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Carotid Intima-Media Thickness as the Cardiometabolic Risk Indicator in Patients with Nonfunctional Adrenal Mass and Metabolic Syndrome Screening

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Background: Our purpose was to show the association of adrenal incidentaloma and metabolic syndrome in consideration of the studies and to detect the increase in the carotid intima-media thickness which is regarded as the precessor of atherosclerosis.

Material/Methods: Eighty-one patients who were diagnosed with adrenal mass were included in the study. Hormonal evaluation, insulin rezistance measurement with the HOMA-IR and 1-mg DST were performed of all patients. The patients were classified as follows: mass size <3 cm (K_1) and mass size of at least 3 cm (K_2). Echocardiography and carotid intima-media thickness of the patients were measured using B-mode ultrasound. Thirty-three healthy individuals were enrolled as the control group.

Results: Mass size of 64.19% K_1, while mass size of the remainder (35.81%) K_2 was calculated. Five of the patients with adrenal mass were detected to have subclinical Cushing syndrome. The remaining 76 patients were accepted as nonfunctional. It was seen with regard to metabolic and biochemical parameters that plasma glucose (p=0.01), insulin (p=0.00) and triglyceride (p=0.012) values of all patients were significantly high compared to those of the control group. It was detected that measured heart rate (p=0.00), end-diastolic diameter (p=0.02), end-systolic diameter (p=0.014) and carotid intima-media thickness (p=0.00) values of the patients with adrenal mass were significantly higher than those of the healthy control group.

Conclusions: We found that the increased insulin resistance, increased risk of cardiovascular disease with the increase in the thickness of carotid intima-media and diastolic disfunction parameters, although the patients with adrenal incidentaloma are nonfunctional.

MeSH Keywords: Adrenocortical Adenoma • Carotid Intima-Media Thickness • Metabolic Syndrome X

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Background

Nonfunctional adrenal masses (NFAMs) are the clinical definition detected in the adrenal glands of patients who applied to clinic for any reason except adrenal pathology, with frequent use of modern imaging techniques and are generally given to benign masses [1]. Through more common use of Computerized Tomography (CT) and magnetic resonance imaging (MRI), it is thought that the estimated prevalence is 3–10%, particularly in actual application [2]. After diagnosing the incidentalome, the mass is categorized according to its diameter, characteristics in imaging, and whether it secretes hormone or not. They are NFAMs, most of which are located singly on the right side and they have a benign character. Apart from this above-mentioned majority that does not secrete hormone (80%), the remainder comprising 15% secrete hormone – primarily cortisol [3,4].

Another important subject discussed nowadays is that NFAMs are a risk indicator of increased cardiometabolic risk [5]. In recent studies it was determined that the frequency of Type 2 diabetes mellitus (DM), obesity, hypertension (HT), impaired glucose tolerance (IGT) and dyslipidemia increase in patients with non functional adrenal incidentaloma (NFAI) [6]. Additionally, observation of many components (especially increased thrombogenic ambient, insulin resistance, hepatosteatosis and abdominal obesity) of the metabolic syndrome (MS) in the patients with NFAM makes us think that different metabolic pathways are impaired [7]. In particular, increasing carotid intima-media thickness (CIMT) of these patient groups compared to that of healthy control groups and observation of impaired Flow-Mediated Dilatation (FMD) caused the studies to further focus on the cardiovascular system [8,9]. In patients NFAI there is an impairment of cardiac morphology and function in echocardiographic examination. Especially diastolic dysfunction can be seen in these patients. Although there are a lot of ecocardiographic studies [10–12] in functional adrenal incidentalomas (Cushing syndrome, primary hyperaldosteronism, pheochromocytoma) there is not enough research of ecocardiographic studies in nonfunctional adrenal incidentalomas. Because we know that cardiac diseases are increasingly observed in patients with subclinical impairment of left ventricular (LV) diastolic function a precursor to overt heart failure [13]. Two ideas emerged basically as a result of these studies. The first one is whether or not the cardiac problems of the patients with adrenal mass are related to hormone secretion, even though the problem cannot be identified, or that the hyperinsulinemic environment developing with unknown mechanisms leads to cardiac function disorder by means of MS. In order to find the answers to these questions, the patients with adrenal mass were detected as having a low adiponectin level, which decreases insulin resistance and high adipocytokine (resistin, IL-6, MCP, leptin, TNF-α) levels, which increase the insulin resistance [14,15]. But the relationship between adrenal mass and cardiometabolic function disorder could not be revealed even under the present conditions.

Our purpose was to show the association of adrenal incidentalome and MS in consideration of the studies that have been performed to date for the patients referred to us due to adrenal incidentalome, and to detect the increase in the CIMT which is regarded as the precessor of atherosclerosis. Furthermore, another important purpose was emphasizing diastolic dysfunction that may develop in the early period, led by underlying various mechanisms even though they are asymptomatic, using detailed echocardiographic parameters which have not been emphasized in the studies performed to date.

Material and Methods

Eighty-one patients who applied to our clinic between 2014 and 2016 were diagnosed with adrenal mass and follow-ups were included in the study. Ethics committee approval of the study was received in the meeting No. 43 on 05.06.2015. Consent forms of all patients were obtained. Firstly, if there were only imaging results (CT, MRG) of the patients who were examined for any reason and detected to have adrenal mass, the existence of adrenal mass was confirmed through MRG examination in our center. The patients who had a history of Type 2 DM, HT, coronary artery disease and dyslipidemia, use drugs, used steroids before or had adrenal mass detected functionally (Cushing syndrome, primary hyperaldosteronism, pheochromocytoma) were excluded from the study.

During the first application from the patients, their clinic histories were questioned, their height/weight, BMI, waist circumference and tension arterial were measured, and their detailed physical examinations were made. Information about APG, insulin, serum, sodium, potassium, cortisol, ACTH, dehydroepiandrostenedione sulphate (DHEA SO4), total cholesterol, LDL-K, HDL-K, triglyceride, plasma rennin activity and aldosterone level of the patients measured in the morning were sent. Insulin resistance of the patients was calculated with the HOMA-IR (mg/dl) formula.

Afterwards, 24-hour urine samples were analyzed for measuring vanillylmandelic acid (VMA), metanephrine (normal interval 74–298 mcg/day), normetanephrine (normal interval 105–354 mcg/day) and cortisol (normal interval <110 mcg/day). The patients who had increased normetanephrine and metanephrine values or adosterone/rennin activity >30 were not included in the study.

A 1-mg DST was conducted after evaluating basal cortisol measurements of the patients. The patients who were determined

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to have cortisol values below 1.8 mcg/dl after DST were accepted as normal. DST was applied to the patients during 2 days, 4×0.5 mg at intervals of 6 hours. The patients who did not have any findings of the physical examination with regard to Cushing syndrome, but were determined to have cortisol values and ACTH values above 1.8 mcg/dl and below 10 pg/ml, respectively, as a result of DST, were accepted as having subclinical Cushing syndrome (SCS). After the existence of adrenal mass of the patients was verified with MRG, the patients were classified into two groups: the patients with mass size <3 cm (K_1) and the patients with mass size of at least 3 cm (K_2).

Lastly, detailed echocardiography (tissue Doppler and diastolic dysfunction parameters) and carotid intima-media of the patients were measured using B-mode ultrasound (VIVID S5 General Electric). The patients were in the left lateral decubital position while measurements were made using two-dimensional, M Mode, C-Doppler and current doppler in concert with the images of parasternal long and short axis, apical four-space and five-space. In line with the suggestions of the American Echocardiography Association, all echos were performed at midday by the same person in order to eliminate the effect of circadian changes on diastolic dysfunction. The diastolic dysfunction parameters of the patients containing E/A, deceleration time (EDEC), and isovolumetric relaxation time (IVRT) were recorded.

The patients were laid on their backs for carotid intima-media measurement provided that their heads tilted toward the back. Similarly, the measurement of left and right carotid arteries was performed by a single physician. The patients were first subjected to general morphological evaluation of both common carotid arteries (CCA),and cervical segments of the internal carotid artery (ICA) after carotid separation under axial and longitudinal plan through B mode gray scale imaging. In both measurements of carotid artery intima-media thickness (CIMT) under longitudinal plan, carotid artery bulbus with 1 cm proximity from the back wall and the area without plaque was viewed, and after zooming in the image, measurement was made between the lumen of intima and hypoechogenic reflection generated by media-adventitia at depth of the reflection and media layer and the average was found.

The control group (n=33) was created by choosing healthy volunteers who applied to our polyclinic. While choosing the control group, it was targeted that age, gender distribution, and BMI values of the control group would equal those of the patient group. The patients who had any acute inflammatory disease and met the exclusion criteria were excluded from the study. The imaging analyses (USG, CT, or MR) of the chosen control group made previously were used to determine that members of the control group did not have any adrenal mass. It was also seen after a 1-mg dexamethasone test that cortisol values of the patients were suppressed.

Fasting plasma glucose, total cholesterol, Low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), triglyceride and uric acid were measured using spectrophotometric method. DHEAs and ACTH values and cortisol values were analyzed using polymerase chain reaction (PCR) method, enzymatic-labeled chemiluminescent immunometric assay method, and chemiluminescence (Beckman DXI 800 autoanalyzer), respectively. PRA and PA levels were measured through radioimmunoassay method. High performance liquid chromotography (HPLC) method was used to analyze urine cortisol and metanephrine values.

Statistical analysis of the data was performed by means of SPSS 19.0 program. Descriptive statistics were produced for demographical characteristics of the patient and control group. Chi-square test was used to evaluate the categorical variables. Continuous variables were evaluated through T-test, Mann-Whitney U test, or ANOVA test. Data were indicated as mean ± standard deviation (μ±SS) or median. $p<0.05$ was accepted as statistically significant.

Results

Demographical and biochemical parameters

In total, 81 patients who were followed up in 2015–2016 and had adrenal incidentalome were included in our study. The frequency of female patients (n=50, 61%) was higher than that of male patients (n=30, 39%). Within the scope of the study, mean mass size of the patients (n=81) with adrenal mass was determined to be 2.5±1.2 cm. Mass size of 64.19% (n= 52, K_1) of the patients was found as <3 cm, while mass size of the remainder (35.81%) (n=29, K_2) was calculated to be at least 3 cm. As a result of the analyses, 5 of the patients with adrenal mass were detected to have SCS. The remaining 76 patients were accepted as nonfunctional. In addition to the patient group, 33 healthy members were included in the study as the healty control group (HC). When other data were analyzed, it was seen that waist circumference measures of both cases with NFAI and SCS increase significantly compared to the control group. With regard to (p=0.00) systolic (p=0.45) and diastolic (p=0.61) blood pressures, no significant difference between these three groups could be found. Considering the mass size and waist circumference, there was no significant difference. It was shown in Table 1 demographic and biochemical parameters of the patients with NFAI and SCS), and the HC group.

It was seen with regard to metabolic and biochemical parameters that plasma glucose (p=0.01), insulin (p=0.00) and triglyceride (p=0.012) values of NFAI and SCS patients were significantly high compared to those of the control group. No significant difference with regard to total cholesterol, LDL cholesterol, and

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Table 1. Demographic and biochemical parameters of the patients with nonfunctional adrenal mass (NFAI) and subclinical Cushing syndrome (SCS), and the healthy control group (HC).

	NFAI (n=76)	SCS (n=5)	HC (n=33)	p
Age (year)	52.09±9.78	49.60±8.64	48.90±8.73	0.09
BMI (kg/m^2)	28.74±4.69	31.80±5.14	27.57±2.53	0.09
Waist circumference (cm)	98.92±11.44	98.60±15.85	85.27±7.41	0.00
SBP (mmHg)	129.±14.96	135±2.87	127.27±9.36	0.44
DBP (mmHg)	79.80±10.14	83.00±13.03	81.90±6.29	0.19
FPG (mg/dL)	96.21±9.97	91.09±9.39	95.60±8.44	0.01
İnsulin (µU/mL)	8.68±9.63	9.60±4.52	3.67±2.05	0.00
HOMA-IR	2.44±2.46	2.19±1.03	0.53±0.54	0.00
Total cholesterole (mg/dL)	196.39±46.5	199.60±60.97	188.81±38.37	0.37
LDL (mg/dL)	122.±36.86	130±51.63	118.06±26.25	0.52
HDL (mg/dL)	46.36±10.68	48.40±10.80	49.12±18.77	0.43
Trigliseride (mg/dL)	159.63±136.96	143.80±29.92	112.75±53.56	0.01
Uric aside (mg/dL)	5.15±1.54	4.14±1.00	5.63±4.65	0.56

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FPG – fasting plasma glucos; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

Table 2. Comparison between the hormonal parameters of the patients with nonfunctional adrenal mass (NFAI) and subclinical Cushing syndrome (SCS).

	NFAI (n=76)	SCS (n=5)	p
Cortisol (µg/dL)	11.41±4.33	13.80±2.39	0.09
ACTH (pg/mL)	20.40±10.28	18.20±7.39	0.58
DHESO4 (µg/dL)	92.19±93.88	60.00±33.49	0.11
Post-DST* Cortisol	1.32±0.90	4.84±0.47	0.00

* Post DST – post dexamethasone suppression test.

HDL cholesterol could be found (p>0.05). Calculated HOMA-IR values of the patients with NFAI (p=0.00) and SCS (p=0.01) were found to be significantly higher than the HC group. When the two groups were classified according to mass size, it was observed that measured plasma insulin (9.41±12.60; 8.36±7.12 p=0.02), HOMA-IR (2.25±3.28; 1.93±1.75 p=0.01) and TG (154.20±198.18; 161.13±78.09 p=0.00) values of K2 were significantly higher than K_1.

Hormonal parameters and pathological diagnosis of the mass

Hormonal parameters of the 3 groups included in the study are shown in Table 2. Whereas no significant difference between morning plasma cortisol values and ACTH values of the patients with NFAI and SCS was found (p=0.09, p=0.51), cortisol (p=0.00) values observed after 1 mg DST were determined to be significantly higher in SCS cases. 24-hour urine cortisol values of these patients were higher than those of the patients with nonfunctional mass. Not surprisingly, (p=0.11) plasma DHESO4 levels of NFAI cases were found to be lower than those of SCS cases. With regard to basal plasma cortisol values and ACTH values, there was no difference between both groups (K_1 and K_2) classified according to mass size, but post-DST cortisol values of the group with at least a 3-cm mass (1.89±1.25; 1.30± 1.15 p<0.05) was significantly higher.

In our 10 patients (%12,3) had undergone surgery due to diameter of the mass. Pathological diagnosis are adenoma (n=6), myelipom (n=3), carcinoma metastasis (n=1).

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Table 3. Echocardiographic measurements of the patients with nonfunctional mass (NFAI) and subclinical Cushing syndrome (SCS), the patients of the healthy control group (HC), and a comparison of their CIMT values.

	NFAI (n=76)	SCS (n=5)	HC (n=33)	p
Heart Rate	77.30±12.56	81.60±7.46	68.84±7.97	0.00
PR (msec)	142.19±25.34	130±17.32	146.48±25.92	0.42
LA (mm)	35.05±3.74	37.60±8.73	32.87±6.13	0.06
EDD (mm)	47.05±3.49	49±2	45.51±3.68	0.04
ESD (mm)	28.17±3.36	29.40±4.09	26.48±3.45	0.02
EF (%)	64.06±4.36	63±1.87	63.03±3.24	0.17
IVS (mm)	10.38±1.47	11.20±2.49	9.75±1.58	0.059
PD (mm)	10.31±1.45	10.80±1.78	9.63±1.29	0.01
EDEC (msec)	213.38±43.35	175.20±41.48	247.84±108.82	0.08
IVRT (msec)	94.90±25.43	97.20±28.55	84.42±20.45	0.02
CIMT (mm)	0.89±0.17	0.84±0.20	0.67±0.15	0.00

LA – left atrium; EDD – snd diastolic diameter; ESD – end systolic diameter; EF – ejection fraction; IVS – interventricular septum; PD – Posterior wall; EDEC – E deceleration time; IVRT – interventricular relaxation time; CIMT – carotid intima-media thickness.

Echocardiographic findings

Echocardiographic findings were shown in Table 3. It was detected that measured heart rate (p=0.00), end-diastolic diameter (EDD) (p=0.02), end-systolic diameter (ESD) (p=0.014) and CIMT (0.893±0.177; 0.67±0.15 p=0.00) values of the patients with adrenal mass were significantly higher than those of the HC group. The same evaluation was valid for NFAI, SCS, and HC groups as well. It was seen that interventricular septum (İVS) thickness of the patients (p=0.00, p=0.047, p=0.022, p=0.00) with NFAI (p=0.05) and SCS (p=0.05) increased significantly compared to septum thickness of the HC group. Similarly, it was observed that posterior wall (PD) thickness of the patients with NFAI and SCS increased (p=0.018) and their interventricular relaxation time (IVRT) extended (p= 0.026) compared to HC patients. In addition, one of the diastolic dysfunction parameters, the E/A rate of only 36% of the HC group corresponded to <1, whereas the E/A rate was <1 among the majority (79%) of the patients with NFAI. Considering all of the parameters between the patients with NFAI and SCS, no significance was seen (p>0.05).

Discussion

In this study we analyzed the hormonal profiles, metabolic parameters, and carotid IMK of the patients who we followed due to adrenal incidentaloma or those diagnosed with it recently; we detected an increase in the insulin resistance and carotid IMK of these patients. Moreover, we found out as a result of the detailed echocardiographic analysis that such patients have diastolic dysfunction, which we associated with hyperinsulinemia.

Regarding the patients who applied to the clinic because of adrenal incidentaloma, apparent insulin resistance, and MS clinic which arises from the metabolic disorders developing due to the insulin resistance are known truths revealed by the studies conducted to date [16]. Additionally, the multi-center study of Montero et al. [3] attended by 1004 adrenal incidentalome patients in 2000 showed that insulin resistance and obesity increased seriously among these patients. Many authors associate this truth with moderately high cortisol levels, even though it has not been demonstrated yet. However, the hyperinsulinemic environment which forms depending on cortisol synthesis was indicated as the real cause in the opposite studies [17]. Furthermore, it was seen in the study of Peppa et al. [18] in 2010 that insulin resistance (HOMA-IR and QUICKI, MATSUDA index) of the patients with NFAI increased compared to the HC group. Similarly, it was determined in our study that the patients with NFAM have increased insulin resistance compared to the HC group. In another study of Damjanoviç et al. [19] attended by 116 patients with adrenal incidentalome, it was seen that waist circumference was apparent even though the BMI of the patient and control groups were matched, and insulin resistance increased when it was calculated through HOMA-IR measurement. In our study it was observed that waist circumference of the patients increased compared to that of the control group despite the matching made to minimize the metabolic and cardiovascular damages arising from BMI differences.

Although most of the adrenal incidentalome cases are mentioned as nonfunctional in the literature, the clinical status which is regarded as a result of the moderate cortisol secretion of the mass, not as a clinical symptom, is qualified as

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subclinical Cushing syndrome, and its rate of incidence in adrenal incidentalome was recorded as 5% [20]. As a consequence of the moderate hormone secretion, impairment of the insulin resistance and lipid parameters, increased waist circumference, and diseases such as osteoporosis are particularly seen among these patients [21]. 37 of the patients with nondiabetic adrenal mass (n=107) were detected to have subclinical Cushing syndrome in the study of Ivovic et al. about this subject in 2012 [22]. When nonfunctional patients (n=70) and patients with SCS (n=37) are compared with the healthy control group (n=35), it was seen that the glucose, insulin, triglyceride, and HOMA-IR of these patients are higher than those of the control group, but such values of the patients with nonfunctional mass and SCS do not change. In our study, SCS incidence was found to be 6% (n=5). It was seen that plasma glucose, insulin, HOMA-IR, and triglyceride values of nonfunctional patients and the patients with subclinical Cushing syndrome are significantly higher than those of the healthy control group (n=33). However, no significant statistical difference with regard to these parameters between the patients with nonfunctional mass and SCS could be found.

Numerous studies about metabolic syndrome and insulin resistance of the patients having nonfunctional adrenal mass were conducted. In addition, HOMA-IR and triglyceride values of the patients with nonfunctional adrenal mass (n=42) and SCS (n=8) were detected to be significantly high, compared to the healthy control group (n=32) in a study of Lazurova et al. [23] in 2011 about the association of adrenal incidentalome metabolic syndrome ($p<0.05$). They classified the patients into two according to their mass size: <3 cm and >3 cm. From the parameters, a significant difference between their cortisol values was seen only after 1 mg dexamethasone suppression. In our study we could not find any significant difference except cortisol as a result of post-DST when we classified according to mass size as <3 cm and >3 cm. We can speak more definitively about this subject by using the other studies, but we can say that mass size is not related to insulin resistance.

The etiology of susceptibility for patients with nonfunctional adrenal mass to cardiovascular diseases is a much-debated issue. Hypotheses asserted for this situation include hyperinsulinemia, undetectable hormone secretion, or a different view including the cytokines, which are determined as high in these patients and raise the insulin resistance [23]. Many authors associated the risk increase seen in the patients with adrenal mass with direct cardiovascular damage (increased IMT, impaired FMD) of these secreted cytokines [24].

In the evaluation of cardiovascular disease risk, increasing carotid IMK was accepted as the indicator of coronary atherosclerosis [25]. IMK is an indicator of the generalized atherosclerosis, including the coronary arteries as well [26]. In particular, increased intima-media thickness was determined in the patients with nonfunctional mass compared to the healthy control group in many studies [8,27]. In our study increased CIMT was seen in the patients with nonfunctional mass.

Until quite recently, diastolic dysfunction could not be understood well as the cause of the heart failure and was generally ignored. On the other hand, invasive and noninvasive methods developed in the last decade eased the understanding of the pathological changes in diastolic function. Diastolic dysfunction is a picture characterized with normal systolic end pressure, but improper increase of the filling pressure, and increase of the diastole end pressure due to the sufficient filling of the left ventricle. Filling capacity of the left ventricle is limited. The left ventricle is not dilated, diastolic pressure increased, and there is normal ejection fraction [28]. Numerous factors should be evaluated and combined with the clinical information to evaluate the diastolic dysfunction. In a study of El Dayem et al. [13], a significant positive correlation between CIMT and diastolic dysfunction was found. In particular, left ventricle end diastolic diameter, IVS (interventricular septum thickness/late diastolic filling rate are correlated with CIMT (RRRRR)). In our study increased CIMT values were found to be significantly high in the patients with mass compared to the control group and the indicators of diastolic function (PD, IVS, EDD, ESD) of this group were impaired as well. These findings can be thought of as a sign of the increased atherosclerosis process and impaired ventricle functions seen among the patients with adrenal incidentalome [8]. Increased heart rate impairs filling and relaxation of the left ventricle, reduces coronary perfusion, raises oxygen consumption, and causes diastolic dysfunction of the left ventricle. Merabet et al. [29] proved the positive effect of the decreased heart rate on diastolic function. In our study the heart rate of the patients with adrenal incidentalome diastolic function of which impaired significantly compared to control group was determined to be significantly higher. These findings may be a preview of the increased atherosclerosis process and impaired diastolic function among our patient group with nonfunctional mass.

Conclusions

In consequence, we see the increased insulin resistance and increased risk of cardiovascular disease with the increase in the thickness of carotid intima-media, although the patients with adrenal incidentalome are nonfunctional. However, we note a different aspect of the cardiac damage using the indicators of the increased atherosclerosis process, as well as impaired diastolic function in this study.

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Conflict of interests

All authors declare that there is no any conflict of interest

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