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*Piotr Głuszko

Vitamin D supplementation in glucocorticoid induced osteoporosis

Suplementacja witaminy D w osteoporozie indukowanej glikokortykosteroidami

Department of Rheumatology, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw
Head of Department: Professor Piotr Głuszko, MD, PhD

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Address/adres:
*Piotr Głuszko
Department of Rheumatology
National Institute of Griatrics,
Rheumatology and Rehabilitation
ul. Spartanska 1, 02-637 Warszawa
tel. +48 (22) 844-87-57
piotr.gluszko@spartanska.pl

Summary

Long-term treatment with glucocorticosteroids leads to negative calcium balance, rapid bone loss, muscle weakness and to an increased risk of osteoporotic fractures. Unlike glukokortykosteroids, active metabolites of vitamin D increase intestinal calcium absorption, inhibits renal calcium excretion, regulates bone mineralisation and protect muscle function. Vitamin D supplementation combined with calcium is widely recommended in early preventive measures and in general management of glucocorticoid-induced osteoporosis (GIO). Vitamin D plays an adjuvant role in the prevention and treatment, but bisphosphonates are used as the gold standard for the pharmacologic management of GIO. In this review, we discuss a rational for vitamin D treatment in GIO and summarise current guidelines indicating calcium and vitamin D supplementation in fracture prevention strategy.

Streszczenie

Długotrwałe leczenie glikokortykosteroidami prowadzi do ujemnego bilansu wapniowego, utraty masy kostnej, osłabienia mięśni i w konsekwencji do wzrostu ryzyka złamań kości. W przeciwieństwie do glikokortykosteroidów, aktywne metabolity witaminy D ułatwiają wchłanianie wapnia w przewodzie pokarmowym, zmniejszają wydalanie wapnia z moczem, biorą udział w procesie mineralizacji kości, wywierają korzystny wpływ na funkcję mięśni. Suplementacja witaminy D i soli wapnia jest powszechnie zalecana zarówno w zakresie prewencji, jak i w leczeniu osteoporozy będącej wynikiem podawania sterydów (GIO). Podawanie witaminy D ma znaczenie pomocnicze w prewencji osteoporozy i w jej leczeniu, albowiem bisfosfoniany są uznawane za „złoty standard" farmakoterapii GIO. W niniejszym opracowaniu przedstawiamy i uzasadniamy celowość podawania witaminy D w leczeniu GIO. Prezentujemy także obecnie obowiązujące rekomendacje wskazujące na potrzebę stosowania witaminy D w ramach strategii zapobiegania złamaniom.

INTRODUCTION

Glucocorticoids (Gcs) are widely used in the treatment of inflammatory diseases including skin, neurologic, pulmonary and rheumatic disorders. While this treatment is very efficient, the chronic use of systemic (oral and parenteral) glucocorticoid therapy is unfortunately associated with common adverse events (AEs) including secondary osteoporosis, osteonecrosis and muscle weakness. All of these adverse events are associated with an increased risk of fractures (1-3). Bone loss is potentially reversible with the tapering or cessation of glucocorticoid therapy and the withdrawal of Gcs treatment may lead to a reduction of fracture risk. A deleterious effect of Gcs on bone metabolism is caused by a direct inhibition of osteoblast differentiation and function, increased osteocyte apoptosis, secondary hypogonadism, negative calcium balance and myopathy (3). The elevated risk of fractures (long-term use of Gcs causes fractures in about 30 to 50% of patients) (1) and other adverse events such as obesity, insulin resistance, diabetes, cataracts and glaucoma, elevated blood pressure and cardiovascular diseases are similar to clinical symptoms of endogenous Cushing's syndrome (2). So far, Gcs-induced adverse events including osteoporosis remain under diagnosed and undertreated in many countries (4).

VITAMIN D AND CALCIUM

International (1, 4, 5) and Polish experts (6) routinely recommend Vitamin D and calcium supplementation in

the prevention and basic management of a primary (7) and secondary osteoporosis, including GIO (4).

Active metabolite of vitamin D, 1,25-dihydroxycholecalciferol increases intestinal calcium absorption, inhibits renal calcium excretion and regulates bone mineralisation. Due to pleiotropic role of vitamin D, low serum concentration of 25(OH)D (< 30 mg/ml) is associated with muscle weakness and atrophy with increased risk of falls (8, 9), osteomalacia, osteoporosis, respiratory infections, diabetes, elevated risk of cardiovascular diseases, autoimmune diseases, dental diseases and risk of cancer (8, 10). Low serum concentrations of 25(OH)D is often observed in elderly people (9, 11) and in patients suffering from rheumatoid arthritis (RA) and lupus (SLE) (12, 13). Most of these patients are at high risk of bone fractures because of the underlying disease and/or advanced age. Moreover, a number of patients with RA and SLE are treated with Gcs. Therefore, vitamin D supplementation in GIO prevention and treatment seems to be quite rational. The dosage of vitamin D should maintain serum concentration of 25(OH)D in the range of 30-50 ng/ml (11). Vitamin D is safe, is contraindicated in patients with hypercalcemia and sarcoidosis (14). Active metabolites alfacalcidol and calcitriol could be effective increasing vertebral BMD in GIO (1), but are not superior to native vitamin D and are not recommended for the prevention or treatment of GIO (1, 4, 5). It is worth noting that most studies and current guidelines advise that vitamin D supplementation should be combined with an adequate calcium intake (4-6, 14). Vitamin D plays an adjuvant role in the primary prevention and treatment, but bisphosphonates are considered to be the gold standard for the pharmacologic management of GIO (4, 5).

Decreased dietary calcium intake (< 400 mg/day) and/or low intestinal absorption, and/or increased urinary excretion (> 0.3 g/24 h) are causing secondary secretion of parathyroid hormone (PTH) and bone resorption (1, 3). The need for calcium and vitamin D supplementation may be particularly relevant in individuals over 65 years (1, 11, 14) and patients receiving long-term Gcs therapy (4, 5). Kanis et al. in the "European guidance" (7) recommend calcium supplementation in daily dose of 0.5-1.2 g and 400-800 IU of vitamin D for all older patients receiving anti-osteoporotic treatment. In majority of patients dietary calcium intake should be preferred. It was also shown in several studies, that calcium alone does not prevent bone loss neither in GIO nor in postmenopausal osteoporosis (1, 14). An adequate calcium supplementation combined with vitamin D is able to preserve BMD in GIO and is recommended for all patients receiving Gcs for 3 months or more (1, 4, 5). According to current evidence, not vitamin D and calcium, but anti-osteoporotic treatment with alendronate, etidronate, risedronate, zolendronic acid and teriparatide decreases rate of vertebral fractures (1, 4, 5). Therefore, in our routine management, anti-osteoporotic medication with bisphosphonates is used with parallel, or even prior to bisphosphonates, supplementation of calcium and vitamin D (1, 6, 14).

VITAMIN D AND MUSCLES

Glucocorticoid-induced muscle wasting is mostly associated with atrophy of fast-twitch muscle fibres (type II fibres). Gcs inhibit protein synthesis and accelerate protein breakdown. There is also some evidence, that Gcs may inhibit the anabolic response to insulin, down regulate Insulin-like Growth Factor-1 and stimulate production of myostatin – a muscle catabolic factor. This complex anti-anabolic action of Gcs leads to muscle atrophy, weakness and increased risk of falls (15).

In contrast to the Gcs action, the effects of vitamin D on muscle may be mediated by de novo protein synthesis, stimulating muscle cell growth (9, 16). Chronic vitamin D deficiency has been associated with malfunction of the musculoskeletal system, because of myalgia, myopathy, sarcopenia and increased risk of falls (16).

Vitamin D supplementation has a positive impact on muscle strength mostly in patients presenting low baseline serum concentration of 25(OH)D and in people over 65 years of age (9). It was found, that vitamin D supplementation in a dose of 700-1000 IU a day reduced the risk of falling among older individuals by 19% (17). In another study performed in community-dwelling elderly 191 women and 187 men, participants received either 1 μg of alfacalcidol/day for 36 weeks or were matched for placebo. After 36 weeks the reduction of the number of fallers reached significance in alfacalcidol-treated subjects with a total calcium intake of more than 512 mg/d (OR = 0.45, 95%) (18).

Based on meta-analysis of controlled trials, Bischoff-Ferrari et al. (16, 17) conclude, that vitamin D supplementation may improve muscle function and may reduce risk of falls.

It is therefore justified, that current guidelines for the management of GIO recommend prevention of falls and use of vitamin D as an important issue (4-6).

VITAMIN D IN CONTEMPORARY GUIDELINES AND RECOMMENDATIONS

Experts from the American College of Rheumatology (5) strongly (level A) recommend calcium intake (supplement + oral intake) of 1200-1500 mg daily and vitamin D supplementation (800-1000 IU) for all patients starting Gcs, for any dose or duration of treatment. During monitoring period serum 25(OH)D concentration should be measured once a year.

In Europe, the Joint IOF-ECTS GIO Guidelines Working Group (4) indicates that bone-protective therapy should begin at the very beginning of Gcs treatment. Dietary means should be used to obtain an optimal calcium intake with the use of supplements if necessary and an adequate vitamin D status (serum 25(OH)D measurements) should be maintained.

Among general measures, the IOF-ECTS Working Group (4) recommend fall risk assessments and good nutrition with calcium and vitamin D. During monitoring period, assessment of adherence to therapy, including calcium and vitamin D, at each visit, has been suggested.

Swiss rheumatologists (Schweizerische Gesellschaft für Rheumatologie) (19) persuade, that all patients exposed to a glucocorticoid (prednisone or equivalent) dose ≥ 5 mg per day for ≥ 3 months should receive 1000-1200 mg of calcium daily combined with 800-1200 IU of vitamin D. Rheumatologists in Hungary recommend calcium and vitamin D supplementation to all patients with GIO receiving anti-osteoporotic treatment (20). In the "Polish guidelines for the diagnosis and management of osteoporosis" (6), we recognize that the sufficient supply of calcium and vitamin D is the cornerstone of prevention and an indispensable element of pharmacological treatment. We also advise measurement of 25(OH)D serum levels in patients. All these recommendations are consistent with the IOF-ESCEO guidelines (4). We wish to add that simply getting more sun (if not contraindicated) seems to be the best natural way to achieve and maintain optimal vitamin D levels.

A note: Neither alfacalcidol nor calcitriol is approved for prevention or treatment of GIO in UE or USA (1, 5).

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