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Analysis between Adrenal MRI Mass Size and 1 mg Dexamethasone Suppression Test in Patients with Adrenal Incidentaloma

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Abstract: This study aimed to investigate the correlation of adrenal magnetic resonance imaging (MRI) mass size and 1 mg dexamethasone suppression test results in patients with adrenal incidentaloma diagnosis. Eighty-six patients (82.6% female) with incidentally discovered adrenal masses, diagnosed and treated in the Department of Endocrinology Bakirkoy Dr. Sadi Konuk Education and Research Hospital between June and August 2017, were included in the analysis. All the patients evaluated for their hormonal functionality. 24-h urinary excretion of cortisol did not correlate with tumor size. But there was a positive correlation between longer adrenal nodule diameter and metanephrine, and there was a negative correlation between shorter adrenal nodule diameter and renin levels. We found that smaller and clinically “silent” tumors often do not demonstrate subclinical hormonal activity.
Keywords: adrenal incidentaloma; adrenal magnetic resonance imaging mass size; metanephrine, renin.

INTRODUCTION

An incidentaloma is a mass in one or both adrenal glands detected accidentally during an imaging study performed for other reasons. The rapid development of modern imaging techniques has led to an increase in incidentaloma diagnosis without clinically apparent hormonal abnormalities (Babińska et al., 2012; Kim et al., 2013; Ekinci et al., 2016). In different studies, the incidence of incidentalomas differs between 1.4% and 8% (Ekinci et al., 2016).

By definition, patients with incidentalomas do not display any physical sign of adrenal hormonal excess; because no clinical suspicion has led to the detection of the adrenal masses. However, although incidentalomas considered hormonally inactive, a.k.a nonfunctional, they have often been associated with a high prevalence of hypertension, dyslipidemia, glucose intolerance, and obesity (Muscogiuri et al., 2011).

It has shown that these incidental adenomas may secrete small quantities of cortisol, and 5-30% of patients with adenomas may have subclinical hypercortisolism (Olsen et al., 2014).

Incidentalomas are a common reason for referral to the endocrine clinics. A series of investigations are usually recommended to exclude catecholamine, cortisol, or aldosterone oversecretion (Theodoraki et al., 2011). The researches show that most of the incidentalomas are nonfunctional and benign adenomas (Ekinci et al.,

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2016). Recently, many studies have been carried out to determine the characteristics of adrenal incidentalomas (Kim et al., 2013, Debono et al., 2014, Libe et al., 2002, Erbil and Barbaros, 2008, Kilinc et al., 2015, Kutbay et al., 2015).

This retrospective observational study aimed to perform an analysis of the correlation of adrenal magnetic resonance imaging (MRI) mass size and hormonal status (incl. 1 mg dexamethasone suppression test) in patients with adrenal incidentaloma.

MATERIALS AND METHOD

This retrospective cross-sectional study was carried out in Bakirkoy Dr. Sadi Konuk Education and Research Hospital after receiving ethical approval from the Ethical Review Board of the same institution. A total of 86 patients with adrenal masses discovered incidentally on MRI recruited from June to August 2017.

The age, patient's gender, MRI based mass size, dexamethasone suppression test result, serum levels of morning basal cortisol, free triiodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), prolactin, adrenocorticotropic hormone (ACTH), haemoglobin A1c (HbA1c), fasting blood glucose, homeostatic model of assessment insulin resistance (HOMA-IR), renin, aldosterone, plasma renin activity, 25-hydroxy vitamin D, dehydroepiandrosterone-sulfate (DHEA-S), progesterone, 24h urine levels of cortisol, vanillylmandelic acid (VMA), metanephrine, normetanephrine, epinephrine, norepinephrine taken from patient medical records.

All venous blood samples draw between 08:00, and 10:00 am. after 12-h fasting. In our hospital, the overnight dexamethasone suppression test is performed by administering low-dose (1 mg, p.o.) dexamethasone at 11 pm the night before. Blood samples for determination of plasma cortisol obtained at 8 am the following morning.

In our hospital, patients instructed on how to collect a 12-hour overnight urine sample. The patients give detailed instructions to void at the start time and collect all urine until the stop time, at which they completed their last void. Patients transfer each voided urine sample to a collection bottle containing a preservative (sodium meta bisulfate; NA2S205, crystal form; reagent ACS grade, Fisher Scientific no. S244).

Paramagnetic particle chemiluminescence method at UniCel DxI800 Immunoassay analyzer (Beckman Coulter Inc, Brea, CA, USA) was used to measure the serum level of 25-hydroxy vitamin D. HbA1c was studied with Premier Hb9210-Primus ultra II device using HPLC (high-performance liquid chromatography) method. Urine concentrations of vanillylmandelic acid (VMA), metanephrine, normetanephrine, epinephrine, and norepinephrine were quantified by liquid chromatography with electrochemical detection. The rest of the biochemical and hormonal parameters were measured using Cobas c501 (Roche Diagnostic, USA), C6000 autoanalyzer (Roche Diagnostic, USA), Immulite 2000 model analyzer using original kits (Siemens Healthcare GmbH, Henkestr, Erlangen, Germany).

The Homeostatic Model Assessment (HOMA) was used to quantify the Insulin Resistance (IR). The approximating equation for IR used a fasting plasma sample and derived by the use of the insulin-glucose product divided by a constant: HOMA-IR = (Glucose (mg/dL) x Insulin) / 405.

Statistical Analysis

Test of normality performed for each variable and Kolmogorov-Smirnov and Shapiro-Wilk tests shown. Since the variables did not have a normal distribution, nonparametric tests preferred for the analyses. To determine the correlation between two data, nonparametric Kendall's Tau-B correlation test used. For testing group differences, Mann-Whitney U for two groups was carried out. Due to the lack of normal distribution, the median and range give for continuous data. Frequency distribution tables interpreted for categorical data. Analyses were carried out with SPSS 22.0 version significance level was $p<0.05$.

RESULTS AND DISCUSSION

Out of 86 patients,17.4% (15 patients) were male and 82.6% (71 patients) were female. The median age was 48.5; where the minimum age was 14 years, and the maximum was 90 years. Of these patients, 58.1% (50 patients) had a nodule in the right adrenal lobe, while 65.1% (56 patients) had a nodule on the left adrenal lobe. 23.3% (20) had nodules in both adrenal lobes (Table 1).

According to incidentaloma size, the median longer nodule diameter was 21 mm while the median shorter nodule diameter was 15 mm. Median basal cortisol level was 14.17 µg/dl. The median cortisol level after 1 mg dexamethasone suppression test was 1.26 nmol/l, with a minimum level of 0.21 nmol/l and a maximum level of 10.88 nmol/l.

Median metanephrine in urine was 56.8 µg/24h, while the minimum level was 2.34 µg/24h, and the maximum level was 143.26 µg/24h. The median renin level was 55.65 pg/mL, with minimum and maximum levels of 21.4 pg/mL and 97 pg/mL, respectively. Median insulin resistance was 3.3 mg/dl, where the minimum and maximum levels were 1.4 mg/dl and 8.9 mg/dl, respectively.

Median, distribution range, minimum, and maximum values of the variables of 86 patients with adrenal incidentaloma shown in Table 2. The relationship between adrenal mass size and 1 mg dexamethasone suppression test results was not statistically significant (see table 3 for p values).

Shorter nodule diameter was statistically significant according to gender. As for mean rank values of the two nodule diameters, they are more significant in females and smaller in males. Other variables were not statistically significant (see table 5 for p values). Longer adrenal nodule diameter was significantly correlated only with metanephrine ($p = 0.001$, Table 4). Shorter adrenal nodule diameter is significantly correlated only with renin ($p = 0.02$, Table 6).

Table 1. Distribution of Incidentaloma Nodules

Site	No (%)
Right lobe	58.1% (50)
Left lobe	65.1% (56)
Both lobes	23.3% (20)

Table 2. Variables of 86 Patients with Adrenal Incidentaloma

Variables	Median	Range	Minimum	Maximum
Age (year)	48.5	76	14	90
Longer Nodule Diameter (mm)	21	74	3	77
Shorter Nodule Diameter (mm)	15	72.5	1.5	74
Basal Cortisol (Urine) (µg/dl)	14.17	36.09	6.78	42.87
Cortisol After Dexamethasone Sup. (nmol/l)	1.265	10.67	0.21	10.88
FT3 (ng/dl)	2.91	2035.22	0.78	2036
FT4 (µg/dl)	2.35	5.42	1.03	6.45
TSH (µIU/ml)	4.585	45.37	0.43	45.8
Prolactin (µg/l)	12.66	41.1	4.5	45.6
ACTH (pg/ml)	16.7	62	5	67
HbA1c (%)	5.95	5.2	3.7	8.9
FBG (mg/dl)	91.5	80	65	145
HOMA_IR (mg/dl)	3.3	7.5	1.4	8.9
Renin (pg/mL)	55.65	75.6	21.4	97
Aldosterone (ng/dl)	19.75	94.1	3.7	97.8
Plasma Renin Activity (ng/ml/h)	12.85	82.51	0.29	82.8
25-Hydroxy Vitamin D (ng/ml)	23	64	3	67
DHEA-S (mg/ml)	72.7	212	8.5	220.5
Progesterone (ng/ml)	2.67	66.8	0.2	67
Cortisol (Urine) (µg)	90.44	595.8	21.4	617.2
VMA (Urine) (mg/24 h)	8.965	85.16	3.24	88.4
Metanephrine (Urine) (µg/24 h)	56.8	143.26	2.34	145.6
Normetanephrine (Urine)(µg/24 h)	192.05	610.4	67.8	678.2
Epinephrine (Urine) (ng/l)	5.635	67.6	0.2	67.8
Norepinephrine (Urine) (pg/ml)	46.2	555.7	11.3	567

FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone; ACTH: adrenocorticotropic hormone; HbA1c: haemoglobin A1c; FBG: fasting blood glucose; HOMA_IR: homeostatic model of assessment_insulin resistance; DHEA-S: dehydroepiandrosterone-sulfate; VMA: vanillylmandelic acid.

Table 3. Correlation between adrenal MRI mass size and 1 mg dexametasone suppression test (n=86)

Variables	Correlation Analysis	Basal Cortisol	1 mg Dexamethason Suppression Test
Longer Nodule Diameter	Correlation Coefficient (r)	.030	.100
	p value	.684	.178
Shorter Nodule Diameter	Correlation Coefficient (r)	-.026	.127
	p value	.725	.091

Table 4. Correlation Between Longer Adrenal Nodule Diameter and Biochemical Parameters

Variables	Correlation Coefficient (r)	*p* value
FT3	-0.03	0.72
FT4	-0.09	0.21
TSH	-0.13	0.09
Prolactin	0.10	0.17
ACTH	-0.06	0.40
HbA1c	-0.06	0.42
FBG	0.11	0.14
HOMA_IR	-0.14	0.07
Renin	-0.09	0.22
Aldosterone	-0.12	0.12
Plasma Renin Activity	0.05	0.46
25-Hydroxy Vitamin D	0.01	0.85
DHEA-S	0.00	0.97
Progesterone	0.00	0.96
Cortisol	-0.04	0.60
VMA	-0.06	0.44
Metanephrine	0.23	0.00*
Normetanephrine	0.07	0.35
Epinephrine	0.13	0.09
Norepinephrine	0.14	0.06

*$p<0.05$; statistically significant.
FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone; ACTH: adrenocorticotropic hormone; HbA1c: haemoglobin A1c; FBG: fasting blood glucose; HOMA_IR: homeostatic model of assessment_insulin resistance; DHEA-S: dehydroepiandrosterone-sulfate; VMA: vanillylmandelic acid.

Table 5. Correlation Between Adrenal MRI Mass Size and 1 mg Dexametasone Suppression Test According to Sex (15 Male, 71 Female; n=86)

	Sex	Mean Rank	Mann-Whitney U test	*p* value
Basal Cortisol	Male	47.50		
	Female	42.65	472.50	0.494
Dexa. Sup. T.	Male	34.57		
	Female	45.39	398.50	0.127
Longer Nodule Diameter	Male	33.33		
	Female	45.65	380.21	0.092
Shorter Nodule Diameter	Male	29.13		
	Female	46.54	317.93	0.014*

*$p<0.05$; statistically significant.

Table 6. Correlation between shorter adrenal nodule diameter and biochemical parameters

Variables	Correlation Coefficient (r)	*p* value
FT3	-0.11	0.16
FT4	0.08	0.32
TSH	-0.08	0.28
Prolactin	0.14	0.07
ACTH	-0.06	0.39
HbA1c	-0.06	0.40
FBG	-0.05	0.54
HOMA_IR	0.05	0.51
Renin	-0.17	0.02*
Aldosterone	0.03	0.66
Plasma Renin Activity	-0.13	0.09
25-Hydroxy Vitamin D	0.02	0.84
DHEA-S	-0.08	0.27
Progesterone	-0.02	0.76
Cortisol	-0.03	0.73
VMA	0.04	0.56
Metanephrine	-0.01	0.88
Normetanephrine	0.08	0.27
Epinephrine	-0.06	0.39
Norepinephrine	0.05	0.50

* $p<0.05$; statistically significant.

FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone; ACTH: adrenocorticotropic hormone; HbA1c: haemoglobin A1c; FBG: fasting blood glucose; HOMA_IR: homeostatic model of assessment_insulin resistance; DHEA-S: dehydroepiandrosterone-sulfate; VMA: vanillylmandelic acid.

In the literature, adrenal incidentalomas were more prevalent in middle-aged and elderly subjects (Ekinci et al., 2016, Debono et al., 2014, Erbil and Barbaros, 2008, Comlekci et al., 2009). The previous studies have shown that ischemia and atrophy related to aging lead to compensatory hyperplasia in the cortical cells. This observation and the increase in the success of radiological procedures can account for this higher prevalence in the elderly. Clinically overt hormone hypersecretion syndromes were mainly shown in young subjects, while adrenal gland malignancies and sCS were more common in older ages (Comlekci et al., 2009).

In our study, the female/male ratio was 4.7 (71 F/15 M), which is similar to another study performed in a Turkish population (Ekinci et al., 2016), whereas higher than the ratio found in the literature.

Since most of the adrenal tumors incidentally discovered, there are no clinical signs of adrenal hormonal excess. But, it is still not clear whether an incidentaloma puts the patient at an increased risk of harmful outcomes. Literature shows that incidentalomas have often been associated with a high prevalence of hypertension, dyslipidemia, glucose intolerance, and obesity (Muscogiuri et al., 2011; Turan et al., 2015). By this, our series had a median insulin resistance value of 3.3 mg/dl, which is higher than usual.

In general, diagnostic workup of adrenal incidentalomas aimed at the detection of malignancy or subclinical hormone excess. Therefore, many authors recommend an array of hormonal assays to search for any hormonal abnormality.

Subclinical Cushing syndrome (SCS) is the most prevalent hormonal abnormality, found at a rate of 5-8% in patients with incidentalomas. Since impaired cortisol secretion with dexamethasone is an earlier sign, the low dose dexamethasone suppression test (ODST) is considered as the screening test in SCS (Babińska et al., 2012). As well as SCS, overt Cushing syndrome is ruled out in patients with a cortisol value of <1.8 µg/dl (50 nmol/l) after the ODST (Babińska et al., 2012).

In our series, the median post ODST cortisol was 1.2 µg/dl, and most of the patients had a value of <1.8 µg/dl. Most probably, this is related to the mass size: Our series had median adrenal nodule diameters of 2.1 cm (longer nodule diameter) and 1,5 cm (shorter nodule diameter).

It has been suggested that tumors of >3 cm are more likely to develop hyperfunction than smaller tumors (Muscogiuri et al., 2011; Morelli et al., 2014; Yılmaz et al., 2009).

We could not find any correlation between adrenal mass size and cortisol secretion after1 mg dexamethasone suppression test. But, we found a correlation between longer adrenal nodule diameter and 24h urinary metanephrine levels. As for shorter adrenal nodule diameter, it has a significant negative correlation with renin.

The positive correlation of adrenal mass size with metanephrine suggests that incidentaloma investigations should include analysis of plasma free metanephrines or urinary fractionated metanephrines, especially from the point of diagnosis of phaeochromocytomas and paragangliomas (van Berkel et al., 2014).

Recent studies have shown that a high percentage of adrenal incidentalomas can be subclinically functioning, causing symptoms milder than those encountered in the well known adrenal hyperfunctioning symptoms (Linos, 2003).

The fear of adrenal carcinoma, which has dictated the investigation of incidentalomas in the past, should leave its place to the dismay of mental function of these usually benign adrenal incidentalomas with coexisting metabolic pathology (Linos, 2003).

CONCLUSION

We found that the relationship between adrenal mass size and 1 mg dexamethasone suppression test results was not statistically significant. Shorter nodule diameter was statistically significant in women, and also it is negatively correlated with serum renin levels. Longer adrenal nodule diameter was significantly correlated only with 24h urinary metanephrine levels.

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