Adrenal incidentalomas and the metabolic syndrome – are there any differences between adenoma and hyperplasia?

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Authors evaluated the prevalence of symptoms of the metabolic syndrome and insulin resistance in 25 patients with adrenal incidentalomas (10 men, 15 women) of the mean age 57.9±15 years. 15 patients had adrenal adenoma determined by CT or MR scan and 10 had unilateral or bilateral hyperplasia. The prevalence of obesity was 72%, arterial hypertension 60%, diabetes mellitus or impaired glucose tolerance 28%, hyperlipidemia 56% and hyperuricemia 20%, respectively, which is more frequent occurrence than that in normal human population. Patients with adrenal adenomas had mildly but significantly higher body mass index (BMI, $p<0.05$) and insulin resistance calculated as HOMA IR ($p<0.05$) and FIRI ($p<0.05$) and significantly higher values of serum ferritin ($p<0.01$). Plasma cortisol values were slightly but not significantly higher in the group with adrenal adenomas. Authors conclude that adrenal adenomas are probably more related to the metabolic syndrome than adrenal hyperplasia.

Key words: adrenal adenoma, adrenal hyperplasia, insulin resistance, ferritin

Cortical adenomas are the most frequent tumors among adrenal incidentalomas. They are usually detected in patients with no clear symptoms of Cushing syndrome, thus clinically can be labeled as nonfunctioning. Recent evidence suggests that many patients with adrenal adenomas exert symptoms of metabolic syndrome such as diabetes mellitus, glucose intolerance or impaired insulin sensitivity, obesity, arterial hypertension, hyperlipidemia and hemostatic abnormalities [1, 2]. On the other hand nonsecreting adrenal adenomas are 2–5 times frequently seen in diabetic, obese patients and patients with arterial hypertension [3]. Some studies demonstrated an increased activity of pituitary-adrenal axis in these patients which can play a role in the pathogenesis of abdominal obesity and insulin resistance [4]. Moreover there are many reports documenting a subtile, possibly transient, autonomous glucocorticoid hypersecretion. Therefore, inapparent cortical adenoma may cause subclinical Cushing syndrome which could put the patients at increased risk of metabolic syndrome [5–8].

In recent literature there are no reports about incidentally discovered bilateral adrenal hyperplasia. The aim of this study was to investigate glucose metabolism and other symptoms of metabolic syndrome in patients with adrenal incidentalomas and compare the results between adrenal adenomas and bilateral adrenal hyperplasia.

Patients and methods

The study group comprised 25 patients (10 men, 15 women) with incidentally discovered adrenal masses detected on CT or MR scan. 15 patients of them had unilateral mass with typical CT characteristics of adenomas, 10 patients had unilateral or bilateral adrenal hyperplasia without adenomatous structures. Mean age of patients was 57.9±15.3 years (median 56 yrs).

Each patient was completely evaluated for adrenal hormonal overproduction, i.e. we rulled out catecholamine overproduction, primary hyperaldosteronism and Cushing syndrome or androgen overproduction. Mean body mass index (BMI) in all group was 28.2±5 kg/m^2, most of patients had BMI in the range of overweight (n=9) or obesity (n=9). Only 7 patients had normal BMI.

Blood samples were collected in the morning for evaluation of: fasting plasma glucose, plasma insulin, total cholesterol (TCH), HDL and LDL cholesterol, triglycerides, uric acid and serum ferritin levels.

Because of exclusion of adrenal endocrinopathies following tests were performed: baseline and postural values of plasma renin activity and plasma aldosterone, following an aldosterone-renin ratio as a screening test, plasma metanephrines and urinary catecholamines for detection of

pheochromocytoma. For demonstration of an androgen overproduction a 17 hydroxyprogesterone and dehydroepiandrosterone sulphate were evaluated as most important adrenal androgens. Patients with adrenal endocrinopathies were excluded from this study.

For detection of possible subclinical Cushing's syndrome we investigated baseline plasma cortisol, ACTH and plasma cortisol after administration of 1 mg of dexamethasone at 11 p.m. (overnight 1 mg dexamethasone suppression test). Adequate suppression was demonstrated when cortisol fell below 138 nmol/l in the morning following the overnight dexamethasone administration [7]. According this criteria none of our patients had signs of subclinical Cushing's syndrome, thus, all were classified as having nonfunctional adrenal masses.

Plasma glucose, lipoproteins, uric acid and ferritin were examined using routine methods, Samples for insulin, plasma cortisol, ACTH were analyzed by commercially available RIA (Immunotech, France).

In non diabetic subjects and in diabetics nontreated with insulin, the insulin resistance index was assessed by the homeostasis model, calculated as follows: homeostasis model assessment of insulin resistance (HOMA IR) = (fasting glucose x fasting insulin)/22.5.

Normal values of HOMA index are in the range 0.7 to 1.4 and the values above 1.4 indicated an insulin resistance.

Besides HOMA index we calculated an index FIRI as follows: FIRI = (fasting glucose x fasting insulin)/25 and the values more than 1.0 indicated the presence of insulin resistance.

Statistical analysis. Continuous variables are summarized as the mean ±SEM. Unpaired t test and Mann Whitney test were used to compare the means between the subgroups of patients. The correlation was assessed using linear regression analysis. Significance was retained for $p<0.05$.

Results

The prevalence of various symptoms of the metabolic syndrome, i.e. arterial hypertension, obesity, diabetes mellitus or impaired glucose tolerance (IGT), hyperlipidemia and hyperuricemia is demonstrated in Table 1.

All symptoms of the metabolic syndrome in the group of patients were more frequent among patients with adrenal incidentalomas compared to prevalence in normal human population. Hypertension was found in 60%, diabetes mellitus or IGT in 28%, hyperlipidemia was seen in 56%, obesity in 72% and hyperuricemia in 20% of patients, respectively.

Insulin resistance based on index HOMA IR was determined in 13 patients, i.e. 52%, each increased HOMA index was associated with increased index FIRI.

Table 1. The prevalence of various symptoms of the metabolic syndrome in patients with adrenal incidentalomas

	N	%
Hypertension	15	60
DM/IGT	7	28
Hyperlipidemia	14	56
Hyperuricemia	5	20
Overweight/obesity	18	72

The patients were divided into two groups. First one consisted of patients with adrenal adenomas and the second of patients with adrenal hyperplasia.

The mean values of evaluated parameters in the whole group of patients and in subgroup with adrenal adenomas and subgroup with adrenal hyperplasia are demonstrated in Table 2.

Table 3 shows the mean values of hormonal parameters in the whole group of patients and in subgroup with adenomas and subgroup with hyperplasia.

Neither between plasma cortisol and lipid profile nor between cortisol and HOMA, FIRI or fasting insulinemia there was detected a statistically significant correlation.

Additionally we couldn't find the correlation between plasma ACTH and parameters of the metabolic syndrome. Both, plasma cortisol and ACTH did not correlate with BMI.

Mean values and the differences between variables are shown in Table 2 and 3.

Table 2. The mean values of evaluated parameters in all patients and in subgroup with adrenal adenomas and subgroup with adrenal hyperplasia

Parameter	all patients	adenoma	hyperplasia	significance
weight /kg/	78.4 ± 2.7	84.4 ± 4	75.5 ± 3	0.05
BMI /kg/m^2/	28.2 ± 1.0	30.7 ± 2	26.7 ± 1	0.05
glycemia /mmol/l/	5.5 ± 0.5	4.9 ± 0.2	5.2 ± 0.3	NS
fasting insulin /uIU/ml/	9.7 ± 2.8	14.2 ± 6.2	6.5 ± 1.4	0.05
HOMA	2.2 ± 0.7	3.5 ± 1.6	1.3 ± 0.3	0.05
FIRI	2.0 ± 0.6	3.1 ± 1.4	1.2 ± 0.3	0.05
Cholesterol /mmol/l/	5.3 ± 0.3	5.3 ± 0.3	5.1 ± 0.4	NS
Triglycerides /mmol/l/	1.9 ± 0.2	1.8 ± 0.3	1.9 ± 0.3	NS
HDL /mmol/l/	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	NS
LDL /mmol/l/	3.2 ± 0.2	3.3 ± 0.2	3.0 ± 0.2	NS
Ferritin /mg/l/	129.6 ± 47	174 ± 69	54.2 ± 7.7	0.01
Uric acid /mmol/l/	362 ± 32	338 ± 36	412 ± 59	NS

Table 3. The mean values of hormonal parameters in all patients and in subgroup with adenomas and subgroup with hyperplasia

Parameter	all patients	adenoma	hyperplasia	significance
Cortisol	408.6 ± 42	441 ± 48	352 ± 79	NS
Cortisol after D	109 ± 30.6	123.5 ± 41.4	86.8 ± 42.1	NS
ACTH	16.8 ± 0.05	17.7 ± 2.4	14.1 ± 1.4	NS

There were no differences in age between the two groups (59±4 years v.s. 55±5 years, NS).

Patients with adrenal adenomas had significantly higher BMI ($p<0.05$) than those with adrenal hyperplasia and slightly but significantly higher insulin resistance calculated as HOMA ($p<0.05$) and FIRI ($p<0.05$).

Both baseline plasma cortisol and plasma cortisol after 1 mg dexamethasone were slightly but not significantly increased among patients with adenomas than among patients with hyperplasia.

There were no significant differences in serum lipid profile and serum uric acid between the two groups. However, patients with adrenal adenomas had significantly higher serum ferritin levels than those with adrenal hyperplasia ($p<0.01$).

Discussion

Nowadays, clinically inaparent adrenal masses, or adrenal incidentalomas are frequently discovered in the course of differential diagnosis of various unrelated disorders. Cortical adenoma is the most frequent type of adrenal incidentaloma accounting for approximately 50% of cases in surgical series and even greater shares in medical series [7]. Unilateral or bilateral adrenal hyperplasia is less frequently found during the CT or MR imaging, but it is frequently seen in autopsy series, mainly in patients with chronic disorders.

Adrenal incidentalomas mainly adenomas are often associated with subtle, possibly transient, autonomous glucocorticoid hypersecretion, which can be involved into the pathogenesis of the metabolic syndrome and its various symptoms.

Incidental adrenal adenomas have variable cortisol secretion rates and a degree of autonomous production [2, 7, 8]. However, the criteria for qualifying subclinical cortisol excess are controversial and we still do not have sufficient evidence to define a reliable standard for the diagnosis of subclinical Cushings syndrome [7].

In our study patients with adrenal masses had more frequent prevalence of arterial hypertension, obesity, diabetes mellitus or IGT, hyperlipidemia and hyperuricemia than values of normal human population which is in agreement with others [5–7, 9]. Patients with subclinical hypercortisolism were ruled out in this study.

Many authors documented an increased prevalence of obesity, insulin resistance or impaired glucose tolerance, arterial hypertension or hyperlipidemia in patients with "nonfunctional adrenal adenomas" suggesting a mild cortisol production [4, 6–8). Study of TAUCHMANOVA et al in patients with subclinical Cushing syndrome documented an increased cardiovascular risk profile, similar that described in overt Cushing's syndrome [2]. In study of VIERHAPPER et al authors examined plasma cortisol levels during oral GTT in 126 patients with adrenal incidentalomas and 129 controls. The prevalence of IGT was significantly higher in patients with incidentalomas. They observed a paradoxical rise in serum cortisol during oGTT which was slightly higher among patients than among controls. [4]. A high prevalence of disturbed glucose tolerance (61%) was found among consecutive patients harboring incidental nonfunctional adrenal adenomas. Authors conclude, that patients with adrenal incidentalomas should be tested for glucose tolerance or insulin sensitivity [9].

The relationship between adrenal incidentalomas and impaired glucose tolerance can be explained by two ways: firstly, as an autonomous and unregulated cortisol secretion, i.e. subclinical Cushing's syndrome. Some authors found a relatively high prevalence of occult Cushing syndrome in patients with Type-2 diabetes mellitus [3, 10, 11]. On the other hand, subclinical hypercortisolism occurs in approximately 5–30% of patients with adrenal incidentalomas [12]. This subclinical Cushing syndrome could put the patient at increased risk of arterial hypertension, obesity, impaired glucose tolerance and dyslipidemia.

Secondly, the alternative hypothesis that adrenal incidentalomas are unrecognized manifestation of the metabolic syndrome has been formulated by REINCKE et al [6]. They observed a proliferative effect of insulin on an adrenal cell line without any effect on cortisol synthesis and suggested that hyperinsulinemia may have a pathogenic role since it occurs in polycystic ovary syndrome. However, it remains to be demonstrated that insulin is able to promote adrenal growth in other experimental models and may stimulate the cortisol synthesis.

According to study of TERZOLO et al, many patients with incidental adrenal adenoma display altered glucose tolerance, that may be explained by reduced insulin sensitivity, and an increased blood pressure levels in comparison with controls [7]. The slight hypercortisolism observed in some of such patients may contribute to this state of insulin resistance. In this study patients with adrenal adenomas being more insulin resistant had mildly increased plasma cortisol compared to patients with adrenal hyperplasia, but the differences were not significant. There are still lack of data comparing the metabolic differences between adrenal adenomas and adrenal hyperplasia. In our study patients with adrenal adenomas had a mildly higher body weight and BMI compared to group of patients with hyperplasia. Fasting plasma glucose and plasma insulin were not significantly different, however patients with adrenal adenomas were more insulin resistant.

The most significant differences found in this study were in plasma levels of ferritin, which was higher in the group with adrenal adenomas than in patients with hyperplasia. There are no references about plasma ferritin levels in patients with adrenal incidentalomas in recent literature. It is only known, that plasma ferritin can be a good indicator of impaired insulin sensitivity. Several studies demonstrated the fact that elevated iron stores were positively associated with the presence of the metabolic syndrome and with insulin re-

sistance [13, 14] and postulated that ferritin could be a marker of the insulin resistance syndrome [15]. Relationship between adenomas and iron stores was described only in some studies in patients with colorectal adenomas. Authors concluded that risk of adenoma recurrence was modestly increased among patients with higher serum ferritin concentration, although it was not confirmed in further studies [16].

We suppose, that higher ferritin levels in patients with adenoma are related mainly to increase insulin resistance and to symptoms of the metabolic syndrome in patients with adenoma rather than to type of adrenal mass. However, it needs more studies on larger group of patients.

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