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Original Article

Bone density in patients with nonfunctional adrenal incidentaloma

Turgut Kültür[1] Aşkın Güngüneş[2] Şenay Durmaz Ceylan[2] Salih Karatlı[3]
Mikail İnal[4] Alper Göncüoğlu[4]

[1]Department of Physical Therapy and Rehabilitation, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey
[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey
[3]Department of Internal Medicine, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey
[4]Department of Radiology, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey

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Corresponding Author: Turgut Kültür, kurgut@hotmail.com

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ABSTRACT

Aims: Adrenal incidentalomas (AI) are adrenal masses that are detected incidentally in imaging studies performed for different reasons in people who do not have any complaints suggestive of adrenal gland disease. The overall prevalence, approximately just over 4%, increases with age. AI is detected in approximately 10% of people over the age of 70. In this context, we thought that CT imaging, which is already used in the diagnosis and follow-up of AI, can contribute to the evaluation of muscle and bone mass without creating additional costs.

Methods: In this retrospective study, 39 patients who were followed up with nonfunctional adrenal incidentaloma (NFAI) by the endocrinology department and 30 healthy individuals with normal adrenal imaging in the abdominal CT examination as the control group were included. Patients with chronic diseases or drug use that may affect bone and muscle mass, and individuals in the postmenopausal period were excluded in this study. Endocrine tests performed to exclude autonomous cortisol secretion, pheochromocytoma and primary hyperaldosteronism; VMA and fractionated metanephrines in 24-hour urine, cortisol values after 1 mg dexamethasone suppression test, baseline serum dehydroepiandrosterone sulfate (DHEAS) levels and plasma aldosterone (ng/dl)/renin (ng/ml/hour) ratio were measured. Autonomous cortisol production was excluded in patients with serum cortisol below 1.8 mcg/dl after 1 mg dexamethasone suppression.

Results: 39 patients with NFAI and 30 healthy volunteers participated in the study. In the NFAI group, 69.2% (n=27) were female and 30.8% (n=12) were male. In the healthy control group 63.3% (n=19) of the people were female and 37.7% (n=11) were male. There was no statistically significant difference between the two groups in terms of gender (p=061). The mean age of the NFAI group is 43 and the mean age of the control group is 49, and there was no statistically significant difference in age between the two groups (p=0.06).

Conclusion: No decrease was found in BMD and paravertebral muscle mass values in the measurements made at L1-3 vertebral level with CT in NFAI patients. Further studies are needed in a larger patient population where the results are evaluated together with the femur and vertebral BMD measurements by DXA method, and muscle strength and performance are evaluated in addition to muscle mass in terms of sarcopenia.

Keywords: Adrenal incidentaloma, bone-mineral density, nonfunctional adrenal incidentalomas, NFAI

INTRODUCTION

Adrenal incidentalomas (AI) are adrenal masses that are detected incidentally in imaging studies performed for different reasons in people who do not have any complaints suggestive of adrenal gland disease. The overall prevalence, approximately just over 4%, increases with age. AI is detected in approximately 10% of people over the age of 70.[1]

Mild cortisol excess (MCE), previously called "subclinical Cushing's syndrome (SCS)", is observed in 15-30% of cases, although most of them are dysfunctional, without the typical clinical features of hypercortisolism.[1] Comorbidities such as type 2 diabetes mellitus and hypertension are common in AI cases. It is thought that this low-grade cortisol excess may be associated with various comorbid conditions (hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, and osteoporosis).[1-3]

There are studies indicating in adipocytokines levels may be associated with insulin resistance. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index, and cardiovascular risk factors in nonfunctional adrenal incidentalomas (NFAI) patients.[4,5]

Intermittent cortisol and mineralocorticosteroid hormone secretion that cannot be detected by routine tests in NFAI patients may be a cause of increased cardiovascular risk, and may even have effects on bone and muscle mass.

There are studies showing that in addition to a decrease in BMD in patients with adrenal incidentaloma and subclinical hypercortisolism, the trabecular bone score (TBS), which is an indicator of increased bone quality and fracture risk, decreases.[6]

On the other hand, is there a negative effect on bone and muscle mass in individuals with NFAI? Our current knowledge is insufficient in answering this question. Therefore, in our study, we aimed to measure bone mineral density and muscle mass quantitatively with CT in cases with NFAI. In this context, we thought that CT imaging, which is already used in the diagnosis and follow-up of AI, can contribute to the evaluation of muscle and bone mass without creating additional costs.

METHODS

In this retrospective study, 39 patients who were followed up with NFAI by the endocrinology department and 30 healthy individuals with normal adrenal imaging in the abdominal CT examination as the control group were included. The study was initiated with the approval of the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 26.06.2019 Decision No: 2019.06.23). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with chronic diseases or drug use that may affect bone and muscle mass, and individuals in the postmenopausal period were excluded in this study.

Endocrine tests performed to exclude autonomous cortisol secretion, pheochromocytoma and primary hyperaldosteronism; VMA and fractionated metanephrines in 24-hour urine, cortisol values after 1 mg dexamethasone suppression test, baseline serum dehydroepiandrosterone sulfate (DHEAS) levels and plasma aldosterone (ng/dl)/renin (ng/ml/hour) ratio were measured. Autonomous cortisol production was excluded in patients with serum cortisol below 1.8 mcg/dl after 1 mg dexamethasone suppression.

Hounsfield unit (HU), absolute contrast washout rate and tumor size were noted.

Calcium, phosphorus, albumin, alkaline phosphatase, parathormone, 25-OH Vitamin D, urea, creatinine, hormone profiles, results of endocrinological dynamic tests, ESR and CRP levels were taken retrospectively from the hospital information system.

The measurements were calculated from CT images.

Bone densities and muscle masses were calculated from the CT images of the patient and control groups by area measurement (millimeter square mm^2) method.

ROI (Region of interest) was selected to cover 2/3 of the corpus area in axial sections at the level of L1 vertebra, bone density (HU) was measured without including the bone cortex in the area (Figure 1).

Fat-containing tissues were removed from the paravertebral area (Figure 2a) in axial sections at the level of the L3 vertebra (Figure 2b), and the lean muscle tissue area was measured (Figure 2c).

Statistical Analysis

Statistical analyzes were performed using the Statistical Package for the Social Science' (SPSS 16.0) program. Descriptive statistics were signified as mean ± standard deviation for numerical variables and as numbers and percentages for nominal variables. Kolmogorov Smirnov and ShapiroWilks tests were used to investigate the normal distribution in numerical variables. In the comparison of two independent groups for a numerical variable, the t-test (students' t-test) was used in the independent groups according to whether they fit the normal distribution or not, and the Mann Whitney-U test was used in those who

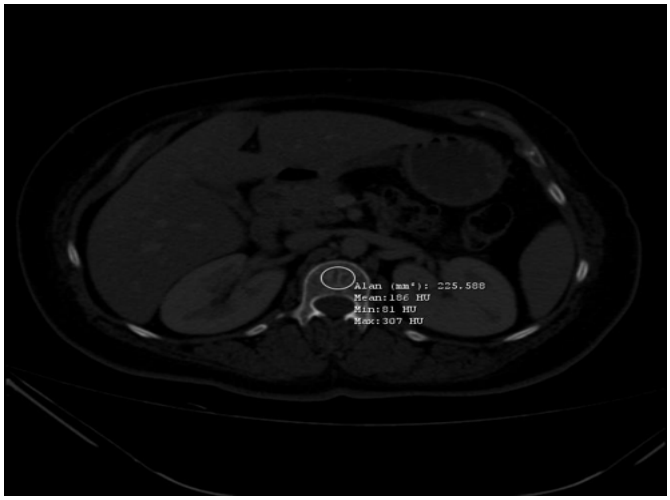

Figure 1. Bone density measurement at L1 vertebra level

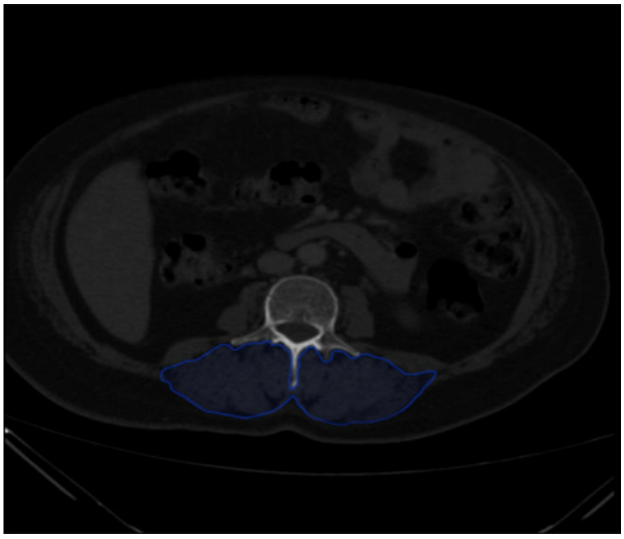

Figure 2a. Paravertebral area measurement at L3 vertebra level

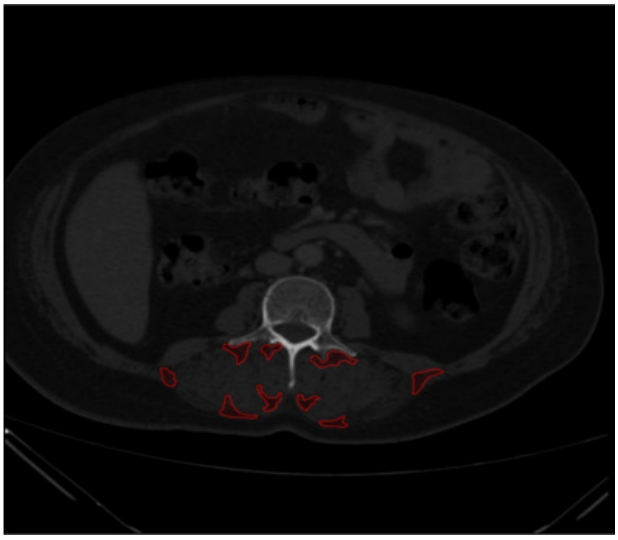

Figure 2b. Fatty tissue within the paravertebral muscles

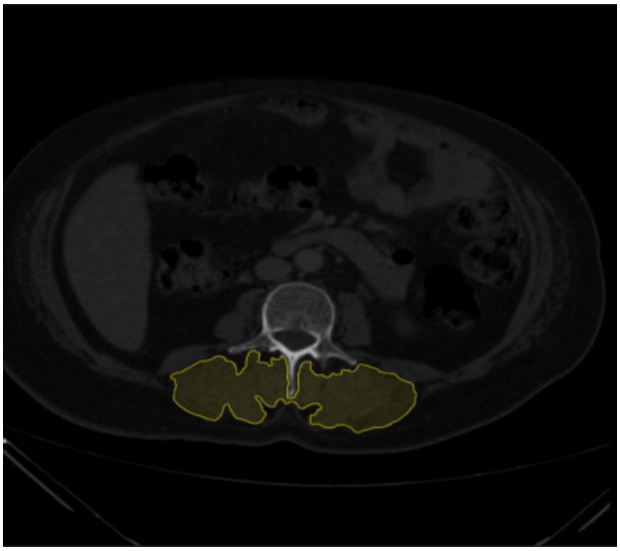

Figure 2c. Fat tissue removed paravertebral muscle tissue

did not fit in with the normal distribution. Chi-square (ChiSquare) test was used to compare nominal variables between groups. Spearman's correlation analysis was used while investigating the relationship between two numerical variables. P<0.05 was considered statistically significant.

RESULTS

39 patients with NFAI and 30 healthy volunteers participated in the study. In the NFAI group, 69.2% (n=27) were female and 30.8% (n=12) were male. In the healthy control group 63.3% (n=19) of the people were female and 37.7% (n=11) were male. There was no statistically significant difference between the two groups in terms of gender (p=061). The mean age of the NFAI group is 43 and the mean age of the control group is 49, and there was no statistically significant difference in age between the two groups (p=0.06) (Table 1a and Table 1b).

There was no significant difference between the groups in serum PTH, Vit D, calcium, phosphorus, albumin, urea, creatinine, sodium, potassium, cortisol, 24-hour urine VMA, normetanephrine/Metanephrine, plasma renin activity, and aldosterone levels (Table 2).

Table 1a. The two group comparisons of demographic characteristics, bone and muscle mass

		NFAI group n=39	Control group n=30	
Age; years		43 (34-50)	49 (28-50)	P=0.064
Sex	Female	27 (69.2%)	19 (63.3%)	P=0.61
	Male	12 (30.8%)	11 (37.7%)	
Bone mass (HU)		205 (102-277)	169 (101-306)	P=0.358
Muscle mass (mm2)		4329 (3289-6687)	4627 (3314-43262)	P=0.506

Table 1b. Demographic characteristics of NFAI and control group

		NFAI group n=39	Control group n=30	
Age, years		43 (34-50)	49 (28-50)	P=0.064
Sex	Female	27 (69.2%)	19 (63.3%)	P=0.61
	Male	12 (30.8%)	11 (37.7%)	

HU: Hounsfield unit

The BMD and muscle mass were similar in both NFAI patients and controls (Table 3).

The mean BMD value in the NFAI group was 205 HU, while it was 169 HU in the control group (p=0.358). The mean muscle mass area was 4329 mm^2 in the NFAI group and 4627 mm^2 in the control group (p=0.506). No correlation was found between muscle and bone measurements and biochemical parameters (Table 4).

Table 2. Comparison of study groups in terms of biochemical parameters

	Study group n=39	Control group n=30	
PTH	38 (22-56)	50.5 (4.2-138)	P=0.384
Vitamin D, ng/ml	12 (2.9-51)	13 (3.2-23)	P=0.691
Calcium, mg/dl	9.4 (8.4-10.3)	9.75 (8.5-10.8)	P=0.231
Phosphorus, mg/dl	3.3 (2.6-4.5)	3.1 (2.3-4.2)	P=0.046
Albumin, g/dl	4.5 (3.6-5.4)	4.7 (3.8-5.5)	P=0.55
Urea, mg/dl	25 (12-38)	25 (17-51)	P=0.433
Creatinine, mg/dl	0.7 (0.5-1.1)	0.7 (0.3-1.1)	P=0.106
Sodium, mmol/L	139 (136-144)	140 (137-145)	P=0.057
Potassium, mmol/L	4.6 (3.5-5.5)	4.4 (3.2-5.3)	P=0.085
Cortisole, ug/dl	11 (3.4-19.8)		
Urine VMA, mg/day	4.55 (2-25)		
Urine metanephrine ug/day	119.5 (27-220)		
Plasma Renin activity, ng/ml/h	1.2 (0.2-7)		
Aldosterone, ng/dl	9.7 (4.6-40)		

Table 3. Muscle and bone mass values of NFAI and control group

	NFAI group n=39	Control group n=30	
Bone mass (HU)	205 (102-277)	169 (101-306)	P=0.358
Muscle mass (mm^2)	4329 (3289-6687)	4627 (3314-43262)	P=0.506

HU: Hounsfield unit

DISCUSSION

In this study, it was indicated that BMD and paravertebral muscle mass measurements made at the L1-3 vertebra level of patients with NFAI were not different from the control group. To our knowledge, this is the first study to quantitatively compare CT with BMD and muscle mass measurements of these two groups.

Glucocorticoids negatively affect bone metabolism through their receptors and ligands on osteoblasts, osteocytes and osteoclasts. Cortisol excess causes differentiation of mesenchymal progenitor cells preferentially to adipocytes, a decrease in the number of osteoblasts, an increase in osteoblast apoptosis and osteoclastogenesis.[7] Bone density loss and osteoporosis are important complications of glucocorticoid excess. However, initial studies reported that BMD measurements in patients with adrenal incidentaloma with autonomic cortisol secretion were not different from controls. In more recent studies, it has been shown that patients with adrenal incidence and subclinical hypercortisolism have a decrease in BMD value, an increase in fracture risk, and a decrease in TBS, which is an indicator of bone quality. Even moderate cortisol excess may have negative effects on bone mineral density (BMD) and bone quality. Moreover, in

Table 4. The correlations between muscle and bone measurements and biochemical parameters

		Age	Ca	P	Alb	D Vit	PTH	Urea	Creatine	Na	K	Cor	VMA	Metanefrin	Renin	Ald
Bone	r	-.38	-.2	-.27	-.41*	-.24	.153	-.06	.007	-.29	-.22	-.01	.201	-.05	-.21	.15
	p	.02	.30	.114	.015	.346	.673	.714	.965	.090	.197	.978	.287	.771	.23	.39
	n	39	36	35	35	17	10	39	38	35	35	30	30	28	32	32
Muscle	r	.37*	-.22	-.02	-.03	.034	-.69*	.042	.190	.273	-.05	-.01	.074	.319	-.17	-.18
	p	.022	.199	.905	.869	.896	.025	.797	.253	.112	.766	.959	.699	.098	.33	.32
	n	39	36	35	35	17	10	39	38	35	35	30	30	28	32	32

Ca: calcium, P: phosphorus, Alb; albumin, Vit D; vitamin D, PTH: parathormone, sKrea: serum creatine, Na: sodium, K: potassium, Cor: cortisole, VMA: vani mandelic acid, Ald: aldosterone

a study, it was reported that TBS was lower in patients with mild cortisol excess compared to patients with NFAI while BMD was similar. Even moderate cortisol excess may have negative effects on bone mineral density (BMD) and bone quality. Moreover, in a study, it was reported that TBS was lower in patients with mild cortisol excess compared to patients with NFAI while BMD was similar.[6-11]

Aldosteron direct effects on bone metabolism through mineralocorticoid receptors. In addition, hyperaldosteronism may cause an increase in extravascular volume, leading to urinary calcium and magnesium excretion and secondary hyperparathyroidism. Moreover, hyperaldosteronism may cause increased oxidative stress by decreasing alpha-1 anti-protease activity and increasing lymphocyte hydrogen peroxide production.[6-11]

Possible reasons for the differences in the results of these studies may be the differences in the criteria used for the diagnosis of mild cortisol excess in the studies, genetic differences, differences in male-female distribution, and gonadal status. In our study, cases with mild cortisol excess were not included. This may be why BMD measurements were similar between the NFAI and control groups. In addition, the effects of cortisol excess on skeleton may differ depending on individual sensitivity to cortisol. The GR polymorphism, changes in co-activator and co-repressor levels, and local cortisol production as a result of 11-beta hydroxysteroid dehydrogenase type 1 activity may be possible causes of this difference. The majority of these studies, which show a decrease in bone mineral density, deterioration in bone quality, and an increased risk of fracture in individuals with adrenal incidental and mild cortisol excess, were conducted in a similar patient population by the same author group. Apart from this, the possible reasons for the differences in the results of the studies in the early period may be the differences in the criteria used for the diagnosis of mild cortisol excess in the studies, the differences in the male-female distribution and gonadal status.[7-10]

There is a positive feedback vicious circle relationship between inflammatory cytokines such as IL-6 and tumor necrosis factor-alpha (TNF-α) in sarcopenia. Sarcopenia may be associated with metabolic syndrome and hyperinsulinemia.[12] The relationship between osteoporosis and metabolic syndrome is controversial, with some studies reporting an association and others not.[13-15]

It has been reported that the increase in proinflammatory cytokines such as TNF-α, IL-6, in patients with NFAI may cause subclinical inflammation and insulin resistance.[13] Increased inflammatory cytokines and insulin resistance are conditions associated with sarcopenia.[12] It has been suggested that increased cortisol in patients with Ai may lead to a decrease in muscle mass.[6] It has also been shown that excess aldosterone causes a decrease in skeletal muscle mass in women.[17] However, the number of studies examining the change in body composition in the adrenal incidentaloma patient group is very few. In a recent study, changes in body composition were investigated by DXA method in patients with adrenal incidentalomas with NFAI and mild cortisol excess and control group. There was no difference between the groups in terms of body composition. However, it has been shown that there is a significant relationship between AI and metabolic syndrome, with an increase in both total fat and body fat index.[18]

In our study, muscle mass was measured only in the paravertebral region and there was no difference between the groups. Measurements were not taken with the DXA method or the bioimpedance method. Again, muscle strength and performance were not evaluated.

Limitations of the study: Our study was conducted in a small patient population.On the other hand, BMD measurements of the femur and vertebrae were not made with the DXA method. Muscle mass was measured only in the paravertebral region, measurements were not taken from other regions. Also, muscle strength and muscle performance were not evaluated for sarcopenia.

CONCLUSION

As a result, no decrease was found in BMD and paravertebral muscle mass values in the measurements made at L1-3 vertebral level with CT in NFAI patients. Further studies are needed in a larger patient population where the results are evaluated together with the femur and vertebral BMD measurements by DXA method, and muscle strength and performance are evaluated in addition to muscle mass in terms of sarcopenia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 26.06.2019, Decision No: 2019.06.23).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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