MODERN APPROACHES TO THE PREVENTION AND TREATMENT OF OSTEOPOROSIS IN RHEUMAOID ARTHRITIS

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Annotation:
This article presents methods of research on the causes of bone loss in patients with rheumatoid arthritis and the factors that increase it, as well as the criteria for its early detection and diagnosis.

Keywords: Osteoporosis, osteopenia, malabsorption, densitometry, rheumatoid arthritis, menopause, osteonecrosis, matrix.

Introduction

The goal of prevention and treatment of osteoporosis (OP) and other metabolic diseases of the skeleton is to reduce the risk of fractures and improve the mechanical properties of bone. The concept of increasing the amount of bone density expands the principles of treating OP. In this context, it is necessary to discuss the effect of calcium on bone tissue.

Calcium is necessary to ensure the bone formation phase in the process of continuous remodeling. It is not possible to directly calculate the optimal dose of calcium for specific patients. However, the body's need for calcium can best be determined as an adequate intake associated with minimal fracture risk.

Calcium is the main component of the food diet and fulfills its biological role both in the ionized state and in the bound state in the form of salts. The role of calcium in maximizing bone mass by age 20-25 is important.

Calcium enters the body only with food products. There are differences in calcium intake due to patients' individual dietary habits. Calcium absorption occurs throughout the intestine, the main part is absorbed in the duodenum and small intestine, in which active and passive absorption mechanisms are involved. Losses in the form of endogenous calcium secretion in the gastrointestinal tract are approximately 100 mg per day. Calcium absorption in young people can be as low as 30%. The main regulator of calcium absorption is vitamin D, but the absorption efficiency of calcium is never 100%. Vitamin D can increase calcium absorption by up to 20%. The main part of the absorbed calcium goes to the bones. During the day, the kidneys filter up to 9000 mg of calcium, about 98% of which is reabsorbed. This process is controlled by parathyroid hormone (PTH). 2% of unabsorbed calcium is determined in urine. Calcium excretion with daily urine should not normally exceed 200 mg. About 500 mg of calcium per day is required to carry out the process of bone formation, as much calcium is released into the plasma as a result of bone resorption [7]. The overall result is the maintenance

of calcium balance, that is, the amount that enters the body compensates for the losses. Calcium losses are increased in older people, leading to negative calcium balance and subsequent development of OP.

The total amount of calcium in blood serum varies between 2.25-2.75 mmol/l or 8.8-10.2 mg/100 ml. About 40% of calcium is associated with proteins, 10% forms complexes with phosphates, sulfates and citrates, and the remaining 50% exists in an ionized form. The concentration of ionized calcium is strictly controlled by the hormone PTG and vitamin D (1,25-dihydroxyvitamin D3). The regulation mechanism of calcium homeostasis is based on the feedback principle. But while it takes days to increase vitamin D production, PTG concentrations rise within minutes in response to a drop in blood calcium.

Studies have shown that high calcium intake reduces bone loss by an average of 1% per year in adults and older adults. There are indications that people with a high calcium intake have a lower incidence of bone fractures. Recker R. et al (2006) demonstrated that an additional 1200 mg of calcium per day reduced the incidence of vertebral fractures in postmenopausal women with low calcium intake [2]. The main mechanism of action of calcium is to suppress bone resorption by reducing PTG levels [11].

Currently, calcium preparations containing high doses of elemental calcium in the form of various salts are used to prevent OP. According to pharmacological standards, one tablet should contain calcium equivalent to 500 mg or 12.5 mmol of ionized calcium in the form of a salt or a combination of salts. Usually, such salt combinations ensure sufficient intake of calcium in the body. 1-2 tablets are prescribed per day, which covers at least 70% of the daily calcium requirement.

The use of vitamin D in the treatment of metabolic diseases of the skeleton, including OP, its deficiency or metabolic disorders occur in primary and secondary osteoporosis. The basis for the use of vitamin D in primary postmenopausal OP is hypoestrogenemia, which impairs intestinal calcium absorption and reduces calcium reabsorption through renal channels. For senile OP, vitamin D deficiency, malabsorption of calcium, suppression of the conversion of 25(OH)D3 to 1,25(OH)2D3 in the kidneys, which leads to the development of secondary hyperthyroidism.

Currently, three groups of vitamin D preparations are used for the prevention and treatment of OP:

1. Active vitamins D2 and D3 - ergocalciferol and cholecalciferol;
2. Structural analogs of vitamin D - taxistin or dihydrotaxysterol;
3. Active metabolites of vitamin D - 1a,25(OH)2D3 (calcitriol) or its analogue - 1a(OH)D3 (alfacalcidol).

Mechanisms of disturbance of calcium-phosphorus balance in RA patients are discussed. As we have shown, which group of patients develop mineral metabolism disorders. RA patients develop negative calcium balance due to increased urinary excretion within 6-12 months after

initiation of GKS therapy. At the same time, hypophosphatemia may develop, contributing to the development of secondary hyperthyroidism, which was found in 26.9% of RA patients. However, vitamin D deficiency, particularly 25(OH)D3, may play an important role in calcium absorption, which was found in 54.5% of RA patients. Prolonged and severe hypokinesia can lead to high excretion of calcium in the urine. It is in these groups of RA patients that it is possible to carefully monitor the state of calcium-phosphorus metabolism and use replacement therapy with calcium-sparing drugs and vitamin D.

Combined Calcium and Vitamin D Preparations in the Prevention of Calcium Metabolism Disorders in Patients with Rheumatoid Arthritis and Taking GKS

Vitrum Calcium + Vitamin D was administered to 18 patients with RA, whose clinical characteristics are shown in Table 1. The average age of the examined patients was 47 years (from 19 to 68), and the duration of the disease was 15.4±5.5 years. All patients received prednisolone from 7.5 to 25 mg per day, depending on the activity of the immune-inflammatory process. The duration of GKS-therapy was from 4 months to 10 years.

Table 1 Clinical characteristics of RA patients receiving Vitrum Calcium

Classification features	Classification	Number of patients
Uniform	Articulated	4
	Articula-vessiral	14
Activity level	Upper (III)	3
	Middle (II)	12
	Slow (I)	3
Immunological status	Seropositive	13
	Seronegative	5
Radiological stages	I - periarticular osteoporosis	1
	II - narrowing of the joint cavity	9
	III - several erosions	5
	IV - ankylosis	3

Total serum calcium was significantly lower in RA patients than in controls

The control group included patients with primary osteoarthritis (2.09±0.15 and 2.35±0.12 mmol/l, respectively, $p<0.05$). Calcium excretion in daily urine was slightly increased in four patients with 3-4 year disease duration and menopause duration not exceeding 3 years. A decrease in daily calcium excretion was observed in patients over 60 years of age who received GCS for more than 5 years and the duration of the disease exceeded 6 years.

Vitrum Calcium was prescribed in a dose of 2 tablets per day, which was equivalent to 1000 mg of elemental calcium and 400 IU of vitamin D3 (cholecalciferol). The peculiarity of this

drug is that it is in the form of calcium carbonate and has high bioavailability. Calcium obtained from oysters is absolutely safe, and its production technology involves a high level of purification from harmful substances such as heavy metals (for example, lead). As a result of continuous administration of Vitrum Calcium for 1.5 months, the serum total calcium level of RA patients was moderately increased compared to baseline (2.23±0.16 mmol/l). It should be noted that there were no statistically significant differences between the total calcium level in the blood of patients with RA and the control group. The initially decreased 24-hour urinary calcium excretion normalized by the end of 6 weeks of treatment. Hypercalciuria was not observed against the background of taking Vitrum Calcium. Other side effects such as allergic reactions were not recorded.

Indications for prescribing Vitrum Calcium in patients with RA are determined by:

1. Long-term acceptance of GKS;
2. High activity of the immune-inflammatory process at the beginning of the disease;
3. Disorders of calcium absorption in people over 60 years old.

Thus, in patients with RA, it is necessary to prevent disturbances of calcium metabolism in cases where it is not possible to completely cancel GKS. In this case, Vitrum Calcium is an effective tool for correcting the calcium balance if taken in a dose of 2 tablets per day. Vitrum Calcium has a stable and strengthening effect on the level of calcium in blood serum. Since side effects are not observed, the drug can be prescribed for a long time.

Active metabolites of vitamin D in the correction of calcium metabolism and bone metabolism in patients with rheumatoid arthritis

In recent years, worldwide interest in issues related to the homeostatic role of vitamin D in the human body has been increasing. In the last two decades, modern concepts of vitamin D have been formed, and it is not considered a vitamin in the classical sense, but a steroid prohormone that has a strong control over calcium metabolism after a series of changes in the liver and kidneys. Currently, it has been proven that 1a,25(OH)2D3 (calcitriol) has a stimulating effect on bone tissue formation processes, because osteoblasts have special receptors for vitamin D. Taking into account the multifaceted effect of vitamin D on bone remodeling processes, bone mineralization and maintenance of calcium homeostasis, preparations based on natural vitamin D and its synthetic analogues and derivatives have been developed for the prevention and treatment of OP. Here we are not talking about polyvitamin complexes, including drugs containing vitamins D2 and D3, but drugs used in clinical practice as monotherapy and complex treatment of OP and other skeletal metabolic diseases.

Two active metabolites of vitamin D are of particular importance in the prevention and treatment of OP: 1α,25(OH)2D3, chemically similar to D-hormone, known as calcitriol, and 1α(OH)D3 (alphacalcidol), a synthetic form of vitamin D. It is a derivative of 1a and is released under the trade name Alfa-D3. The mechanism of action of both drugs, which are active metabolites of vitamin D, consists in binding to specific receptors, which increases the

absorption of calcium in the intestine, stops the proliferation of parathyroid cells and reduces the production of parathyroid hormone, reduces the perforation of trabecular plates, enhancing bone regeneration, synthesis of bone matrix, increasing muscle strength, improving neuromuscular transmission, thereby reducing the risk of falls.

Alfacalcidol has several advantages over other vitamin D metabolites and natural forms. The main advantage of alfacalcidol is that it is actually a prodrug, that is, after entering the body, it turns into an active form, and by taking it twice a day, a stable concentration in the blood is maintained, which prevents the development of transient hypercalcemia. At the same time, the drug is convenient for long-term use in outpatient practice. Alfacalcidol overdose is unlikely, as the 25-hydroxylation of the drug slows down with an increase in the level of 1α,25(OH)2D3 in the blood. Also, alfacalcidol can be prescribed to correct phosphorus-calcium metabolism in patients with renal failure, since hydroxylation is not required in the renal parenchyma. Calcitriol has a more hypercalcemic effect, while alfacalcidol is considered to have a good effect on bone tissue.

19 patients with RA, whose complex therapy included prednisolone in doses not exceeding 10 mg per day and received for at least 6 months, and who were diagnosed with OP or osteopenia by densitometric examination, Alfa-D3-Teva drug It was prescribed in the morning and evening at a dose of 0.25 μg. On the 7-10th and 14-16th days of taking the drug, the total blood calcium level and daily calcium excretion were monitored. Hypercalcemia and hypercalciuria were not observed during the control period.

Analysis of biochemical markers of bone metabolism showed that in the group of patients with RA who received GKS (8.92±5.73 nM/nM creatinine, n=19) and in the group who did not receive GKS (8.06±4, 19 nM/nM creatinine, n=17) showed higher urinary excretion of DPD, and when compared with the control group, no reliable difference was found between the mean values. After 3 months of treatment with Alfa-D3-Teva, a significant decrease in urinary DPD excretion was noted in a group of patients with RA receiving GKS, but DPD levels remained high and did not reach normal values.

Thus, Alfa-D3-Teva can be used at a dose of 0.5 μg per day for at least 3 months to suppress bone resorption in RA patients treated with GKS.

Of the 22 RA patients whose blood levels of 25(OH)D3 were measured, 12 had a significant decrease. These patients were prescribed Alfa-D3-Teva at a dose of 1.0 μg per day for 3 months. The description of the group is given in the table below.

Table – 2 Characteristics of RA patients with low blood 25(OH)D3 levels (x ± SD)

Indicators	Patients with low RA 25(ON)D3 (n=12)	RA patients 25(ON)D3 (n=10)	P
Age	65,6±9,0	59,6+11,0	>0,05
Duration of the disease, years	8,2+5,8	6,9±4,1	>0,05
Activity, degree	1,9±0,79	1,9±0,8	>0,05

Stage I	3,0±0,85	2,4±0,7	<0,05
Functional joint deficiency, level	2,0±0,6	1,9±0,6	>0,05
Duration of menopause, years	15,9±7,5	10,5±9,4	>0,05
Number of patients receiving GKS	6	6	
SOE mm/s	33±17	28,4±18,3	>0,05
SRO, mg/ml	268±428	447±1014	>0,05
Calcium content in total blood,	1,99+0,14	2,15±0,24	<0,05
Daily excretion of calcium in urine, mmol/l.	3,3±2,7	3,9±2,3	>0,05
Inorganic phosphorus, mmol/l	1,35±0,12	1,26±0,05	>0,05
Daily excretion of phosphorus in	19,05±6,4	20±4,5	>0,05
T-criterion	-3,0±1,1	-3,29±1,5	>0,05
Z-criterion	-1,07±1,28	-1,5+1,25	>0,05

It was found that patients with significantly reduced levels of 25(OH)D3 in the blood were about 6 years older than patients with normal levels, and the duration of menopause was on average 5 years longer. RA patients with low blood 25(OH)D3 levels had higher levels of functional limitation (FNS) and lower total blood calcium levels. According to KM (calcium metabolism) indicators, both groups did not differ.

Table – 3 Dynamics of calcium metabolism in patients with RA under the influence of 3 months of therapy with alpha-calcidol (x ± SE)

Indicators	Before starting therapy (n=12)	After 3 months of treatment (n=9)	P
25(ON)D3} mmol/l	7,8±7,1	27,8±3,3	< 0,001
Calcium content in total blood, mmol/l	1,99±0,14	2,06±0,11	>0,05
Daily excretion of calcium in urine, mmol/day.	3,3±2,7	6,81±2,45	<0,01

Active metabolites of vitamin D in the correction of calcium metabolism and bone metabolism in patients with RA. In recent years, there has been increasing interest in issues related to the homeostatic role of vitamin D in the human body throughout the world. Over the past two decades, the modern understanding of vitamin D has evolved not as a vitamin in the classical sense, but as a steroid pro-hormone. After a series of changes in the liver and kidneys, it is able to exert a strong regulatory effect on calcium metabolism and perform important biological functions at the level of other organs and tissues. Currently, it has been proven that 1a,25(OH)2D3 (calcitriol) has a positive effect on the processes of bone tissue formation, because osteoblasts have specific receptors for vitamin D.

Taking into account the multifaceted effect of vitamin D on the processes of bone remodeling, bone mineralization and maintenance of calcium homeostasis, drugs for the prevention and treatment of osteoporosis (OP) and other bone metabolic diseases have been developed based on natural vitamin D and its synthetic analogues. It should be noted here that we are not talking about polyvitamin complexes, but about drugs that are used in clinical practice for OP and other bone metabolic diseases in the form of monotherapy or complex therapy.

In the prevention and treatment of OP, special attention is paid to the metabolite forms of two active vitamin D: 1a,25(OH)2D3, chemically similar to D-hormone and non-proprietary name calcitriol, and 1a(OH)D3 (alphacalcidol), a synthetic derivative of 1a , trade name Alfa-D3. The mechanism of action of these two drugs consists in binding to specific receptors, thereby increasing the absorption of calcium in the intestine, suppressing the proliferation of parathyroid cells and reducing the production of parathyroid hormone, increasing the synthesis of bone matrix and improving the quality of bone, increasing muscle strength, neuromuscular o It reduces bone resorption by improving mobility and reducing the risk of falls.

Alfacalcidol has several advantages over other vitamin D metabolites and native forms. The main advantage of alfacalcidol is that it is a pro-drug, that is, it is a substance that changes into an active form after entering the body, and when taken twice a day, it provides a stable blood concentration, which prevents the development of temporary hypercalcemia. Therefore, the drug is convenient for long-term use in outpatient practice. The probability of an overdose of alfacalcidol is low, because the hydroxylation of the drug at the 25-position slows down with an increase in the level of 1α,25(OH)2D3 in the blood serum. In addition, alfacalcidol can be prescribed to correct phosphorus-calcium metabolism in patients with renal failure, as it does not require hydroxylation in the renal parenchyma. Calcitriol has a more hypercalcemic effect, and alfacalcidol has a good effect on bone tissue.

19 patients with RA who received prednisolone at a dose of 10 mg/day for at least 6 months and who were diagnosed with OP or osteopenia according to densitometric examination, Alfa-D3-Teva 0.25 mcg morning and evening ordered. Total blood calcium level and daily calcium excretion were monitored on 7-10 and 14-16 days of drug administration. Hypercalcemia and hypercalciuria were not observed within the specified period.

Analysis of biochemical bone metabolism markers in RA patients receiving GKS (8.92±5.73 pM/tM creatinine, n=19) and those not receiving GKS (8.06±4.19 pM/tM creatinine, n= 17) showed increased excretion of DPD in urine. Compared with the control group, no significant difference was found between the average indicators. Against the background of therapy with alpha-D3-, in RA patients receiving GKS, a significant decrease in urinary DPD excretion was observed for 3 months, but the level of DPD remained high and did not reach normal values. Thus, the use of Alfa-D3-Teva at a dose of 0.5 μg/day for at least 3 months can suppress bone resorption in RA patients treated with GKS.

25(OH)D3 levels were significantly reduced in 12 of 22 RA patients. These patients were prescribed Alfa-D3-Teva at a dose of 1.0 μg/day for a period of 3 months. The description of the group is given in Table 55.

Patients with significantly reduced 25(OH)D3 levels were approximately 6 years older and had an average of 5 years longer menopause duration than patients with normal levels. RA patients with low 25(OH)D3 levels showed higher functional capacity limitation (FNS) and lower total blood calcium levels. According to the parameters of calcium metabolism, both groups did not differ.

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