Long-term outcome after adrenalectomy for incidentally diagnosed subclinical cortisol-secreting adenomas

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Background. *The management of subclinical cortisol-secreting adenomas (SCSAs) is controversial, and available evidence to assess the superiority of an operative versus a nonoperative approach is lacking. The aim of this work was to report the postoperative results and the long-term outcomes for patients with incidentally diagnosed SCSAs and to compare the results with those of patients who underwent an operation for cortisol-secreting adenomas (CSAs).*

Methods. *From 1994–2011, 107 consecutive patients underwent laparoscopic unilateral adrenalectomy for either an SCSA (n = 39) or a CSA (n = 68). Preoperatively, all patients underwent standardized clinical, hormonal, and imaging assessments. Patients were followed up for ≥2 years with serial assessments of body weight, blood pressure, and glycated hemoglobin, HbA1c.*

Results. *Operative resection of SCSAs and CSAs did not significantly differ regarding operative time, conversion rate, overall operative and medical morbidity, and duration of stay. For SCSAs, the comparison between preoperative status and 2-year assessment showed a median weight loss of 6% (P < .001), a decrease in the median HbA1c of 15% (P < .001), and an improvement or normalization of blood pressure in 50% of the patients. The same significant beneficial metabolic effects of the operation with even greater improvement were observed in patients with CSAs.*

Conclusion. *Laparoscopic unilateral adrenalectomy for SCSA is associated with low morbidity, no mortality, and significant improvement of various aspects of metabolic syndrome. Until additional evidence from prospective randomized controlled studies is obtained, laparoscopic unilateral adrenalectomy should be considered a valid option in the care of patients with SCSA. (Surgery 2016;160:397-404.)*

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Since it was first described in 1992,[1] laparoscopic adrenalectomy (LA) has become the standard procedure for the operative management of most adrenal tumors.[2,3] Today, LA is performed by experienced teams with very low mortality and morbidity rates of <15%. Nevertheless, the laparoscopic approach has led to an increased rate of adrenalectomies, which are possibly associated with more liberal indications.[4] Furthermore, the widespread use of high-quality, cross-sectional imaging has led to the more frequent diagnosis of asymptomatic adrenal lesions, ie, adrenal incidentalomas.[5]

After complete hormonal and imaging work-up, 5–30% of incidentalomas are found to be associated with subclinical hypercortisolism.[6,7] This condition is of growing interest and has been associated with some nonspecific, long-term consequences of cortisol excess, including hypertension, weight gain, diabetes, or cortisol-induced osteopenia. The treatment of subclinical cortisol-secreting adenomas (SCSAs), ie, operative resection versus

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medical treatment of metabolic disorders, remains controversial because of the lack of high-quality prospective randomized controlled trials.

There is no clear consensus from the National Institutes of Health or other European medical societies[8-10] regarding the management of subclinical autonomous glucocorticoid oversecretion. There is a lack of available evidence to demonstrate the superiority of an operative versus a nonoperative approach for the management of patients with SCSAs.

The aim of the present study was to report the postoperative results and long-term outcomes for patients with SCSAs and to compare these results with those for patients who underwent an operation for cortisol-secreting adenomas (CSAs).

PATIENTS AND METHODS

Study population. From June 1994 to August 2011, 107 consecutive patients underwent laparoscopic unilateral adrenalectomy for either an SCSA ($n = 39$) or a CSA ($n = 68$) at the Cochin Hospital, Paris, France, a tertiary referral center for adrenal disease. SCSAs were defined as adrenal incidentalomas without clinical Cushing's syndrome and with normal 24-hour urinary free cortisol (UFC), but with an abnormal response to a 1-mg dexamethasone (DEX) suppression test. CSAs were defined as tumors with clinical signs of Cushing's syndrome, elevated UFC, elevated late-night serum cortisol level, and low basal plasma adrenocorticotrophin.

Preoperative workup and care. Before the operation, all patients underwent clinical examination, hormonal measurements, and imaging workup as recommended by the guidelines of the French Endocrine Society.[9-11] Clinical evaluation was conducted within 6 weeks before the operation and included a physical examination, arterial blood pressure measurement after 30 minutes of rest using an oscillometric semiautomatic device, and weight assessment. High blood pressure was defined as a systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg.

Preoperative biochemical evaluation was performed according to a routine standardized procedure[12-14] and included measurements of 24-hour UFC (Normal value <69–248 nmol/24h), basal plasma adrenocorticotrophin (Normal value <13–15 pmol/L), late-night serum and/or salivary cortisol, and a 1-mg overnight DEX test. Inadequate cortisol suppression after the 1-mg overnight DEX test was defined by the cutoff value of 1.8 μg/dL(50 nmol/L) to achieve a sensitivity rate >95%.[11] In addition, glycated hemoglobin (HbA1c) and fasting blood glucose levels were determined for all patients. Diabetes was defined by an HbA1c level of >6.5% or by the need for a specific treatment.[10] Measurements of urinary metanephrine, normetanephrine, androgens, steroid precursors, renin, and aldosterone were routinely performed.

Since 2008, imaging workup has included at least a dedicated adrenal multirow detector computed tomography (CT) scan with magnetic resonance imaging (MRI) or ^{18}F-fluorodeoxyglucose positron emission tomography (PET) when required by the clinical situation or CT-scan atypical findings. According to each attending's discretion, ^{131}I-6-β-iodomethyl-norcholesterol scintigraphy was performed when discrepant results were obtained after repeat hormonal measurements. Scintigraphy confirmed the controlateral gland extinction or ruled out a bilateral disease.

Demographic, clinical, radiologic, and pathologic characteristics were obtained from a prospectively maintained database with an additional retrospective review of the biochemical and metabolic data.

Operative technique and perioperative care. The lateral transabdominal laparoscopic approach was used in all patients as previously described.[1,3,15] First, the main adrenal vein was divided before gland mobilization. Then, the gland was mobilized together with all of the periadrenal fat tissue to prevent tumor disruption. All the patients received prophylaxis for deep venous thrombosis. A normal diet and full mobilization were initiated on the first postoperative day.

Postoperative complications were defined according to the Clavien–Dindo classification.[16] The patients were not treated preoperatively, but received postoperative glucocorticoid substitution until normalization of an adrenocorticotropic hormone (ACTH) stimulation test. Postoperative follow-up consisted of standardized clinical, biochemical, and hormonal evaluation at 3 months, every 6 months for 2 years, and annually thereafter. Improvement in blood hypertension was defined as a normalization of blood pressure with the cessation of treatment, a reduction of the daily dosage of ≥50% in the case of monotherapy, or a reduction of the number of antihypertensive drugs in the case of therapy with multiple medications.

Statistical analysis. Values are expressed as the median and interquartile or percentage as appropriate. According to the distribution of variables, the χ^2 or Fisher exact tests were used to compare

Table I. Patient characteristics

	Overall n = *107*	*SCSA* n = *39*	*Clinical CSA* n = *68*	*SCSA versus CSA* P
Clinical characteristics				
Age (y)	42 (35–58)	59 (48–65)	38 (30–47)	<.001
Women (*n*)	94 (87.8%)	29 (74.3%)	65 (95.6%)	.004
Right-sided lesion (*n*)	38 (35.5%)	20 (51%)	18 (26%)	.16
BMI (kg/m^2)	26 (23–31)	27 (23–32)	26 (23–30)	.45
ASA I and II (*n*)	94 (87.8%)	33 (84.6%)	61 (89.7%)	.60
High blood pressure (*n*)	64 (59.8%)	20 (51.2%)	44 (64.7%)	.25
Patient with antihypertensive treatment (*n*)	56 (52.3%)	18 (46.1%)	38 (55.9%)	.33
Median number of medications	2 (1–5)	1.8 (1–4)	2 (1–5)	.65
Diabetes (*n*)	43 (40.19%)	11 (28.2%)	33 (47.1%)	.067
HbA1c (%)	6.3 (5.5–6.5)	5.9 (5.7–6.3)	6.4 (6.1–6.6)	<.001
Biologic characteristics				
UFC (μg/24h)	1.43 (0.7–3.57)	0.64 (0.47–0.77)	2.83 (1.67–5.83)	<.001
1-mg overnight DEX test (pg/mL)	99 (65–175)	58 (52–75)	143 (98–212)	<.001
Serum cortisol cycle				
Abnormal (*n*)	85 (79.4%)	17 (43.5%)	68 (100%)	<.001
ACTH (pg/mL)	6 (4–8)	8 (7–13)	4 (2.5–7)	<.001
ACTH <15 pg/mL (*n*)	101 (94.5%)	35 (89.7%)	66 (97%)	.19

SCSA, Subclinical cortisol-secreting adenoma; *CSA*, cortisol-secreting adenoma; *BMI*, body mass index; *ASA*, American Society of Anesthesiology; *HbA1c*, glycated hemoglobin; *UFC*, urinary free cortisol; *DEX*, dexamethasone; *ACTH*, adrenocorticotropic hormone.

the differences in discrete or categorical variables, and the *t* test or Wilcoxon rank sum test were used for continuous variables. Differences between the matched groups were evaluated using the Wilcoxon signed ranks test for continuous variables and the McNemar χ^2 test for paired proportions for categorical variables. All tests were 2-sided. The data were analyzed using STATA 11 statistical software (Stata Statistical Software: Release 11; Stata Corporation, College Station, TX).

RESULTS

Patient and tumor characteristics. Patient and tumor characteristics are summarized in Tables I and II. Briefly, the majority of patients were women ($n = 94$; 87.8%) with a median age of 42 years (35–58 years). At diagnosis, patients with SCSAs were significantly older (with a median age of 59 years versus 38 years; $P < .004$) compared with patients with CSAs. Otherwise, the features of the 2 groups' clinical presentations did not differ; features included lesion side, American Society of Anesthesiology (ASA) score, body mass index (BMI), preoperative blood pressure, or treatment. As expected and by definition, patients with SCSAs had less frequently elevated UFC, abnormal 1-mg DEX suppression test, abnormal serum cortisol, and ACTH when compared with patients with clinical Cushing's syndrome.

Tumor characteristics are detailed in Table II. On CT scan, tumors in patients with SCSAs were significantly larger (3.5 cm versus 3 cm; $P = .004$) than those in patients with CSAs. On the adrenal CT scan, the median spontaneous density was significantly higher for CSAs than SCSAs, with a significantly greater value of contrast enhancement absolute washout, as recently reported by Chambre et al.[17] No other significant differences were observed regarding the results of MRI, ^{131}I-6-β-iodomethyl-norcholesterol scintigraphy, or ^{18}F-fluorodeoxyglucose PET when performed. On the ^{18}F-fluorodeoxyglucose PET scans, the adrenal-to-liver maximum standardized uptake value (SUV) ratio was <1.45 in all instances, as previously reported for benign lesions.[18] Additionally, the adrenal SUV was always lower than that of the liver.

Intra- and postoperative results. Intra- and postoperative results are summarized in Table III. Briefly, the 2 groups did not differ significantly regarding operative time, conversion rate, overall morbidity rate, operative morbidity rate, medical morbidity rate, or duration of stay. There was no mortality in either group. On pathologic examination, tumor size was observed to be greater for SCSAs than for CSAs without significant difference (3.8 cm versus 3.4 cm; $P = .07$). The diagnosis of benign adenoma (Weiss score <3) was confirmed

Table II. Tumor characteristics

	Overall n = *107*	*SCSA* n = *39*	*Clinical CSA* n = *68*	*SCSA versus CSA* P
Tumor size on CT scan (cm)	3.2 (2–9)	3.5 (2–5.8)	3 (2–9)	.004
Dedicated adrenal CT scan (*n*)	97 (90.6%)	37 (94.8%)	60 (88.2%)	.4
Spontaneous density (HU)	14 (7–24)	8 (4–13)	21 (10–33)	<.001
<10 HU (*n*)	31 (31.9%)	19 (51.4%)	12 (20%)	—
10–20 HU (*n*)	35 (36.2%)	18 (48.6%)	17 (28.3%)	
>20 HU (*n*)	31 (31.9%)	0 (0%)	31 (51.7%)	
Absolute wash-out value (%)	63 (55–70)	61 (54–64)	67 (59–73)	.01
>60% (*n*)	66 (62%)	20 (51%)	48 (71%)	.05
Relative wash-out value (%)	63 (55–70)	51 (44–57)	51.5 (46.5–56)	.95
>40% (*n*)	86 (80%)	33 (84%)	52 (77%)	.33
MRI (*n*)	44 (41.1%)	19 (48.7%)	25 (36.7%)	.31
In/out phase decrease intensity >20%	24 (54.5%)	13 (68.4%)	11 (44%)	.19
Iodomethylnorcholesterol scintigraphy (*n*)	44 (41.1%)	26 (66.6%)	18 (26.5%)	<.001
Normal bilateral uptake (*n*)	1 (2.3%)	1 (3.8%)	0	.70
Asymmetric bilateral uptake (*n*)	4 (9.1%)	4 (15.4%)	0	
Unilateral uptake (*n*)	39 (88.6%)	21 (80.8%)	18 (100%)	
^{18}F-fluorodeoxyglucose PET	37 (34.6%)	22 (56.4%)	15 (22%)	<.001
Maximum SUV	4.3 (2.2–5)	4.2 (2.4–4.7)	4.1 (2.2–5.5)	.77

SCSA, Subclinical cortisol-secreting adenoma; *CSA*, cortisol-secreting adenoma; *CT*, computed tomography; *HU*, Hounsfield unit; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography; *SUV*, standardized uptake value.

Table III. Intra- and postoperative results

	Overall n = *107*	*SCSA* n = *39*	*Clinical CSA* n = *68*	*SCSA versus CSA* P
Operative duration (min)	85 (75–100)	80 (70–105)	88 (75–98)	.80
Conversion to open operation (*n*)	1 (0.93%)	0	1 (1.4%)	.70
Overall morbidity (*n*)	11 (10.3%)	4 (10.2%)	7 (10.3%)	.47
Clavien-Dindo Grade 2	6	2	4	—
Clavien-Dindo Grade 3	4	1	3	
Clavien-Dindo Grade 4	1	1	0	
Operative morbidity (*n*)	10 (9.3%)	4 (10.2%)	6 (8.8%)	.92
Parietal complications	4	2	2	—
Hematoma	2	1	1	
Intra-abdominal collection	4	1	3	
Medical morbidity (*n*)	5 (4.7%)	2 (5.1%)	3 (4.4%)	.19
Pulmonary (chest infection, pleural effusion)	1	1	0	—
Venous thromboembolism	3	0	3	
Cardiac insufficiency	1	1	0	
Mortality	0	0	0	—
Duration of stay (d)	5 (4–7)	5 (4–7)	5 (4–7)	.27
Tumor size on pathology (cm)	3.5 (3–4)	3.8 (3–4.7)	3.4 (2.9–3.9)	.07
Duration of hydrocortisone substitution therapy (mo)	24 (10–64)	12 (5–24)	28 (16–70)	.001
Hydrocortisone substitution therapy >24 mo (*n*)	58 (54%)	15 (38%)	43 (63%)	.02

SCSA, Subclinical cortisol-secreting adenoma; *CSA*, cortisol-secreting adenoma.

in all instances. Patients with CSAs required significantly longer hydrocortisone substitution therapy than those with SCSAs (28 months versus 12 months; $P = .001$).

Evolution of anthropometric, glycemic, and hemodynamic parameters following an operation. Following an operation, modifications in metabolic and anthropometric parameters were prospectively recorded for at least the first 2 years, with a median follow-up of 42 months (ranging from 26–180 months; Table IV). Compared with the baseline measurement, improvement was significant for weight, glycemic profile, and blood pressure as early as 6 months following an

Table IV. Evolution of anthropometric, glycemic, and hemodynamic parameters following an operation

	SCSA n = *39*			*Clinical CSA* n = *68*		
	At diagnosis	*At 24 mo*	P	*At diagnosis*	*At 24 mo*	P
Weight (kg)	80 (61–87)	70 (58–82)	<.001	70 (62–79)	60 (56–70)	<.001
Variation (%)	6 (2.5–8)			10.5 (2–17.8)		
High blood pressure (*n*)	20 (51.3%)	10 (25.6%)	.002	44 (64.7%)	9 (13.4%)	<.001
Variation	50%			80%		
HbA1c (%)	5.9 (5.7–6.3)	5 (4.5–5.5)	<.001	6.4 (6.1–6.6)	5.4 (5.1–5.8)	<.001
Variation (%)	15.4 (5.2–21.3)			15.7 (10.3–21.5)		
Diabetes (*n*)	11 (28.2%)	4 (10,2%)	.016	33 (47.1%)	3 (4.4%)	<.001

SCSA, Subclinical cortisol-secreting adenoma; *CSA*, cortisol-secreting adenoma; *HbA1c*, glycated hemoglobin.

operation, with continuous improvement for up to 2 years.

For SCSAs, at 24 months after an operation, the median weight loss was 6% of preoperative weight ($P < .001$); the median decrease in HbA1c was 15.4% ($P < .001$); an overall improvement in blood pressure was observed in 50% of patients; and antihypertensive therapy was stopped in 20% of patients. For CSAs, 24 months after an operation, the median weight loss was 10.5% of preoperative weight ($P < .001$); the median decrease in HbA1c was 15.7% ($P < .001$); an overall improvement in blood pressure was observed in 80% of patients; and treatment was stopped in 52% of patients. With the definition of diabetes based on elevated HbA1c, 60% of patients with SCSAs and 91% of patients with CSAs were no longer diabetic 24 months after an operation. The benefits of an operation were significantly more important in patients with CSAs than in patients with SCSAs.

DISCUSSION

With the widespread use of multirow, cross-sectional imaging, adrenal lesions are being identified with increasing frequency.[19] The prevalence of incidentally detected adrenal lesions, so-called *incidentalomas*, is approximately 2–4% and appears to increase with age.[19,20] Over time, progress has been made in the selection of patients for an operation, and the routine resection of all incidental adrenal lesions is no longer advocated.

After complete clinical, radiologic, and biologic workup, LA has become a consensual procedure for treating secreting lesions, including pheochromocytoma, Conn's adenomas, or CSAs. LA is selectively proposed for nonsecreting lesions according to their risk of malignancy,[8,19] which is based on size, spontaneous density, and contrast enhancement absolute wash-out on CT scan. The management of subclinical CSAs, ie, incidentally diagnosed adrenal adenomas associated with clinically silent hypercortisolism, is controversial, because the long-term risks of this hormonal oversecretion are not clearly defined.[21,22]

In the present study, among patients with SCSAs, 61.5% were overweight; 51.2% had high blood pressure; and 28.2% were diabetic. After at least a 24-month follow-up, LA for SCSA was shown to result in significant improvements in several components of metabolic syndrome, including weight loss, decreased HbA1c, and improved blood pressure. Overall, these results favor laparoscopic operative resection for the management of subclinical Cushing's syndrome. As expected, the same beneficial metabolic effects of an operation, with even greater improvement, were also observed in patients with CSAs.

For patients with clinical Cushing's syndrome, operative resection has been associated with reduced cardiovascular risk,[23,24] decreased blood pressure and weight gain, as well as improvement of glucidic balance.[25-27] Nevertheless, the situation is more complex for patients presenting with SCSAs.

First, the clinical relevance and diagnostic criteria for SCSAs are still a matter of debate. This is especially true for the cut-off level of inadequate cortisol suppression after the 1-mg overnight DEX test. The 50-nmol/L cut-off chosen in the present study is very sensitive (<95%) but less specific (<80%). It is unclear if the use of 131-iodomethyl-norcholesterol has some additional value for the management of patients with suspected SCSA. It was selectively used when discrepant hormonal measurements were obtained in patients having undergone serial biochemical evaluations. In that setting, ^{131}I-6-β-iodomethyl-norcholesterol scintigraphy appeared helpful for the decision of operating, in case of increased homolateral gland uptake together with contralateral gland extinction.

Table V. Results of the main studies reporting the operative management of SCS

Authors/y	Study design	Patients with SCS	Median follow-up	Significant improvement for patients with SCS			
				Blood pressure	Glucose metabolism	Overweight/ obesity	Quality of life
Rossi[30]/2000	Prospective nonrandomized	12	36	Yes	Yes	Yes	NA
Midorikawa[31]/2001	Prospective nonrandomized	4	NA	Yes	Yes	No	NA
Bernini[32]/2003	Prospective nonrandomized	6	12	No	NA	No	NA
Erbil[24]/2006	Retrospective	11	12	Yes	No	No	NA
Mauclère-Denost[29]/2009	Prospective nonrandomized	8	12	No	No	No	NA
Toniato[22]/2009	Prospective randomized	45	92	Yes	No	No	NA
Guerrieri[21]/2010	Retrospective	47	48	Yes	Yes	Yes	NA
Chiodini[33]/2010	Retrospective	41	48	Yes	Yes	Yes	NA
Miyazato[23]/2011	Retrospective	55	36	Yes	Yes	No	NA
Akaza[13]/2011	Prospective	16	NA	Yes	Yes	Yes	NA
Iacobone[34]/2012	Prospective	35	54	Yes	Yes	Yes	Yes
Perysinakis[35]/2012	Retrospective	29	77	Yes	Yes	Yes	NA

SCS, Subclinical Cushing's syndrome; *NA*, not available.

Overweight, diabetes, or hypertension associated with cortisol oversecretion represent nonspecific symptoms, which are increasingly encountered in Western countries. In this context, among patients in the general population with metabolic syndrome, it is likely that the prevalence of SCSAs is low, even though the prevalence may be underestimated. Nevertheless, this asymptomatic condition seems to be clearly associated with an increased cardiovascular risk.[28]

Whether intervention or medical treatment is the best treatment option for SCSAs remains controversial because of the lack of powered randomized controlled studies. There is no clear consensus treatment from the National Institutes of Health or other European medical societies[8,9] regarding the management of SCSAs. Several studies designed to assess the benefits of an operation in subclinical Cushing's syndrome are summarized in Table V. In these studies, there is a trend in favor of operative treatment with concordant evidence regarding blood hypertension and glucose metabolism but with less convincing data regarding weight loss.[13,21-24,29-36]

The only prospective randomized controlled trial including 45 patients reported significant improvements in several parameters of metabolic syndrome after an operation for SCSA when compared with control patients subjected to conservative medical treatment.[22] The operative resection of SCSAs aims to prevent the detrimental long-term consequences of low-dose cortisol excess. The benefits of an operation cannot be hampered by postoperative complications and should, therefore, be restricted to experienced operative teams with very low morbidity and zero mortality rates.[2,3]

In a recent systematic review, Iacobone et al[36] confirmed the trend toward a beneficial effect of an operation in several metabolic aspects of subclinical hypercortisolism; however, they also emphasized the heterogeneity and low quality of most available studies. In this review, which included 230 patients from 7 studies, the benefits to weight, blood pressure, and diabetes mellitus after adrenalectomy for SCSA appeared substantial.

As a bariatric operation, LA for SCSA can be viewed as a metabolic operation that might improve cardiovascular risk factors, BMI, bone mineral density, high blood pressure, glucose and lipid profiles, and possibly long-term overall survival. Furthermore, Iacobone et al[34] showed that in addition to improvements in cardiovascular and metabolic risk factors, adrenalectomy significantly improved the quality of life for patients with SCSAs, as assessed by the SF-36 questionnaire.

Surprisingly, the median duration for steroid supplementation in our study was 12 months. This is 2 times longer than the 6-month duration reported in another experience of operative treatment for SCSA.[37] This strongly suggests that a more rapid reduction of cortisol substitution may have helped reduce the overall duration of supplementation.

We are aware of several limitations to the present study. First, patients with SCSAs considered for an operation were not compared with a controlled group of patients with SCSAs undergoing medical management of their metabolic syndrome. However, this would only be possible

within a prospective randomized controlled trial with prolonged follow-up. Second, the evaluation of clinical and biologic improvement following LA does not accurately assess the quality of life, rates of cardiovascular events, or osteoporotic complications that might represent additional end points. Addressing these issues would require a prospective randomized controlled study including a large number of patients who are followed for several years.

In conclusion, when performed by an experienced team, LA for incidentally diagnosed SCSAs is associated with low morbidity and no mortality. Furthermore, LA results in significant long-term improvements in several components of metabolic syndrome, ie, weight, HbA1c, and blood pressure. This work provides additional evidence that when viewed as a metabolic operation, LA may benefit patients with SCSAs. While waiting for the results of a forthcoming prospective randomized controlled study, we should consider LA a valid option for the care of patients with SCSAs, especially for those with moderate-to-severe metabolic syndrome.

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