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Original Article

Determination of Cardiovascular Risk Factors Which Accompany Non-Functional Adrenal Incidentalomas

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ABSTRACT

Objective: The frequency of detecting adrenal masses is increasing day by day. The basic approach is to evaluate whether these masses are hormonally active or not and to evaluate if they have malignant potential. There are doubts that most of these masses, which are known to be nonfunctional, produce some active metabolites. In this study, we aimed to investigate the cardiovascular risk factors of nonfunctional adrenal incidentalomas.

Methods: 305 patients who were admitted to the Endocrinology and Metabolic Diseases Polyclinics with an incidentally detected adrenal mass between January 2006 and 2011 were included. Demographic characteristics, co-morbidities, drugs, and laboratory parameters were analyzed retrospectively. It was divided into two groups. Our group with nonfunctional adrenal adenoma, were compared with a community-based study; Turkey Diabetes, Hypertension, Obesity and Endocrinology Diseases Prevalence Study-2 (TURDEP-2).

Results: Adrenal masses were divided into two groups as functional and non-functional. The patients in the first group were younger (46.2±12.1 years, p=0.0001), had larger masses with malignant appearance. The patients in the second group were compared with TURDEP-2. When the patients with non-functional adrenal adenoma compared with the general community, hypertension and obesity were observed more frequently in our patient group; 66.2%-31.3% and 61.8%-36%, respectively.

Conclusion: It is controversial whether non-functional adrenal incidentalomas increase cardiovascular risk or not. Subclinical Cushing Syndrome is the most common hormonal disorder. The insidious cortisol autonomy is thought to be responsible for this. In our study, cases with nonfunctional adrenal mass were found to be more obese and hypertensive compared to the general population.

INTRODUCTION

Incidentally detected adrenal masses are increasing day by day in the clinic. The increase in the number of examinations such as computed tomography and magnetic resonance imaging is thought to be responsible for this situation.[1-3]

Approach to these patients; is the hormonal state of the mass and to make the distinction between benign or malignant. The size and appearance characteristics of these masses may be helpful in determining the presence of malignancy.[1]

In functional screening, serum glucocorticoid, mineralocorticoid and urine catecholamine levels are examined in the routine. It is reported that even adenomas that do not function with current screening tests can produce some active hormone metabolites and function.

These metabolites are thought to cause an increase in cardiovascular risk.[4] Due to the increased incidence of adrenal incidentalome recently and having serious doubts that the masses secrete some active hormone metabolites not yet measured by routine methods, it is aimed by this study to determine cardiovascular risk factors in adenomas which thought to be nonfunctional.[5] Cardiovascular risk factors were determined in these cases, and it is planned to compare the findings with recent general population-based studies.

MATERIALS AND METHODS

Between January 2006-2011, 305 patients were analyzed retrospectively who were incidentally detected adrenal mass while being examined for any reason at the Endocrinology and Metabolic Diseases Polyclinics.

Demographic characteristics of the cases such as age, gender, body mass index (BMI), smoking, family history, co-morbidities such as diabetes, hypertension, coronary artery disease, cerebro-vascular disease, peripheral artery disease, and the duration of exposure, and the drugs they used, were recorded. Fasting and postprandial plasma glucose values, lipid parameters, kidney and liver functions, blood counts were examined in the laboratory. In terms of whether it is humorally active or not; Measurement of catecholamines in 24-hour urine, Dexamethasone suppression test (DST) with 1 mg dexamethasone, if hypertension is present, PA/PRA is checked for malignancy or benign. They were the patients evaluated with the size and radiological feature.of the mass.

Cases were divided into two groups according to whether the mass was functional or not. General demographic data and parameters determining the risk of cardiovascular disease (CVD) were compared in the two groups above-sided. Following, the data of cases with adrenal masses which do not function are compared with Turkey Diabetes, Hypertension, Obesity and Endocrinology Diseases Prevalence Study-2 (TURDEP-2) data.

SPSS 17.0 package program was used for statistical analysis. Chi-Square test or Fisher test statistics were used for the comparison of categorical variables, Student T test and Mann Whitney U test were used to compare continuous measurements between groups.

RESULTS

A total of 305 cases were included in the study. Our patients in our database are evaluated in two groups as patients with non-functional mass 255 (83.6%), and patients with functional mass 50 (16.4%). The majority of our cases were cases with nonfunctional adrenal mass (p=0.0001). 46% of functional adrenal masses were glucocorticoid-secreting adenoma, 28% was pheochromocytoma, 26% was aldosteronoma, and 91.9% of non-functional adrenal masses were adrenal adenomas. It was observed that the most common imaging method used in diagnosis was CT (69%). It was observed that functional and non-functional tumors were diagnosed with similar imaging methods (p=0.051).

234 patients who carry a functionally inactive adrenal adenoma were detected. Our cases were compared as patients with functionally inactive adrenal adenoma and those with functionally active adrenal adenoma. The general characteristics of the cases are summarized in Table 1. A significant difference was found between functional and non-functional adenoma groups in terms of benign/malignant appearance (p=0.001). 91.5% (n=279) of the patients had a single adrenal lesion. Multiple adrenal tumors were detected at the rate of 8.5% (n=26).

When the adenoma was separated and evaluated in terms of functional status, no significant difference was observed between the patients' height, weight, BMI, gender, and whether the mass was right, left or bilateral (p>0.05). The mean age of the non-functional adenoma group was higher than the functional group (p=0.0001). Masses in the functional group were larger and malignant (p=0.001, p=0.0001) (Table 1).

When the history data were examined, it was observed that DM and HT were more common in those with functional adenomas as can be predicted; p=0.006 and p=0.001, respectively. No significant difference was observed in fasting plasma glucose, postprandial plasma glucose, total cholesterol, HDL-cholesterol and triglyceride values between the groups (Table 2).

When the TURDEP-2 data and non-functional adenoma group data were compared, no difference was found in terms of DM frequency. The frequency of hypertension in our patient group is 66.2% and 31.3% in TURDEP-2 data. HT is more common in the non-functional group than in the general population (p=0.0001). It was observed that the non-functional adenoma group smoked more (p=0.004). When the cases were divided into two in terms of body mass index, it was found that the non-functional group was more obese than the general population (p=0.0001) (Table 3).

Compared with TURDEP-2 data, the prevalence of smok-

Table 1. Comparison of the general characteristics of cases with functional and non-functional adenomas

	Non-Functional adenoma (n=234)	Functional adenoma (n=50)	p
Age (year)	54.6±11.6	46.2±12.1	0.0001
Gender (Female, %)	169 (72.2)	40 (80.0)	0.180
Height (cm)	159.6±8.3	158.6±8.2	0.462
Weight (kg)	80.5±14.9	81.5±20.6	0.723
Body Mass Index (BMI)	31.5±6.6	32.2±8.8	0.545
*Tumor Diameter (mm)	25 (5-92)	30 (6-150)	0.001
Direction Information			
Right (%)	108 (46.2)	30 (60.0)	0.208
Left (%)	105 (44.9)	17 (34.0)	0.308
Bilateral (%)	21 (9.0)	3 (6.0)	0.852
Malignant appearance (%)	13 (5.6)	14 (28.0)	0.0001

Mean±Standard Deviation. BMI: Body Mass Index *median (minimum-maximum).

Table 2. Accompanying cardiovascular risk factors according to the functional status of adenoma and comprasion of diseases

	Functional status		
	Non-Functional adenoma (n=234) (n, %)	Functional adenoma (n=50) (n, %)	p
Smoking	96 (41.4)	17 (34.7)	0.241
DM presence	62 (26.5)	23 (46.0)	0.006
HT presence	155 (66.2)	44 (88.0)	0.001
CAD presence	25 (10.7)	5 (10.0)	0.561
CVA presence	14 (6.0)	1 (2.0)	0.222
HLD presence	45 (19.2)	7 (14.0)	0.258

DM: Diabetesmellitus; HT: Hypertansion; CAD: Coronary artery disease; CVA: Cerebrovascular accident; HLD: Hyperlipidermia.

Table 3. Comparison of comorbidities of non-functional incidental adrenal adenomas with TURDEP-2 data

	Non-Functional adenoma (n=234) (n, %)	TURDEP-2 (%)	p
Smoking (n,%)	96 (41.4)	21.7	0.004
BMI (%)			0.0001
<30 kg/m^2	73 (38.2)	64	
>30 kg/m^2	118 (61.8)	36	
DM (n, %)	62 (26.5)	16.5	0. 055
HT (n, %)	155 (66.2)	31.3	0.0001

DM: Diabetesmellitus; HT: Hypertension; BMI: Body mass index; TURDEP-2: Turkey Diabetes, Hypertension, Obesity and Endocrinology Diseases Prevalence Study-2.

ing and HT were found to be more common in both men and women; p=0.0001 and p=0.0001, respectively. In the non-functional adenoma group, the proportion of women with a BMI of 30 and above was higher than the rate observed in TURDEP-2 (p=0.001) (Table 4).

DISCUSSION

The incidence of adrenal masses among endocrine tumors is gradually increasing due to many factors.[6] The most important step in the approach to adrenal masses is determining the hormonal status and potential malignancy. [5] Subclinical cushing syndrome, insufficiency of the data, metabolic disorder-adrenal adenoma relationship prevents to come to definite conclusions to approach to adrenal incidentalomes unlike the other incidentalomas. When the literature is reviewed, adrenal incidentalomes are usually detected in middle-aged women.[3,4,5,7] In the light of the data obtained from autopsy series, the aging process may increase the probability of adrenal mass formation. Due to hypoperfusion which occurs in adrenal cortex with aging, hyperplasia occurs in the cortex cells, and this may lead to

Table 4. Comparison of non-functional adenoma group and TURDEP-2 cohort data by gender

	Non-functional adenoma	TURDEP-2	p
DM n (%)			
Female	48 (28.4)	17.2	0.062
Male	14 (21.5)	16	0.362
HT n (%)			
Female	116 (68.6)	30.9	0.0001
Male	39 (60.0)	32.3	0.0001
Obesity (VKİ≥30) n (%)			
Female	99 (69.7)	44.2	0.001
Male	19 (38.8)	27.3	0.071
Smoking n (%)			
Female	57 (34.1)	9.9	0.0001
Male	39 (60.0)	31.5	0.0001

DM: Diabetesmellitus; HT: Hypertension; BMI: Body mass index/kg/m^2; TURDEP-2: Turkey Diabetes, Hypertension, Obesity and Endocrinology Diseases Prevalence Study-2.

the development of adrenal mass.[8,9] Cardiometabolic risk factors such as insulin resistance, prediabetes, DM, HT, obesity and endothelial dysfunction can often be detected in patients with adrenal incidentalome. There are many studies in the literature on this subject.[10-13] It is thought that some of the non-functional adrenal adenomas can secrete autonomous cortisol. However, limited information is available about the possible harmful effects of this mild hypercortisolemic state.[7,14-17]

The critical issue is whether Subclinical Cushing Syndrome predisposes arterial hypertension, obesity or diabetes, which are the classic features of fully developed endogenous hypercortisolism and metabolic syndrome.[18,19] Increased levels of proinflammatory mediators such as IL-6, resisting, TNF-alpha, monocyte chemotactic protein-1 in patients with non-functional adrenal incidentaloma (NFAI) are thought to play a role in the pathogenesis of unsolvable subclinical inflammation between insulin resistance, metabolic syndrome and increased cardio metabolic risk. Again, in NFAI patients, the decrease in adiponectin levels was associated with a decrease in insulin sensitivity, and it was stated that this association could be related with undetected hypercortisolism.[20,21] Speculations are made on this subject. Two in vivo studies, it is suggested that increased release of functional corticotropin receptors and enzymes were associated with both increased cytochrome p-450 enzyme activity and endogencortisol production, and were associated with clinically and biochemically undetectable increased adrenal steroid production, which have metabolic impairment effects.[22,23]

Subclinical hypercortisolism has been observed in a significant percentage of NFAI patients in multiple studies, which has been associated with sustained autonomic cortisol release, including an increased prevalence of hypertension, dyslipidemia, impaired fasting glucose or type 2 DM and a high risk of osteoporotic fractures. Although many of the usual signs of the syndrome are missing in these patients with subclinical cushing syndrome, one or more of the effects of continuous autonomous cortisol secretion can be seen and it is not always easy to detect the presence of hypercortisolism.[12,24,25,26] A remarkable improvement in blood pressure levels was detected after surgical removal of adenoma in patients with subclinical cushing syndrome.[27]

In our study, patients with an incidentally detected adrenal mass appealed to the Endocrinology and Metabolic Diseases Polyclinics between January 2006 and 2011 are examined. Their demographic characteristics, history and laboratory parameters are retrospectively examined. Also dimensions and directions of the tumors, hormonal and malignancy conditions are analyzed. As in many studies in the literature, the most common endocrine adrenal mass in this study has been non-functional adrenal adenomas (76.7%).[7] Computed tomography was determined to be the most frequent method (69%). In Adrenal Tumor group data published 10 years ago, the most frequent method is ultrasonography.[7] The metabolic problems faced by our patients with non-functional adrenal adenoma, respectively were; hypertension (66.2%), DM (26.5%), hyperlipidemia (19.2%) and coronary artery disease (10.7%).When the history of our patients was examined, it was observed that DM and HT were more common in patients who had functional tumors, similar to the literature.[3-5] There was no difference between the groups in terms of fasting and postprandial plasma glucose and lipid parameters. When the patients with non-functional adrenal adenoma and those with functional adrenal masses were compared, there was no difference between the groups in terms of BMI, gender, direction of the mass, bilateralness, while the average age of patients with non-functional adrenal adenoma was higher. It was observed that the mass size of the patients in the functional group was larger and more malignant, which is supported by other studies.[4,5] In line with the literature, diabetes and hypertension were observed more in our cases with functional adenoma than in the non-functional group.[3-6,13,24]

It is suggested that adenomas, which are thought to be nonfunctional or proved by the current methodology, actually secrete poorly active hormone metabolites at an unmeasurable level or not routinely measured, and cause metabolic problems with subclinical disorders. Based on this information, in the next phase of our study, it was questioned whether patients with non-functional adenoma had increased cardiometabolic risk factors compared to healthy controls. For this purpose, TURDEP-2 community study data were used.[28]

TURDEP-2 is recently a very important community-based study of cardiovascular disease and its risks, conducted with the support and auspices of the Turkish Ministry of Health in our country. Age, height, weight, BMI, obesity, known DM, new DM, known HT, new HT, smoking, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) were evaluated on randomly selected healthy adults who express the general population. The prevalence of diabetes was 13.7% and obesity prevalence was found to be 32% in the Turkish adult population. There was an increase in the incidence of obesity (BMI>30 kg/m^2) and DM development with increasing age in both women and men. The ratio of IFG in men and IGT is higher in women.

The incidence of hypertension is around 30% and it has been found that there is no difference between men and women and urban-rural, and the frequency of HT and new HT increases with age.[28] When we compare the results of the TURDEP-2 study, there was no difference between the groups in terms of the incidence of diabetes, while the prevalence of hypertension and smoking was higher in both genders in patients with nonfunctional adrenal adenoma. Considering our patient group with non-functional adrenal adenoma in general, a significant difference was observed in terms of obesity (BMI≥30) with the TURDEP-2 cohort. Our study group was found to be overweight. When the cases were divided according to gender, it was determined that this difference was due to the women in our group. Our data support the previous studies in the literature and

show that people with non-functional adrenal mass have a risk of metabolic disorders and therefore cardiovascular disease.[28] Studies investigating insulin resistance, BMI and abdominal fat in cases with NFAI have also shown that high total body mass and abdominal fat are excessive in those with non-functional adrenal mass. It has been suggested that cortisol hypersecretion and insulin resistance may be responsible for the total body mass distribution.[21,29] Because we don't have a control group in our study, our data were compared with the data on prevalence studies which have been made in Turkey.[28,30,31] As a result, hypertension, obesity, and smoking were found to be higher in patients with non-function adrenal adenoma compared to the general population average. Our results support the knowledge that people with non-functional adrenal adenomas are as prone to metabolic disorders as individuals with SCS. In the literature, there are publications stating that autonomic cortisol release shows a steady step in patients with adrenal adenomas, and even adenomas detected as non-functional with laboratory facilities may have an insidious, low-amplitude but high-frequency and continuous cortisol release, which may increase the risk of metabolic disorders and cardiovascular disease.[20,32,33] Adrenal incidentaloma is a middle-aged group disease that is more common in women. Determination of hormonal activity and benign/malignant potential are the most important evaluation steps. The most common type of adrenal incidentaloma is nonfunctional adrenal adenoma and the most common hormonal disorder is Cushing Syndrome. It is uncommon for a dysfunctional adenoma to show clinically significant hormone secretion. However, SCS development may be observed during the follow-up. It can generally be seen in patients with relatively large tumor size at the time of diagnosis and in patients who followed up for a long time. Interestingly, similar metabolic disorders can be observed in non-functional adenomas. Autonomous release of insidious cortisol or the like may be responsible for this situation. For these reasons, patients with non-functional adrenal adenoma should be followed up in terms of cardiometabolic problems that may develop.

Ethics Committee Approval

Başkent University Medical and Health Sciences Research Board 12/09/2012-KA12 / 207.

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Conflict of Interest

None declared.

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Non fonksiyonel Adrenal İnsidentalomalara Eşlik Eden Kardiyovasküler Risk Faktörlerinin Belirlenmesi

Amaç: Adrenal kitlelerin saptanma sıklığı her geçen gün artmakta ve bu kitlelerin hormonal olarak aktif olup olmadığı veya malignite potansiyeli taşıyıp taşımadığının değerlendirilmesi temel yaklaşımdır. Büyük çoğunluğunun nonfonksiyonel olduğu bilinen bu kitlelerin bazı aktif metabolitler ürettiğine dair kuşkular mevcuttur. Bizde bu çalışmada nonfonksiyonel adrenal insidentalomaların kardiyovasküler risk faktörlerini araştırmayı amaçladık.

Gereç ve Yöntem: Endokrinoloji ve metabolizma hastalıkları polikliniklerinde, Ocak 2006-2011 tarihleri arasında, tesadüfen saptanan adrenal kitle ile başvuran, 305 hasta alındı. Demografik özellikler, eşlik eden hastalıklar, ilaçlar, laboratuvar parametreleri geriye dönük olarak analiz edildi. İki gruba ayrıldı. Nonfonksiyonel adrenal adenom olan grubumuz toplum bazlı bir çalışma olan Türkiye Diyabet, Hipertansiyon, Obezite ve Endokrinolojik Hastalıklar Prevalans Çalışması-2 (TURDEP-2) ile karşılaştırıldı.

Bulgular: Adrenal kitleler fonksiyonel ve non fonksiyonel olmak üzere 2 gruba ayrıldı. Birinci gruptaki hastalar daha genç (46.2±12.1 yıl, p=0.0001), kitleleri daha büyük ve malign görünümdeydi. İkinci gruptaki hastalar TURDEP-2 ile karşılaştırıldı. Non fonksiyonel adrenal adenomu olan hastalar genel toplum ortamasıyla karşılaştırıldığında, hipertansiyon ve obezite bizim hasta grubumuzda daha sık izlendi; sırasıyla %66.2-%31.3 ve %61.8-%36.

Sonuç: Non fonksiyonel adrenal insidentalomaların kardiyovasküler riski artırıp artırmadığı tartışmalıdır. Subklinik Cushing sendromu en sık görülen hormonal bozukluktur. Sinsi kortizol otonomisinin bundan sorumlu olduğu düşünülmektedir. Bizim çalışmamızda da nonfonksiyonel adrenal kitle saptanan olgular genel topluma göre daha obez ve hipertansif bulunmuştur.

Anahtar Sözcükler: Adrenal insidentaloma; kardiyovasküler risk; subklinik Cushing sendromu.