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Clinical, Biochemical, and Radiological Retrospective Analysis in Patients with Adrenal Incidentaloma – A Secondary Publication

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Abstract: *Objective:* To evaluate the epidemiological, demographic, clinical features, treatment approaches, and survival of patients followed up for adrenal incidentaloma. *Methods:* Data from 46 patients who were treated and followed up due to adrenal incidentaloma in the Endocrinology Department of Mersin University Health Research and Application Hospital between 2010 and 2014 were retrospectively analyzed. *Results:* Of the cases included in the study, 13 were male, 33 were female, and the mean age was 54.09 ± 10.7 years. The most common reason for admission was abdominal pain in 34.78% of the patients, the most commonly diagnosed radiological method was dynamic adrenal CT in 60.87%, and the most common location was the left adrenal gland. The mean lesion diameter was between 26.8 ± 16.5 mm. The frequency of hypertension was 50%, obesity 47.8%, type 2 diabetes 21.7%, osteoporosis 42.8%, and metabolic syndrome 41.3%. According to hormonal evaluation results, non-functional adrenal adenoma (NFAA) was found in 82.61%, subclinical Cushing's syndrome (SCS) in 15.21%, and aldosteronoma in 2.1%. Myelolipoma, pheochromocytoma, and adrenocortical adenoma were diagnosed in 8 cases undergoing adrenalectomy. One patient died due to liver failure. No hormonal activation or growth in lesion size was detected during the follow-up of the patients. *Conclusion:* Due to the very different pathological and radiological appearances of adrenal incidentaloma, it is important to evaluate demographic, etiological, clinical, laboratory, and radiological data as a whole in the treatment and follow-up.

Keywords: Adrenal incidentaloma; Subclinical Cushing's syndrome; Non-functional adrenal adenoma; Diagnosis; Treatment

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1. Introduction

Adrenal incidentalomas (AI) refer to masses incidentally detected in the adrenal gland through radiological imaging methods in patients presenting for various reasons, and they can present with a range of pathologies [1-4]. The incidence varies between 1.4% and 8%. It has been observed that the prevalence of AI increases with increasing

age, with a prevalence of 1% in patients under 30 years old and reaching 7%–10% in those over 70 years old [1]. About 80% of AIs are composed of benign non-functional adrenal cortical adenomas. However, they can also occur in primary or metastatic malignancies [2].

Due to the serious effects of AI on morbidity and mortality, it is important to differentiate benign and non-functional masses from malignant and hormone-secreting masses. Diagnosis is made using non-invasive, high-resonance imaging techniques such as ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI). Positron emission tomography (PET) evaluates the metabolic activity of adrenal glands as well as morphological imaging. It is particularly useful in assessing regional and distant metastases, especially in primary tumors or in combination with primary tumors. Radiological features are indicative in determining the histological type. Fine needle aspiration biopsy and cytological evaluation can be useful in distinguishing between adrenal tumors and metastatic adrenal tumors. Tumor size is an important parameter considered for benign-malignant differentiation. As tumor size increases, the probability of malignancy also increases [2,3,7]. A detailed history (sweating, palpitations, headache, etc.), physical examination (purple striae, central obesity, buffalo hump, moon face, hypertension, etc.), and laboratory examination (hypokalemia, etc.) are indicative of functional adenoma. Since endocrine hyperfunction is associated with serious morbidity, cortical and medullary functions are evaluated with basal values and dynamic tests [2-10].

In the treatment, adrenalectomy is recommended for non-functional adrenal lesions larger than 4 cm due to the increased risk of carcinoma. Unless contraindicated, all secretory AIs (pheochromocytoma, cortisol-secreting adenoma, aldosterone-secreting adenoma) are surgically removed regardless of their size. AIs smaller than 4 cm and radiologically appearing as benign adenomas are recommended for radiological follow-up every 3–6 months. During follow-up, surgical excision should be considered if tumor growth exceeds 1 cm or hormonal activation occurs. Currently, the follow-up beyond 5 years in stable non-functional adrenal lesions is uncertain [3-9].

With the widespread use of imaging techniques along with modern technology, the frequency of encountering AIs has increased, yet studies on this subject are still limited. Prospective and randomized clinical studies on the diagnosis and treatment of AI patients in the literature are not sufficient. Therefore, a specific diagnosis, follow-up, and treatment protocol have not been established.

This study aims to retrospectively evaluate the general demographic data, clinical characteristics, and applied treatments of AI patients followed and treated in the Endocrinology Department of Mersin University Health Research and Application Hospital.

2. Materials and methods

In this study, the demographic, clinical, radiological, and biochemical data of 46 patients who were diagnosed and followed up for AI at the Department of Endocrinology, Mersin University Faculty of Medicine Hospital between 2010 and 2014 were evaluated. Ethical approval was obtained from the Mersin University Ethics Committee with decision number 2014/84 dated 24th April 2014.

2.1. Patient selection

AI cases under the age of 18 and cases with a diagnosis of cancer were excluded after evaluation.

2.2. Demographic characteristics and physical examination findings of the patients

Detailed medical histories of all patients, reasons for admission, physical examination findings including height, weight, body mass index (BMI), waist circumference, arterial blood pressure, and presence of phenotypic

characteristics of Cushing's syndrome were recorded during admission and follow-up.

The lowest value measured between the xiphoid process and the umbilicus was recorded for waist circumference measurement. BMI was calculated using the formula weight/height^2 (kg/m^2). Those with a BMI between 18.5–24.9 kg/m^2 were considered normal weight, those between 25.0–29.9 kg/m^2 were considered overweight, and those with a BMI of 30 kg/m^2 or higher were considered obese.

2.3. Radiologic examinations performed on the patients

Dynamic adrenal CT or MRI findings were recorded for patients at their initial visit and during follow-up.

To assess osteoporosis, bone mineral density measurement was performed using dual-energy X-ray absorptiometry (DEXA) in addition to blood parameters. Patients' bone mineral densities were recorded using T and Z-scores. The T-score was used to diagnose osteoporosis in postmenopausal women and men over 50 years old. The Z-score was used to diagnose osteoporosis in premenopausal women and men under 50 years old. Accordingly, a Z-score of -2.0 SD or lower was considered as "lower bone mass than expected for chronological age," and above -2.0 was considered as "normal bone mass for chronological age."

2.4. Biochemical parameters examined

Biochemical parameters including lipid profiles (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), fasting plasma glucose, and HbA1c levels in patients diagnosed with diabetes mellitus were measured using routine laboratory methods and recorded. Fasting plasma glucose < 100 mg/dl was considered normal.

To determine the insulin resistance, fasting plasma glucose and fasting insulin levels were recorded, and the HOMA formula was used: HOMA = fasting insulin (μU/mL) × fasting plasma glucose (mg/dl). A value above 2.7 was considered insulin resistance. In evaluating accompanying metabolic syndrome in patients, the NCEP-ATP III metabolic syndrome diagnostic criteria were used.

2.5. Hormonal parameters examined

To detect cortisol excess, the overnight 1 mg dexamethasone suppression test (DST), which is considered a standard test for screening hypercortisolemia, was performed. In cases where suppression did not occur in the 1 mg DST, plasma levels of dehydroepiandrosterone sulfate (DHEA-S), adrenocorticotropic hormone (ACTH), and cortisol were examined for subclinical Cushing's syndrome (SCS). For the diagnosis of pheochromocytoma, 24-hour urine measurements of metanephrine, normetanephrine, and vanillylmandelic acid (VMA) excretions were measured. Renin activity and aldosterone levels were examined for adrenal adenomas secreting aldosterone in patients with hypertension or hypokalemia.

Based on the results of the evaluations performed in patients, they were classified as SCS, Cushing's syndrome, primary hyperaldosteronism, pheochromocytoma, and non-functional adrenal adenomas (NFAA). In patients with a serum cortisol concentration below 50 nmol/L (1.8 μg/L) in the low-dose 1 mg DST, the presence of cortisol hypersecretion was ruled out. Patients with a serum cortisol concentration above 50 nmol/L were considered definite SCS if abnormalities were detected in at least two of the criteria listed below. Other patients were classified as NFAA.

2.6. Follow-up

Comparative imaging features were recorded during patients' initial presentation, at 6 months, and subsequently during annual follow-ups, including the lesion's direction, whether the imaging characteristics were consistent with adenoma, homogeneity, size, and any increase in lesion size during follow-up. Additionally, biochemical

and hormonal values at 6-month or annual intervals were also examined.

2.7. Statistical analysis

Statistical analysis of the data was performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of the data was assessed using the Kolmogorov-Smirnov test. Data showing normal distribution were presented as mean ± standard deviation, while those not showing normal distribution were presented as median minimum–maximum).

3. Results

Table 1 shows the demographic, clinical, radiological, and laboratory parameters of the patients. Thirteen (28.3%) patients were male, and thirty-three (71.7%) were female. The mean age at diagnosis was 54.09 ± 10.7 years (range: 29–74 years), with the most common reason for admission being abdominal pain in 34.78% of patients, and the most commonly used diagnostic radiological method being dynamic adrenal CT in 60.87% of cases. While 76.08% of adrenal masses were determined as adenoma by radiological methods, 13.04% were non-adenoma, 6.52% were myelolipoma, and 4.35% were interpreted as cysts. Of the lesions detected radiologically, 18 (39.1%) were located in the right adrenal gland, 24 (52.2%) in the left adrenal gland, and 4 (8.7%) were bilateral, with tumor sizes ranging from 9 mm to 90 mm (mean 26.8 ± 16.5 mm).

At the initial presentation, the mean BMI was 30.2 ± 4.9, the mean waist circumference was 100.8 ± 11.0 cm, with a hypertension frequency of 50% (n = 23), type 2 diabetes mellitus frequency of 21.7% (n = 10), and dyslipidemia frequency of 28.26% (n = 13). The mean HOMA value used to determine insulin resistance was calculated as 1.93 ± 1.35 with insulin resistance detected in four cases.

Regarding hormonal evaluation, the mean 24-hour urinary VMA value was 5.96 ± 2.96 mg/day, metanephrine value was 120.7 ± 91.7 μg/day, and normetanephrine was 273.33 ± 343.28 μg/day. Only three patients had values above the normal range. Among the 23 patients with hypertension or hypokalemia, the mean plasma aldosterone concentration was 8.49 ± 7.21 and plasma renin activity was 3.05 ± 4.38. The mean plasma aldosterone concentration/plasma renin activity ratio was 6.60 ± 6.05. In one patient, this ratio was found to be 26, and aldosteronoma was diagnosed after a saline suppression test. The mean serum cortisol concentration after 1 mg DST was 55.60 ± 87.35 nmol/L, and the mean morning (08:00) serum cortisol concentration was 346.2 ± 135.7 nmol/L. Serum cortisol concentration after 1 mg DST was above 50 nmol/L (1.8 μg/dL) in nine patients (19.5%). Basal morning DHEA-S levels were below normal limits in 10 cases (21.7%), and ACTH levels were below 10 pg/mL in 13 patients. Following hormonal evaluation, one patient (2.1%) was diagnosed with aldosteronoma, seven patients (15.2%) with SCS, and thirty-eight patients (82.6%) with NFAA.

Table 1. Demographic, radiologic, and biochemical data of the patients included in the study

Variables	Number (*n*)	Percent (%)
Gender		
Male	13	28.3
Female	33	71.7
Age (median)	54.0 ± 10.7	
Male	60.3 ± 9.4	
Female	61.6 ± 10.3	
Reasons for admission		
Abdominal pain	16	34.7
Right side pain	5	10.8
Thorax CT	3	6.5
Feeling of bloating in the abdomen	3	6.5
Hepatic steatosis	3	6.5
Renal transplant preparation	2	4.3
Cholecystectomy preoperative control USG	2	4.3
Control USG	2	4.3
Hypertension	2	4.3
Dysuria	1	2.1
Cyst in the liver	1	2.1
Nausea and vomiting	1	2.1
Nephrolithiasis	1	2.1
Viral hepatitis	1	2.1
Female contraception	1	2.1
Thoracic MRI for low back pain	1	2.1
Renal donor preparation	1	2.1
Radiological examination		
MRI	18	39.1
CT	28	60.9
Mass localization		
Right	18	39.1
Left	24	52.2
Bilateral	4	8.7
Radiological tumor size (median mm) according to MRI		
1 cm and below	2	4.3
1–4 cm	10	21.7
4–6 cm	5	10.8
6 cm and above	1	2.1
Radiological tumor size (median mm) according to CT		
1 cm and below	2	4.3
1–4 cm	22	47.8
4–6 cm	3	6.5
6 cm and above	1	2.1

Table 1 (Continue)

Variables	Number (*n*)	Percent (%)
Diagnosis according to the radiological method		
Adenoma	35	76.0
Non-adenoma	6	13.0
Myelolipoma	3	6.5
Cyst	2	4.4
Body mass index (median)	30.2 ± 4.9	
Normal weight	6	13.4
Overweight	18	39.2
Obese	22	47.8
Waist circumference (median, cm)	100.8 ± 11.0	
Female	100.9 ± 11.5	
Male	100.6 ± 10.1	
Concomitant diseases		
Hypertension	23	50.0
Type 2 diabetes mellitus	10	21.7
Dyslipidemia	13	28.2
Metabolic syndrome	19	41.3
HOMA reference range	0.4–6	
Median	1.9 ± 1.4	
DEXA		
Normal	2	4.3
Osteopenia	12	26.8
Osteoporosis	10	21.7
Hormonal tests VMA (reference range)	1.7–16.9	
Median (mg/day)	5.9 ± 3.0	
Metanephrine (reference range)	7–381	
Median (μg/day)	120.7 ± 91.7	
Normetanephrine (reference range)	21–2,350	
Median (μg/day)	273.3 ± 343.3	
Aldosterone concentration (reference range)	1.2–33.5	
Median	8.5 ± 7.2	
Plasma renin activity (reference range)	0.15–16	
Median	3.1 ± 4.4	
Cortisol 1 mg post DST (reference range)	9–574	
Median (μg/dL)	55.6 ± 87.3	
Morning cortisol (reference range)	9–574	
Median (nmol/L)	346.2 ± 135.7	

When comparing patients diagnosed with NFAA and SCS, the prevalence of type 2 diabetes mellitus (DM; 23.6% and 14.2%, respectively), osteoporosis (36.36% and 33.33%, respectively), and dyslipidemia (28.9% and 28.5%, respectively) was higher in NFAA group. The prevalence of metabolic syndrome, obesity, and hypertension was more frequent in the SCS group (**Figure 1**).

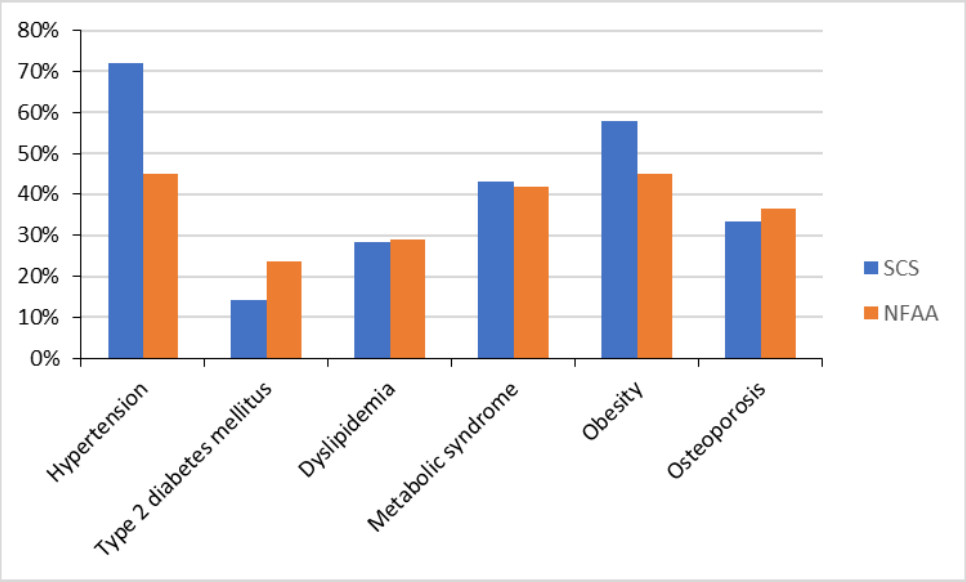

Figure 1. Comparison of comorbidity rates in patients with SCS and NFAA

After the initial visit, 8 patients (4 cases of SCS, 1 case of aldosteronoma, 2 cases with progression in lesion size, and 1 case with suspicion of malignancy) underwent surgery (**Figure 2**). Postoperative pathology results revealed 1 myelolipoma, 1 pheochromocytoma, and 6 adrenocortical adenomas.

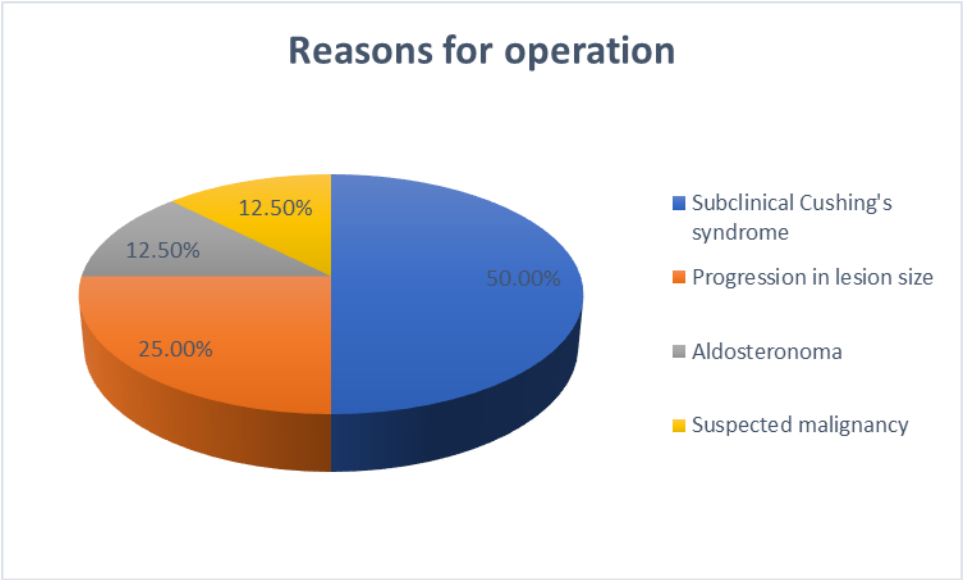

Figure 2. Reasons for operation

During follow-up, 21 patients (45.7%) had one follow-up visit, 9 (19.6%) came for follow-up twice, 11 (23.9%) came for follow-up 3 times, 2 (4.3%) came for follow-up 4 times, and 3 (6.5%) came for follow-up 5 times. The mean BMI at the second visit was calculated as 29.7 ± 4.7 with 4 patients (16%) classified as normal weight, 11 (44%) as overweight, and 10 (40%) as obese. At the third visit, the mean BMI was calculated as

30.1 ± 5.3. Four patients (23.5%) were normal weight, 4 (23.5%) were overweight, and 9 (52.9%) were obese. During the 6-month and annual follow-up, except for two patients, the lesion size remained stable in all cases. One patient died due to liver failure. The annual hormonal evaluation did not reveal hormonal activation.

4. Discussion

AI encompasses a heterogeneous spectrum of pathologies, with adrenocortical adenoma being the most common. Technological advancements in radiology have led to an increased detection rate of AIs, resulting in a higher incidence of subclinical diseases being identified [1-7]. Patients with adrenal tumors can present with various clinical scenarios. They may present with endocrinological symptoms, symptoms suggestive of pheochromocytomas such as headaches, palpitations, and hypertension, nonspecific symptoms related to the adrenal tumor such as pain, weight loss, discomfort due to mass effect, or entirely asymptomatic findings unrelated to the adrenal mass [5,7,8]. In this study, the most common reason for patients with AI to seek medical attention was abdominal pain.

Several studies have reported that AIs are most frequently found in the fifth and seventh decades of life, with no significant age difference observed between men and women [1,9,10]. In this study, the mean age was 54.09 ± 10.7 (range: 29–74) years. The mean age for female patients was 51.6 ± 10.3 (range: 28–74) years, while for male patients, it was 60.3 ± 9.4 (range: 43–73) years. The higher incidence and earlier onset of AIs in females observed in this study may be interpreted as women seeking medical attention more frequently and at an earlier age.

Adrenal masses are localized in the right adrenal gland in 50%–60% of cases, in the left adrenal gland in 30%–40% of cases, and bilaterally in 10%–15% of cases. The more frequent use of USG for imaging may lead to a higher detection rate of adrenal masses in the right adrenal gland due to the inadequacy of USG in visualizing the left adrenal gland compared to CT. However, both CT and autopsy series have shown a similar distribution between the two adrenal glands [7,10,11]. In this study, the localization of the mass was recorded based entirely on adrenal CT or MRI findings, thus enabling the detection of masses in the left adrenal gland as well.

In patients with overt clinical symptoms, basal testing or DSTs provide reliable results in diagnosing Cushing's syndrome. However, in SCS, the level of cortisol excess varies among patients, making the diagnostic sensitivity and specificity of the criteria controversial. There is no gold standard test that can be universally applied to all patients with SCS [12]. Although urinary-free cortisol excretion is a guiding test for diagnosing Cushing's syndrome, its sensitivity is low in detecting mild hypercortisolism [1,3,6,11,13]. Mantero *et al*. found a mild elevation in urinary free cortisol excretion in 69 (75%) of 92 patients diagnosed with SCS [10], Reincke *et al*. found it in only 1 (13%) of 8 patients with SCS [13], and Morioka *et al*. found a mild elevation in urinary free cortisol excretion in 2 (29%) of 7 patients with SCS [14]. In this study, all patients diagnosed with SCS showed increased urinary-free cortisol excretion, with a fivefold increase observed in one patient and a mild increase observed in urinary-free cortisol levels in the other six patients.

In patients with SCS, plasma ACTH suppression has been reported at varying rates in previous studies. Morioko *et al*. reported a suppression rate of 100% [14], while Rossi and Libe found it to be 42% [15,16]. Kasperlik-Zaluska *et al*. showed that in 33 out of 98 patients with AIs, plasma ACTH concentration was below the defined normal limit [17]. In this study, plasma ACTH suppression was observed in 28.2% (n = 13) of all patients with Ais. Among the 7 patients diagnosed with SCS, ACTH suppression was detected in 71.4% (5 out of 7 patients). Additionally, in 8 cases (17.3%) that were considered normal according to the diagnostic criteria, plasma ACTH concentration was also suppressed.

The low-dose DST is considered the most accurate test for diagnosing subclinical hypercortisolism. Generally, in studies, a diagnosis of SCS is made when at least two abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis are present [18-20]. In this study, the definitive diagnosis of SCS was based on the failure of serum cortisol concentration to be suppressed during the low-dose 1 mg DST, and at least 2 parameters were considered to be present to prevent false positives. DSTs can be used not only to screen for hypercortisolism but also to determine its level.

In the largest series of AI conducted by Mantero *et al*., the prevalence of SCS was determined to be 9.2% [10]. Ambrosi *et al*. reported a prevalence of 12% in a study involving 32 patients [22], while Rossi *et al*. found this rate to be 24% among patients with AI [15]. Çömlekçi *et al*. determined the prevalence of SCS to be 12.5% in a study involving 376 patients [23]. In this study, the prevalence of SCS was found to be 15.2%.

Despite the uncertainties in the investigation process of SCS, it is believed that many patients with clinically silent adrenal adenomas may be exposed to slight cortisol excess [23]. In these patients, long-term complications of Cushing's syndrome, such as hypertension, obesity, and diabetes, which are defined within the metabolic syndrome, may be encountered [1-10]. In a multicenter study of 1,004 patients with AI conducted in Italy, the prevalence of hypertension was found to be 42%, obesity prevalence was 28%, and diabetes prevalence was 10% [24]. Another study by the Italian Study Group, which examined 887 patients, reported hypertension at 46%, obesity at 36%, and diabetes at 21% [13]. In a study of 376 patients with AIs conducted in Turkey, the prevalences of hypertension, metabolic syndrome, type 2 diabetes mellitus, and hyperlipidemia were found to be 54.9%, 48.1%, 18.4%, and 59.6%, respectively [22]. In this study, the prevalence of hypertension in patients with AIs was 50%, obesity prevalence was 47.8%, diabetes mellitus prevalence was 21.7%, and metabolic syndrome prevalence was 41.3%.

In a study conducted by Yener *et al*. in Turkey, which evaluated 273 patients, including 231 with NFAA and 42 with SCS, the prevalence of hypertension, dyslipidemia, metabolic syndrome, prediabetes, type 2 diabetes mellitus, and cardiovascular disease was found to be 54%, 59%, 47%, 23%, 18%, and 8%, respectively [25]. In the same study, the prevalence of hypertension was 68.2% in SCS and 51.7% in NFAA; dyslipidemia prevalence was 58.9% in SCS and 59.1% in NFAA; metabolic syndrome prevalence was 52.6% in SCS and 45.9% in NFAA; prediabetes prevalence was 24.3% in SCS and 22.9% in NFAA; type 2 DM prevalence was 16.6% in SCS and 18.7% in NFAA; and cardiovascular disease prevalence was 19.5% in SCS and 6.7% in NFAA. While the prevalence of hypertension, metabolic syndrome, and cardiovascular disease was higher in the SCS group, statistically significant differences were only found in the rate of cardiovascular disease between the two groups [25]. In this study, when NFAA and SCS were evaluated separately, the prevalence of hypertension and obesity was found to be higher in the group with SCS.

Osteoporosis is a complication that may arise due to excess cortisol; however, studies on bone mineral density in patients with clinically silent AIs have conflicting results [26]. Some researchers have found a decrease in bone mass in gonadal or hypogonadal patients with SCS, while others have found no difference in bone mineral density between patients and control groups [15,27-29]. In this study, the prevalence of osteoporosis was 35.71% and osteopenia prevalence was 42.86% in patients with AI. The prevalence of osteoporosis was 36.363% in patients with NFAA and 33.33% in patients with SCS, with no statistically significant difference between the two groups.

In conclusion, due to the diverse pathological and radiological appearances of AIs, it is important to evaluate demographic, etiological, clinical, laboratory, and radiological data as a whole in the treatment and follow-up process. Multicenter studies with subgroup analysis will be instrumental in determining better treatment and follow-up algorithms.

Authors contribution

The authors contributed equally to this work.

Disclosure statement

The authors declare no conflict of interest.

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