Skeletal Diseases in Cushing's Syndrome: Osteoporosis versus Arthropathy

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Abstract

Structural and functional impairment of the skeletal system remains an important cause of morbidity and disability in patients with Cushing's syndrome (CS). Glucocorticoid (GC) excess inhibits bone formation and calcium absorption from the gut, increases bone resorption, and alters the secretion of gonadotropin and growth hormones, cytokines and growth factors influencing bone. Both overt and subtle endogenous hypercortisolism affect bone, leading to vertebral fractures in up to 70% of patients. Fracture risk is related to age at onset, duration and severity of the disease and individual susceptibility to GCs that is genetically determined. Bone mineral density (BMD) measurement at the lumbar spine should be performed as a screening test in all patients with CS due to the preferential loss of trabecular bone induced by GCs. The higher risk of fractures at comparable BMD values with controls suggests that bone quality features, not assessed by routine BMD approaches, are also important and should be addressed when indicated applying specific radiological means. Successful treatment of GC excess is associated with improvement in bone mass which, although delayed and often incomplete, reduces the risk of osteoporotic fractures. Bisphosphonates can induce a more rapid improvement in BMD than cortisol normalization alone and can be used in patients with increased risks for further fractures and/or persistent hypercortisolemia to prevent further bone loss. Anabolic agents have not as yet been systemically used. Avascular necrosis, mainly of the femoral neck, and growth arrest in children are the most common skeletal disorders unrelated to osteoporosis encountered in patients with endogenous hypercortisolism.

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Introduction

Glucocorticoids (GCs) exert multiple effects on bone and GC-induced osteoporosis is the commonest cause of secondary osteoporosis. However, the effects that GCs exert on bone metabolism are hampered by the specific effects of the underlying disease that GCs are prescribed for. Recently, a substantial amount of data has been gathered from studies looking at the effects that GC excess exerts on bone denoted of any other confounding factors such as in cases of endogenous hypercortisolism (Cushing's syndrome; CS). This paper addresses the pathogenesis, incidence, prediction and treatment of osteoporosis in patients with CS and discusses other less common, related arthropathies encountered in such patients.
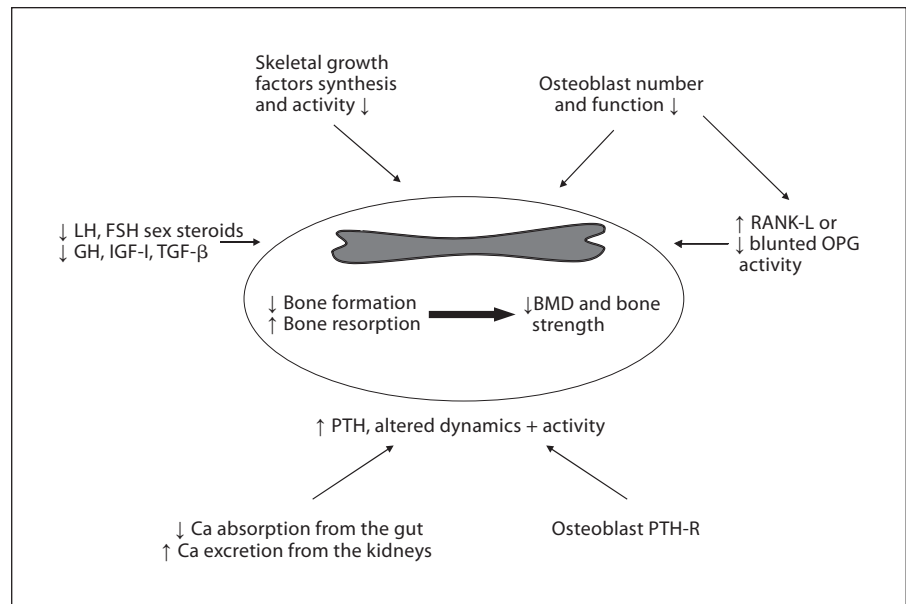
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Fig. 1. Pathogenesis of GC-induced bone loss.

Osteoporosis

Pathogenesis (fig. 1)

The multifactorial pathogenesis of bone loss in CS depends on direct and indirect effects of GCs on bone that are not restricted to bone mineral density (BMD) alone, but also involve bone architecture, geometry and the rate of bone remodeling units (BRU), important components that together determine bone strength [1].

Sustained and prolonged hypercortisolism leads to a rapid early phase of BMD decline due to excessive bone resorption, which is followed later on by a slower and more progressive phase of impaired bone formation [2]. Besides their direct effect on BRU, GCs also reduce calcium absorption from the gastrointestinal tract due to opposition of vitamin D action and inhibition of renal tubular calcium reabsorption [2]. GCs also influence the production and action of other hormones that regulate bone and calcium metabolism such as gonadotropins, growth hormone (GH) and insulin-like growth factor-I (IGF-I) [2, 3]. In patients with CS, a significant reduction of lumbar spine bone density develops before involvement of the peripheral skeleton [4] because of a rapid loss of the trabecular bone [5]. The catabolic effects of GCs on muscle also contributes to fracture risk due to an increased incidence of falls secondary to muscle weakness, and loss of the stimulatory effect of muscular contraction on bone formation [2].

GC Effects on Bone at the Cellular Level

The initial event of GC effect on bone is stimulation of osteoblastic cells to increase the production of RANKL (receptor activator of NF-kappa B-RANK-ligand, which enhances osteoclastogenesis) and reduce the production of osteoprotegerin, the natural antagonist of RANKL [1]. Furthermore, GCs may act directly or through the increased expression of macrophage-colony-stimulating factor on the osteoclasts, prolonging their life span, explaining the early rapid phase of bone loss [1]. However, the most detrimental effect of GCs on bone metabolism is a profound reduction in osteoblast number and function, leading to suppression of bone formation and subsequent reduction of the amount of bone replaced in each remodeling cycle [1]. GC excess impairs osteoblastic cell differentiation by inhibiting Wnt-β-catenin signaling, and inducing the overexpression of Notch receptors thereby enhancing apoptosis of osteoblasts and osteocytes by activating caspase 3 [6]. Osteocyte apoptosis may be an additional important mechanism in GC induced fractures while the disruption of the osteocyte-canalicular network may result in a detection failure of signals that normally stimulate the replacement of damaged bone [7]. Thus, a substantial effect of GCs on osteocytes might account for a disproportionate loss of bone strength in relation to bone mass. Recent evidence has also implicated the GC-induced leukine zipper gene transcriptional factor as a crucial factor by regulating osteoblast maturation and bone turn-over [8].

Risk of Fractures

Approximately 30–67% of patients with CS develop fractures, mainly at the vertebrae, leading to back pain, kyphosis and loss of height [9]. The number of collapsed vertebral bodies is correlated to age at disease onset, disease duration, and urinary free cortisol levels at diagnosis even in patients with long-term cured CS [9]. In a significant number of patients, fractures may be completely asymptomatic and even develop in those with normal BMD values [10]. Men appear to be more susceptible than women, with the crucial period of developing a fracture being 2 years prior diagnosis [11]. Although it was initially suggested that the risk was higher in patients with adrenal CS this finding has not been replicated by subsequent studies [1].

Besides clinically obvious CS, a significant number of patients are increasingly being identified with alterations of cortisol secretory dynamics without exhibiting the classical signs or symptoms of CS. These patients constitute the so-called subclinical CS (SCS), mainly due to functioning adrenal adenomas, with an estimated prevalence higher than that of clinically obvious CS (0.8/1,000 vs. 1/500,000) [1]. Although not replicated consistently, several studies have documented that patients with SCS have reduced BMD and that this is more prominent in postmenopausal women [1, 12].

Individual Susceptibility to Osteoporosis

Not all individuals exposed to endogenous hypercortisolism develop osteoporosis and fractures [2]. Between the speculated mechanisms subjects carrying the N363S GC receptor polymorphism are thought to exhibit a higher sensitivity to GCs [13]. Alternatively, the activity of 11β-hydroxysteroid dehydrogenase type 1 enzyme, which acts to convert inactive cortisone to cortisol and is expressed in osteoblasts, is enhanced by GCs and leads to osteoblastic dysfunction [14].

Biochemical Markers of Bone Turnover

The net effect of bone apposition markers in patients with CS reveals a picture of reduced synthesis of new bone. Markers of bone formation, particularly osteocalcin, are substantially reduced, correlate with disease activity and increase with restoration of eucortisolism. Other markers of bone formation have shown greater variability [15], while bone resorption markers exhibit substantial variation and thus are not used routinely [1].

Bone Mass

In CS there is uncoupling between bone apposition (reduced) and resorption (normal/increased) leading to severe bone loss, especially in trabecular sites, with an estimated risk of osteoporosis of 60–70% [9]. Measurement of BMD by DEXA, particularly at the lumbar spine, presents the initial method of assessment. Vertebral CT scan can also be used to assess osteoporosis in these patients [5].

Bone Architecture

Fracture risk among prior GC users can be partly explained by BMD and the thresholds of BMD for vertebral fractures are higher in patients treated with oral GC, suggesting that other factors besides BMD may also operate [16]. Indeed, bone strength is also determined by instinct properties of bone tissue such as microdamage accumulation, bone matrix proteins and degree of mineralization, and bone turn over effects. These features are currently best accessed by peripheral quantitative computed tomography which can distinguish cortical from trabecular bone, measure the geometric properties of long bones, and estimate bone strength by calculating polar strength strain index [16]. When this method was recently applied in 10 women with CS, it revealed that all these indices were lower in patients with CS compared to controls but only in premenopausal women, suggesting a strength loss mechanism and explaining the presence of fractures even in patients with normal BMD [16]. Since the ultrasound velocity is influenced both by the organic and nonorganic bone compounds, quantitative ultrasound could be a useful tool for assessing the multifactorial bone involvement in CS; however, longitudinal studies are lacking [5].

Risk Factor Stratification

The number of collapsed vertebrae was reported to directly relate to age at disease onset, disease duration and severity based on urinary free cortisol levels, even in cured patients [5]. These parameters along with lumbar BMD measurements and possible means of assessing bone quality, and the cortisol-to-DHEAS ratio should be taken into consideration to identify patients at high risk and offer appropriate intervention [17]. Assessment of muscular strength is also highly important as muscular weakness is associated with increased fracture risk.

Therapy

The ultimate target is to prevent fractures. Appropriate interventions include calcium and vitamin D intake of 1,500 mg and 800 IU daily, respectively. Urinary cal-

cium excretion has to be considered to avoid the development of nephrolithiasis. Administration of sex steroids has a place in the management of hypogonadal patients receiving GCs and particularly in those with SCS [1, 2]. Similarly, GH replacement may exert a beneficial effect on bone turnover in significant number of patients with CS and GH deficiency [5]. However, this particular treatment has not been extensively used. Due to the increased fracture risk, a proactive preventing approach including lifestyle changes, such as tobacco cessation and reduction in alcohol consumption, exercise program, and restriction of sodium intake in the presence of hypercalciuria should be undertaken [2]. The cure of CS is reported to restore normally coupled bone metabolism and remarkably improve BMD [1]. However, normalization may take several years and may not always be complete although the fracture risk is substantially reduced over the first years following treatment [1]. In order to shorten the time of BMD recovery, particularly in high-risk patients, the use of aledronate and clodronate exhibit a higher BMD increase compared to untreated patients, suggesting that these drugs may induce a more rapid improvement in bone density than cortisol normalization alone [1]. As patients with GC induced osteoporosis have a higher risk for fractures, it has been recommended that treatment with bisphosphonates should be started with T-scores lower than –1 SD [2]. Estrogens are a reasonable approach in hypogonadal premenopausal women and in combination with bisphosphonates have additive effects on osteocyte survival, acting synergistically on the same transduction pathway although at different levels [2].

Due to the substantial reduction of bone formation, treatment with an anabolic agent that promotes bone formation and reduces vertebral and non-vertebral fractures, such as PTH, has also been suggested [2]. Although the use of teriparatide has not been yet explored in endogenous CS it has been repeatedly shown to be beneficial in patients with exogenous GC-induced osteoporosis [2]. Another potential therapeutic target is the RANK-RANKL-OPG system particularly after the development of a human monoclonal antibody to RANKL (denosumab) that has been shown to reduce all osteoporotic fractures in postmenopausal patients [18].

Arthropathies (table 1)

Arthopathies related to CS are relatively rare and usually accompany osteoporosis. Abundant pseudocallus formation is frequently seen around stress fractures in

Table 1. Skeletal manifestation of Cushing's syndrome

Osteoporosis, predominantly of trabecular bones
Spontaneous symptomless fractures of ribs, pubic and ischial rami, foot bones and vertebrae
Healing of fracture with abundant pseudocallus formation
Osteonecrosis (avascular necrosis) of head of femur and humerus, distal femur and vertebrae
Suppression of growth velocity in children

the ribs, pelvis and end plates of collapsed vertebrae and is considered the hallmark of GC-induced osteoporosis [19]. Microscopically, there is a reduction in osteoblastic activity and production of a cartilaginous callus that becomes highly mineralized in an amorphous fashion [20]. Such fractures can also develop in the feet, pubic and ischial rami and uncommonly in long bones resembling pseudofractures of osteomalacia [19]. Osteonecrosis of the femoral head is most commonly encountered following exogenous GC administration although cases following endogenous hypercortisolism are increasingly being recognized; occasionally both femurs and several other joints may be involved [1, 19]. Growth failure, weight gain and pubertal arrest are the hallmarks of CS in children and growing adolescents leading to reduced final adult height [5]. Children with hypercortisolism also develop a reduction in peak bone mass, which presents a major determinant of long-term risk of osteoporosis [5].

Conclusion

Endogenous hypercortisolism exerts a detrimental effect on bone and substantially increases the risk for spinal fractures secondary to osteoporosis. High-risk patients need to be identified and offered appropriate treatment at an early stage.

Disclosure Statement

The authors have nothing to declare.

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