CLINICAL STUDY

Atherosclerotic risk factors and complications in patients with non-functioning adrenal adenomas treated with or without adrenalectomy: a long-term follow-up study

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Abstract

Objective: Despite the increased prevalences of hypertension, type 2 diabetes mellitus (T2DM), hyperlipidemy, and obesity in patients with non-functioning adrenal adenomas (NFAAs), there is a paucity of data on long-term atherosclerotic morbidity as well as the long-term cardiovascular effects of adrenalectomy in these patients.

Design, patients, and methods: This retrospective study includes the results of baseline and follow-up investigations of 125 patients (29 males and 96 females; mean age 60.1 years) with NFAAs referred for endocrine evaluation between 1990 and 2001. Of the 125 patients, 47 underwent unilateral adrenalectomy, while 78 patients were followed conservatively. These patients were reinvestigated after a mean follow-up time of 9.1 (5–16) years in 2006, with special emphasis on laboratory and other atherosclerotic risk factors (ARF), vascular events, and interventions.

Results: The prevalences of hypertension, impaired glucose tolerance or T2DM, hyperlipidemy, and obesity were 82, 43, 58, and 50%, and 89, 58, 82, and 50% at baseline and follow-up, respectively. None of the investigated ARF prevalences were different between patients treated and not treated with adrenalectomy, and between patients with and without subclinical Cushing's syndrome. The prevalences of angina pectoris, acute myocardial infarction, coronary, and peripheral arterial interventions or cerebrovascular stroke did not differ significantly between patients treated and not treated with adrenalectomy.

Conclusion: Our study confirms previous investigations reporting markedly increased prevalences of various ARF in patients with NFAAs. Adrenalectomy performed in these patients failed to decrease the prevalence of ARF and atherosclerotic morbidity.

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Introduction

Adrenal incidentalomas are mostly (in 70–80% of cases) non-functioning adrenal adenomas (NFAAs) which do not cause classical clinical signs and symptoms of hormone excess syndromes (1–4). However, 5–47% of the NFAAs show mild cortisol oversecretion without symptoms of Cushing's syndrome referred to as subclinical autonomous glucocorticoid hypersecretion or subclinical Cushing's syndrome. The prevalence of subclinical Cushing's syndrome among patients with NFAAs depends on the criteria used to define it. The lack of a golden standard, however, makes the diagnosis of subclinical hypercortisolism uncertain (3, 5–14).

Several lines of evidence suggest that in addition to cortisol-producing adrenal adenomas causing overt Cushing's syndrome, NFAAs are also associated with an increased atherosclerotic risk (15). The increased prevalence of various biochemical disturbances and accompanying diseases such as type 2 diabetes (T2DM) and hypertension is thought to be resulted from a mild glucocorticoid overactivity of these tumors. Unfortunately, this mild glucocorticoid excess cannot be always detected with a sufficient degree of sensitivity and specificity.

Autonomous cortisol hypersecretion may cause a variety of metabolic derangements and disorders, such as arterial hypertension, impaired glucose tolerance (IGT) and T2DM, hypercholesterolemia, hypertriglicer-idemia, hyperuricemia, and obesity. An increased prevalence of these metabolic disorders has been reported in patients with subclinical Cushing's syndrome (16–24). Mild autonomous cortisol hypersecretion caused by seemingly silent adrenal adenomas has

also been suggested as a new possible cause of metabolic syndrome (16, 25, 26).

These metabolic disorders are well-known risk factors for atherosclerosis. It was shown that surgical treatment of endogenous hypercortisolism reduces mortality and morbidity (18, 21, 27, 28). However, there is a lack of long-term follow-up studies that investigate the issue of whether patients with incidentally discovered adrenal adenomas, either hormonally inactive or only moderately active, could benefit from adrenalectomy in terms of cardiovascular morbidity and mortality.

The aim of our present study was to investigate the prevalence of various atherosclerotic risk factors (ARF), both at baseline and at least 5 years later in patients with NFAAs. Further aim of this work was to study whether adrenal surgical intervention could have an impact on atherosclerotic morbidity and mortality of these patients.

Subjects and methods

The results of clinical, laboratory, and imaging investigations of patients with NFAAs referred for evaluation to our endocrine unit at Semmelweis University between 1990 and 2001 were retrospectively analyzed. The initial imaging modalities were usually ultrasonography and computed tomography. All patients underwent complete clinical, radiological, and hormonal evaluation during their baseline investigation. Serum cortisol concentrations were measured from blood samples collected at 0800 and 2400 h, as well as after a low-dose (1 mg) dexamethasone suppression test. Hormonal investigations also included the measurements of serum DHEA sulfate, aldosterone, 17-hydroxyprogesterone, testosterone, plasma ACTH concentration, and plasma renin activity. The 24-h urine collection was performed for the determination of vanillylmandelic acid excretion. Nuclear magnetic resonance imaging and cholesterol- or MIBG-scintigraphy were performed if indicated. In case of a suspicion for primary aldosteronism, saline suppression test and, in some patients, selective adrenal vein sampling for aldosterone and cortisol measurements were also performed.

Based on the results of these investigations, patients with classic hormone excess syndrome (primary hyperaldosteronism, adrenal Cushing's syndrome, and pheochromocytoma) and those with a tumor greater than 4 cm commonly underwent adrenal surgery. Adrenal surgery was also performed if the possibility of adrenal malignancy persisted even after repeated laboratory and imaging investigations. Adrenal malignancy was frequently suspected in patients with tumors greater than 4 cm with irregular contours and a CT attenuation value greater than 10 HU, or with inhomogenities suggesting intratumoral necrosis or hemorrhage. However, several patients with a tumor diameter smaller than 4 cm were subjected to adrenalectomy when CT or MRI morphology not unequivocally suggested a benign lipid-rich adrenal lesion. In some other cases with a tumor size smaller than 4 cm, the patient expressed a strong preference for surgical intervention, especially when laparoscopic operation for symptomatic gallbladder stones offered the choice of simultaneous laparoscopic adrenalectomy.

In 2006, 171 patients diagnosed with NFAAs between 1990 and 2001 were invited in letter for an ambulatory follow-up medical investigation. Of the 171 invited patients, 113 patients were re-examined using our re-investigation protocol. Patients were instructed to present all of the medical documents including the results of all laboratory and imaging examinations and hospitalization records. Our re-investigation protocol consisted of a detailed medical and drug history, physical examination including blood pressure, body weight, and height measurements, as well as detailed laboratory and basal hormone investigations. The protocol was approved by the local ethics committee. All of the patients with an abdominal CT performed 2 or more years earlier underwent adrenal computed tomography. The CT diagnosis of adrenal adenoma was based on the following criteria: mass size usually lower than 4 cm, homogeneity, regular well-defined margins, and attenuation values less than 10 HU on unenhanced CT and, when using a 10- to 15-min delayed enhanced CT, a threshold value of 50–60% of the initial enhancement (3). In addition, all of the relevant medical documents of 12 further patients (four patients treated and eight not treated with adrenalectomy), who could not attend our clinic for the follow-up examination, were obtained either from the patients or their relatives, and the data were subsequently verified during a consultation with their family doctors. The reasons for the non-attendance were hemiparesis caused by ischemic cerebrovascular stroke (one patient), severe chronic obstructive pulmonary disease (one patient), and severe ischemic heart disease (one patient), deaths from malignant non-adrenal tumors (two patients), from severe chronic obstructive pulmonary disease (one patient), from cardiovascular disease (five patients), and from unknown cause (one patient).

Of the 125 patients with NFAAs having follow-up examinations or presenting follow-up data, 47 patients underwent unilateral adrenalectomy between 1990 and 2001. Histological examination revealed a benign adrenocortical adenoma in each patient. The remaining 78 patients were treated conservatively, without adrenalectomy. Of the 46 patients whose follow-up data were not available, 15 patients had unilateral adrenalectomy between 1990 and 2001 according to earlier records. Baseline plasma cortisol concentrations at 0800, 2400 h and after low-dose dexamethasone test as well as tumor diameters were not different between patients who were and were not available for follow-up investigations.

At the ambulatory follow-up visit, all of the 113 patients underwent fasting blood sampling for detailed laboratory measurements including complete blood cell count, hepatic and kidney functions, detailed lipoprotein, and hormone measurements. Patients on anti-hyperlipidemic medications and those who had total cholesterol greater than 5.2 mmol/l, low density lipoprotein cholesterol greater than 2.6 mmol/l or triglycerides greater than 1.7 mmol/l were considered to have hyperlipidemia.

Patients with a previous definitive diagnosis of diabetes mellitus and those on antidiabetic medications were regarded as diabetic. All of the other patients underwent an oral glucose tolerance test (OGTT, 75 g glucose diluted in 250 ml water). IGT and diabetes mellitus were defined according to the criteria of WHO (1999) (29). Diabetes mellitus was diagnosed when fasting plasma glucose exceeded 7.0 mmol/l or the glucose response after OGTT at 120 min was 11.1 mmol/l or greater. IGT was diagnosed when blood glucose levels at 120 min after OGTT were between 7.8 and 11.0 mmol/l. Laboratory results obtained during the baseline in-hospital examination including fasting, postprandial or after OGTT plasma glucose concentrations were reviewed and each patient was reclassified as normal, having IGT or diabetes mellitus according to the 1999 WHO criteria (29). Patients regularly taking antihypertensive medications and patients repeatedly having blood pressure greater than 140/90 mmHg were considered to have hypertension (30).

Subclinical Cushing's syndrome was diagnosed in patients without overt clinical signs and symptoms of Cushing's disease with at least one of the following two criteria: i) midnight serum cortisol concentration greater than 5 μg/dl and ii) plasma cortisol concentration greater than 3.6 μg/dl after low-dose dexamethasone suppression test.

For the comparison of the prevalences of hypertension and diabetes mellitus in our patients to that of the general Hungarian population, a large, community-based sample obtained in primary care facilities in four Hungarian counties was used. This database was shown to broadly represent the Hungarian general population, as virtually all Hungarian inhabitants are registered at family doctors (31).

Statistical analysis

Statistical analysis was performed using Statistica package (version 7.0, Statsoft Inc., Tulsa, Oklahoma, USA). A value of $P < 0.05$ was considered to be significant. The relative frequencies of each atherosclerotic event and disease recorded at follow-up were compared between patient groups treated with and without adrenalectomy, using chi-square analysis and Fisher's exact test. The frequencies of metabolic disorders and hormonal parameters were compared with t-test and Mann–Whitney U-test.

Results

The main clinical characteristics of the 125 patients with NFAAs, who participated in the follow-up examination or presented follow-up data are summarized in Table 1. There were no statistically significant differences in age and sex ratios between patients treated and not treated with adrenalectomy. The median follow-up time for all patients was 9.1 years (range, 5–16 years), and patients with and without adrenalectomy had similar follow-up times (Table 1). However, the baseline diameter of adrenal tumors of patients who underwent adrenalectomy was significantly larger when compared with that found at baseline in patients without subsequent adrenalectomy.

At the baseline endocrine investigation, plasma cortisol concentrations at 0800 and 2400 h, as well as after a low-dose dexamethasone test failed to show differences between patients subsequently treated and not treated with adrenalectomy (Table 2).

Table 3 shows the prevalences of various ARF in patients with NFAAs both at baseline and at the follow-up. The prevalences of risk factors and laboratory data at the time of follow-up were compared with the baseline data, and these parameters were also compared in the two groups of patients treated and not treated with adrenalectomy. As shown in Table 3, the prevalences of hypertension at baseline were very high in both groups (86 and 80% in patients with and without subsequent adrenalectomy, respectively), and this high prevalence persisted at the time of follow-up

Table 1 Main clinical characteristics of the 125 patients with non-functioning adrenocortical adenomas who participated in the follow-up examination or presented follow-up data.

	All patients	Patients with adrenalectomy	Patients without adrenalectomy	Difference between patients with and without adrenalectomy
Number of patients	125	47	78	
Male/female	29/96	8/39	21/57	NS
Age of patients at baseline, year	51.8±9.9	50.6±7.2	52.5±11.2	NS
Age of patients at follow-up, year	60.9±9.9	60.0±7.1	61.4±11.3	NS
Baseline tumor diameter, mm	26.0±11.9	33.4±10.8	21.5±10.2	$P < 0.0001$
Follow-up time, year	9.1±3.1	9.4±3.6	8.8±2.8	NS

Data are given as means and SDs. NS, not significant.

Table 2 Baseline hormonal findings in patients with non-functioning adrenocortical adenomas subsequently treated and not treated with adrenalectomy.

	Patients with subsequent adrenalectomy	Patients without subsequent adrenalectomy	Difference between patients with and without adrenalectomy
Midnight plasma cortisol (µg/dl)	2.6 ± 1.7	3.1 ± 2.6	NS
Morning plasma cortisol (µg/dl)	9.8 ± 5.8	10.9 ± 4.6	NS
Plasma cortisol after low-dose DXM (µg/dl)	2.2 ± 2.4	1.9 ± 0.7	NS
Plasma ACTH (pg/ml)	33.9 ± 18.5	23.3 ± 12.9	NS

Data are given as means and SDs. NS, not significant.

without significant differences between the two groups. Patients undergoing adrenalectomy were slightly more obese at baseline than those who were not treated with adrenalectomy, but the difference was not statistically significant. At the time of follow-up, the BMI was slightly increased in both groups without any significant differences between the two groups. When compared with baseline, the prevalence of hyperlipidemia and the number of patients treated with lipid-lowering drugs increased significantly at the time of follow-up in the two groups of patients with and without adrenalectomy. Plasma total cholesterol concentrations in both groups showed a significant decrease at the time of follow-up when compared with those measured at baseline. There were no statistically significant differences in the frequency of usage of lipid-lowering drugs (Table 3) between patients treated and not treated with adrenalectomy.

When compared with baseline, the prevalence of T2DM increased, whereas the prevalence of impaired glucose tolerance decreased significantly during the follow-up period in patients both with and without adrenalectomy (Table 3). Surgical removal of the adrenal adenoma failed to influence the prevalence of T2DM. At the time of follow-up, there were no statistically significant differences in the concentrations of plasma glucose, in the frequencies of usage of antidiabetic agents (Table 3), between patients treated and not treated with adrenalectomy.

When compared with the data obtained from a large cohort representing the Hungarian general population (31), the prevalences of hypertension and diabetes mellitus were significantly higher in patients with NFAAs both at baseline (Table 4) and at the time of follow-up (Table 5). These prevalences were significantly increased also in patients treated with surgery when compared with the general population (data not shown).

The number of various atherosclerotic events, as well as the number of coronary and peripheral arterial interventions occurring after the diagnosis of NFAA and adrenalectomy in the surgical group is presented in Table 6. No statistically significant differences were found in the prevalences of these events and interventions between patients treated and not treated with adrenalectomy. In addition, the cardiovascular

mortality was also similar in the groups of patients treated and not treated with adrenalectomy.

Thirteen of the 125 patients (10.4%) with NFAAs qualified for subclinical Cushing's syndrome, of which two patients fulfilled both criteria. Midnight plasma cortisol concentrations but not those measured at 0800 h or after a low-dose dexamethasone test were significantly higher in patients with subclinical Cushing's syndrome when compared with those found in patients without subclinical Cushing's syndrome (Table 7). Five of the 13 patients with subclinical Cushing's syndrome were treated with surgery. Mean tumor diameter in all patients with subclinical Cushing's syndrome and in those who were operated on did not differ from that found in patients without subclinical Cushing's syndrome. In addition, the occurrence of metabolic and cardiovascular risk factors was similar in patients with and without subclinical Cushing's syndrome. One of the patients diagnosed initially with subclinical Cushing's syndrome developed suppressed plasma ACTH concentration at follow-up without any signs and symptoms of hypercortisolism. No other major changes were detected in any of the laboratory parameters of these patients at the follow-up visit. There were no significant differences in any other laboratory parameters or in the prevalences of incident vascular events and interventions between patients with and without subclinical Cushing's syndrome (not shown in tables).

Discussion

The long-term benefit attained from surgical intervention is one of the most important unresolved issues regarding the management of patients with incidentally discovered adrenal tumors. Patients with adrenal masses causing unambiguous hormonal overactivity and those with suspected malignancy are clearly candidates for surgical interventions. Although the prevalence of metabolic abnormalities and accompanying disorders resulting in an increased atherosclerotic risk are high among patients with NFAAs and especially in those causing subclinical hypercortisolism (15, 16), the cause and effect relationship between

Table 3 Prevalence of atherosclerotic risk factors and laboratory abnormalities at baseline and at the time of follow-up in patients with non-functioning adrenocortical adenomas treated and not treated with adrenalectomy.

	All patients (n=113)			Patients with adrenalectomy (n=43)			Patients without adrenalectomy (n=70)			Difference between patients with and without adrenalectomy	
	At baseline	At follow-up	P-value	At baseline	At follow-up	P-value	At baseline	At follow-up	P-value	At baseline (P-value)	At follow-up (P-value)
Number (percent) of patients with hypertension	93 (82%)	101 (89%)	NS	37 (86%)	38 (88%)	NS	56 (80%)	63 (90%)	NS	NS	NS
BMI (kg/m²)	29.7±5.3	30.2±5.2	NS	30.8±5.1	31.2±5.3	NS	29.0±5.2	29.5±4.8	NS	NS	NS
Number (percent) of patients with obesity	56 (50%)	56 (50%)	NS	27 (63%)	26 (60%)	NS	29 (41%)	30 (43%)	NS	0.027	NS
Number (percent) of patients with hyperlipidemia	66 (58%)	93 (82%)	<0.0001	24 (56%)	39 (91%)	<0.0001	42 (60%)	54 (77%)	<0.05	NS	NS
Total cholesterol, mmol/l	6.1±1.2	5.3±1.1	<0.0001	5.9±1.4	5.4±1.2	NS	6.1±1	5.3±1.1	<0.0001	NS	NS
Triglycerides, mmol/l	1.9±1.1	1.9±1.1	NS	1.9±1.1	2.1±1.4	NS	2.0±1.1	1.9±0.8	NS	NS	NS
Number (percent) of patients on antihypertensive therapy	80 (71%)	93 (80%)	NS	31 (71%)	33 (77%)	NS	49 (70%)	60 (86%)	<0.05	NS	NS
Number (percent) of patients on statin therapy	6 (5%)	33 (29%)	<0.05	4 (9%)	12 (28%)	<0.05	2 (3%)	21 (30%)	<0.05	NS	NS
Number (percent) of patients on fibrate therapy	1 (0.8%)	7 (6%)	NS	1 (2%)	3 (7%)	NS	0	4 (6%)	NS	NS	NS
Number (percent) of patients with IGT	26 (23%)	11 (9%)	<0.05	15 (35%)	7 (16%)	<0.05	11 (16%)	4 (6%)	NS	<0.05	NS
Number (percent) of patients with T2DM	23 (20%)	54 (48%)	<0.0001	4 (9%)	18 (42%)	<0.001	19 (27%)	36 (51%)	<0.05	<0.05	NS
Plasma glucose, mmol/l	5.7±1.2	6.1±2.3	NS	5.4±1.1	5.9±1.9	NS	5.8±1.3	6.2±2.6	NS	NS	NS
Prevalence of oral antidiabetic medication	8 (7%)	30 (27%)	<0.05	2 (5%)	12 (28%)	<0.05	6 (9%)	18 (26%)	<0.05	NS	NS
Prevalence of insulin therapy	1 (0.8%)	6 (5%)	NS	0	1 (2%)	NS	1 (1%)	5 (7%)	NS	NS	NS
Prevalence of OAD+insulin therapy	9 (8%)	36 (32%)	<0.05	2 (5%)	13 (30%)	<0.05	7 (10%)	23 (33%)	<0.05	NS	NS

Data are given as means and SDs. NS, not significant; IGT, impaired glucose tolerance; T2DM, type 2 diabetes.

Table 4 Prevalences of high blood pressure and type 2 diabetes mellitus in patients with non-functioning adrenocortical adenomas at baseline and in the general Hungarian population.

Sex	Patients with non-functioning adrenocortical adenomas at baseline		General Hungarian population		Difference between patients with non-functioning adrenocortical adenoma and general Hungarian population	
	Females	Males	Females	Males	Females	Males
Number of patients	89	24	23 000	22 079		
Mean age of patients, year	50.8	53.4				
Age range, year			45–54	45–54		
Number (percent) of patients with hypertension	72 (81%)	21 (87%)	6184 (27%)	5877 (27%)	$P<0.0001$	$P<0.0001$
Number (percent) of patients with type 2 diabetes	16 (18%)	7 (29%)	982 (4%)	1595 (7%)	$P<0.0001$	$P<0.0001$

adrenal adenoma and increased atherosclerotic risk has not been clearly established.

Our present study, in accordance with other reports (18), demonstrates that the prevalences of several ARF are increased in patients with NFAAs. At the time of diagnosis, the prevalences of hypertension, T2DM, obesity, and hyperlipidemia in our patients were comparable with those reported in the majority of other series (6, 10, 16–18, 21–26, 32). Among several clinical, biochemical, and hormonal parameters investigated in our study, adrenal tumor diameter was the only parameter influencing significantly the decision between surgical and non-surgical treatment of our patients with NFAAs.

It is presently unclear how surgical removal of NFAAs may affect the increased atherosclerotic risk of these patients. The few follow-up studies of patients with non-functioning adrenal tumors have been focused on the prevalence of growth of tumor mass or change in hormonal activity (33–36), but the prevalence of various cardiovascular events has not been evaluated in these patients. It has been shown that the atherosclerotic risk decreases, but not returns to normal after the cure of overt (28) and subclinical Cushing's syndrome (27). However, only a few studies investigated the postoperative changes in various clinical and metabolic parameters reflecting atherosclerotic risk in patients with non-functioning adrenal tumors (18, 22). Insulin resistance has been shown to be improved in some, but not all patients after unilateral adrenalectomy in patients with non-functioning adrenal tumors including those presenting with subclinical hypercortisolism (21).

When comparing patients with and without adrenalectomy, detailed investigations of various plasma lipoprotein fractions, basal plasma glucose, serum

Table 5 Prevalences of hypertension and type 2 diabetes mellitus in patients with non-functioning adrenocortical adenomas without adrenalectomy at the time of follow-up and in the general Hungarian population.

Sex	Patients with non-functioning adrenocortical adenomas without adrenalectomy at the time of follow-up		General Hungarian population		Difference between patients with non-functioning adrenocortical adenomas without adrenalectomy at the time of follow-up and general Hungarian population	
	Females	Males	Females	Males	Females	Males
Number of patients	53	17	19 799	16 691		
Mean age of patients (year)	60.5	63.2				
Age range (year)			55–64	55–64		
Number (percent) of patients with hypertension	47 (89%)	16 (94%)	9716 (49%)	7414 (44%)	$P<0.0001$	$P<0.0001$
Number (percent) of patients with type 2 diabetes mellitus	25 (47%)	11 (65%)	2082 (11%)	2347 (14%)	$P<0.0001$	$P<0.0001$

Table 6 Cardiovascular/cerebrovascular morbidity and mortality at the time of follow-up in patients with non-functioning adrenocortical adenomas treated and not treated with adrenalectomy.

	Patients with adrenalectomy (*n*=47)	Patients without adrenalectomy (*n*=78)	Difference between patients with and without adrenalectomy (*P* value)
Number (percent) of patients with cardiovascular morbidity	16 (34%)	25 (32%)	0.8
Number (percent) of major cardiovascular events	9 (19%)	13 (17%)	0.7
Number (percent) of patients with angina pectoris	7 (15%)	9 (12%)	0.58
Number (percent) of patients with acute myocardial infarction	2 (4%)	9 (12%)	0.16
Number (percent) of cardiovascular mortality	2 (4%)	3 (4%)	0.9
Number (percent) of patients with coronary interventions	1 (2%)	6 (8%)	0.2
Number (percent) of patients with percutaneous transluminal coronary angioplasty	1 (2%)	3 (4%)	0.6
Number (percent) of patients with coronary bypass surgery	0	4 (5%)	0.1
Number (percent) of intervention for peripheral arterial stenosis/occlusion	7 (15%)	5 (6%)	0.1
Number (percent) of patients with cerebrovascular stroke	7 (15%)	12 (15%)	0.9

insulin, and C-peptide concentrations did not indicate any metabolic benefit from the surgical removal of NFAAs. This finding was in accordance with the lack of differences in the prevalences of cardiovascular adverse events and vascular interventions between patients with and without adrenalectomy. Among several parameters investigated in the present study, plasma total cholesterol was the only ARF, which showed a decrease at the time of follow-up, but this change proved to be independent of adrenal surgery and could be related to the more frequent usage of lipid-lowering agents, especially statins, at the time of follow-up.

To our best knowledge, this is the first study in patients with NFAAs, which investigated not only the

Table 7 Baseline hormonal findings in patients with non-functioning adrenocortical adenomas with and without subclinical Cushing's syndrome.

	Patients without SCS	Patients with SCS	Difference between patients with and without SCS
Midnight plasma cortisol (μg/dl)	2.4±1.4	6.0±3.9	<0.05
Morning plasma cortisol (μg/dl)	10.4±5.2	11.6±5.1	NS
Plasma cortisol after low-dose DXM (μg/dl)	1.8±0.7	3.1±3.0	NS
Plasma ACTH (pg/ml)	26.1±16.8	21.2±14.7	NS

Data are given as means and SDs. SCS, subclinical Cushing's syndrome; NS, not significant.

baseline atherosclerotic risk profile and its short-term change after adrenalectomy, but also the prevalence of long-term adverse cardiovascular events. Most importantly, our results indicate that despite the highly increased atherosclerotic risk parameters, surgical removal of the non-functioning adrenal adenoma failed to lower the prevalence of various adverse vascular events.

Our present study has some important limitations which should be taken into account. It is important to note that the prevalence of hypertension in our patients with NFAA was very high even at baseline (80%). The most probable explanation for this observation is that in several cases, ultrasonography or computer tomography were performed preferably in hypertensive patients to search for secondary causes of high blood pressure. The relatively low number of patients, especially the low number of patients with subclinical Cushing's syndrome represents another important limitation of our study. However, the long follow-up period should be considered as a strength of the study which may, at least partially, compensate for the relatively small patient cohort. Further limitations are the retrospective nature of this study and the lack of usage of standardized drug treatment protocol. However, the medical treatment of the patients during the follow-up period was managed mainly by the patients' general practitioners according to the general treatment practices. Our analysis revealed an absence of significant differences in the usage of various drug treatments between patients treated and not treated with adrenalectomy. Nevertheless, we cannot exclude the possibility of minor differences,

for example, in the intensities of various drug treatments or in the compliance of these patients.

Our observations support the possibility that the association between NFAAs and the high prevalence of adverse atherosclerotic risk profile does not necessarily reflect a cause and effect relationship, as these metabolic abnormalities may persist for a long period of time after surgical removal of the NFAAs. It is possible that the lack of improvement of adverse atherosclerotic risk profile after adrenal surgery may be the consequence of persisting abdominal obesity and insulin resistance, similar to those observed during a long-term follow-up of patients after curative surgery for pituitary Cushing's disease (28).

In conclusion, our results clearly indicate that adrenalectomy performed in patients with non-functioning adrenocortical adenomas failed to normalize or improve the adverse metabolic profile and the increased prevalence of hypertension, T2DM, dyslipidemia, and obesity during a 9-year period of postoperative follow-up. Adrenalectomy in these patients did not result in a decrease of atherosclerotic morbidity and mortality. Nevertheless, a large prospective, randomized study may be needed to explore more definitively the long-term outcome of adrenalectomy on adverse metabolic profile as well as on atherosclerotic mortality and morbidity in these patients. This prospective trial should focus also on the differences in the long-term consequences of adrenocortical adenomas with and without the laboratory abnormalities of subclinical Cushing's syndrome.

Declaration of interest

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