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*Lucyna Papierska, Waldemar Misiorowski, Michał Rabijewski, Piotr Dudek, Małgorzata Gietka-Czernel

Vitamin D status in patients treated with intravenous ibandronate – a cohort study

Stężenie witaminy D u chorych leczonych dożylnie ibandronianem – badanie kohortowe

Department of Endocrinology, Medical Centre of Postgraduate Education, Warsaw
Head of Department: prof. Wojciech Zgliczyński, MD, PhD

S u m m a r y

Osteoporosis is a social disease, which in individual cases leads to disability and generates high costs of the treatment of its complications. Its treatment before the fractures occur should be conducted in as great as possible group of patients. Therefore we need unambiguous standards for therapeutic action. We posses wide options of antiresorptic agents and bisphosphonates are the most important among them. However, for successful treatment of osteoporosis, proper supplementation of calcium and vitamin D is necessary. Polish guidelines recommend using of 800-1000 units in Autumn and Winter; in people older than 65 vitamin D3 should be administered all over the year. Patients with osteoporosis may need greater doses, also given twelve month a year. In Poland OTC preparations of calcium + vitamin D contain usually 200-400 unit of cholecalciferol, so provide the lowest recommended dose after taken at least two tablets per day for healthy adults. However, it may be an insufficient dose for people with osteoporosis, especially if they have additionally disorders of gastrointestinal tract and taking antiulcer drugs.

In 100 consecutive women with upper gastrointestinal tract disorders referred to our clinic for intravenous ibandronate treatment, which were at least six month before admission treated with calcium and vitamin D, we measured serum 25OHD3 concentrations. We found that only in 8 of them the concentrations were normal (i.e. > 30 ng/ml), so we qualified them to undertake the antiresorptic treatment. The average concentration of 25OHD3 in our group was 17.91 ng/ml (± 4.04), and in most cases (69%) was lower than 20 ng/ml. In ten women concentration was lower than 10 ng/ml and evident signs of muscle weakness were present. These women had the lowest BMD in the group and secondary hyperparathyroidism. Most of examined women were treated with 200-800 units of vitamin D per Day. Only 10 patients used 1000-2000 units daily – 8 of them had serum 25OHD3 in normal ranges.

The results of this simple study shows that doses used in Poland, derived mainly from compound preparations are insufficient for proper supplementation of vitamin D.

Key words: vitamin D, vitamin D deficiency, osteoporosis

S t r e s z c z e n i e

Osteoporoza jest chorobą społeczną, prowadzącą w indywidualnych przypadkach do niesprawności i generująca wysokie koszty leczenia powikłań. Jej leczenie w okresie przed wystąpieniem złamań powinno być prowadzone u jak największej grupy chorych, stąd potrzebne są jednoznaczne schematy postępowania terapeutycznego. Dysponujemy coraz szerszą paletą leków antyresorpcyjnych, wśród których najważniejsze miejsce zajmują bisfosfoniany. Niezbędnym warunkiem powodzenia terapii antyresorpcyjnej jest jednak zapewnienie odpowiedniej podaży wapnia i witaminy D. Zalecenia dotyczące suplementacji witaminy D w Polsce mówią o 800-1000 IU podawanych w okresie jesienno-zimowym, a u osób po 65. roku życia przez cały rok. Chory z niską masą kostną może wymagać dawek większych, również stosowanych całorocznie. Dostępne w Polsce bez recepty preparaty złożone, z wapniem i witaminą D zawierają najczęściej 200-400 IU cholekalcyferolu, co pozwala na zapewnienie podstawowego zapotrzebowania dla osoby zdrowej dopiero przy stosowaniu dwóch tabletek, a może być niewystarczające dla chorego z osteoporozą, szczególnie jeżeli towarzyszą jej choroby przewodu pokarmowego i przewlekłe stosowanie leków przeciwwrzodowych.

U 100 kolejnych kobiet z osteoporozą pomenopauzalną i chorobami górnego odcinka przewodu pokarmowego, kierowanych do naszej Kliniki w celu dożylnego leczenia ibandronianem, które przez co najmniej sześć miesięcy otrzymywały preparaty wapnia i witaminy D, oceniano stężenie 25OHD3 w surowicy. Stwierdzono, że u jedynie 8 z nich stężenie to było prawidłowe (tj. > 30 ng/ml), czyli uprawniające do podjęcia leczenia antyresorpcyjnego. Średnie stężenie 25OHD3 w grupie wynosiło 17,91 ng/ml (± 4,04), a w większości przypadków (69%) było niższe od 20 ng/ml. U 10 kobiet stężenie było niższe

niż 10 ng/ml i występowało ewidentne osłabienie siły mięśni. Kobiety te miały najniższą w badanej grupie gęstość mineralną kości i wtórną nadczynność przytarczyc.

Stosowane przez 90% badanych przez co najmniej pół roku dawki witaminy D wynosiły 200-800 IU. Jedynie 10 kobiet zażywało 1000-2000 IU dziennie i u 8 z nich stwierdzono prawidłowe stężenia 25OHD3. Wyniki tego prostego badania pokazują, że stosowane w Polsce dawki witaminy D3, pochodzącej często z preparatów złożonych o niskiej jej zawartości, są najczęściej niewystarczające dla prawidłowej suplementacji.

Słowa kluczowe: witamina D, niedobór witaminy D, osteoporoza

INTRODUCTION

Osteoporosis is a social disease, with serious individual and social consequences as well as high costs, therefore must be cured as efficiently as possible. Modern antiresorptive drugs provide powerful decrease of bone resorption, however for their proper action sufficient supply of calcium must be provided. Vitamin D increases calcium absorption, enhances bone mineralization and also is necessary for proper muscle function and strength (1, 2). Therefore the proper medication of osteoporosis must include vitamin D supplementation.

Synthesis of vitamin D in skin decreases with ageing, especially in countries with low exposition to a sun. In Poland from October to April skin synthesis of vitamin D is extremely low, and even in summer the widespread use of UV filters and low outdoor activity of most of our patients also lead to common D3 deficiencies (3). Dietary restrictions in patients suffering from gastrointestinal disorders contribute to this problem. Calcium absorption can be diminished by prolonged use of proton pump inhibitors. This class of medication was described as decreasing bone mineral density and increasing risk of hip fracture (4, 5).

Polish guidelines for vitamin D supplementation were recently provided by scientific research team, based on previously obtained epidemiological data on vitamin deficiency in Europe, including Poland. Vitamin D deficits were found in Winter in 90% women in OPTIFORD project (5) and in another studies it is estimated on 30-80% depending on the season and the cut-off point for 25OHD3 concentration (3). According to these data polish group of experts decided to recommend to take 800-1000 IU daily from October to April in all adults. For people who already have osteoporosis medication with vitamin D is recommended all over the year (3, 6). However, the most popular in Poland preparations of Calcium + vitamin D prescribing to people with osteoporosis contain mainly 200-400 IU per tablet. Ordered once or twice daily they don't provide sufficient dose of cholecalciferol. Moreover many patients omit daily use of these preparations as they are sure that the basic and sufficient antiosteoporotic medication is antiresorptive drug.

Hundreds of patients with osteoporosis and gastrointestinal problems are recently referred to our Clinic in order to treat parenterally with bisphosphonates or Denosumab. However, for reasons mentioned above we weren't convinced that sufficient doses of vitamin D were previously used by our patients.

MATERIAL AND METHODS

In order to asses status of vitamin D in "ready to antiresorptive treatment" patients we examined 100 consecutive postmenopausal osteoporotic women referred to our clinic for intravenous treatment with ibandronate. Taking the anamnesis we assessed their dietary intake of calcium, concomitant diseases and medication.

The excluding criteria were: existence of concomitant diseases and drugs affecting bone mass and calcium/D3 metabolism (hyperthyreosis, untreated hypothyreosis, hyperparathyreosis, liver cirrhosis, renal diseases, malabsorption syndromes, anticonvulsant drugs). Including criteria were: osteoporosis confirmed by BMD measurement of lumbar spine and femoral neck, with or without fractures, existing pathology of upper gastrointestinal tract, chronic treatment with proton pump inhibitors and at least 6 month medication with calcium and D3 preparations. We evaluated Ca, P, creatinine in blood and 24 urine samples as well as PTH-intact and 25OHD3 levels in blood.

RESULTS

Group characterization

The age of examined women was 57-78 yr, they were 6-30 yr after menopause. None of them currently used HRT, 17 was HRT users in the past (more than 5 yrs before hospitalization, for 0.5-5 yrs). BMI of patients were 23.2 (± 4.7).

The reason for intolerance of oral bisphosphonates were: gastritis (53%), esophagitis (18%) or peptic ulcer (29%).

Women were treated for 3-29 months with proton pump inhibitors: omeprasole (62 persons – 62%) 20-40 mg daily or pantoprasole (38 persons – 38%) 20-80 mg daily. 90 (90%) women used 200-800 IU vitamin D daily and only 10 (10%) 1000-2000 IU daily for 7-24 months (on average 12 months). Calcium intake in diet alone achieved 300-700 mg daily and supplied by medication 500-1000 mg daily (mostly 500 mg daily)

The bone mineral density was low in the whole group, all patient met WHI criteria for osteoporosis. T scores were on average -2.95 (± 0.62) for lumbar spine and -2.72 (± 0.95) for femoral neck. However these measurements were performed in various health centers, using Lunar or Hologic systems, so they weren't comparable.

37 (37%) of examined women had previous fractures: 20 wrist fracture, 16 vertebral fracture and 1 hip fracture. All the fractures occured at least one year before current hospitalization.

Vitamin D levels

Generally 25OH D_3 levels in all group were very low – on average 17.91 ng/ml (± 4.04). In 69 (69%) patients were even lower than 20 ng/ml. Only in 8 (8%) of examined women the levels of 25OH D_3 were proper, ie > 30 ng/ml (34.7 ± 2.9 ng/ml) (all of them used at least 1000 IU of vitamin D daily). 23 (23%) patients had "intermediate" concentrations of 25OHD3 – defined in literature as insufficiency not deficiency. 10 (10%) patients had 25OHD concentrations even lower than 10 ng/ml.

PTH levels

The levels of PTH were elevated in 10 patients with extremely low 25OHD3 concentrations (78.05 pg/ml ± 4.31). In the whole group however PTH was normal (53.35 pg/ml ± 23.55). We haven't found an evident correlation between PTH and 25OH D_3 ($r = -0.48$; $p = 0.11$).

Clinical outcomes

In 10 women with 25OHD_3 concentrations < 10 ng/ml we found an evident symptoms of muscle weakness and muscle cramps in anamnesis. They also have elevated PTH levels (78.05 pg/ml ± 4.31) and the lowest BMD among examined women (e.g.: T score L1/L4 -3.6 vs -2.95 in the whole group and T score f.neck -3.1 (± 0.42) vs -2.72 (± 0.95) in the whole group).

DISCUSSION

The treatment of osteoporosis is apparently easy, as we posses some antiresorptive agents with strongly confirmed antifracture efficiency. With addition of proper doses of calcium and vitamin D such medication should be convenient ant effective. Then why many patients don't achieve any BMD gain during therapy? Perhaps their supply with vitamin D is insufficient or we actually try to cure osteomalacia not osteoporosis?

Our date indicates that women with osteoporosis (more than one third of them with established osteoporosis with fractures) in fact for at least half a year hadn't take any efficient medication for improvement of bone density and resistance for fractures. Usage of very low doses of vitamin D don't lead to achieve proper 25OHD3 blood concentrations. Additionally, in patient with gastrointestinal disorder who are protracted users of proton pump inhibitors the calcium absorption can be diminished, as the acidic environment in the stomach facilitates the release of ionized calcium from insoluble calcium salts (7, 8). (However the further absorption takes place mainly in intestines and some data questioned the importance of previous ionization (3). The proper vitamin D action is particularly necessary in these patients for enhancing calcium absorption from gastrointestinal tract as well as for increase in tubular renal calcium reabsorption (9). Our data showed that in Poland we unfortunately use too low doses of cholecalciferol to achieve these goals. Strongly disturbing is observation, that among 100 women qualified to treatment with antiresorptive agents 10 actually have osteomalacia not osteoporosis. In such cases using of antiresorptive even could exacerbate disturbances of calcium metabolism. Possessing various excellent antiresorptic drugs we often forget about the simple, basic rule: there will be no success in antifracture treatment if patient is D_3 deficient.

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Address/adres:
*Lucyna Papierska
Department of Endocinology,
Medical Centre of Postgaduate Education, Bielański Hospital
ul. Cegłowska 80, 01-809 Warszawa
tel./fax: +48 (22) 834-31-31
e-mail: klinendo@cmkp.edu.pl