

Bone metabolism disorders in endogenous Cushing syndrome

Zaburzenia metabolizmu kostnego w endogennym zespole Cushinga

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- Cushing's disease
- Cushing syndrome
- cortisol
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ABSTRACT

Endogenous Cushing syndrome (CS) leading to an overproduction of cortisol is a major cause of secondary osteoporosis. Bone complications in CS, even though they not only reduce the quality of life but also increase mortality, are still underdiagnosed. Hypercortisolemia results, among others, in reduced bone mineral density (BMD). However, an increased risk of fracture in CS may occur in bones with only a slight reduction or even normal BMD. The disease is usually insidious, prolonging the period of hypercortisolemia before diagnosis. Therefore, skeletal complications such as reduced BMD, osteoporosis, and fractures are common in CS. Osteoporosis has a prevalence of 40-70%, osteopenia 80-85%, and fractures 30-70% in patients with CS (1, 2). Fractures usually involve the lumbar and thoracic vertebrae, hips, ribs, and pelvis as the trabecular bone is mainly affected. The most common pathogenesis of CS leading to bone lesions remains a topic of many researches. Chronic hypercortisolemia leads not only to the reduction of BMD but also to changes in bone microarchitecture. Increased resorption and inhibited bone formation are the main mechanisms described in CS. Reversal of changes in bone mineral density after recovery from CS has been observed. Surgical treatment of pituitary or adrenal tumors should be the first line of treatment. However, vitamin D and calcium supplementation as well as treatment with antiresorptive drugs seems to be also essential. In this paper, we present a review of the current literature on bone complications in endogenous CS.

SŁOWA KLUCZOWE:

- choroba Cushinga
- zespół Cushinga
- kortyzol
- osteoporoza

STRESZCZENIE

Endogenny zespół Cushinga (CS) prowadzący do zwiększonego wydzielania kortyzolu jest główną przyczyną wtórnej osteoporozy. Powikłania kostne w CS, mimo że nie tylko obniżają jakość życia, ale także zwiększają śmiertelność, są wciąż niedostatecznie diagnozowane. Hiperkortyzolemia skutkuje się m.in. zmniejszeniem gęstości mineralnej kości (BMD). Jednakże zwiększone ryzyko złamań może wystąpić nawet w kościach z niewielkim zmniejszeniem lub nawet prawidłowym BMD. Choroba ma zwykle podstępny przebieg, co wydłuża okres trwania hiperkortyzolemii przed postawieniem rozpoznania. Dlatego też powikłania szkieletowe takie jak obniżone BMD, osteoporoza czy złamania kostne są częste w CS. Częstość występowania osteoporozy wynosi 40-70%, osteopenii 80-85% i złamań 30-70% u pacjentów z CS (1, 2). Złamania dotyczą najczęściej kręgow łędźwiowych i piersiowych, bioder, żeber i miednicy, ponieważ uszkodzeniu ulega głównie kość bełeczkową. Najczęstsza patogenezą CS prowadząca do zmian kostnych pozostaje tematem badań. Przewlekła hiperkortyzolemia prowadzi nie tylko do zmniejszenia BMD, ale również do zmian w mikroarchitekturze kości. Zwiększona resorpcja i zahamowanie tworzenia kości to główne mechanizmy opisywane w CS. Po wyzdrowieniu z CS obserwowane jest odwrócenie zmian gęstości mineralnej kości. Leczenie chirurgiczne guzów przysadki lub nadnerczy powinno być pierwszą linią leczenia. Istotną wydają się również suplementacja witaminą D i wapniem, jak również leczenie lekami antyresorpcyjnymi. W niniejszej pracy przedstawiono przegląd aktualnej literatury dotyczącej powikłań kostnych w CS.

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Introduction

Glucocorticoids play an important role in the development and proper functioning of many human tissues. The most important glucocorticoid is cortisol, which is produced in the adrenal cortex. The main factor controlling cortisol secretion is adrenocorticotropic hormone (ACTH). ACTH secretion from the anterior pituitary is regulated by the hypothalamus and central nervous system via two neurotransmitters: corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP).

Endogenous CS is caused by the excessive production of cortisol. The first description of CS was published by Harvey Cushing in 1912, based on his report of 12 cases of patients with a characteristic appearance (3). CS belongs to a group of rare diseases, with an estimated incidence of 0.7-2.4 new cases per 1,000,000 people per year. The increased incidence is usually seen in women in the fourth decade of life. The approximate ratio of females to males with CS is 3:1 (4-6). However, the incidence of CS seems to be underestimated, particularly in obese individuals with poorly controlled hypertension and diabetes (7). Endogenous hypercortisolemia can be divided into ACTH-dependent and ACTH-independent (4, 7, 8). The ACTH-dependent form accounts for 70-80% of all cases of CS (9). The most common cause of endogenous hypercortisolemia is Cushing disease (CD), which represents 80% of all CS cases. Ectopic Cushing syndrome covers the remaining 20% of the ACTH-dependent form. It is most commonly caused by small-cell lung cancer or bronchial carcinoid, but it can also result from a neuroendocrine tumor localized in virtually any organ (7).

The ACTH-independent form of Cushing's syndrome is the result of autonomous cortisol production by adrenal tumors and micro- or macroglandular hyperplasia of the adrenal cortex.

This study aims to review the literature on bone disorders and skeletal metabolism in patients with endogenous hypercortisolemia.

Clinical features and diagnosis

The clinical picture of CS varies from mild to severe manifestations and includes changes in fat distribution (central obesity, buffalo hump, moon facies), thin skin with striae and increased bruising, hypertension, dyslipidaemia, glucose intolerance/diabetes, psychiatric disorders, and osteopenia/osteoporosis (10). Screening tests are preceded by a strong clinical suspicion of CS and include late-night salivary and/or serum cortisol, 24-hour urinary free cortisol, or low-dose dexamethasone suppression test (9). If the clinical course of hypercortisolemia is severe, a markedly elevated serum or urine cortisol concentration is sufficient to make the diagnosis. After confirmation of hypercortisolemia, it is necessary to differentiate between the ACTH-dependent and ACTH-independent form of CS.

Bone complications in CS are common and clinically significant. Already H. Cushing in his report in 1934 drew attention to the severity of osteoporosis in a patient's spine (11). Clinically, osteopenia/osteoporosis may be associated with low back pain, limited mobility, and a reduction in the patient's height (12). Dual-energy X-ray absorptiometry (DXA) is used to assess the severity of osteoporosis. It is the most commonly used test to measure BMD and fracture risk and is usually performed at the femoral neck and lumbar spine (L1-L4) (13).

The pathogenesis of bone loss in endogenous Cushing syndrome

Hypercortisolemia has negative effects on bone metabolism and it mainly affects trabecular bone (14). Glucocorticoid-induced osteoporosis is one of the most common causes of secondary osteoporosis. The end result of glucocorticoid excess is mineral loss from bone and increased bone fragility. The changes in osteoporotic bone are caused by the higher rate of bone turnover in the trabecular bone due to its greater surface volume area-to-volume ratio. In addition, trabecular bone is more sensitive to glucocorticoid excess than cortical bone (15). Multifactorial bone loss occurring in CS is associated with indirect and direct effects of glucocorticosteroids on bone. Glucocorticosteroids increase collagen matrix degradation by reducing the number and function of osteoblasts. Apoptosis of osteoblasts and osteocytes results in a reduced number of osteoblasts. The role of osteocytes as mechanoreceptors is to transmit information to the bone surface. When glucocorticoids are in excess, caspase-3 is activated, resulting in osteocyte apoptosis. This mechanism of reduced osteocyte number is responsible for increased bone fragility (16). In addition, hypercortisolemia reduces the production of new osteoblastic cells and impairs the differentiation of stromal cells towards the osteoblastic lineage (15). Decreased bone formation occurs due to reduced osteoblast function and impaired osteoblastogenic differentiation. In long-term hypercortisolemia, excessive bone resorption occurs, leading to a rapid decline in BMD. This is followed by a slower phase of impaired bone formation. In addition, hypercortisolemia affects the impaired absorption of calcium from the gastrointestinal tract and inhibits of calcium reabsorption in the renal tubules leading to secondary hyperparathyroidism. Glucocorticoids also affect the production and regulation of other hormones: gonadotropins, growth hormone (GH), and insulin-like growth factor-I (IGF-I) (17).

In addition, glucocorticoids increase the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) and decrease the expression of osteoprotegerin (OPG) (16). However, RANKL and OPG levels do not reflect the bone status of patients (18, 19). Increased OPG levels are noted in patients with chronic hypercortisolemia, even after successful surgical treatment. However, the source of increased OPG levels appears to be the vascular endothelium, which affects the cardiovascular profile of patients more than bone metabolism (20).

Glucocorticosteroids also have a catabolic effect on the muscular system, leading to its weakening and consequently exerting an atrophic effect on the muscles and bones (21, 22). Bone loss is more commonly reported in regions of the skeleton with predominantly barrel-shaped bone such as the lumbar spine (23, 24). However, an increased risk of non-vertebral (65%) and hip (130%) fractures has also been reported (25, 26). Unfortunately, the exact mechanisms of osteoporosis in hypercortisolemia are still not fully understood.

Clinical characteristics of bone disease

There is a consensus in the literature that CS is related to lower bone mass compared to the healthy population. The term "bone changes" is commonly used. It includes osteopenia, osteoporosis, and BMD below the normal range for age and sex. Bone mineralization disorders are a major

factor affecting patients' quality of life. In the literature, bone changes are described in 42-100% of patients with CS (6, 12, 27, 28). The incidence of osteoporosis and osteopenia is increased in patients with endogenous hypercortisolemia and is estimated at 40-70% and 80-85%, respectively (1). However, according to Lekamwasam et al., other criteria should be established in relation to the DXA T-score, which should lead to an even higher diagnosis of osteoporosis in this group of patients (29).

Bone fractures

Bone fractures may occur in patients with osteoporosis, osteopenia, or with normal BMD. Tauchamanova et al. point out that symptomatic fractures were reported in 52% of patients, with spinal fractures being the most common (76%). Non-traumatic vertebral fractures mainly affect the thoracic and lumbar vertebrae and occur at a rate in 30-70% of cases (30). Case series with the incidence of vertebral fractures ranging from 15.3%-55.5% have been described in the literature (13, 31-33). Fractures of multiple vertebrae in the spine are usually noted. This is related to the greater amount of trabecular bone in the lumbar spine. In the hip, where there is less trabecular bone and greater cortical bone, the effect of glucocorticosteroids is less harmful and osteopenia is less severe (2).

Fractures due to hypercortisolemia are noted in the first few years of disease while densitometric improvement is observed within 2 years of recovery (30, 34, 35). Fractures in CS patients can often occur spontaneously or as a result of low-energy trauma.

A report from Denmark looking at fracture rates after both low-energy and high-energy injuries shows a higher risk of fractures in the 2 years immediately before diagnosis and after recovery. The report showed that patients with CS have five times more low-energy fractures (30). In the study by Futo et al., no fractures were found after treatment, whereas symptomatic or asymptomatic fractures before treatment affected 35% of CS patients (36).

The literature suggests that the reduction in bone mass relative to peak bone mass is 10-25% (12, 28, 36, 37). There appears to be little reduction in BMD in the arms or legs compared to the lumbar spine and femoral neck. This confirms the barrel-like nature of bone loss. However, the ultra distal part of the forearm, which is rich in trabecular bone, showed increased BMD (36).

Bone loss and fracture risk depending on the etiology of Cushing syndrome

The literature is inconsistent about the most common cause of CS leading to fractures. According to The European Registry on Cushing's Syndrome (ERCUSYN), vertebral fractures are more common in the ectopic CS compared to CD. The ERCUSYN study has also shown that the incidence of vertebral fractures is similar in CD and adrenal Cushing syndrome (ACS). However, according to one of the most recent papers by Naguib et al., osteoporosis is more common in ACS than in CD (62,5% vs 26,3%). Minetto et al. highlight the lower BMD only at the lumbar spine in patients with ACS compared to CD, while BMD at the hip was comparable (2). Ohmori et al. also suggest an increased incidence of osteoporosis in ACS, but these data have not been confirmed in other studies (31). Rahaman et al. show no difference

in the severity of osteoporosis between patients with different etiologies of CS while emphasizing the lowered Z-score in patients with CS (38). Trementino et al. came similar conclusions after analyzing 52 patients with CD – found a similar prevalence of osteoporosis and fractures in CD and ASC (13). Likewise, Apaydin et al. showed no association between the etiology of endogenous hypercortisolemia and vertebral fractures (1).

Bone loss and fracture risk depending on gender and gonadal status

Literature unanimously indicates that fractures are more common in men with CS. A higher incidence of fractures of the spine and ribs was found in men than in women: 52% vs. 18%, respectively. Both the European Registry on CS and Girdali et al. show a higher prevalence of corticoid-related osteoporosis of the spine and bone fractures in men compared to women (28, 39). Girdali et al. also highlight the more severe clinical course of CS in men (39).

It is worth mentioning that hypercortisolemia affects the gonadal axis, resulting in hypogonadism which is another mechanism leading to loss of BMD (40).

Tauchamanova et al. equate the incidence of fractures in non-menstruating and properly menstruating women with CS and conclude that hypercortisolemia and its effects cannot be compensated by normal gonadal function. Tauchamanova et al. also report a higher incidence of vertebral fractures in patients with overt hypercortisolemia (69%) than in those with subclinical CS (57%) (12). In addition, Karavitaki et al. found no differences between premenopausal regularly menstruating women with newly diagnosed CS and the control group, compared with non-menstruating women who were found to have reduced BMD (41). However, Trementino et al. report a protective role of estrogen on bone loss, but do not correlate fracture risk with gonadal status (13).

In children, the characteristic symptom of CS is the arrest of sexual maturation and stunted growth. This leads to a reduction in final height and a decrease in peak bone mass, increasing the risk of osteoporosis (42). The decreased bone mass appears to improve after the remission of hypercortisolemia (43). However, even patients in remission, there is an increased incidence of spinal injury, especially if the disease has developed before growth is complete (15).

Predictors of bone loss

There are several predictors of vertebral fractures and bone mineral density loss in CS. One of such predictor is urinary cortisol concentration, but data on the correlation between urinary and plasma cortisol on BMD loss and fracture risk are conflicting. Some literature data report that urinary and plasma cortisol concentrations are predictors of fractures (1, 32), while others deny this association (41, 44).

Trementino et al. link bone fractures with bone demineralisation and urinary free cortisol levels. They show no correlation with age, sex, BMI, hormonal status, disease etiology, or midnight blood cortisol levels (1). Researchers show a positive correlation of disease duration with the incidence of periprosthetic fractures but no correlation with vertebral fractures was demonstrated (13). However, a positive correlation between BMI and BMD in patients with hypercortisolemia

is apparent. This protective effect is most evident in the lumbar spine (15, 36, 44). Tauchmanova et al. also link morning cortisol and testosterone levels with lumbar BMD. However, they do not show an association with increased fracture incidence (12). In a study by Minetto et al. and Ohmori et al. a correlation between the dehydroepiandrosterone sulphate (DHEAS) levels and BMD of the femoral neck and lumbar spine was observed (2, 31).

On the other hand, Futo et al. negated the correlation between fractures, BMD, and cortisol levels and showed a positive correlation with age and Z-score reduction; so a greater deficit in BMD was found in younger patients (36).

There are papers in the literature estimating the interval between symptom onset, diagnosis, and symptom severity. The estimated duration of the disease ranged from 9-70 months (12, 36, 44-46). This suggests a long duration of disease before diagnosis and therefore a long period of hypercortisolemia leading to the development of symptoms. The prevailing opinion is that the duration of the disease does not affect the severity of the bone lesions. In the series studied, it is difficult to determine the exact onset of the disease, as this is based on the patient's recollection (44, 47). No association between the presence of diabetes and bone fractures or reduced BMD has been reported in the literature (1, 28).

The ERCUSYN study did not distinguish differences in BMD between the different etiologies leading to CS. In the European CS Registry, 25% of patients with normal BMD had bone fractures, but fractures were registered more frequently when osteoporosis was present (28). In the literature, lower BMD at the lumbar spine was associated with a higher risk of fracture (12, 13). However, Belaya et al. found no association between lumbar spine BMD and increased fracture risk (48).

Treatment of osteoporosis in CS

Percutaneous vertebroplasty (PVP) and kyphoplasty (PKP) are the main neurosurgical procedures used for osteoporotic vertebral compression fractures (OVCF). However, their use in CS remains controversial. PVP and PKP reduce pain and allow rapid rehabilitation (49, 50). Side effects of these minimally invasive procedures include spinal cord compression, nerve root damage, and neurological complaints, but also infection or congestion (51). Conservative management, pain relief, stabilisers, and anti-osteoporotic treatment should be the first choice (52). In addition, lifestyle changes should be made: strengthening exercises, prevention of falls, cessation of alcohol and smoking, and a balanced diet rich in calcium and vitamin D supplementation (53). However, there are currently no clear guidelines for the treatment of osteoporosis induced by endogenous hypercortisolism. Some papers emphasise the use of vitamin D and calcium, but not bisphosphonates (54). In contrast, Di Somma et al. showed an improvement in bone mineral density in patients receiving alendronate compared with placebo (55). Teriparatide and denosumab reduce the risk of vertebral fractures more than oral bisphosphonates. However, the effect of treatment was not apparent in nonvertebral fractures (56, 57).

The effect of CS treatment on bone disorders

Pocock et al. were the first to present two cases of BMD improvement after successful endogenous CS surgery.

They described an increase in BMD of up to 20% over a 24-months (58). Another landmark study was the data from Manning et al. who reported a complete improvement in BMD over 10 years following the cure of CS (59). Later studies confirmed the complete reversibility of BMD changes even in 3-5 years after surgery (36, 60, 61). However, data on the complete healing rate for BMD remain inconsistent. Kawamata et al. report an improvement in mineral density especially in the lumbar spine only after surgery for adrenal adenoma (62).

Conclusions

Abnormalities in bone metabolism in CS lead to decreased BMD, osteopenia, and osteoporosis, especially in trabecular bone. CS lesions most commonly affect the vertebrae of the spine and the femoral neck, due to the increased proportion of trabecular bone in these areas. However, the literature is inconsistent regarding which cause of endogenous hypercortisolemia is the most common cause of bone lesions. The protective role of oestrogens is still controversial. According to the literature, the influence of other predictors such as urinary and plasma cortisol levels, age, BMI, hormonal status, gender, and even disease duration on BMD loss and fracture risk is conflicting. Due to the many inconsistencies in the literature, further work evaluating the effect of endogenous hypercortisolemia on bone metabolism seems indicated.

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