clear Cushing phenotype; thus, they can be labeled as nonfunctioning from a clinical viewpoint. However, autonomous and unregulated cortisol secretion, not fully restrained by pituitary feedback, may be demonstrated in some cases by a detailed endocrine workup (16) and depicted *in vivo* by iodocholesterol scintigraphy (17, 18). The terms preclinical Cushing's syndrome (7) or subclinical Cushing's syndrome (19) have often been used interchangeably in the literature. As proposed by Ross (19), the term subclinical Cushing's syndrome is probably more accurate not implying any assumption on the evolution toward clinically overt hypercortisolism, which is an infrequent event (13, 14, 20, 21).

The diagnostic criteria of subclinical Cushing's syndrome and its possible detrimental effects are matter of controversy (5, 14, 21). It is reasonable to anticipate that subclinical Cush-

Abbreviations: BMI, Body mass index; CT, computed tomography; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; UFC, urinary-free cortisol; WHO, World Health Organization.

ing's syndrome could put the patient at increased risk of arterial hypertension, obesity, impaired glucose tolerance, and dyslipidemia. These features are shared by the metabolic syndrome and overt Cushing's syndrome (22, 23). The relationship between these diseases and unsuspected adrenal adenomas has been investigated in autopsy studies that produced controversial results (1).

The alternative hypothesis that adrenal incidentalomas are an unrecognized manifestation of the metabolic syndrome has also been formulated by Reincke *et al.* (24). They observed a proliferative effect of insulin on an adrenal cancer cell line without any effect on cortisol synthesis and suggested that hyperinsulinemia may have a pathogenetic role since it occurs in polycystic ovary syndrome (24). However, it remains to be demonstrated that insulin is able to promote adrenal growth in other experimental models and, in parallel, may stimulate cortisol synthesis.

In a multiinstitutional survey performed in Italy, which collected 1004 patients with adrenal incidentaloma between 1980 and 1995, the prevalence of arterial hypertension, diabetes, and obesity was 41%, 10%, and 28%, respectively (12). However, the interpretation of these data is partially confounded by the retrospective nature of the study, possibility of a referral bias, and large prevalence of these diseases in the general population.

The present study was designed to investigate some possible consequences of subclinical Cushing's syndrome on glucose and lipid metabolism and blood pressure in a series of patients with incidental adrenal adenoma.

Subjects and Methods

Subjects

Subjects were drawn from a series of consecutive patients with adrenal incidentaloma, *i.e.* an adrenal mass discovered serendipitously by abdominal ultrasound or computed tomography (CT) scan performed for the evaluation of unrelated diseases. An adrenal mass was considered incidental if signs or symptoms suggestive of adrenal hypersecretion were absent. Exclusion criteria were severe or resistant arterial hypertension, defined according to World Health Organization (WHO) criteria (25), a history of paroxysmal hypertension, or hypertension associated with hypokalemia. In the hypertensive patients included in the study, abdominal imaging study was requested for some complaint that did not relate to the study of hypertension. Patients with known extraadrenal malignancies were also excluded from the study. From the overall series of adrenal incidentalomas, only the patients with a presumed cortical adenoma were selected for the study. The diagnosis of cortical adenoma rested on the following CT criteria: size less than 4.0 cm, regular shape with well-defined margins, and homogenous and hypodense content (1). Concerning this last variable, an attenuation value of 10 or less, Hounsfield units on unenhanced CT scan, and 30 or less Hounsfield units on enhanced CT scan were considered as suggestive of an adrenal adenoma (26, 27). In all patients abdominal CT scans

were performed at the Radiology Department of our hospital and the scans were reviewed by an experienced radiologist. The diagnosis of adenoma was confirmed by a repeat CT scan after 6 months. During the follow-up, the mass size did not increase in any patient. The patient selection was also based on the results of an initial endocrine evaluation requiring normal 24-h urinary excretion of catecholamines and vanillyl mandelic acid to exclude silent pheochromocytoma (1, 12–14) and normal plasma aldosterone to plasma renin activity ratio to exclude normokalemic hyperaldosteronism (12–14). The following general criteria were also required for the enrollment: 1) age less than 70 yr, 2) normal fasting glucose levels according to American Diabetes Association recommendations (28), 3) no previous history of fasting hyperglycemia or impaired glucose tolerance (IGT), 4) no medications or concomitant relevant illnesses, and 5) body mass index (BMI) less than 30 kg/m². Three patients reported sporadic consumption of alcoholic beverages and eight patients were current or past smokers.

From a total of 83 patients with adrenal incidentaloma referred to our center from 1996 to 1999, 41 patients were selected (Table 1). Patients with pheochromocytoma (n = 4), adrenal carcinoma (n = 2), myelolipoma (n = 3), cyst (n = 2), or metastasis of extraadrenal tumors (n = 1) were excluded. Thirty other patients with adrenal adenoma were excluded because of advanced age (n = 12), elevated BMI (n = 5), previous history of fasting hyperglycemia (n = 15) or IGT (n = 3). In five of these patients coexisted more than one exclusion criteria. A group of 41 patients with multinodular euthyroid goiter and TSH concentration within the normal range (0.4 to 4.0 mU/liter) served as controls. All these subjects were off medication and physical exam, standard biochemical, and radiological evaluation excluded other relevant diseases. Five subjects reported sporadic consumption of alcoholic beverages, and 11 subjects were current or past smokers. They were selected according to the same general inclusion criteria of patients with adrenal incidentaloma to obtain a careful matching by gender, age, and BMI to perform a 1:1 case-control analysis (Table 1). Both patients and controls were studied within 3 months following diagnosis of their adrenal mass or thyroid goiter, respectively. A group of normoglycemic patients with overt Cushing's syndrome sustained by adrenal adenoma and no previous history of fasting hyperglycemia or IGT, and a BMI less than 30 kg/m² served as comparison with patients bearing incidental adrenal adenoma who qualified for subclinical Cushing's syndrome. The study was designed in agreement with the Declaration of Helsinki and was approved by the local Ethical Committee. The patients and subjects volunteered for the study and gave their informed consent. Either patients or controls were all hospitalized for the study.

Materials and methods

The patients with adrenal incidentaloma and controls underwent physical examination, chest radiograph, electrocardiogram, routine laboratory evaluation, and an oral glucose tolerance test (OGTT). At 0830 h, after a 10- to 12-h overnight fast and 30 min after cannulation of an antecubital vein kept patent by slow infusion of isotonic saline, subjects received a 75-g OGTT. Blood samples were collected at -15, 0, 30, 60, 90, and 120 min for the measurement of plasma glucose and insulin concentrations. Patients with overt Cushing's syndrome underwent only measurement of fasting glucose and insulin levels. Diagnosis of IGT or diabetes mellitus following the OGTT was made according to WHO criteria (29). The whole-body insulin sensitivity index (ISI) derived from the OGTT was calculated in patients and controls according to the formula developed by Matsuda and DeFronzo (30).

All patients underwent the following endocrine workup aimed to

TABLE 1. Demographic and clinical data of the patients with incidental adrenal adenoma and controls

Subjects (m/w)	Age (yr)	BMI (kg/m ²)	Systolic blood pressure (mm Hg) ^a	Diastolic blood pressure (mm Hg) ^b
Patients (9/32)	54.0 ± 10.7 (19–69)	23.8 ± 2.4 (19.0–29.0)	135.4 ± 15.5 (115.0–170.0)	82.9 ± 9.1 (70.0–104.0)
Controls (9/32)	52.2 ± 11.6 (21–69)	23.5 ± 2.8 (17.8–29.6)	125.0 ± 15.6 (110.0–170.0)	75.3 ± 6.6 (60.0–85.0)

Data are given as mean ± SD and range.

^a *P* = 0.003, patients *vs.* controls.

^b *P* < 0.0001, patients *vs.* controls.

study the hypothalamic-pituitary-adrenal axis: 1) measurement of serum cortisol at 0800 h and 1200 h, 2) measurement of the 24-h excretion of urinary-free cortisol (UFC), 3) measurement of plasma ACTH at 0800 h, 4) overnight low-dose dexamethasone suppression test (1 mg, orally, at 2300 h with measurement of serum cortisol at 0800 h the following morning). Premenopausal women were studied in the early follicular phase of the menstrual cycle. In control subjects, only measurement of serum cortisol in the morning and at midnight and measurement of 24-h UFC excretion was performed. Normal ranges of serum and urinary cortisol and plasma ACTH were determined as previously reported (16). Adequate dexamethasone suppression was demonstrated when cortisol fell below 138 nmol/liter the morning following dexamethasone administration (31). Subclinical Cushing's syndrome was defined as previously reported (16). Briefly, elevated UFC, failure of cortisol to suppress after 1 mg dexamethasone, suppressed ACTH concentrations, and disturbed cortisol circadian rhythm were the criteria considered. The association of at least two of these criteria qualified a patient for subclinical Cushing's syndrome (16). The diagnosis of overt Cushing's syndrome rested on classical clinical and hormonal features and CT evidence of an adrenal adenoma (23). In all Cushing patients, hypoadrenalism ensued after surgical removal of the adrenal adenoma and no relapse of the disease was observed during a 2-yr follow-up.

Assays

Plasma glucose levels were measured by standard enzymatic colorimetric tests (Hitachi 747 Instrument, God-Pap, Boehringer Mannheim, Meylan, France). Serum insulin was measured by a two-site immunoenzymometric assay (Aia-Pack IRI TOSH, distributed by Eurogenetics, Torino, Italy). The sensitivity of the assay was 14 pmol/liter; the intra- and interassay coefficients of variation were between 2.7–4.6% and 4.5–7.0%, respectively. Total serum cholesterol, high-density lipoprotein cholesterol, and serum triglycerides were measured by routine clinical chemistry methods (Dry Chemistry Vitros, Ortho System). Hormonal variables were measured in the same laboratory by RIA or immunoradiometric assay methods, using commercially available kits, as previously described (16). All samples for an individual subject were determined in a single assay in duplicate. Intra- and interassay coefficients of variation for all hormone variables were less than 8% and 12%, respectively.

Statistical analysis

Statistical analysis was performed with the Statistica for Windows (Statsoft Inc., Tulsa, OK) software package. Normal distribution of con-

tinuous variables was tested with the Wilk-Shapiro's test. We used the two-tailed *t* test for the normally distributed variables and the two-tailed Mann-Whitney test for the other ones. Ordinal variables were analyzed by χ^2 test. Bonferroni adjustment for multiple comparison was performed when appropriate. Correlation analyses were determined by calculating the Spearman's *R* coefficient. Levels of statistical significance were set at *P* less than 0.05. The results are expressed as mean plus or minus SD and range. A multiple regression analysis was performed to determine which variables predicted postchallenge glucose levels. The candidate predictive variables were age, BMI, and midnight cortisol levels. Age and BMI were tested because of the well-known effect of these variables on glucose tolerance in the general population (32), and midnight cortisol was chosen because it is considered as the most sensitive index of hypercortisolism (33). The ISI during the OGTT was not selected as a candidate variable because postchallenge glucose is included in the formula used to calculate the ISI (30).

Results

The plasma glucose and insulin levels during the OGTT in patients and controls are presented in Fig. 1. Fasting and 30-min glucose levels were not different between patients and controls whereas the 60-, 90-, and 120-min levels were significantly increased in patients (Fig. 1 and Table 2). Plasma insulin concentrations were higher during the OGTT in patients than in controls, but levels of statistical significance were not attained (Fig. 1 and Table 2). The ISI during the OGTT was significantly reduced in patients, compared with controls, whereas no difference in the lipid pattern was observed between the two groups (Table 2). Compared with controls, patients with incidental adrenal adenoma had significantly higher midnight serum cortisol and 24-h UFC excretion (Table 1). Fifteen patients (36%) reached the WHO criteria for IGT and two other patients (5%) reached those for diabetes, and 14% of the controls qualified for IGT (*P* = 0.01). Family history of diabetes was known in 32% of patients and 33% of controls (*P* = NS). In the patients, the ISI during the OGTT was significantly correlated with midnight cortisol ($r = -0.66$, *P* = 0.005). Either systolic or diastolic blood pressure was higher in patients than in controls (Table 2). No

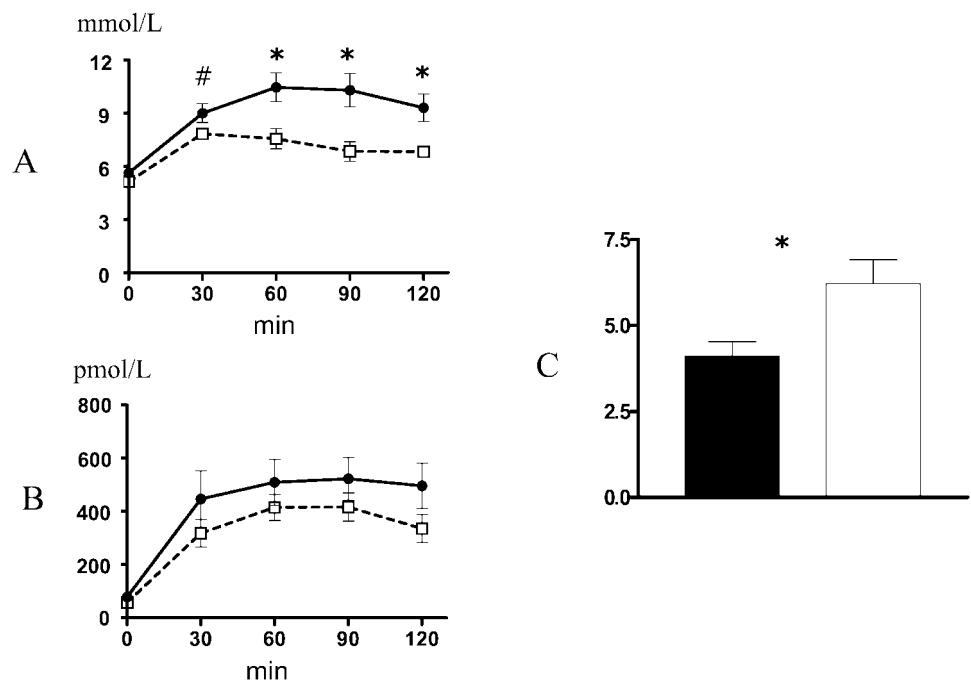


FIG. 1. A, Plasma glucose levels before and after a 75-g glucose load in patients with adrenal incidentaloma (solid line) and control subjects (dotted line). B, Serum insulin levels before and after a 75-g glucose load in patients (solid line) and control subjects (dotted line). C, The ISI during the OGTT in patients (solid bar) and control subjects (open bar). #, *P* < 0.05; *, *P* = 0.01.

significant correlation was found between either systolic or diastolic blood pressure and demographic, metabolic, or hormonal variables. In a multiple regression model, 2-h glucose was associated with BMI ($\beta = 0.39$, $P = 0.01$) and midnight cortisol values ($\beta = 0.47$, $P = 0.003$). The model accounted for 36% (r^2) of the total variation ($P = 0.002$). Twelve patients qualified for subclinical Cushing's syndrome according to the criteria previously developed (16). The comparison of these patients with those with nonfunctioning adenoma yielded significant differences as to 24-h UFC excretion, midnight serum cortisol, 2-h glucose, serum triglycerides, and the ISI during the OGTT (Table 3). The comparison between the patients with subclinical Cushing's syndrome and those with overt Cushing's syndrome yielded significant differences as to age, 24-h UFC excretion, midnight serum cortisol, and fasting insulin (Table 4).

Discussion

Adrenocortical adenomas account for the majority of adrenal masses discovered serendipitously, the so-called adrenal incidentalomas (1, 12). By definition, these patients do not display any overt physical sign of cortisol excess because no clinical suspicion of adrenal disease led to the detection of the adrenal mass. The unexpected finding of an adrenal mass offers the possibility of early treatment of a potentially dangerous disease. However, it remains to be elucidated whether an incidental adrenal adenoma puts the patient at increased risk for an unfavorable outcome (5). There is a wealth of data on the endocrine features of these tumors that

may secrete cortisol autonomously and in slight excess causing the subclinical Cushing's syndrome (1, 7–14, 16, 19, 21). However, there is scant information on the detrimental effects, if any, of this mild hypercortisolemic state (13–15, 21). The critical issue is whether subclinical Cushing's syndrome may predispose to diseases such as arterial hypertension, obesity, or diabetes that are classical features of full-blown endogenous hypercortisolism (23) and cluster in the metabolic syndrome (22).

The present data demonstrate a high prevalence of IGT (36%) or previously undiagnosed diabetes mellitus (5%) in patients with incidental adrenal adenoma in comparison with a group of sex-, age-, and BMI-matched controls. The control subjects were chosen among patients with euthyroid multinodular goiter who presented at our clinic during the same period. These subjects are not fully normal and may possibly be considered at higher risk of metabolic complications than general population because previous phases of subclinical hyperthyroidism should not be ruled out. This consideration strengthens the meaning of our results. The observed frequency of altered glucose tolerance is remarkably higher in our patients than that found in a population-based study in northern Italy (34). In this epidemiologic analysis, the prevalence of IGT, or previously undiagnosed diabetes mellitus, ranged from 3.7% between 45 and 54 yr to 11.1% between 65 and 74 yr (34). The alteration in glucose metabolism observed in our patients is hardly explained by a selection bias for the following reasons. First, both patients and controls were enrolled only if they had normal fasting

TABLE 2. Hormonal and metabolic data of the patients with incidental adrenal adenoma and controls

	Patients	Controls	P
UFC (nmol/24 h)	286 ± 212 (37–968)	185 ± 29 (94–342)	0.005
Midnight cortisol (nmol/liter)	152 ± 94 (55–474)	88 ± 25 (55–143)	0.0001
Fasting glucose (mmol/liter)	4.96 ± 0.61 (3.77–6.03)	4.88 ± 0.58 (3.33–5.71)	NS
Fasting insulin (pmol/liter)	67 ± 34 (21–148)	59 ± 32 (18–163)	NS
2-h glucose (mmol/liter)	7.43 ± 2.49 (3.38–17.54)	6.10 ± 1.44 (4.01–9.49)	0.01
2-h insulin (pmol/liter)	470 ± 338 (86–1478)	365 ± 247 (90–982)	NS
ISI	4.3 ± 1.7 (1.6–7.1)	5.7 ± 2.5 (2.3–11.1)	0.01
Triglycerides (mmol/liter)	1.27 ± 0.70 (0.54–4.04)	1.08 ± 0.51 (0.44–2.82)	NS
Total cholesterol (mmol/liter)	5.83 ± 1.15 (3.51–8.32)	5.70 ± 1.01 (3.51–8.01)	NS
HDL cholesterol (mmol/liter)	1.52 ± 0.51 (0.82–2.68)	1.50 ± 0.43 (0.56–2.53)	NS

Data are given as mean ± SD and range. HDL, High-density lipoprotein; NS, not significant.

TABLE 3. Clinical, hormonal, and metabolic data of the patients with nonfunctioning adrenal adenoma (n = 29) and patients with subclinical Cushing's syndrome (n = 12)

	Nonfunctioning adenoma	Subclinical Cushing	P
Age (yr)	54.9 ± 11.0 (19.0–69.0)	53.1 ± 11.5 (24.0–68.0)	NS
BMI (kg/m ²)	23.6 ± 2.2 (19.0–29.0)	24.2 ± 2.8 (19.1–27.5)	NS
UFC (nmol/24 h)	229 ± 142 (37–579)	457 ± 271 (127–968)	0.002
Midnight cortisol (nmol/liter)	102 ± 28 (55–143)	229 ± 110 (66–474)	0.0001
Systolic (mm Hg)	132.5 ± 11.5 (115–155)	139.7 ± 18.5 (120–170)	NS
Diastolic (mm Hg)	82.0 ± 9.0 (70.0–104.0)	84.5 ± 9.8 (70.0–100.0)	NS
Fasting glucose (mmol/liter)	4.88 ± 0.55 (3.77–5.60)	5.24 ± 0.69 (4.05–6.0)	NS
Fasting insulin (pmol/liter)	59.5 ± 35.9 (20.8–148.5)	73.9 ± 30.8 (24.4–110.5)	NS
2-h glucose (mmol/liter)	7.02 ± 1.76 (3.38–10.1)	8.72 ± 3.16 (5.71–17.54)	0.04
2-h insulin (pmol/liter)	413.3 ± 353.0 (86.1–1478)	536.7 ± 355.9 (150.0–1229)	NS
ISI	5.2 ± 1.4 (2.6–7.1)	2.9 ± 1.2 (1.6–5.2)	0.0001
Triglycerides (mmol/liter)	1.06 ± 0.4 (0.54–1.88)	1.73 ± 0.95 (0.84–4.04)	0.006
Total cholesterol (mmol/liter)	5.85 ± 1.19 (3.49–8.3)	5.57 ± 0.81 (4.34–7.08)	NS
HDL cholesterol (mmol/liter)	1.69 ± 0.56 (0.82–2.68)	1.41 ± 0.36 (1.13–2.12)	NS

Data are given as mean ± SD and range. HDL, High-density lipoprotein; NS, not significant.

TABLE 4. Clinical, hormonal, and metabolic data of the patients with subclinical (n = 12) or overt (n = 11) Cushing's syndrome

	Subclinical Cushing	Overt Cushing	P
Age (yr)	53.1 ± 11.5 (24.0–68.0)	35.0 ± 16.0 (14.0–61.0)	0.005
BMI (kg/m ²)	24.2 ± 2.8 (19.1–27.5)	24.4 ± 3.4 (19.0–24.4)	NS
UFC (nmol/24 h)	457 ± 271 (127–968)	1917 ± 1128 (303–4166)	0.001
Midnight cortisol (nmol/liter)	229 ± 110 (66–474)	568 ± 174 (328–902)	0.0001
Systolic (mm Hg)	139.7 ± 18.5 (120–170)	139.2 ± 11.7 (120–158)	NS
Diastolic (mm Hg)	84.5 ± 9.8 (70.0–100.0)	90.0 ± 12.2 (70.0–117.0)	NS
Fasting glucose (mmol/liter)	5.24 ± 0.69 (4.05–6.0)	4.89 ± 0.51 (3.88–5.6)	NS
Fasting insulin (pmol/liter)	73.9 ± 30.8 (24.4–110.5)	124.1 ± 59.5 (47.3–236.0)	0.03
Triglycerides (mmol/liter)	1.73 ± 0.95 (0.84–4.04)	1.14 ± 0.53 (0.56–1.98)	NS
Total cholesterol (mmol/liter)	5.57 ± 0.81 (4.34–7.08)	5.74 ± 1.82 (3.7–9.36)	NS
HDL cholesterol (mmol/liter)	1.41 ± 0.36 (1.13–2.12)	1.45 ± 0.37 (0.87–1.93)	NS

Data are given as mean ± SD and range. HDL, High-density lipoprotein; NS, not significant.

glucose levels according to the American Diabetes Association recommendations (28). Second, subjects with previously known fasting hyperglycemia or IGT were excluded from the study. Third, the frequency of family history of diabetes was similar between patients and controls. Moreover, both patients and controls with obesity, defined as BMI greater than 30 kg/m² (35), were excluded from the study. It is generally accepted that insulin sensitivity decreases as a function of body fat (36); in fact, only 19% of subjects with a BMI less than 30 kg/m² were found to be insulin resistant in a large series of Caucasian individuals of all ages (37).

The present results confirm and extend those of Fernandez-Real *et al.* (38), who found a prevalence of IGT or unknown diabetes of 61% among patients with nonfunctioning adrenal tumors. However, the results of that study were not adjusted for body weight, and no control group was included (38). The altered glucose tolerance observed in our patients may be due to reduced insulin sensitivity because the ISI during the OGTT (30) was significantly lower in patients than in controls. We disclose the limit of not having employed the euglycemic clamp, the best available standard for the measurement of insulin action (39). However, the ISI during the OGTT developed by Matsuda and DeFronzo (30) was validated as a simple and reasonable estimate of whole-body insulin sensitivity.

In the present study, several lines of evidence suggest a causal relationship between hypercortisolism and the combination of altered glucose tolerance and reduced insulin sensitivity observed in our patients. First, the group of patients did not differ from that of control subjects as to the factors known to influence insulin sensitivity (age, body weight, fasting glucose, etc.), but the patients were hypercortisolemic, compared with controls. Even if the amount of cortisol excess was insufficient to give a clear Cushing phenotype, the markers of cortisol secretion were significantly different between patients and controls studied under analog conditions of stress induced by hospitalization.

Second, 2-h postchallenge glucose levels were correlated in a multiple regression model with BMI and midnight cortisol values. The relationship with BMI is expected because BMI is a strong predictor of IGT in the general population (32). The relationship with midnight serum cortisol is very interesting because midnight cortisol is admittedly considered the most sensitive marker of endogenous glucocorticoid excess (33). The significant inverse correlation found between the ISI and midnight cortisol values favors the view that the subclinical hypercortisolism is able to impair glucose metabolism through reducing insulin sensitivity.

Third, 2-h postchallenge glucose levels were significantly higher in the patients who qualified for subclinical Cushing's syndrome than in the patients with nonhypersecreting adenoma. Furthermore, the ISI during the OGTT was significantly reduced in the patients with subclinical Cushing's syndrome, compared with the other patients. These differences were independent of BMI values that were similar between the two groups of subjects. The elevation in triglyceride levels observed in the patients with subclinical Cushing's syndrome is another evidence of reduced insulin sensitivity in such subjects (40).

That the metabolic abnormalities were not exclusive of the patients with subclinical Cushing's syndrome is because cortisol secretion by incidental adrenal adenomas shows a spectrum of intensity, ranging from normal secretion to various degrees of excess over the physiological daily production rate (13, 16, 21). The stringent criteria used for the ascertainment of subclinical Cushing's syndrome have conceivably selected only the patients with more than minimal cortisol excess.

The patients with overt Cushing's syndrome were hyperinsulinemic in comparison with the patients with subclinical Cushing's syndrome, notwithstanding that they were younger than the other ones. The amount of cortisol excess found in subclinical Cushing's syndrome was quite small in comparison with that of the classic variant, but fasting glucose and BMI were comparable between the two groups. These findings suggest that the more severe hypercortisolism is, the higher the circulating level of insulin, which is a surrogate of insulin sensitivity (39). Our data support the view that cortisol excess is able to influence insulin levels independently of obesity, which is otherwise a prominent clinical feature of Cushing's syndrome and may contribute *per se* to hyperinsulinemia (41).

The effect of glucocorticoids *in vivo* appears to include both impaired insulin-dependent glucose uptake in the periphery and enhanced gluconeogenesis in the liver (42). On the other hand, central action of glucocorticoids may enhance vagal stimulation of insulin secretion (43). The balance of these effects may be important in determining whether insulin resistance is accompanied by compensatory hyperinsulinemia, or hyperglycemia, in Cushing's syndrome (44).

Blood pressure, either systolic or diastolic, was significantly increased in patients with incidental adenomas than in controls. However, we did not disclose any significant correlation between blood pressure and the metabolic or endocrine variables. A straight relationship between insulin resistance,

and the resultant hyperinsulinemia, and blood pressure does not occur with secondary hypertension (45). It is conceivable that cortisol excess and reduced insulin sensitivity may contribute to the pathogenesis of hypertension by means of complex reciprocal interplay with genetic and environmental factors in our patients. Pertinently, the pathophysiology of hypertension in Cushing's syndrome remains poorly understood, and most studies failed to detect any relationship between pressure levels and markers of cortisol secretion (46).

In conclusion, patients with adrenal adenoma of incidental discovery frequently display some features of the metabolic syndrome, such as impaired glucose tolerance, increased blood pressure, and high triglyceride levels. The present data allow us to hypothesize that the subtle autonomous cortisol secretion of these adrenal adenomas may cause an acquired condition of insulin resistance in otherwise normoglycemic and nonobese subjects. To the best of our knowledge, this is the first demonstration in a case-controlled analysis that subclinical Cushing's syndrome may be associated with metabolic alterations. Further studies are needed to clarify whether these patients are at increased risk of cardiovascular disease morbidity and mortality as was demonstrated in the general population (47). This issue is critical to select the optimal management of these patients which, at present, remains largely empirical (1, 5, 8, 13, 14, 20, 21).

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