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Current indications for prevention and therapy of steroid-induced osteoporosis in men and women

Obowiązujące wskazania do prewencji i leczenia osteoporozy posteroidowej u mężczyzn i kobiet

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Abstract

Steroid-induced osteoporosis is a textbook example of the secondary type of this medical condition. Glucocorticosteroids suppress bone formation by their direct and indirect effect on osteoblasts, osteoclasts and osteocytes, increasing their resorption and, eventually, leading to negative bone balance. A clinical problem arises regarding the fact that approximately 50% of patients on chronic steroid therapy undergo asymptomatic bone fractures. The treatment mode includes minimising the dose of administered steroids, encouraging an improved lifestyle and supplementation with adequate calcium and vitamin D_3 doses. Bisphosphonates are a group of medical agents used both to prevent and treat steroid-induced osteoporosis, although new therapies have also become available in recent years.
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Key words: *steroid-induced osteoporosis, men, women, treatment, prevention*

Streszczenie

Osteoporoza posteroidowa jest modelowym przykładem osteoporozy wtórnej. Glukortykosteroidy poprzez bezpośredni i pośredni wpływ na osteoblasty, osteoklasty oraz osteocyty hamują formowanie kości, zwiększając ich resorpcję, doprowadzając finalnie do ujemnego bilansu kostnego. Problem kliniczny narasta w związku z faktem, że około 50% pacjentów długotrwale stosujących steroidy ulega asymptomatycznym złamaniom kości. Leczenie pacjentów polega na minimalizowaniu dawki stosowanych steroidów, poprawie stylu życia i suplementacji adekwatną dawką wapnia i witaminy D_3. Bisfosfoniany są najlepiej przebadaną grupą leków stosowanych zarówno w prewencji, jak i terapii osteoporozy posteroidowej, choć znajdują też zastosowanie nowe formy terapii.
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Słowa kluczowe: *osteoporoza posteroidowa, mężczyźni, kobiety, leczenie, prewencja*

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Introduction

Glucorticosteroids were discovered early in the 20th century. The first reports on the effects of cortisol on bone tissue were presented by Cushing in 1932 [1]. Cortisone was isolated in 1936–1940 and cortisol in 1939 [2, 3]. However, the development of a synthesis of derivatives of those compounds, with much stronger immunosuppressive and anti-inflammatory effects but with smaller mineralcorticoid activity, led to their broad application in the therapy of numerous diseases, including autoimmunological, rheumatological, gastrological and neoplasmic diseases and in cases of organ transplantation [4].

An analysis, carried out in the UK of 1.6 million prescriptions for oral steroids issued over a ten year period, showed these agents are used in 0.9% of the general population and in approximately 2.5% of patients aged 70 to 79, i.e. the time when adverse symptoms may overlap with changes related to the ageing process [5]. Although glucocorticosteroids are important therapeutic agents, their adverse effects, manifested during their chronic use, should be kept in mind, including their unfavourable effects on bone tissue. Our knowledge regarding the necessity of prophylactics is still unsatisfactory, which is why prophylactic treatment has been proposed to only 5% of subjects on oral glucocorticosteroid therapy [5].

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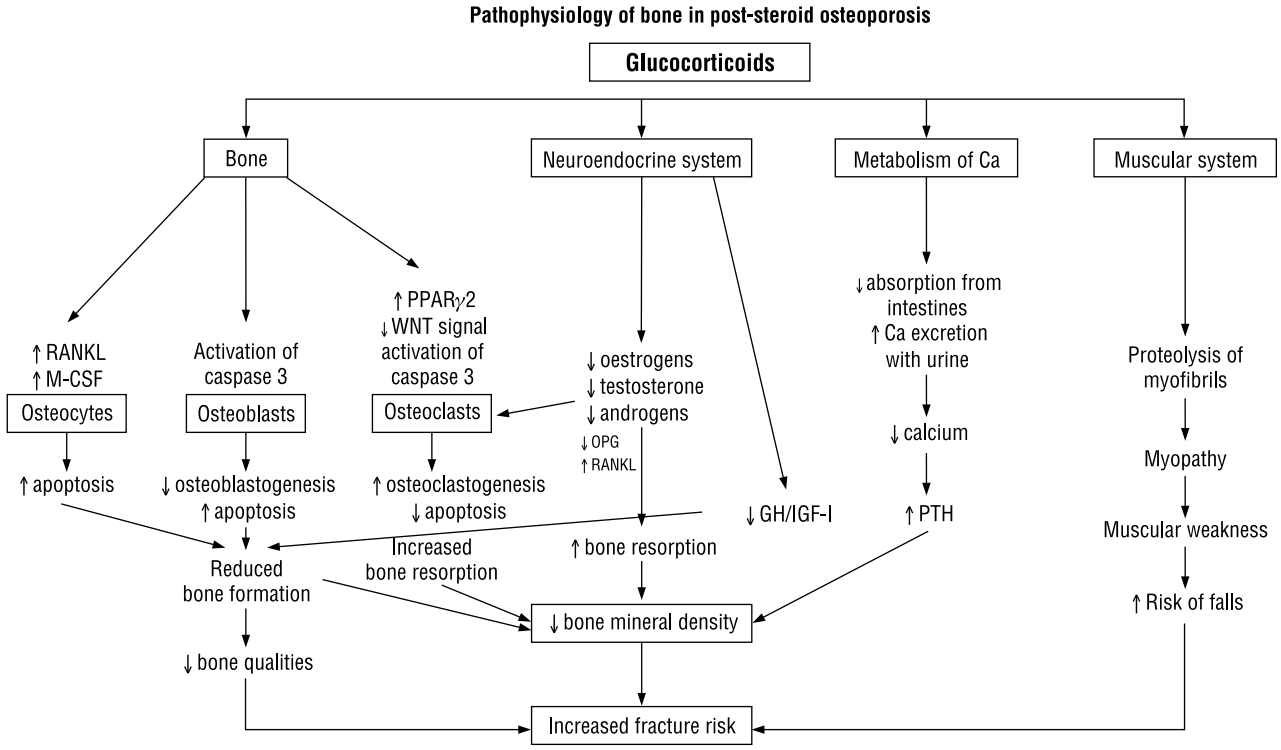

Figure 1. *Pathophysiology of changes in steroid-induced osteoporosis according to Canalis et al. [8] with own modification*
Rycina 1. *Zmiany patofizjologiczne w osteoporozie posteroidowej na podstawie pracy Canalis i wsp. [8] w modyfikacji własnej*

Aetiopathogenesis

Steroid-induced osteoporosis is a textbook example of secondary osteoporosis [6, 7]. Glucocorticosteroids, via their direct and indirect effects on osteoblasts, osteoclasts and osteocytes, inhibit bone formation, increasing their resorption and, eventually, leading to negative bone balance [8] (Fig. 1). In direct steroid effects on osteoclasts, the role of the recently discovered RANKL--osteoprotegerin system is emphasised, while the PPARγ2 system, Wnt signal and caspase-3 activation influence the activities that steroids exert on osteoblasts. Caspase-3 activation plays an important role in enhancing the apoptosis of osteocytes, until quite recently regarded as inactive bone tissue cells [9]. The process of bone mass loss, observed in the course of steroid therapy, begins rapidly during the first few months, then slows after the first year of treatment, to finally stabilise at an annual rate of 2–5% [10, 11].

Fracture risk

The fact that 30–50% of steroid-administered patients experience asymptomatic bone fractures is a significant clinical problem of chronic steroid therapy, i.e. therapy lasting longer than three months [12, 13]. There is a positive correlation between daily dose and fracture risk. The fracture risk rises rapidly 3–6 months after the onset of steroid therapy, dropping down again when the therapy ceases [14].

Glucocorticoids increase the risk of all fractures in all age groups, including young people, regardless of bone mineral density, earlier fractures in history or gender [8, 12]. A meta-analysis of a population of 42,000 men and women found that bone density changes, resulting from steroids used both currently and previously, increased the fracture risk, especially with regards to the femoral neck. The risk of fractures is higher in younger subjects than in women after the menopause, irrespective of earlier fracture episodes [12]. According to epidemiological data, subjects exposed to system steroids experience a doubling in the incidence of femoral neck and forearm fractures, while spinal fracture rates are higher than in the untreated population [15].

It is also known that spinal fracture is an independent risk factor of subsequent fractures, as well as those in other areas [14]. The fracture risk rises at even such a small daily dose of prednisolone as 2.5–7.5 mg; additionally, a relationship has been demonstrated between the fracture risk and the cumulative dose [16, 17]. An analysis of a group of 244,235 female patients vs. an identical control group found that the annual risk of fractures at a prednisolone dose of 2.5–7.5 mg/day was 1.77 (CI 1.55–2.02), rising to 2.27 at a dose of 7.5 mg (CI 1.94–

–2.66) [18]. When using an agent equivalent to prednisolone at a dose of 10 mg/day over a period longer than 90 days, the risk of femoral neck fracture is seven times higher and the risk of spinal fracture is 17 times higher [19].

Van Staa et al. [18] emphasised that in predisposed subjects, even a dose of less than 2.5 mg may increase fracture risk. Faced with this data, it is a particular challenge to precisely determine a dose which would leave bone tissue unaffected.

This fact has influenced the final approach to steroid-induced bone fracture risk, including also the calculators evaluating ten year fracture risk, namely that steroids used for at least three months are a significant fracture risk factor [20–24].

It should be underlined that the levels of prophylactics, even in such prophylactics-oriented countries as the UK (14%) or Iceland (51%), are unsatisfactory [18, 25].

We must remember that most diseases in which steroid administration is indicated themselves increase the risk of osteoporosis, for example rheumatoid, chronic pulmonary and inflammatory intestinal diseases or the post-transplantation period [26–28].

No increased fracture risk has been demonstrated with the use of nasal or local steroid application (e.g. as an ointment) or in inhalatory forms, except the daily dose corresponding to 7.5 mg of prednisolone (an equivalent of 1,875 μg of budesonide or beclomethasone [29].

It has, however, been demonstrated that bone mineral density (BMD) is lower both with chronic application of inhalatory steroids with intermediate doses of oral steroids, and with continuous, combined use of inhalatory steroids with oral steroids [30–32]. Following clinical observations and according to steroid doses, asthmatic patients were divided into groups of low, medium and high risk of osteoporosis [33]. The low risk group included patients taking inhalatory steroids, equivalent to a daily beclomethasone dose $\leq$ 800 μg/ /day in adults or $\leq$ 400 μg/day in children. The medium risk group featured patients with asthma, receiving inhalatory steroids in a dose $>$ 800 μg/day in adults and $>$ 400 μg/day in children. The high risk group comprised patients using systemic steroids four times a year or in daily oral doses, both as chronic therapies. This group included subjects using nasal and inhalatory steroids in combination with their oral forms.

Prophylactics and therapy

Even though the understanding of steroid therapy complications continues to grow, neither osteoporosis prophylactics nor treatment of the disease is yet optimal [34]. However, the situation, viewed in the context of the last few years, has demonstrated some improvement. An evaluation of patients treated during 1995 to-1998 against others treated 2001 to 2003 found out that the number of densitometric examinations tripled and the quantity of drugs used doubled.

In turn, it has been found in the United States that only 10% of patients on oral steroid therapy had had densitometry performed, while only 15% of patients had been receiving treatment other than hormonal replacement therapy (HRT) [35].

It is worth emphasising that only one in three patients had received any information about the countermeasures against osteoporosis necessary with steroid administration, only half of them had been receiving appropriate doses of calcium, and only one third had received sufficient vitamin D supplementation [36]. Bearing all this in mind, doctors should be regularly reminded about the need for prevention with prior densitometric evaluation of bone status being performed in patients before steroid therapy application.

The goals of post-steroid osteoporosis treatment include preservation of bone mineral density, counteracting bone mass loss, post-fracture pain control, muscular force increase and improved lifestyle [10]. The American Society of Rheumatology introduced recommendations in 2001 concerning both the prevention and therapy of post-steroid osteoporosis. All steroid-using patients should receive supplementation with calcium preparations (approximately 1 g daily) and with vitamin D (800 IU/d). Patients treated with medium and high doses of glucocorticosteroids should receive active forms of vitamin D (e.g. alphacalcidiol 1 μg/d or calcitriol 0.5 μg/d), in addition to calcium supplementation.

Regarding the treatment of both men and postmenopausal women, bisphosphonates is the therapy of choice, while in cases of hypogonadism, it is hormonal replacement therapy [10]. Alendronate, risedronate and teriparatide are the medical agents approved in Europe for osteoporosis treatment in men with increased fracture risk [37–39]. Indications for osteoporosis prophylactics and treatment implementation in the course of steroid therapy differ greatly, despite numerous attempts at systematisation [40–49] (Table I). All the recommendations emphasise the need for prevention during continuous use of oral steroids. Intermittent therapy is still the subject of debate as to the best therapeutic protocols. A similar situation is seen with inhalatory steroids, taking into account the scarcity of data on an increased fracture risk in the course of their application [32, 50]. The divergent recommendations result from differences in particular health care systems, the varying availability of densitometric examinations, and fairly strong evidence for the efficacy of post-steroid osteoporosis therapy [42]. In the UK, primary prevention protocols are recommended in all men and women over

Table I. *Recommendations for treatment of post-steroid osteoporosis (comparison of data in the USA, UK and Denmark) (acc. to [41, 43, 48])*

Tabela I. *Rekomendacje leczenia osteoporozy posteroidowej (porównanie zaleceń Stanów Zjednoczonych, Wielkiej Brytanii i Danii) [41, 43, 48]*

	American Society of Rheumatology	Royal College of Physicians (UK)
Steroid dose	≥ 5 mg/day for ≥ 3 months	Each dose for ≥ 3 months
Primary prevention criteria	All patients	Age ≥ 65 years or with fractures in history
Indications to secondary prevention	BMD T-score < –1	BMD T-score ≤ –1.5 *(≤ –2.5 following Danish recommendations for patients receiving < 7.5 mg of prednisolone)*
Ca and vitamin D supplementation	All patients	Patients with insufficient supplementation of calcium in diet and/or with vitamin D deficiency

the age of 65 and all patients with fractures in their history, while in the USA, it concerns every person starting steroid therapy. In the UK, recommendations cover subjects using oral steroids for at least three months with an unspecified dose limit, while in the United Sates, this recommendation applies to subjects receiving steroids for at least six months at a dose ≥ 5 mg of prednisolone. Similar differences occur in imaging examinations. The American recommendations indicate the need for densitometric evaluation of all patients before therapy implementation, emphasising the role of the examination in monitoring. In the UK on the other hand, densitometry is not a requirement in primary prevention but should be performed to qualify patients to secondary prevention. In US recommendations, a densitometry T-score ≤ –1.0 (≤ –1.5 in UK) requires pharmacological intervention. Polish recommendations have been systematised, taking into account local experience and the particular needs of our country [40, 45].

Bisphosphonates

These agents are most frequently used both for prophylactics of steroid-induced osteoporosis and to treat the disease [9, 43, 44, 51]. Etidronate is registered in Europe and in Canada only, while alendronate, risedronate and zoledronate are widely applied [9]. The data shows that a statistically significant anti-fracture effect in the spine is observed after 24 months of alendronate, and after 12 months of etidronate or risedronate administration [52–54]. Such agents as clodronate, ibandronate and pamidronate improve BMD, but there is no proper data concerning their possible anti-fracture effects [55, 56]. Intravenous forms of these drugs, especially ibandronate (and recently also zoledronate) have attained a proper position in the treatment of osteoporosis, the latter also in the treatment of osteoporosis in men. Intravenous forms are particularly useful in cases of intolerance to oral bisphosphonates or in concomitant absorption disorders. In steroid-using patients, a more effective BMD improvement has been demonstrated, both in the spine and in the femoral neck, in the course of a three-year i.v. ibandronate therapy, combined with a calcium supplement vs. the effect of alphacalcidol plus calcium [56].

Table II. *Approved therapies of post-steroid osteoporosis*

Tabela II. *Zaakceptowane formy leczenia osteoporozy posteroidowej*

	Dose	Route of administration
Alendronate	5 or 10 mg daily 70 mg once a week	Oral
Etidronate	400 mg daily for two weeks, every three months	Oral
Risedronate	5 mg daily 35 mg once a week	Oral
Zoledronate	5 mg once a year (in women and men)	Intravenous infusion
Teriparatide	20 μg daily	Subcutaneous

Moreover, a certain reduction has been demonstrated in the number of patients with spinal fractures in the group treated with i.v. ibandronate vs. alphacalcidol (8.6% vs. 22.8%; $p < 0.05$). Recently, beside the above-mentioned drugs, zoledronate and teriparatide have been approved for the treatment of post-steroid osteoporosis (Table II).

It has been demonstrated that zoledronate, administered once a year at an intravenous 5 mg dose, increases BMD in the spine and in the proximal femur much more effectively than risedronate, both in prevention (steroids < 3 months) and in treatment (steroids ≥ 3 months). In the course of an annual observation, only eight new spinal fractures were noted in 771 patients and no statistically significant differences were observed between the group submitted to prevention and the group

submitted to therapy. Taking into account the frequently observed concomitance of other diseases in steroid-treated patients, which means there are increased quantities of administered drugs, the incidence of adverse effects may be higher than average. Therefore, it is assumed that steroid therapy could increase the risk of mandibular necrosis or atypical fractures [57, 58]. Moreover, because it is possible that bisphosphonates can permeate through the placenta in premenopausal women, their use should be approached with particular caution.

Calcium and vitamin D and its active metabolites

Calcium and vitamin D applications play a significant role in the course of steroid therapy. Cochrane's database analysis indicates a statistically significant participation of calcium and vitamin D in BMD improvement, both in the spine and in the femoral neck [59]. Even beyond this, calcium and native vitamin D have routinely been used in many studies looking at the prevention and treatment of post-steroid osteoporosis [47].

Active forms of vitamin D play a significant role in steroid-induced osteoporosis. It has been found that calcitriol, administered in doses of 0.5–1 μg daily, improves BMD, particularly in the lumbar spine [60–62], although the obtained results were not always satisfactory [63]. No such effects of the active forms of vitamin D have been found regarding the fracture risk in steroid-treated patients. Similarly, alphacalcidol, in doses from 0.25 to 1 mg daily, protects against bone mass loss in the spine and, according to some reports, also in the forearm and the femoral neck [64–66]. Although a decreased risk of spinal and extravertebral fractures was observed after two years of using alphacalcidol with calcium, , the results obtained from a three-year observation were not statistically significant [67]. Comparing the effect of alendronate with that of alphacalcidol, a more efficient improvement of BMD was observed in the lumbar spine, following bisphosphonate therapy [68, 69]. The evidence which would indicate any supremacy of the active forms of vitamin D over that of the native form of vitamin D is rather weak. Therefore, neither alphacalcidol not calcitriol has been approved for the therapy of post-steroid osteoporosis in Europe or North America.

When using active forms of vitamin D, calcium concentration in serum and in daily urine volume should be monitored for the possibility of hypercalcaemia or hypercalciuria. It should also be kept in mind that steroids can themselves enhance calcium escape with urine. It should be emphasised as well that the favourable pleiotropic effects of native vitamin D are highlighted in the Polish therapeutic recommendations [70–71].

Other forms of therapy

Other forms of therapy recommended during chronic steroid administration include calcitonin, oestrogens and fluorine [72]. An analysis of Cochrane's base found that the favourable effect of calcitonin in post-steroid osteoporosis consists in counteracting bone mass loss in the spine and the forearm, with no effect on the femoral neck. No benefits have been confirmed in terms of spinal or extravertebral fracture risk [73]. Despite information as to the strong, favourable, anabolic effects of the parathormone and its formal approval to the therapy of post-steroid osteoporosis, PTH agents are not commonly used [74]. In steroid-treated women, an increased BMD has been observed in the lumbar spine after one year of PTH administration and in the femoral neck after two years [75–76]. Studies have reported that postmenopausal women, receiving oral prednisolone and HRT, who were administered teriparatide at a dose of 40 μg/d i.e. the human, recombined PTH with molecule of 1–34 amino acids, obtained an increase in spine BMD after one year of therapy. That effect was maintained for another year after drug withdrawal. In turn, in the femoral neck, despite PTH withdrawal after one year of therapy, a statistically significant increase was also found after three years of the still continued study.

Comparing the effects of teriparatide at a dose of 20 mg/day against those of alendronate, a higher and statistically significant increase in spine BMD was already being observed after six months, while a similar effect in the femoral neck was obtained only after one year of therapy [77]. BMD changes were comparable in women, both before and after the menopause, as well as in men [78]. It should be emphasised that, after PTH, the incidence of fractures was lower than after alendronate (0.6% vs. 6.1%, respectively; $p < 0.005$). It has been noted that the positive effect of the parathormone on BMD in women is better expressed in post-steroid than in post-menopausal osteoporosis, what may be associated with the way PTH suppresses steroid effects on osteoblastogenesis and on the apoptosis of osteoblasts and osteocytes [9].

Another study again demonstrated that advantage, comparing the effect of a 36-month therapy with teriparatide to the effect of 36-month alendronate administration on BMD improvement in the spine and in the femoral neck, as well as on the reduction of vertebral fracture risk [79]. This found that, in both therapies, early changes of certain bone metabolism markers correlated with BMD increased after 18 months [80]. As expected, bone metabolism markers changed according to the activity of the received drug (PTH being an anabolic agent, whereas alendronate is an antiresorptive agent) [80-81].

Despite certain differences in the approach to patients in the course of chronic steroid therapy, significant roles have been assigned to: 1) primary prophylactics; 2) bisphosponates as first-line therapy; and 3) supplementation with calcium and vitamin D [82–83].

The roles of bone metabolism markers and of densitometric examinations in the monitoring are not absolutely clear, although spine densitometry at the stage of therapy implementation may have significance for the decision regarding prevention options. It seems that not only is the appropriate implementation of prophylactics important, but so also is regularity of its application. It has been found that the prophylactics of bone mass loss is suboptimal when oral steroids are used [84].

A positive correlation has been demonstrated between bisphosphonate therapy withdrawal in patients on chronic steroid therapy and young age, a large number of concomitant diseases, and the unavailability of densitometric examination.

Understanding the disease is a very important element in the prophylactics of osteoporosis, especially post-steroid osteoporosis. A programme based on identifying patients with risk factors, a proper education, a planned care system and control of recommendations after one year of their application, has been shown to considerably improve the knowledge of patients about osteoporosis. Additionally, increased vitamin D concentrations and better physical activity have been observed in these patients. In 91% of patients in the high risk group, an implementation of prophylactic treatment brought about an improvement in bone mineral density of the lumbar spine and the femoral neck [85].

Regarding the prophylactics of post-steroid osteoporosis, in addition to a proper diet or calcium and vitamin D substitution, a considerable role can be attributed to physical activity, prevention of falls and minimising the steroid dose, while keeping it therapeutically effective. If possible, the oral mode should be replaced by another form of administration, e.g. inhalation.

In the treatment of osteoporosis, cost-effectiveness should be regarded as a very important factor. It has been demonstrated that the relatively high cost of bisphosphonates is cost-effective in the group of patients with high fracture risk [86]. This group includes elderly patients (those expected to survive at least five years), younger patients with fractures in their history, those with small body weight, rheumatoid arthritis or who are using high doses of steroid.

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