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Occult Cushing's Syndrome in Type-2 Diabetes

BOGDAN CATARGI, VINCENT RIGALLEAU, AGATHE POUSSIN, NATHALIE RONCI-CHAIX, VERONIQUE BEX, VINCENT VERGNOT, HENRI GIN, PATRICK ROGER, AND ANTOINE TABARIN

Departments of Endocrinology (B.C., A.P., V.B., N.R.-C., P.R., A.T.) and Nutrition (V.R., V.V., H.G.), Institut de Recherche en Nutrition Humaine en Aquitaine, University Hospital of Bordeaux, 33604 Pessac, France

Subclinical Cushing's syndrome (SCS) caused by adrenal incidentalomas is frequently associated with overweight and insulin resistance. Metabolic syndrome X may therefore be a clue to the presence of CS. However, the incidence of CS in this situation remains unknown. We have conducted a prospective study to evaluate the prevalence of occult CS in overweight, type-2 diabetic patients devoided of specific clinical symptoms of CS.

Two hundred overweight, type-2 diabetic patients, consecutively referred for poor metabolic control (HbA_{1C} > 8%), were studied as inpatients. A first screening step was performed with the 1-mg overnight dexamethasone suppression test (DST) using a revised criterion for cortisol suppression (60 nmol/liter) to maximize the sensitivity of the procedure. A second confirmatory step of biochemical investigations (midnight plasma cortisol concentration, plasma cortisol circadian rhythm, morning plasma ACTH concentration, 24-h urinary free cortisol, and 4-mg iv DST) was performed in patients with impaired 1-mg DST. A third step of imaging studies was performed according to the results of second-step investigations.

Fifty-two patients had impaired 1-mg DST. Among these, 47 were further evaluated. Thirty were considered as false positives of the 1-mg DST, whereas 17 displayed at least one additional biological abnormality of the hypothalamic-pituitary-adrenal axis. Definitive occult CS was identified in four patients (2% of the whole series) with Cushing's disease (n = 3) and surgically proven adrenal adenoma (n = 1). Definitive diagnosis remains to be established in seven additional patients (3.5%) with mild occult CS associated with unsuppressed plasma ACTH concentrations and a unilateral adrenal tumor of 10–29 mm in size showing prevalent uptake at radiocholesterol scintigraphy.

In conclusion, a relatively high prevalence of occult CS was found in our study. Further studies are needed to evaluate the impact of the cure of occult CS on obesity and diabetes mellitus in these patients. Such studies might provide a rationale for systematic screening of occult CS in this population. (*J Clin Endocrinol Metab* 88: 5808–5813, 2003)

EXCESSIVE AND SUSTAINED hypercortisolism results in the entire spectrum of metabolic syndrome X (abdominal obesity, insulin resistance, dyslipidemia, and hypertension). Consequently, glucose intolerance or type-2 diabetes secondary to insulin resistance occurs in approximately 80% of patients with Cushing's syndrome (CS) (1). Although frequently not associated with hypercortisolism, metabolic syndrome X may conversely be a clue to the presence of CS.

Subclinical CS (SCS) is another entity that occurs in approximately 5–30% of patients with adrenocortical incidentaloma (2). These patients display various degrees of cortisol hypersecretion and autonomy that are usually less intense than that seen in CS. Although patients with SCS do not display the specific clinical symptoms of CS, a subsequent number present with features of metabolic syndrome X, such as overweight, increased waist-to-hip ratio (WHR), elevated blood pressure, and hyperglycemia (3). Furthermore, studies conducted in patients with adrenal incidentaloma and SCS suggest that the subtle autonomous and cortisol overproduction may participate in the pathogenesis of these abnormalities (3–8), and the prevalence of adrenocortical adenomas found in autopsy series is 2- to 5-fold increased in diabetics and obese subjects (9). Elsewhere, one retrospective study found that inapparent Cushing's disease (CD), from a clinical point of view, might occur in diabetic patients and participate to the physiopathology of hyperglycemia (10); but, to the best of our knowledge, no prospective study about the prevalence of CS in a large cohort of diabetic patients is available.

We therefore hypothesized that a number of overweight patients with type-2 diabetes may harbor occult CS of pituitary and/or adrenal origin.

The aim of the present study was to prospectively evaluate the prevalence of CS of various intensities, in a large cohort of overweight type-2 diabetic patients, and poor metabolic control. Because SCS in series of adrenal incidentalomas do not present with the full spectrum of biochemical abnormalities of CS, but is associated with more subtle disturbances of the hypothalamic-pituitary-adrenal (HPA) axis (11, 12), standard biochemical tests used to diagnose overt CS might not be accurate in such instances. Consequently, we used a three-step diagnostic strategy, including a first-screening step based on the overnight 1-mg dexamethasone suppression test (DST) with revised criterion for cortisol suppression to maximize the sensitivity of the screening procedure.

Subjects and Methods

Subjects

Two hundred consecutive overweight or obese type-2 diabetic patients [151 women and 49 men; age, 58.6 ± 10.7 yr (range, 22–84); body mass index (BMI) > 25 kg/m^2], referred for poor metabolic control (HbA_{1C} > 8%; normal, <6%), were studied as inpatients. Their main characteristics are shown in Table 1. When admitted to our care unit, one hundred fifty patients (75%) were treated with at least one antidiabetic

Abbreviations: BMI, Body mass index; CD, Cushing's disease; CS, Cushing's syndrome; CT, computed tomography; DM, diabetes mellitus; DST, dexamethasone suppression test; HbA1c, glycosylated hemoglobin; HPA, hypothalamic-pituitary-adrenal; SCS, subclinical Cushing's syndrome; UFC, urinary free cortisol; WHR, waist-to-hip ratio.

TABLE 1. Clinical and metabolic features of the patients studied (n = 200)

	Variable
Age (yr)	58.6 ± 10.7
Males/females	49/151
Duration of diabetes (yr)	10.5 ± 8.4
HbA1c (%)	10.8 ± 1.8
BMI (kg/m^2)	33.9 ± 6.5
M	32.7 ± 5.5
F	34.4 ± 6.7
WHR	1.0 ± 1.5
M	1.0 ± 0.1
F	0.9 ± 0.1

Data are given as mean ± SEM and range.

oral drug, 19 (9.5%) were treated with insulin, and 11 (5.5%) with a combined therapy. In addition, one hundred forty-three patients (71.5%) were treated with at least one antihypertensive drug.

All patients underwent careful clinical examination, and none of them displayed specific symptoms of hypercortisolism, such as weakness associated with proximal muscle wasting, skin atrophy, ecchymoses, or purple striae. History examination excluded exogenous glucocorticoid intake and other factors known to affect the DST (drugs, alcoholism, obvious depression, or pregnancy). None of patients had severe nephropathy (creatinine clearance < 30 ml/min), hypoglycemia unawareness, or severe associated acute illness. All patients had an apparently normal sleep-wake cycle.

The protocol study was approved by the department ethics staff, and informed consent was obtained from all patients.

Materials and protocols

All subjects were admitted to our care unit in the afternoon, and a heparin-lock catheter was inserted to avoid stress-induced cortisol released caused by venipuncture during endocrine evaluation. The second day after admission, all patients underwent a first-screening step using the overnight 1-mg DST (1 mg dexamethasone was administered orally at 2300 h, and blood samples were collected on the following morning at 0800 h for determination of plasma cortisol concentration).

Patients who failed to suppress serum cortisol less than 60 nmol/liter (2.1 μg/dl) were proposed a second-step biological evaluation of the HPA axis. This evaluation included three segments.

Blood samples. Blood samples were withdrawn at 0800 h and 2400 h for the measurements of cortisol and ACTH concentrations. The circadian rhythm of plasma cortisol was calculated as (2400-h value/0800-h value) × 100 concentrations (13). A value above 50 was considered as abnormal. The normal range for cortisol and ACTH plasma concentrations at 0800 h were 200–700 nmol/liter and 2–14 pmol/liter, respectively. According to the results obtained in our department in a cohort of 27 control obese patients (data not shown), midnight cortisol concentrations were considered normal when less than 71 nmol/liter.

Urine samples. Twenty-four-hour urine collection was performed for urinary free cortisol (UFC) measurement. The normal range for 24-h UFC was 20–100 μg/24 h.

DST (iv 4-mg). Briefly, dexamethasone was infused iv for 4 h, starting at 1100 h at a rate of 1 mg/h, using an iv infusion pump. Blood samples were withdrawn every 4 h until 0800 h the next day (14). Cortisol suppression was assessed on the latter value (normal range obtained in 12 control subjects, <27–66 nmol/liter).

A third-step imaging investigation was performed when the result of second-step biochemical investigations displayed at least one abnormal result.

Imaging studies

Complementary imaging, abdominal computed tomography (CT) or pituitary MRI, was performed when the results of the second-step biological evaluation were consistent with ACTH-independent or -dependent hypercortisolism, respectively (1). Both procedures were performed in equivocal cases. When abdominal CT showed an adrenal tumor more than 1 cm in diameter, a ^{131}I-6β-iodomethylnorcholesterol scintigraphy (37 MBq Norchol-131; CIS Bio International, Gif sur Yvette, France) was performed without dexamethasone administration. Adrenal imaging was performed using a γ-camera equipped with a high-energy, parallel-hole collimator. Posterior and anterior abdominal images (15 min/image) were performed on d 5 after tracer injection. Three types of iodocholesterol uptake were defined: unilateral uptake concordant with the adrenal mass, bilateral symmetrical uptake, and bilateral asymmetrical uptake.

Assays

The hormonal variables were determined in the hospital reference laboratory using commercially available kits. Plasma cortisol concentrations were determined by a solid-phase RIA (Coat-a-Count, Los Angeles, CA); plasma ACTH concentrations were determined using the Brahms (Berlin, Germany) kit (after immediate centrifugation, plasma was collected into a pre-chilled tube); UFC was determined using a Cis Bio International (Paris, France) kit.

Statistical analysis

Results are given as means ± SEM. For statistical purposes, the value corresponding to the limit of detection of assays was used for undetectable concentrations (27 nmol/liter for serum cortisol, 1.1 pmol/liter for ACTH). Comparison between variables was performed using the Mann-Whitney *U* test and Student's *t* test. Correlation coefficients were determined by Pearson's ρ test. The level of statistical significance was set at $P < 0.05$.

Results

Fifty-two patients (26% of the whole series) failed to suppress plasma cortisol less than 60 nmol/liter during the 1 mg overnight DST. There was no correlation between the value of glycosylated hemoglobin [HbA1c and the results of the 1-mg overnight DST ($r^2 = 0.001$, $P = 0.67$)] (Fig. 1). Among the 52 patients, 47 were further evaluated, whereas five refused further endocrine evaluation.

Thirty patients (15% of the whole series) did not display any other biochemical abnormality of the HPA axis and were considered as false positives of the 1-mg DST. The post-1-mg-DST plasma cortisol in these patients was 124.2 ± 17.9 nmol/liter (range, 66–552). At least one associated biochemical abnormality of the HPA axis was found in the remaining 17 patients (8.5%), who had a post-1-mg-DST plasma cortisol of 186.9 ± 39.1 nmol/liter (range, 62–687). Sixteen of these 17 patients had two associated abnormalities of the HPA axis.

Further complementary imaging investigation and follow-up were declined by three of these 17 patients. Two had elevated midnight cortisol (403 and 276 nmol/liter, respectively) and nonsuppressible cortisol after 4-mg iv DST (0800 h post-DST plasma cortisol = 147 and 81 nmol/liter, respectively). The third had mild elevated 24-h UFC (308 μg/24 h), elevated midnight cortisol (113 nmol/liter), and nonsuppressible cortisol after 4-mg iv DST (292 nmol/liter). Denied alcoholism that could have led to alcohol-induced pseudo-CS was strongly suspected in this patient (15).

No pituitary or adrenal tumor was found in three of the 14 patients who underwent imaging studies. All three patients had elevated midnight plasma cortisol (255, 198, and 183 nmol/liter), whereas impaired suppression to the 4-mg iv DST (0800-h plasma cortisol = 83 and 343 nmol/liter) was found in two. The origin of the biochemical abnormalities of the HPA axis in these patients remains unknown.

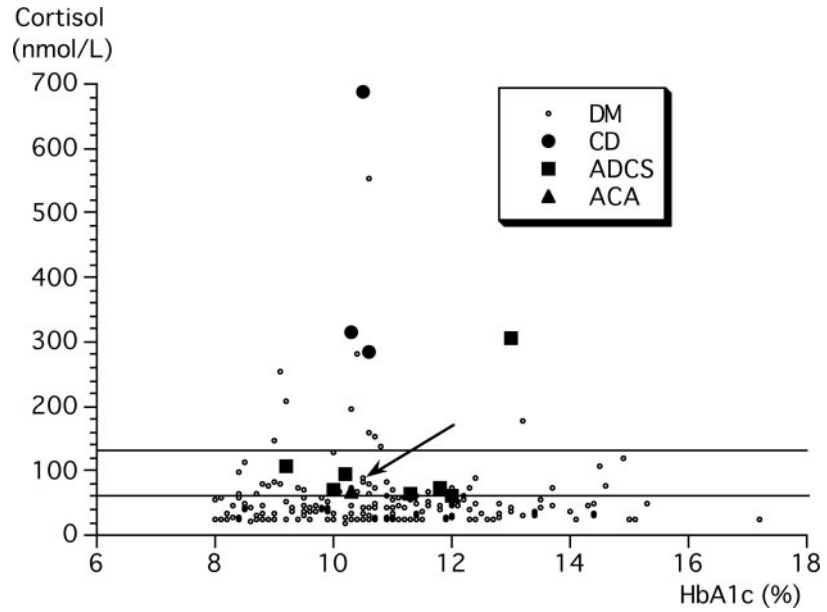

FIG. 1. Plasma cortisol levels after the overnight 1-mg DST *vs.* HbA1c in 200 consecutive overweight type-2 diabetic patients. *Horizontal lines* indicate threshold for normal suppression (60 and 138 nmol/liter, 2.1 and 5 μg/dl, respectively). Among 52 patients with type-2 DM, occult CS was subsequently confirmed in four patients [three had CD; one had an adrenal cortical adenoma (ACA), *arrow*]. Seven patients had possible adrenal-dependent CS (ADCS).

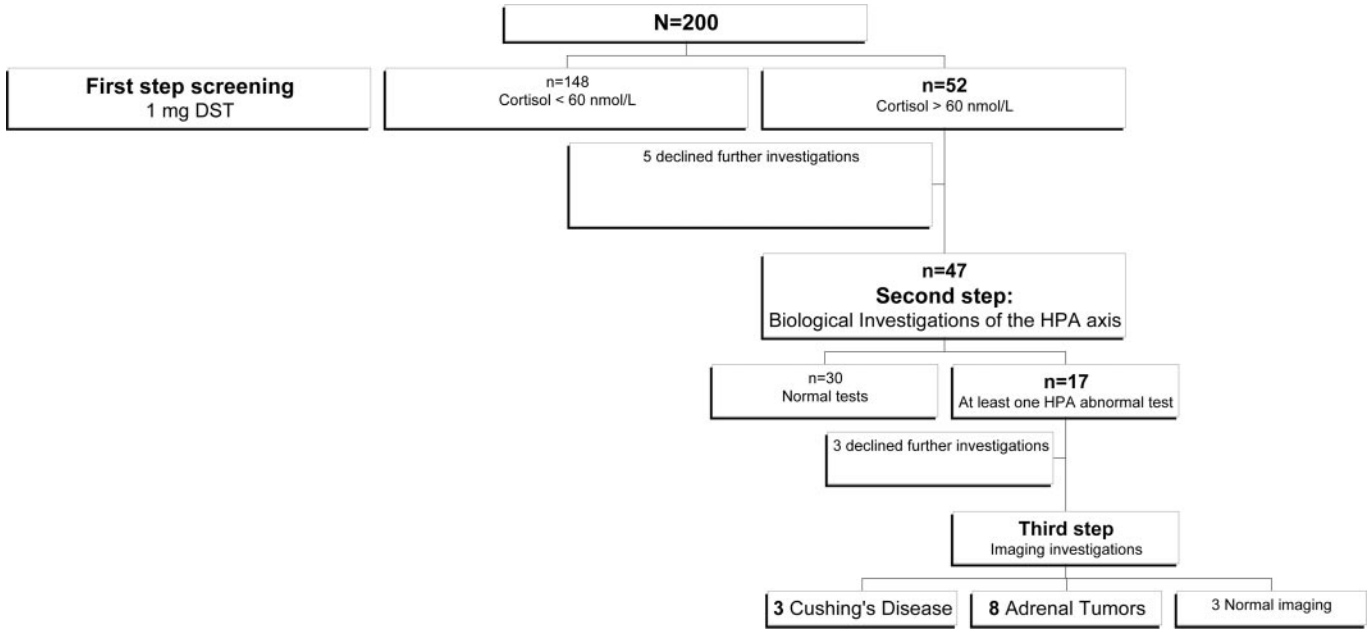

FIG. 2. Results of the screening strategy for occult CS in 200 overweight type-2 diabetic patients. Second-step biochemical investigations included morning plasma cortisol and ACTH concentrations, midnight plasma cortisol, cortisol percent ratio, 24-h UFC, and 4-mg iv DST.

Abnormal imaging studies were obtained in the remaining 11 patients (5.5% of the whole series). Three patients proved to have pituitary CD attributable to a pituitary microadenoma (1.5% of the whole series). Histological diagnosis of CD was obtained in two patients. One patient, with an obvious 10-mm pituitary tumor at MRI, could not be operated because of severe sphenoidal bone dysplasia. In this case, the diagnosis of CD was established using bilateral inferior petrosal sinus sampling for ACTH measurement.

Eight patients (4% of the whole series) had an adrenal tumor ranging from 1.0–3.0 cm in size (Fig. 2). CT scanning features in these patients were consistent with an cortical adenoma (9). Iodocholesterol scintigraphy revealed unilateral and concordant uptake in one case and asymmetrical (enhanced) uptake on the side of the tumor in other cases (Table 2).

The three patients with CD were treated with pituitary surgery, radiotherapy, and ketoconazole alone or in association. The 3.0-cm adrenal adenoma with unilateral scintigraphic uptake was surgically removed. In the latter patient, a postoperative adrenocortical insufficiency occurred and was treated by oral replacement therapy for 6 months. Six months after treatment of occult CS, a mean 5.5% reduction in body weight, associated with a 2.5% reduction in HbA1C, was noted in the four patients treated for occult CS; while oral antidiabetic medications were resumed in one patient and

TABLE 2. Main characteristics of patients with occult CS

Patient	Gender	Age	1-mg DST	24-h UFC (20–100 μg)	F 0 h (<71 nmol/liter)	F% (<0.5)	ACTH (2–14 pmol/liter)	4-mg DST	Adrenal tumor at CT scan size (mm)/side	Radiocholesterol uptake at scintigraphy
Adrenal										
1	F	51	75[a]	25	206[a]	0.51[a]	3.7	72[a]	10/Right	Bilateral asymmetric
2	M	66	64[a]	75.5	140[a]	0.24	3.0	76[a]	19/Left	Bilateral asymmetric
3	F	50	62[a]	38	97[a]	0.23	2.1	77[a]	29/Right	Bilateral asymmetric
4	F	57	70[a]	73	215[a]	0.41	3.7	109[a]	25/Right	Bilateral asymmetric
5	M	52	307[a]	12.7	233[a]	0.47	5.4	301[a]	15/Left	Bilateral asymmetric
6	M	64	95[a]	32.9	186[a]	0.32	4.6	51	20/Left	Bilateral asymmetric
7	M	66	67[a]	28.5	92[a]	0.14	2.2	75[a]	30/Right	Unilateral concordant
8	F	60	108[a]	29	175.5[a]	0.41	3.2	91[a]	18/Left	Bilateral asymmetric
Pituitary									MRI characteristics Size (mm)	
9	F	66	315[a]	268[a]	462[a]	0.65[a]	12.7	225[a]	9	
10	F	70	687[a]	62.4	398[a]	0.63[a]	4.7	124[a]	9	
11	F	29	284[a]	132[a]	405[a]	0.56[a]	7.3	197[a]	10	

F % ratio was determined as serum cortisol 2400/F0800. Occult CS was confirmed in patients 7, 9, 10, and 11.
[a] Values outside the normal range.

TABLE 3. Characteristics and comparison of patients with nonsuppressible plasma cortisol after the 1-mg DST, according to the presence of occult CS

Variable	Occult CS + DM	DM	*P* value
Age	57.4 ± 11.7	58.7 ± 10.7	NS
Duration of diabetes (yr)	15.4 ± 13.0	10.2 ± 7.9	NS
BMI (kg/m^2)	34.0 ± 6.9	33.9 ± 6.2	NS
WHR	0.9 ± 0.1	1.0 ± 0.1	NS
HbA1c (%)	10.8 ± 1.1	10.8 ± 1.8	NS
SBP (mm Hg)	139.5 ± 21.7	145.3 ± 20.6	NS
DBP (mm Hg)	81.8 ± 14.0	83.1 ± 11.2	NS
Cortisol after 1-mg DEX (nmol/liter)	194.0 ± 58.4	111.6 ± 13.4	0.04
UFC (μg/24 h)	70.4 ± 22.2	37.3 ± 5.1	0.04
Cortisol 0800 h (nmol/liter)	513.2 ± 76.0	486.9 ± 130.8	NS
Cortisol 1200 h (nmol/liter)	237.2 ± 38.4	174.6 ± 16.9	NS
Cortisol percent ratio (%)	47.1 ± 7.5	37.0 ± 3.4	NS
ACTH 0800 h (pmol/liter)	4.8 ± 0.9	6.7 ± 0.6	NS
Cortisol after 4-mg iv DEX (nmol/liter)	127.1 ± 23.9	58.3 ± 4.8	0.0002

Data are given as mean ± SEM. One patient with suspected denied alcoholism and pseudo-CS was excluded from the analysis. DEX, Dexamethasone; NS, not significant.

the insulin daily dose was dramatically reduced in an other patient. The adrenal tumor was not removed in the seven remaining patients.

Overall, the overnight 1-mg DST allowed 100% sensitivity for the screening of occult CS when plasma cortisol was less than 60 nmol/liter with 78% specificity. Use of the "classical" 138-nmol/liter plasma cortisol threshold would have reduced the number of false positives (specificity, 94%), but the seven unoperated patients with an adrenal mass associated with enhanced uptake on the side of the tumor, at iodocholesterol scintigraphy, would have been ignored (sensitivity, 36%).

Among patients who underwent second-step investigations, morning plasma cortisol after the 1-mg DST, the 24-h UFC, and plasma cortisol after the 4-mg iv DST were significantly more elevated in the group of 11 patients with SCS. Midnight plasma cortisol also tended to be higher in patients with SCS, without reaching statistical significance (Table 3).

Discussion

Among 200 patients with type-2 diabetes and overweight, 11 patients had definitive biochemical abnormalities of the HPA axis associated with imaging and possibly scintigraphic evidence of a tumor. Among these, three patients (1.5% of the whole series) had CD. The prevalence of occult CD in diabetic patients found in this series is similar to that quoted in a previous (but retrospective) report (10). The lack of specific signs of CS in these three patients could be explained by their mildly elevated 24-h UFC excretion. UFC was even normal in one patient during the first urine collection, as observed in approximately 10–20% of patients with CD when multiple urine collections are performed (16). Elevated UFC levels found in subsequent urine collections in this patient (data not show) are consistent with variable hormonogenesis of the pituitary adenoma.

Whether or not these cases would have progressed toward overt CS remains hypothetical. Although subclinical CD is rare (17), it is common, in experienced teams in the field of CS, to occasionally recruit patients with paucisymptomatic CD (18). Clinical observation of recurrence of CD in patients with previously successful pituitary surgery obviously also shows that the onset of clinical signs of hypercortisolism may be delayed for years, in comparison with biochemical abnormalities. Therefore, whether these patients had preclinical *vs.* subclinical CD remains debatable.

Eleven patients displayed subtle biochemical abnormalities of the HPA axis that were consistent with a mild degree of hypercortisolism (elevated midnight plasma cortisol contrasting with normal UFC) (19) and secretory autonomy (nonsuppression after iv 4-mg DST) and that were associated with CT scanning features consistent with adrenocortical adenoma. Demonstration that these patients have adrenal-dependent occult CS requires adrenal insufficiency after adrenalectomy and pathological examination of the gland removed. Only one patient, with the largest tumor, was operated and fulfilled these criteria. Therefore, definitive diagnosis of occult CS of pituitary or adrenal origin was obtained in four patients, *e.g.* 2% of patients of these series.

Definitive diagnosis of the origin of occult CS remains to be determined in the remaining seven patients with an adrenal tumor, at CT scanning, that were not operated. The lack of suppression of plasma ACTH does not favor the hypothesis of adrenal-dependent hypercortisolism and may suggest ACTH-dependent CS with unilateral adrenal hyperplasia or nonfunctioning adrenocortical nodule. Elsewhere, studies of patients with adrenal incidentalomas associated with SCS have revealed a wide spectrum in the degree of hypercortisolism and autonomy (7, 13, 20–25). Dissociation in the results of biochemical investigations of the HPA axis is often noted (13) and, consequently, the "usual" biological criterion used at the different diagnostic steps of overt CS might not always be indicative in this instance (7). Indeed, contrary to patients with cortisol-secreting adenomas responsible for overt CS, plasma ACTH in patients with adrenal-dependent SCS might not be suppressed, as exemplified in the patient of our series who had removal of the adrenal tumor followed by transient postoperative adrenal insufficiency. This emphasizes the need for additional tools to better define SCS and its etiology in equivocal cases. In addition to biochemistry, iodocholesterol scintigraphy can be used to assess the functional status of adrenocortical tumors. In previous studies conducted in patients with adrenal incidentalomas, we and others have shown that unilateral and/or predominant uptake on the side of the tumor is usually associated with a greater degree of cortisol secretory autonomy (12, 26) and is correlated with the occurrence of adrenal insufficiency after removal of the tumor (13, 23, 27). Although diabetes and its attendant vascular disease may induce *per se* ischemic nonfunctioning adrenocortical nodules (9), scintigraphic evidence of preferential or exclusive radioiodine uptake on the side of the tumor in our patients supports a causal relationship between the tumor and biochemical abnormalities of the HPA axis (23, 25). In the absence of HPA axis evaluation after removal of the tumor, additional procedures, such as plasma ACTH response to CRH (2, 20, 22, 28) or iodocholesterol scintigraphy after dexamethasone administration (25), might have been helpful to definitively ensure the origin of occult CS in the patients with small adrenal tumors.

Three patients displayed at least two biochemical abnormalities of the HPA axis without evidence of a tumor. Negative imaging in front of subtle alterations of the HPA axis suggests several hypotheses. One of these is occult CD with negative pituitary MRI. Another possibility is nontumorous, functional activation of the HPA axis, as observed in pseudo-CS (29). Indeed, abnormalities of the HPA axis function are common in diabetic patients, even in the absence of ketoacidosis. These include slightly higher plasma cortisol levels than nondiabetics (30) and increases in contraregulatory hormone secretion (31). Subjects with abdominal obesity, and especially women, may also have slightly increased activity of the HPA axis together with blunted cortisol circadian variability (32), increased nocturnal cortisol secretion (33), and higher ACTH and cortisol concentration after HPA stimulation (34). Furthermore, true depression, a frequent finding in diabetic patients (35), might also contribute to the functional activation of the HPA axis. Finally, the inpatient status of patients of our series during biochemical investigations might have contributed to HPA axis activation in susceptible individuals (16, 36).

Using our criterion for the 1-mg DST, 15% of patients displayed impaired cortisol suppression, contrasting with normal complementary biochemical investigation of the HPA axis, including a 4-mg iv DST. Although we did not perform systematic imaging studies in these patients, the possibility that they harbor a milder degree of occult CS is unlikely, and these patients probably represent false positives of the 1-mg DST. Obviously, the low cut-off value that we used for post-1-mg DST cortisol concentration might contribute to this poor specificity, especially in the setting of type-2 diabetes, abdominal obesity, and in-patient investigation as discussed above. Although lowering the threshold will invariably result in a decrease in specificity, recent controversy has emerged with regard to the cut-off values to be used (11, 37). Indeed, the classical 138-nmol/liter cut-off value was elaborated in the 60's and based on fluorometric assays that overestimate serum cortisol concentrations, as compared with current immunoassays (38). A more deep suppression of plasma cortisol has been quoted in recent studies (39); and, using current immunoassays, serum cortisol concentrations, after 1-mg DST, higher than 50–60 nmol/liter may indicate subtle alterations of the HPA axis (37). We showed in a previous study that, among patients with adrenal incidentalomas, a cortisol post-1-mg-DST more than 60 nmol/liter (2.1 μg/dl) was strongly correlated with other abnormalities of the HPA axis and unilateral uptake during noriodocholesterol scintigraphy (12). In the present series, the historical 138-nmol/liter (5 μg/dl) threshold would have missed seven patients with occult CS. One must note, however, that these cases of false negatives with the classical post-dexamethasone cortisol cut-off value correspond to the seven patients that were not operated and in whom the diagnosis of occult CS remains to be definitively established.

Cortisol excess impairs insulin action at different sites and increases liver gluconeogenesis (40, 41). Several reports suggest that removal of adrenal incidentalomas associated SCS improves insulin sensitivity, glucose metabolism (6, 20), and cardiovascular risk (3). Whether or not occult CS is responsible for the anthropometric and metabolic abnormalities displayed by the patients of our series is a critical issue that questions the usefulness of (and how aggressively we should diagnose) occult CS in type-2 diabetes mellitus (DM). Evaluation of the metabolic impact of the cure of occult CS was outside the scope of the present study. However, after 6 months of follow-up, a 5.5% relative weight reduction was observed, and withdrawal of antidiabetic medications could

be performed in patients successfully treated for occult CS. Further-controlled and long-term follow-up studies are needed to confirm the improvement of obesity and diabetes after cure of occult CS and, hopefully, provide information about subgroups of patients in whom this improvement is likely to occur.

In conclusion, prospective screening in overweight adult patients with type-2 diabetes revealed a 2% prevalence of definitive occult CS attributable to CD and cortisol-secreting adrenal adenoma. Possible adrenal-dependant occult CS was found in an additional 3.5% of diabetic patients. Although the proportion of patients with occult CS in this population is low, it should be interpreted in the light of the increasing prevalence of metabolic syndrome and type-2 diabetes in Western countries. Alternatively, this study was performed on an in-patient basis, and the prevalence of occult CS that we found might not apply to an ambulatory patient population.

Further prospective and controlled studies are needed to evaluate the anthropometric and metabolic impact of the cure of occult CS. Such studies might provide a rationale for a systematic screening of occult CS in obese patients with DM. In this perspective, our study supports the use of the 1-mg DST with revised cut-off criterion for post-test plasma cortisol value. Because of the relatively poor specificity of this revised procedure, complementary biochemical investigations are required to confirm occult CS in patients with apparent impaired HPA axis suppressibility.

Acknowledgments

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Address all correspondence and requests for reprints to: Antoine Tabarin, Department of Endocrinology, University Hospital of Bordeaux, Avenue de Magellan, 33604 Pessac, France. E-mail: antoine.tabarin@chu-bordeaux.fr.

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