ACADEMIC JOURNAL OF HEALTH

ORIGINAL ARTICLE

Frequency of Metabolic Syndrome in Adrenal Incidentalomas

ABSTRACT

Objectives: Adrenal incidentalomas (AI) are adrenal tumors discovered incidentally during imaging. While the metabolic effects of high cortisol levels are well-documented, the association between AI and metabolic syndrome (MetS) remains underexplored. This study investigates the frequency of MetS in patients with AI and compares it to a healthy control group.

Methods: This cross-sectional, single-center study was conducted from January 2018 to January 2019 and involved 50 patients with AI and 50 age- and sex-matched healthy controls. We compared waist circumference, blood pressure, fasting plasma glucose (FPG), and MetS prevalence between groups.

Results: Patients with AI had significantly higher waist circumference (p=0.001), FPG levels (p=0.007), and both systolic (SBP) and diastolic (DBP) blood pressure values (p=0.001; p=0.006, respectively) compared to controls. Similarly, patients with non-functioning adrenal adenomas (NFA) also exhibited increased waist circumference (p=0.002), FPG levels (p=0.005), SBP (p=0.001), and DBP (p=0.017) compared to the control group. The frequency of MetS was significantly higher in both the AI (p=0.039) and NFA (p=0.023) groups compared to controls.

Conclusion: Our study found a higher prevalence of MetS among patients with AI and NFA, as well as increased waist circumference, FPG levels, and blood pressure in these groups. These findings suggest that patients with AI should be regularly screened for MetS and cardiovascular diseases to manage and reduce long-term health risks.

Keywords: Adrenal incidentalomas, cardiovascular diseases, metabolic syndrome

Adrenal incidentalomas (AI) are adrenal masses identified incidentally during imaging studies performed for reasons unrelated to adrenal pathology (1). While most AI are benign and non-functional, their discovery raises questions about their potential health impacts, particularly regarding metabolic health.

Metabolic syndrome (MetS) is a multifaceted health condition marked by a group of interrelated risk factors, such as abdominal obesity, elevated fasting plasma glucose (FPG), hypertension, and dyslipidemia. Collectively, these factors greatly enhance the likelihood of developing type 2 diabetes mellitus (DM) and cardiovascular disease (CVD) (2). MetS is linked to several chronic conditions and represents a significant public health challenge.

Hypercortisolism, either due to endogenous conditions like Cushing's syndrome or exogenous sources, is known to contribute to insulin resistance, obesity, hypertension, impaired glucose tolerance, and dyslipidemia (3,4). Recent research indicates that even mild, subclinical elevations in cortisol levels—such as those seen in non-functioning adrenal adenomas (NFA)—can be associated with metabolic disturbances not detected by standard diagnostic tests or resulting from intermittent hormone secretion (5,6).

Given these potential metabolic effects, it is important to investigate whether AI is linked to an increased prevalence of MetS compared to healthy individuals. Our study aims to evaluate the frequency of MetS among patients with AI and compare it to a control group of healthy volunteers. Through this evaluation, we seek to underscore the need for regular MetS and cardiovascular disease screening in patients with AI to manage and mitigate long-term health risks.

METHODS

Between January 2018 and January 2019, 50 patients with AI were admitted to the Endocrinology outpatient clinics, and 50 healthy volunteers were included as a control group.

Ebru Aydoğan[1]

Hüseyin Demirci[2]

Muhammed Erkam Sencar[3]

Sema Hepşen[2]

Erman Çakal[2]

[1]*Department of Occupational Medicine, Hacettepe University Hospitals, Ankara, Türkiye*
[2]*Department of Endocrinology and Metabolism, Ankara Etlik City Hospital, Ankara, Türkiye*
[3]*Department of Endocrinology and Metabolism, Medicana International Ankara Hospital, Ankara, Türkiye*

Corresponding author:
Ebru Aydoğan
✉ ebruu_erd@hotmail.com

Received: June 14, 2024
Revisioned: November 26, 2024
Accepted: November 28, 2024

Cite this article as: Aydoğan E, Demirci H, Sencar ME, Hepşen S, Çakal E. Frequency of metabolic syndrome in adrenal incidentalomas.Acad J Health 2024;2(2):57-60.

DOI: 10.14744/ajh.2024.63825

Informed consent was obtained from all participants, and the study adhered to the Declaration of Helsinki. The study received written approval from the Clinical Research Ethics Committee of the University of Health Sciences.

Patients were included if they had unilateral or bilateral adrenal masses ⩾1 cm and <4 cm in diameter with benign tumor characteristics. Exclusion criteria included: age younger than 18 years, pregnancy, alcoholism, drug abuse, hepatic or renal insufficiency (Child-Pugh score B or C and creatinine clearance <60 mL/min), drug use that could increase blood glucose levels or weight, secondary causes of obesity, severe neuropsychiatric disorders, sepsis or severe illness, proven CVD, and malignancy. The presence of MetS was categorized based on the NCEP/ATP III diagnostic criteria.

Height was recorded using a standard height measurement scale, with no headgear or footwear. Body weight was recorded using a standard scale, with all accessories removed to ensure an accurate reading. Body mass index (BMI) was subsequently calculated. Waist circumference was measured using a non-elastic tape measure. Blood pressure was measured with a sphygmomanometer on the left arm at heart level after the patient had been seated and rested for 10 minutes. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings were taken during this period.

Demographic information (age, gender), presence of comorbidities, and diagnoses of comorbidities (e.g., DM, hypertension (HT)) were recorded. The initial complaint leading to the detection of the adrenal lesion by imaging was also noted.

To assess hormonal activity, plasma cortisol, ACTH, a 1 mg dexamethasone suppression test (DST), 24-hour urine-free cortisol (UFC), plasma aldosterone, renin activity, and 24-hour urine metanephrines were measured. The aldosterone-to-renin ratio was calculated using the formula: plasma aldosterone concentration/renin activity. The results from hormonal screening tests and, if necessary, confirmation tests (pheochromocytoma (Feo), mild autonomous cortisol secretion (MACS), primary hyperaldosteronism (PHA), NFA, Cushing's syndrome (CS)) were recorded. The localization and size of the lesions were determined from CT and MRI reports used for imaging.

Statistical Analysis

The data were imported into Statistical Package for the Social Sciences (SPSS) version 20.0 for analysis. To evaluate the distribution of the data, the Kolmogorov-Smirnov test was conducted. Descriptive statistics were presented as means±standard deviations (SD) for normally distributed quantitative data, medians with interquartile ranges (IQR) for non-normally distributed quantitative data, and frequencies (n) with percentages (%) for categorical data. For comparisons involving parametric data, the Student's t-test was utilized, while the Mann-Whitney U test was used for non-parametric data. The Pearson chi-square and Fisher's exact tests were employed for categorical data analysis, with statistical significance set at $p<0.05$. Relationships between two normally distributed numerical variables were assessed using Pearson's correlation, whereas Spearman's correlation was used for variables not meeting the normality assumption.

RESULTS

The AI and control groups were comparable in terms of age and sex (p=0.633; p=0.310, respectively). The NFA and control groups showed no significant differences in age and sex (p=0.752; p=0.534, respectively). In terms of functionality, 82% (n=41) were NFA, 12% (n=6) were MACS, 4% (n=2) were PHA, and 2% (n=1) were CS. Due to the small sample size of functional adrenal adenomas (n=9), their data were not included in the statistical evaluation in comparison with NFA and the control group. Characteristics of AI and NFA are presented in Table 1 and Table 2.

When comparing AI and NFA patients to controls, although BMI showed no significant difference, waist circumference was notably greater in both the AI and NFA groups (p=0.001; p=0.002, respectively). FPG levels were elevated in the AI and NFA groups compared with controls (p=0.007; p=0.005, respectively). SBP and DBP were significantly elevated in the AI group (p=0.001; p=0.006, respectively). Similarly, SBP and DBP were significantly elevated in the NFA group (p=0.001; p=0.017, respectively).

The prevalence of MetS was 48% (n=24) in the AI group, 52.5% (n=21) in the NFA group, and 28% (n=14) in controls, which was higher in the AI and NFA groups (p=0.039; p=0.023, respectively). LDL-C, TG, and HDL-C levels were similar between the AI and NFA groups compared to the controls. Table 3 summarizes the numerical information regarding the comparison of the NFA groups with the controls in terms of anthropometric measurements, biochemical values, blood pressure measurement results, and MetS frequency. No significant correlation was found between 1 mg DST,

Table 1. Demographic and clinical characteristics of the adrenal incidentaloma group

	AI (n=50)	Control (n=50)	p
Age	53.4±8.9	54.7±8.5	0.633
Gender			0.310
Female	66% (n=33)	56% (n=28)	
Male	34% (n=17)	44% (n=22)	
Functionality			
NFA	82% (n=41)		
MACS	12% (n=6)		
CS	2% (n=1)		
PHA	4% (n=2)		
Settlement			
Unilateral	84% (n=42)		
Bilateral	16% (n=8)		

AI: Adrenal incidentaloma; MACS: mild autonomous cortisol secretion; PHA: primary hyperaldosteronism; NFA: nonfunctional adrenal adenoma; CS: Cushing syndrome.

Table 2. Demographic characteristics of nonfunctional adrenal adenoma group

	NFA (n=41)	Control (n=50)	p
Age	54.1±7.6	54.7±8.5	0.752
Gender			0.534
Female	58% (n=24)	56% (n=28)	
Male	42% (n=17)	44% (n=22)	

NFA: Nonfunctional adrenal adenoma.

Table 3. Comparison of anthropometric measurement, biochemical values, blood pressure measurement results and metabolic syndrome frequency between the nonfunctional adrenal adenoma group and the control group

	NFA (n=41)	Control (n=50)	p
BMI (kg/m^2)	30.8±5.9	29.6±4.5	0.145
Waist circumference (cm)	95.6±14.3	84.8±9.3	0.002*
FPG (mg/dL)	124±66	93.6±22.9	0.005*
LDL-C (mg/dL)	137±33	131±35	0.392
HDL-C (mg/dL)	47±15	47±10	0.289
TG (mg/dL)	161±114	185±102	0.377
SBP (mmHg)	128.8±14.4	116.8±14.4	0.001*
DBP (mmHg)	77.8±10.8	71.9±10.2	0.017*
MetS (n %)	21 (52.5%)	14 (28%)	0.023*

NFA: Nonfunctional adrenal adenoma; BMI: body mass index; FPG: fasting plasma glucose; LDL-C: LDL cholesterol; HDL-C: HDL cholesterol; TG: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure; MetS: metabolic syndrome; *p<0.05.

basal cortisol, UFC, and DHEA-S levels and the results of FPG, LDL-C, HDL-C, TG, BMI, waist circumference, SBP, and DBP measurements in adrenal incidentaloma patients.

DISCUSSION

Considering that the prevalence of AI has increased over the years due to the widespread use of abdominal imaging modalities and that the prevalence of NFA has also increased, it is extremely important to evaluate whether the prevalence of MetS, which increases mortality, has risen in these patients. We showed that the frequency of MetS was increased in AI and NFA patients compared to the controls.

Similar to our study, Peppa et al. (3) found that, in 46 AI patients of similar age and BMI, the frequency of MetS, FPG levels, insulin levels, insulin resistance (IR), SBP, and DBP were increased in all types of AI. Studies on AI patients revealed a higher prevalence of DM and impaired glucose metabolism among them (4,5). Therefore, they recommended that AI patients be tested for glucose tolerance (5). Terzolo et al. (7) also found SBP and DBP to be higher in AI patients.

Ribeiro Cavalari EM et al. (8) found a high prevalence of MetS in NFA patients. In this study, as in ours, waist circumference, FPG levels, SBP, and DBP were higher in NFA patients compared to controls, but no significant difference was observed in plasma lipid levels. In another study, while BMI showed no significant difference, NFA patients had greater waist and hip circumference compared to the controls (9). In a study comparing NFA patients with a control group, a higher prevalence of HT, resistant HT, and more antihypertensive drug use were found in NFA patients (10).

The reason why waist circumference was higher in NFA and AI patients despite having similar BMI to the controls may be due to visceral adipose tissue accumulation resulting from low-grade autonomic cortisol excess. The effects of glucocorticoids (GC) are linked to adipose tissue metabolism, and their effects are more pronounced in visceral adipose tissue. This may be related to the development of MetS, metabolic risk factors, and CVD risk due to increased visceral fat accumulation in AI and NFA patients (11,12). Some large studies have shown that waist circumference, an indicator of visceral adiposity, has a better prognostic value than BMI, an indicator of general adiposity, in predicting CVD risk (13,14). Therefore, increased waist circumference alone may be considered a CVD risk factor in patients with AI and NFA.

Peppa et al. (2) also observed significant improvement in cardiometabolic risk factors after adrenalectomy in patients with AI and NFA. In another study, the NFA group exhibited elevated levels of leptin and resistin, along with reduced levels of adiponectin, compared to the control group. This suggests that additional factors may be contributing to abdominal obesity and increased waist circumference (15).

Adrenal steroid profile studies using mass spectrometry have shown that NFA patients secrete lower levels of GC that cannot be measured or captured by standard cortisol assays (16). Cortisol is a potent glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) agonist. Adrenal tumors may persistently secrete low levels of GR or MR agonists, which can contribute to the increased incidence of hypertension. Furthermore, a genotype related to ACE gene polymorphism, which is associated with increased risk of HT and cardiovascular issues, is more common in NFA patients compared to controls. This ACE gene polymorphism in AI and NFA may be associated with an increased frequency of hypertension (17). Additionally, the hypothalamic-pituitary-adrenal axis, which regulates the circadian rhythm of endogenous cortisol secretion, also influences blood pressure patterns throughout the day (18). Dysregulation of this axis in these patients could contribute to the development of hypertension (19,20).

The limitation of our study is that functional adrenal adenomas could not be statistically compared with NFA and the control group due to the small sample size.

A growing body of data suggests that adrenal incidentalomas are associated with autonomic cortisol secretion, which leads to various cardiometabolic disorders such as central obesity, HT, and DM, and these are associated with increased CVD risk and mortality. In our study, we found an increased prevalence of MetS, high waist circumference, high FPG levels, and increased SBP and DBP values in patients with AI and NFA. In conclusion, we think that patients with AI should be screened for MetS and cardiovascular diseases.

Ethics Committee Approval: This study was conducted with the permission of the University of Health Sciences Dışkapı Yıldırım Beyazıt Education and Research Hospital Clinical Research Ethics Committee (decision no: 60/19, date: 25.02.2019)

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.A.; Design – E.A., E.Ç.; Supervision – E.Ç., H.D.; Resource – E.A.; Materials – E.A.; Data Collection and/or Processing – E.A., S.H., M.E.S.; Analysis and/or Interpretation – E.A.; Literature Review – E.A:, H.D.; Writing – E.A.; Critical Review – H.D.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

Disclosures: This original article's abstract attended the Ahi Evran 4th International Conference on Scientific Research held on April 26-28, 2024 / Kırşehir Ahi Evran University, Kırşehir, Türkiye.

REFERENCES

1. Young WF Jr. Clinical practice the incidentally discovered adrenal mass. N Engl J Med 2007;356(6):601-10. [CrossRef]
2. Lemieux I, Després JP. Metabolic syndrome past, present and future. Nutrients 2020;12(11):3501. [CrossRef]
3. Peppa M, Koliaki C, Raptis SA. Adrenal incidentalomas and cardiometabolic morbidity an emerging association with serious clinical implications. J Intern Med 2010;268(6):555-66. [CrossRef]
4. Androulakis II, Kaltsas GA, Kollias GE, Markou AC, Gouli AK, Thomas DA, et al. Patients with apparently nonfunctioning adrenal incidentalomas may be at increased cardiovascular risk due to excessive cortisol secretion. J Clin Endocrinol Metab 2014;99(8):2754-62. [CrossRef]
5. Barutçu S, Tuna MM, Kılınç F, Pekkolay Z, Soylu H, Tuzcu A. Non functioning adrenal incidentalomas may be associated with insulin resistance. J Clin Exp Invest 2014;5(4):589-91. [CrossRef]
6. Krzyżewska K, Niemczuk E, Myśliwiec BJ, Junik R. Glucose metabolism disorders in patients with non-functioning adrenal adenomas single-centre experience. Endokrynol Pol 2017;68(4):416-21. [CrossRef]
7. Terzolo M, Pia A, Alì A, Osella G, Reimondo G, Bovio S, et al. Adrenal incidentaloma a new cause of the metabolic syndrome. J Clin Endocrinol Metab 2002;87(3):998-1003. [CrossRef]
8. Ribeiro Cavalari EM, de Paula MP, Arruda M, Carraro N, Martins A, de Souza K, et al. Nonfunctioning adrenal incidentaloma a novel predictive factor for metabolic syndrome. Clin Endocrinol Oxf 2018;89(5):586-95. [CrossRef]
9. Cansu GB, Sarı R, Yılmaz N, Özdem S, Çubuk M. Markers of subclinical cardiovascular disease in nonfunctional adrenal incidentaloma patients without traditional cardiovascular risk factors. Exp Clin Endocrinol Diabetes 2017;125(1):57-63. [CrossRef]
10. Arruda M, Mello RCE, Pessoa de Paula M, Fernandes DMF, Furtado BG, Alves CMC, et al. The presence of nonfunctioning adrenal incidentalomas increases arterial hypertension frequency and severity and is associated with cortisol levels after dexamethasone suppression test. J Hum Hypertens 2017;32(1):3-11. [CrossRef]
11. Nicklas BJ, Penninx BW, Cesari M, Kritchevsky SB, Newman AB, Kanaya AM, et al; Health Aging and Body Composition Study. Association of visceral adipose tissue with incident myocardial infarction in older men and women the Health Aging and Body Composition Study. Am J Epidemiol 2004;160(8):741-9. [CrossRef]
12. Kuk JL, Katzmarzyk PT, Nichaman MZ, Church TS, Blair SN, Ross R. Visceral fat is an independent predictor of all-cause mortality in men. Obesity Silver Spring 2006;14(2):336-41. [CrossRef]
13. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries the INTERHEART study case-control study. Lancet 2004;364(9438):937-52. [CrossRef]
14. Mohammadifard N, Nazem M, Sarrafzadegan N, Nouri F, Sajjadi F, Maghroun M, et al. Body mass index, waist-circumference and cardiovascular disease risk factors in Iranian adults Isfahan healthy heart program. J Health Popul Nutr 2013;31(3):388-97. [CrossRef]
15. Akkus G, Evran M, Sert M, Tetiker T. Adipocytokines in non-functional adrenal incidentalomas and relation with insulin resistance parameters. Endocr Metab Immune Disord Drug Targets 2019;19(3):326-32. [CrossRef]
16. Arlt W, Biehl M, Taylor AE, Hahner S, Libé R, Hughes BA, et al. Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. J Clin Endocrinol Metab 2011;96(12):3775-84. [CrossRef]
17. Harman E, Karadeniz M, Biray C, Zengi A, Cetinkalp S, Ozgen AG, et al. The relation of adiponectin and tumor necrosis factor alpha levels between endothelial nitric oxide synthase angiotensin-converting enzyme transforming growth factor beta and tumor necrosis factor alpha gene polymorphism in adrenal incidentalomas. J Endocrinol Invest 2009;32(11):881-8. [CrossRef]
18. Pecori Giraldi F, Toja PM, De Martin M, Maronati A, Scacchi M, Omboni S, et al. Circadian blood pressure profile in patients with active Cushing›s disease and after long-term cure. Horm Metab Res 2007;39(12):908-14. [CrossRef]
19. Walker BR, Stewart PM, Shackleton CH, Padfield PL, Edwards CR. Deficient inactivation of cortisol by 11 beta-hydroxysteroid dehydrogenase in essential hypertension. Clin Endocrinol Oxf 1993;39(2):221-7. [CrossRef]
20. Watt GC, Harrap SB, Foy CJ, Holton DW, Edwards HV, Davidson HR, et al. Abnormalities of glucocorticoid metabolism and the renin-angiotensin system a four-corners approach to the identification of genetic determinants of blood pressure. J Hypertens 1992;10(5):473-82. [CrossRef]