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REVIEW ARTICLE

Unveiling the hidden impact: Subclinical hypercortisolism and its subtle influence on bone health

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Abstract

In recent years, advancements in imaging technologies have led to an increased detection rate of adrenal incidentalomas (AI), with age demonstrating a significant correlation with their incidence. Among the various forms of functional adrenal incidentalomas, subclinical hypercortisolism (SH) stands out as a predominant subtype. Despite the absence of typical symptoms associated with Cushing's syndrome, both domestic and international research consistently establishes a robust link between SH and diverse metabolic irregularities, including hypertension, lipid metabolism disorders, glucose metabolism abnormalities, and disruptions in bone metabolism. Individuals with SH face an elevated risk of cardiovascular events and mortality, highlighting the clinical significance of addressing this condition. Prolonged exposure to elevated cortisol levels poses a significant threat to bone health, contributing to bone loss, alterations in bone microstructure, and an increased susceptibility to fractures. However, comprehensive reviews addressing bone metabolism changes and associated mechanisms in SH patients are currently lacking. Furthermore, the profound impact of concurrent SH on the overall health of the elderly cannot be overstated. A comprehensive understanding of the skeletal health status in elderly individuals with concomitant SH is imperative. This article aims to fill this gap by offering a detailed review of bone metabolism changes and associated mechanisms in SH patients arising from AI. Additionally, it provides a forward-looking perspective on research concerning skeletal health in elderly individuals with concurrent SH.

KEYWORDS
bone health, bone metabolism, subclinical hypercortisolism

1 | INTRODUCTION

Subclinical hypercortisolism (SH) is characterized by dysregulated activity within the hypothalamus-pituitary–adrenal (HPA) axis, leading to elevated cortisol secretion independent of adrenocorticotropic hormone (ACTH) regulation.[1–3] Despite the absence of overt symptoms of cortisol excess, individuals with SH are predisposed to metabolic disturbances, cardiovascular complications, and elevated mortality risks compared to the general population or those with nonfunctioning adrenal tumors (NFA).[4–7] Excessive cortisol levels are widely acknowledged as a significant threat to bone health, contributing to bone loss, alterations in

bone microarchitecture, and an increased risk of fractures, observed in both endogenous and exogenous hypercortisolism.[8–10] Osteoporosis and fractures are definitive complications associated with clinical Cushing's syndrome (CS).[11] Over the past two decades, numerous studies have revealed an increased incidence of osteoporosis and fractures in individuals with SH, particularly those with adrenal incidentaloma (AI), compared to both NFA patients and the general population.[12–15] These studies, predominantly cross-sectional or retrospective, primarily explore the relationship between adrenal-derived SH and bone metabolism on an international scale. Additionally, epidemiological surveys indicate a relatively elevated prevalence of subclinical hypercortisolism among the elderly, particularly in those aged over 60.[16] The coexistence of SH in the elderly significantly heightens the potential risk to bone health. This article provides a comprehensive review of bone metabolism alterations and related mechanisms in patients with SH induced by AI. Additionally, it offers insights into the prospective exploration of skeletal health in elderly individuals with concurrent SH.

2 | OVERVIEW OF SH

SH constitutes a cluster of clinical syndromes characterized by an elevation in autonomous cortisol secretion, distinctly lacking the classical signs and symptoms associated with overt hypercortisolism, such as centripetal obesity, a polycythemic appearance, purplish skin texture, skin bruising, sloughing, and proximal muscle weakness. Various terms have been employed to describe this phenomenon of endogenous hypercortisolism, including "preclinical Cushing's syndrome," "subclinical hypercortisolism," and "subclinical Cushing's syndrome".[1,17,18] Despite the 2016 European Society of Endocrinology (ESE) guidelines introducing the concept of "autonomous cortisol secretion" and emphasizing the necessity of monitoring dynamic hormone level changes due to alterations in the hypothalamus-pituitary–adrenal (HPA) axis, the term "subclinical hypercortisolism" remains widely utilized.[19] To date, the overnight 1 mg dexamethasone suppression test (DST) has been extensively conducted in clinical settings as the primary screening test, recommended by both national and international guidelines.[19,20] The 2016 guidelines for adrenal incidentalomas propose a serum cortisol level >138 nmol/L after overnight 1 mg DST (5.0 μg/dL) as the primary diagnostic criterion for autonomous cortisol secretion, with a sensitivity of approximately 83.3% and a specificity of up to 100%.[19] Despite the convergence on common principles, distinct diagnostic cut-points persist among different countries or regions, contributing to ongoing debates regarding specific diagnostic criteria.[20–22] In the context of China, a diagnostic cut-point of 50 nmol/L (1.8 μg/dL) is commonly employed for SH, with a recommendation to integrate other HPA axis-related indicators for a comprehensive assessment. This divergence in cut-points underscores the need for a nuanced approach to diagnosis, considering regional variations and enhancing the comprehensiveness of evaluations for accurate assessments of SH.

In recent years, the widespread use of imaging tests has significantly increased the detection rate of AI compared to previous years, with the prevalence of AI in the adult population estimated at approximately 4% to 7%.[17,19] The incidence of AI varies depending on the data source, such as autopsy, surgical, or radiological data.[17] Autopsy data suggest an increasing incidence of AI with age, with some studies indicating a prevalence exceeding 15% in individuals aged 70 and above.[23] In a large-scale retrospective cohort study conducted in Japan, which investigated all recorded cases of primary adrenal cortical tumors in the Pathological Autopsy Annuals from 1973 to 1984 ($n = 321,847$ cases), the age distribution chart revealed a peak incidence in the 60s.[24] SH is the most common type of functional adrenal incidentaloma, accounting for approximately 20% to 30% of its etiological classification.[17,19] Epidemiological data suggest that the prevalence of SH in the general population is around 0.08% to 0.2%. Moreover, the incidence of SH in individuals aged 60 and above further increases, reaching up to 0.2% to 2.0%.[17–19] Additionally, SH often remains concealed within common diseases such as obesity, diabetes mellitus, and hypertension, with studies indicating that the prevalence of SH can be as high as 10.8% in patients with diabetes mellitus, hypertension, obesity, and osteoporosis.[25]

Individuals with SH often present without the characteristic signs and symptoms of hypercortisolism, and the progression to overt hypercortisolism is rare (occurring in less than 0.1% of cases). Nevertheless, the prolonged exposure to endogenous cortisol oversecretion is frequently associated with the development of multiple metabolic disorders, resembling the profile observed in patients with overt hypercortisolism.[26] The chronic elevation of cortisol levels significantly elevates the risk of diverse health complications, encompassing diabetes mellitus, hypertension, dyslipidemia, and disruptions in bone metabolism, thereby contributing to cardiovascular complications.[5,7,27] Recent statistics indicate that 64% to 100% of individuals with increased cortisol levels experience impaired bone health. Notably, the incidence of asymptomatic vertebral compression fractures in SH patients can be up to four times higher than in individuals with NFA.[11,28] Consequently, it is imperative to underscore the importance of emphasizing skeletal health and conducting thorough assessments of bone metabolism in individuals diagnosed with SH. This proactive approach becomes particularly crucial in managing the multifaceted health implications associated with prolonged cortisol elevation in these patients.

3 | MAIN MECHANISMS OF BONE DESTRUCTION CAUSED BY SH

The pathophysiological mechanisms underlying osteoporosis and fracture occurrence in patients with SH closely resemble those observed in CS. Despite the comparatively mild cortisol excess associated with SH, it can exert detrimental effects on bone health.

1. Direct Adverse Effects of SH on Bone. SH directly impacts bone health through glucocorticoid overactivity. Receptors on

osteoblasts, osteoclasts, and bone cells respond to excessive glucocorticoids, leading to imbalances in mesenchymal stem cell (MSC) differentiation, resulting in decreased osteoblasts and increased apoptosis, inhibiting bone formation.[9,29,30] Additionally, glucocorticoids induce heightened osteoclast activity, promoting accelerated bone resorption. This effect is mediated by alterations in the ratio of receptor activator of NF-kB ligand (RANKL) to osteoprotegerin produced by osteoblasts.[31] The net consequence is an imbalance in bone remodeling dynamics, favoring bone loss and fragility.

2. Indirect Adverse Effects of SH on Bone. Beyond direct consequences, excess glucocorticoids from SH disrupt calcium metabolism, attenuating intestinal calcium absorption and stimulating renal tubular calcium excretion, resulting in unfavorable calcium balance and aberrant bone mineralization.[11,27] Secondly, glucocorticoids play a pivotal role in lipid metabolism. They induce the decomposition of fat into glycerol and free fatty acids, either directly or by facilitating the lipolytic actions of catecholamines and growth hormone. Furthermore, they promote the conversion of free fatty acids and the synthesis of very low-density lipoproteins, thereby influencing organismal lipid metabolism. Elevated glucocorticoid levels have been associated with increased total cholesterol and triglycerides, coupled with decreased HDL-cholesterol levels. Lipid metabolism abnormalities have been reported in a substantial percentage of CS patients, ranging from 12% to 72%.[7,11] In hyperlipidemia, lipid oxidation products can induce reactive oxygen species, triggering oxidative stress. This, in turn, inhibits osteoclastogenesis and fosters bone resorption, ultimately contributing to the development of osteoporosis.[32]

   Furthermore, it is well-established that the intricate regulation of bone remodeling involves a complex interplay of factors operating at both systemic and local levels. Critical systemic regulators encompass parathyroid hormone (PTH), calcitriol, and various hormones including growth hormone, glucocorticoids, thyroid hormones, and sex hormones. In addition to these, insulin-like growth factors (IGFs), prostaglandins, transforming growth factor-beta (TGF-β), bone morphogenetic proteins (BMP), and cytokines play pivotal roles in orchestrating this nuanced regulatory network.[33] The detrimental impact of SH on bone metabolism may also arise from the excessive inhibition of the hypothalamus-pituitary–adrenal axis and the hypothalamus-pituitary-growth hormone axis due to elevated cortisol levels.[34,35] However, the specific underlying mechanisms remain inconclusive.

3. Impact of SH on Bone Conversion Indexes. Currently, both domestic and international research on bone turnover markers in patients with SH mainly focus on the changes in blood PTH and osteocalcin levels in SH patients. PTH is a calcium-regulating hormone and is also considered one of the markers for bone resorption. Studies have found that blood PTH levels in female patients with AI combined with SH are slightly higher than in NFA patients.[36] However, some studies suggest that no significant changes in PTH levels are observed in SH patients.[37,38] Osteocalcin, a marker of bone formation, has also been a subject of investigation in SH. Comparative analyses have revealed that SH patients exhibit lower blood osteocalcin levels when compared to both healthy controls and NFA patients.[15,36] This supports the notion that bone formation activity is inhibited, and osteoblast apoptosis is increased in SH patients.[9] However, negative results have also been reported.[37] The inconsistency in these studies may be attributed to several reasons. Firstly, there were variations in the number of participants and their relatively small sample sizes in different studies. Secondly, some studies did not adjust for confounding factors affecting bone metabolism. Lastly, differences in the diagnostic criteria for SH among various studies also contribute to the disparate results. It is important to note that the aforementioned markers are not highly specific bone turnover markers. N-terminal procollagen of type I collagen (P1NP) and β-C-terminal telopeptide of type 1 collagen (β-CTX) are more specific markers for bone turnover. However, research on changes in P1NP and β-CTX in SH patients is relatively limited, and further investigation is needed.

4 | IMPACT OF SH ON FRACTURE OCCURRENCE

Currently, most studies indicate a significantly increased risk of fractures in patients with SH. However, the correlation between changes in bone density and the risk of fractures in SH patients remains inconsistent.

1. Risk of Fracture in SH. Numerous international studies have focused on the risk of fractures in SH patients, with evidence suggesting fracture risks ranging from 46.3% to 82.4%. Vertebral fractures in SH patients often manifest as asymptomatic fractures.[10] A prominent cross-sectional study conducted by Chiodini and colleagues in Italy found a significantly higher incidence of vertebral fractures in SH+ patients compared to healthy controls and SH− AI patients ($p < 0.001$).[12] The study also utilized the Spinal Deformity Index (SDI), a reliable tool for assessing the long-term risk of vertebral fractures, calculated by cumulatively measuring the deformity of each vertebra. Chiodini et al. observed a significantly higher SDI in SH+ patients compared to healthy controls and SH− AI patients (95% CI: 3.94–13.41, $p < 0.001$), indicating a substantial increase in the risk of vertebral fractures. Furthermore, longitudinal cohort studies suggest that SH patients may experience asymptomatic vertebral fractures over the course of their illness.[39–41] Another longitudinal study followed 444 AI patients (271 females, 173 males) for over 2 years and reported 126 new vertebral fractures.[41] The study found a significantly increased risk of vertebral fractures (10-fold increase, 95% CI: 3.39–31.12, $p < 0.001$) when serum cortisol levels after a 1 mg dexamethasone suppression test exceeded 2.0 μg/dL. Some studies have also found that the incidence of

fractures can be significantly reduced after surgical removal of adrenal tumors, indirectly suggesting the harmful effects of SH on bone.[42] However, there is currently a lack of clinical controlled trials on whether surgical resection of AI can improve the fracture risk of SH. Salcuni et al.'s comparative analysis of 32 surgically treated and 23 conservatively treated SH patients assessed bone density and vertebral fracture occurrence at baseline and follow-up. Results showed that postoperative lumbar spine bone density increased, and the incidence of new vertebral fractures was significantly lower in the surgical group compared to the conservative treatment group (9.4% vs. 52.2%, $p<0.001$). Surgical treatment reduced the fracture risk associated with SH by 30%, with a relative risk of 0.7 (95% CI: 0.01–0.05, $p=0.008$), indirectly suggesting the detrimental impact of SH on bone.[40] However, the metabolic disturbance in surgically treated SH patients exhibited varying degrees of improvement, and conflicting conclusions exist due to short evaluation periods and biases, leaving the long-term outcomes and impact on patients' quality of life unclear. Currently, there is a lack of clinical controlled trials in this regard.

2. Non-Vertebral Fractures in SH Patients. While most studies on fractures in SH patients focus on vertebral fractures, a few isolated case reports mention nonvertebral fractures in various anatomical sites. Poonuru et al. reported 10 cases of incomplete distal limb fractures in patients with hypercortisolism, with five cases attributed to SH.[43] These patients presented with nonvertebral fractures in different locations, including the elbow, tibia, fibula, and metatarsal bones, suggesting the need to assess the occurrence of incomplete fractures in SH. However, these are individual case reports, and further multicenter clinical studies with larger sample sizes are needed to validate these findings.
3. Changes in SH Bone Density Are Not Correlated with Fracture Incidence. The relationship between changes in bone density and the incidence of fractures in SH has been a subject of extensive investigation. Traditionally, dual-energy X-ray absorptiometry (DXA) has been employed to assess bone density in patients with SH, with a consistent finding of reduced bone density, particularly in trabecular bone structures like the vertebrae and femoral neck. A comprehensive clinical review published by the European Society of Endocrinology in 2016 synthesized existing data, highlighting the adverse impact of excess cortisol on trabecular bone structure.[10] Contrary to the anticipated association between decreased bone density and increased fracture risk, some intriguing observations challenge this conventional understanding. Notably, some individuals with SH manifest vertebral fractures even in the presence of normal or only mildly reduced bone density.[39,40,44] This incongruity raises a critical point: relying solely on bone density indices may not be a reliable predictor for fractures in SH patients. The intricate interplay of various factors, including bone quality, microarchitecture, and perhaps other systemic effects of cortisol, may contribute to the occurrence of fractures independently of changes in bone density. The Trabecular Bone Score (TBS) is a method of evaluating the closeness of bone microstructure, it has been found that the TBS of SH patients was significantly lower than that of NFA patients ($p<0.0001$), the TBS was positively correlated with the degree of cortisol overdose, and the occurrence of fracture in SH patients was correlated with lower TBS with an OR of 4.8, suggesting that patients with SH's bone microstructure is damaged and bone mass is decreased, causing a decrease in bone strength followed by fractures.[45] In summary, while the majority of studies have demonstrated a prevalent reduction in bone density in SH patients, caution is warranted when assuming a direct correlation with fracture risk. The multifaceted nature of bone health in the context of excess cortisol necessitates a more nuanced understanding that goes beyond conventional assessments of bone density alone. Further research is imperative to elucidate the intricate mechanisms underlying fractures in SH patients and to refine our predictive models for fracture risk in this population.

5 | THE IMPACT OF SH ON BONE DENSITY

Diminished bone mass and osteoporosis are well-documented complications of overt Cushing's syndrome. Presently, extensive research has delved into alterations in bone density among individuals with SH, placing particular emphasis on SH triggered by AI. However, existing research findings exhibit a certain degree of variability.

Predominantly, the majority of studies point towards a reduction on BMD, as measured by DXA, among patients with SH. A retrospective multicenter study conducted in Italy in 2009, involving 287 AI patients, including 85 patients with concomitant SH (SH+) (mean age 62.9 ± 9.9 years, female/male ratio 53/32) and 202 patients without SH (SH−) (mean age 61.2 ± 11.4 years, female/male ratio 123/79), as well as 194 healthy controls (mean age 61.1 ± 13.7 years, female/male ratio 104/90), utilized DXA to gauge lumbar spine and femoral neck bone density. Results indicated a significantly lower bone density in the SH+ group compared to the SH− group and the healthy control group, while no significant difference in bone density was observed between the SH− group and the healthy control group.[12] Consistent conclusions were drawn in other studies as well.[10,36] While research on the relationship between SH and bone density in Asian regions is relatively limited, a multicenter retrospective study in South Korea in 2019 found that lumbar spine bone density in female AI patients with concomitant SH (including pre- and postmenopausal women) was lower than in those without SH ($p<0.001$). The study suggested a negative correlation between bone density in premenopausal women and cortisol levels after suppression with 1 mg dexamethasone.[42] There are also relevant clinical studies in China that observed a decrease in BMD in patients with SH. Additionally, a few studies utilizing quantitative computed tomography (QCT) to assess bone density in SH found that the vertebral, femoral neck, and radial 1/3 bone densities were significantly lower in the SH group, with a reduction of up to 33%.[46]

While the majority of studies observe a decrease in bone density in SH patients, some research suggests that, compared to healthy controls, the reduction in bone density in certain SH patients is not statistically significant. For instance, a study in 2001 assessed lumbar spine and femoral neck bone density in 27 AI patients, revealing no significant differences in lumbar spine bone density between AI patients and the healthy control group. Moreover, no significant differences were observed in lumbar spine and femoral neck bone density between patients with and without concomitant SH.[47] In addition, no significant differences in lumbar spine and femoral neck BMD were similarly observed between patients with and without combined SH.[37] A South Korean study in 2019 also found that although bone density decreased in female AI patients with concomitant SH, no significant decrease was observed in male patients.[42] However, these studies have inherent limitations, including a small sample size and a relatively young age of the subjects, potentially introducing bias into the results.

Current research on bone metabolism in SH predominantly relies on foreign data. Despite certain limitations in the studies, the preponderance of research results suggests a decrease in bone density in SH patients, particularly in trabecular bone density. It is noteworthy that although a decrease in bone density is observed in SH patients, it is primarily confined to a reduction in bone mass and does not reach the threshold for osteoporosis.[44]

6 | THE IMPACT OF SH ON BONE HEALTH IN THE ELDERLY

With the accelerating aging population, the preservation of bone health in the elderly has become a crucial public health concern. Age-related disturbances in bone remodeling contribute to an elevated ratio of bone resorption to bone formation, resulting in progressive bone loss. In elderly individuals experiencing sustained autonomic cortisol elevation, particularly those diagnosed with SH, the risk of bone destruction is further heightened. Additionally, the diminished ability of the elderly to effectively respond to stress stimuli exacerbates these deleterious effects. Elderly individuals with SH may encounter a spectrum of challenges, including cognitive function decline, disorders in the immune system, and an increased susceptibility to frequent fractures, mobility issues, and chronic pain. These adversities significantly impede daily life activities and compromise self-care capabilities. A comprehensive study conducted by Chiodini et al. involving 85 patients with SH (SH+) and 202 patients without SH (SH−), all with an average age exceeding 60 years, underscored the substantial impact of SH on bone health. The bone density of the SH+ group was markedly lower than that of both the SH− group and healthy controls, as reported in the study.[12] This underscores the potential heightened risks posed by the coexistence of SH in elderly individuals for their skeletal health. However, it is noteworthy that the aforementioned studies did not exclusively focus on elderly patients, and as of now, there is a lack of specific research addressing the impact of SH on skeletal health in the elderly population. In light of the expanding aging demographic, it becomes imperative to undertake targeted investigations to unravel the intricate relationship between subclinical hypercortisolism and bone health specifically in the elderly. Such research endeavors would not only enhance our understanding of the physiological mechanisms at play but also pave the way for tailored interventions and healthcare strategies aimed at preserving and promoting skeletal health in this vulnerable demographic.

7 | CONCLUSION

In summary, the sustained and mild elevation of cortisol levels observed in SH emerges as a significant factor detrimentally affecting bone health. While existing research on bone mass alterations in SH presents some variability, a predominant consensus among studies confirms that SH is associated with a decline in trabecular bone mass, heightening the susceptibility to fractures, particularly vertebral fractures. Current investigations primarily focus on the relationship between SH and fracture risk in patients with AI. However, future inquiries should extend their reach to explore the impact of pituitary-derived SH on bone metabolism, broadening our understanding of the comprehensive effects of SH on skeletal health. Furthermore, imperative to advancing our understanding is the initiation of high-quality clinical trials aimed at determining whether the surgical removal of adrenal incidentalomas can ameliorate abnormal bone metabolism in SH patients. This avenue of research holds the potential to provide valuable insights into therapeutic interventions for improving bone health in individuals with SH. A more nuanced comprehension of the intricate relationship between SH and bone health in the elderly is crucial for comprehensive patient care. In conclusion, safeguarding bone health in individuals with SH necessitates dedicated clinical attention and emphasis. The early identification, precise diagnosis, and timely intervention in SH are pivotal for preventing osteoporosis, averting pathological fractures, enhancing patient prognosis, and ultimately improving the overall quality of life.

AUTHOR CONTRIBUTIONS

Lou Yuan completed the collection and analysis of relevant literature and drafted the manuscript as the main writer of the review. Ren Luping, Chen Huan, and Zhang Tian participated in the analysis and sorting of literature materials. Pan Qi was the architect of the concept and the person in charge of the project and guides the writing of the paper. All authors have read and approved the content of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to declare.

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