High prevalence of smoking in patients with adrenal incidentalomas: causality or case selection?

Henrik Olsen^{1,2}, Albin Kjellbom^{1,2}, Magnus Löndahl^{1,2} and Ola Lindgren^{1,2}

¹Department of Endocrinology, Skane University Hospital, Lund, Sweden and ²Department of Clinical Sciences Lund, Endocrinology, Faculty of Medicine, Lund University, Lund, Sweden

Correspondence
should be addressed
to H Olsen

Email
henrik.olsen@med.lu.se

Abstract

Objective: Autonomous cortisol secretion and possible autonomous cortisol secretion (ACS/pACS) are associated to an increase of cardiovascular risk factors such as hypertension, diabetes mellitus and dyslipidaemia. To our knowledge, the prevalence of smoking, another well-established risk factor for cardiovascular disease, has not been studied in detail in people with ACS/pACS or adrenal incidentalomas.

Methods: Patients with adrenal incidentalomas were examined with the 1-mg overnight dexamethasone suppression test (cortisol_{ONDST}). Information about current smoking was collected from the patient's records.

Results: We studied 1044 patients, of whom 370 (35%) were current smokers. Of these, 22% had bilateral AI compared to 12% of the non-smokers ($P < 0.001$). Among patients with unilateral adrenal incidentalomas, smokers had larger adrenal incidentalomas than non-smokers (22 mm vs 19 mm, $P < 0.001$). Smokers also more often had cortisol_{ONDST} ≥ 50 nmol/L than non-smokers, 54% vs 40% ($P < 0.001$), a finding independent of the size of the adrenal incidentaloma in patients with unilateral adrenal incidentalomas.

Conclusions: In the present study of patients with adrenal incidentalomas, the prevalence of current smoking was higher than in the general population. Furthermore, smokers had larger unilateral adrenal incidentalomas, more often bilateral adrenal incidentalomas, and more frequently ACS/pACS. Whether smoking is a risk factor for adrenal incidentalomas and ACS/pACS or our findings are due to case selection needs to be further studied.

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Introduction

Adrenal incidentalomas are frequently found at imaging examinations and may cause autonomous cortisol secretion (ACS) and possible autonomous cortisol secretion (pACS) (1). ACS/pACS has been linked to increased cardiovascular morbidity and mortality (2, 3, 4). Furthermore, ACS/pACS is associated with increased cancer mortality (5) as opposed to overt Cushing syndrome (6). The reason for this difference is not known, although selection bias might be involved. Smoking is an important risk factor for both cancer and cardiovascular disease, but smoking habits among patients with adrenal incidentalomas have not been comprehensively

investigated. Our aim was, therefore, to study the prevalence of smoking in relation to morphology and cortisol secretion in a large consecutive geographically well-defined group of patients with adrenal incidentalomas.

Methods

Patients examined for adrenal incidentalomas at Helsingborg Hospital and the departments in Malmö and Lund of Skane University Hospital between January 1, 2005 and September 15, 2015 were included in the

absence of one or more of the following exclusion criteria: presence of a metastatic malignancy; adrenal incidentalomas smaller than 1 cm; non-adenoma lesions such as myelolipomas, haemorrhages and cysts; biochemical results supporting pheochromocytoma, primary hyperaldosteronism, or clinical Cushing's syndrome; oral corticoid treatment more than single doses in the past 3 months; use of inhalation steroids or medication affecting dexamethasone metabolism and systemic oestrogen treatment. Medical history was collected from patient records. Current smokers were defined as daily smokers and thus did not include occasional smokers. Data on previous smoking was not collected as this was not available in most records. All patients were examined with the 1-mg overnight dexamethasone suppression test (cortisol_{ONDST}). Basal ACTH was collected in the majority of the patients. The size of the adrenal incidentalomas was defined as the maximal axial diameter and adrenal incidentalomas considered bilateral in patients with a lesion with the minimal size of 1 cm in both adrenal glands. The CT scans were evaluated by the clinical radiologists and confirmed by two of the authors (A K, H O). The study was approved by the Ethics Committee, Lund, Sweden. Informed consent was not required due to the nature of the study.

Laboratory analyses

Plasma cortisol was analysed using a one-step competitive immunoassay (Roche Diagnostics). The reference range was (171–536 nmol/L), the coefficient of variation (CV) 2.1% at 94.9 nmol/L, and the detection limit 0.5 nmol/L. Plasma ACTH was analysed using two two-step immunometric sandwich assays (Cobas®), Roche Diagnostics and Nichols Institute Diagnostics, CA, USA). The reference range for Roche assay was 1.6–13.9 pmol/L, the CV 5.4% at 1.1 pmol/L, and the detection limit 0.23 pmol/L, and 2.0–10.0 pmol/L, 9% at 8.0 pmol/L, and 2.0 pmol/L, respectively for the Nichols Institute Diagnostics assay. The latter was used in the department in Malmö from the start of the study period until 20/2/2012.

Data analyses

Results for ACTH achieved with the assay from Nichols Institute Diagnostics was only used to separate patients into groups with ACTH <2.0 pmol/L or ≥2.0 pmol/L because of the low precision.

Statistical analyses

The statistical analysis was performed using PASW statistics 25 (SPSS Inc.). Results are expressed as medians and ranges. Comparisons of categorical data between groups were made using Chi-squared test or Fisher's exact test as appropriate and comparisons of continuous data between groups with the Mann–Whitney *U*-test. Multivariable logistic regression was used to study the prevalence of cortisol_{ONDST} ≥50 nmol/L according to whether the adrenal incidentaloma was unilateral or bilateral and whether the patient was a smoker or non-smoker, adjusted for age. The same analysis was also performed with the patients grouped by gender and into four age groups. Confidence intervals for binomial data were calculated with the Clopper–Pearson test. Multivariable logistic regression was used among patients with unilateral AI to study the prevalence of cortisol_{ONDST} ≥50 nmol/L in smokers vs non-smokers, adjusted for gender, age, BMI, and size of the adrenal incidentaloma. Multivariable logistic regression was also used among patients with unilateral adrenal incidentaloma to study the prevalence of ACTH <2.0 pmol/L in smokers vs non-smokers, adjusted for gender, age, BMI, size of the adrenal incidentaloma, and cortisol_{ONDST}. Cortisol_{ONDST} was ln-transformed in this analysis. To study whether the total smoking exposure is associated to whether the adrenal incidentalomas was bilateral, cortisol_{ONDST}, and the size of the unilateral incidentalomas, these three factors were studied in smoker and non-smokers separately. Univariable logistic regression was used to study the relation between age and whether the adrenal incidentaloma was unilateral or bilateral and whether cortisol_{ONDST} was <50 or ≥50 nmol/L in smokers and non-smokers. Univariable linear regression was used to study the relation between age and size of the unilateral adrenal incidentaloma in smokers and non-smokers. A *P*-value <0.05 was considered to indicate statistically significant differences.

Results

We screened 1594 patients consecutively examined for adrenal incidentalomas, and of these 550 were excluded based on the exclusion criteria, and thus, 1044 patients were included, of which 370 (35%) were current smokers. The prevalence of smoking declined during the study period in males from 41% (38 of 93) during 2005–2008 to 25% (36 of 145) during 2013–2015 (*P*=0.009), but was unchanged in women, 35% (43 of 124) and 39%

Clinical Study	H Olsen and others	Smoking in adrenal incidentalomas	183:3	337
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(86 of 222) ($P=0.45$), respectively. Smokers were younger, had lower BMI, more often bilateral adrenal incidentalomas, larger unilateral adrenal incidentalomas, lower ACTH and higher cortisol_{ONDST} than non-smokers, although the prevalence's of treated hypertension, diabetes mellitus, and dyslipidaemia were lower among smokers. Patient's characteristics are given in Table 1. Of the patients with bilateral adrenal incidentalomas, three or more nodules were present in 22 patients and of these 7 were smokers. The indications for the imaging examinations are given in Table 2.

The prevalence of cortisol_{ONDST} ≥ 50 nmol/L in smokers and non-smokers with unilateral or bilateral adrenal incidentalomas are given in Fig. 1. The prevalence of cortisol_{ONDST} ≥ 50 nmol/L was increased in smokers in both unilateral and bilateral adrenal incidentalomas. Table 3 gives the prevalence of smoking according to gender and age group in the background population as reported by Ali *et al.* (7) and in patients divided into groups whether they had unilateral or bilateral adrenal incidentalomas and whether they had cortisol_{ONDST} < 50 nmol/L or cortisol_{ONDST} ≥ 50 nmol/L. In multivariable analysis, the risk of having bilateral adrenal incidentalomas was higher in smokers (OR: 2.1, $P < 0.0001$) and increased with age (OR: 1.2 for 10 years increase in age, $P = 0.03$) but was independent of gender. Among patients with unilateral adrenal incidentalomas, the relations of smoking to ACTH < 2.0 pmol/L and cortisol_{ONDST} ≥ 50 nmol/L, adjusted for gender, age, the size of the AI, and BMI, are given in Table 4.

The probability of harbouring bilateral adrenal incidentalomas increased with age in smokers (32% increase per 10 years increase, $P = 0.03$) but was not related

to age in non-smokers (11% increase per 10 years increase, $P = 0.37$). The size of the adrenal incidentaloma in patients with unilateral adrenal incidentalomas was independent of age in both smokers (-0.07 mm per 10 years increase, $P = 0.89$) and non-smokers (0.09 mm per 10 years increase, $P = 0.76$). The prevalence of cortisol_{ONDST} ≥ 50 nmol/L increased with age in both smokers (71% increase per 10 years, ($P < 0.0001$) and non-smokers (78% increase per 10 years, $P < 0.0001$).

Missing data

Basal ACTH was measured with the Roche and Nichols methods in 576 and 185 patients, respectively, and was thus not available in 283 patients.

Discussion

The frequency of current smokers in our population varied with gender, age and time of enrolment in a similar pattern as in the general population (7, 8). In the study by Ali *et al.*, 27 963 persons living in our county (Skåne), randomly selected from the population registry, answered a postal questionnaire (7). The subjects categorized themselves into one of the four categories: daily smoker, intermittent (non-daily) smoker, stopped smoking and never smoked. The prevalence of smoking among our patients with unilateral adrenal incidentalomas was approximately twice and among patients with bilateral adrenal incidentalomas approximately three times that reported by Ali *et al.* (7). For instance, in our female patients between 55 and 64 years of age, the smoking prevalence

Table 1 Characteristics of all patients and patients divided into two groups according to whether they were current smokers or non-smokers.

	All patients	Non-smokers	Smokers	P
n	1044	674	370	
Gender (% females)	59	56	64	0.009
Age (years)	64.8 (24.4–88.7)	66.3 (24.4–88.7)	61.5 (24.7–88.2)	< 0.0001
BMI (kg/m ²)	27.4 (12.8–55.2)	28.1 (12.8–50.4)	26.5 (15.0–55.2)	< 0.0001
Bilateral (%)	16	12	22	0.0001
Size of the unilateral AI (mm)	20 (10–72)	19 (10–70)	22 (10–72)	0.0002
Cortisol (nmol/L)	473 (131–1299)	473 (131–1299)	472 (157–1244)	0.81
ACTH* (pmol/L)	3.1 (< 0.23 –26.0)	3.7 (< 0.23 –26.0)	2.0 (< 0.23 –11.0)	< 0.0001
Cortisol _{ONDST} (nmol/L)	46 (9–487)	43 (9–487)	53 (11–449)	< 0.0001
Cortisol _{ONDST} ≥ 50 (%)	45	40	54	< 0.0001
Treatment for hypertension (%)	52	57	44	< 0.0001
Diabetes mellitus (%)	19	21	15	0.017
Treatment for dyslipidaemia (%)	31	35	23	< 0.0001

*ACTH levels measured with the method with best accuracy (Roche method) was available in 576 (55%) of the patients.
P-values are significance level for smokers compared to non-smokers.

Table 2 Indications for imaging stratified by smoking status.

Indications for the imaging examinations	All patients	Non-smokers	Smokers
Abdominal pain including pain in the side (%)	487 (47)	319 (47)	168 (45)
Cancer including examining for suspected cancer (%)	97 (9)	64 (9)	33 (9)
Chest pain and dyspnoea (%)	78 (7)	56 (8)	22 (6)
GI bleeding (%)	24 (2)	15 (2)	9 (2)
Haematuria (%)	54 (5)	36 (5)	18 (5)
Trauma (%)	38 (4)	24 (4)	14 (4)
Aortic aneurysm including examination for suspected aneurysm (%)	23 (2)	16 (2)	7 (2)
Study (%)	4 (0)	3 (0)	1 (0)
Other indications (%)	234 (22)	138 (20)	96 (26)
Not available (%)	5 (0)	3 (0)	2 (1)
Total	1044	674	370

was 42% in people with unilateral adrenal incidentalomas and 57% in those with bilateral adrenal incidentalomas as compared to 20% in the cited study (7). Corresponding data for men at the same age were 28, 55, and 19%, respectively (7). Current smoking, thus, seems to be more prevalent in our patients than in the general population, independent of gender and age. In our study, smokers

had bilateral adrenal incidentalomas approximately twice as often as non-smokers, a finding comparable to that previously described by Hao *et al.* (9). Further, in people with unilateral adrenal incidentalomas, the tumours were larger among smokers. Smoking habits were also linked to cortisol_{ONDST} with smokers having cortisol_{ONDST} ≥50 nmol/L more often, both among patients with unilateral and bilateral adrenal incidentalomas. We have identified six studies that have reported the prevalence of smoking in patients with or without ACS/pACS (10, 11, 12, 13, 14, 15). Only two of these reported an increased prevalence of smoking among patients with ACS/pACS (14, 15). However, all these studies were considerably smaller than ours and differences in smoking habits between groups were not adjusted for plausible confounding factors such as gender and age. We had not the possibility to separate former smokers from never smokers. The differences in the prevalence of bilateral adrenal incidentalomas, the size of the unilateral AI and the prevalence's of cortisol_{ONDST} ≥50 nmol/L between smokers and never smokers may therefore be larger than the reported differences between smokers and non-smokers. It could be suspected that the increased prevalence of ACS/pACS found in smokers could be explained by an activation of the HPA-axis, but the lower ACTH found in smokers contradicts this.

Figure 1

The prevalence's of cortisol_{ONDST} ≥50 nmol/L in patients divided into four groups according to whether they had unilateral or bilateral adrenal incidentalomas and whether they were smokers or non-smokers. **P* < 0.0001 compared to non-smokers with unilateral adrenal incidentaloma, adjusted for age. ***P* = 0.033 compared to non-smokers with unilateral adrenal incidentaloma, adjusted for age. ****P* = 0.027 compared to non-smokers with unilateral adrenal incidentaloma, adjusted for age. *****P* = 0.009 compared to non-smokers with bilateral adrenal incidentalomas, adjusted for age. The prevalence of cortisol_{ONDST} ≥50 nmol/L was increased in smokers independently of whether the adrenal incidentaloma was unilateral or bilateral.

We can only speculate whether the relation between smoking and adrenal incidentalomas may be causal or not. Smoking has chronologically the possibility to be causal to an adrenal incidentaloma (16) and smoking has been linked to colorectal adenomas and Warthin's tumours in the salivary glands and among the endocrine glands to thyroid nodules and functional ovarian cysts (17, 18, 19, 20). The very high prevalence of smokers among patients with adrenal incidentalomas was further increased among patients with ACS/pACS, suggesting that smoking may be a causal factor for adrenal incidentalomas and ACS/pACS. The lack of data on duration of smoking, number of cigarettes smoked daily and former smokers hampers

Table 3 The prevalence's of smoking in genders and different age groups in the general population and in patients divided into groups whether they had unilateral or bilateral adrenal incidentalomas and whether they had cortisol_{ONDST} <50 nmol/L or cortisol_{ONDST} ≥50 nmol/L.

Age group, years	General population*	Unilateral				Bilateral				
		Cortisol _{ONDST} <50		Cortisol _{ONDST} ≥50		Cortisol _{ONDST} <50		Cortisol _{ONDST} ≥50		
		% Smokers (95% CI)	n	% Smokers (95% CI)	n	% Smokers (95% CI)	n	% Smokers (95% CI)	n	p
Males										
24-54	14.2/19.4	44 (31-59)	54	30	10	44	9	67	3	0.45
55-64	18.5	25 (16-35)	81	35 (21-50)	46	50	10	60	10	0.02
65-80	11.2	19 (11-29)	79	30 (20-42)	70	15	13	50 (30-70)	26	0.003
81-83	-	0	5	10	10	50	2	0	3	NA
Females										
25-54	17.9/24.4	49 (38-60)	84	59 (42-75)	37	50	8	75	8	0.19
55-64	19.8	25 (16-36)	79	61 (49-72)	72	36	11	80	10	0.04
65-80	10.7	19 (13-28)	119	33 (24-42)	107	38	13	53 (35-70)	34	0.0002
80-89	-	13	8	21	19	100	1	33	3	0.49

*The data on smoking prevalence's in the general population is the data reported by Ali *et al.* (7). For the age groups up to 54 years, the data from the general population is given for the age groups 35-44 and 45-54 years.

The 95% CI is calculated in the groups with a minimum of 25 subjects.

P-values are the significance levels for the prevalence's of smoking compared to patients with unilateral adrenal incidentalomas and cortisol_{ONDST} <50, adjusted for age.

NA, Not applicable.

the possibility to relate the total smoking volume of each patient to their adrenal incidentaloma and cortisol_{ONDST}. However, people usually start smoking as adolescents or young adults as reported by Douglas *et al.* who found that the median age for smoke initiation was 19 years and that initiation of smoking after the age of 24 years was rare (21). The duration of smoking is thus strongly correlated to the age of the patients. The presence of bilateral adrenal incidentalomas increased with age in smokers but not in non-smokers, which thus indicates that the total load of smoking may be of importance. On the contrary, we found no differences in the relations of age to the size of unilateral adrenal incidentalomas or cortisol_{ONDST} ≥50 nmol/L between smokers and non-smokers to further support this. However, the low proportion of smokers below 50 years of age corresponding to a duration of smoking below 30 years may limit the possibility to detect this. An explanation for the increased prevalence of cortisol_{ONDST} ≥50 nmol/L in smokers may be an effect of smoking on dexamethasone metabolism, but two earlier studies reported no effect of smoking on the dexamethasone levels (15, 22). The relation between AI and smoking may alternatively be non-causal. An adrenal incidentaloma is defined as an adrenal enlargement detected at an imaging examination performed for another indication than a suspected adrenal disease. Smoking is linked to increased morbidity in general, which might lead to a higher frequency of imaging examinations in smokers, plausibly leading to an increased detection rate in smokers harbouring an AI. Increased smoking habits may also explain the increased incidence cardiovascular risk factors in patients with an adrenal incidentaloma considered to be non-functional (12). A selection bias due to hormone levels may also occur. This is possible if the coexistence of the two risk factors, hormonal alterations, and smoking enhance the risk for disease not simply additively but synergistically, which is the case for other cardiovascular risk factors (23). Thus, the detection rate may be increased due to high morbidity in smokers with ACS/pACS. As smoking is a well-known risk factor for cancer, our data may also explain the somewhat unexpected finding of malignancy being the cause of increased mortality in patients with ACS in one study (5).

Although, our observations are strengthened by our large study population and the high validity of the variables studied, several limitations, including its cross-sectional design, provide no possibility to study causality. As previously discussed, data on former smokers, duration of smoking, amount of daily smoking in smokers and the use of snuff tobacco were not available.

Table 4 Multivariable logistic regression for whether cortisol_{ONDST} was <50 nmol/L or ≥50 nmol/L and whether ACTH was ≥2.0 pmol/L or <2.0 pmol/L in patients with unilateral adrenal incidentalomas.

	OR for cortisol _{ONDST} ≥50 nmol/L	OR for ACTH <2.0 pmol/L
Gender (female vs male)	1.32 (0.98–1.78)	2.19 (1.41–3.41)
Age (10-year increase)	1.69 (1.46–1.96)	0.87 (0.72–1.06)
Smoker (yes vs no)	1.68 (1.21–2.33)	2.75 (1.80–4.20)
BMI (increase 5 kg/m ²)	0.80 (0.69–0.91)	0.99 (0.83–1.18)
Size (increase 10 mm)	1.85 (1.52–2.22)	1.55 (1.22–1.95)
Cortisol _{ONDST} (increase 100%)	Not analysed	2.01 (1.55–2.61)

The number of patients included in the analysis of the OR for cortisol_{ONDST} ≥50 nmol/L and the OR for ACTH <2.0 pmol/L are 861 and 638, respectively.

In summary, in the present population-based study, the prevalence of current smoking was higher than in the general population. Furthermore, smokers had larger unilateral AI, more often bilateral AI and ACS/pACS. Whether smoking is a risk factor for adrenal incidentalomas and ACS/pACS or our findings are due to case selection needs to be further studied.

Declaration of interest

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

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