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REVIEW

Adrenocortical incidentalomas and bone: from molecular insights to clinical perspectives

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Abstract

Adrenal incidentalomas constitute a common clinical problem with an overall prevalence of around 2–3%, but are more common with advancing age being present in 10% of those aged 70 years. The majority of these lesions are benign adrenocortical adenomas (80%), characterized in 10–40% of the cases by autonomous cortisol hypersecretion, and in 1–10% by aldosterone hypersecretion. Several observational studies have shown that autonomous cortisol and aldosterone hypersecretion are more prevalent than expected in patients with osteopenia and osteoporosis: these patients have accelerated bone loss and an increased incidence of vertebral fractures. In contrast to glucocorticoid action, the effects of aldosterone on bone are less well understood. Recent data, demonstrating a concomitant co-secretion of glucocorticoid metabolites in patients with primary aldosteronism, could explain some of the metabolic abnormalities seen in patients with aldosterone hypersecretion. In clinical practice, patients with unexplained osteoporosis, particularly when associated with other features such as impaired glucose tolerance or hypertension, should be investigated for the possible presence of autonomous cortisol or aldosterone secretion due to an adrenal adenoma. Randomized intervention studies are needed, however, to investigate the optimum interventions for osteoporosis and other co-morbidities in these patients.

Keywords: Adrenal · Incidentaloma · Autonomous cortisol hypersecretion · Primary aldosteronism · Bone · Osteoporosis

Introduction

The term adrenal incidentaloma refers to any clinically unsuspected adrenal lesion that is detected incidentally during imaging for other indications [1, 2]. With widespread use of imaging techniques, adrenocortical incidentalomas constitute a common clinical problem with a prevalence of more than 10% in people 70 years or more [1–6]. Adrenal incidentalomas can be benign or malignant, functioning or non-functioning, unilateral or bilateral. The vast majority are benign adrenocortical adenomas (ACA, 80%) [1, 2] with the most frequent endocrine dysfunction being "autonomous cortisol hypersecretion", previously termed "subclinical Cushing's syndrome" [1, 2, 7–10], while primary aldosteronism (PA) seems to be the most frequent hormonal secretion in Korean population with adrenal incidentaloma [11]. Depending on definitions used, the prevalence of excess cortisol secretion among these adrenocortical lesions ranges from 10 to 40%. In contrast, the frequency of aldosterone hypersecretion varies from 1% to 10% according to various tests used [1, 2, 6, 12, 13]. Recent data, however, indicate that excess cortisol secretion

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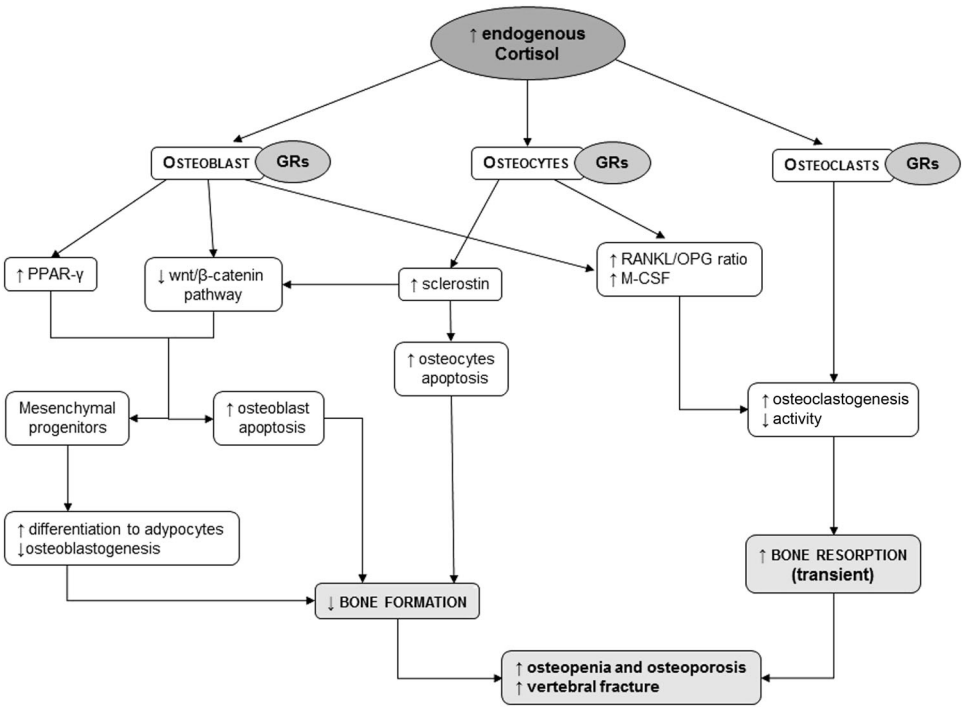

Fig. 1 Direct effects of cortisol excess on bone metabolism. Endogenous glucocorticoid excess negatively affect osteoblast, osteocytes, and osteoclast, which expressed glucocorticoid receptors (GRs). These actions include an upregulation of peroxisome proliferator-activated receptor (PPAR)-γ [23] and an inhibition of the wingless (wnt)/β-catenin signaling pathway [24–26], leading to mesenchymal progenitor cells differentiating preferentially into adipocyte that results in a decreased number of osteoblasts and in an increasing of osteoblast apoptosis and a consequent reduction of bone formation [28]. This mechanism is also stimulated by sclerostin produced by osteocytes [30]. Another key mechanism is the increase of the receptor activator for NF-κB ligand (RANKL)/osteoprotegerin (OPG) ratio produced by osteoblasts and osteocytes [32–34] that, together with the increased macrophage colony-stimulating factor (M-CSF) [36], stimulates osteoclastogenesis and bone resorption

is also seen in PA, and that this may account for some of the metabolic abnormalities seen in these patients [14]. Furthermore, the cut-off used to define whether an adrenocortical incidentaloma is "functioning" or "non-functioning" is important, since patients with apparently non-nonfunctioning adrenal incidentalomas, as defined by a serum cortisol post dexamethasone of <1.8 µg/dL, still have excess risk of what may be reasonably considered to be cortisol-dependent co-morbidities [15].

The estimated cost of fragility fracture in the UK was £2.3 billion in 2011, but with this rising to a predicted cost of £6 billion by 2036, mostly due to the cost of hip fracture [16]. Bone loss and osteoporosis are well-established complications of glucocorticoid excess, be it from endogenous Cushing's syndrome or exogenous sources [17]. Given the wide prevalence of adrenal incidentaloma with low-grade cortisol-excess (1–4% of the aging population), it is important to understand what effect there may be on bone health, as this may have a very significant impact at the population level. In light of this, many studies over the past two decades have sought to investigate the effect of subclinical hypercortisolism on bone health in patients with adrenal incidentalomas.

The aim of this article is to outline the known effects of cortisol and aldosterone on bone and summarize the main studies that have assessed bone health in patients with adrenal incidentalomas.

Methods

A literature search was conducted in PubMed in English language, in order to identify publications on adrenal incidentalomas and bone until the end of June 2018. We collected, analyzed, and qualitatively resynthesized data regarding the effects cortisol and aldosterone on bone metabolism, as well as studies that have assessed bone health in patients with adrenal incidentalomas. We present in turn updated information regarding the mechanisms of action of cortisol and aldosterone on bone and clinical evidence from patients with adrenal incidentalomas with autonomous cortisol hypersecretion or hyperaldosteronism or both. We also discuss clinical implications and provide recommendations on appropriate management.

Cortisol hypersecretion and bone

Effects of cortisol on bone metabolism: mechanisms of action

Glucocorticoids are important for bone development by affecting osteoblast differentiation [18, 19], but excessive quantities seem to have a negative impact on bone health [20] and this impact will be analyzed here. In patients with adrenal incidentalomas with increased secretion of glucocorticoid to levels insufficient to cause classic Cushing's syndrome, the "sub-clinical" levels may still be sufficient to increase the risk of vertebral fractures due to a decrease of bone mineral density (BMD) and bone quality [20, 21].

Evidence showing the effect of glucocorticoid on bone deriving primarily from in vitro and in vivo models of mouse treated with glucocorticoid. Osteoporosis induced by glucocorticoid excess is due mainly to a direct effect on cells involved in bone remodeling (osteoblast, osteocytes, osteoclast, and their precursors) [20], which express the glucocorticoid receptors (GRs) that mediated the main action of cortisol [22]. The principal effect of the cortisol excess is a reduction of bone formation through a suppression of osteoblast activity mediated by an upregulation of peroxisome proliferator-activated receptor (PPAR)-γ [23] and an inhibition of the wingless (wnt)/β-catenin signaling pathway (Fig. 1) [24–26]. These mechanisms favor the differentiation of mesenchymal progenitors to adipocytes instead of osteoblasts, resulting in a decreased number of osteoblasts and in an increasing of osteoblast apoptosis [27, 28]. Cortisol excess stimulates the expression in osteocytes of sclerostin which seems to be a key role in the inhibition of the wnt pathway in osteoblast (Fig. 1) [29, 30]. In mouse models of glucocorticoid-induced osteoporosis, it has been showed that the treatment with anti-sclerostin antibody prevented the reduction of bone mass and strength in comparison to placebo [30]. Moreover, the treatment with these antibodies prevented osteocytes from apoptosis in rodents [31]. The suppression of osteoblasts differentiation associated with an increased osteoblasts and osteocytes apoptosis causes a reduction of bone formation (Fig. 1).

Cortisol excess favors also bone resorption through an alteration of the receptor activator for NF-κB ligand (RANKL)/osteoprotegerin (OPG) ratio produced by osteoblasts and osteocytes (Fig. 1) [32–34]. RANKL is a regulator of recruitment, activation, and survival of osteoclasts, whereas OPG acts as a decoy receptor for RANKL preventing its interaction with RANK and causing the inhibition of osteoclastogenesis [35]. An in vivo mouse model demonstrated that glucocorticoids treatment decreased secretion of OPG rather than elevating RANKL expression in osteocyte cells [34]. The modified RANKL/OPG ratio by cortisol increases the RANKL activity and promotes the bone resorption (Fig. 1) [32–34]. Moreover, glucocorticoids stimulate the production of the macrophage colony-stimulating factor that stimulates osteoclastogenesis together with RANKL [36]. However, this effect of bone resorption is only transient and usually decreases over time due to a suppression of osteoblasts and osteocytes activity [37]. Therefore, the decrease in bone formation rather than increase in bone resorption plays a key role in osteoporosis induced by cortisol excess [19, 28].

It should be noted that the severity of the skeletal effect of hypercortisolism could due to individual sensitivity to cortisol that may modify the overall phenotype observed. Some of the variability in sensitivity in different tissues in the same individual may be mediated by the repertoire of co-activators and co-repressors that are present in a given tissue. Moreover, evidence suggests that at least some of the variable sensitivity to glucocorticoids in bone is conferred by polymorphisms of the GR [38]. Moreover, local regeneration of cortisol by 11-beta hydroxysteroid dehydrogenase type 1 (11βHSD1) may contribute further to these effects [39].

Hypercortisolism influences mineral and bone metabolism also through indirect effects mediated by calcium (Ca^{2+}) and parathyroid hormone (PTH) [20]. Cortisol reduces intestinal Ca^{2+} absorption and increases renal Ca^{2+} excretion, with a final Ca^{2+} negative balance that may deteriorate bone mineralization. Opposing dates are reported regarding PTH levels, a marker of bone resorption, in patients with adrenal incidentaloma and two studies by the group of Chiodini showed that in female patients with adrenal incidentaloma autonomous cortisol hypersecretion and autonomous cortisol hypersecretion had higher PTH levels in comparison to patients with inactive adrenal masses [40, 41]. Higher levels of PTH in these patients were not shown by studies from other groups [42, 43]. However, regardless of an increase plasma levels, PTH correlated inversely with femoral BMD [40, 42, 43]. More consistently observed are lower blood osteocalcin levels, a marker of bone formation, in patients with autonomous cortisol hypersecretion in comparison to patients with inactive adrenal incidentaloma or healthy controls [40–42, 44]. The decrease of osteocalcin levels is due to the inhibition of osteoblastic activity and increase of osteoblastic apoptosis caused by cortisol excess [20]. However, this finding was not confirmed by other studies [43, 45]. It is important to note that the discordance observed between studies on PTH and osteocalcin levels is likely due to the small sample size of the studies and the different criteria used for the definition of autonomous cortisol hypersecretion [21].

Taken together, it is clear that the overall level of cortisol secretion needed to have deleterious effects differs by tissue and by individual, but that over time even subtle increases

of endogenous cortisol secretion has a net effect favoring bone loss.

Clinical evidence from patients with adrenal incidentaloma and autonomous cortisol hypersecretion

Evidence for the effect of cortisol hypersecretion on bone health also comes from clinical studies too. Although glucocorticoids impair bone turnover with inhibition of osteoblastic activity [40, 42, 46], in patients with adrenal incidentalomas initial BMD studies did not find significant differences between those deemed to have autonomous cortisol secretion and controls [40, 47, 48]. Two studies assessing more homogeneous populations with adrenal incidentalomas, one including eugonadal males [45] and one including post-menopausal women [43], demonstrated significantly decreased BMD in patients with autonomous cortisol hypersecretion compared to those without. This decrease was, however, mainly within the limits of osteopenia and not sufficient to be classed as osteoporosis [43].

Several observational studies from one Italian center provide data that autonomous cortisol hypersecretion in patients with ACA is associated not only with accelerated bone loss but also with increased incidence of vertebral fractures [49–51]. Chiodini et al. included only women (70 patients and 84 controls) to avoid gender-related effects on bone and divided participants according to premenopausal and postmenopausal status. Subclinical hypercortisolism was associated with higher prevalence of fractures and reduced volumetric bone mass at the lumbar spine, independent of gonadal status. BMD, however, was mainly affected by menopausal status [49]. Another retrospective study, including 287 patients with adrenal incidentalomas and 194 controls, showed that BMD was significantly lower in lumbar spine and femoral neck in patients with autonomous cortisol hypersecretion than non-functioning adenoma and controls. Fracture prevalence and spinal deformity index were also significantly higher in those with subclinical hypercortisolism regardless of age, gender, menopausal status, and BMD [50]. In a prospective study by the same group, 103 consecutive patients with adrenal incidentalomas were followed-up in order to evaluate the fracture risk over time. It was shown that the group of patients with autonomous cortisol hypersecretion had a higher rate of vertebral fractures (82%) compared to baseline (56%), regardless of age, gender, body mass index (BMI), BMD, and menopause, and this incidence was higher than that seen in patients with non-functioning adrenal incidentalomas [51]. It is likely that the fractures reported in these studies are being disclosed by very sensitive methodologies, since in routine clinical practice such a high rate of clinically significant fractures is not usually seen.

Interestingly, fracture risk was not directly predicted by BMD, as 40% of fractures occurred in patients with normal or only slightly reduced BMD [50, 51]. Therefore, it is possible that both bone mass and bone quality may be disordered. In further study from the same group, bone microarchitecture was assessed by measurement of the trabecular bone score (TBS) in patients with adrenal incidentalomas and concluded that bone quality in autonomous cortisol hypersecretion is altered [52]. Furthermore, it was shown that a combination of low TBS and low BMD was highly predictive for fractures, while the converse was true for those with a normal TBS plus high BMD, in whom a lower rate of fractures was observed [52]. A very recent study provided evidence that patients with mild autonomous cortisol secretion presented significantly decreased TBS, but not BMD when compared with patients with non-secreting incidentalomas [53]. TBS may be proved as a promising, non-invasive, inexpensive tool for the routine assessment of these patients in clinical practice.

A meta-analysis including six relevant studies has shown that patients with bilateral ACA had a higher prevalence of autonomous cortisol hypersecretion compared to patients with unilateral incidentalomas of the same size as the largest of the bilateral adenomas [54]. Only one study from this analysis investigated bone parameters in patients with unilateral vs. bilateral adrenal incidentalomas and reported a higher prevalence of fractures in those patients with bilateral adenomas. Interestingly, this higher prevalence remained significant even after adjusting for subclinical hypercortisolism, BMI, age, and lumbar spine BMD [55].

When managing patients with adrenal incidentaloma in clinical practice, it would be very useful to know which biochemical parameter of cortisol hypersecretion is the most reliable for predicting increased fracture risk. However, this is difficult as the diagnosis of autonomous cortisol secretion itself is still a matter of debate [56]. It is worth noting that the Italian group with the most studies on the topic is based on the presence of two out of the following three alterations for the diagnosis of subclinical hypercortisolism: (1) increased urinary free cortisol (UFC) levels (>193.1 nmol/24 h); (2) unsuppressed serum cortisol levels after 1-mg overnight dexamethasone (Dex) suppression test (serum cortisol after Dex >82.8 nmol/L); and (3) low adrenocorticotropic hormone (ACTH) levels (<2.2 pmol/L) [43, 45, 49–52].

A recent study from Italy found that serum cortisol levels after 1 mg dexamethasone-suppression test greater than 2.0 mg/dL (55 nmol/L) are independently associated with both prevalent and incident of vertebral fracture as well as with an increased risk of new vertebral fractures at diagnosis and during follow-up [57]. This association between the degree of biochemical cortisol hypersecretion and the risk for vertebral fracture was expected and is in accordance

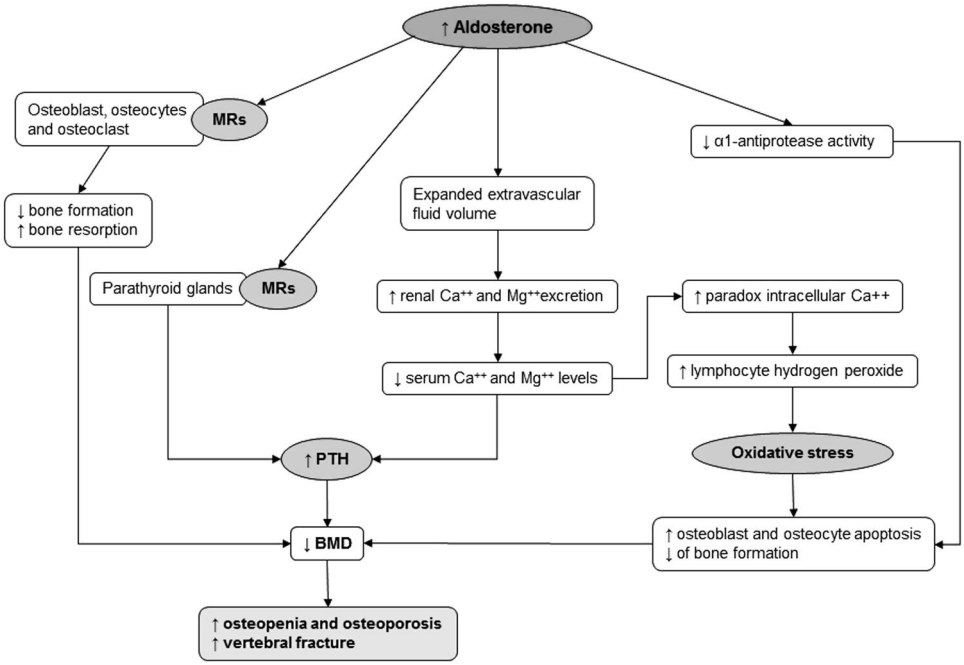

Fig. 2 Mechanisms of action of aldosterone on bone metabolism. Aldosterone excess could affect bone turnover directly by binding mineralcorticoid receptors (MRs) expressed in osteoclasts, osteocytes, and osteoblasts [67]. Furthermore, aldosterone regulate PTH synthesis and secretion through the MRs expressed in cells of parathyroid glands [69, 70]. Indirectly, aldosterone excess regulates bone metabolism through parathyroid hormone (PTH) and oxidative stress. Hyperaldosteronism expands the extravascular fluid volume that causes a marked increase of urinary excretion of calcium (Ca^{2+}) and magnesium (Mg^{2+}) in the distal tubule of the nephron, with a progressive reduction of serum Ca^{2+} and Mg^{2+} levels. The resulting hypocalcemia and hypomagnesemia stimulate the secretion of PTH, with a consequent secondary hyperparathyroidism, which induces bone resorption and a reduction of the bone mineral density (BMD) [61]. Moreover, aldosterone excess reduces plasma α1-antiprotease activity and increases lymphocyte hydrogen peroxide production, promoting a condition of oxidative stress resulting in increased osteoblast and osteocyte apoptosis, and reduction of bone formation [61, 81]

with previous studies, most of which come from a single Italian group [43, 45, 49–52]. Interestingly, this association was independent of BMD and supports the notion that reduced bone quality is the most significant parameter leading to skeletal fractures as a consequence of cortisol excess [52]. 24-h UFC and plasma ACTH levels were shown to be not statistically associated with fracture risk. A potential explanation for plasma ACTH not being a useful marker is the differing sensitivity of various tissues to glucocorticoids: bone tissue may be affected even before suppression of hypothalamic–pituitary–adrenal axis is evident [57].

Surgical treatment of ACA in small groups of patients with autonomous cortisol hypersecretion has been associated with improvement of various parameters, including weight, blood pressure, glucose, and lipid metabolism [58, 59]. However, here the data are still too limited, and some studies report no benefit. The European guidelines on the management of adrenal incidentaloma recommend adrenalectomy only in the minority of cases, and based on careful individualized treatment decisions. Recent data showed a 30% reduction of vertebral fracture risk after adrenalectomy in selected patients [60]; this finding is potentially important and underlines the pathophysiological association between cortisol hypersecretion, reduced bone quality, and fractures in patients with ACA. However, it is important to note that the majority of studies on bone in patients with adrenal incidentaloma come from one group [45, 49–51, 55, 57, 58] and before making wide-ranging treatment recommendations it is crucial to have larger studies in various populations.

PA and bone

Effects of aldosterone on bone metabolism: mechanisms of action

Contrary to the well-studied mechanisms, which underline the link between autonomous cortisol secretion and bone, less is known regarding the link between hyperaldosteronism and osteoporosis.

Over the last two decades, several small studies have demonstrated that aldosterone excess is likely to affect bone

turnover through a direct effect on bone cells and through indirect mechanisms via PTH and oxidative stress [61–66] (Fig. 2).

The direct effect of aldosterone on bone metabolism is still poorly understood. Mineralocorticoid receptors (MRs) are expressed in human and rat osteoclasts, osteocytes, and osteoblasts [67, 68], suggesting a direct effect of aldosterone on bone turnover. MRs are present also in normal and adenomatous parathyroid tissue [69, 70]. Furthermore, a positive association between the aldosterone/renin ratio and serum PTH concentration has been demonstrated in normal individuals [71], suggesting that aldosterone may directly regulate PTH synthesis and secretion (Fig. 2). Moreover, in vivo and observational human studies suggest that MR antagonists (MRA) have a beneficial effect on bone metabolism. In rat models, treated with aldosterone and salt for 4–6 weeks, bone loss was attenuated after administration of the MRA spironolactone [61, 72, 73]. Similarly, patients with PA treated with spironolactone showed decreased urinary calcium loss and improved BMD [74–76]. However, a recent single-center, double-blind, randomized, placebo-controlled trial demonstrated no effects of eplerenone on bone turnover markers in patients with primary hyperparathyroidism, suggesting that MR antagonism may not be relevant in primary hyperparathyroidism, but could have efficacy in condition of hyperparathyroidism secondary to hyperaldosteronism [77].

The interaction between MR and bone has been further examined in animal models. In rats treated with aldosterone and salt, there was a significant increase in urinary and fecal excretion of Ca^{2+} and magnesium (Mg^{2+}), with a consequent progressive reduction of plasma ionized Ca^{2+} and Mg^{2+} levels [61]. Urinary losses of Ca^{2+} and Mg^{2+} were the result of expanded extravascular fluid volume resulting in decreased resorption of sodium (Na^{+}), Ca^{2+}, and Mg^{2+} in the proximal tubule of the nephron with a consequent increase of their excretion in the distal tubule. Because aldosterone stimulates Na^{+} resorption, but not that of Ca^{2+} and Mg^{2+} at the distal tubule, this causes a marked increase of Ca^{2+} and Mg^{2+} excretion [78, 79], with the lowering of Ca^{2+} and Mg^{2+} leading to secondary hyperparathyroidism, stimulating bone resorption and a significant reduction of BMD and cortical bone strength (Fig. 2) [61, 80].

In the same rat model, a significant reduction of plasma α1-antiprotease activity and an increase of lymphocyte hydrogen peroxide production was reported after aldosterone-sodium treatment for 1–6 weeks in comparison to the control group [61, 80, 81]. The authors hypothesized that aldosterone promotes a systemic condition of oxidative stress and inflammation that could result in increased osteoblast and osteocyte apoptosis, and reduced bone formation (Fig. 2) [82, 83].

In conclusion, hyperaldosteronism affects bone turnover through several direct and indirect mechanisms, most of which act through an increase of serum PTH levels.

Clinical evidence from patients with adrenal incidentaloma and hyperaldosteronism

Evidence regarding the link between hyperaldosteronism and bone metabolism is also derived from several observational studies. Aldosterone hypersecretion can be detected in 1–10% of patients with adrenal incidentalomas [1, 2]. Together with bilateral adrenal hyperplasia (BAH), the aldosterone-producing adenomas (APA, also termed "Conn adenoma") represent more than 90% of cases of PA; the remaining cases of PA are due to unilateral adrenal hyperplasia and aldosterone-producing carcinoma [84]. Several observational studies showed significantly higher PTH levels, lower serum Ca^{2+} levels, and higher urinary Ca^{2+} excretion in patients with PA in comparison to those with essential hypertension (EH) [63, 64, 74, 85–87], and a higher prevalence of osteoporosis [63–66, 74, 88].

Salcuni et al. [63] reported the first association between hyperaldosteronism and osteoporosis in patients with APA. In 11 patients with APA there was decreased BMD at the lumbar spine, total and femoral neck (13%, 8% and 11%, respectively), an increased prevalence of osteoporosis (73% vs. 20%) and a higher incidence of vertebral fractures (46% vs. 13%), in comparison to 15 patients with non-functioning incidentalomas. Moreover, the increased urinary Ca^{2+} excretion and elevated PTH levels found in APA patients were reversed after adrenalectomy or spironolactone treatment [63].

The reversibility of secondary hyperparathyroidism in PA patients after surgical or medical treatment was supported by two other observational studies [85, 86]. Ceccoli et al. [85] compared PA patients (46 with APA and 70 with BAH) with 110 EH patients, finding significant increases in PTH levels and urinary Ca^{2+} excretion, and decreased serum Ca^{2+} levels (with comparable vitamin D concentrations). Interesting, PTH levels were higher in patients with APA than in those with BAH [85]. Similarly Pilz et al. [86] showed higher PTH levels in a small group of patients with PA (5 APA and 5 BAH) compared to 182 with EH; moreover, they observed that the normalization of PTH levels was more pronounced in patients operated for APA than those treated with MRA for BAH. It is important to note that in both studies the PA group had significantly higher blood pressure than the EH group, and that arterial hypertension itself can increase urinary Ca^{2+} excretion with consequent secondary hyperparathyroidism [89]. Nevertheless, a larger observational study demonstrated higher urinary Ca^{2+} excretion, lower serum Ca^{2+} levels, and higher

PTH levels in 73 patients with PA in comparison to 73 patients with EH and 40 healthy controls [64], without differences in blood pressure between PA and EH groups, suggesting that aldosterone itself may be involved in the stimulation of PTH secretion in PA. No differences were seen in anthropometric and biochemical characteristics between patients with APA and BAH [64].

Another observational study comparing 105 consecutive patients with hypertension, of whom 44 with APA and 61 with EH, showed that in the APA group there were significantly higher plasma PTH levels compared to the EH group ($P < 0.001$), despite similar urinary Ca^{2+} excretion and vitamin D levels [87]. Similar to previous studies, PTH levels were normalized in patients with APA after adrenalectomy. Moreover, the authors demonstrated the expression of the PTH receptor, at mRNA and protein levels, in APA tissues and speculated that PTH, by acting on these receptors, may contribute to hyperaldosteronism despite the suppression of the angiotensin–renin system [87].

Very recently, Salcuni et al. observed a higher prevalence of PA in a group of 322 consecutive subjects screened for osteoporosis who were not taking drugs affecting bone and mineral metabolism and who had no prior diagnosis of secondary osteoporosis, compared to a non-osteoporotic control group (5.2% vs 0.9%, $P = 0.066$). The prevalence of PA was higher still in those who also had osteoporosis and hypertension (13.9%), fracture and hypertension (14.8%), fracture and hypercalciuria (11.1%), and osteoporosis, hypertension, and hypercalciuria (26.1%), emphasizing the potential interplay between PA and bone [88]. In this study, osteoporosis was associated with PA (OR = 10.42; 95% CI 1.21–90.91), as well as age (OR = 1.06; 95% CI 1.03–1.09) and BMI (OR = 1.11; 95% CI 1.05–1.17), but not with EH (OR = 1.23; 95% CI 0.72–2.1) [88].

Another recent study including 56 PA patients, 16 of whom had APA, and 56 matched healthy controls identified PA as a risk factor for vertebral fractures independently of blood pressure, glycated hemoglobin, and lipid levels [65]. There were no differences in the vertebral fracture rate in patients with APA in comparison to those with BAH, despite higher aldosterone plasma levels in patients with APA. Contrary to previous observational studies [63, 64, 88], there were no significant differences in PTH levels and BMD in PA patients compared to controls [65]. This discrepancy could be due to the design of the study, which focused on vertebral and not cortical bone [65]. A large population-based study suggested that PA was associated with higher risk of bone fracture; however, a reduced risk of fracture in women with both APA or BAH after MRA treatment was not observed, a result which might reflect the duration of disease [66].

However, similar to what is observed in autonomous cortisol secretion, the majority of data regarding PA and bone metabolism came from observational studies of a small cohort of patients evaluated in a single center. Multicenter observational studies and randomized interventional studies, which investigate the efficacy of MRA or adrenalectomy for the prevention of osteoporosis, are urgently needed.

Very recent data suggest the potential role of co-secretion of mild glucocorticoid excess in the development of co-morbidities in patients with PA. Using mass spectrometry-based analysis of the 24-h urinary steroid metabolic profiling a concomitant presence of mild glucocorticoid metabolite excess was demonstrated in a large proportion of patients with PA (provocatively termed by the authors as "Connshing's" syndrome) [14]. Interesting, in the group of patients with co-secretion of aldosterone and cortisol, metabolic parameters such as increased BMI, insulin resistance, diastolic blood pressure, waist circumference, and high-density lipoprotein were associated with cortisol levels and not with aldosterone levels [14]. Arlt et al. [14, 90] suggested that the co-secretion of cortisol in patients with PA may contribute in the pathogenesis of co-morbidities observed in these patients, including osteoporosis. However, prospective randomized studies are needed to confirm this result, and to assess whether those patients with PA identified as having the glucocorticoid-rich metabolic profile but who do not undergo surgery, need glucocorticoid antagonist in addition to MRA to counteract the adverse metabolic risk [14].

Conclusion and implications for management

Adrenocortical incidentalomas constitute a common clinical problem with a prevalence of up to 10% in elderly [1–4], mostly being represented by benign ACA and often being associated with corticosteroid excess [1, 2, 7–9].

Several observational studies have shown that ACA with autonomous cortisol hypersecretion is more prevalent than expected in patients with osteopenia and osteoporosis and that the autonomous cortisol hypersecretion is associated with accelerated bone loss and increased incidence of vertebral fractures [49–51]. Similarly, hyperaldosteronism is associated with a higher prevalence of osteoporosis [63–66, 74, 88]. Contrary to what is known about glucocorticoid action, the effects of aldosterone on bone metabolism are less well understood and seem mostly due to an indirect effect through the increase of urinary Ca^{2+} excretion, leading to compensatory secondary hyperparathyroidism [61, 63, 64, 85]. However, recent data using urinary steroid metabolic profiling have shown a mild cortisol co-secretion

in a subgroup of patients with APA and that it may account for some of the metabolic abnormalities seen in these patients, including osteoporosis [14, 90].

The recent European Society of Endocrinology (ESE)/ European Network for the Study of Adrenal Tumors (ENSAT) guidelines suggest screening of patients with ACA and autonomous cortisol secretion for vertebral fractures at least once at the time of diagnosis (by re-evaluation of CT images or by X-ray), while no consensus was reached by the experts concerning the assessment of BMD with dual-energy X-ray absorptiometry (DXA) [1]. The data summarized above suggest that BMD may not be accurate for fracture risk assessment in patients with ACA and autonomous cortisol secretion, and that TBS may be more useful, or at the very least used in combination.

In everyday clinical practice, patients with unexplained osteoporosis, particularly when associated with other metabolic symptoms (impaired glucose tolerance, hypertension, or hypercalciuria), should be investigated for the possible presence of adrenal incidentaloma associated with autonomous cortisol secretion or aldosterone hypersecretion. Thus, patients with ACA and osteopenia, osteoporosis or vertebral fractures might benefit from therapeutic adrenalectomy or when it is not possible from specific medical treatment, such as glucocorticoid antagonist therapy or MRA, to mitigate against the co-morbidities due to hormone excess [1, 12, 14]. Furthermore, it is possible that patients with PA, who do not undergo surgery, might need also glucocorticoid antagonist in addition to MRA if they have a glucocorticoid metabolite profile [14]. All these suggestions are derived from observational studies; more data, especially from prospective, randomized, controlled intervention trials, are needed to investigate further the optimum surgical or medical interventions to ameliorate osteoporosis and other co-morbidities due to ACA associated with autonomous cortisol secretion or hyperaldosteronism.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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