

# Osteoporosis and adrenal incidentaloma: To be or not to be?

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## ABSTRACT

**Introduction.** Adrenal incidentaloma is a more frequent diagnosis during the last decades since the relative access to abdominal ultrasound, computed tomography or magnetic resonance imagery is higher.

**Aim.** Our aim is to focus on the relationship between bone status (BS) in patients diagnosed and confirmed with adrenal incidentaloma.

**Method.** This is a mini-review of the literature. Most of the included papers were published during the last 5 years. The main research tool is PubMed database.

**General data.** BS is affected in adrenal incidentaloma mainly through persistent autonomous cortisol production which is called (even lately the term is not encouraged) “subclinical Cushing’s syndrome” with a prevalence of 0.2 up to 2% in unselected series of adult people. TBS (Trabecular Bone Score) in both men and women is negatively correlated with plasma cortisol after 1 mg dexamethasone suppression test. There is 2.2% decrease of TBS if subclinical Cushing’s syndrome is confirmed opposite to clear non-functioning pattern of the adrenal incidentaloma. Bone mineral density based on DXA at central sites (lumbar spine and femoral neck) was similar between the subject with unilateral and bilateral incidentaloma. The presence of subclinical hypercortisolism is positively correlated with a higher risk of osteoporosis and fragility fractures. Recently the term of “high risk” patients with adrenal incidentaloma has been introduced in order to describe the subgroup with autonomous cortisol secretion that has an increased risk of cardiovascular morbidities, infections and fractures (even independently of DXA - bone mineral density).

**Conclusion.** The main contributor to BS, as well as to the cardiometabolic damage, remains the autonomous cortisol secretion in adrenal incidentaloma with a potential improvement after adrenalectomy and without a specific anti-osteoporotic medication in this particular situation.

**Keywords:** adrenal tumour, osteoporosis, fracture, cortisol

## Abbreviations

BS = bone status

DXA = Dual-Energy X-Ray Absorptiometry

TBS = Trabecular Bone Score

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## Article History:

Received: 14 November 2019

Accepted: 2 December 2019

## INTRODUCTION

Adrenal incidentaloma is a more frequent diagnosis during the last decades since the relative access to abdominal ultrasound, computed tomography or magnetic resonance imagery is higher (1,2) (Figure 1). The incidence is expected to rise due to technological progress (1,2). The finding has an age-dependent pattern (2,3). The diagnosis actually includes two aspects: one is the radiological or imaging detection through any of the mentioned procedures, and the other aspect is related to the clinical and endocrine assessment that finally decides that the incidental tumour is a “true” incidentaloma meaning that overall there is a negative secretor profile and the route to its detection was accidental (4,5). However, a possible or a probable autonomous cortisol production is included and thus some long term complications might be expected, ignored or considered “idiopathic” or just “age-related” as seen in subjects diagnosed with high blood pressure, hyperlipemia and osteoporosis especially in menopausal women (1,5,6). The lesion typically has at least 10 millimetres (mm) (6). The hormonal workup includes: morning plasma cortisol and ACTH, cortisol circadian rhythm, salivary plasma cortisol, 24-hour urinary free cortisol, plasma/urinary metanephrines and normetanephrines, adrenal androgens, aldosteron and aldosteron/renin ratio (6). Some drugs if they are co-administered might alter the results of the assays and a level of awareness is necessary among practitioners (1,6).



**FIGURE 1.** Abdominal ultrasound on a menopausal woman showing a right adrenal tumour of 1.53 by 1.97 cm (an adrenal incidentaloma)

## AIM

Our aim is to focus on the relationship between bone status especially osteoporosis in patients diagnosed and confirmed with adrenal incidentaloma

after both radiological and endocrine evaluation.

## MATERIAL AND METHOD

This is a mini-review of the literature. Most of the included papers were published during the last 5 years. The main research tool is PubMed database. The general data is grouped around several key points based on a clinical approach. A number of 33 papers have been included based on clinical relevance.

## GENERAL DATA

### Adrenal incidentaloma

The prevalence of adrenal incidentaloma is up to 3% based on unselected series of general population (4). The percent increases to 10% after the age of 70 years (4). The radiological (unselected speaking about endocrine pattern) includes: 80% of cases are adenomas derived by adrenal cortex with benign features displaying a completely negative endocrine profile (most of them) or autonomous cortisol secretion (between 10% and 50%) or aldosterone excessive secretion (between 1% and 10%) (4). The excess of pure adrenal androgens is extremely rare in cases without other secretions and these cases are not usually asymptotically at presentation so they can barely fit to the diagnosis of adrenal incidentaloma (7,8). The cortisol excess (even subclinical) is more frequent in subjects with bone loss or vertebral fractures (4,9).

### Autonomous secretion of cortisol

The persistent cortisol secretion, even mild, is autonomous and it underlines the typical long term complications of subclinical hypercortisolism which is found positive in one third up to half of the cases confirmed with adrenal incidentaloma (10). The main clinical aspects are the fact that classical phenotype of Cushing's syndrome is lacking (10,11). However, morbidities like obesity, type 2 diabetes mellitus or impaired glucose tolerance, hyperlipemia, osteoporosis, and high blood pressure are typically found after the age of 50 years and they may be considered as age-related, but not necessarily incidentaloma-related (10). There is a fine line between establishing the real cause of these conditions and their follow-up may show an unexplained worsening thus most probably tumor-related, while adrenalectomy may associate an improvement of the parameters so the connec-

tion with the tumor endocrine profile is confirmed (10,12).

### Glucocorticoid osteoporosis

Despite the fact that typical Cushing's syndrome is not found, chronic cortisol exposure affects the bone and glucocorticoid osteoporosis is the most common form of secondary type (13,14,15). The source of cortisol may be endogenous as adrenal and pituitary tumour derived or exogenous since glucocorticoids are used in many rheumatologic, dermatological, lung, etc conditions (13,14,15). Regardless the origin of the glucocorticoids excess, the mechanisms of bone loss includes reduced bone formation and increased bone resorption which is time-dependent as well as dose-dependent (16,17,18). DXA (Dual-Energy X-Ray Absorptiometry) is a useful tool to evaluate the bone loss but sometimes it underestimates the fracture risk (16).

### Bone status (BS)

BS is affected in adrenal incidentaloma mainly through persistent autonomous cortisol production which is called (even lately the term is not encouraged) "subclinical Cushing's syndrome" with a prevalence of 0.2 up to 2% in unselected series of adult people (19). One study published in 2018 by Kim BJ et al. showed that TBS (Trabecular Bone Score) in both men and women is negatively correlated with plasma cortisol after the use of 1 mg dexamethasone suppression test (20). Moreover, there is 2.2% decrease of TBS if subclinical Cushing's syndrome is confirmed opposite to clear non-functioning pattern of the adrenal incidentaloma (20). TBS have a tendency to correlate with the values of plasma cortisol after mentioned suppression test (20). The statistical quality of the data is higher in women (20).

Another study on 152 subjects with adrenal incidentaloma (2/3 had unilateral lesions and 1/3 had bilateral lesions) showed that among them 20% had subclinical Cushing's syndrome (more frequent in bilateral tumours) but the bone mineral density based on DXA at central sites (lumbar spine and femoral neck) was similar between the subgroups (21). Another meta-analysis based on 6 studies including 1239 patients with adrenal incidentaloma showed that metabolic complications

as well as osteoporosis do not differ if the incidentaloma is uni or bilateral (22). On the other hand, the presence of subclinical hypercortisolism is positively correlated with a higher risk of osteoporosis and fragility fractures versus patients with negative secretor profile and adrenal incidentaloma (23). Recently the term of "high risk" patients with adrenal incidentaloma has been introduced in order to describe the subgroup with autonomous cortisol secretion that has an increased risk of cardiovascular morbidities, infections and fractures (even independently of DXA - bone mineral density (24).

## DISCUSSION

The influence of BS in adrenal incidentaloma is also directly due to the presence of obesity, type 2 diabetes mellitus and hyperlipemia as potential contributors to increased risk of vertebral fractures, not necessarily through hypercortisolism (25,26). Also, the data regarding the non-cortisol hormones of the adrenal cortex is controversial. The lesions like lipomas and cysts are irrelevant to BS (27). The effect of aldosterone excess over BS is less understood up to present time (3). It seems that clear aldosterone overproduction causes a deterioration of bone microarchitecture as shown by low TBS (28). Some authors suggested that a higher activity of the sympathetic activity induces skeleton status damage (29). Other secondary causes of osteoporosis related to concomitant endocrine tumours with overproduction of different hormones like pituitary adenomas including prolactinomas are described in addition to adrenal incidentalomas but this is a rare event (30,31).

The main contributor to BS, as well as to the cardiometabolic damage, remains however the autonomous cortisol secretion in adrenal incidentaloma with a potential improvement after adrenalectomy and without a specific anti-osteoporotic medication in this particular situation (32,33).

## CONCLUSION

Adrenal incidentaloma and osteoporosis, respective fragility fractures are still an open topic; up to this moment the correlation is based on autonomous cortisol secretion as main contributor.

*Conflict of interest:* none declared  
*Financial support:* none declared

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