

Glucocorticoid-induced osteoporosis

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Abstract: Long-term treatment with glucocorticoids can result in drug-related complications, among which osteoporosis is one of the most frequently encountered problems. Each patient treated with a dose of 7.5 mg or more of prednisone daily for at least 3 months can be affected. During the prolonged steroid use bone formation is inhibited while its resorption increases and negative calcium balance with secondary hyperparathyroidism occurs. In the affected bone, multiple focuses of osteomalacia and avascular necrosis are also described. The bone fracture risk is much higher than it can be suspected on the basis of bone mineral density (BMD) assessment. Therefore, in glucocorticoid-treated patients with only slightly decreased BMD (osteopenia according to the WHO criteria) treatment with antifracture agents should be initiated as soon as possible. Indication for therapy is a T-score of -1.5 . Calcium supplementation with vitamin D represents an initial step of prevention and treatment. A first-line treatment effective in preventing bone fractures involves aminobisphosphonates such as alendronate and risedronate. Other effective agents are also estrogens, testosterone, selective estrogen receptor modulators and anabolic agents (parathyroid hormone, dehydroepiandrosteron, strontium ranelate).

Key words: corticotherapy, glucocorticoid-induced osteoporosis

INTRODUCTION

Several lines of evidence indicate that long-term glucocorticoid treatment is the most common cause of secondary osteoporosis. Osteoporotic vertebral fractures have already appeared in the first historic description of hypercortisolemia in Cushing's disease [1]. Every textbook of pharmacology highlights the bone complications of long-term treatment with anti-inflammatory doses of glucocorticoids. However, physicians, though aware of the threat in theory, recommend osteoporosis prophylaxis in less than half the patients treated with steroids, and only 15% of patients receive an effective antiresorptive treatment [2,3]. However, regardless of the initial state of the bones, glucocorticoids result in inducing the largest increase in fracture frequency described in osteoporosis; and already within the first year of steroid therapy [4]. The most effective way to prevent this increase is the introduction of antiresorptive treatment already in the first weeks of glucocorticoid administration.

How do glucocorticoids influence the bone tissue?

Glucocorticoids are necessary in the metabolism of osseous cells. Physiological Cortisol at physiological levels stimulate

osteoblasts to collagen synthesis and condition an appropriate pace of recruitment and osteoclasts maturation [5]. However, glucocorticoids administered in pharmacological doses inhibit the maturation of bone-forming cells, diminishing the collagen, osteocalcin, Gla protein, and alkaline phosphatase synthesis, and inhibit the mineralization of the bone-forming matrix. In response to glucocorticoids, osteoblasts undergo accelerated apoptosis. Glucocorticoids inhibit the osteoclast recruitment and decrease their activity, thus in the area of osseous tissue a primary resorption inhibition is observed. Indeed, resorption acceleration occurs. It results from secondary hyperparathyroidism and hypogonadism as a consequence of long-term steroid therapy [6]. As a result of high glucocorticoid levels in osteoblasts, the synthesis of osteoprotegerin is inhibited, and RANKL production is stimulated, which also significantly stimulates resorption [7]. The collagenase III synthesis, a metalloprotease involved in collagen degradation, also increases. Nevertheless, in the morphometry of bones in glucocorticoid-induced osteoporosis, a decrease in bone tissue trabeculae thickness dominates, unlike postmenopausal osteoporosis, in which their integrity is disrupted [8].

In most patients the gastrointestinal tract calcium absorption significantly decreases during long-term steroid therapy. As a result of the renal tubular calcium reabsorption inhibition, the calciuria increases. A negative calcium balance leads to a constant parathyroid stimulation and a rise of serum parathormone (PTH) levels (secondary hyperparathyroidism). During chronic steroid therapy, increased as well as decreased 25OH and 1.25OHD₃ serum levels were observed. This depends on the level of parathyroid stimulation and calcium supply. Even the vitamin D₃ level rise does not break the negative

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calcium balance; this suggests the development of receptor D resistance as a result of corticotherapy [9,10].

An aseptic osteonecrosis occurs in 4–25% of patients undergoing long-term steroid therapy. The most frequent localizations of these abnormalities are: femoral head, head of the humerus and distal femoral epiphysis [11]. The catabolic effect of steroids concerns also the muscular tissue; its long-term administration leads to a decrease in muscle strength and mass. This increases the risk of falls and also leads to the positive influence of antigravity muscle tension on bone turnover weakening [12].

The alterations in bone tissue occurring in individuals on long-term steroid therapy are very complex and do not consist of a mere decrease in bone mineral density (BMD). The complex of these disorders may be described as a “metabolic bone disease in chronic hypercortisolemia”.

Corticotherapy indications and glucocorticoid-induced osteoporosis development risk

The anti-inflammatory and immunosuppressive effects of glucocorticoids are used in the treatment of many inflammatory and autoimmune diseases. In most cases the therapy duration is over 3 months, and an average dose is usually ≥ 7.5 mg of prednisone per day. Already the basic disease, in its natural course, increases the risk for bone mass loss and fractures.

Bronchial asthma and chronic obstructive pulmonary disease are the classical indications for long-term corticotherapy. Other respiratory tract diseases treated with glucocorticoids (for example sarcoidosis, allergic alveolitis and other interstitial lung diseases) are much less frequent. In the respiratory tract diseases, inhaled glucocorticoids are used more and more often, and prednisone doses do not often exceed 5 mg. It has, however, been shown that inhaled glucocorticoids inhibit the bone formation and increases fracture risk. The treatment is long-term and in exacerbation, high doses parenteral or oral glucocorticoids are being administered. In effect a total dose is reached, which significantly increases fracture risk. Additionally ketoacidosis, present in respiratory tract diseases, accelerates bone mass loss, and an increased cough or dyspnea induced, intercostal muscles and diaphragm tension, result in more frequent costal fractures.

Patients with rheumatoid arthritis and other rheumatic diseases, including connective tissue disorders, represent another group of individuals treated with long-term glucocorticoids. In these diseases high levels of proinflammatory factors such as interleukins 1 and 6 or tumor necrosis factor result in a gradual bone mass loss; mainly, however not uniquely, in the regions of ongoing inflammation process. Due to the joint pain and rigidity, patients have difficulty in moving, which increases the risk for falls and fractures. When introduced steroid therapy accelerates the bone mass loss, increasing however the patient's fitness, which prevents falls.

Treatment of a shorter duration, usually lasting several months, but employing higher, i.e. several dozen-milligram doses of prednisone; is used by dermatologists (atopy, pem-

phigus dermatitis), hematologists (thrombocytopenia), endocrinologists and ophthalmologists (infiltrative edematous exophthalmos). Even a therapy of 3 months' duration significantly increases the fracture risk. In the case of a coexisting malignant exophthalmia and hyperthyroidism, bone tissue resorption is additionally enhanced by the excess of thyroid hormone.

Glucocorticoid-induced osteoporosis in the gastrointestinal tract disease is accompanied by particularly pronounced osteomalacia, which is subject to calcium absorption disorders (ulcerative colitis, Crohn's disease), or vitamin D hepatic metabolism disorders (primary biliary cirrhosis). In glomerular nephritis with renal insufficiency, vitamin D renal hydroxylation disorders and secondary hyperparathyroidism occur. Intravenous glucocorticoid “pulses”, employed in malignant exophthalmia and renal diseases, have less influence on bone tissue paradoxically, as very high doses act outside the genome, binding with the cell membrane and altering the bone formation cell metabolism to a lesser extent [13].

Corticotherapy and BMD: fracture risk

For effective prophylaxis of bone disorder management and treatment in patients with long-term steroid therapy it is necessary to answer the question: what glucocorticoid dose and administered for how long, will increase fracture risk? As studies regarding the development of glucocorticoid-induced osteoporosis showed, these negative alterations in bone tissue occur already in the first months and even weeks of exposition to glucocorticoids. Most authors demonstrated that a dose of ≥ 7.5 mg prednisone, administered for 3 months significantly decreases BMD. Such a dose induces a significantly pronounced vertebral body bone mass loss, however not until the 3rd to 6th month from glucocorticoid administration, but the increase of compressive fracture risk occurs already earlier [4]. This risk however increases also with long-term (over 1 year) administration of an equivalent of a 5 mg prednisone dose once a day, and according to some authors, even due to a several-year administration of inhaled glucocorticoids [14,15]. The fracture risk with oral glucocorticoids increases with the rise of the daily and cumulating dose. With a dose of 2.5 mg prednisone daily, a risk for a vertebral body compression fracture, for example is 1.55, and with the dose >7.5 mg it rises to 5.2. [16]. A similar relation was found with inhaled glucocorticoids. The fracture risk increases with: female sex, low body mass (body mass index <20 kg/m²), cigarette smoking, falls and old fractures. If the main disease is rheumatoid arthritis treated with steroids, it is an additional risk factor [17]. A particularly pronounced osteoporosis risk is related to the administration of intramuscular depot agents.

A shortage of glucocorticoids, as in patients with primary or secondary renal cortex insufficiency, inhibits osteoblasts activity and decreases the velocity of physiological bone tissue remodeling [11]. It therefore seems that hydrocortisone replacement doses should not increase the fracture risk, and should even have a positive effect on the bone quality. How-

ever epidemiologic data showed that in Addison's disease (primary adrenal insufficiency) patients receive too high doses of glucocorticoids resulting in subclinical hypercortisolaemia [18]. The insulin resistance and cardiovascular complications risk may rise as a result, and bone mass may decrease. It must be kept in mind that a prednisone dose regarded as significant for fracture risk increase, 7.5 mg/d, is equivalent to 30 mg of hydrocortisone, frequently used in Addison's disease. Hydrocortisone doses of <20 mg/d were recommended for secondary adrenal insufficiency patients so far; currently some authors recommend them also in primary insufficiency [19]. They however slightly decrease BMD, but it seems that their influence on fracture risk is practically negligible.

The decrease of BMD and the fracture risk increase are particularly pronounced in the first six months of steroid therapy. Bones with the greatest percentage of a metabolically active spongy bone: vertebral bodies, ribs, pubic symphysis, are especially susceptible to fractures. Steroid therapy also increases the risk for long bones fractures (proximal femoral epiphysis, radius). The fractures heal slowly, often with an excessive periosteal reaction [11].

The risk for fracture in a glucocorticoid treated patient is disproportionately higher than the BMD value may imply. This has been stressed in antifracture efficacy of the bisphosphonates study, during the analysis of fracture frequency in the placebo treated group [20]. A group of post menopausal women with long-term steroid therapy was studied for one year. Symptomatic and asymptomatic fracture frequency in the placebo treated group was 17.3%, though their BMD was decreased as compared to values equivalent for osteopenia according to the WHO criteria (T-score [BMD of patient examined to a mean bone density of the ratio calculated for young subjects] was 1.8) [21]. In the study on antifracture risedronian efficacy, the fracture percentage in females and males with glucocorticoid-induced osteoporosis was 15% with a mean T-score of 1.7 [22]. However, in postmenopausal women with a similar BMD (equivalent to a diagnosis of osteopenia based on absorptiometry) the fracture incidence is ≤1% a year. In glucocorticoid-induced osteoporosis a high fracture risk is a BMD independent factor that may influence the decision about initiation of antifracture treatment. Taking a 20% fracture risk in 10 years as the therapeutic intervention limit, each patient with an initial diagnosis of "osteopenia" will have exceeded that limit. In the most recent Polish guidelines, in which the above mentioned limit for antifracture treatment was adopted, the current glucocorticoid therapy is considered a BMD independent, strongest and requiring a therapeutic intervention risk factor.

In the guidelines regarding glucocorticoid-induced osteoporosis it has been stressed that corticotherapy is of an „actual" character. What is therefore the meaning of the previous glucocorticoid therapy for bones?

Discontinuation of long-term steroid therapy, as a successful treatment of Cushing's disease, induces a gradual bone mass increase and a fracture risk decrease [15,23]. In young individuals the bone tissue renovation process takes place

without disruption; the main role being played by normal sex hormones levels and high calcium supply. In postmenopausal women and post-andropause men, or with the occurrence of other risk factors it is advised to maintain the antiresorptive treatment (according to classical standards for postmenopausal or involution osteoporosis). In new guidelines concerning indications for antifracture treatment it has been found that the previous steroid therapy is not a fracture increasing risk factor. It must, however, be kept in mind that a patient during glucocorticoid treatment could suffer from multiple vertebral body fractures, which through disrupting the vertebral column equilibrium, limit the ability to move and increase the fall incidence. A fracture during steroid therapy is the next fracture important risk factor, even when the glucocorticoid therapy is discontinued. Moreover, it has to be stressed that because of the recurrent nature of several diseases treated with glucocorticoids, the patient for the rest of his life has to take into account the possibility of another course of this therapy.

The therapeutic threshold in glucocorticoid-induced osteoporosis: when to treat?

The data presented here undoubtedly show that in patients treated with long-term anti-inflammatory glucocorticoid doses, the therapy should be introduced already with a very limited bone mass loss.

During the last decade when formulating management guidelines for glucocorticoid-induced osteoporosis, different indications for treatment commencement were suggested. In 1998 in Great Britain it was proposed that the treatment be started together with steroid therapy, if the patient's BMD is decreased in such a way that the T-score is less than 1.5. If there is a negative score, but higher than 1.5, prophylaxis was advised (Ca/D₃, hormone replacement therapy), and for a positive T-score, only observation. In the case when after a year of prophylactic treatment or observation BMD decreased by 4% in the lumbar spine and by 7% in the femoral neck, treatment was advised [24]. A completely different approach was adopted by the American College of Rheumatology in 2001, which recommends antifracture treatment in all postmenopausal females and males, if a prednisone administration of ≥5 mg for >3 months is scheduled. With the ongoing therapy, the treatment should be introduced at the T-score greater than 1.0 [25]. On the other hand, according to Australian guidelines the therapeutic threshold limit is a T-score of 2.5 standard deviations, and prophylaxis is recommended only between 1 and 2.5. Among prophylaxis drugs, apart from calcium and vitamin D, bisphosphonates and hormone replacement therapies are listed [26]. This standard recommends introducing antifracture drugs already with osteopenia, according to the WHO criteria (what is called „prophylactic"). The history concerning fractures has been regarded in these standards, first of all; each patient beginning steroid therapy, had he suffered from an osteoporotic fracture earlier, should be treated with osteoporosis treatment regardless of the result of bone densitometry. Secondly, patient management, with no fractures till

the present day, was dependent not only on the initial bone mass, but also on the dose of glucocorticoids administered. When the initial BMD is less than 80% peak bone mass (about 1.7 standard deviation), treatment is recommended. If it is higher, therapy is recommended for patients receiving >5 mg prednisone per day [27].

The Canadian Osteoporosis Society recommends introducing antiresorptive bisphosphonate treatment in all patients who planned to receive ≥ 7.5 mg prednisone for >3 months. This approach is to be independent of BMD, which is only assessed to evaluate a long-term therapy effect. [28].

The above mentioned standards, regardless of which densitometric criteria are adopted as the therapeutic limits, have one common point; it is not only the densitometry test result that decides about the introduction of antifracture therapy. The speed of bone mass loss (assessed after repeated densitometry), the history looking at previous fractures, as well as the doses and duration of glucocorticoid administration, are also important. A similar approach to this problem is also presented by Polish guidelines, currently in preparation; the therapeutic decision according to these recommendations should be based on obtaining the fracture risk. This risk is assessed based on densitometry test results and other risk factors; including previous fractures and the family history (femoral neck fracture in parents). In this standard, corticotherapy is regarded the most important, increasing more than twice the fracture risk independent factor. It results in qualifying to the treatment a patient who based on BMD and other risk factors would only have an indication for osteoporosis prophylaxis.

It means practically that all patients with osteopenia, according to the WHO criteria, treated for >3 months with a dose of ≥ 7.5 mg prednisone, should have antiresorption treatment introduced.

Glucocorticoid-induced osteoporosis treatment

The anti-inflammatory doses of glucocorticoids result in a negative calcium balance. In order to avoid its consequences (osteomalacia, osteomalacia, secondary parathyroid hyperactivity) from the very first days of steroid therapy, it is necessary to initiate calcium and vitamin D₃. Such treatment allows for a appropriately balanced calcium equilibrium, it does not however induce a satisfactory BMD increase (slight alterations are seen only in the first year of treatment) [29]. According to Ringe's recommendations, a patient who begins steroid therapy should have 0.5–1.0 g elemental calcium and 1.0 μ g alfacalcidol or 0.59 μ g calcitriol, administered [30]. Active metabolites (alfacalcidol, calcitriol) not only increase BMD, but also decrease fracture risk due to steroid therapy [31,32]. For a decrease of hypercalciuria it may be favourable to start thiazide diuretics, or if contraindicated (glucocorticoid-induced diabetes, hypercholesterolaemia), indapamide group drugs application. An antifracture effect of such a treatment has not been documented yet, it is however justified, as it counteracts a negative calcium balance [33].

Bisphosphonates are the group of the strongest antifracture potential in osteoporosis treatment, including glucocorticoid-induced osteoporosis. First generation bisphosphonates, with the weakest antiresorptive effect have already been described as drugs inhibiting the post steroid bone mass loss. In the case of treatment with etidronate, pamidronate or klodronate there is a risk of a non sufficient mineralization of the newly formed bone tissue, which in the case of a patient with post-steroid osteomalacia present, is a very serious threat. Aminobisphosphonates with a strong antiresorptive potential, with no risk of a demineralization increase, act through the mechanism of cholesterol synthesis inhibition in the osteoclast, thus disturbing the effect of the breaking down of the bone cell. The results of the GIOP study demonstrated that alendronate administration increases the bone mass and decreases the risk for vertebral body fracture in patients on long term steroid therapy [34]. Risedronate studies showed a significant BMD increase and a vertebral body fracture risk decrease in patients treated with glucocorticoids [22,35]. The limitation in the above mentioned drugs administration may be due to their irritating effect on gastrointestinal tract mucous membrane. The cited studies did not demonstrate an increased frequency of inflammation and ulcerations in the upper gastrointestinal tract. There is however a likelihood of a combined risk of stomach abnormalities, due to a combined treatment with an aminobisphosphonate and nonsteroidal anti-inflammatory drugs. Such a combined use of drugs with negative adverse effects on the mucous membrane of the upper gastrointestinal tract can be observed for example in patients with rheumatoid arthritis. The introduction of aminobisphosphonate tablets administered once a week (alendronate or risedronate) or once a month (ibandronate) may effectively decrease the incidence of adverse effects. Intravenous aminobisphosphonates, i.e. ibandronate (once every 3 months) and zoledronate (once a year), have also been used for osteoporosis treatment recently. A study published in 2006, which confirmed the antifracture activity of zoledronate, concerned postmenopausal females. As these drugs principle of action is the same as of oral aminobisphosphonates, they can be expected to be as effective in patients on steroid therapy [36]. It must be kept in mind that aminobisphosphonates are a group of drugs with the earliest documented antifracture efficacy in postmenopausal osteoporosis, and the only ones with documented antifracture effects in glucocorticoid-induced osteoporosis. Their administration, therefore, not only improves the densitometry test result, but also brings a measurable benefit reflected by a decrease in the fracture risk.

As a result of long-term steroid therapy, the sex hormones release is inhibited, being an additional factor to decrease bone mass; mainly through the mechanism of resorption activation. Hormone replacement therapy may be the osteoporosis and fracture prophylaxis in this case. Reid et al. [37] found a BMD and lean body mass rise in males treated with prednisone after testosterone intramuscular injections. Lukert et al. [38] demonstrated that as a result of hormone replacement therapy the BMD fall can be decreased in glucocorticoids treated females, and Hall et al. [39] obtained the same effect in females re-

ceiving prednisone for rheumatoid arthritis. Estrogen receptor specific modulator has a similar effect. A 2-year duration treatment with tamoxifen inhibits the post steroid bone mass loss in females who started estrogen receptor specific modulator administration together with the introduction of the prednisone treatment [40].

Calcitonin has an antiresorptive effect through osteoclast activity inhibition, as it adheres to the receptor on their surface. Unfortunately, it also increases the negative calcium balance resulting from steroid therapy, as it diminishes the intestinal calcium absorption and calcium reabsorption from glomerular filtrate in renal tubules. For patients with vertebral body fractures during corticotherapy, the calcitonin analgesic effect is very important. Calcitonin has the strongest analgesic effect with nasal application; its classical adverse effects: hot flashes, vertigo, nausea, vomiting, are observed less frequently than with intramuscular administration. A positive effect of calcitonin on post steroid bone mass loss inhibition, applied nasally or in injections, has been demonstrated in several studies, the results however are not synonymous. Its fracture risk reducing action in patients on long-term steroid therapy has not been demonstrated yet. In most recommendations, calcitonin is mentioned as a third-line drug, after bisphosphonates and hormone replacement therapy [41].

Knowing that as a result of anti-inflammatory doses steroid therapy there is a strong bone formation inhibition it may be expected that drugs inhibiting the bone tissue resorption will not be sufficient for an effective therapy. It may therefore be beneficial to administer anabolic drugs (in monotherapy or together with an antiresorptive agent) which activate osteoblasts. Glucocorticoid-induced osteoporosis treatment with anabolic steroids, reasonable from a pathophysiological point of view, has rarely been discussed in available data. An attempt of nandrolone treatment in females has been noted, as a result of which a radius BMD rise has been observed [42]. Dehydroepiandrosterone, in "pharmacological" (100–200 mg) or physiological (25–50 mg/d) doses, results in levels of the bone formation markers and the BMD rise in the vertebral body and the femoral neck [43,44]. The recombinant human growth hormone increases the bone and muscular mass and has a strong anabolic effect; it may however increase the risk of glucocorticoid-induced diabetes [45].

Parathormone at physiological levels has an anabolic effect on the bone tissue; it activates bone formation. After glucocorticoid-induced osteoporosis treatment with the recombinant fragment of human PTH (teriparatide) an activation of bone formation was achieved (osteocalcin level increase) and a lumbar spine BMD rise [46]. The administration of PTH together with hormone replacement therapy in postmenopausal women enhances this effect [47]. However in some patients treated with glucocorticoids in anti-inflammatory doses PTH levels are already initially increased, secondary to a negative calcium balance. Calcium and vitamin D deficiency replacement which helps prevent from secondary hyperparathyroidism is a determinant of teriparatide therapy efficacy. Another problem related to parathormone therapy is the limited therapy duration;

approved therapy duration is 18–24 months. This restriction has been introduced as a result of observations of rats which experienced osteosarcoma more often when treated with teriparatide for their whole lives. Bone mineral density, rising rapidly during therapy, decreases equally rapidly upon treatment discontinuation; therefore the necessity of the antiresorptive drug therapy continuation. It has been demonstrated that hormone replacement therapy and PTH may act synergistically, but the simultaneous PTH and alendronate administration limits the teriparatide positive effect. Aminobisphosphonate treatment should therefore be initiated upon the completion of parathormone therapy [48].

So far no studies concerning the use of strontium ranelate, which apart from its antiresorptive effect activates bone formation in patients on glucocorticoids, have been published. Due to its dual mechanisms it may become, along with aminobisphosphonates, a commonly used drug in glucocorticoid-induced osteoporosis treatment in the future.

SUMMARY

Glucocorticoid-induced osteoporosis is an extremely severe, bone metabolic disease, in the development of which complex pathomechanisms take part. It leads to fractures much more often than postmenopausal osteoporosis; it may also be accompanied by osteomalation or aseptic bone necrosis. The pace of bone tissue alterations is the greatest in the first year of steroid therapy, therefore it is advised to introduce the treatment or prophylaxis of glucocorticoid-induced osteoporosis, even with a nonsignificant BMD decrease. For fracture prevention calcium with active vitamin D metabolites, hormone replacement therapy and aminobisphosphonates are being employed. The latter, alendronate and risedronate, are at present first-line drugs in glucocorticoid-induced osteoporosis treatment. An increase in the significance of anabolic drugs such as parathormone and strontium ranelate, is to be expected in the future.

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