“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
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Evaluation of mineral metabolism and osteoporotic fractural risk in patients with non-functioning adrenal tumors with or without mild autonomous cortisol secretion

THESIS ABSTRACT

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Introduction [1-5,11-15]

My motivation for the PhD thesis [1-5] is based on the following elements:

1. Heterogeneity of terms and standard diagnosis criteria over time for adrenal incidentalomas (AIs). Various definitions, associated terminology and standard protocols of diagnosis had been released over time, being one of the most dynamic fields among other endocrine tumors. In October 2022, when I started my PhD research, the latest guideline in the field of AIs had been released in 2016 (Europe) [6] and many concerns around the designed terms and testing criteria of mild cortisol over-production accompanied this concept. In the meantime, in 2023, a rethinking of the concept was pinpointed amid a novel European guideline, which clearly imposed the category of "mild autonomous cortisol secretion" (MACS) [7]. Early after its release, a new wave of concerns has been raised due to the fact that further clarifications are needed [8,9], for instance, the value of additional (combined) hormonal markers or new thresholds for post-dexamethasone cortisol testing (DST-cortisol) to identify novel sub-categories of different multidisciplinary risks.

2. COVID-19 pandemic and post-pandemic peak for incidentalomas detection due to a massive imaging procedures use. As mentioned, it was the third pandemic year when I started my PhD research, and the medical community had witnessed a hidden wave of medical outcomes: the detection of accidentally detected tumours/masses among a dramatic application of various imaging investigations for the infection. Thus, AIs were more frequently identified upon thoracic-abdominal scans, and the topic became "resourceful" as a real-life setting.

3. Bone-adrenal interplay: a gap in the current evidence. While osteoporosis and adrenal tumours are well-established chapters in the endocrinology domain, their interplay in individuals with apparently non-functional adrenal tumours (NFATs) ± MACS remains a matter of debate. In the rather traditional landscape of cortisol-related bone impairment, AIs do not involve a standard cause of secondary osteoporosis. Most tumours are generally designed as "non-functioning", while one third are not entirely "non-secretor" (MACS-positive). But, both mild hormonal-positive and -negative tumours have been found to associate increased risks regarding various osseous and non-osseous ailments. Notably, osteoporosis/osteopenia was identified in up to 20-40% of the individuals confirmed with NFATs, and even 40-60% in certain MACS subgroups [10,11].

4. Paucity of evidence-based-medicine with regard to osteoporosis in the individuals confirmed with this type of tumours. Overall, osteoporosis and osteoporotic fractures (OP-FRs) remain the least studied complications in these tumours as opposite to cardiovascular and metabolic complications in NFATs/MACS. Exploration of mineral metabolism and fracture risk is restrained to a limited number of studies so far, so I analysed calcium-phosphorus metabolism assays, circulating bone turnover markers (BTMs), bone mineral density (BMD) at central Dual-Energy X-Ray Absorptiometry (DXA) sites and FRAX (Fracture Risk Assessment Tool)-based estimations and choose a population that does not bring an additional bias by gender and age distribution (menopausal adults) [11-15].

5. Trabecular bone score (TBS) and adrenal tumours: crossing the bridge to type 2 diabetes. The introduction of novel tools to assess diabetic bone disease (e.g. TBS) is hardly studied in this kind of tumours (less than ten well-designed studies have been prior published in NFATs-related TBS), which otherwise might associate a higher risk of type 2 diabetes as well, and the osseous damage might come *via* this co-morbidity rather that being a direct cortisol consequence [15].

6. FRAXplus: new tool and potential tool in AIs/NFATs/MACS. The newly launched fracture risk estimator, FRAXplus offered me an extraordinary opportunity since the model might become very important in these patients, noting their lumbar BMD and the co-diagnosis of type 2 diabetes may require both an adjustment of OP-FR risk, so this is currently the first step in this specific area. To my best aware, less than five studies have addressed conventional FRAX in subjects with AIs, and none in FRAXplus [13].

7. Exploring the circulating adipo-myokines panel: a signature of modern medicine. The "boom" of testing biomarkers such as adipo-myokines involves all kind of ailments, but a rather limited experience in AIs had been published so far, so this represented one of the most important objectives to be addressed during this PhD research. [15].

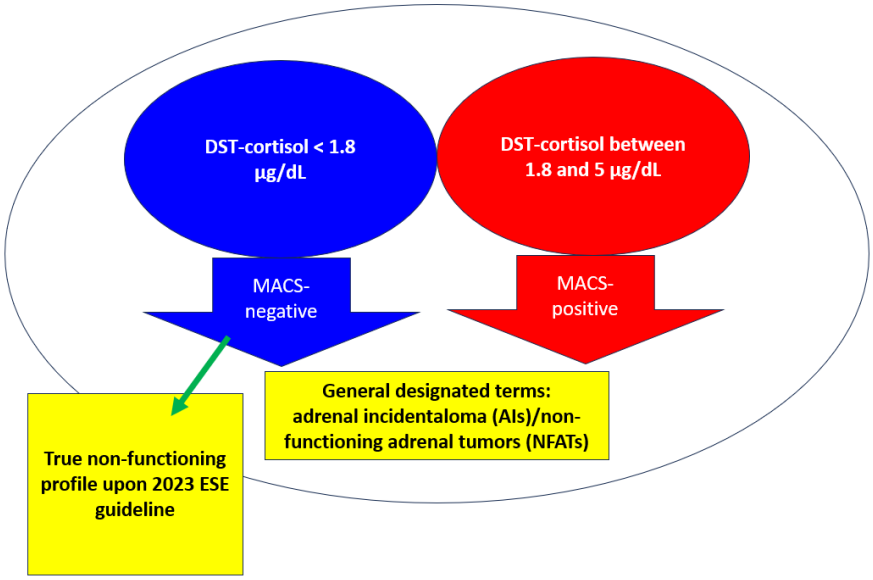
I. General considerations: updated state of knowledge

1. Modern conceptual landscape in AIs/NFATs/MACS [1-5,11-15]

The radiological point of view concerns AIs as a strictly accidental imaging finding, however, the endocrine point of view also relates to a negative hormonal profile and a low expected rate of growth, generally designed as NFATs. The overall prevalence of AIs is 2%

(between 1% and 8.7%, up to 10-20% in certain population subgroups). AIs prevalence increases with age, reaching up to 7–10% in patients older than 70 (female predominance), MACS prevalence being between 5% and 30% of AIs [1,7]. (Figure 1)

Figure 1. Visualization of current terminology in the landscape of adrenal incidentalomas



2. Hormonal profile: from conventional to alternative markers [3,5]

Over time, several diagnosis criteria for MACS have been proposed, being centred on the lack of serum cortisol suppression amid DST use with various cutoffs, currently, being agreed for a value >1.8 and <5 µg/dL, in the absence of the clinical phenotype highly suggestive for Cushing's syndrome (CS). DST-cortisol (upon 1-mg DST) is the mostly used test for the primary screening; alternatively, 2 days of 2 mg (low-dose) DST testing may be applied in selected cases (LDDST) [3,5]. In addition, in NFATs/MACS might be found a decreased or low-normal basal morning plasma adrenocorticotropic hormone (ACTH), an elevated midnight serum cortisol or late-night salivary cortisol (LNSC), and/or an increased urinary free cortisol (UFC), which otherwise are not currently regarded as standard diagnosis criteria, as opposite to DST-cortisol. Moreover, a low dehydroepiandrosterone sulfate level (DHEAS) may help MACS recognition [3,5].

In 2025, we published a literature update aiming to evaluate the diagnosis relevance of 1-mg DST in subjects with AIs/NFATs/MACS by exploring different cutoffs DST-cortisol with respect to the cardio-metabolic outcomes, the importance of adding supplementary

biomarkers to DST-cortisol, as well as DST variability over time (e.g. switch between categories: MACS-free, MACS-positive, or overt CS) [3].

The final sample-focused analysis (n=13, N=4203 patients, female-to-male ratio of 1.45) showed that alternative DST-cortisol cutoffs (0.87, 0.9, 1.2, and 1.4 μg/dL) largely varied among the studies, being reflected in different risk ratios for cardio-metabolic and renal complications. After adjusting for age, only the prevalence of cardiovascular disease remained significantly higher in >0.9 μg/dL versus ≤0.9 group (OR=2.23). Multivariate analysis found that DST-cortisol between 1.2 and 1.79 μg/dL was independently associated with hypertension (OR=1.55, 95% CI: 1.08-2.23, p=0.018), diabetes (OR=1.60, 95%CI: 1.01-2.57, p=0.045), and their combination (OR=1.96, 95%CI:1.12-3.41, p=0.018) after adjusting for age, gender, obesity, and dyslipidaemia [3,5].

A higher DST-cortisol was associated with a lower estimated glomerular filtration rate (eGFR), independently of traditional cardiovascular risk factors. Post-adrenalectomy eGFR improvement was more pronounced in younger individuals, those with lower eGFR before surgery, and with a longer post-operative follow-up. DST-cortisol (n=1) was strongly associated with AIs size and weakly associated with age, body mass index (BMI) and eGFR. Cortisol level increased by 9% (95% CI:6%-11%) for each 10 ml/min/1.73m² decrease in eGFR. A lower DST-cortisol was associated with a faster post-adrenalectomy function recovery; the co-diagnosis of diabetes reduced the likelihood of this recovery (OR=24.55, p=0.036). Additional biomarkers assays (n=5) showed effectiveness only for lower DHEAS to pinpoint MACS amid AIs (n=2, cutoffs of <49.31 μg/dL, respectively, <75 μg/dL), and lower ACTH (n=1, <12.6 pmol/L) [3,5].

Longitudinal analysis of DST' results (n=3) revealed that: 22% of MACS-negative tumours switched to MACS-positive after a median of 35.7 months (n=1), respectively, 29% (n=1) after 48.6 ± 12.5 months, 11.8% (n=1) after 40.4 ± 51.17 months. A multifactorial model of prediction showed the lowest risk of switch (2.4%) in individuals <50 years with unilateral tumour and DST-cortisol <0.45 μg/dL. In the subgroup of subjects without cardio-metabolic comorbidities at first presentation, 25.6% of them developed ≥1 comorbidities during surveillance [3,5].

To summarize, the importance of exploring the domain of AIs/NFATs/MACS relates to an increasing detection in aging population, hence, the important role of their optimum

hormonal characterization and identifying/forestalling associated outcomes. DST remains the key tool for identifying MACS amid AIs. DST-cortisol serves as an independent predictor of cardio-metabolic consequences, kidney dysfunction, while adrenalectomy may correct them in both MACS and NFATs, especially in younger population (not all studies agreed). Moreover, it serves as a predictor of switching MACS-free into MACS-positve during surveillance [3,5].

3. Associated bone spectrum [1]

As part of my early PhD research, I reviewed prior studies in the matter of AIs/NFATs/MACS-related bone health. The main findings represent an insight of the current state of knowledge. This review, based on a search from Inception until February 2023 included 40 original studies, a total of 3046 patients with female prevalence (female-to- male ratio of 1921:1125), aged between 20.5 and 95.5 years old [1].

The 30 years-based analysis showed that 37 studies provided DXA-based parameters; another 5 studies reported bone micro-architecture, including TBS, spinal deformity index, and high-resolution peripheral quantitative computed tomography; 20 cohorts included data on BTMs, while 4 longitudinal studies followed subjects between 1 and 10.5 years old (surgical versus non-adrenalectomy arms). DST-cortisol was inversely associated with BMD (not all studies agreed). TBS predicted incidental vertebral fractures (VFx) regardless of BMD, being associated with DST-cortisol independently of age and BMD. Low BTMs were identified in MACS-positive across several studies. The highest prevalence of MACS-related osteoporosis was 87.5%, while the VFx prevalence varied: pre-menopause (42.5%), post-menopause (78.6%), and adult males (72.7%) depending on the study, with a 10-fold increased incidental VFx risk up to a 12-fold increased risk after a 2-year follow-up. No specific medication against osteoporosis is indicated in MACS, but adrenalectomy (according to four studies) should be part of a long-term strategy [1].

To conclude, according to our bone profile study of published data (that remains, to our knowledge, one of the largest on its kind), tumours considered AIs/NFATs, including the subgroup designated as having MACS, include a large panel of osseous complications from lower BMD and TBS to blunt BTMs and a higher prevalence of osteoporosis and/or VFx compared to (non-AIs) controls, but there is no general consensus. Moreover, while a more

severe bone damage is expected in MACS-positive versus MACS-negative subjects, there is no definitive distinction in this specific matter [1].

Overall, the level of evidence remains far from generous in this bone-adrenal interplay; there are still no homogenous results, which might be a consequence of different investigation clusters with respect to adrenal profile and bone exploration that have been used over time. Moreover, distinct population sub-groups might show distinct OP-FRs risk. Whether overlapping influence of type 2 diabetes might alter the direct interpretation of cortisol effects is still an open matter. However, awareness is mandatory, and bone assessments should be an essential element of the management in these adults [1].

4. Metabolic interplay: focus on type 2 diabetes [2,4]

One of the most important interplays in AIs/NFATs/MACS comes with type 2 diabetes co-diagnosis, which also influences the bone spectrum. As an important extension to the bone field, the co-presence of diabetes, especially in menopausal women, makes mandatory the use of TBS for bone health screening [4]. In 2024, we published a large analysis with the objective to highlight the most recent data with concern to the glucose profile, particularly, type 2 diabetes, in NFATs/MACS. To our aware, this large and complex comprehensive review covered the most important aspects according to the recent publications in the field of MACS/NFATs-related type 2 diabetes across our methods (n=37 studies, N=17,391 individuals, aged between 14 and 96 years) [2].

The main take-home messages are: most data come from retrospective (n=14) and cross-sectional studies (n=13) and only 3 prospective studies were identified. The analysed population showed that the female population was slightly more frequent (female-to-male ratio of 1.47), but the results in the glucose profile did not show a specific gender-related burden in these adults. MACS prevalence amid all AIs/NFATs was 10% to 30%. Most studies sustain a higher type 2 diabetes prevalence in MACS (12% to 44%) versus MACS-free. However, a few studies also showed a similar rate (up to 45%). Prediabetes may be more frequent in MACS versus MACS-negative or generally in AIs versus tumour-free controls (no homogenous results) [2].

Four studies introduced a CS sub-group and, paradoxically, only half of them confirmed a more severe glucose profile versus MACS/NFATs. The longest period of follow-

up with concern to the glycaemic profile was of 10.5 years, and one cohort showed a significant increase in the type 2 diabetes rate at 17.9% compared to the baseline value of 0.03%. Inconsistent data coming from six studies enrolling 1,039 individuals that underwent adrenalectomy (N=674), respectively, conservative management (N=365) pinpointed the impact of adrenalectomy in AIs/NFATs/MACS that improved the regulation of the glucose metabolism after adrenalectomy versus baseline, respectively, versus conservative management (n=3) [2].

Noting these data, awareness of the type 2 diabetes in NFATs/MACS represents the key factor as transversal and longitudinal approach in daily practice, and this potentially impacts the AIs-related diabetic bone disease, as shown by the value of TBS [4].

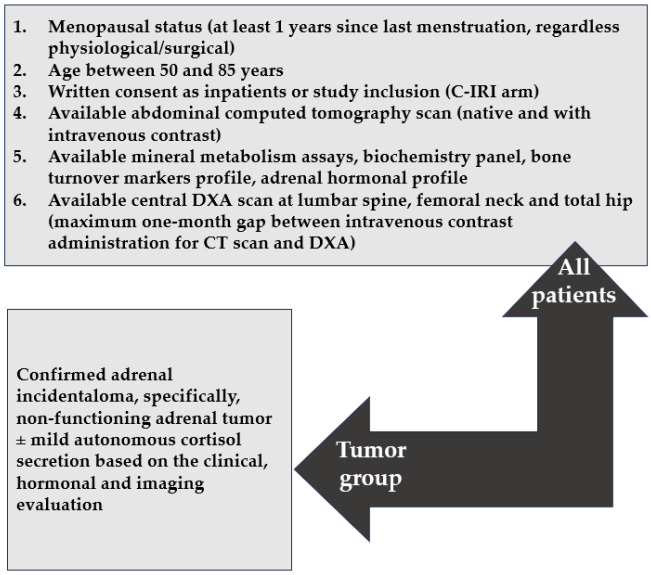
II. Original research [11-17]

2. Material and Methods [11-17]

Study design: a retrospective, real-life study amid a clinical setting in a university hospital (tertiary centre of endocrinology) provided "CORE DATA" [11,12]. Collateral analyses included a multicentric, retrospective analysis [13,14]. An additional segment included a prospective study of circulating irisin testing ("C-IRI" analysis) [15].

Study population: adult menopausal females, who were hospitalized in the mentioned hospitals and confirmed with the diagnosis of NFATs/AIs ± MACS. (Figure 2)

Figure 2. Inclusion criteria [11-17]



Exclusion criteria [11-17]

I. Endocrine and metabolic panel:

1. Overt (clinically manifested) Cushing's syndrome of any type/origin
2. Suspected or confirmed (active or prior) endocrine tumors (acromegaly, prolactinoma, pheochromocytoma, Conn syndrome, primary hyperparathyroidism)
3. Neuroendocrine neoplasia
4. Multiple endocrine neoplasia
5. Active thyroid dysfunction (hyperthyroidism or hypothyroidism)
6. Congenital adrenal hyperplasia
7. Turner syndrome
8. Suspected or confirmed imaging features of primary or secondary adrenal malignancy (abdominal lymph nodes involvement, necrosis, inhomogeneous mass, irregular borders, high attenuation, slow washout after contrast, >10 Hounsfield unites on non-contrast CT diameter > 4 cm, tumor necrosis/hemorrhage)
9. Adrenal masses such as cysts, adrenal hemorrhage, myelolipoma, lipoma
10. Type 1 diabetes
11. Secondary diabetes

II. Multidisciplinary panel:

1. Bone metabolic conditions: Paget disease, osteogenesis imperfecta, bone metastases
2. Chronic kidney disease
3. Prior or active (suspected or confirmed) malignancy
4. Active infections or inflammatory diseases
5. Rheumatoid arthritis, lupus, scleroderma

III. Specific adrenal assays:

1. Second-day plasma cortisol after 1 mg dexamethasone administration of ≥ 5 μg/dL
2. Registration time of the morning cortisol and ACTH assays outside the window between 6.00. and 7.30. a.m.
3. Connshing syndrome (primary hyperaldosteronism with mild autonomous cortisol secretion)
4. Abnormal levels of plasma/24-hour urinary metanephrines/normetanephrines, aldosterone/renin ratio, creatinine/urea (confirmed during the hospitalization that provided the adrenal panel)

IV. Medications and prior surgery:

1. Specific anti-osteoporotic medication (bisphosphonates, denosumab, teriparatide, romosozumab)
2. Corticotherapy
3. Insulin therapy
4. Glucagon-like peptide-1 receptor agonists drugs
5. Adrenalectomy
6. Bariatric surgery
7. Hormone replacement (menopausal) therapy (e.g. estrogens, progestative)

Study protocol: menopausal women who were identified with AIs at computed tomography (CT) scan were assessed regarding inclusion/exclusion criteria and then checked for available DXA for a maximum one month-gap between CT scan and DXA evaluation, respectively, for the panel of DST/mineral metabolism results.

Study assessments included adrenal, bone and glucose profile. (Table 1)

Table 1. Brief presentation of studied parameters [11-15]

Parameter/variable	Method/manufacturer
Demographic features (age, years since menopause), comorbidities (type 2 diabetes, hypertension, dyslipidaemia), prior fragility fractures	medical records and evaluation during hospitalization
Total calcium, phosphorus, magnesium, total alkaline phosphatase, fasting glucose, creatinine	photometry (Roche)
PTH, P1NP, osteocalcin, CrossLaps, cortisol, ACTH	ECLIA (Roche)
25-hydroxyvitamin D	CLIA (DiaSorin)
Glycated haemoglobin A1c	turbidimetry (Roche)
Central (lumbar, femoral neck, total hip) DXA	GE Lunar Prodigy device
Trabecular Bone Score	TBS iNsight software

FRAX allowed the calculation of 10-year major osteoporotic fracture risk (MOF)/hip fracture risk (HF) ± femoral neck BMD for Romanian population. In addition, FRAXplus estimated 10-y-MOF/HF adjustment for lumbar BMD, respectively, for type 2 diabetes, which is applicable only by mandatorily using femoral neck BMD [11-15]. (Figure 3)

Figure 3. FRAX and FRAX-plus estimations [11-15,18,19]

MOF = major osteoporotic fracture	HF = hip fracture
10-y-MOF = 10-year fracture risk assessment for major osteoporotic fracture	10-y-HF = 10-year fracture risk assessment for hip fracture
10-y-MOF+BMD = 10-year fracture risk assessment for major osteoporotic fracture; calculation with femoral neck BMD (conventional FRAX)	10-y-HF+BMD = 10-year fracture risk assessment for hip fracture; calculation with femoral neck BMD (conventional FRAX)
10-y-MOF-BMD = 10-year fracture risk assessment for major osteoporotic fracture; calculation without femoral neck BMD (conventional FRAX)	10-y-HF+BMD = 10-year fracture risk assessment for hip fracture; calculation without femoral neck BMD (conventional FRAX)
10-y-MOF+BMD+L = 10-year fracture risk assessment for major osteoporotic fracture; calculation with femoral neck BMD and adjustment for lumbar BMD (FRAXplus)	10-y-HF+BMD+L = 10-year fracture risk assessment for hip fracture; calculation with femoral neck BMD and adjustment for lumbar BMD (FRAXplus)
10-y-MOF+BMD+DM = 10-year fracture risk assessment for major osteoporotic fracture; calculation with femoral neck BMD and adjustment for T2DM (FRAXplus)	10-y-HF+BMD+DM = 10-year fracture risk assessment for hip fracture; calculation with femoral neck BMD and adjustment for T2DM (FRAXplus)

3. ACTH as pointer of menopausal bone health [11]

Working hypothesis: a low or suppressed ACTH (e.g. below the threshold of 10 - 15 pg/mL) had been found to be associated with a higher risk of multilayered co-morbidities in AIs/NFATs (regardless MACS-positive or MACS-negative). ACTH assay is not a current standard, neither a guideline approach has been released until present day to mandatorily integrate this hormone testing in the final case decision with respect to the individuals who are conformed with AIs. This remains a part of a patient-focused modern clinical approach and it might provide an index of suspicion from the very first endocrine (adrenal) evaluation, before performing a specific assessment of the bone status in one patient. In addition, osseous-focused investigations are not mandatory in this kind of tumours according to current protocols, except for the people who already present the conventional panel of OP-FRs risks [20-24]. We hypothesized that an ACTH cutoff below and above the level of 10 pg/mL might point out a distinct spectrum of mineral metabolism anomalies and OP-FRs risk in menopausal women who are co-diagnosed with AIs [11].

Objective: we aimed to evaluate the complex relationship between the bone status and ACTH (with the 10 pg/mL cutoff) in menopausal adults confirmed with AIs, taking into account, on one hand, mineral metabolism-related assays, BTMs, DXA-BMDs/T-scores, respectively, on the other hand, hormonal and imaging profile of these tumours [11].

Material and methods: this study belongs to CORE DATA (single-centre, retrospective analysis). In this study, “bone impairment” included DXA-BMD categories according to non-normal results (osteoporosis + osteopenia). We also used the category “suppressed ACTH” for the subjects with a morning baseline ACTH value less than 10 pg/mL, and designated group S (ACTH < 10 pg/mL) and group nonS (ACTH ≥ 10 pg/mL) [11].

Results: the cohort (N=84, age: 61.49±7.86 years) associated a type 2 diabetes rate of 18%, hypertension of 75%, and dyslipidaemia of 78%. Median ACTH was 11.89 pg/mL. MACS prevalence was 30.95%. Mean largest tumour diameter (LTD) was 2.25±0.99 cm [11].

ACTH statistically significantly correlated with DST-cortisol (r = -0.301, p=0.024) and LTD (r= -0.434, p<0.001). ROC analysis for bone resorption marker CrossLaps showed an AUC of 0.647 (p = 0.05) with highest Youden index for the cut-off 0.32 ng/mL (sensitivity 87.50%, specificity 39.50%) [11].

Bone impairment was found in 65% of patients, OP-FRs prevalence was 4.76%. Lowest mean T-score (-1.12±1.00) showed osteopenia and median TBS pointed a partially degraded microarchitecture [median (IQR): 1.320 (1.230, 1.392)]. FRAX and FRAXplus estimations correlated with BMDs at all three central DXA sites, regardless of ACTH. Patients with a low ACTH (group S) displayed similar bone/adrenal features when compare to those with normal ACTH, except for a higher MACS rate (45.45% versus 21.57%, p=0.021), and a larger LTD (2.67±0.98 versus 1.98±0.92 cm, p=0.003). Fracture estimation showed that only in patients with low ACTH, 10-y-MOF adjusted for lumbar BMD was lower that 10-y-MOF adjusted for diabetes (p=0.036), and 10-y-HF was lower when adjusted for lumbar BMD (p=0.007). ACTH correlated with lumbar BMD (r=0.591, p=0.002) only in the group S, suggesting its potential usefulness as a bone biomarker in these cases. On the other hand, MACS-negative subjects with low ACTH versus MACS-free with normal ACTH showed higher CrossLaps levels (0.60±0.27 versus 0.42±0.21 ng/mL, p=0.022), implying an elevated bone resorption even in patients with tumours which are regarded as non-secretor based on DST-cortisol [11].

To conclude, a subgroup of subjects diagnosed with NFATs/MACS might be prone to skeletal damage, and biomarkers such as ACTH (specifically, a suppressed ACTH) might serve as a surrogate pointer to help refining a higher OP-FR risk in daily practice.

4. Unilateral versus bilateral tumors: bone status analysis [12]

Osteoporosis and associated fragility fractures have been confirmed more often in certain population subgroups diagnosed with NFATs/AI, especially MACS-positive (but not exclusive). However, a multilayered panel of contributors (other than persistent endogenous hypercortisolism) is co-present, such as menopausal status, male hypogonadism, type 2 diabetes, vitamin D deficiency, etc. [25]. Generally, one out of ten patients diagnosed with an adrenal tumor has bilateral masses (the reported prevalence of bilateral adrenal incidentalomas varies between 7.5% and 15%) [26-28]. A heterogeneous landscape of data had shown discordant results concerning the estimation of a higher risk of the osseous and non-osseous complications in bilateral versus unilateral tumors [29-31].

Working hypothesis: globally, despite a guideline-based strategic workup, real-life settings have shown a suboptimal evaluation in AIs patients regarding the bone disease burden in bilateral versus unilateral tumors and we intended to bridge this gap [12].

Objective: to analyze (blood) mineral metabolism assays (including BTMs), central DXA, and the 10-year fracture risk estimation based on FRAX and FRAXplus in menopausal patients who were confirmed with unilateral versus bilateral tumors, regardless of MACS profile [12].

Material and methods: this study belongs to CORE DATA. In this analysis, we assigned the group with unilateral (UT group) versus bilateral tumors (BT), according to CT scan findings [12].

Results: The cohort (N=129; mean age: 62.39±7.9 years; menopause duration: 13.7±8 years) included UT (62.22%) and BT (31.78%) groups with a similar age, years since menopause, type 2 diabetes prevalence (35.23% versus 36.59%), hypertension (73.6% versus 75.5%), BMI, fasting glycemia, and glycated hemoglobin A1c ($p>0.5$). The borderline significance for morning plasma cortisol was higher in UTs versus BTs [median (IQR): 13.9 (11.16, 15.00) versus 10.10 (8.88, 12.95) µg/dL; $p=0.05$] and the MACS-positive rate (24.45% versus 36.59%; $p=0.051$). LTD was similar (2.26±0.97 versus 2.51±0.87 cm; $p=0.175$), as well as was DST-cortisol [1.27 (1.01, 1.95) versus 1.52 (0.92, 2.78) µg/dL; $p=0.357$]. BTMs, and DXA-BMD/T scores were similar in the UT versus BT groups [12].

The most prevalent DXA categories were osteopenia (50.82%) and normal (41.38%). The rate of bone impairment was similar: 72.13% versus 58.62%. Out of the 25.58% females

who were found to be MACS-positive, 54.55% were in the UT group and 45.45% were in the BT group. Age, menopause duration, rate of analyzed comorbidities, BMI, BMDs, and FRAX/FRAXplus (lumbar BMD adjustment)-based probabilities were similar between the UT and BT groups (including the sub-analysis for MACS-positive versus MACS-negative groups) [12].

Diabetic patients were all MACS-positive. A higher PTH level in the MACS-positive UT versus MACS-positive BT groups (36.32±9.21 versus 51.65±9.58 pg/mL; p=0.01) was found, with the mean 25-hydroxyvitamin D showing an overall mild insufficiency (24.2±12.73 versus 26.16±9.89 ng/mL; p=0.694). In UTs, LTD statistically significantly correlated with baseline ACTH (r= −0.391; p<0.001) and DST-cortisol (r=0.306; p < 0.001), while in BTs, the largest diameter of the two tumors showed a positive correlation with DST-cortisol (r=0.309; p=0.012) [12].

Overall, the findings of this real-life setting (similar age, years since menopause, and diabetes and MACS-positive rates) might explain the bone features in UT group versus BT group, noting that ACTH/DST-cortisol measurements showed no difference. The study population was associated with a generally low fragility fracture prevalence and 10-year fracture risk probabilities, which might act as a bias in this distinct clinical exploration. We need a 360-degree perspective of the bone health assessment in these patients to help the overall case management. To our best knowledge, this study adds to the limited number of prior studies regarding bone impairment in bilateral versus unilateral AIs/NFATs/MACS.

5. Novel tools for fracture risk adjustment: FRAXplus [13]

The tools to estimate the 10-year probability of fractures have been developed to assist the clinicians in everyday practice for detecting the high-risk individuals who should undergo a further specific evaluation of the bone status and then promptly start a medication against osteoporosis. Many (but not all) of the fracture risk-related contributors are already captured by the conventional FRAX model; yet, novel insights are brought by an improved algorithm version of the current model, namely, FRAXplus, which is currently under beta testing and it is expected to offer a wider perspective of the risk evaluation via introducing new inputs such as lumbar BMD, the history of fall or type 2 diabetes duration [18,19].

While conventional algorithm allows the risk estimation by using or not the results

regarding the femoral neck BMD according to central DXA scan, many individuals, including those diagnosed with MACS-positive/negative profile, might display the lumbar BMD as the most affected DXA site, hence, a fracture risk underestimation might be registered amid traditional evaluation. The estimation using lumbar BMD has been recently added to the model (FRAXplus) [13].

Working hypothesis: to address the current lack of data, we hypothesized the utility of recently launched FRAXplus and used it for the patients with AIs/NFATs, a study which was published in 2025 and represented the first study in the field of FRAXplus in the world, and, of course, the first study in adrenal tumors-related FRAXplus estimation [13].

Objective: to analyze the fracture risk in menopausal females diagnosed with low BMD at central DXA (non-normal results) and (MACS-negative) AIs/NFATs versus tumor-free controls under the FRAXplus model perspective [13].

Material and Methods: this was a multicentric retrospective study. We included 66 menopausal women, 50% of them had non-MACS AIs (group A), and 33 (tumor-free) controls (group B) and sub-included group A1 (N=14/33 subjects with normal DXA), and A2 (19/33 subjects with lowest T-score <-1), respectively, group B1 (14/33) had normal DXA, and group B2 (19/33) with low BMD [13].

Results. The sub-groups were age, BMI- and years since menopause-matched, as well BMD-matched (A versus B, A1 versus B1, A2 versus B2). FRAX analysis showed similar results for 10-year probability between these groups A and B, A2 and B2, while lumbar BMD adjustment showed statistically significant lower risk in group A1 versus B1 ($p=0.013$) for MOF, but not for HF ($p=0.064$) [13].

The analyzed subgroups were age-, years since menopause-, and BMI-match, as well as BMDs-match (group A versus B, A1 versus B1, and A2 versus B2), and this is particularly important in order to highlighting the differences that might be found when estimating the 10-year probability of fracture in the mentioned cohorts. While the estimated risk for MOF/HF according to the conventional model mostly showed a lower value in the groups with higher BMD (non-normal DXA) versus the groups with normal DXA and similar risk between the BMD-matched sub-groups (except for 10-year HF risk, which statistically significant decreased in A1 versus B1 group), the 10-year probability of MOF as adjusted according to the use of lumbar BMD showed heterogeneous results: females with tumors versus controls (A

versus B), respectively, the sub-groups with non-normal DXA (A2 versus B2) showed a similar fracture risk, while the sub-groups with normal BMD (A1 versus B1) displayed a lower risk in tumor group than controls which might prove that current model overestimates the fracture risk as oppose to using lumbar BMD for the risk estimation [13].

To conclude, we introduced a pilot study in FRAXplus model and AIs/NFATs diagnosed in menopausal females with or without low BMD at central DXA assessment, using this fracture risk calculator with lumbar BMD adjustment. FRAXplus algorithm might be a better discriminator for fracture risk in these patients since we found that in age-, BMI-, and years since menopause-matched subgroups, patients with normal DXA and MACS-free AIs display a lower 10-year probability of major osteoporotic fractures than controls upon lumbar BMD adjustment [13].

6. Conventional assessment of mineral metabolism and fracture risk [14,16,17]

Working hypothesis: current controversies showed an abnormal bone profile and a higher OP-FR risk in menopausal females confirmed with AIs/NFATs/MACS, but there is a heterogenous spectrum of influence [14].

Objective: to perform a traditional analysis of the mineral metabolism assays, BTMs, and DXA results in subjects confirmed with these tumors versus (tumor-free) controls [14].

Material and methods: This was an observational, multi-centric, real-world community setting. In this analysis, we studied patients with AIs versus (AIs-free/tumor-free) controls, and then the subjects with AIs were included in two sub-groups: subjects without MACS (DST-cortisol < 1.8 μg/dL) and individuals with confirmed MACS (DST-cortisol between 1.8 and 5 μg/dL) [14].

Results: Demographic features of both baseline groups (N=39 versus N=95) were similar 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), BMI (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 BMDs were similar between AIs and controls. A statistically significant lower osteocalcin 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 (p=0.035). Of note, a tendency for correlation with total hip BMD was found, too. To conclude, decreased osteocalcin might be the signature of mild cortisol anomalies in AIs, while DXA-BMD and conventional FRAX algorithm revealed similar parameters in AIs group versus controls, as found between MACS and MACS-free subgroups [14].

I extended this early PhD research to a larger single-centre experience (CORE DATA) and presented the final results as abstracts for two poster presentations, which were awarded with ESCEO-IOF Young Investigator Award at WCO-IOF-ESCEO 2026 Prague, the world's leading clinical conference on bone, joint and muscle health [16,17].

One analysis was cross-sectional, specifically: demographic characteristics (N=461) were similar among three groups [MACS (N=33), NFATs/MACS-negative (N=80), and controls (N=348)]: age (61.19±8.15 versus 61.29±8.40 versus 61.60±7.80 years, p=0.926), years since menopause (13.30±8.33 versus 13.53±8.47 versus 13.27±8.19 years, p=0.978). BMI was statistically significant different across these 3 groups (p=0.018), being highest in MACS group (31.25±6.11 kg/m^2), intermediate in the NFATs/MACS-free group (29.10±5.51 kg/m^2), and lowest in controls (28.13±5.32 kg/m^2). BTMs were similar among MACS-positive, MACS-free, and (tumor-free) controls [17].

The prevalence of OP-FRs was 12.1% in MACS, 7.5% in MACS-free, and 8.4% in controls, with no significant differences (p=0.715). BMDs and TBS were similar among these groups. However, the distribution of DXA categories was statistically significantly different (p=0.031), with osteoporosis being more prevalent in MACS (33.3%) and NFATs/MACS-negative (30.7%) groups compared to controls (18.3%), while osteopenia remained the most frequent DXA category across all groups [17].

Hence, in postmenopausal women with adrenal tumors, MACS was associated with a higher BMI and an increased prevalence of osteoporosis at central DXA, according to standard evaluation in menopause, despite similar BMDs values, BTMs, TBS and OP-FRs prevalence compared with MACS-negative patients and, respectively, (tumor-free) controls [17].

In addition, 119 postmenopausal women with AIs/NFATs were included in a longitudinal analysis: 89.1% were managed conservatively and 10.9% underwent adrenalectomy (age groups at baseline: 60.9±7.2 versus 54.2±6.9 years, p=0.074). Mean

follow-up duration was 28.5±19.1 months. Postoperative adrenal insufficiency occurred in 7.7% (surgery group). Lumbar and femoral neck BMD changes showed no-between group differences. Total hip T-score change in non-surgery group (-1.05±1.04 to -1.04±0.92) was statistically significantly lower than found in surgery group (-1.75±0.29 to -1.60±0.56, p=0.023). BTMs' changes between the groups were similar after follow-up. Thus, in postmenopausal women with AIs/NFATs, adrenalectomy was associated with an improvement of total hip DXA results with similar BTMs change [16].

7. Placing TBS and irisin testing in the clinical frame [15]

Modern approach of the musculoskeletal health assessment in daily practice expanded beyond BMD at central DXA, for instance, to the lumbar DXA-derived TBS or hip geometry, and to emergent biomarkers, others than traditional BTMs, such as adipokines and exerkines (myokines) assays [32-34]. They might contribute to the bone formation/resorption process, either directly or indirectly via crossroads with glucose metabolism, chronic inflammation and oxidative stress [35-38]. Among this panel, irisin is a novel muscle-released hormone, which had been placed in relationship with multiple metabolic pathways under physiological and pathological circumstances (e.g. physical exercise/training or cold exposure, respectively, sarcopenia, diabetes, osteoporosis, obesity, cancers, etc.), but so far, its testing is not standardized [15,39-41].

Working hypothesis: irisin level might be influenced by the co-presence of AIs/NFATs in menopause, noting that the landscape of co-morbidities in NFATs/AIs varies from a higher cardio-metabolic risk to an increased risk of osteoporosis and OP-FRs. To date, only a limited number of studies (n<10) approached the topic of non-BMD assessment, particularly, TBS, in individuals with AIs [42-45], and even fewer (n=1) studied the blood/circulating irisin profile in these subjects [15,46].

Objective: to assess the current gap of the musculoskeletal health evaluation beyond BMD, we aimed to explore TBS and circulating irisin in relationship with the adrenal status in patients diagnosed with AIs [15].

Material and methods: This was a prospective, single-center, clinical, exploratory and pilot study, between October 2024 and December 2025 (C-IRI analysis). In addition to prior inclusion/exclusion criteria, in this study, the individuals with previous medication against

diabetes of any type, not just insulin, at any moment in time, were ruled out, as well as those with prevalent/incident OP-FRs. After specific informed consent was signed for this specific study protocol, the blood tests were performed: fasting assays (after 8 to 12 h of fasting), as well as 75-gram oral glucose tolerance test in subjects who were not previously known with diabetes or had a fasting glycaemia of less than 125 mg/dL (N=81) [15].

Results: Irisin testing (ELISA) was performed in 81 menopausal women (mean age of 63.26±8.82 years, 15.86±9.5 years since menopause, BMI of 30.69±5.76 kg/sqcm. 33.33% of them had NFATs/MACS (group AIs) and 66.67% were (tumor-free) controls (group C), with similar age, years since menopause and BMI. Type 2 diabetes prevalence was: 66.67% versus 68.52% (p=0.865). TBS correlated with lumbar BMD/T-score (N=33), while age and lumbar BMD were independent TBS predictors (N=81), but not type 2 diabetes, nor the tumor diagnosis. TBS correlated with 5-year-age groups (r=-0.273, p=0.003) [15].

Irisin statistically significantly correlated with osteocalcin (r= -0.252, p=0.007), P1NP (r= -0.187, p=0.049) and CrossLaps (r= -0.209, p=0.026) in tumor-free controls. In AIs group, a higher irisin statistically significantly associated with a higher DST-cortisol (r=0.716, p<0.001) and a lower ACTH (r= -0.438, p=0.041). The rate of low TBS (based on 1.350 cutoffs) was of 48.15% versus 38.89% in group AIs versus C. In AIs group, patients with low TBS had a lower osteocalcin, P1NP and CrossLaps than those with normal TBS, with similar rate of type 2 diabetes and MACS-positive prevalence (between 25% and 28%) [15].

Notably, the median glycated hemoglobin A1c (5.78% versus 5.93%, p=0.94) and median HOMA-IR (1.53 versus 1.42, p=0.948) suggested a certain level of glucose control in both studied groups, which might not be reflected in severely damaged bone microarchitecture, as shown by TBS. Irisin may be one of the additional factors in these tumors to reflect the associated hormonal burden [15].

8. Concluding remarks and personal contributions

In the current PhD research, across five original studies and five sample-based analyses of prior published data, we delved into the topic of bone health in menopausal women diagnosed with AIs/NFATs/MACS according to the prior mentioned methodology. Generally, we highlight the importance of exploring the domain of AIs/NFATs, which relates to an increasing detection in aging population, large variations of definition criteria over time and a

sub-optimal hormonal characterization in relationship with various osseous outcomes, while new tools of assessment (e.g. TBS, FRAXplus, circulating muscle/fat-originating molecules) are finding their place in the exploration of these tumors amid daily endocrine practice.

Concluding remarks based on the original studies:

The first study showed that more than half of the consecutive menopausal women with AIs/NFATs (regardless MACS) have osteoporosis/osteopenia, while 18% of the menopausal women over 50 had type 2 diabetes, 75% had hypertension and 78% had dyslipidemia of any type. The rate of prevalent OP-FRs in anti-osteoporotic drugs-naïve patients was 5%. Mean T-score shows osteopenia and partially degraded lumbar DXA-derivate TBS. One third of consecutive patients with AIs displays MACS. MACS prevalence is higher and the largest tumor diameter is increased if ACTH is suppressed below the threshold of 10 pg/mL, but standard bone panel remained unchanged in the groups based on this ACTH cutoff. FRAX/FRAX-plus estimations correlated with BMDs at all central sites (lumbar spine, femoral neck, total hip), regardless MACS (based on standard DST-cortisol criteria) or regardless ACTH level (an alternative pointer of the hormonal anomalies in these tumours). If ACTH is suppressed (< 10 pg/mL), 10-year probability of MOF adjusted for lumbar BMD is lower than the estimation adjusted for type 2 diabetes, while the risk for HF based on conventional FRAX becomes lower when adjusted for lumbar BMD (via FRAXplus). FRAXplus might take into account the diabetes effect in diabetic subgroup diagnosed with these tumors, rather than cortisol-related impact on the fracture risk. Patients with MACS-negative tumors and low ACTH versus those MACS-negative with unsuppressed/normal ACTH have higher CrossLaps, which suggests that ACTH is potentially a marker of bone resorption in cases with DST-cortisol < 1.8 µg/dL [11].

The second study adds value to a very limited number of prior studies regarding bone impairment in bilateral versus unilateral AIs/NFATs/MACS. We identified that unilateral versus bilateral gland involvement rate was 68.22% versus 31.78%, a slightly higher rate of bilateral disease than prior reported in unselected populations (10%). Unilateral versus bilateral AIs/NFATs involve a similar prevalence of hypertension (72.70% versus 75.60%), dyslipidemia (79% versus 73.30%), type 2 diabetes (35.23% versus 36.59%), bone impairment (72.13% versus 58.62%), prevalent OP-FRs (3.41% versus 4.88%, most fractures being vertebral), as well as DST-cortisol and ACTH levels. In UTs, largest tumor diameter

statistically significantly and negatively correlated with baseline ACTH and positively with DST-cortisol, while in BTs, the largest diameter of the two tumors showed a positive correlation with DST-cortisol. MACS-positive status concerns slightly more often bilateral (36.59%) than unilateral AIs (25.58%), with a similar largest tumor diameter (between 2.2 and 2.5 cm). Diabetic patients were all MACS-positive. Blood assays of the mineral metabolism revealed a similar profile between the groups (including BTMs), except for a higher PTH in MACS-positive-BT versus MACS-positive-UT, but with intra-normal variations amid a general mild vitamin D insufficiency [12].

The third study (which actually received a publication date before the two prior mentioned studies [11,12]) represents, to the best of our knowledge, the first of this kind due to the novelty of using FRAXplus for fracture risk estimation (with improved inputs such as lumbar BMD). This approach seems particularly useful in patients who present incongruences in the level of BMD deterioration between the central DXA sites or subjects with less described conditions in terms of associated OP-FRs risk as found in the field of adrenal tumors in menopause [13]. Our findings showed that patients with normal DXA and (MACS-free) AIs display a lower 10-year probability of MOF than controls upon lumbar BMD adjustment due to potential asymmetrical involvement of the bone mass between central DXA sites. Moreover, we might speculate that the current classification of MACS/MACS-free tumours might not cover all hormonal aspects and a mild hormonal activity may not be reflected by the current definition that only takes into consideration DST-cortisol to define MACS/MACS-free [13]. In addition, OP-FR risk estimation relates to the overall management: currently, the presence of osteoporosis/OP-FR in a menopausal woman with AIs does not necessarily indicate an adrenalectomy (unless other key findings are co-identified such as an elevated cardiovascular and metabolic risk or increased size at serial imaging evaluation), yet, an unexplained bone loss and/or incidental fractures during follow-up in such patient might raise the issue of surgery (independently of other indications for the adrenal removal) in order to preventing the fracture risk increase [13].

The fourth study explored a standard AIs-related bone health in menopause and highlighted that lower levels of the bone formation marker osteocalcin, and similar BMDs at central sites, respectively, 10-year absolute fracture risk (conventional FRAX algorithm) were found in AIs versus (AIs-free) controls, while sub-groups of AIs (MACS-positive versus

MACS-free) were not distinct amid these mineral metabolism assays, BTMs and OP-FR risk estimation [14].

A study extension to more than 400 patients showed that MACS was associated with a higher BMI and an increased prevalence of osteoporosis at central DXA, despite similar BMDs values, BTMs, TBS and OP-FRs prevalence compared with MACS-free patients and (tumor-free) controls [16]. In addition, 119 postmenopausal women were included for a longitudinal analysis: 89.1% were managed conservatively and 10.9% underwent adrenalectomy, and followed for a mean 28.5 months. Postoperative adrenal insufficiency rate was 7.7%. Total hip T-score change in non-surgery group was statistically significantly lower than found in surgery group, which suggests that surgery might help the bone outcome [17].

The fifth study was a pilot analysis to assess circulating irisin and TBS in patients with AIs/NFATs versus (tumor-free) controls. TBS correlated with lumbar BMD, while the patients with lower TBS (< 1.350) showed lower BTMs than those with normal TBS in the tumor group, while MACS prevalence was similar in low versus normal TBS sub-groups (25%). Irisin did not directly associate with TBS, but it correlated with BTM's profile in controls, while in tumor group showed a strong correlation with DST-cortisol and ACTH levels (with opposite effects). Overall, this was a study population with a relatively good glucose profile control (due to strict inclusion/exclusion criteria), a bone microarchitecture damage might be less involved. In this particular instance, TBS may be potentially connected with both: the mild hormonal (cortisol) impairment and glucose profile anomalies. These data offered an exploratory perspective rather than a practical point for the clinicians, but it might represent the first step for the clinical frame and every day practice. So far, the type 2 diabetic population and/or osteoporotic population harboring these tumors are treated based on the traditional recommendations for the general population with these ailments, regardless the presence of the tumor, and a shift of a multi-layered approach is expected for the following years [15].

We acknowledge the limitations of this research, as mentioned, and further research should include larger sample size with prospective and longitudinal designs and more diverse population regarding age/gender. A larger panel of assays in the adrenal field (e.g. metabolomics, LNSC, DHEAS), as well as adipo-myokines testing in relationship with NFATs/MACS profile might improve the bone assessment. Specific interventional strategies

to address osteoporosis in these patients versus adrenalectomy are yet to be clarified. The incidental fractures upon FRAXplus estimation requires long-term surveillance of the real-life impact and validation in the clinical field. Multimodal algorithms to include multi-layered aspects (BTMs, BMDs, TBS, irisin etc.) might help the clinical decision, case-finding strategies and decision-making.

Personal contributions and core-findings are:

1. The first study worldwide to address FRAXplus. An expansion of this type of analysis is massively expected for the following years.
2. The second study worldwide to address irisin testing in AIs/NFATs and the first to combine TBS analysis. An exploration of the circulating biomarkers originating from muscle/fat tissue represents a cutting-edge topic nowadays.
3. The first study in Romanian population to apply FRAX versus FRAXplus.
4. We addressed several elements that have been studied across a very limited number of prior publications: TBS, traditional FRAX and bilateral tumors in AIs/NFATs/MACS.
5. The conventional panel (BTMs, BMDs) in MACS-positive versus MACS-negative, versus (AIs-free) control might be found similar and this does not exclude the co-presence of a bone damage, only that combined assessment tools or alternative tools of exploration might be necessary.
6. Suppressed ACTH might serve as surrogate marker of bone resorption in tumor cases with normal DST-cortisol.
7. Two third of these tumors were unilateral. The presence of bilateral tumors does not influence the prevalence of conventional osseous health issues.
8. Overall, no clear negative bone impact was confirmed in MACS-positive versus MACS-free, so DST-cortisol might not capture the true essence of the bone effects.
9. FRAXplus might show a better fracture predictor than conventional FRAX, especially if low ACTH or co-diagnosis of type 2 diabetes. The adjustment for diabetes should be preferred in diabetic sub-groups, the adjustment for lumbar BMD should be preferred to the conventional model due to incongruence in lumbar versus femoral neck bone mass deterioration, especially in a menopausal population with a relatively low fracture risk.

This research opens new doors for a better tumor burden characterization and understanding of outcomes that are less studied (e.g. osteoporosis versus cardio-metabolic

complications), so that will make space for novel drugs intervention (e.g. low-dose metyrapone) or a multi-step decision of adrenalectomy. One of the main challenges comes from a single hormone-based definition criteria (DST-cortisol), which might not epitomize the bone spectrum, especially in menopause.

DXA remains the gold standard for diagnosis of osteoporosis, but conflicting effects on bone mass are caused by cortisol-induced low BMD versus stationary or even high BMD in type 2 diabetic population, especially if obesity is co-present. Thus, DXA-BMD might not be able to encapsulate the true OP-FR risk in this instance and alternative assessments might find their place. While we confirmed a 30% rate of MACS across these tumors, MACS-related osteoporosis might not be obvious at standard/conventional evaluation.

Delving into bone health investigation amid menopause and AIs showed a less than homogenous picture and refining the case management stands on a tailored decision. Somehow, NFATs/MACS stand in the middle, between primary (menopause-related) osteoporosis and glucocorticoid-related osteoporosis, with a potential overlap of diabetic bone disease in one third of cases. Hence, the solution is rather to integrate all these potential contributors rather than taking them separately and acknowledge that current tools for bone evaluation should be multimodal.

We may ignore the bone chapter in the wider landscape of AIs/NFATs/MACS complications, or smoothly integrate it for the purpose of increased quality of life and decrease disease burden.

In addition, while only exploratory at this point, novel circulating biomarkers, especially those muscle- and fat-originating, might help navigating the complex cross-talk muscle/fat-bone-adrenal.

I trust that my PhD thesis and associated publications embody the fascinating and challenging bone-adrenal cross-domain.

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Portfolio of scientific works during PhD research

1. WOS/Clarivate full-length articles: standard PhD criteria

1. **Trandafir AI**, Sima OC, Manda D, Costachescu M, Cumpata V, Valea A, Schipor SV, Nistor C, Popescu A, Preda EM, Carsote M. Musculoskeletal Assessment in Patients with Adrenal Incidentalomas: Should We Integrate the Trabecular Bone Score and/or Circulating Irisin? Diagnostics (Basel). 2026;16(5):761. (correspondence to Preda EM, Carsote M)
   doi:10.3390/diagnostics16050761. PMID: 41828037.
   https://pubmed.ncbi.nlm.nih.gov/41828037/
   Impact factor = 3.3; Q1, PubMed index; first author
   WOS profile:
   https://www.webofscience.com/wos/woscc/full-record/WOS:001714573000001
2. **Trandafir AI**, Carsote M, Costachescu M, Sima OC, Florescu AF. Mineral Metabolism Assays, Central DXA, and Fracture Risk Probabilities in Menopausal Patients with Non-Functional Adrenal Tumours with/Without Mild Autonomous Cortisol Secretion: Does the Presence of Unilateral Versus Bilateral Tumours Matter? Life (Basel). 2025;15(10):1639. (correspondence to Carsote M)
   doi:10.3390/life15101639.
   PMID:41157311.
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   Impact factor = 3.4; Q1, PubMed index; first author
   WOS profile:
   https://www.webofscience.com/wos/woscc/full-record/WOS:001604585200001
3. **Trandafir AI**, Sima OC, Ionovici N, Manda D, Costachescu M, Carsote M. The relationship between bone health status of post-menopausal women with non-functional adrenal tumours/mild autonomous cortisol secretion and their baseline morning adrenocorticotropic level. Diagnostics (Basel). 2026;16(2):180. (correspondence to Ionovici N)
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   Impact factor = 3.3; Q1; PubMed index; first author
   WOS profile:
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4. Stanciu M, Sima OC, Costachescu M, Valea A, Nistor C, **Trandafir AI**, Tanasescu D, Nistor TVI, Ciobica ML, Carsote M. Assessment of the 10-Year Probability of Fracture Using Femoral Neck (FRAX) and Lumbar BMD (FRAXplus) in Menopausal Women with Non-Functioning Adrenal Tumours: Where We Stand Today (A Study-Focused Analysis). J Clin Med. 2025;14(7):2302. (correspondence to Valea A, Nistor C, **Trandafir AI**)
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5. **Trandafir AI**, Carsote M. Dexamethasone Suppression Testing in Patients with Adrenal Incidentalomas with/Without Mild Autonomous Cortisol Secretion: Spectrum of Cortisol

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doi:10.3390/biomedicines13092169.
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Impact factor = 3.9; Q1; PubMed index; first author and correspondent author
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6. **Trandafir AI**, Carsote M, Florescu AF. An Analysis of Post-Adrenalectomy Dynamics in MACS (Mild Autonomous Cortisol Secretion)-Positive Adrenal Tumours: The Biomarkers and Clinical Impact. J Clin Med. 2025;14(15):5217. (correspondence to Carsote M)
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Impact factor = 2.9; Q; PubMed index; first author
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7. **Trandafir AI**, Stanciu M, Valea A, Sima OC, Nistor C, Iliescu MG, Ciobanu I, Popa FL, Carsote M. Mineral metabolism assays and osteoporotic fracture risk evaluation in menopausal population diagnosed with adrenal incidentalomas: a sub-analysis of PRECES study. Balneo and PRM Research Journal. 2024;15(2):692. (correspondence to Nistor C, Iliescu MG, Ciobanu I)
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Impact factor = 1.1; Q3; first author
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https://www.webofscience.com/wos/woscc/full-record/WOS:001268347000013
8. **Trandafir AI**, Ghemigian A, Ciobica ML, Nistor C, Gurzun MM, Nistor TVI, Petrova E, Carsote M. Diabetes Mellitus in Non-Functioning Adrenal Incidentalomas: Analysis of the Mild Autonomous Cortisol Secretion (MACS) Impact on Glucose Profile. Biomedicines. 2024;12(7):1606. (correspondence to Ciobica ML, Nistor C)
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Impact factor = 3.9; Q1; PubMed index; first author
WOS profile:
https://www.webofscience.com/wos/woscc/full-record/WOS:001276495000001
9. **Trandafir AI**, Sima OC, Gheorghe AM, Ciuche A, Cucu AP, Nistor C, Carsote M. Trabecular Bone Score (TBS) in Individuals with Type 2 Diabetes Mellitus: An Updated Review. J Clin Med. 2023;12(23):7399. (correspondence to Nistor C)
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10. **Trandafir AI**, Stanciu M, Albu SE, Stoian VR, Ciofu I, Persu C, Nistor C, Carsote M. Management of Adrenal Cortical Adenomas: Assessment of Bone Status in Patients with (Non-Functioning) Adrenal Incidentalomas. J Clin Med. 2023;12(13):4244. (correspondence to **Trandafir AI**, Stanciu M)
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Impact factor = 3; Q1; PubMed index; first author and correspondent author
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2. Other scientific works during PhD years (selective)

Full-length articles indexed in WOS/Clarivate

1. **Trandafir AI**, Gheorghe AM, Sima OC, Ciuche A, Petrova E, Nistor C, Carsote M. Cross-Disciplinary Approach of Adrenal Tumours: Insights into Primary Aldosteronism-Related Mineral Metabolism Status and Osteoporotic Fracture Risk. Int J Mol Sci. 2023;24(24):17338. (correspondence to Gheorghe AM, Nistor C)
doi:10.3390/ijms242417338.
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Impact factor = 4.9; Q1; PubMed index; first author
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Poster presentations at international conferences/congresses

1. **Trandafir A**. Bone health outcome following adrenalectomy versus conservative management in 119 postmenopausal women with non-functional adrenal tumours. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO), 16-19 2026 April, Prague, Czech Republic. Abstract book (page 263; poster number P283) https://www.wco-iof-esceo.org/programme
2. **Trandafir A**. Bone profile in postmenopausal women with adrenal tumours according to cortisol secretion status: a cross-sectional study. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO), 16-19 2026 April, Prague, Czech Republic. Abstract book (page 266; poster number P287) https://www.wco-iof-esceo.org/programme
3. **Trandafir AI**, Carsote M. Bone health assessment in menopausal women with adrenal incidentalomas: a single Balkan country experience. The 38th Balkan Medical Week, organized by The Romanian National Section of the Balkan Medical Union, 5-6 June 2025, Bucharest, Romania. https://umbalk.org/wp-content/uploads/2025/06/PROGRAM-CONGRES-pentru-website-3.pdf. Abstract book in Archives of The Balkan Medical Union, The Official Journal of the Balkan Medical Union. New Series. June 2025; Volume 60, Supplement 1: page S40-S41 (E4). ISSN 1584-9244 (print), ISSN-L 1584-9244, 2558-815X (online) https://umbalk.org/
4. **Trandafir AI**, Sima OC, Nistor C, Dumitrascu A, Costachescu M, Petrova E. Beyond back pain: mild autonomous cortisol secretion complicated with vertebral fractures. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-

ESCEO), 10-13 2025 April, Rome, Italy. Abstract book (page 589; poster number P893) WCO25-AbstractBook.pdf

5. **Trandafir AI**, Petrova E, Gheorghe AM, Sima OC, Dumitrascu A. Bilateral nodular adrenocortical disease and decision making for antiosteoporotic medication. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO), 11-14 2024 April, London, United Kingdom. Abstract book (page 245; poster number P267) WCO24-AbstractBook.pdf
6. **Trandafir AI**, Gheorghe AM, Sima OC, Rentea ED, Nistor C, Bugala NM, Diaconu OA, Scrieciu M. Premature ovarian failure and osteoporosis. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO), 4-7 2023 May, Barcelona, Spain. Abstract book (page 243; poster number P266) WCO23-AbstractBook.pdf

Poster and oral presentations at national conferences/congresses

1. **Trandafir AI**, Petrova E, Carsote M. Osteoporoza in contextul secretiei autonome de cortizol (MACS) si al hiperparatiroidismului primar. Al 33-lea Congres National al Societatii Romane de Endocrinologie. Stiinta, Colaborare si Dezvoltare. 29 June-2 July 2025, Timisoara, Romania. Volum de rezumate (pdf). pag 204-207 (PP73) www.sre.ro.
2. Gheorghe AM, Manda D, Loghin-Oprea N, Schipor SV, Cumpata V, Voicu G, **Trandafir AI**, Sima OC, Popescu A, Costahescu M, Petrova E, Suveica L, Carsote M. Correlations in the clinical approach of circulating irisin: a clinical study in postmenopausal women. The 27th National Symposium of Psychoneuroendocrinology, organized by Romanian Society of Psychoneuroendocrinology in partnership with "Stefan cel Mare" University of Suceava & the Academy of Medical Sciences, "Behavioural Implications of Neuroendocrine Disorders", 9-10 October 2025, Suceava, Romania https://neuroendocrinologie.ro/
3. **Trandafir AI**, Dumitrascu A, Nistor C, Petrova E, Voicu G, Chirita C, Carsote M, Ghemigian A. Bilateral sporadic nodular adrenocortical disease: does trabecular bone score serve a reflection of mild autonomous cortisol secretion? The 31st National Congress of the Romanian Society of Endocrinology. 25-28 June 2023, Oradea, Romania. Abstract book. PO66: 171-172. https://www.sre.ro/2023-congresul-national-de-endocrinologie-program/
4. **Trandafir AI**, Dumitrascu A, Voicu G, Nistor CE, Petrova E, Ghemigian A, Carsote M. Statusul osos in tumorile adrenale nefunctionale. Al XVI-lea Congres al Asociatiei de Endocrinologie Clinica din Romania (AECR) „Patologia tumorala, autoimuna si enzimatica in endocrinologie", 5 Septembrie 2023, Eforie Nord, Romania https://www.aecr.ro/

Awards

1. **ESCEO-IOF Young Investigator Award** on behalf of International Osteoporosis Foundation (IOF) and European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), awarded at World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2026 Prague (signed award certificate by Professor Nicholas C. Harvey and Professor Jean-Yves Reginster as co-Presidents)
2. **"Professor Dr. Rodica Dascalu" Award** on behalf of AECR (Association of Clinical Endocrinology in Romania), awarded at The XVIth Congress of AECR, 3-5 September 2023, Eforie Nord, Romania for the oral presentation of the scientific work "Bone status in non-functioning adrenal tumours"