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Contemporary Solutions to the Importance of Vitamin D in the Prevention of Osteoporosis in Postmenopausal Women

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Abstract: The review provides information on vitamin D requirements for normal bone mineralization, phosphorus-calcium and bone metabolism, as well as the pleiotropic effects of D-hormone; the methods of laboratory examination of vitamin D in blood serum are described, the norm, deficiency and deficiency criteria of vitamin D in the human body are given. The role of drugs for the treatment of osteoporosis and mainly vitamin D in complex treatment was analyzed in elderly patients with decreased bone mineral density (BMD) and microarchitectural disturbances. According to the results of the study, a combination of 70 mg of alendronic acid and 5600 IU of cholecalciferol in one tablet (Fosavance® forte) was shown to be acceptable in the majority of patients with a moderate intake of calcium from food without additional calcium supplements. The antiresorptive effect of alendronic acid and the sufficient amount of vitamin D contribute to the faster conversion of vitamin D to D-hormone and to a significant increase in the fractional absorption of calcium from the small intestine. Once-weekly use of Fosavance Forte is more effective in normalizing vitamin D levels and, in combination with calcium and vitamin D supplementation, leads to statistically significant increases in spine and hip BMD compared to conventional osteoporosis therapy. It is paid for the safety of medication use, in particular, the rare adverse events, as well as the possibility of prescribing therapy for osteoporosis immediately after a fracture. The achievements of modern medicine in the field of treatment and prevention of infectious diseases (use of antibiotics, vaccination), medical examination and prevention programs, as well as significantly increasing the level of surgical support for urgent and planned operations have increased significantly. population life expectancy, especially in developed countries [1, 2]. The growing number of elderly people in the population presents a new challenge to medicine: to maintain their activity, independence and quality of life as much as possible.

Key points: Methods of studying vitamin D in blood serum, vitamin D status: deficiency, deficiency, normal, extraskeletal effects of D-hormone.

Risk of decreased cognitive function with the development of arterial hypertension (AH), cardiovascular diseases (CHD) and cerebrovascular diseases with the development of atherosclerosis, heart failure, type 2 diabetes (DM), peripheral arterial diseases, dementia. , cancer, as well as falls and fractures. Depending on a combination of genetic predisposition, lifestyle, and risk factors, an older person is prone to some age-related diseases. In this regard, it seems necessary to identify risk groups for the development of certain diseases among elderly people in order to prevent and treat irreversible complications before they develop.

Low-traumatic fractures caused by osteoporosis are associated with acute and chronic pain, disability, limited movement to the point of complete immobilization, reduced quality of life, and, in some cases, complete social isolation. The lifetime risk of hip, radius, and vertebral fractures is comparable to the risk of cardiovascular disease [3]. Statistically, women over 45 with low-traumatic fractures due to osteoporosis have longer hospital stays due to other conditions (such as diabetes, myocardial infarction, and breast cancer). With the exception of lung cancer, low-

traumatic fractures remove more healthy life expectancy (adding DALYs (Disability-Adjusted Life Years)) than any other cancer [5, 6].

In the elderly, vitamin D deficiency significantly increases the risk of fractures [7-9]. This is because patients with vitamin D deficiency have poor bone mineral density (BMD), weak muscles, and unsteady gait; they are more likely to lose balance and fall [10, 11]. Some clinical guidelines for the treatment of osteoporosis, particularly in Canada and the United States, include routine determination of vitamin D levels since 2010 [12, 13], as vitamin D levels are associated with an adequate response to osteoporosis therapy. is important for [14, 15].]. Experts in the UK and Europe caution against mass screening of the population, but recommend testing serum vitamin D levels in people with bone disease [16, 17].

Methods of studying vitamin D in blood serum

There are about 40 metabolites of vitamin D [18]. Most of them, with rare exceptions, have very short half-lives and therefore are not of clinical interest [19]. The longest half-life for local vitamin D cholecalciferol (the time when the concentration of the drug in the body decreases by 50%) is 21 to 30 days [20, 21]. Biologically active D-hormone (1,25 (OH) 2D3) is destroyed after 4-15 hours [22, 23] and, unlike native vitamin D, determined in nmol/l, with pmol/l will be measured. Thus, the natural level of vitamin D most accurately reflects the body's supply of vitamin D obtained from food or supplements and formed by ultraviolet (UV) radiation. The result of the study of local vitamin D can be presented in the form of nmol / l and ng / ml, and a serum level of 2.5 nmol / l corresponds to 1 ng / ml [16].

Immunoassay methods are widely used for the determination of vitamin D [16]. Modern automated systems allow rapid testing of large quantities of samples almost on the same day of biomaterial submission. In addition to the need for standardization and calibration, among the disadvantages of the method, it is not possible to separate ergocalciferol (D 2) and cholecalciferol (D 3). However, D2 is usually almost never detected in humans, except when the patient takes D2 as part of a nutritional supplement or medication.

Tandem mass spectrometry allows isolation of D 2 and D 3 , but this method is more labor intensive and expensive. The number of samples analyzed each day is significantly lower.

Effects of vitamin D on the human skeleton

Vitamin D (cholecalciferol / ergocalciferol) is necessary for the development and maintenance of the functions of the musculoskeletal system throughout human life. In the early twentieth century, the discovery of vitamin D was associated with the treatment of rickets in children [24]. Ergocalciferol is a sterol of yeast and fungi produced by UV radiation and can enter the human body with plant products. Cholecalciferol is synthesized in the skin under the influence of UV rays and is also found in oily fish (salmon, mackerel, herring) [25]. Cholecalciferol and ergocalciferol are biologically inert and require hydroxylation in the liver and kidneys to convert to D-hormone (1,25(OH)2D), which mainly interacts with steroid hormones [26-28] and nuclear receptors in different ways. makes a secret. human tissues [29]. Vitamin D helps the absorption of calcium in the small intestine. In the absence of vitamin D, only 10–15% of calcium and 60% of phosphorus are absorbed from food, whereas with normal vitamin D levels, 30–40% of calcium and 80% of phosphorus are absorbed [29 , 30]. In addition, D-hormone stimulates calcium reabsorption in the kidneys [31]. By interacting with D-hormone receptors on osteoblasts, 1,25(OH)2D increases the expression of receptor-activating kappa-beta ligand (RANKL), which in turn promotes the differentiation of monocytes into mature osteoclasts [29-31] .

Extraskeletal effects of D-hormone

The widespread distribution of the D-hormone receptor in the human body [32] has led to a number of studies and hypotheses about the extraskeletal effects of vitamin D. American Endocrine Association in 2012, based on a systematic review of the literature. , published a formal opinion on the extraskeletal effects of vitamin D [33] (Table 1).

Thus, at present, the effect of vitamin D/hormone on bone tissue remains the most proven and clinically relevant.

Vitamin D status: deficient, deficient, normal

Due to the high prevalence of vitamin D deficiency in the elderly [7–9], conventional methods for determining reference intervals are not applicable in this age group. When making a decision about the need for therapeutic intervention, they pay more attention to information about the mineralization of bone tissue or a number of biochemical indicators.

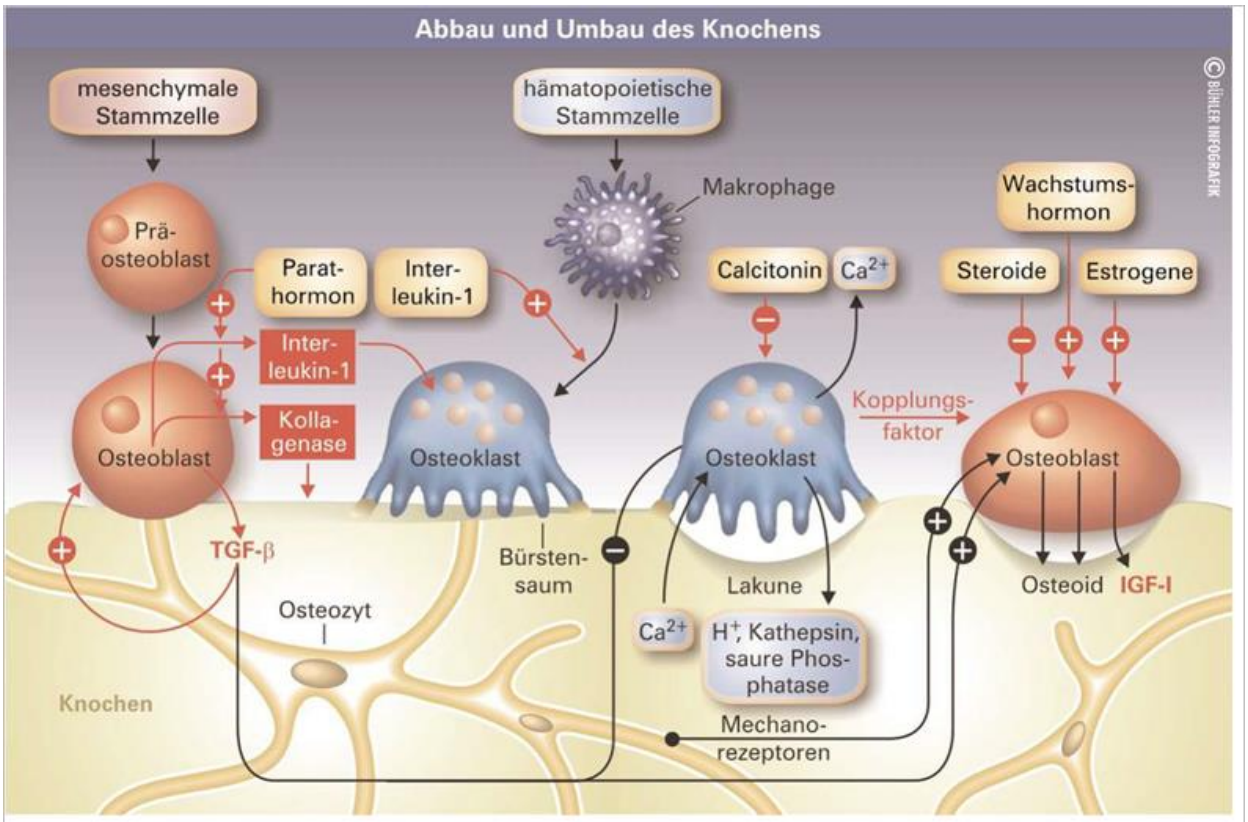

ABB. 1: OSTEOBLASTEN UND OSTEOKLASTEN sind zwei für den Knochen wesentliche Zelltypen. Sie stehen in enger Beziehung und sind für den ständigen dynamischen Knochenumbau (remodeling) verantwortlich [80].

With vitamin D deficiency, intestinal absorption of calcium and phosphorus is reduced, which leads to relative calcium deficiency and subsequent increase in parathyroid hormone (PTH) [35, 36]. In secondary hyperparathyroidism, the amount of calcium is maintained within normal limits due to the mobilization of calcium from bone tissue and an increase in phosphorus in the urine. Increased osteoclast activity mediated by PTH produces localized areas of weak bone and leads to a systemic loss of BMD as measured by dual-energy X-ray absorptiometry (DXA) with the development of osteopenia and osteoporosis. Phosphaturia, in turn, leads to a decrease in phosphorus levels. All these together create prerequisites for the destruction of mineralization of the skeleton [37]. In children, growth plates do not close and mineral does not accumulate, so vitamin D deficiency and skeletal mineralization disorders lead to bone deformities. And in adults, since the growth zones are already closed and the mineral component is obtained, osteomalacia is manifested by a decrease in BMD and may not be diagnosed. According to some reports, patients with severe vitamin D deficiency experience bone pain, muscle weakness, and may increase the risk of falls [37].

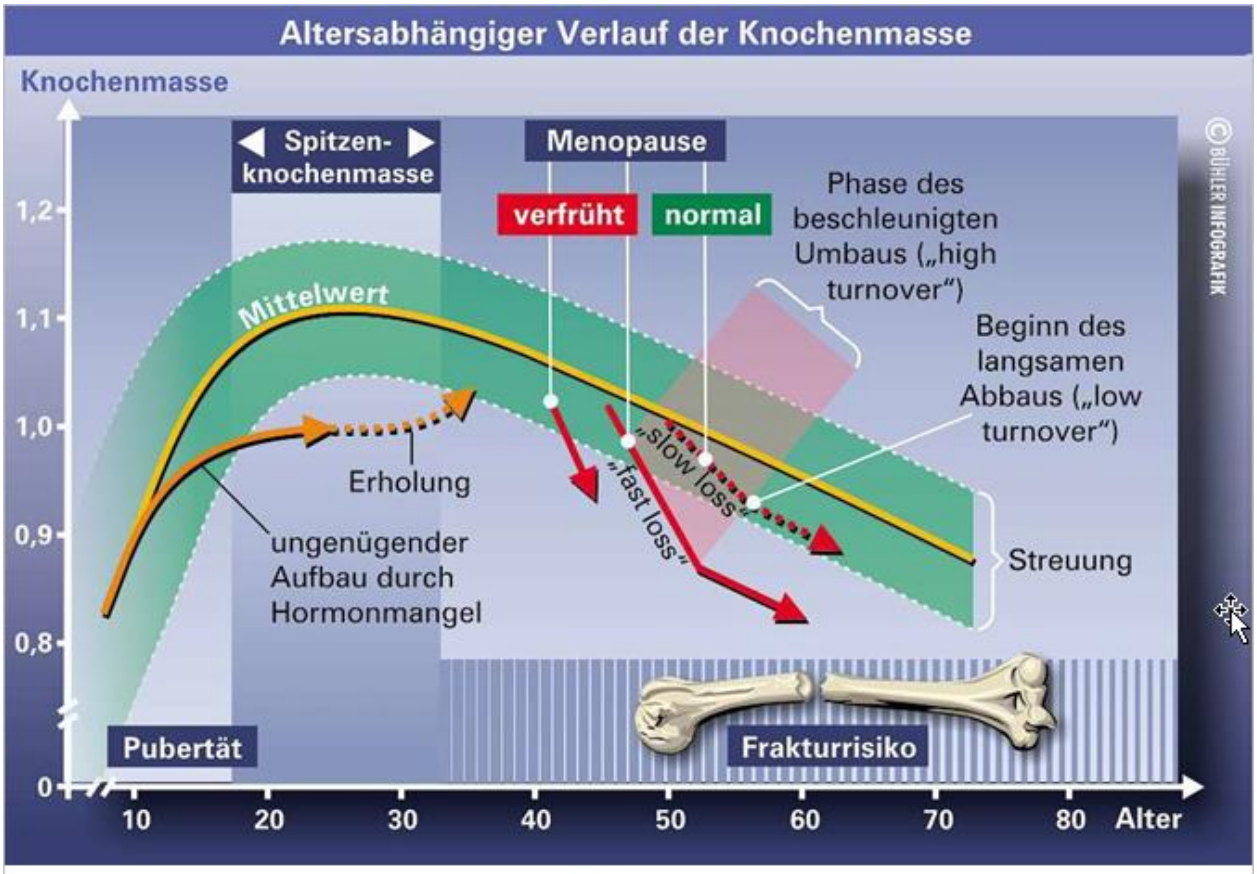

ABB. 2: EINE FRAGE DES ALTERS Während bei Kindern und Jugendlichen die anabolen Prozesse im Knochen dominieren, übersteigt im Verlauf des dritten Lebensjahrzehnts der Knochenabbau die Knochenneubildung [145].

Determining the critical level of vitamin D that must be maintained for optimal bone metabolism is difficult. Several studies have been conducted to determine the association of vitamin D levels with key indicators of bone mineralization and metabolism. Histomorphometric studies of iliac bones obtained from autopsies of 675 men and women showed impaired mineralization (large surface, area, and osteoid thickness) with serum vitamin D levels less than 25 nmol/L. Some changes in osteoid, although less pronounced, were observed when vitamin D levels were less than 50 nmol/L [38]. There is a relationship between vitamin D and PTH levels: when vitamin D levels are between 25 and 50 nmol/l, PTH levels decrease significantly and then reach a plateau [39]. Patients with vitamin D levels below 25 nmol/L have higher markers of bone turnover, as well as a plateau after this value [40].

However, the definition of vitamin D deficiency, insufficiency, and normal levels still varies in clinical guidelines and consensuses in different countries. Table 2 lists the latest recommendations published in Europe [41], UK [16] and USA [25]. There is also no consensus on the dosage of vitamin D for patients of different ages. When used prophylactically in postmenopausal women and elderly men, a daily dose of 600 to 2000 IU of vitamin D is recommended [16, 25, 41] or intermittent vitamin D intake (once a week, once a month, or (maximum) 1 time (100,000 IU) every 4 months). 4,000–10,000 IU of vitamin D per day is considered safe but is rarely recommended [25, 41]. Occasional high doses of vitamin D, particularly 300,000 IU once, may induce hypercalcemia, and 500,000 IU annually increases the risk of low-traumatic fractures [16, 25]. For established vitamin D deficiency, 50,000 IU of vitamin D once weekly for 6 [16] or 8 weeks [25] followed by a daily or intermittent maintenance dose is recommended.

In general, the intake of vitamin D does not depend on food intake and does not require any special conditions, including a certain amount of fat in food. However, almost all clinical recommendations

for the treatment of osteoporosis in postmenopausal women and elderly men do not include the use of vitamin D supplements as monotherapy for osteoporosis [12, 13, 17].

In postmenopause, there is a change in the processes of bone metabolism: accelerated bone formation and bone destruction [42], the latter significantly predominates, which leads to bone loss in each cycle of bone remodeling. Population-based studies have shown that elevated levels of a marker of bone formation (osteocalcin) and a marker of bone resorption may be independent predictors of rapid BMD loss and increased fracture risk, but these data have not been validated for use in daily clinical practice. [43–45].

Thus, drugs for the treatment of osteoporosis should affect bone turnover, while vitamin D complements the main therapy, affecting mineralization and phosphorus-calcium metabolism.

Treatment of osteoporosis with drugs

The decision to prescribe therapy for the prevention of low-traumatic fractures is made in the following cases: a fracture of a large bone or spine in a post-menopausal woman or a man over 50 years old, including with minimal damage, including a fall. own height; Fracture Risk Assessment Tool (FRAX) calculator (http://www.shef.ac.uk/FRAX/tool.aspx?country=13) for each age group with high probability of low trauma fractures or DXA data when osteoporosis is diagnosed [12, 13, 17]. Each of the three points listed has its own meaning. It is important that the absence of a decrease in BMD by DXA is not a contraindication for the initiation of osteoporosis therapy in patients with a low traumatic fracture history by FRAX or a high fracture risk for this age group.

The most commonly used antiresorptive drugs reduce the activity and lifespan of osteoclasts (bisphosphonates, BP) or reduce the formation of osteoclasts (denosumab) and accordingly destroy bone [46–51]. Antiresorptive drugs do not affect bone formation independently. However, the processes of bone metabolism in adults are interconnected, therefore, with a decrease in bone destruction, a decrease in bone formation is observed very quickly. In general, bone turnover in postmenopausal women returns to premenopausal levels.

As an alternative to the drugs listed above, anabolic therapy (teriparatide) can be used. In this case, bone formation increases significantly, but very soon there is an increase in the level of signs of bone destruction in the blood due to the conjugation of the processes of bone tissue formation and resorption [52]. Anabolic therapy allows the synthesis of new bone tissue, but there are limitations regarding the duration of use (1.8-2 years) and the cost of treatment, so, as a rule, antiresorptive therapy is prescribed after it.

The increased interest in strontium ranelate in the early years after its introduction was mainly due to a slight dissociation of bone turnover with increased bone formation and suppression of bone loss obtained in animal studies and one phase III study in humans. was [53-56] . In subsequent studies, these results were not confirmed, and strontium ranelate at a dose of 2 g per day showed a weak antiresorptive effect: a 14% decrease in the level of a marker of bone formation (N-terminal propeptide of type 1 collagen) (p). = 0.005) at 3 months, 18.8% at 6 months, and an overall reduction in bone resorption symptoms of 11% (p = 0.013) [57]. As an explanation of the drug's mechanism of action, bone density and weight have been proposed according to strontium content [58, 59]. 2012, 2013 The European Medicines Agency (EMA) introduced restrictions on the use of strontium ranelate. This drug is not recommended for patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease, poorly controlled hypertension [60], history of thrombosis and thromboembolism, including risk factors for thrombosis [61].

Active metabolites of vitamin D (alfacalcidol) and D-hormone (calcitriol) are widely used in the Russian Federation [27], but currently these drugs are not recommended as monotherapy for patients with osteoporosis [12, 13, 17].

Salmon calcitonin is also not recommended for long-term treatment of osteoporosis due to low efficacy and a slightly increased risk of cancer.

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