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Alternative cutoffs for cortisol post-Dexamethasone suppression testing: is there a practical point for the bone health evaluation?

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Abstract

Background: Current guideline-based stratification in the non-secretory adrenal tumors (ADTs) involves the second-day (post-Dexamethasone testing) plasma cortisol (D-C) threshold of <1.8 μg/dL to determine a non-functional profile and another one for a mild cortisol secretion (cortisol between 1.8 and 5 μg/dL). *Objective*: To analyze the bone status in terms of mineral metabolism, circulating biomarkers of bone turnover and bone mineral density in menopausal women with ADTs by comparing two population subgroups, according to distinct thresholds for D-C, which are out of the current guidelines (1.4 μg/dL and 0.9 μg/dL, respectively). *Patients, Materials and Methods*: A retrospective analysis was conducted in ADT-positive menopausal women. *Results*: Final analysis included 109 adults: ADT-1 group (52.3%; D-C: ≤1.4 μg/dL) *vs.* ADT-2 group (47.7%; D-C: 1.4–5 μg/dL) and ADT-3 group (20.2%; D-C: ≤0.9 μg/dL) *vs.* ADT-4 group (79.8%; D-C: 0.9–5 μg/dL), respectively. ADT-1 group *vs.* ADT-2 group was at similar age (60.14±8.56 *vs.* 60.08±11.85 years), menopause duration (13.85±7.41 *vs.* 14.19±8.54 years), body mass index (30.78±6.20 *vs.* 29.23±6.73 kg/m^2), and obesity rate (56% *vs.* 35.9%). Mineral metabolism assays showed no between-group difference. Both groups experienced a vitamin D deficiency according to 25-hydroxyvitamin D (23.69±10.42 *vs.* 25.35±9.98 ng/mL, *p*=0.481). Except for femoral neck T-score within ADT-1 group (-1.22±1.11), all the other dual energy X-ray absorptiometry (DXA) categories were normal. The prevalence of osteoporosis diagnosis was similar: 24.5% *vs.* 35.4%, with lower fracture rate (3.5% compared to 21.2%, *p*=0.005). ADT-3 group compared to ADT-4 group showed a similar bone health status. Half of patients suffered from obesity (50% *vs.* 46.4%, *p*=0.775). A borderline significance was attributed to a higher total hip T-score in ADT-3 group *vs.* ADT-4 group (-0.23 *vs.* -0.87, *p*=0.06), both with intra-normal values, and a lower fracture rate (0% *vs.* 14.9%, *p*=0.053). Osteoporosis diagnosis displayed a statistically significant decrease in the prevalence in ADT-3 group *vs.* ADT-4 group: 5.6% *vs.* 35.4% (*p*=0.042). *Conclusions*: Menopausal adults with D-C >0.9 μg/dL should be mandatory tested for osteoporosis, and those with D-C >1.4 μg/dL should be additionally screened for osteoporotic fractures, while age is not different among the subgroups with different cutoffs.

Keywords: adrenal tumor, incidentaloma, cortisol, ACTH, osteoporosis, surgery.

Introduction

Adrenal incidentalomas associate an increasing detection rate in contemporary medical era due to a large access at abdominal imaging investigations such as ultrasound, magnetic resonance imaging or (contrast-enhanced) computed tomography (CT) [1–3]. After the accidental radiological finding, a complete adrenal hormonal panel is mandatory to be performed, and most of these tumors are non-functional (70% to 95%) and do not involve a true oncological profile [4–6]. In this instance, the underlying pathological report involves an adrenocortical adenoma, and this is suggested by biochemical and hormonal assays in addition to imaging features, and only exceptionally confirmed post-adrenalectomy, since surgery is less likely required [7–9]. Non-conservative approach is essential for the tumors with a larger diameter than 4 cm, with significant size increase during follow-up or those associating a cutoff cortisol of >5 μg/dL after low-dose Dexamethasone drug administration amid suppression testing [10–12].

Most patients who are identified with adrenal incidentalomas are adults, females being more affected than males [13–15]. The overall prevalence of 1% to 5% is higher in certain population subgroups such as the cohorts with cardiovascular, metabolic and osseous comorbidities (up to 10–20% in consecutive preselected individuals based on comorbidities) [16–18]. Noting than menopausal women are more frequently diagnosed than females of reproductive

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age, the overlapping complications like osteoporosis and/or osteoporotic (fragility) fractures might be caused by a mild hormonal activity of the tumor, as well as the physiological hypoestrogenic status amid menopause [19–22].

Current guideline-based stratification in the non-secretory adrenal tumors (ADTs) involves apparently non-functional ADTs in patients with a second-day plasma cortisol measurement <1.8 μg/dL after 1 mg Dexamethasone testing and mild autonomous cortisol secretion if this hormone assay is found between 1.8 and 5 μg/dL [23–26].

Aim

Recent evidence showed that other thresholds of post-testing cortisol might point out a higher relative risk of tumor-related ailments [27–32], this being a knowledge gap which we aimed to address in this research. Our objective was to analyze the bone status in terms of the mineral metabolism-related parameters, circulating value of biomarkers for bone turnover and bone mass [specifically, bone mineral density (BMD)] in post-menopausal subjects diagnosed with a tumor of non-functional adrenal type by comparing two population subgroups, according to distinct thresholds for post-Dexamethasone testing cortisol levels, which are out of the current guidelines (1.4 μg/dL and 0.9 μg/dL, respectively).

Patients, Materials and Methods

A retrospective, cross-sectional, observational analysis was conducted in adults following menopause starting, subjects who were also confirmed with non-functional adrenal (incidentalomas) tumors, between October 2024 and February 2026.

Study population

The enrolled patients followed:

Inclusion criteria: age between 50 and 80 years; menopausal status; signed informed consent by each patient during hospitalization according to the hospital protocol; confirmed adrenal incidentaloma based on a complete hormonal testing and imaging characterization at abdominal CT.

Exclusion criteria: secretory ADTs/non-ADTs of any origin; Cushing disease/syndrome; cortisol >5 μg/dL (amid the mentioned Dexamethasone test); prior or concurrent diagnosis of cancer, osteoporosis, type 1 diabetes; previous adrenalectomy, bariatric surgery; incomplete hormonal panel and/or imaging profile of the adrenal mass; non-interpretable or non-available BMD/T-score at conventional dual energy X-ray absorptiometry (DXA); suspected malignancy at clinical exam, hormonal assessment and/or CT [33]; prior/concurrent exposure to glucocorticoids, insulin therapy, anti-obesity drugs, and anti-osteoporotic medication.

Study assessments

All included patients underwent abdominal CT and were found with unilateral or bilateral ADTs. The largest diameter of the single mass or bilateral tumors was registered (Figure 1).

Hormonal evaluation for the adrenal profile was performed and the adults who were found with non-secretory (apparently non-functional) tumor based on cortisol post-Dexamethasone testing of maximum 5 μg/dL were enrolled.

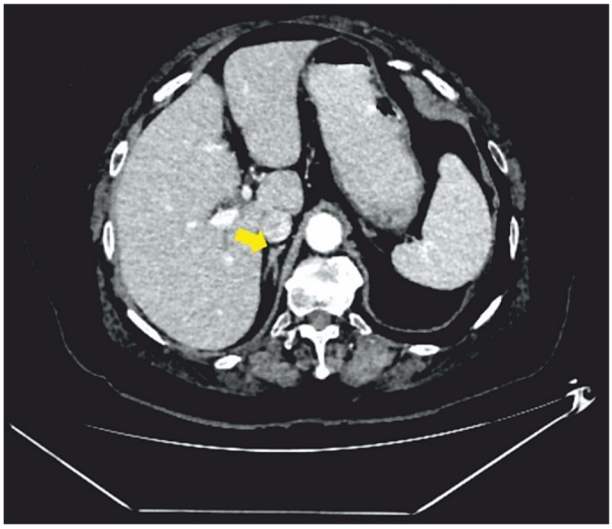

Figure 1 – ***Computed tomography (arterial phase, transverse plane): right adrenal incidentaloma (yellow arrow) of 1.2 cm (non-functioning adrenocortical adenoma of the cortex) in a 68-year-old female.***

The data collection involved the biochemical panel (serum total calcium, phosphorus); hormonal spectrum [adrenocorticotropic hormone (ACTH), morning plasma cortisol at baseline and second-day value after 1 mg overnight (low-dose) screening Dexamethasone testing, as well as parathormone (PTH) and blood vitamin D]; circulating biomarkers [bone formation (procollagen type 1 *N*-terminal propeptide (P1NP), alkaline phosphatase (ALP), osteocalcin) and bone resorption (CrossLaps)]. Medical records of the individuals provided the age, menopause duration (years since last menstruation), the history of diseases and medication as mentioned above, including previous osteoporotic (fragility) fractures. Moreover, central DXA (GE Lunar Prodigy) and thoracic–lumbar spine profile X-ray (as screening for asymptomatic vertebral fractures) were performed. All imaging captures (DXA scans, abdominal CT, X-ray) and electronic/digital medical records of prior osteoporotic fractures were re-analyzed by a skilled radiologist. Obesity was defined at a BMI of 30 kg/m^2 or higher, while osteoporosis diagnosis was based on T-score of -2.5 or below [34, 35].

Study protocol

The patients were analyzed based on two pairs of sub-groups: those with a cortisol ≤1.4 μg/dL *vs.* those with a cortisol value between 1.4 and 5 μg/dL, and the individuals with tumors and a cortisol level ≤0.9 μg/dL *vs.* adults with cortisol level >0.9 and <5 μg/dL, respectively (Figure 2).

Statistical analysis

The original data collection was performed in Excel, then imported in Statistical Package for the Social Sciences (SPSS). The mean ± standard deviation (SD) was applied for parameters with normal distribution, respectively, median/interquartile interval for those with non-normal distribution. *P*-value <0.05 was statistically significant.

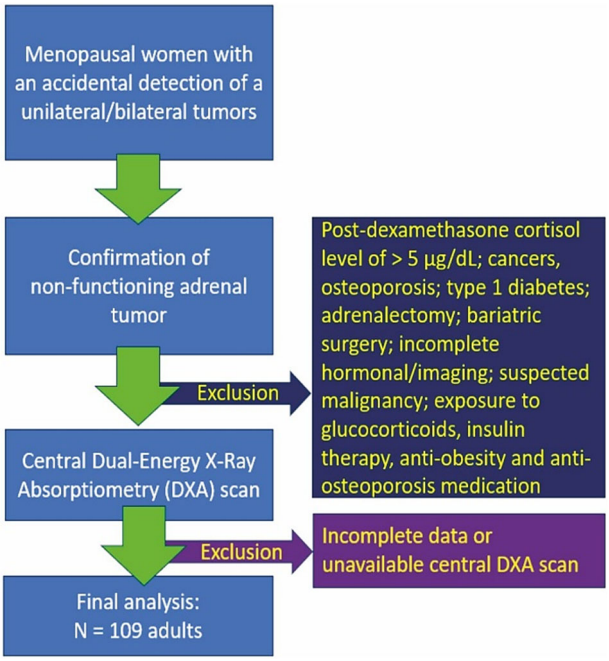

Figure 2 – ***Flowchart of the study protocol.***

Ethical aspects

The enrolled individuals were waived from the informed consent for this study due to its retrospective design, but they signed the informed consent during hospitalization to anonymously use their medical records. Ethical boards approved the study (hospital and university).

Results

One hundred and nine adults with ADTs were grouped based on the two mentioned cutoffs on the second day following Dexamethasone administration at 11.00 p.m.:

- ADT-1 group: 57 individuals with cortisol ≤1.4 µg/dL;
- ADT-2 group: 52 individuals with cortisol between 1.4 and 5 µg/dL;
- ADT-3 group: 22 individuals with cortisol ≤0.9 µg/dL;
- ADT-4 group: 87 individuals with a cortisol between 0.9 and 5 µg/dL.

ADT-1 group *vs.* ADT-2 group showed a statistically significant decreased largest tumor diameter (1.88±0.80 *vs.* 2.95±1.17 cm, $p<0.001$), and ADT-3 group *vs.* ADT-4 group (1.59±0.64 *vs.* 2.56±1.13 cm, $p<0.001$), respectively (Table 1).

Table 1 – ***Profile according to the study groups***

Parameter, unit, normal ranges	ADT-1 group	ADT-2 group	*p*-value	ADT-3 group	ADT-4 group	*p*-value
ACTH [pg/mL]; mean ± SD Normal: 3–66 pg/mL	16.28±10.60	12.33±11.38	0.066	17.69±11.43	13.59±10.94	0.131
Cortisol* [µg/dL]; mean ± SD Normal: 6.2–19.4 µg/dL	13.00±5.55	14.14±6.76	0.339	12.47±4.92	13.81±6.42	0.364
Cortisol** [µg/dL]; mean ± SD Normal: <1.8 µg/dL	0.99±0.25	2.69±1.06	<0.001	0.73±0.13	2.08±1.11	<0.001
Unilateral tumors [*n*, %]	38, 67.9%	28, 56%	0.209	13, 61.9%	53, 62.4%	0.970
Largest diameter of the tumor [cm]; mean ± SD	1.88±0.80	2.95±1.17	<0.001	1.59±0.64	2.56±1.13	<0.001

*Means baseline morning plasma cortisol; **Means cortisol following 1 mg overnight Dexamethasone. ACTH: Adrenocorticotropic hormone; ADT: Adrenal tumor; *n*: No. of patients; SD: Standard deviation.

The analysis based on the 1.4 µg/dL level of the second-day plasma cortisol identified two groups with similar ($p>0.05$ for each) variables, as follows: age (60.14±8.56 *vs.* 60.08±11.85 years), menopause duration (13.85±7.41 *vs.* 14.19±8.54 years), body mass index (BMI) (30.78±6.20 *vs.* 29.23±6.73 kg/m^2), and obesity rate (56% *vs.* 35.9%). The mineral metabolism assays showed no between-group difference, while both groups experienced a vitamin D deficiency according to the average values of serum 25-hydroxyvitamin D: 23.69±10.42 *vs.* 25.35±9.98 ng/mL ($p=0.481$) (Table 2).

Table 2 – ***Mineral metabolism and bone status in menopausal females with non-functioning ADTs associating a post-Dexamethasone testing cortisol ≤1.4 µg/dL (ADT-1 group) vs. those with a cortisol 1.4–5 µg/dL (ADT-2 group)***

Parameter, unit, normal ranges	ADT-1 group	ADT-2 group	*p*-value ADT-1 *vs.* ADT-2
Number of patients [*n*, %]	57, 52.3%	52, 47.7%	
Age [years]; mean ± SD	60.14± 8.56	60.08± 11.85	0.974
Years since menopause; mean ± SD	13.85± 7.41	14.19± 8.54	0.864
BMI [kg/m^2]; mean ± SD	30.78± 6.20	29.23± 6.73	0.264
Obesity [*n*, %]	28, 56%	14, 35.9%	0.059
Serum total calcium [mg/dL]; mean ± SD Normal: 8.4–10.2 mg/dL	9.44± 0.44	9.56± 0.41	0.153
Serum phosphorus [mg/dL]; mean ± SD Normal: 2.3–4.7 mg/dL	3.52± 0.53	3.72± 0.57	0.075
PTH [pg/mL]; mean ± SD Normal: 15–65 pg/mL	51.05± 17.56	44.34± 17.92	0.136
25-hydroxyvitamin D [ng/mL]; mean ± SD Normal: >30 ng/mL	23.69± 10.42	25.35± 9.98	0.481
P1NP [ng/mL]; mean ± SD Normal: 20.25–76.31 ng/mL	46.33± 16.96	54.61± 24.71	0.166
ALP [U/L]; mean ± SD Normal: 35–104 U/L	74.26± 29.47	77.06± 22.96	0.615
Osteocalcin [ng/mL]; mean ± SD Normal: 15–46 ng/mL	20.97± 11.51	22.16± 12.47	0.694
CrossLaps [ng/mL]; mean ± SD Normal: 0.33–0.782 ng/mL	0.417± 0.24	0.451± 0.29	0.612
Lumbar BMD [g/cm^2]; mean ± SD	1.055± 0.16	1.073± 0.15	0.638
Lumbar T-score; mean ± SD Normal: +1 to -1	-1.01± 1.29	-1.09± 1.55	0.789
Femoral neck BMD [g/cm^2]; mean ± SD	0.849± 0.14	0.856± 0.12	0.844
Femoral neck T-score; mean ± SD Normal: +1 to -1	-1.22± 1.11	-1.06± 1.02	0.557

Parameter, unit, normal ranges	ADT-1 group	ADT-2 group	*p*-value ADT-1 *vs.* ADT-2
Total hip BMD [g/cm^2]; mean ± SD	0.939± 0.17	0.932± 0.14	0.865
Total hip T-score; mean ± SD Normal: +1 to -1	-0.61± 1.17	-0.86± 1.17	0.375
Fragility fractures [*n*, %]	2, 3.5%	11, 21.2%	0.005
Osteoporosis diagnosis [*n*, %]	12, 24.5%	17, 35.4%	0.458

ADT: Adrenal tumor; ALP: Alkaline phosphatase; BMD: Bone mineral density; BMI: Body mass index; *n*: No. of patients; P1NP: Procollagen type 1 *N*-terminal propeptide; PTH: Parathormone; SD: Standard deviation.

DXA-based BMDs also confirmed similar levels, noting that, except for the femoral neck mean T-score within ADT-1 group (-1.22±1.11), all the other five DXA categories showed normal results. The prevalence of osteoporosis diagnosis according to the lowest T-score at DXA was similar: 24.5% *vs.* 35.4% in ADT-1 group *vs.* ADT-2 group. On the other hand, the fractures rate was statistically significantly higher in the group with higher post-Dexamethasone cortisol: 21.2% *vs.* 3.5% (p=0.005) (Figure 3).

ADT-3 group *vs.* ADT-4 group showed similar bone health status, as assessed by the study protocol. Almost half of the patients suffered from obesity (50% *vs.* 46.4%, p=0.775). Hypovitaminosis D was reflected by the reduced average serum 25-hydroxyvitamin D within each group (Table 3).

Table 3 – ***Bone health in females with non-functioning ADTs associating a post-Dexamethasone testing cortisol ≤0.9 µg/dL (ADT-3 group) vs. 0.9–5 µg/dL (ADT-4 group)***

Parameter, unit, normal ranges	ADT-3 group	ADT-4 group	*p*-value ADT-3 *vs.* ADT-4
Number of patients [*n*, %]	22, 20.2%	87, 79.8%	
Age [years]; mean ± SD	58.18± 8.23	60.60± 10.64	0.324
Years since menopause; mean ± SD	12.07± 7.89	14.55± 7.80	0.284
BMI [kg/m^2]; mean ± SD	30.08± 4.84	30.11± 6.87	0.980
Obesity [*n*, %]	10, 50%	32, 46.4%	0.775
Serum total calcium [mg/dL]; mean ± SD Normal: 8.4–10.2 mg/dL	9.46± 0.44	9.52± 0.43	0.639
Serum phosphorus [mg/dL]; mean ± SD Normal: 2.3–4.7 mg/dL	3.47± 0.44	3.65± 0.57	0.235
PTH [pg/mL]; mean ± SD Normal: 15–65 pg/mL	49.89± 16.65	47.19± 18.46	0.599
25-hydroxyvitamin D [ng/mL]; mean ± SD Normal: >30 ng/mL	23.51± 7.63	24.72± 10.79	0.612
P1NP [ng/mL]; mean ± SD Normal: 20.25–76.31 ng/mL	48.27± 12.77	51.42± 23.67	0.661
ALP [U/L]; mean ± SD Normal: 35–104 U/L	76.44± 15.12	75.53± 28.14	0.901
Osteocalcin [ng/mL]; mean ± SD Normal: 15–46 ng/mL	19.47± 7.27	22.15± 12.87	0.474
CrossLaps [ng/mL]; mean ± SD Normal: 0.33–0.782 ng/mL	0.370± 0.11	0.451± 0.29	0.358
Lumbar BMD [g/cm^2]; mean ± SD	1.10± 0.17	1.05± 0.16	0.333
Lumbar T-score; mean ± SD Normal: +1 to -1	-0.75± 1.33	-1.12± 1.43	0.331
Femoral neck BMD [g/cm^2]; mean ± SD	0.912± 0.14	0.841± 0.13	0.115
Femoral neck T-score; mean ± SD Normal: +1 to -1	-0.71± 1.07	-1.22± 1.05	0.150
Total hip BMD [g/cm^2]; mean ± SD	0.990± 0.13	0.920± 0.16	0.185
Total hip T-score; mean ± SD Normal: +1 to -1	-0.23± 1.06	-0.87± 1.17	0.060
Fragility fractures [*n*, %]	0	13, 14.9%	0.053
Osteoporosis diagnosis [*n*, %]	1, 5.6%	28, 35.4%	0.042

ADT: Adrenal tumor; ALP: Alkaline phosphatase; BMD: Bone mineral density; BMI: Body mass index; *n*: No. of patients; P1NP: Procollagen type 1 *N*-terminal propeptide; PTH: Parathormone; SD: Standard deviation.

A borderline significance was attributed to a higher total hip (average) T-score in the group with lower *vs.* higher post-Dexamethasone cortisol (-0.23 *vs.* -0.87, p=0.06), both with intra-normal values, as well as a lower rate of osteoporotic fractures (0% *vs.* 14.9%, p=0.053). Osteoporosis diagnosis, as provided by central DXA, displayed a statistically significant decreased prevalence in ADT-3 group *vs.* ADT-4 group: 5.6% *vs.* 35.4% (p=0.042) (Figure 4).

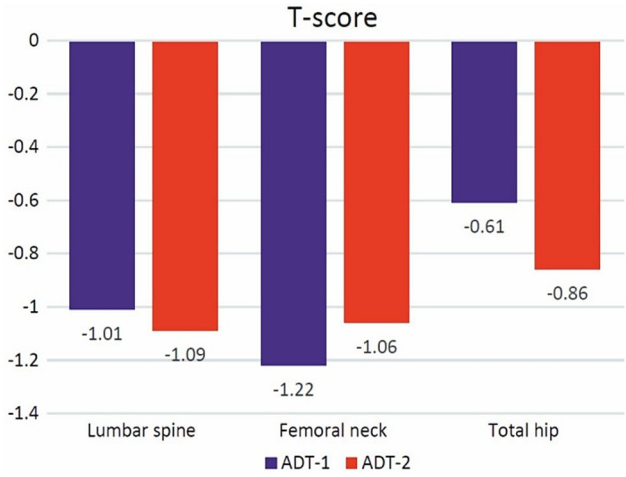

Figure 3 – ***Analysis of T-scores in ADT-1 vs. ADT-2 groups. ADT: Adrenal tumor.***

Figure 4 – ***Analysis of T-scores in ADT-3 vs. ADT-4 groups.***

Bone parameters were similar in ADT-1 group *vs.* ADT-3 group and ADT-2 group *vs.* ADT-4 group, respectively (Table 4).

Table 4 – ***The comparison between the groups with lower cortisol (below the selected cutoffs: ≤1.4 μg/dL vs. ≤0.9 μg/dL) and between the groups with a higher cortisol level (>1.4 μg/dL vs. >0.9 μg/dL), respectively***

Parameter, unit, normal ranges	*p*-value ADT-1 *vs.* ADT-3	*p*-value ADT-2 *vs.* ADT-4
Age [years]	0.360	0.790
Years since menopause	0.441	0.850
BMI [kg/m^2]	0.651	0.523
Obesity rate [*n*, %]	0.649	0.262
Serum total calcium [mg/dL]	0.860	0.515
Serum phosphorus [mg/dL]	0.742	0.495
PTH [pg/mL]	0.821	0.506
25-hydroxyvitamin D [ng/mL]	0.949	0.776
P1NP [ng/mL]	0.729	0.591
ALP [U/L]	0.779	0.757
Osteocalcin [ng/mL]	0.667	0.997
CrossLaps [ng/mL]	0.538	0.992
Lumbar $L_{1–4}$ BMD [g/cm^2]	0.381	0.591
Lumbar $L_{1–4}$ T-score	0.482	0.917
Femoral neck BMD [g/cm^2]	0.223	0.604
Femoral neck T-score	0.197	0.487
Total hip BMD [g/cm^2]	0.374	0.778
Total hip T-score	0.291	0.970
Fragility fractures [*n*, %]	0.374	0.348

ADT: Adrenal tumor; ALP: Alkaline phosphatase; BMD: Bone mineral density; BMI: Body mass index; *n*: No. of patients; P1NP: Procollagen type 1 *N*-terminal propeptide; PTH: Parathormone.

Discussions

In this analysis of 109 menopausal females confirmed with apparently non-functional adrenal incidentalomas, we applied two unconventional thresholds for cortisol (following low dose of Dexamethasone administration), which represents the current standard diagnosis (for the values of 1.8 μg/dL) [26]. Thus, we selected two novel cutoffs based on prior published data. Specifically, Araujo-Castro *et al.* [27] published a multi-centric, retrospective, observational study in 2023 aiming to analyze the cardio-metabolic outcomes in 593 adults with non-functioning adrenal incidentalomas, and 74.5% of them were integrated within the subgroup with cortisol ≤1.4 μg/dL. The individuals with a cortisol >1.4 μg/dL were older than those with a lower cortisol, but, after adjustment for age, the cardio-metabolic profile was similar [27]. In the present analysis, we identified a lower rate for the subjects with a cortisol ≤1.4 μg/dL after Dexamethasone testing (ADT-1 group; 52.3%), and they had similar age with the group presenting a cortisol above this cutoff (ADT-2 group; 47.7%). Moreover, we found a lower tumor diameter in the group with lower cortisol level (1.88±0.80 *vs.* 2.95±1.17 cm, $p<0.001$), but with similar total blood calcium, PTH, circulating vitamin D, circulating bone biomarkers and BMDs at DXA. The osteoporosis prevalence was 24.5% *vs.* 35.4% ($p=0.458$), with a statistically significant lower fracture rate (21.2% *vs.* 3.5%, $p=0.005$).

Additionally, when applying the 0.9 μg/dL cutoff, the prior mentioned study identified that 69.5% of the patients had a cortisol above 0.9 μg/dL with a statistically significant increased age and rate of cardiovascular disease [27]. In our study, 79.8% of the patients had cortisol >0.9 μg/dL (ADT-4 group) and they had a similar age and bone status with ADT-3 group. However, they presented a slightly lower T-score at total hip (-0.87 *vs.* -0.23, $p=0.06$), a higher rate of fractures (14.9% *vs.* 0%, $p=0.053$), and a statistically significant increase osteoporosis prevalence of 35.4% *vs.* 5.6% ($p=0.042$). The tumor size increased as well (2.56±1.13 cm *vs.* 1.59±0.64 cm, $p<0.001$).

These findings suggest that a lower cortisol level than required according to the guideline-based definition (0.9 μg/dL or 1.4 μg/dL) offered a distinctive perspective with respect to the osteoporosis/osteoporotic fracture prevalence, thus the need of DXA screening in females with a higher cortisol level. The screening for vertebral fractures, as shown by the spine profile X-ray might not be enough, and an improved detection rate might be provided by vertebral fracture assessment or opportunistic vertebral fractures evaluation during CT scan [36–41].

Longitudinal data might help understanding the risk of further developing osteoporosis/fragility fractures in association with changes of cortisol levels. For example, Ahn *et al.* [42] analyzed the impact of age on the post-Dexamethasone cortisol values across a retrospective, four-centric cohort study in 1063 Korean patients confirmed with adrenal incidentalomas, between 2003 and 2022. Age was found to associate a statistically significant non-linear effect on these cortisol levels ($p<0.001$), with a higher risk of progression to elevated level in individuals who were followed for more than five years *vs.* < two years ($p<0.001$), both in subjects with non-functional tumors and those with mild excess of cortisol as designed for autonomous cortisol secretion nowadays [42].

Limitations of the current analysis potentially include the design and cohort rather small size. Of important note, a supplementary analysis of the cardio-metabolic outcomes, not only osseous, in cross-sectional and longitudinal studies to compare surveillance *vs.* surgical intervention might highlight the overall health burden that comes with these tumors. For instance, a similar single-center study revealed diabetes risk was higher in adults experiencing mild cortisol excess *vs.* true non-functioning masses [odds ratio (OR) 7.81, $p=0.04$] and after a 28-month median of post-surgery follow-up, the weight statistically significant improved, while pre-operatory post-Dexamethasone cortisol was a predictor of this improvement (OR of 1.88, $p=0.04$) [43]. In our analysis, we identified similar BMI values between the groups, notably with a mean level within obesity or overweight category (ADT-1 group *vs.* ADT-2 group of 30.78±6.20 *vs.* 29.23±6.73 kg/m^2, $p=0.264$ and 30.08±4.84 *vs.* 30.11±6.87 kg/m^2, $p=0.08$, respectively). The rate of obesity involved 32% to 56% of the patients, depending on the study group.

Further metabolomics analysis might include other molecules involved in the steroidogenesis to potentially correlate with osseous complications in patients diagnosed with non-functional adrenal incidentalomas [44–46]. For example, Prinzi *et al.* [47] identified in a single-center, retrospective study on 171 patients with adrenal incidentalomas that a suppressed Dehydroepiandrosterone-sulphate value below the cutoff 0.5 μg/mL statistically significantly predicted as an independent marker a cortisol

between 1.8 and 5 μg/dL [47]. To date, this hormonal assay is not currently mandatory to define these mentioned categories of adrenal incidentalomas, neither baseline ACTH testing (which might prove suppressed as response to cortisol anomalies [26, 48–53]. Additionally, studies in radiomics and deep learning machines are under development to provide multimodal algorithms that estimate osteoporotic status based on tumors' imaging features [54–62]. Predictive models to integrate the clinical, hormonal and imagery-based data seem a promising alternative. Opposite to the AI-generated spectrum, a tailored decision in each case confirmed with adrenal incidentaloma remains the basis of clinical practice nowadays depending on age, gender, menopausal status, comorbidities and patients' options and preference [63–66]. Moreover, genetic characterization of non-functional ADTs has recently gained a massive interest, while, currently, most of these incidentalomas are detected in individuals who do not harbor a specific mutational frame, except for bilateral adrenal disease and some genetic syndromes [67–73].

Conclusions

Menopausal adults with D-C >0.9 μg/dL should be mandatory tested for osteoporosis, and those with D-C >1.4 μg/dL should be additionally screened for osteoporotic fractures, while age is not different among the subgroups with different cutoffs.

Conflict of interests

The authors declare no conflict of interests.

Institutional Review Board Statement

The Ethics Committee of Scientific Research of Carol Davila University of Medicine and Pharmacy, Bucharest, Romania approved this study (Approval No. 7634 from 4 April 2025) and C.I Parhon National Institute of Endocrinology, Bucharest, Romania (Approval No. 37 from 22 September 2025).

Informed Consent Statement

Patient consent was waived due to retrospective design.

Data Availability Statement

No other data are available.

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