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# Subclinical Cushing's syndrome in adrenal incidentalomas — possible metabolic consequences

## Subkliniczny zespół Cushinga w przypadkowo stwierdzonych guzach nadnerczy — następstwa metaboliczne

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**Abstract**

**Introduction:** The presence of subclinical Cushing's syndrome (SCS) and some features of the metabolic syndrome were evaluated in adrenal incidentaloma patients.

**Material and methods:** 165 patients were studied. Plasma cortisol, ACTH, DHEA-S, 17-OH-P, aldosterone, renin activity and 24-h urinary methoxycatecholamines were measured. Fasting concentrations of glucose, insulin, triglycerides, T-chol., HDL-chol. and LDL-chol. were determined and the FIRI and QUICKI indices were calculated. Blood pressure, WHR and BMI were determined in all patients. Forty healthy volunteers were the controls.

**Results:** 133 patients had unchanged endocrine function, 32 demonstrated hormonal disturbances without clinical symptoms (in 26 nonclinical hypercortisolism). The WHR and blood pressure in the SCS group were significantly higher than in the patients with nonfunctioning adenoma (NA). T-chol and LDL-chol were significantly higher, but HDL-chol was significantly lower, in the SCS than in the NA patients. Fasting insulin level was significantly higher in the SCS than in the NA patients and controls, while fasting glucose level was comparable. QUICKI was significantly lower in the SCS and NA patients than in the controls, while FIRI was significantly higher in the SCS group.

**Conclusions:** In incidentaloma patients, hormonal function of the adrenal gland should be estimated because some of them present subclinical hyperfunction. These patients frequently display features of metabolic syndrome such as insulin resistance, hypertension, high triglycerides, T-chol and LDL-chol levels. Subtle autonomous cortisol secretion may be the cause of these features. **(Endokrynol Pol 2013; 64 (3): 186–191)**

***Key words:*** *adrenal incidentaloma, subclinical hypercortisolism, metabolic changes*

**Streszczenie**

**Wstęp:** Celem pracy było zbadanie występowania subklinicznego zespołu Cushinga(SCS) oraz ocena ewentualnych zmian metabolicznych z nim związanych u pacjentów z guzami nadnerczy typu incydentaloma.

**Materiał i metody:** Przebadano 165 pacjentów. W surowicy oceniano stężenia: kortyzolu, DHEA-S, ACTH, 17-OH-P, aldosteronu, aktywności reninowej osocza oraz badano dobowe wydalanie z moczem metoksypochodnych amin katecholowych. Ponadto oceniano stężenia glukozy, insuliny, całkowitego cholesterolu, triglicerydów, cholesterolu frakcji HDL i frakcji LDL, a także wskaźniki insulinooporności i wrażliwości FIRI i QUICKI. U wszystkich pacjentów badano ciśnienie tętnicze oraz wskaźniki WHR i BMI. Czterdziestu zdrowych ochotników stanowiło grupę kontrolną.

**Wyniki:** Prawidłową czynność nadnerczy miało 133 pacjentów z incydentaloma, zaburzenia hormonalne bez objawów klinicznych stwierdzono u 32 chorych (u 26 subkliniczna hiperkortyzolemia). W grupie z SCS stwierdzono istotnie wyższy WHR oraz wartości ciśnienia tętniczego w porównaniu do grupy z gruczolakami niewydzielającymi (NA).

Stężenia całkowitego cholesterolu i cholesterolu frakcji LDL były istotnie wyższe zaś cholesterolu frakcji HDL istotnie niższy u pacjentów z SCS niż u osób z NA. Stężenie insuliny na czczo było istotnie wyższe w grupie z SCS w porównaniu z grupą z NA , natomiast wartości glikemii w obu grupach nie różniły się istotnie. Wskaźnik QUICKI był istotnie niższy w grupie z SCS i NA w porównaniu z grupą kontrolną, FIRI był istotnie wyższy u pacjentów z SCS.

**Wnioski:** Badanie czynności nadnerczy u pacjentów z guzami typu incydentaloma jest istotne ponieważ u tych chorych często pojawiają się zaburzenia metaboliczne, takie jak insulinooporność, nadciśnienie oraz zaburzenia lipidowe w postaci podwyższonego stężenia cholesterolu, triglicerydów i cholesterolu frakcji LDL. Przyczyną tego stanu może być subkliniczna, autonomiczna nadczynność nadnerczy. **(Endokrynol Pol 2013; 64 (3): 186–191)**

***Słowa kluczowe:*** *incydentaloma nadnerczy, subkliniczna hiperkortyzolemia, zaburzenia metaboliczne*

## Introduction

Adrenal masses discovered by imaging studies performed for unrelated reasons have become a common clinical problem. In the vast majority of cases, these masses are not hypersecreting adrenocortical adenomas. Some of them may show minor endocrine abnormalities with subclinical hyperfunction or malignancy

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[1–5]. Subclinical hypercortisolism is the commonest hormone abnormality detected in patients with adrenal incidentalomas. Prevalence varies from 1 to 47%, with an average frequency of 8% [1,3,6–10]. In some patients, minimal abnormalities in cortisol secretion have been shown, for example slight elevations of urinary cortisol, low levels of plasma ACTH or lack of serum cortisol inhibition during a low dose dexamethasone suppression test. This functional status is commonly defined as pre- or subclinical Cushing's syndrome (SCS). By definition, patients with SCS lack the overt physical stigmata of Cushing's syndrome. The diagnosis comes to light after a detailed biochemical work-up [11–15]. The risk of progression from subclinical to overt CS is rare and debated [4, 9, 10].

Recent studies have added new evidence that SCS predisposes to atherosclerosis and related cardiovascular complications. Subjects with adrenal incidentaloma who met the criteria for SCS had sustained and adverse cardiovascular and metabolic risk compared to controls matched for gender, age and body mass index [13, 16]. Several studies have supported a pathogenic role of cortisol in metabolic syndrome [17–19]. Patients with adrenal incidentaloma, especially those with SCS, have a higher prevalence of hypertension, obesity, diabetes mellitus, hyperlipidemia and osteopenia than the general population [10, 16, 20]. Whether these features typical of metabolic syndrome have an impact on the long- term morbidity of patients with SCS remains to be determined.

The aims of the present study were to evaluate the presence of SCS in a cohort of patients with incidentally discovered adrenal adenomas, and to investigate some possible consequences of SCS on selected metabolic parameters.

## Material and methods

165 consecutive patients (123 females and 42 males, mean age 56 ± 13.7 years) with adrenal incidentalomas (153 unilateral and 12 bilateral, with mean diameter 3.6 cm, range 0.5–9.0 cm) were seen at the Department of Endocrinology, Diabetology and Isotope Therapy of Wroclaw Medical University. Part of the patient population has been described in a previous study [21]. The design of our study was approved by the Ethics Committee of the Medical University.

All incidentalomas were discovered by abdominal ultrasound or computed tomography (CT) performed for the evaluation of unrelated disorders. The diagnosis of adrenal adenoma was based on CT or magnetic resonance . Endocrine evaluation consisted of baseline measurements of plasma cortisol (F) at 8 a.m. and midnight, morning adrenocorticotropin (ACTH), aldosterone, renin activity, dehydroepiandrosterone sulphate (DHEA-S), 17-hydroxyprogesterone (17-OH-P), 24-h urinary free cortisol (Fur-24) and metanephrines as well as an overnight low-dose dexamethasone suppression test (1 mg, orally, at 11-p.m. with measurement of serum F at 8a.m. the following morning).

The criteria for subclinical Cushing´s syndrome were: absence of clinical signs of cortisol excess and two abnormalities in the regulation of the hypothalamic-pituitary-adrenal axis (failure to suppress serum cortisol by 1 mg dexamethasone, and the combination of a low ACTH, DHEA-S and elevated Fur-24).

The fasting concentrations of glucose, insulin, triglycerides (TG) and total cholesterol (T-chol) and high density lipoprotein-cholesterol (HDL-chol) were determined by standard procedures and low density lipoprotein cholesterol (LDL-chol) was evaluated by Friedewald's formula. Insulin resistance and insulin sensitivity were evaluated using the FIRI and QUICKI indices with the following validated formulas: the fasting insulin resistance index — FIRI = [$G_0$( mmol/L) + $I_0$ (mU/L)/25] and the quantitative insulin sensitivity check index — QIUICKI = 1/[log ( $I_0$) + log ($G_0$)], where $I_0$ is the fasting insulin in μIU/mL and $G_0$ fasting glucose in mg/dL.

Blood pressure (BP), waist to hip ratio (WHR) and body mass index (BMI) were determined in all patients. Hypertension was diagnosed when the diastolic blood pressure was above 90 mm Hg and systolic pressure above 140 mm Hg. In patients receiving antihypertensive treatment, the diagnosis and evaluation of severity of hypertension were determined from pretreatment values. The WHR was determined as the ratio between the smallest circumference of the torso and the maximal circumference of the hips at the extension of the buttocks. A BMI of 25–30 kg/m$^2$ was considered overweight, and above 30 kg/m$^2$ obesity. All the patients were hospitalised and none showed signs of overt endocrine dysfunction on physical examination or were taking any hormonal medication.

Forty persons matched for gender, body mass index and age were enrolled as controls. They were from a group of patients referred to the Department of Gastroenterology for abdominal ultrasound examination for similar reasons as the group of our patients and who were found to be unaffected by any relevant disorder.

### *Statistical analysis*

The statistical significance of differences between different sample groups was calculated using Student's *t*-test and the Mann-Whitney *U* test. Correlation coefficients were determined using Spearman's rank correlation. The results are presented as the mean ± *SD*. Statistical significance was defined as $p < 0.05$.

**Table I.** *Clinical and hormonal features in patients with subclinical Cushing's syndrome (SCS) and hormonal nonfunctioning adenomas (NA) (mean ± SD)*

**Tabela I.** *Podstawowe parametry kliniczne i hormonalne u pacjentów z subklinicznym zespołem Cushinga (SCS) i u pacjentów z guzami nieczynnymi hormonalnie (NA) (średnia ± SD)*

| | SCS n = 29 | p | NA n = 133 | Reference range |
|---|---|---|---|---|
| Morning serum F [ng/mL] | 214 ± 125 | ns | 180 ± 53 | 94–260 |
| Midnight serum F [ng/mL] | 180 ± 101 | *** | 41.2 ± 15.7 | 18–127 |
| F- urine exretion [μg/24h] | 104 ± 56 | *** | 39.6 ± 14.9 | 21–85 |
| ACTH [pg/mL] | 7.2 ± 2.2 | *** | 18.5 ± 10.1 | 0–46 |
| DHEA-S [mg/dL] | 44.7 ± 23.2 | *** | 126.3 ± 74.9 | 35–430 |
| Mean diameter of adrenal tumour [cm] | 2.7 ± 0.8 | * | 3.4 ± 1.5 | |

*p < 0.05, ***p < 0.001, ns — not significant; F — cortisol; ACTH — adrenocorticotropin; DHEA-S — dehydroepiandrosterone sulphate

## Results

Of the 165 patients, 133 had hormonal nonsecreting adenomas (NA) and 32 had secreting tumours. Subclinical Cushing´s syndrome (SCS) was found in 26 patients with secreting tumours, according the criteria previously described. Clinical and biochemical features of patients with SCS and NA are shown in Table I. In the remaining six patients with secreting tumours, we recognised medullary hyperfunction in four, and primary hyperaldosteronism in the other two cases. These six patients were excluded from the study.

The differences in plasma and urinary cortisol in SCS and NA are shown in Figure 1.

The BMIs in patients with adrenal adenomas and in the control group were comparable. About 70% of them were overweight and/or obese. WHR was significantly higher in the group with SCS than in the control group (Table II).

Diastolic blood pressure was significantly higher in the patients with SCS than in NA and controls, and systolic blood pressure was higher in SCS and NA than in controls, despite antihypertensive treatment (Table II).

We observed significantly higher serum levels of T-chol, LDL-chol and a decreased level of HDL-chol in the patients with SCS compared to the NA group and controls. Fasting serum glucose levels were comparable in the patients with incidentaloma and controls, but fasting serum insulin levels were significantly higher in the SCS group than in the NA patients and the controls. FIRI was higher in the SCS than in the NA patients and controls and QUICKI was significantly lower (Table II). Selected indices of insulin resistance in SCS, NA and controls are set out in Figure 2.

Mean adrenal tumour size was significantly higher in NA than in the SCS patients (Table II).

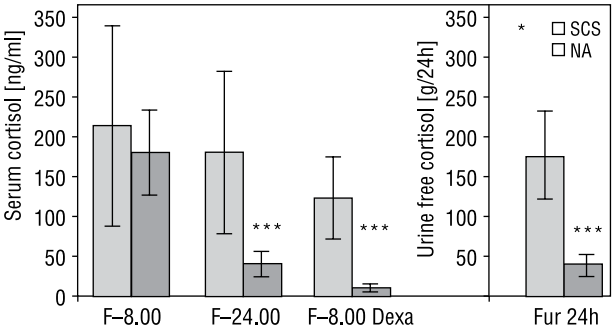


**Figure 1.** *Plasma cortisol concentrations, urine cortisol excretion and the result of an overnight low-dose dexamethasone suppression test in patients with subclinical Cushing's syndrome (SCS) and non-functioning adrenal adenomas (NA); ***p < 0.001*

*F-8.00 — serum cortisol concentration at 8.00 a.m.*

*F-24.00 — midnight serum cortisol concentration*

*Fur 24h — 24-h urinary excretion of free cortisol*

*F-8.00 Dexa — serum cortisol concentration at 8.00 a.m. after an overnight low-dose dexamethasone suppression*

**Rycina 1.** *Stężenie kortyzolu w surowicy, wydalanie z moczem oraz jego wartości w teście z dexametazonem u pacjentów z subklinicznym zespołem Cushinga (SCS) oraz nieczynnymi gruczolakami nadnerczy (NA); ***p < 0.001*

*F-8.00 — stężenie kortyzolu w surowicy o godz. 8.00*

*F-24.00 — stężenie kortyzolu w surowicy o północy*

*Fur 24h — 24-godzinne wydalanie wolnego kortyzolu z moczem*

*F-8.00 Dexa — stężenie kortyzolu w surowicy o godz. 8.00 po podaniu wieczorem małej dawki deksametazonu*

We did not observe any correlation between the tumour diameter and hormonal activity in patients with SCS.

## Discussion

A clinically unapparent adrenal mass discovered by chance in the course of diagnostic evaluation is com-

**Table II.** *Selected clinical and metabolic features in patients with adrenal incidentalomas: hormonal non-functioning adenomas (NA) and subclinical Cushing's syndrome ( SCS) and in the control group*

**Tabela II.** *Wybrane cechy kliniczne i metaboliczne u pacjentów z incydentaloma nadnerczy: z hormonalnie nieczynnymi gruczolakami ( NA), subklinicznym zespołem Cushinga( SCS) i w grupie kontrolnej*

| | SCS (1) | p 1 vs. 2 | NA (2) | Control group (3) | p 1 v. 3 | p 2 v. 3 |
|---|---|---|---|---|---|---|
| | n=29 | | n=133 | n=40 | | |
| Age (years) | 58 ± 14 | ns | 56 ± 14 | 52.2 ± 0.8 | ns | * |
| BMI [kg/m$^2$] | 28.6 ± 7.8 | * | 27.0 ± 4.4 | 27.8 ± 6.9 | ns | ns |
| WHR | 0.93 ± 0.1 | *** | 0.82 ± 0.1 | 0.85 ± 0.08 | ** | ** |
| Fasting glucose [mg/dL] | 98 ± 27 | ns | 90 ± 16 | 86.7 ± 14.3 | ns | ns |
| Fasting insulin [$\mu$IU/mL] | 19.5 ± 5 | *** | 7.0 ± 2.0 | 8.7 ± 3.5 | *** | ** |
| FIRI | 4.2 ± 2.0 | *** | 1.4 ± 0.45 | 1.76 ± 0.7 | *** | *** |
| QUICKI | 0.13 ± 0.01 | *** | 0.2 ± 0.1 | 0.28 ± 0.05 | *** | *** |
| T- chol [mg/dL] | 238. ± 35 | *** | 216 ± 35 | 213 ± 28 | ** | ns |
| HDL-chol [mg/dL] | 36 ± 9 | *** | 50 ± 11 | 50.1 ± 14.2 | *** | ns |
| LDL-chol [mg/dL] | 170 ± 32 | *** | 137 ± 34 | 137.9 ± 26.6 | *** | ns |
| Triglicerides [mg/dL] | 162 ± 56 | ns | 148 ± 50 | 136 ± 63.2 | * | ns |
| Systolic BP [mm/Hg] | 147 ± 18.3 | ns | 142 ± 18.5 | 127 ± 21 | *** | *** |
| Diastolic BP [mm/Hg] | 96 ± 6.4 | *** | 85 ± 13 | 82.5 ± 9.1 | *** | ns |

*p < 0.05; **p < 0.01; ***p < 0.001; ns — not significant; WHR — waist-to-hip ratio; BP — blood pressure; FIRI — fasting insulin resistance index; QUICKI — quantitative insulin sensitivity check index

monly known as an adrenal incidentaloma [1, 13, 16]. Because of their great heterogeneity, what has been called a disease of modern technology is actually a cluster of diseases. Cortical adenoma is the most frequent tumour among adrenal incidentalomas. It is often associated with subtle, possibly transient, autonomous glucocorticoid hypersecretion. The prevalence of hypercortisolism in clinically unapparent adrenal masses has been reported to range from 5 to 47% or from 1 to 9% with an average frequency of 8% in different studies with varying study protocols and diagnostic criteria [1, 3–5, 14, 22, 23]. Because most of these patients do not show a clinical pattern of manifest hypercortisolism, rather only an abnormal regulation of the hypothalamic-pituitary axis, the term 'subclinical Cushing's syndrome' has been widely used. This term was first introduced by Charbonnel et al. in 1981 [6] to describe patients with adrenal incidentalomas and autonomous glucocorticoid production, but without specific signs and symptoms of overt Cushing's syndrome. A recently proposed term is subclinical autonomous glucocorticoid hypersecretion (SAGH) [3].

Subclinical Cushing's syndrome (SCS) was found in 26 (15.7%) of 165 patients with adrenal adenomas and was the most frequent hormonal abnormality found at entry in our patients. This is in line with the data of other authors [1, 7, 19, 23]. Therefore we shall discuss our results in the light of findings reported for

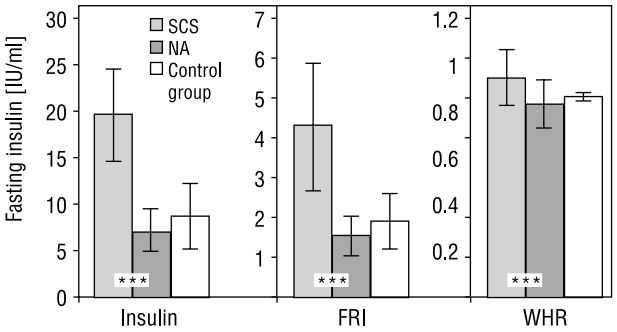


**Figure 2.** *Selected indices of insulin resistance in patients with subclinical Cushing's syndrome (SCS), nonfunctioning adrenal adenomas (NA) and in the control group; WHR — waist-to-hip ratio; FIRI — fasting insulin resistance index; ***p < 0.001*

**Rycina 2.** *Wybrane wskaźniki insulinooporności u chorych z subklinicznym zespołem Cushinga, nieczynnymi gruczolakami nadnerczy (NA) i w grupie kontrolnej; WHR — wskaźnik talia–biodra, FIRI — fasting insulin resistance index; ***p < 0,001*

patients with both SCS and adrenal incidentalomas. Patients with adrenal incidentalomas, especially those with SCS, have a higher prevalence of hypertension (40–90% of cases), obesity (35–50%), hyperlipidemia (50%), osteopenia (40–50%) and diabetes mellitus or glucose intolerance (20–75%) than the general population [1, 4, 10]. Chronic cortisol excess has been implicated in central obesity, systemic arterial hypertension, impaired glucose tolerance, insulin resistance, altered lipid

profile and hypercoagulability [13, 21]. Cross-sectional and case–control studies indicate that the degree of metabolic abnormalities in patients with adrenal incidentalomas is directly related to the severity of the hypercortisolism [13, 19, 22, 23].

A total of 119 (72%) of our patients were hypertensive and 111 (67%) overweight or obese (BMI 26–35 kg/m$^2$). Our data demonstrates significantly higher WHR in patients with SCS than in the group with NA and in controls, although they were matched for BMI. The WHR is a reliable index of abdominal obesity. Altered body fat distribution and increased visceral abdominal fat may be important in the development of the metabolic syndrome in patients with SCS.

Insulin levels and FIRI were significantly higher and QUICKI was significantly lower in patients than in the controls, especially in the SCS group, suggesting enhanced insulin resistance. The patients did not differ from the controls with regard to the factors known to influence insulin sensitivity (age, body weight, fasting glucose levels), but some of the patients were hypercortisolaemic compared to the controls.

Our data supports the view that cortisol excess can influence insulin levels independently of obesity which is otherwise a prominent clinical feature of Cushing's syndrome and may itself contribute to hyperinsulinaemia [16]. Subtle cortisol hypersecretion by apparently non-functioning adrenal adenomas might be the cause of insulin resistance and other features of the metabolic syndrome in such patients. However, Reincke et al. [7] proposed adrenal incidentaloma as an insulin-mediating tumoural manifestation of the metabolic syndrome, similar to the insulin-mediated ovary overgrowth seen in polycystic ovary disease. This hypothesis was based on the observation that insulin has a mitogenic effect on adrenocortical cells without affecting cortisol synthesis.

We observed higher serum levels of triglycerides in the patients with SCS than in the controls. The levels of T-chol. and LDL-chol. were significantly higher, and level of HDL-chol. significantly lower, in SCS than in NA patients and the controls. The elevation in triglycerides levels observed in SCS patients is another indication of reduced insulin sensitivity in hypercortisolism [14]. Lipid disturbances are indicative of increased atherosclerotic risk in the patients. Our observations are comparable with those reported in the majority of other series [12, 17, 22, 23].

Systolic and diastolic blood pressures were significantly higher in patients with SCS than in the controls. Systolic blood pressure in the NA group was comparable to that in the SCS group, but diastolic BP was significantly lower. Seventy five percent of our patients were hypertensive. The pathogenesis of hypertension related to cortisol excess is probably multifactorial and is not completely understood; however, repeated observations of improved blood pressure control after treatment of hypercortisolism may confirm the link between these features [4, 13, 19]. Some studies have failed to detect any relationship between blood pressure levels and cortisol secretion [16, 23].

In contrast to recent reports, no relationship between tumour size and adrenocortical function or ACTH levels was observed in our study. Tumour mass diameter in the SCS group of patients was significantly smaller than in the group with non-functioning adenomas. This finding does not confirm the observations of other authors that the size of the tumour (especially when greater than 3 cm) may be considered as a risk factor of adrenal hyperfunction [1–3]. Adrenal tumour diameter was the only parameter influencing the decision between surgical treatment and/or follow-up observation of our patients.

## Conclusions

In patients with incidentally discovered adrenal masses, hormonal function of the adrenal gland should be evaluated because some of them may present subclinical hyperfunction. Our results show that most adrenal incidentalomas are mainly NA and SCS is the most frequent hormonal abnormality. However, clinically silent hypercortisolism is not completely asymptomatic. SCS is associated with a higher prevalence of insulin resistance, hypertension, dyslipidemia (high triglycerides, T-chol and LDL-chol levels) and obesity. Subtle autonomous cortisol secretion of these adrenal adenomas may cause an acquired condition of insulin resistance in normoglycaemic patients.

Chronic mild endogenous cortisol excess may have an important systemic effect on the human body.

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