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ORIGINAL PAPER

Carotid intima media thickness is increased and associated with morning cortisol in subjects with non-functioning adrenal incidentaloma

Serkan Yener · Sinan Genc · Baris Akinci · Mustafa Secil · Tevfik Demir · Abdurrahman Comlekci · Senem Ertilav · Sena Yesil

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Abstract Data regarding cardiovascular risk in subjects with non-functioning adrenal adenoma are limited. The objectives of this study are to investigate carotid intima media thickness (IMT) as an indicator of atherosclerosis in subjects with non-functioning adrenal incidentaloma (AI) and to evaluate the factors that could be associated with IMT. Forty-nine subjects without findings of hypercortisolism or other adrenal gland disorders, 34 body mass index (BMI)-unmatched controls (C) and 18 BMI-matched controls (BC) were enrolled. Participants underwent hormonal evaluation including morning cortisol, adrenocorticotrophic hormone (ACTH), post dexamethasone suppression test cortisol (DST), dehydroepiandrosterone sulfate (DHEAS), and urinary free cortisol. Anthropometric and metabolic parameters and carotid IMT were measured. AI group had increased BMI, blood pressure, waist circumference, post DST cortisol, uric acid, and homeostasis model assessment (HOMA) levels when compared with C. Blood pressure, uric acid and, post DST cortisol remained significantly elevated in AI versus BC. Average IMT was increased significantly in AI versus C (0.74 mm vs. 0.68 mm, $P = 0.029$) and insignificantly elevated in AI versus BC (0.74 mm vs. 0.67 mm, $P = 0.086$). In all participants, IMT was correlated with age, BMI, HOMA, waist circumference, morning cortisol, and uric acid. Morning cortisol was independently associated with HOMA levels in both AI group and all participants. Increased IMT in non-functioning AI was a consequence of insulin resistant state associated with subtle cortisol autonomy rather than a direct effect of cortisol. The correlation between morning cortisol and IMT may be associated with the effect of hypothalamus–pituitary–adrenal axis disturbances on vasculature.

Keywords Adrenal incidentaloma · Carotid IMT

S. Yener (✉) · B. Akinci · T. Demir · A. Comlekci · S. Ertilav · S. Yesil
Division of Endocrinology and Metabolism, Department of Internal Medicine, Dokuz Eylul University, Inciralti, Izmir 35340, Turkey
e-mail: serkan.yener@deu.edu.tr

B. Akinci
e-mail: baris.akinci@deu.edu.tr

T. Demir
e-mail: tevfik.demir@deu.edu.tr

A. Comlekci
e-mail: comlekci@deu.edu.tr

S. Ertilav
e-mail: senem.ertilav@deu.edu.tr

S. Yesil
e-mail: sena.yesil@deu.edu.tr

S. Genc · M. Secil
Department Radiology, Dokuz Eylul University, Inciralti, Izmir 35340, Turkey
e-mail: sinan.genc@deu.edu.tr

Introduction

The previous studies have demonstrated a variety of anthropometric and metabolic disturbances in subjects with adrenal incidentalomas (AIs). The burden of disturbances showed diversity from impaired glucose tolerance and visceral obesity to increased levels of intima media thickness (IMT) of common carotid arteries (CCA) [1–8]. These were mostly described in subjects with subclinical or overt Cushing Syndrome and the severity of disturbances was associated with the degree of cortisol excess.

The degree of autonomous cortisol production in AI is a continuum from subtle autonomy of subclinical Cushing Syndrome (sCS) to completely pathological secretion that can be seen in Cushing Syndrome [4, 9]. In spite of the lack of recent data regarding cortisol secretion dynamics in subjects with non-functioning AI, in a previous study, it was demonstrated that steroid production in inactive adrenocortical tumors are not overtly different from those of sCS [10]. In spite of the highest incidence of non-functioning AI among adrenal masses [11], data regarding cardiovascular risk factors in this particular group are limited. Terzolo et al. demonstrated that subjects with non-functioning AI had similar blood pressure, glucose, and insulin levels but preserved insulin sensitivity index when compared with patients with sCS [8]. In a recent study, Ermetici et al. showed that levels of several adipocytokines were higher in patients with non-functioning AI than in healthy subjects [2].

Because of the previous data demonstrating increased central fat distribution in subjects with AI similar with the subjects with overt Cushing Syndrome [12] and the presence of novel studies demonstrating higher levels of several adipocytokines [2] and impairment of cardiac morphology [1] in subjects with non-functioning AIs, we aimed to investigate IMT of CCA as an indicator of atherosclerosis in subjects with non-functioning AI and compare the findings with body mass index (BMI)-matched and BMI-unmatched controls. We also aimed to investigate anthropometric, metabolic, and hormonal factors that could be associated with IMT values.

Materials and methods

Subjects with incidentally discovered adrenal mass whom were diagnosed between January 2007 and June 2008 at Dokuz Eylul University, Division of Endocrinology and Metabolism, were invited for the study. Intuitional review board and local ethical committee approvals were obtained. All of the participants gave written consent. At the first visit, a confirmatory computed tomography (CT) scan was performed and adenoma was diagnosed if the following criteria were met: (i) regular shape with well-defined margins and homogenous, (ii) attenuation value of 10 or less Hounsfield units on unenhanced CT scan, and (iii) 30 or less Hounsfield units on enhanced CT scan. If CT scan failed to confirm the diagnosis, magnetic resonance imaging was performed.

After confirming the presence of an adrenal adenoma, subjects (n = 75) were invited for the second visit. Detailed physical examination was performed. Patients with a history of diabetes, coronary artery disease, peripheral artery disease, cerebrovascular events, angina pectoris, intermittent claudication, who were on oral contraceptives, anti-coagulants, anti-obesity drugs, oral anti-diabetics, glucocorticoids, or insulin were excluded (n = 16). Patients with signs or symptoms of Cushing Syndrome, hypokalemia with hypertension suggesting primary hyperaldosteronism, sustained hypertension with adrenergic symptoms suggesting pheochromocytoma were excluded (n = 5). Among participants with AI, 15 patients had hypertension all of whom were well-controlled with single anti-hypertensive agent.

The initial hormonal evaluation included morning cortisol, dehydroepiandrosterone sulfate (DHEA-S), adrenocorticotrophic hormone (ACTH), plasma renin activity, and aldosterone. Subsequently, urinary free cortisol (UFC) and urinary catecholamines were measured and overnight 1 mg dexamethasone suppression test (DST) was performed (normal ranges; normetanephrine: 88–444 μg/day, metanephrine: 52–341 μg/day, and UFC < 110 μg). Patients with increased urinary normetanephrine and metanephrine or increased aldosterone/renin ratio (>30) were excluded (n = 5).

The suppression in overnight DST was adequate when morning cortisol fell below 1.8 μg/dl. When post DST cortisol was over 1.8 μg/dl, 2 day 2 mg dexamethasone suppression test involving the administration of 0.5 mg oral dexamethasone given every 6 h for 48 h was performed and adequate suppression was achieved. The patients with suppressed post-DST cortisol levels were accepted to have nonfunctional adenoma if they additionally had at least one of the following criteria: (i) morning DHEA-S levels ≥ 40 μg/dl, (ii) non-suppressed ACTH (≥5 pg/ml), or (iii) UFC < 110 μg/day.

The eligible patients (n = 49) were evaluated after 8–10 h fasting between 8.00a.m and 9.00a.m at the third visit. Height (m), weight (kg), waist circumference (WC) (cm), and blood pressure were measured. Subsequently, IMT of CCA was evaluated. The same examiner who was unaware of the clinical status throughout the study performed the sonographic measurements. Ultrasonographic images of the right and the left CCA of each case at the lower 1/3 cervical region proximally and 1 cm above the carotid bulb distally in longitudinal plane were obtained. IMT of CCA measurements of the proximal and distal CCA posterior wall were done manually by the provided distance measurement system of the sonography device after magnification of the images. Three measurements were made in a non-neighboring fashion within an approximately 1 cm segment both from the left and right CCA proximal and distal portions. IMT values were then calculated by obtaining the arithmetic means of the measured values. After IMT measurements blood samples were collected.

The control subjects (C) (n = 34) were randomly selected from hospital staff. They were not affected by any

disease or acute inflammatory conditions. Control subjects underwent a CT scan to confirm that they did not have adrenal masses. They were screened with 1 mg DST and adequate suppression was achieved in all individuals. After excluding endogen hypercortisolism, similar investigational procedure was applied. In order to compare the patients with BMI-matched subjects, a subgroup (BC, n = 18) was generated from healthy controls by including the individuals with BMI levels over 25 kg/m^2.

Fasting plasma glucose, total cholesterol, high density lipoprotein cholesterol (HDL-C), triglyceride, and uric acid were measured by Roche/Hitachi D/P Modular System Autoanalyzer (Roche Diagnostics, Basel, Switzerland). Low density lipoprotein cholesterol (LDL-C) was calculated. Insulin, cortisol, DHEAS, and ACTH were measured using chemiluminescence enzyme immunoassay kits (Immulite, Diagnostic Products Corporation, Los. Angeles, USA). Urine free cortisol and metanephrines were measured by high performance liquid chromatography (Agilent Technologies, Santa Clara, USA). The degree of insulin resistance was calculated from the homeostasis model assessment (HOMA).

Variable distributions were assessed by the Kolmogorov–Smirnov normality test. According to the variable distribution, one way-ANOVA was used for comparison of groups. Categorical variables were compared by using the chi-square test. Correlation analyses were performed using Spearman's or Pearson's coefficients according to distribution of the variable. Regression analysis was employed to assess correlations between studied parameters. Statistical analysis was performed using Statistical Package of Social Science (SPSS), version 11.0 for Windows. Data were expressed as mean ± standard deviation (S.D.) or median (interquartile range). A P value < 0.05 was accepted as statistically significant.

Results

Characteristics of participants are shown in Table 1. There were seven patients with multiple adrenal adenomas. Right adrenal adenomas were more common (30/26). Mean adenoma diameter was 18.9 ± 6.3 mm.

Age, gender, and diastolic blood pressure (DBP) were similar between groups. When compared with BMI-unmatched healthy controls (C), patients with AI had increased BMI ($P < 0.001$), increased systolic blood pressure (SBP) ($P < 0.001$), and mean arterial pressure (MAP) ($P = 0.006$) and increased waist circumference ($P < 0.001$). When patients were compared with BMI-matched controls (BC), SBP ($P = 0.002$) and MAP ($P = 0.008$) were found to be significantly elevated.

Table 1 Characteristics of study participants

	AI (n = 49)	C (n = 34)	BC (n = 18)	*P* (AI versus C)	*P* (AI versus BC)
Age	52.7 ± 10.2	49.2 ± 7.2	49.3 ± 7.3	0.085	0.201
Gender (M/F)	35/14	29/5	14/4	0.399	0.999
BMI (kg/m2)	28.8 ± 4.2	24.8 ± 3.2	27.1 ± 2.5	<0.001	0.135
SBP (mm-Hg)	120 (110–125)	110 (95–120)	110 (90–120)	<0.001	0.002
DBP (mm-Hg)	80 (70–80)	80 (60–80)	75 (60–80)	0.312	0.216
MAP (mm-Hg)	98.5 (90.6–102.5)	90 (80–100)	90 (77–97)	0.006	0.008
Waist (cm)	92.9 ± 10.2	81.1 ± 10.9	88.4 ± 8.0	<0.001	0.224
Glucose (mg/dl)	95.3 ± 13.2	92.1 ± 11.3	92.0 ± 11.2	0.254	0.358
İnsulin (μIU/ml)	8.6 ± 5.2	6.0 ± 4.4	7.0 ± 5.3	0.012	0.183
HOMA	1.55 (0.84–3.26)	1.19 (0.46–1.94)	1.25 (0.61–2.06)	0.017	0.216
Uric acid (mg/dl)	4.7 ± 1.3	3.4 ± 0.9	3.6 ± 0.9	<0.001	0.012
T.cholesterol (mg/dl)	215.1 ± 30.7	217.5 ± 38.8	227.1 ± 31.6	0.752	0.164
LDL-C (mg/dl)	136.3 ± 27.7	139.4 ± 33.3	146.8 ± 24.9	0.649	0.164
HDL-C (mg/dl)	51.1 ± 11.8	55.1 ± 12.4	54.3 ± 11.3	0.150	0.334
Triglyceride (mg/dl)	120 (92–169)	106 (83–140)	113 (91–148)	0.190	0.871
Right CCA IMT (mm)	0.73 ± 0.15	0.65 ± 0.13	0.65 ± 0.14	0.024	0.084
Left CCA IMT (mm)	0.75 ± 0.16	0.68 ± 0.16	0.68 ± 0.16	0.048	0.106
Aver. CCA IMT (mm)	0.74 ± 0.15	0.68 ± 0.14	0.67 ± 0.15	0.029	0.086

Data is expressed as mean ± S.D or median (interquartile range). *AI* Adrenal incidentaloma group, *C* Healthy controls, *BC* BMI-matched controls, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *MAP* Mean arterial pressure, *T. cholesterol* Total cholesterol, *LDL-C* Low density lipoprotein cholesterol, *HDL-C* High density lipoprotein cholesterol, *CCA* Common carotid artery, *Aver* Average, and *IMT* Intima media thickness

Table 2 Hormonal evaluation of study participants

	AI (n = 49)	C (n = 34)	BC (n = 18)	*P* (AI versus C)	*P* (AI versus BC)
ACTH (pg/ml)	14.0 ± 5.3	14.7 ± 6.1	16.2 ± 7.8	0.930	0.734
Cortisol (μg/dl)	13.9 ± 5.5	11.9 ± 5.0	10.8 ± 3.7	0.113	0.043
DHEAS (μg/dl)	63.6 (42.4–108.0)	78.7 (57.8–126.5)	113.5 (61.1–144.2)	0.091	0.025
Post DST cortisol (μg/dl)	1.21 ± 0.33	1.05 ± 0.12	1.03 ± 0.11	0.011	0.012

Data is expressed as mean ± S.D or median (interquartile range). *ACTH* Adrenocorticotrophic hormone, *DHEAS* Dehydroepiandrostenadione sulfate, *DST* Dexamethasone suppression test, *AI* Adrenal incidentaloma group, *C* Healthy controls, *BC* BMI-matched controls

Parameters of hormonal evaluation are demonstrated in Table 2. Plasma ACTH levels were similar in groups. DHEAS levels were reduced in AI versus C ($P = 0.092$) and AI versus BC ($P = 0.025$), while post DST cortisol was significantly elevated in AI when compared with C ($P = 0.011$) and BC ($P = 0.012$). Urinary cortisol was 39.8 ± 29.9 μg/day in AI group.

Metabolic characteristics of patients and healthy controls are shown in Table 1. Fasting plasma glucose and lipid values were similar in groups. When compared with C group HOMA levels were elevated in AI group ($P = 0.017$). Serum uric acid levels were also higher ($P < 0.001$). When patients were compared with BC it was demonstrated that uric acid levels remained significantly elevated while HOMA levels were comparable.

Left, right, and average IMT of CCA were significantly elevated in AI group when compared with C (average IMT: 0.74 ± 0.15 mm vs. 0.68 ± 0.14 mm, $P = 0.029$). Although comparison of AI versus BC revealed increased IMT in AI group, the result was not statistically significant (0.74 ± 0.15 mm vs. 0.67 ± 0.15 mm, $P = 0.086$).

In all participants, average IMT was significantly correlated with age ($r = 0.651$, $P < 0.001$), waist circumference ($r = 0.337$, $P = 0.003$), BMI ($r = 0.269$, $P = 0.020$), morning cortisol ($r = 0.290$, $P = 0.017$), HOMA ($r = 0.241$, $P = 0.036$), and uric acid levels ($r = 0.303$, $P = 0.009$). Morning cortisol was found to be correlated with age ($r = 0.281$, $P = 0.016$), HOMA ($r = 0.309$, $P = 0.008$), uric acid ($r = 0.239$, $P = 0.046$), and average IMT ($r = 0.290$, $P = 0.017$). In linear regression analysis, after adjusting for age, BMI, morning cortisol, waist circumference, MAP, HOMA, and uric acid, age was shown to be the independent variable associated with common carotid artery IMT ($\beta = 0.823$, $P = 0.001$). After adjusting for age, BMI, morning cortisol, MAP, and waist circumference, morning cortisol ($\beta = 0.231$, $P = 0.028$) and waist circumference ($\beta = 0.400$, $P = 0.033$) were the independent variables associated with HOMA levels. When the regression analysis was limited to the AI group, morning cortisol ($\beta = 0.427$, $P = 0.001$) and BMI ($\beta = 0.460$, $P = 0.019$) were the independent factors related with HOMA.

Discussion

In this study, we showed that subjects with non-functioning AI featured increased carotid artery IMT when compared with healthy controls. We also showed that AI group had higher but not statistically significant IMT when compared with BMI-matched healthy individuals. Morning cortisol was related with IMT. However, age was the only independent factor.

It has been demonstrated that adrenal adenomas are associated with a variety of metabolic problems related with the degree of cortisol excess. In studies evaluating patients with sCS several anthropometric and metabolic disturbances have been demonstrated [4, 5, 7, 8]. Furthermore, improvements were achieved after the removal of the adenoma [13]. However, most of the adrenal adenomas are non-functioning and the data in terms of metabolic problems or cardiovascular risk in this particular group are limited. In a previous study, Terzolo et al. demonstrated similar blood pressure, glucose, and insulin levels but preserved insulin sensitivity index in non-functioning AI when compared with sCS [7]. In two recent reports Ermetici et al. [1, 2] demonstrated elevated levels of several adipocytokines and impairment of cardiac morphology when compared with BMI-matched controls. However, both studies had some limitations such as the demonstration of some alterations in hypothalamic–pituitary–adrenal (HPA) axis [2] or the inclusion of patients with diabetes [1]. In addition to the scanty data of cardiovascular risk factors, cortisol secretion dynamics are also inexplicit in non-functioning AI. A previous study by Midorikawa et al. [10] demonstrated that the levels of in vitro steroid production in hormonally inactive adrenocortical tumors are not overtly different from those of sCS and/or overt Cushing syndrome suggesting cortisol autonomy in even clinically and hormonally silent adrenal tumors. In our study, significantly elevated post-DST cortisol levels and decreased DHEAS levels in AI group might be associated with subtle autonomy in non-functioning AI. However, further investigations with dynamic tests should be applied for more accurate estimations.

There is considerable literature on stress as a potential cause of cardiovascular disease through HPA axis activation and neuroendocrine mediators such as cortisol [14]. Caerphilly study demonstrated that cortisol:testosterone ratio was found to be associated with incident ischemic heart disease [15]. Several studies suggested that plasma cortisol levels correlate with the degree of coronary artery disease [16, 17]. On the other hand, various studies have found that morning cortisol levels were associated with metabolic syndrome components [18, 19]. Glucocorticoids cause insulin resistance by affecting multiple systems. They increase turnover between stored energy and freely available fuel for mitochondrial oxidation [20]. They both impair insulin-dependent glucose uptake in the periphery and also enhance gluconeogenesis in the liver [21]. Furthermore, they may increase vagal stimulation of insulin secretion with their central action [22]. It has been shown that positive association was present between skeletal muscle myoblast expression of glucocorticoid receptor and levels of insulin resistance, BMI, percent body fat and blood pressure [23]. Elevated concentrations of cortisol and increased tissue sensitivity to glucocorticoids are likely to increase glucocorticoid hormone action and metabolic syndrome risk. In this study, we showed that morning cortisol levels were elevated and independently associated with HOMA levels in subjects with AI. These data suggest that subtle cortisol autonomy in non-functioning AI is responsible for metabolic disturbances.

Carotid IMT has been extensively used to estimate cardiovascular events in both healthy individuals and also in subjects with risk factors. The early increase in IMT reflects the ongoing adaptive/maladaptive process to elevated intravascular shear stress [24]. Several anthropometric and metabolic findings such as age, elevated blood pressure, central obesity, hyperlipidemia, and insulin resistance have been shown as independent determinants of IMT in different populations [25–27]. There is no study evaluating carotid artery IMT in non-functioning AI and there is only one study in subjects with sCS [5]. Tauchmanova et al. demonstrated that IMT of common carotid artery was increased in subjects with sCS and associated with several anthropometric and metabolic variables but not with HPA axis parameters. In non-functioning AI group, we demonstrated a significant increase of carotid artery IMT when compared with BMI-unmatched subjects and an insignificant increase when compared with BMI-matched controls. Although IMT values are quite similar in both control groups, probably the small number of subjects in BMI-matched group has led to insignificant results. Direct cardiovascular effects of cortisol excess have not been clearly established. It has been shown that exogenous glucocorticoids are associated with impaired cholinergic vasodilatation via disturbances in endothelial nitric oxide system [28]. However, it must be noted that studies in animals have shown the atheroprotective effects of medium-term glucocorticoid receptor agonist therapy in mice [29] and rabbits [30]. The data regarding cardiovascular risk in both Cushing Syndrome and sCS emphasized the role of metabolic disturbances [5, 31, 32]. In our study, there was a linear correlation between morning cortisol and IMT values and furthermore IMT values were also increased in AI group when compared to BMI-matched controls. However, we did not demonstrate any of the HPA axis parameters as an independent factor for IMT values. Only age was shown as an independent determinant of IMT levels consistent with the current literature. We suggest that increased level of carotid artery IMT among subjects with non-functioning AI is a consequence of insulin resistant state and metabolic syndrome rather than a direct effect of cortisol. More evidence is needed to speculate about a primary effect of cortisol on endothelial system.

Conclusion

We showed that non-functioning AI was associated with increased risk for cardiovascular events by means of metabolic disturbances and increased carotid artery IMT. The higher trend of IMT when compared with even BMI-matched subjects and the linear correlation between morning cortisol and IMT may be associated with the direct effect of HPA axis alterations on vasculature beyond metabolic disturbances. We suggest that increased carotid artery IMT was a consequence of insulin-resistant state associated with subtle cortisol autonomy of non-functioning AI rather than a direct effect of cortisol secretion.

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