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Research article

Mineral metabolism assays and osteoporotic fracture risk evaluation in menopausal population diagnosed with adrenal incidentalomas: a sub-analysis of PRECES study

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Abstract: Adrenal incidentalomas (AIs) are clinically silent adrenal masses that are unintentionally found during various abdominal imaging procedures. Our objective was to evaluate the bone profile in menopausal females diagnosed with AI versus a non-AI control group. This was an observational, retrospective, multi-centric, case-control study, a sub-analysis of PRECES study ("Parameters of Romanian Patients with Endocrine Conditions with or without Endocrine Surgery: real-world-evidence and retrospective study"), a multi-centric, Romanian collaborative in the field of endocrinology and connected specialities (real-world community setting). Inclusion criteria: women in menopause between 40 and 85 years. Ex-clusion criteria: active endocrine tumours or cancers, prior or current medication against osteoporosis. Assessments included bone turnover markers, central DXA, FRAX-based os-teoporotic fracture risk evaluation. AIs were defined as having a value of second day plas-ma morning cortisol after 1-mg dexamethasone suppression test of < 1.8 μg/dL [without mild autonomous cortisol secretion (MACS free), as seen in control group that did not display the imaging evidence of an adrenal tumour] or between 1.8 and 5 μg/dL (MACS sub-group). Results: Demographic features of both groups (N=39 versus 95 patients) were simi-lar in terms of age (60.95±10.46 versus 61.55±7.2 years), years since menopause (14.92±10.32 versus 14.52±8.85 years), body mass index (28.03 versus 27 kg/sqcm); (p>0.1 for each). Osteopenia was the most prevalent DXA category in each group (43.6% versus 53.7%), followed by osteoporosis (20.5% versus 22.1%), while lumbar, total hip, femoral neck BMD were similar between AIs and controls. A

statistically significant lower osteocal-cin in subjects with AIs, with a median (Q1, Q3) of 16.5 (11.96-20.09) ng/mL compared with the value in control groups of 23.17 (15.9-31.46) ng/mL (p=0.003) was found. In AIs group, serum baseline morning cortisol positively correlated with lumbar Z-score, and correlation coefficient reached a statistical significance (p = 0.035). Of note, a tendency for correlation with total hip BMD was found, too. To conclude, decreased osteocalcin might be the signa-ture of mild cortisol anomalies in AIs, but DXA-BMD and FRAX algorithm revealed similar parameters in AI group versus controls, as found between MACS and MACS free sub-groups.

Keywords: study, osteoporosis, adrenal incidentaloma, hormone, surgery, cortisol, functional, FRAX, bone turnover marker

1. Introduction

Adrenal incidentalomas (AIs) are clinically silent adrenal masses that are unintentionally found during various imaging procedures. According to study criteria, the overall prevalence of AI ranges from 1% to 8.7% [1-3]. The incidence of AI rises with age, with the majority of cases occurring in females [4,5]. Up to 30% of AI patients express biochemical indicators of subtle hypersecretion of cortisol by the adrenal gland without the typical signs or symptoms of overt Cushing's syndrome [6,7]. According to the most recent guidelines, this entity is known as mild autonomous cortisol secretion (MACS)[8].The 1-mg dexamethasone suppression test (DST) is the standard dynamic test for defining MACS, however, there are differences in the cut-offs for the second-day plasma cortisol, ranging from 1.8 to 5 μg/dL[9,10].

The natural history of patients with adrenocortical adenomas that appear to be silent is currently unknown, despite recent evidence suggesting a link with hypertension, diabetes mellitus, obesity, and dyslipidaemia. A higher risk of cardiovascular events and mortality was associated with cortisol levels in patients with MACS [11]. Additionally, there is disagreement over whether MACS has any meaningful clinical impact at all according to some authors [12]. Although the relationship between MACS and clinical complications, such as osteoporosis and fragility fractures is not unanimously sustained, understanding the degree of bone involvement in AI patients could be crucial to their care [13]. Some studied showed a reduced bone mineral density (BMD) in AI [14-16]. Actually, there may be a link between a decline in BMD and even an increased risk of vertebral fractures in these patients [17,18]. Regarding the bone turnover, several studies found that MACS patients had a decreased bone formation as indicated by serum osteocalcin [19-21]. Different researches, however, did not confirm a decline of this parameter [22]. There are differences in the data regarding bone resorption as well, indicating it can be elevated, normal, or even decreased based on different serum bone turnover markers [23-25]. Managing patients with incidentally discovered adrenal masses (incidentalomas) represents a challenge, as well as the decision of adrenalectomy versus conservative approach. The most appropriate course of action for treating AI patients is still up for debate, and it might also depend on whether they exhibit a mild hormonal hypersecretion [26,27].

Our objective was to evaluate the bone profile in menopausal females diagnosed with AI versus a non-AI control group.

2. Results

After applying the inclusion and exclusion criteria, we enrolled 39 subjects with non-functional adrenal incidentalomas (AIs, group A) and 95 controls (group B).

2.1. Baseline characteristics

Subjects with AIs had no statistically significant differences compared with controls in terms of baseline characteristics, including age, body mass index (BMI), metabolic syndrome, and comorbidities such as diabetes mellitus or impaired fasting glucose,

hypertension, dyslipidaemia, or metabolic syndrome. ACTH and basal plasma morning cortisol levels, as well as thyroid function and serum electrolytes were similar between groups. (Table 1)

Table 1. Baseline characteristics of subjects with AIs compared with controls (AI=adrenal incidentalomas, Q=first quartile, Q3=third quartile, SD=standard deviation)

Parameter, unit	Subjects with AIs	Controls	p-value
Age, years (mean ± SD)	60.95±10.46	61.55±7.2	0.745
Age at menopause, years (median, Q1, Q3)	47 (44-50)	48 (43-51)	0.750
Years of menopause (mean ± SD)	14.92±10.32	14.52±8.85	0.818
Current smoking (number, %)	8 (20.5%)	20 (21.1%)	0.944
BMI, kg/m^2 (median, Q1, Q3)	28.03 (24.8-33.4)	27 (24-31)	0.109
Hypertension (number, %)	32 (82.1%)	64 (67.4%)	0.087
Dyslipidemia (number, %)	26 (66.7%)	57 (60%)	0.470
Type 2 diabetes mellitus, (number, %)	10 (25.6%)	20 (21.1%)	0.563
Impaired fasting glucose (number, %)	5 (12.8%)	4 (4.2%)	0.070
Metabolic syndrome (number, %)	15 (38.5%)	28 (29.5%)	0.311
ACTH, pg/mL (median, Q1, Q3)	11.88 (7-20.48)	18.30 (12.16-27.17)	0.125
Cortisol, μg/dL (mean±SD)	13.87±5.47	11.93±3.14	0.447
TSH, μUI/mL (median, Q1, Q3)	1.5 (0.68-2.3)	1.69 (1.05-2.90)	0.254
Free-T4, pmol/L (mean±SD)	13.49±3.14	14.74±2.95	0.125
Sodium, mmol/L, (median, Q1, Q3)	141 (138-143)	141 (138.5-142)	0.658
Potasium, mmol/L, (median, Q1, Q3)	4.4 (4.19-4.7)	4.32 (4.08-4.60)	0.352

In terms of mineral metabolism, there were no statistically significant differences between the two groups. (Table 2)

Table 2. Biochemical calcium metabolism parameters in subjects with AIs versus controls (AI=adrenal incidentalomas, Q1=first quartile, Q3=third quartile, SD=standard deviation)

Parameter, unit	Subjects with AIs	Controls	p-value
Total serum calcium, mg/dL (median, Q1, Q3)	9.60 (9.28-10.2)	9.5 (9.3-9.8)	0.262
Ionized serum calcium, mg/dL (median, Q1, Q3)	4.20 (4.05-4.3)	4.15 (3.95-4.27)	0.195
Serum phosphorus, mg/dL (mean±SD)	3.60±0.63	3.70±0.56	0.430
Serum magnesium, mg/dL (mean±SD)	1.96±0.22	1.96±0.17	0.440
Total serum protein, g/dL (mean±SD)	7.32±0.44	7.43±0.50	0.242
25-hydroxyvitamin D, ng/mL (mean±SD)	17.88±7.26	20.63±9.42	0.083
PTH, pg/mL (mean±SD)	49.19±28.05	51.55±23.55	0.349

2.2. Bone status evaluation in AIs

Osteoporosis and osteopenia had similar prevalence between AIs subjects and controls. (Table 3)

Table 3. Prevalence of osteoporosis and osteopenia in the studied groups

DXA category	Subjects with AIs	Controls	p-value
Normal (number, %)	14 (35.9%)	23 (24.2%)	0.376
Osteopenia (number, %)	17 (43.6%)	51 (53.7%)	
Osteoporosis (number, %)	8 (20.5%)	21 (22.1%)	

We further analysed lumbar, femoral neck and total hip BMD, T-scores and Z-scores according to central DXA with similar values. (Table 4)

Table 4. Bone status in subjects with AIs compared with controls (AI=adrenal incidentalomas, BMD=bone mineral density; Q1=first quartile, Q3=third quartile, SD=standard deviation)

Parameter		Subjects with AIs	Controls	p-value
Lumbar	BMD, g/cm^2 (mean±SD)	1.049±0.17	1.017±0.19	0.383
	T-score (mean±SD)	-0.97±1.42	-1.23±1.40	0.331
	Z-score (median, Q1, Q3)	0 (-1 – 0.5)	-0.40 (-1.1 – 0.4)	0.362
Femoral neck	BMD, g/cm^2 (median, Q1, Q3)	0.888 (0.801 – 0.995)	0.868 (0.782 – 0.934)	0.287
	T-score (median, Q1, Q3)	-1.05 (-1.6 – -0.22)	-1.2 (-1.8 – -0.7)	0.278
	Z-score (median, Q1, Q3)	-0.1 (-0.57 – 0.67)	-0.1 (-0.6 – 0.3)	0.661
Total Hip	BMD, g/cm^2 (mean±SD)	0.955±0.19	0.946±0.15	0.829
	T-score (mean±SD)	-0.35±1.42	-0.48±1.20	0.645
	Z-score (median, Q1, Q3)	0.5 (-0.45 – 1.35	0.1 (-0.3-0.9)	0.284

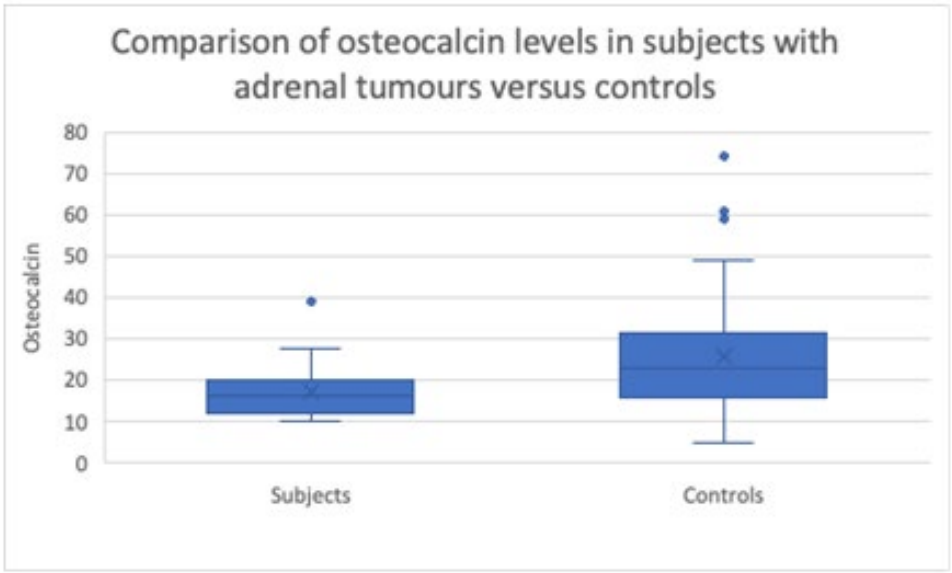
Major osteoporotic and hip fracture risk was also assessed and found to be similar. (Table 5)

Table 5. Fracture risk based on FRAX evaluation in subjects with AIs and controls (AI =adrenal incidentalomas, BMD=bone mineral density; Q1=first quartile, Q3=third quartile)

Parameter	Subjects with AIs	Controls	p-value
Major osteoporotic fracture risk, % (median, Q1, Q3)	3.7 (2.9 – 6)	3.6 (2.8 – 5.3)	0.994
Major osteoporotic fracture risk with BMD adjustment, % (median, Q1, Q3)	3.55 (2.77 – 4.95)	3.7 (2.9 – 4.9)	0.674
Hip fracture risk, % (median, Q1, Q3)	0.6 (0.3 – 1.3)	0.6 (0.4 – 1.6)	0.476
Hip fracture risk with BMD adjustment, % (median, Q1, Q3)	0.4 (0.2 – 1.17)	0.6 (0.3 – 1.4)	0.219

The analysis of bone turnover markers revealed a statistically significant lower osteocalcin level in subjects with AIs, with a median (Q1, Q3) of 16.5 (11.96-20.09) ng/mL, compared with 23.17 (15.9-31.46) ng/mL in controls. (Figure 1)

Figure 1. Osteocalcin evaluation across the two studied groups (p = 0.003)



Additionally, serum bone turnover markers revealed a tendency of lower CrossLaps and P1NP in AIs group versus control. (Table 6)

Table 6. Serum bone turnover markers in AIs versus controls (Q=quartiles)

Parameter, unit	Subjects with AIs	Controls	p-value
Crosslaps, ng/mL (median, Q1, Q3)	0.34 (0.23 – 0.52)	0.46 (0.31 – 0.60)	0.053
Osteocalcin, ng/mL (median, Q1, Q3)	16.5 (11.96 – 20.09)	23.17 (15.9 – 31.46)	**0.003**
P1NP, ng/mL (median, Q1, Q3)	40.58 (24.16 – 51.26)	49.51 (36.01 – 71.57)	0.056
Alkaline phosphatase, U/L (median, Q1, Q3)	71 (57 – 99)	75.5 (66.5 – 96.25)	0.265

In AIs group, serum baseline morning cortisol level positively correlated with lumbar Z-score, and correlation coefficients reached a statistical significance (p = 0.035). Of note, a tendency for correlation with total hip BMD was found, too. (Table 7)

Table 7. Correlations between cortisol levels and bone status parameters in subjects with AIs (BMD=bone mineral density)

Parameters	Correlation Coefficient	p-value
Cortisol and crosslaps	-0.298	0.246
Cortisol and osteocalcin	0.024	0.931
Cortisol and P1NP	-0.145	0.710
Cortisol and alkaline phosphatase	-0.322	0.109
Cortisol and lumbar BMD	0.160	0.375
Cortisol and lumbar T-score	0.220	0.219
Cortisol and lumbar Z-score	0.369	**0.035**
Cortisol and femoral neck BMD	-0.118	0.526
Cortisol and femoral neck T-score	0.017	0.928
Cortisol and femoral neck Z-score	0.198	0.284
Cortisol and total hip BMD	-0.443	0.050
Cortisol and total hip T-score	-0.212	0.369
Cortisol and total hip Z-score	-0.130	0.586

Cortisol level after DST negatively correlated with P1NP level (r = -0.857, p = 0.014). (Table 8)

Table 8. Correlations between cortisol value after DST and serum bone markers in subjects with AIs

Parameters	Correlation Coefficient	p-value
Cortisol after suppression test and crosslaps	-0.172	0.659
Cortisol after suppression test and osteocalcin	-0.571	0.084
Cortisol after suppression test and P1NP	-0.857	**0.014**
Cortisol after suppression test and alkaline phosphatase	0.337	0.310

2.3. Mild autonomous cortisol secretion (MACS) in AIs

A further analysis was performed on subjects with AIs: with MACS (N = 8, 20.5%), and MACS-free (N = 31, 79.5%). Baseline characteristics in subjects with MACS compared with MACS-free were similar, except for the number of smokers, which was higher in subjects MACS sub-group. (Table 9)

Table 9. Baseline characteristics of AIs subjects with MACS and MACS free (AI=adrenal incidentalomas, ACTH=Adrenocorticotropic Hormone; BMI=body mass index; MACS=mild autonomous cortisol secretion, Q1=first quartile, Q3=third quartile, SD=standard deviation, TSH=Thyroid Stimulating Hormone)

Parameter, unit	AI with MACS	AI without MACS	p-value
Age, years (mean±SD)	59.75±7	61.26±11.26	0.722
Age at menopause, years (mean±SD)	45.75±3.61	47.13±4.68	0.445
Years of menopause (mean±SD)	14.88±7.12	14.94±11.10	0.988
Current smoking, (number, %)	4 (50%)	4 (12.9%)	**0.021**
BMI, kg/m^2 (mean±SD)	30.4±4.68	28.54±5.16	0.365
Hypertension, (number, %)	6 (75%)	26 (83.9%)	0.560
Dyslipidaemia, (number, %)	6 (75%)	20 (64.5%)	0.575
Type 2 diabetes mellitus, (number, %)	2 (25%)	8 (25.8%)	0.963
Impaired fasting glucose, (number, %)	1 (12.5%)	4 (12.9%)	0.976
Metabolic syndrome, (number, %)	4 (50%)	11 (35.5%)	0.452
ACTH, pg/mL (median, Q1, Q3)	9.56 (8.01 – 13.35)	12.3 (5.75 – 21)	0.611
Cortisol, μg/dL (mean±SD)	15.13±4.63	13.47±5.74	0.465
TSH, μUI/mL (mean±SD)	0.99±0.92	1.86±1.14	0.068
Sodium, mmol/L, (median, Q1, Q3)	139 (138 – 141)	142 (138 – 143)	0.375
Potasium, mmol/L, (median, Q1, Q3)	4.27 (4.11 – 4.84)	4.5 (4.2 – 4.7)	0.393

Biochemical parameters regarding calcium metabolism were similar in both subgroups. (Table 10)

Table 10. Biochemical parameters of mineral metabolism parameters in subjects with AIs with and without MACS (AI=adrenal incidentalomas, MACS=mild autonomous cortisol secretion, PTH=parathormone; Q1=first quartile, Q3=third quartile, SD=standard deviation)

Parameter, unit	AI with MACS	AI without MACS	p-value
Total serum calcium, mg/dL (mean±SD)	9.66±0.67	9.75±0.59	0.719
Ionized serum calcium, mg/dL (median, Q1, Q3)	4.1 (4.05 – 4.55)	4.2 (4.04 – 4.3)	0.857
Serum phosphorus, mg/dL (mean±SD)	3.33±0.27	3.67±0.67	0.122
Serum magnesium, mg/dL (mean±SD)	1.84±0.33	1.98±0.20	0.215
Total serum protein, g/dL (mean±SD)	7.19±0.44	7.35±0.44	0.188
25-hydroxyvitamin D, ng/mL (mean±SD)	19.25±6.72	17.41±7.54	0.574
PTH, pg/mL (mean±SD)	48.88±14.36	49.31±32.41	0.976

In terms of bone status, subjects with AI and MACS had a higher prevalence of osteopenia and osteoporosis than subjects without MACS. (Table 11)

Table 11. The prevalence of osteoporosis and osteopenia in AIs subjects with MACS compared with those without MACS (AI=adrenal incidentalomas, MACS=mild autonomous cortisol secretion)

DXA category	AI with MACS	AI without MACS	p-value
Normal (number, %)	1 (12.5%)	13 (41.9%)	0.292
Osteopenia (number, %)	5 (62.5%)	12 (38.7%)	
Osteoporosis (number, %)	2 (25%)	6 (19.4%)	

No differences were observed regarding DXA evaluation. (Table 12)

Table 12. DXA assessment in MACS subgroup compared with subjects without MACS (AI=adrenal incidentalomas, BMD=bone mineral density; MACS=mild autonomous cortisol secretion, Q1=first quartile, Q3=third quartile, SD=standard deviation)

Parameter, region		AI with MACS	AI without MACS	p-value
Lumbar	BMD, g/cm^2 (mean±SD)	1.062±0.17	1.046±0.17	0.819
	T-score (mean±SD)	-0.77±1.23	-1.01±1.48	0.671
	Z-score (median, Q1, Q3)	0.22±1.03	-0.24±1.25	0.346
Femoral neck	BMD, g/cm^2 (median, Q1, Q3)	0.808±0.15	0.908±0.14	0.090
	T-score (median, Q1, Q3)	-1.26±0.65	-0.88±1.10	0.366
	Z-score (median, Q1, Q3)	-0.28±0.72	0.11±0.90	0.257
Total Hip	BMD, g/cm^2 (mean±SD)	0.855±0.20	0.994±0.17	0.100
	T-score (mean±SD)	-1.08±1.25	-0.06±1.41	0.109
	Z-score (median, Q1, Q3)	-0.07±1.17	0.61±1.03	0.165

FRAX evaluation showed a similar calculated risk in MACS and MACS free individuals with AIs. (Table 13)

Table 13. Fracture risk in patients with and without MACS according to FRAX calculator (AI=adrenal incidentalomas, MACS=mild autonomous cortisol secretion, Q1=first quartile, Q3=third quartile)

Fracture risk assessment	AI with MACS	AI without MACS	p-value
Major osteoporotic fracture risk, % (median, Q1, Q3)	3.25 (3.12 – 4.50)	3.8 (2.60 – 6.10)	0.695
Major osteoporotic fracture risk with BMD adjustment, % (median, Q1, Q3)	4.05 (3.25 – 8.1)	3.35 (2.62 – 4.77)	0.135
Hip fracture risk, % (median, Q1, Q3)	0.55 (0.32 – 1.07)	0.70 (0.30 – 2.00)	0.720
Hip fracture risk with BMD adjustment, % (median, Q1, Q3)	0.90 (0.27 – 1.85)	0.30 (0.20 – 1.07)	0.156

Serum bone turnover markers in AIs sub-groups showed similar values. (Table 14)

Table 14. Serum bone turnover markers in AIs patients with and without MACS (AI=adrenal incidentalomas, MACS=mild autonomous cortisol secretion, Q1=first quartile, Q3=third quartile)

Bone turnover marker	AI with MACS	AI without MACS	p-value
Crosslaps, ng/mL (median, Q1, Q3)	0.30±0.08	0.40±0.19	0.152
Osteocalcin, ng/mL (median, Q1, Q3)	15.26±2.72	18.01±8.21	0.316
P1NP, ng/mL (median, Q1, Q3)	29.55±19.35	42.75±12.95	0.441
Alkaline phosphatase, U/L (median, Q1, Q3)	89.80±51.48	78.55±27.39	0.475

3. Discussion

Across this study we investigated AIs menopausal patients versus controls. In order to achieve this, BMD and serum bone turnover in female AI patients were assessed. We observed altered osteoblastic activity, as indicated by decreased osteocalcin levels in group A versus B, according to prior published data [19,24,28]. This result is consistent with the observation that an excess of glucocorticoids promotes osteoblastic apoptosis and suppresses osteoblastic differentiation and activity. Other studies, however, did not confirm this decline of osteocalcin [29,30]. The data regarding bone resorption exhibit great variability, contingent upon the specific bone turnover marker that has been evaluated. It has been reported that CrossLaps (bone resorption marker) has either increased or decreased levels in AIs [19,30].CrossLaps levels in our series did not differ between the AIs and control groups.

There were no statistically significant differences between patients with AIs and controls in terms of lumbar, femoral neck, or hip BMD analysis, nor in terms of the prevalence of patients classified according to DXA categories based on T-score. Following the division of AI patients into two groups based on the presence or absence of MACS, we did not detect a decreased BMD at any site between these two sub-groups. Additional cross-sectional studies did not report any BMD reduction in AIs patients with MACS [32,33]. In contrast, other authors identified that patients with AIs had lower BMD versus apparently healthy controls [22,34-36]. Effects of mild cortisol hypersecretion on bone mass are not gender-specific, as suggested by the lower BMD observed in male AI patients with MACS [29]. Notably, we exclude patients with active malignancies or specific anti-cancer or anti-metastasis therapy in order to exclude their potential bone influence, including in bone turnover assessment [37,38]. However, patients with mild or subclinical hyperthyroidism were not excluded and this might change the overall bone assays (e.g. subjects with levothyroxine replacement therapy; yet, the patients with prior thyroid cancer were excluded) [39,40]. Similarly, patients with functional parathyroid tumours were excluded for the same rational [41]. Another potential influence on bone turnover might come from the co-presence of various rheumatologic disorders [42].

As a whole, the ladies with MACS had a higher prevalence of osteoporosis than those MACS free, as expected [43-45].

FRAX algorithm was used to analyse the absolute risk of fracture at 10 years; there was no statistically significant difference between each of the evaluated two sub-groups; of note AIs do not stand for a traditional cause of secondary osteoporosis as quantified by FRAX [46]. Subtle hypersecretion of cortisol influences bone metabolism and increases the risk of fragility fracture; however, the exact method of assessing these aspects is still a matter of debate. There is a higher than expected frequency of MACS-related vertebral fractures in male patients (72.7%), pre-menopausal patients (42.5%), and menopausal women (78.6%) versus healthy controls [17,18,47]. Potentially, bone microarchitecture might be more affected than BMD in AIs [48-52]. These differences between cross-sectional studies could have various reasons. Firstly, various criteria for the diagnosis of MACS might explain the different results. Some studies use DST at varying doses and cut-offs, occasionally combining this with low ACTH, high urine-free cortisol values, or increased midnight salivary cortisol level [53,54]. A cross-sectional analysis in a short series might not capture these fine details and subtle variations across a large range of BMD distribution [55-58] and this stands for a further topic to be studied on a larger scale.

The limitations of our study include a relatively small sample size; also, the control group had an ultrasound, computed tomography or magnetic resonance imagery done at abdominal level in order to exclude an adrenal tumor, an aspect that varied across the centers. Moreover, between March 2020 and early 2023 COVID-19 pandemic refined the medical reality, including with respect to bone health and we did not take into consideration the potential influence of a coronavirus infection amid bone status in terms of turnover or limited physical activity, etc.[59-62]. Moreover, cancer screening protocols were done according to the patients' primary health care; no routine assessment was particularly applied amid the study. Complex rehabilitation in these cases is the key for the increase the quality and life and long term benefits [63,64].

4. Materials and Methods

4.1. Study design

This was an observational, retrospective, multi-centric, case-control study. This was a sub-analysis of PRECES study (**"P**arametersof **R**omanianPatients with **E**ndocrine **C**onditionswith or without **E**ndocrine **S**urgery: real-world-evidence and retrospective study**")**, a multi-centric, Romanian collaborative in the field of endocrinology and connected specialities (real-world community setting).

4.2. Subjects

We analysed menopausal female patients diagnosed with AIs versus controls without adrenal incidentalomas, based on the following inclusion and exclusion criteria. (Table 15)

Table 15. Inclusion and exclusion criteria (DXA=Dual-Energy X-Ray Absorptiometry)

Inclusion criteria	Exclusion criteria
▪ Time-frame of admission: between January 2013 and December 2023 ▪ Age between 40 and 85 years ▪ Confirmed menopausal status ▪ Available DXA results ▪ Informed consent on admission according to local hospital protocol	• Clinically manifested Cushing's syndrome • Pheochromocytoma • Primary aldosteronism • Multiple endocrine neoplasia • Adrenal carcinoma • Primary hyperparathyroidism • Myelolipomas, lipomas, cysts, adrenal metastases • Active neoplasia

▪ Available specific endocrine data in order to sustained the diagnosis of non-functional adrenal incidentaloma	• Congenital adrenal hyperplasia • Type 1 diabetes mellitus • Paget's disease • Bone metastases • Osteogenesis imperfecta • Turner syndrome • Acromegaly • Prior specific therapy against osteoporosis • Glucocorticoid therapy

4.3. Assessments

The patients' age, menopausal status, and history of any medical and surgical conditions were collected (including the parameters from FRAXhttps://frax.shef.ac.uk/FRAX/), as well as parents' medical background on osteoporosis. On admission, each patient underwent blood tests including the following parameters: glucose, glycated haemoglobin, uric acid, sodium, potassium, total calcium, ionized calcium, phosphorus, magnesium, total protein, 25-hydroxyvitamin D (25OHD), parathormone (PTH), alkaline phosphatase, crosslaps, osteocalcin, aminoterminalpropeptide of type I procollagen (P1NP), adrenocorticotropic hormone (ACTH) and cortisol, respectively, thyroid function in terms of TSH (Thyroid Stimulating Hormone) and freeT4 (thyroxine).

AIs were first diagnosed based on intravenous contrast abdominal computed tomography. Additionally, the diagnosis of non-functional adrenal incidentalomas was based on clinical characteristics (lack of fully manifested Cushing's syndrome), basal ACTH, cortisol, aldosterone, renin, plasma and urinary metanephrines and normetanephrines levels. Non-functional AI were classified as tumours with MACS and without MACS, based on DST, namely, the second day plasma morning cortisol less than 1.8 μg/dL included AI without MACS while a value between 1.8 and 5 μg/dL was defined as MACS.

All patients underwent Dual-Energy X-Ray Absorptiometry (DXA) using a GE Lunar DXA device. Fracture risk was assessed using the FRAX® tool available for Romania (https://frax.shef.ac.uk/FRAX/tool.aspx?lang=ro). Normal DXA result was defined based a for a T-score at least or above -1, osteopenia for a T-score between -1 and -2.5, and osteoporosis for a T-score at least -2.5.

4.4. Statistical analysis

MicrosoftExcel 16.81 (Microsoft) was used to create the data base and SPSS Statistics 29.0.2.0. was used for statistical analysis. After testing for normality of distribution using the Kolmogorov-Smirnov test, continuous numerical data was compared using the student's t-test for normally distributed data and Mann-Whitney U test for non-normal distributions. Comparison of categorical variables was done based on frequencies and the chi-square test. The relationships between numerical variables were assessed with the Pearson or Spearman's correlation, based on the normality of distribution. The level of significance for rejecting the null hypothesis was $p\text{-value} < 0.05$.

4.5. Ethical aspects

Each patient agreed to anonymously use their medical record as a retrospective analysis according to each university hospital that has been admitted. Further on the retrospective data collection by investigators has been approved by each Local Ethical Committee as shown at the end of the article.

4. Conclusions

Lower levels of the bone formation marker such as osteocalcin, and similar BMD at central sites, respectively, 10-year absolute fracture risk, as determined by the FRAX algorithm were found in menopausal women with AIs versus controls, while sub-groups of AIs with MACS or MACS free were not distinct amid mineral metabolism assays and osteoporotic fracture risk.

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Informed Consent Statement: The data were retrospectively collected. The patients agreed for anonymous use of their medical records while being hospitalized according to each hospital regulations.

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