

ORIGINAL ARTICLE

Could a nonfunctional adrenal incidentaloma be a risk factor for increased carotid intima-media thickness and metabolic syndrome



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KEYWORDS

Adrenal incidentaloma;
Insulin resistance;
Carotid intima media thickness

Abstract

Background: This study was designed to detect the potential association of a nonfunctional adrenal incidentaloma (NFAI) with insulin resistance and associated metabolic disturbances, with a subsequent increase in cardiovascular risk factors.

Methods: Eighty-three NFAI patients and 56 volunteers (controls) without any adrenal abnormalities on computed tomography (CT) were included. Fasting blood glucose (FBG), fasting insulin, lipid profiles, uric acid, homocysteine, fibrinogen, high sensitivity C-reactive protein (hs-CRP), and adiponectin levels were measured in both groups. Blood pressure (BP), waist circumference, body mass index (BMI), and carotid intima media thickness (CIMT) were evaluated in both the patients and volunteers.

Results: There were no significant difference between the NFAI and control groups with respect to age, sex, BMI, waist circumference, systolic and diastolic BP, smoking, concomitant disease, and medications. Fasting insulin and glucose levels and homeostasis model of assessment-insulin resistance (HOMA-IR) scores were significantly higher in the NFAI group as compared with those in the control group ($p < 0.01$). The frequency of metabolic syndrome in the NFAI group was higher than that in the control group ($p < 0.01$). All the lipid fractions, except triglyceride (TG), ($p < 0.05$), homocysteine ($p = 0.01$), and fibrinogen levels ($p < 0.001$), were significantly higher in the NFAI group as compared with the levels in the control group. There were no significant differences between the NFAI and control groups in terms of uric acid, hs-CRP, and adiponectin levels. The CIMT values in the NFAI group were significantly higher than those in the control group (0.74 ± 0.14 vs. 0.53 ± 0.09 , $p < 0.001$). The mean CIMT value showed a statistically positive correlation with age ($r = 0.245$, $p = 0.004$); the HOMA-IR score ($r = 0.490$, $p < 0.001$); and FBG ($r = 0.521$, $p < 0.001$), fasting insulin ($r = 0.432$, $p < 0.001$), total cholesterol (TC) ($r = 0.267$, $p = 0.002$), and fibrinogen ($r = 0.398$, $p < 0.001$) levels in the NFAI group.

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Conclusions: The results indicated that the NFAI patients had an elevated risk of insulin resistance, with metabolic syndrome and increased CIMT values. Long-term follow-up studies should be designed to evaluate postsurgical alterations in metabolic parameters and cardiovascular risk factors in NFAI patients.

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PALABRAS CLAVE

Incidentaloma suprarrenal;
Resistencia a la insulina;
Grosor de la íntima-media carotídea

¿Puede ser un incidentaloma suprarrenal no funcional un factor de riesgo de aumento del grosor íntima-media carotídeo y de síndrome metabólico?

Resumen

Antecedentes: Este estudio se diseñó para detectar la posible asociación del incidentaloma suprarrenal no funcionante (ISNF) con resistencia a la insulina y trastornos metabólicos asociados, con un incremento subsecuente en los factores de riesgo cardiovascular.

Métodos: Se incluyó a 83 pacientes con ISNF y a 56 voluntarios (controles) sin anomalías suprarrenales en la tomografía computarizada (TC). Se determinaron en ambos grupos los valores de glucemia en ayunas (GA), insulina en ayunas, perfiles lipídicos, ácido úrico, homocisteína, fibrinógeno, proteína C reactiva de alta sensibilidad (PCRas) y adiponectina. Se evaluaron la presión arterial (PA), el perímetro de la cintura, el índice de masa corporal (IMC) y el grosor íntima-media carotídea (GIMC) tanto en los pacientes como en los voluntarios.

Resultados: No había una diferencia significativa entre los grupos con ISNF y de control en cuanto a edad, sexo, IMC, perímetro de la cintura, PA sistólica y diastólica, tabaquismo, enfermedades concomitantes y medicamentos. Las concentraciones de insulina y glucosa en ayunas y las puntuaciones del modelo homeostático de evaluación de la resistencia a la insulina (HOMA-IR) fueron significativamente mayores en el grupo con ISNF que en el de control ($p < 0,01$). La frecuencia de síndrome metabólico fue mayor en el grupo con ISNF que en el de control ($p < 0,01$). Los valores de todas las fracciones lipídicas, excepto los de triglicéridos (TG) ($p < 0,05$), homocisteína ($p = 0,01$) y fibrinógeno ($p < 0,001$), fueron significativamente mayores en el grupo con ISNF que en el de control. No hubo diferencias significativas entre los grupos con ISNF y de control en las concentraciones de ácido úrico, PCRas y adiponectina. Los valores del GIMC en el grupo con ISNF fueron significativamente mayores que los del grupo de control ($0,74 \pm 0,14$ frente a $0,53 \pm 0,09$; $p < 0,001$). El valor medio del GIMC mostró una correlación estadísticamente positiva con la edad ($r = 0,245$; $p = 0,004$); la puntuación del HOMA-IR ($r = 0,490$; $p < 0,001$), y la GA ($r = 0,521$; $p < 0,001$), la insulina en ayunas ($r = 0,432$; $p < 0,001$), el colesterol total (CT) ($r = 0,267$; $p = 0,002$) y el fibrinógeno ($r = 0,398$; $p < 0,001$) en el grupo con ISNF.

Conclusión: Los resultados indicaban que los pacientes con ISNF tenían un riesgo elevado de resistencia a la insulina, con síndrome metabólico y aumento de los valores del GIMC. Deben diseñarse estudios de seguimiento a largo plazo para evaluar los cambios posquirúrgicos de los parámetros metabólicos y los factores de riesgo cardiovascular en pacientes con ISNF.

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1. Introduction

An adrenal incidentaloma (AI) refers to a mass detected incidentally on radiological imaging performed for reasons other than adrenal pathology. The European Society of Endocrinology clinical practice guideline recommends that all patients with AIs should be tested for cortisol excess using the overnight 1 mg dexamethasone suppression test, hyperaldosteronism in the presence of hypertension or unexplained hypokalemia, and the presence of a pheochromocytoma.¹ Previous data showed that among incidentalomas, the frequency of nonfunctioning adenomas, subclinical Cushing's syndrome (CS), pheochromocytomas, aldosteronomas, and

adrenocortical carcinomas were 80%, 5%, 5%, 1%, and <5%, respectively.²

Previous research suggested that the presence of an AI was related to metabolic syndrome and that hyperinsulinemia was a predisposing factor in adrenal tumorigenesis.³ On the other hand, a number of studies reported that a nonfunctional adrenal incidentaloma (NFAI) may cause hypertension, insulin resistance, obesity, and hyperlipidemia, with a subsequent increase in cardiovascular risk.^{4,5}

This study was designed to detect the potential association of NFAIs with insulin resistance, with associated metabolic disturbances and cardiovascular risk factors.

2. Subjects and methods

Eighty-three patients with NFAs and 56 individuals (control group) without any adrenal lesions were included in this study. The control group consisted of volunteers who underwent abdominal computed tomography (CT) for an indication other than adrenal pathology and were found to have normal adrenals. All the volunteers were free of any diseases that could affect metabolic parameters. The exclusion criteria were patients younger than 18 y; patients with diabetes mellitus or malignancies; and patients with a history of myocardial infarctions and/or heart failure, strokes or peripheral vascular disease, acute or chronic inflammatory diseases, and suspected or known psychiatric disorders. Patients who were pregnant or who used glucocorticoids were also excluded.

The adrenocorticotrophic hormone (ACTH) and plasma cortisol levels of the patients with AIs were tested in the morning (08:00 h). The patients' aldosterone and plasma renin activity in a standing position were tested, in addition to their creatinine, dopamine, vanillylmandelic acid, metanephrine, and normetanephrine levels in 24-h urine and dehydroepiandrosterone sulfate levels in serum. The overnight low-dose dexamethasone suppression test (1 mg, orally at 23:00 h, with measurement of fasting serum cortisol at 08:00 h the following morning) was performed to detect adrenal hyperfunctioning. Suppression was accepted as adequate if the morning cortisol levels were lower than 1.8 $\mu\text{g}/\text{dL}$. The 24-h urinary free cortisol (24-h UFC) level was also measured to exclude subclinical Cushing's syndrome (CS). Patients with post-dexamethasone suppression test (PDST) cortisol levels of $<1.8 \mu\text{g}/\text{dL}$, normal 24-h UFC findings [reference range (RR): 38–208 nmol/day], and ACTH levels $\geq 10 \text{ pg}/\text{ml}$ were included. Only biochemically proven nonfunctional tumors were included.

All the participants were screened for diabetes using glycated hemoglobin (HbA1c) and fasting blood glucose (FBG) tests. Patients with FBG $\geq 126 \text{ mg}/\text{dL}$ (7.0 mmol/L) and HbA1c $\geq 6.5\%$ were excluded. To exclude diabetes in patients with impaired fasting glycemia (100–125 mg/dL), the oral glucose tolerance test was performed. Twenty-one patients with impaired fasting glycemia or glucose tolerance were included after exclusion of diabetes using both, the HbA1c test and oral glucose tolerance test.

Ethical approval was obtained from the local ethics committee of Ankara University Faculty of Medicine, Ankara (06-176-12, March 2012).

The indications for CT imaging in the AI patients and controls included the evaluation of ureteral and renal stones; an incidentally found adrenal mass in chest CT during follow-up for pulmonary nodules (included when the nodule was stable and considered benign); differential diagnosis of a focal hepatic mass found on ultrasound (included if the lesion was considered as a hemangioma or focal spared area in a fatty liver); follow-up for a pancreatic pseudocyst; undifferentiated abdominal pain (usually performed for differential diagnosis of irritable bowel syndrome from structural causes); and adrenal lesions incidentally found on abdominal ultrasound in patients with abdominal pain (included when no vascular, malignant, infectious, or inflammatory etiology was

found and the pain was not attributable to an adrenal mass).

Medical histories were obtained, and physical examinations were performed by physicians who were specifically trained in endocrinology and metabolism diseases. Arterial hypertension was diagnosed in patients with systolic blood pressure (BP) $\geq 140 \text{ mmHg}$ and/or diastolic BP $\geq 90 \text{ mmHg}$ and in patients receiving antihypertensive therapy.⁶ The patient's waist circumference was measured using a flexible tape placed on a horizontal plane at the level of the iliac crest.⁷ The body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters. Metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III.⁸ Systolic and diastolic BPs were measured twice in the sitting position, with an interval of 15 min using standard sphygmomanometers of appropriate sized adult cuffs, following a rest period for 30 min.

Blood samples were centrifuged for 15 min at 3000 cycle/min, and the plasma on the top was extracted. The extracted plasma samples were preserved in Eppendorf tubes (volume: 1.5 ml) and kept frozen at -80°C . FBG, fasting insulin, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), uric acid, homocysteine, fibrinogen, C-reactive protein (CRP), and adiponectin levels were evaluated.

The FBG level was measured with the aid of a Roche P800 device using an enzymatic method (RR: 74–100 mg/dL.) Fasting insulin levels were measured with the Roche E170 electrochemiluminescence immunoassay (ECLIA) (RR: 74–16 $\mu\text{IU}/\text{ml}$). The levels of TC, LDL, HDL, and TG were measured with Roche P800 using the photometric method. A cholesterol level of $<200 \text{ mg}/\text{dL}$ was defined as normal whereas levels of 200–239 mg/dL and $>240 \text{ mg}/\text{dL}$ were considered borderline high and high, respectively. For LDL, a reference value of $<100 \text{ mg}/\text{dL}$ was defined as optimal, whereas values of 100–129 mg/dL, 130–159 mg/dL, 160–189 mg/dL, and $>190 \text{ mg}/\text{dL}$ were considered acceptable, borderline high, high, and very high, respectively. For HDL and TG, the reference values were defined as 40–60 mg/dL and $<150 \text{ mg}/\text{dL}$, respectively. High sensitive CRP levels are measured using the photometric method (RR: 0–3 mg/L). Fibrinogen levels were measured using an Amax 190 (Trinity, USA) device using the coagulometric method (RR: 2.38–4.98 g/Dl). Homocysteine levels were measured with the aid of an Immulite 2 (Siemens, Germany) device using the Clia method (RR: 5–14 $\mu\text{mol}/\text{L}$). Adiponectin levels were measured with the aid of an RIA device using an enzyme-linked immunoassay (Biovendor, Czech Republic), and the lower reference value was established as 9 $\mu\text{g}/\text{dL}$.

In both groups, homeostasis model of assessment-insulin resistance (HOMA-IR) scores were calculated using the formula (FBG [mg/dL] \times fasting insulin [mIU/ml])/405.⁹

The carotid intima media thickness (CIMT) values of the patients and volunteers were determined by the same investigator using an ultrasonography device with a 7.5-MHz linear probe. In the first 2 cm distal to the carotid bulb, three measurements of a 1-cm segment were obtained. The measurements were obtained where the CIMT was greatest and mean of the values were accepted as the CIMT.

2.1. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM Corp., NY, USA). Categorical data were compared using a chi-square test and Fisher's exact test. Group data with a normal distribution were compared using the Student's *t* test or an analysis of variance, and nonparametric data were compared using the Mann–Whitney *U* test or Kruskal–Wallis test. Values were expressed as mean \pm standard deviation or median as appropriate. Spearman's correlation test was performed for continuous variables without a normal distribution, and Pearson's correlation test was performed for variables with a normal distribution. Independent linear factors were determined using linear regression, with backwards elimination. For results, a *p* value of <0.05 was considered statistically significant.

3. Results

Eighty-three NFAl patients (26 males [31.3%] and 57 females [68.7%]) and 56 volunteers (24 males [42.9%] and 32 females [57.1%]) were enrolled.

As shown in Table 1, there were no differences between the NFAl and control groups with respect to age, sex, BMI, waist circumference, systolic and diastolic BP, smoking history, presence of hypertension, and dyslipidemia.

Fasting insulin levels, FBG, HbA1C, and HOMA-IR scores were significantly higher in the NFAl group as compared with those in the control group ($p < 0.001$). The FBG level was not associated with fasting morning (08:00 h) ACTH and cortisol levels. The TC ($p = 0.009$), LDL-C ($p = 0.03$), HDL-C ($p < 0.001$), homocysteine ($p = 0.01$), and fibrinogen levels ($p < 0.001$) were all higher in the NFAl group as compared with those in the control group. The prevalence of metabolic syndrome was increased in the NFAl group ($p = 0.04$). There were no significant between-group differences in the LDL-C/HDL-C and TC/HDL-C ratios or the TG, uric acid, CRP, and adiponectin levels (Table 2). Eighteen of the 21 (85%) patients with impaired fasting glucose or glucose tolerance were in the NFAl group ($p < 0.01$).

The median size of the adenomas (maximal diameter) was 20 mm (12–50 mm). The maximal diameter of the adenoma was not associated with FBG, insulin, HOMA-IR scores, lipid profiles, adiponectin, CRP, fibrinogen, homocysteine, ACTH, basal cortisol, PDST cortisol levels, BMI, waist circumference, or CIMT values.

The median PDST cortisol level in the NFAl group was 0.9 $\mu\text{g/dL}$ (0.45–1.47 $\mu\text{g/dL}$). There was a positive correlation between the PDST cortisol level and FBG ($r = 0.69$, $p < 0.001$). However, fasting insulin levels, HOMA-IR scores, lipid profiles, adiponectin, CRP, fibrinogen, homocysteine, BMI, waist circumference, and CIMT values were not associated with morning cortisol, ACTH, or PDST cortisol levels.

Table 1 Demographic and clinical characteristics of NFAl and control groups.

	NFAl (<i>n</i> = 83)	Controls (<i>n</i> = 56)	<i>p</i>
Age (years)	55.16 \pm 8.73	53.19 \pm 10.37	NS
Male/female	26/57	24/32	NS
Body mass index (kg/m ²)	30.20 \pm 4.97	28.89 \pm 4.59	NS
Waist circumference (cm)	101.15 \pm 12.04	98.37 \pm 10.59	NS
Systolic blood pressure (mmHg)	122.23 \pm 15.68	126.25 \pm 11.41	NS
Diastolic blood pressure (mmHg)	76.33 \pm 10.27	75.18 \pm 12.24	NS
Hypertension			
Present, <i>n</i> (%)	39 (47.0%)	18 (32.1%)	NS
Absent, <i>n</i> (%)	44 (53.0%)	38 (67.9%)	
Dyslipidemia			
Present, <i>n</i> (%)	44 (53.0%)	38 (67.9%)	NS
Absent, <i>n</i> (%)	39 (47.0%)	18 (32.1%)	
Metabolic syndrome^a			
Present, <i>n</i> (%)	33 (39.8%)	13 (23.2%)	0.04
Absent, <i>n</i> (%)	50 (60.2%)	43 (66.8%)	
Smoking status			
Smoker (ex/current), <i>n</i> (%)	34 (41.0%)	17 (30.4%)	NS
Non-smoker, <i>n</i> (%)	49 (59.0%)	39 (69.6%)	
BMI groups			
18–24.9 kg/m ²	10 (12.0%)	6 (10.7%)	NS
25–29 kg/m ²	33 (39.8%)	31 (55.4%)	
≥ 30 kg/m ²	40 (48.2%)	19 (33.9%)	

NS: not significant.

^a Metabolic syndrome was defined according to The "National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)" criteria (8).

Table 2 Biochemical data of NFAI and control group.

	NFAI	Controls	<i>p</i>
Fasting blood glucose (mg/dL)	93.14 ± 10.12	77.00 ± 9.57	<0.001
Fasting insulin (μIU/ml)	13.58 ± 6.82	7.61 ± 4.83	<0.001
HOMA-IR score	3.02 ± 1.57	1.37 ± 0.99	<0.001
HbA1c (%)	5.42 ± 0.36	5.19 ± 0.25	<0.001
Total cholesterol (mg/dL)	204.34 ± 47.12	184.71 ± 45.12	0.009
LDL (mg/dL)	128.13 ± 34.79	115.03 ± 34.57	0.03
HDL (mg/dL)	49.07 ± 12.31	41.38 ± 11.39	<0.001
LDL-C/HDL-C ratio	2.71 ± 0.81	2.88 ± 0.88	NS
Total/HDL-C ratio	4.31 ± 1.1	4.63 ± 1.2	NS
Triglyceride (mg/dL)	147.73 ± 77.07	137.33 ± 78.72	NS
Homocysteine (μmol/L)	15.72 ± 27.74	10.97 ± 5.13	0.01
Fibrinogen (g/L)	3.67 ± 0.80	3.09 ± 0.68	<0.001
Uric acid (mg/dL)	5.02 ± 1.25	4.67 ± 1.34	NS
C-reactive protein (mg/L)	5.86 ± 9.43	4.56 ± 5.75	NS
Adiponectin (μg/dL)	27.07 ± 11.54	24.14 ± 11.40	NS

Data were expressed as mean ± SD.

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL: low density lipoprotein; HDL: high density lipoprotein.

The mean 24-h UFC level was 77.9 ± 20.6 nmol/day. The 24-h UFC level was not associated with FBG, insulin, HOMA-IR scores, lipid profiles, adiponectin, CRP, fibrinogen, homocysteine, BMI, waist circumference, or CIMT values.

The HOMA-IR scores showed a positive correlation with the CIMT value ($r=0.533$, $p<0.001$) and FBG ($r=0.582$, $p<0.001$), fasting insulin ($r=0.975$, $p<0.001$), TG ($r=0.225$, $p=0.008$), fibrinogen ($r=0.282$, $p=0.001$), and uric acid ($r=0.209$, $p=0.013$) levels.

The CIMT in the NFAI group was significantly higher than that in the control group (0.74 ± 0.14 vs. 0.53 ± 0.09 , $p<0.001$) (Table 3 and Fig. 1).

In the NFAI group, the CIMT showed a statistically positive correlation with age ($r=0.245$, $p=0.004$), FBG levels ($r=0.521$, $p<0.001$), fasting insulin levels ($r=0.432$, $p<0.001$), HOMA-IR scores ($r=0.490$, $p<0.001$), TC levels ($r=0.267$, $p=0.002$), and fibrinogen ($r=0.398$, $p<0.001$) levels. Cortisol, ACTH, 24-h UFC, and PDST cortisol levels were not associated with the CIMT values. When age, sex, BMI, smoking behaviors, waist circumference, LDL-C, uric acid, adiponectin, CRP, homocysteine, fibrinogen levels, and HOMA-IR variables were evaluated using the linear regression method with backwards elimination, age ($\beta=0.004$ [0.001–0.06]), HOMA-IR scores ($\beta=0.037$ [0.22–0.52]), and fibrinogen ($\beta=0.052$ [0.020–0.83]) levels were independent risk factors for CIMT.

In the control group, age ($r=0.23$, $p=0.01$), TC ($r=0.26$, $p=0.002$), and LDL-C ($r=0.21$, $p=0.01$) levels were positively correlated with the CIMT.

4. Discussion

In the present study, we observed that fasting insulin levels, FBG levels, HOMA-IR scores, and the frequency of metabolic syndrome were significantly higher in NFAI patients when compared with age-, sex-, and BMI-matched controls. In addition, TC, LDL-C, and HDL-C levels were elevated in the

NFAI group as compared with that in the control group. There were no significant between-group differences in TG levels.

Previous studies reported the presence of insulin resistance in patients with NFAs.^{4,10,11} In one study, the area under the curve for glucose after an oral glucose tolerance test was significantly higher in patients with CS and NFAs as compared with that of a control group.¹² Their data indicated that NFAs may represent an intermediate state between normal and pathological and that they may be caused by subtle cortisol hypersecretion.¹² Consistent with previous data, insulin resistance was associated with the PDST cortisol level in the AI patients in the study of Papanastasiou et al.¹³ Another study also reported insulin resistance in patients with NFAs, even when PDST cortisol levels were lower than $1.8 \mu\text{g/dL}$.¹⁴ A significant improvement in plasma glucose and systolic BP levels after an adrenalectomy was reported in NFAI patients and patients with subclinical CS (SCS).¹⁰

Although debate surrounds the screening and diagnosis of SCS,^{15–19} the overnight 1 mg PDST is widely recommended as the first-line screening test.^{15–19} A second confirmatory test, including late night salivary cortisol, 24-h UFC, or late night serum cortisol, was recommended in a number of guidelines.^{17,19} As a strength of our study, we evaluated morning ACTH levels, PDST cortisol levels, and 24-h UFC levels to exclude SCS in the NFAI group. The FBG level was positively correlated with the PDST cortisol level, but no cortisol secretion-related parameters were associated with fasting insulin levels or HOMA-IR scores. However, we did not assess the adrenal function in the control group. Thus, a subtle difference in cortisol metabolism between-groups may have been overlooked.

In the present study, fibrinogen and homocysteine levels were elevated in the NFAI group as compared with those in the control group, and HOMA-IR showed a positive association with fibrinogen levels. This data may support the presence of a proinflammatory state in NFAI patients, which may be associated with insulin resistance. Our results

Table 3 Carotid intima media thicknesses in NFAI and control groups.

	Adrenal incidentaloma	Control	<i>p</i>
CIMT right (mm)	0.74 ± 0.15	0.52 ± 0.10	<0.001
CIMT left (mm)	0.75 ± 0.14	0.53 ± 0.06	<0.001
CIMT mean (mm)	0.74 ± 0.14	0.53 ± 0.09	<0.001

CIMT: carotid intima media thicknesses.

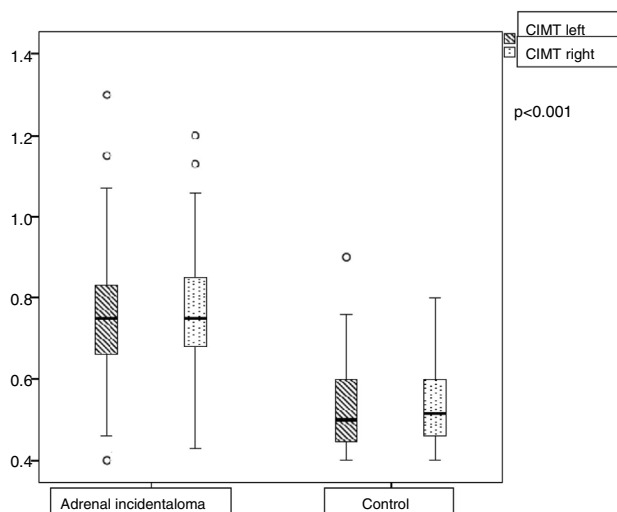


Figure 1 Comparison of carotid intima media thickness (CIMT) in the nonfunctional adrenal incidentaloma (NFAI) group and the control group.

suggest that subtle cortisol secretion may not be the only factor responsible for insulin resistance in NFAI patients.

It is well known that high levels of LDL-C are atherogenic, whereas high HDL-C levels are cardioprotective.^{20,21} Previous studies suggested that high LDL-C/HDL-C and TC/HDL ratios were predictors of increased cardiovascular risk.^{22,23} Some studies reported controversial results regarding the levels of lipid fractions in NFAIs.^{24–26} In our study, TC, LDL-C, and HDL-C levels were all significantly increased in the NFAI group as compared to controls. On the other hand, the LDL-C/HDL-C and TC/HDL ratios of the two groups were not different. The CIMT showed a statistically positive correlation with TC levels.

An important finding of our study was the higher CIMT values in the NFAI group as compared with those in the control group. A limited number of previous studies evaluated CIMT, which is an indicator of premature atherosclerosis, in NFAI patients.^{24,26–29} In one study, epicardial fat thickness, the left ventricular mass index, and CIMT were significantly higher in NFAI patients when compared with those in controls.²⁶ The authors suggested that subclinical inflammation, insulin resistance, and altered cytokine levels in these patients may represent possible mechanisms of increased cardiovascular risk in this population. In another study, the frequency of hypertension in NFAI patients was higher than that in controls, and CIMT was increased among NFAI patients as compared with that in controls.²⁷ In other research, CIMT was not significantly different between NFAI and BMI-matched controls.²⁹ In the same study, CIMT was correlated

with age, BMI, HOMA-IR scores, waist circumference, morning cortisol, and uric acid levels in all the participants. Consistent with previous data, our results showed that NFAIs were associated with insulin resistance, which may give rise to an increase in cardiovascular risk. We found no relationship between CIMT, PDST cortisol, 24-h UFC, and ACTH levels. However, as mentioned already, the possibility of a subtle difference between the two groups in cortisol secretion status cannot be ruled out.

In the present study, the plasma fibrinogen level was significantly higher in the NFAI group as compared with that in the controls, and it was an independent risk factor for increased CIMT. A previous study showed that elevated fibrinogen levels were associated with an increased risk of thromboembolic events and cardiovascular diseases in overt CS patients due to increased cortisol secretion.³⁰ Consequently, fibrinogen levels of NFAI patients may serve as an indicator of cardiovascular risk.

Previous studies reported decreased plasma adiponectin levels in clinical situations related to insulin resistance.^{31,32} Increased levels of adiponectin were reported in AI patients, independent of visceral obesity.³³ However, in another study, adiponectin levels of female CS patients and controls were not significantly different.¹⁹ In our study, there were no differences in the levels of adiponectin in the NFAI patients and controls and no relationship between the CIMT and adiponectin levels.

A major limitation of our study was the absence of data about fat distribution, although the BMI and waist circumference were comparable in the two groups. In addition, we did not assess adrenal functions in the control group. Thus, a subtle difference in cortisol metabolism between the groups may have been overlooked.

In summary, we demonstrated that patients with NFAIs had an increased risk of insulin resistance and metabolic syndrome, in addition to elevated CIMT values. Patients with NFAIs merit closer follow-up in terms of insulin resistance and cardiovascular risks. When evaluating surgical indications for patients with NFAIs, the presence of metabolic syndrome, lipid profiles, glucose levels, fibrinogen levels, and CIMT may be used as indicators of the risk of cardiovascular diseases. Long-term follow-up studies should be designed to evaluate postsurgical alterations in metabolic parameters and cardiovascular risk factors in NFAI patients.

5. Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

6. Funding

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7. Conflict of interest

There is no conflict of interest for each author and there is no source of any support for the study.

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