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Influence of drugs on vitamin D and calcium metabolism

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In the past, interactions between drugs and vitamin D have received only little or no attention in the health care practices. However, since more and more drugs are used for the treatment of patients, this topic is increasingly relevant. Several drugs can interfere with the vitamin D and bone metabolism. Drugs that activate the pregnane X receptor can disrupt vitamin D metabolism and vitamin D function. Beside this, the medication oriented supplementation of vitamin D can ameliorate the pharmacologic action of some drugs, such as bisphosphonates, cytostatics and statins.

Introduction

Vitamin D has long been known for its effects on calcium and bone metabolism. Vitamin D deficiency causes a lack of bone mineralization, which manifests as rickets in children and osteomalacia in adults.[1,2] However, it is now becoming increasingly clear that the "sunshine vitamin" has a much broader range of actions in the human body than believed before. Its physiological effects are not only limited to bone. Besides its well-known effects on calcium/phosphate homeostasis, vitamin D influences muscle function, cardiovascular homeostasis, the immune response and the nervous function.[3] A deficiency of vitamin D has been associated with muscle weakness and a high incidence of various chronic diseases such as cardiovascular disease, cancer, multiple sclerosis, and type 1 and 2 diabetes.[4]

Interactions between drugs and vitamin D have received only little or no attention in the medical and pharmaceutical world in the past. Since more and more drugs are used for the treatment of patients, this topic is increasingly relevant. As such interactions impact the health of the patient and the action and side effects of the drug, physicians and pharmacists should pay more attention to this fact in the future. As vitamin D deficiency leads to bone damage, it is particularly important to ensure an adequate vitamin D supply in cases of pre-existing osteoporosis or during long-term intake of drugs that promote the development of bone damage. Even after bone damage has already occurred, therapeutic use of vitamin D is often not considered.[5]

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A number of drugs are known to interfere with the vitamin D metabolism through activation of the pregnane X receptor and thereby causing vitamin D deficiency.[6,7] Through prevention or treatment of vitamin D deficiency, the risk of drug-induced bone damage, such as that caused by antiepileptic agents, glucocorticoids, anti-estrogens or antiretroviral drugs, can be reduced.[8] For adequate bisphosphonate response in osteoporosis therapy a sufficient vitamin D status must be ensured.[9] Initial studies indicate that vitamin D also has an effect on the lipid-lowering activity of statins (HMG-CoA reductase inhibitors) and the antibacterial effect of antituberculotic agents.[10,11]

The following article discusses the mechanisms of an interaction between vitamin D and the relevant drug groups. In many cases, monitoring of serum 25-hydroxy-vitamin D [25(OH)D] levels and compensation of vitamin D deficiency can contribute to reducing the risk of adverse drug reactions and/or improving the efficacy of various drugs.

Pregnane X Receptor Mediated Interactions

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxy-vitamin D [25(OH)D]. 25(OH)D is the major circulating form of vitamin D and is used to determine a patient's vitamin D status.[3] 25(OH)D is metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to its active form, 1α,25-dihydroxy-vitamin D [1,25(OH)$_2$D].[2] Both 25(OH)D and 1,25(OH)$_2$D are oxidized by hydroxylases (CYP24A1, CYP3A4) at position 24 of the side chain. The resultant metabolites are physiologically inactive and are excreted as acids following further metabolic stages. Expression of the 24-hydroxylases is partially dependent on the calcium and parathyroid hormone levels in the blood and partially regulated by 1,25(OH)$_2$D itself. In this way, the concentration of circulating 1,25(OH)$_2$D and thus both calcium and phosphate homeostasis in the blood is strictly regulated.

Various drugs can interfere in this balance through activation of the pregnane X receptor (PXR). In 1998 the pregnane X receptor (PXR) of mouse was first identified as a member of the nuclear receptor (NR) superfamily on the basis of its sequence homology with other NRs. Human PXR (hPXR) was found subsequently and named steroid and xenobiotic receptor (SXR) or pregnane-activated receptor.[12,68,69] The Pregnane X receptor (PXR) plays an important role in detoxifying xenobiotics and drugs. It is an

Table 1. Drugs that activate the pregnane-X-receptor (PXR) (selection)

PXR-Ligands	Examples
Antiepileptics	Phenytoin, Carbamazepine
Antineoplastic drugs	Cyclophophamide, Taxol, Tamoxifen
Antibiotics	Clotrimazole, Rifampicin
Anti-inflammatory agents	Dexamethasone
Antihypertensives	Nifedipine, Spironolactone
Antiretroviral drugs	Ritononavir, Saquinavir
Endocrine drugs	Cyproterone acetate
Herbal medicines	Kava kava, St. John's wort (Hyperforin)

intracellular receptor, which is expressed in the cells of the gastrointestinal tract, the kidneys and the liver and shows 60% homology with the vitamin D receptor in the DNA-binding domains. The pregnane X receptor can thereby bind to vitamin D-responsive elements (VDRE) at the DNA and, as a transcription factor, affect the expression of genes whose expression is normally regulated by vitamin D. PXR-ligands are structurally diverse and include a wide variety of pharmaceutical agents, such as antiepileptics, anti-inflammatory agents or antiretroviral drugs (**Table 1**). Commonly used herbal medicines can also activate PXR, such as St John's wort and kava kava.[6,7,12]

Through activation of the pregnane X receptor, expression of the 24-hydroxylases is upregulated, leading to increased degradation of 25(OH)D and $1,25(OH)_2D$ (**Fig. 1**). It is still unclear whether other effects of vitamin D are "imitated" by activation of the pregnane X receptor. In addition to the 24-hydroxylases, the ligands of the pregnane X receptor induce other cytochrome P450 enzymes, which are involved in the biotransformation of numerous active substances (e.g., CYP2C9 and CYP3A4).

Antiepileptic Drugs

It was documented more than 40 y ago that institutionalized children who were on multiple anti-seizure medications developed rickets that was resistant to normal vitamin D therapy.[13] As a result of their disease and the associated tendency to fall, patients with epilepsy are at higher risk of bone fractures. In addition, many antiepileptic drugs (AEDs) promote the pathogenesis of AED-induced bone disease, which is detected in up to 50% of patients undergoing long-term antiepileptic treatment. The risk of bone fractures is two to six times higher in patients with epilepsy than in the average population and comparable to that seen in patients undergoing long-term glucocorticoid therapy.[5,14-16]

AED-induced disturbances of bone integrity are mainly influenced by the type, dosage and duration of the antiepileptic therapy. A dose-dependent increase in the risk of fractures was particularly observed during therapy with carbamazepine, oxcarbazepine, clonazepam, Phenobarbital, phenytoin, primidone, and valproic acid. The risk of AED-induced bone disease was greater with inducers of cytochrome P450 (CYP), i.e., carbamazepine, phenobarbital, phenytoin and primidone, than with other antiepileptic agents.[15,16]

AED-induced disturbances of bone metabolism are usually accompanied by a fall in the 25(OH)D level, hypocalcemia, secondary hyperparathyroidism, and increased bone turnover with a decrease in bone density. In the pathogenesis of AED-induced bone disease, a central role is played by the pharmacokinetic interaction between the AEDs and vitamin D: the enzyme inducers carbamazepine, phenobarbital, phenytoin, and primidone can activate the pregnane X receptor, which then upregulates expression of the 24-hydroxylases, which can cause vitamin D deficiency.[7,12,16]

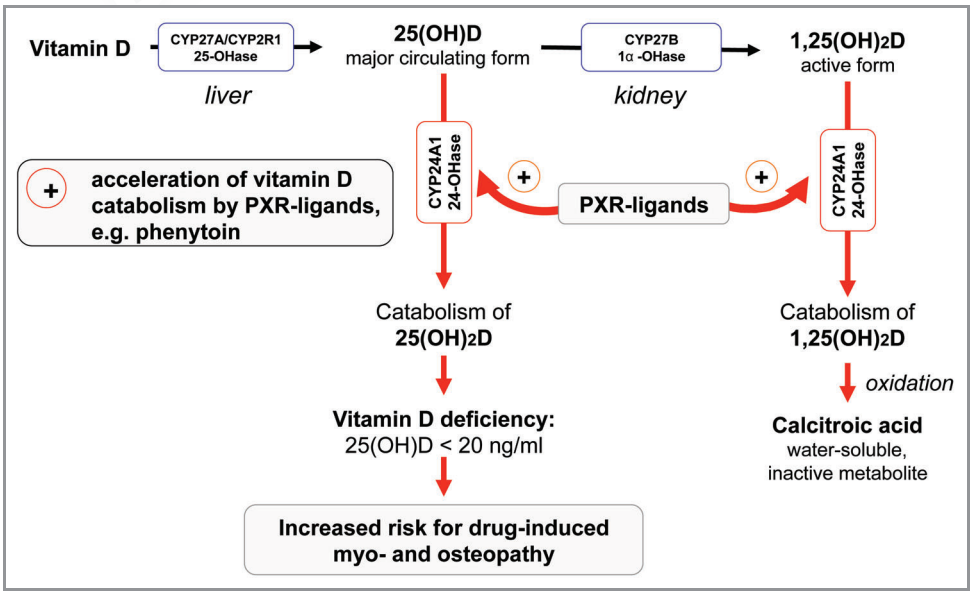

Figure 1. PXR-mediated drug-induced degradation of vitamin D (proposed model according to Pascussi, 2005 and Holick, 2006).

Table 2. Possible factors in the pathogenesis of AED-induced bone disease (selection), according to references 15 and 17

Probable mechanism	Antiepileptic agents (examples)
Increased vitamin D breakdown • Pregnane X receptor-mediated induction of microsomal enzymes in the liver; Results: decrease of 25(OH)D and 1,25$(OH)_2$D, increase of parathyroid levels, increased bone turnover	Carbamazepine, phenobarbital, phenytoin, primidone
Changes in the calcium balance • Reduced intestinal calcium absorption • Renal-tubular dysfunction, leading to increased renal calcium and phosphate losses	Phenytoin, Valproic acid
Change in the parathyroid hormone balance • Hyperparathyroidism • Reduced cellular sensitivity to parathyroid hormone	Various antiepileptic agents Phenobarbital*, phenytoin*
Change in the calcitonin balance • Inhibition of calcitonin secretion	Phenytoin
Direct effect on osteoblasts or osteoclasts • Inhibition of osteoblasts • Stimulation of osteoclasts • Inhibition of osteocalcin secretion in osteoblasts	Carbamazepine, phenytoin Valproic acid, carbamazepine Phenytoin
Increased bone turnover (irrespective of vitamin D and parathyroid hormone levels)	Valproic acid, phenytoin, carbamazepine
Vitamin K deficiency due to increased vitamin K metabolism (with influence on the vitamin K-dependent modification of matrix proteins)	Phenytoin*
Change in the sex hormone balance • Change in the synthesis or metabolism of sex hormones, increased levels of the sex hormone-binding proteins, modulation of aromatase activity	Various antiepileptic agents

*in animal studies.

AED-induced bone disease can also occur even with more modern AEDs, such as gabapentin, lamotrigine and levetiracetam, which have little or no effect on the activity of the cytochrome enzyme, as other mechanisms are probably also involved in the development of this bone damage (**Table 2**). Valproic acid-induced osteopathy, for example, cannot be explained by an induction of 24-hydroxylases, as valproic acid inhibits cytochrome P450 enzymes and is not a ligand of the pregnane X receptor.[8]

Prophylaxis with vitamin D is recommended for all subjects using AEDs.[7,15] Due to increased catabolism of vitamin D, higher than normally recommended doses (up to 7,000 IU per day) of vitamin D are required for optimal effect, particularly for those with low vitamin D levels, high risk of bone disease and/or with documented low bone mineral density (BMD). In general, in patients undergoing antiepileptic treatment, vitamin D status should be monitored once to twice annually, based on the serum 25(OH)D level (target: 30–60 ng/mL [75–150 nmol/L]). Any deficiency should be treated as required with targeted supplementation in order to prevent osteopathy. For those with documented vitamin D deficiency, treatment with 50,000 IU vitamin D/week for 8 weeks is recommended, followed by 50,000 IU of vitamin D every 2 to 4 weeks thereafter.[3,7,15]

Glucocorticoids

Glucocorticoid-induced osteoporosis is one of the most significant forms of drug-induced osteopathy. During long-term glucocorticoid therapy, 30 to 50% of patients develop osteoporosis. Disturbances of bone mineralization are therefore always likely during long-term glucocorticoid therapy, irrespective of the route of administration (oral, parenteral, inhalation); children, adolescents and postmenopausal women are particularly at risk. Impaired bone metabolism is also possible during treatment with low-dose or intermittently administered glucocorticoids.[18,19]

The fracture risk depends on the daily glucocorticoid dose administered. A retrospective data evaluation of a British patient collective showed that the risk of spinal fractures in patients who took less than 2.5 mg prednisolone equivalent daily (Cushing threshold) of a glucocorticoid, was already 55% higher than in patients not treated with glucocorticoids. In patients on doses of between 2.5 and 7.5 mg prednisolone equivalent daily, the risk of spinal fractures was already more than twice as high as that seen in control patients (relative risk [RR]: 2.59). If more than 7.5 mg prednisolone equivalent was taken daily, the risk of spinal fractures increased by more than 5-fold (RR 5.18) and the risk of hip fractures was 2.3 times higher than in patients who were not taking glucocorticoids.[20-22] According to current evidence, there is no safe threshold dose below which glucocorticoids have no effect on bone integrity.[18]

Various factors contribute to the development of glucocorticoid-induced osteoporosis: glucocorticoids increase osteoclast activity through raised expression of RANK (receptor activator of [nuclear factor kappa B] NFκB) ligand and a reduced production of osteoprotegerin and they reduce the development and differentiation of osteoblasts. Furthermore, glucocorticoids reduce the production of sex hormones, thereby reducing their positive effect on the bones. Glucocorticoids also reduce intestinal calcium absorption and concurrently increase renal calcium excretion; this can lead to a fall in serum calcium levels.[18] Glucocorticoids thus influence the function of osteoblasts and osteoclasts via various direct and indirect effects and some of these effects counteract those of vitamin D (**Table 3**). Some

Table 3. Effect of glucocorticoids and vitamin D hormone on bone metabolism (selection)

Effect on	Glucocorticoids	Vitamin D hormone
Osteoblasts	Differentiation ↓ Osteoblastogenesis ↓	Differentiation ↑ Osteoblastogenesis ↑
Calcium homeostasis	Intestinal absorption ↓ Renal excretion ↑	Intestinal Absorption ↑ Renal excretion ↓
Sex hormones	Production ↓	Production ↑
Bones	Absorption ↑	New formation ↑

glucocorticoids (e.g., dexamethasone) also cause increased degradation of 25(OH)D and 1,25$(OH)_2$D due to activation of the pregnane X receptor.

In patients with multiple sclerosis high-dose and short-term intravenous glucocorticoid regimens can cause a decrease in bone formation. Multiple sclerosis (MS) is generally associated with reduced bone mass and higher frequency of osteoporosis. The results of a small study with 41 women on glucocorticoid therapy, who were recently diagnosed with systemic lupus erythematodes, multiple sclerosis, rheumatoid arthritis or asthma bronchiale indicate, that 1-α-hydroxycholecalciferol (0,5–1,0 μg/d) treatment appears to be effective in preventing glucocorticoid-induced bone loss by reducing secondary hyperparathyroidism and stimulating bone formation.[23]

During long- and short-term glucocorticoid therapy, the vitamin D status should always be monitored, especially in patients with multiple sclerosis and bronchial asthma, by means of laboratory tests and any deficiency corrected by means of targeted supplementation, in order to reduce the risk of glucocorticoid-induced disturbances of bone metabolism.

Beyond that, clinical evidence suggests an important role of vitamin D deficiency as a modifiable risk factor in MS. Low circulating levels of 25(OH)D have been found in MS patients, especially during relapses, suggesting that vitamin D could be involved in the regulation of the clinical disease activity.[24] 1,25$(OH)_2$D, the most important form of vitamin D metabolically, possesses pronounced anti-inflammatory and immunomodulatory properties. In MS patients, vitamin D as an add on therapy to interferon β-1b has been shown to reduce MRI disease activity.[25]

Patients undergoing glucocorticoid treatment of bronchial asthma could derive a further benefit from vitamin D supplementation. Patients with low 25(OH)D levels suffered considerably more often from respiratory infections than patients with normal 25(OH)D levels.[26,27] In a study with children suffering from bronchial asthma, the association between 25(OH)D levels, lung function and the antiasthmatic medicine was investigated. The lower the 25(OH)D levels, the poorer the lung function values of the children and the higher the glucocorticoid doses with which the children were treated. Corticosteroid use and worsening airflow limitation were associated with lower 25(OH)D serum levels in asthmatic patients. A possible explanation for this is that 1,25$(OH)_2$D modulates the expression of cytokines with marked anti-inflammatory and anti-allergic properties (e.g., interleukin 10). In vitro studies also showed that vitamin D can enhance the immunosuppressive function of dexamethasone.[28]

Further studies are required, however, to investigate whether vitamin D supplementation in patients with bronchial asthma actually reduces the frequency of respiratory infections and improves the anti-inflammatory effect of inhaled glucocorticoids.[29]

Bisphosphonates

Bisphosphonates are among the most frequently prescribed drugs in osteoporosis therapy. In addition, they are used successfully in the treatment of Paget disease of bone, bone metastases of solid tumors, multiple myelomas and hypercalcemia of malignancy. Based on their structure, bisphosphonates can be divided into two groups: the amino-substituted bisphosphonates, alendronic acid, ibandronic acid, risedronic acid, zoledronic acid and pamidronic acid and the non-nitrogen-containing bisphosphonates, etidronic acid and clodronic acid.

Bisphosphonates accumulate at the bone surface and are particularly absorbed in regions with increased bone turnover from osteoclasts. Through the action of various mechanisms, they subsequently lead to apoptosis of the osteoclasts and thus inhibit bone resorption.[8,30] The main adverse effects of bisphosphonates include gastrointestinal disturbances (e.g., mucosal inflammation, diarrhea, flatulence), acute-phase reactions (flu-like symptoms, such as a feeling of exhaustion, muscle and bone pain), nephrotoxic complications (e.g., damage to the tubular system) and osteonecrosis of the jaw bones.

In patients with vitamin D deficiency and an insufficient calcium intake, bisphosphonate therapy without concurrent vitamin D supplementation can lead to hypomagnesemia and hypocalcemia, sometimes resulting in tetany and severe disturbance of bone mineralization. Hypocalcemia was mainly observed after intravenous administration of bisphosphonates such as zoledronic acid. Hypocalcemia can result in a rise in the parathyroid hormone level (reference range 12–65 ng/L) and secondary hyperparathyroidism. On the one hand, increased parathyroid hormone levels can impair the efficacy of the bisphosphonates on bone, as parathyroid hormone is a potent stimulator of osteoclast activity. On the other hand, in the bone micromilieu, parathyroid hormone increases the production of cytokines and growth factors, which can promote tumor growth.[8,31,32]

The effect of vitamin D status on parathyroid hormone levels and the efficacy of bisphosphonate therapy on bone density was investigated in a study with 112 postmenopausal women. Over half of the women had a vitamin D deficiency [25(OH)D $<$ 70 nmol/L]. Women with a serum 25(OH)D level $>$ 70 nmol/L had significantly lower parathyroid hormone levels than women with a vitamin D deficiency (mean 41 vs. 61.7 ng/L, $p < 0.0001$). In the women with low parathyroid hormone levels ($\leq$ 41 ng/L), the bone density in the hip region increased to a significantly greater extent during bisphosphonate therapy than in women with parathyroid hormone levels $>$ 41 ng/L (+2.5% vs. –0.2%, $p = 0.04$). After the women had been divided into two groups on the basis of their vitamin D status ($<$ or $>$ 70 nmol/L), there was still a difference in the increase in bone density in the hip area, although the difference was not significant ($p = 0.08$). The bone density in the lumbar spine was not affected by either the parathyroid hormone or the 25(OH)D level. These data suggest that optimal 25(OH)D serum levels may lead to further reduction in bone loss at the hip in patients on bisphosphonates.[33]

In a further study with 1,515 postmenopausal women with osteoporosis, who were treated with alendronic acid, risedronic acid or raloxifene, significantly poorer therapy results were seen with regard to a change in bone density at the hip and spine in patients with an initial vitamin D deficiency [25(OH)D $<$ 20 ng/mL]. Women with vitamin D deficiency had a

significantly higher risk of bone fractures than women with normal vitamin D status (adjusted odds ratio 1.77; 95% CI 1.20–2.59; p = 0.004). Optimal vitamin D repletion seems to be necessary to maximize the response to anti-resorbers in terms of both BMD changes and anti-fracture efficacy.[34,35]

In a recent study with 210 postmenopausal women with low bone mineral density, treated with bisphosphonates, patients with a mean 25(OH)D ≥ 33 ng/ml had a ~4.5-fold greater odds of a favorable response ($p < 0.0001$). 25(OH)D level was significantly associated with response: a 1 ng/ml decrease in 25(OH)D was associated with ~5% decrease in odds of responding (odds ratio = 0.95; 95% CI, 0.92–0.98; p = 0.0006). Patients with a mean 25(OH)D ≥ 33 ng/ml had a substantially greater likelihood of maintaining bisphosphonate response. This threshold level of 25(OH)D is higher than that considered adequate by the Institute of Medicine, arguing that higher levels may be required for specific therapeutic outcomes.[9] Optimal vitamin D status, defined by estimated maximum PTH suppression, does not occur until at least 25OHD levels ≥ 40 ng/ml.[36]

For optimal bone health and to avoid secondary hyperparathyroidism, many experts now take a baseline 25(OH)D level in the range of 40–60 ng/ml (100 to 150 nmol/L). In patients on bisphosphonate therapy to treat osteoporosis or on bisphosphonate treatment for cancer, the vitamin D status should be monitored once to twice annually (target: 25(OH)D 40–60 ng/mL) and any deficiency corrected as necessary by targeted supplementation (e.g., with 4,000–7,000 IU vitamin D daily, or 50,000 IU vitamin D/week for 8 weeks, followed by 50,000 IU of vitamin D every 2 to 4).

Antiretroviral Drugs

In persons infected with the human immunodeficiency virus (HIV), the osteoporosis risk is more than three times higher than in persons not infected with HIV.[37] The increased risk in HIV-infected persons is partially due to the fact that the HI virus impairs bone integrity. It has been shown that glycoproteins of HIV-1 (p55-gag, gp120) impair bone calcium utilization and reduce osteoblast activity. In infected macrophages, HIV-1 induces the production of macrophage colony-stimulating factor (M-CSF), which, together with the RANK ligand, increases osteoclastogenesis. Upregulation of proinflammatory cytokines [e.g., tumor necrosis factor α (TNFα)] can additionally induce osteoblast apoptosis and thus further increase the risk of viral damage to the bone cells.[38,39]

The risk of osteopathy is additionally increased by antiretroviral therapy. Disturbances of vitamin D metabolism, particularly an increased vitamin degradation due to induction of CYP3A4, appear to play a major role. Vitamin D deficiency is frequently observed in HIV-infected patients: in a study with 1,077 HIV-infected patients, 91% of subjects had a suboptimal calcidiol level and one third actually had severe vitamin D deficiency [25(OH)D < 10 ng/mL]. In this study, the risk of severe vitamin D deficiency was significantly increased by intake of the non-nucleoside reverse transcriptase inhibitor efavirenz.[37,40] In individuals infected with HIV, vitamin D deficiency has negative effects not only on the bones, but also on viral load and disease progression.[41]

Against this background, vitamin D administration in individuals infected with HIV appears appropriate, in order to reduce the risk of drug-induced osteopathy. Vitamin D may also reduce the mitochondrial toxicity of antiretroviral virostatic drugs, whose effects include muscle pain and lipid metabolism disorders.

Anti-Estrogens

The anti-estrogens include the following:

- aromatase inhibitors, such as anastrozole, letrozole, and exemestane,
- the estrogen receptor antagonist, fulvestrant and
- the selective estrogen receptor modulators, tamoxifen and toremifene.

All these active substances are used in the treatment of estrogen receptor-positive breast cancer. As aromatase inhibitors block estrogen synthesis and thus markedly reduce estrogen levels, treatment with these active substances also results in a severe reduction of the effect of estrogens on bone. Estrogens promote intestinal calcium absorption and bone mineralization; above all, however, they inhibit osteoclast activity. During aromatase inhibitor therapy, up to 50% of women report bone and muscle pain. Intake of aromatase inhibitors reduces bone density and increases the risk of bone fractures. Similar effects are likely following administration of a pure estrogen receptor antagonist; no data are yet available, however, on the long-term effect of fulvestrant on bones.[42-44]

Selective estrogen receptor modulators have estrogenic or anti-estrogenic effects, depending on the tissue. Whereas tamoxifen reduces the effects of estrogens in the breast, its effect on bone more closely resembles that of an estrogen receptor agonist and it shows a certain antiresorptive effect. Nevertheless, a decrease in bone density was observed in various studies during tamoxifen therapy, particularly in pre-menopausal women. Further side effects occurring in association with tamoxifen are bone and muscle pain and a rise in serum triglyceride levels.[45-47]

Aromatase inhibitor associated arthralgia limits adherence to therapy in breast cancer. The pathophysiology may involve vitamin D status. Vitamin D deficiency is associated with a syndrome of musculoskeletal symptoms with generalized non-specific musculoskeletal pain and stiffness, as well as impaired muscle strength and function that is similar to that induced by aromatase inhibitors therapy.[44] Hypovitaminosis D has been suggested as an underlying etiology in individuals with persistent, nonspecific musculoskeletal pain, comparable with the symptoms of osteomalacia.[48] In addition to musculoskeletal symptoms, vitamin D deficiency has been implicated in accelerated bone loss in women with breast cancer receiving aromatase inhibitors therapy.[49] A possible mechanism of AI-induced musculoskeletal symptoms and their improvement with vitamin D supplementation is that reduction in joint estrogen levels may unmask subclinical vitamin D deficiency. Estrogen increases activity of 1-α hydroxylase responsible for conversion of 25(OH)D to the biologically active $1,25(OH)_2D$.[50,51] In addition estrogen

increases expression of the Vitamin D receptor and VDR gene via activation of ERK 1/2 signaling pathway Increasing vitamin D substrate via higher doses may increase the active hormone 1,25-dihydroxyvitamin D with resultant reduction in joint symptoms.[52,53]

A prospective study with 290 women investigated the effect of vitamin D status on the occurrence of arthralgia during treatment with aromatase inhibitors, such as anastrozole, letrozole and exemestane.[39] At baseline, 90% of the women had a calcidiol value < 30 ng/ml (75 nmol/L). Despite vitamin D supplementation with 800 IU daily and, depending on the baseline value, sometimes with an additional 16,000 IU every two weeks, adequate 25(OH)D levels were only achieved in half the women within a three-month period. During the course of the study, there was an increase in joint pain (mean 1.16 points SD 2.66; $p < 0.001$) and the increase was significantly ($p = 0.02$) attenuated in those that reached concentrations of 25(OH)D of ≥ 40 ng/ml, with a lower risk of incident arthralgia [OR 0.12 (0.03 to 0.40)]. A target concentration of 40 ng/ml 25(OH)D may prevent development of AI-induced arthralgia but higher loading doses are required to attain this level in women with deficiency at baseline.[54]

In a pilot study the prevalence of suboptimal vitamin D status in 60 women initiating adjuvant therapy with letrozole for breast cancer was assessed, and determined, whether the supplementation of 50,000 IU vitamin D per week could reduce musculoskeletal symptoms and fatigue associated with aromatase inhibitors therapy. Baseline 25(OH)D levels were obtained, and women were started on letrozole. Four weeks later, women with baseline 25(OH)D levels ≤ 40 ng/mL were started on vitamin D supplementation of 50,000 IU per week. At week 16, after 12 weeks on high-dose vitamin D, 25(OH)D levels were measured. At baseline, 63% of women exhibited vitamin D deficiency [25(OH)D: < 20 ng/mL] or insufficiency [25(OH)D: 20–29 ng/mL]. 25(OH)D levels > 40 ng/mL were achieved in all 42 subjects who received for 12 weeks 50,000 IU vitamin D per week, with no adverse effects. Furthermore, the vitamin D therapy with 50,000 IU vitamin D/week resulted in clinically significant improvement in disability from joint symptoms.[55,56] This early data on vitamin D supplementation under aromatase inhibitors therapy look promising, but results from larger clinical trials are needed.

Cytostatic Agents

Emerging evidence in the literature suggests a high prevalence of vitamin D deficiency [as defined by serum 25(OH)D levels of < 20 ng/mL] as well as an association between lower 25(OH)D serum levels and higher mortality in breast cancer. The prognosis for patients with early-stage breast cancer was less favorable if their 25(OH)D levels were below 20 ng/mL.[57-59]

Santini and colleagues observed that 25(OH)D levels fell considerably further in breast cancer patients on anti-tumor treatment with anthracyclines and taxanes, so that it can be assumed that almost all breast cancer patients have a vitamin D deficiency.[59] A plausible hypothesis may be, that some of the antineoplastic drugs, such as taxol are ligands of the pregnan X receptor and thereby enhances the catabolism of 25(OH)D and $1,25(OH)_2D$, leading to vitamin D deficiency.[6,7,12] Vitamin D deficiency promotes in cancer patients the occurrence of inflammation of the oral mucosa (mucositis) and disturbances in the sense of taste (dysgeusia) during chemotherapy. According to case studies, mucocutaneous side effects (e.g., stomatitis) and dysgeusia, such as occurred in cancer patients during chemotherapy with docetaxel, carboplatin and trastuzumab (TCH regimen) or with fluorouracil, folic acid and oxaliplatin (FOLFOX6 regimen), was successfully treated with vitamin D supplementation.[60]

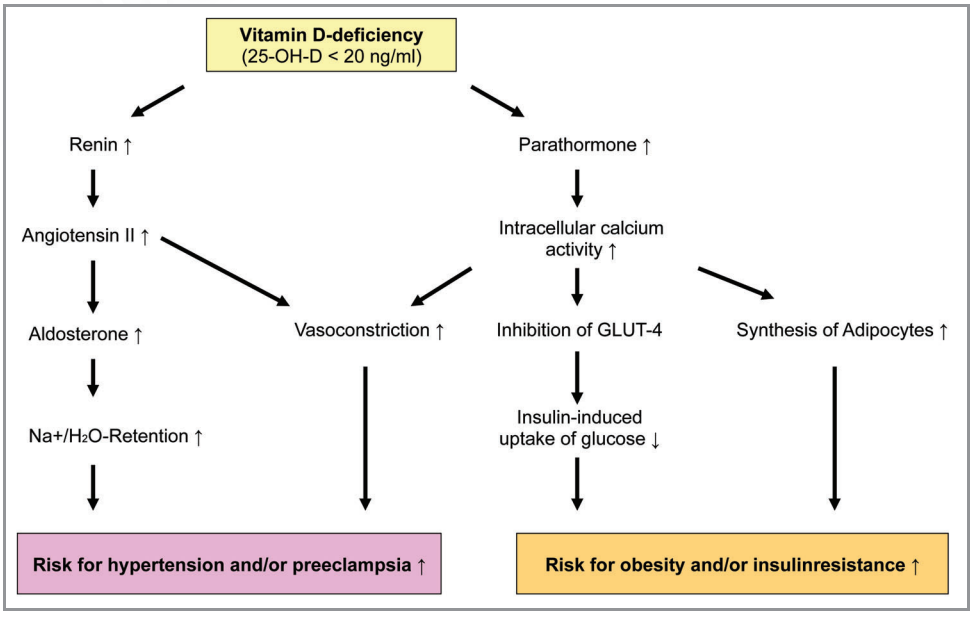

Figure 2. Vitamin D-deficiency and development of hypertension and insulin resistance (possible mechanisms).

If one considers that some cytostatic agents (e.g., methotrexate)[5] can also have a bone-damaging effect and breast cancer patients often undergo anti-estrogen therapy after chemotherapy, it appears appropriate to undertake regular monitoring of the vitamin D status in breast cancer patients.[5,48-56] In order to obtain a comprehensive picture of the vitamin D status of these severely ill patients, additional determination of the parathyroid hormone level can also be beneficial.

Antihypertensive Drugs

Vitamin D deficiency is an independent risk factor for hypertension. Epidemiological and clinical studies have long shown an association between inadequate exposure to sunlight, vitamin D deficiency and hypertension or increased plasma-renin activity. This is additionally underlined by the fact that mean blood pressure values are lower in summer than in winter. Persons with vitamin D insufficiency [25(OH)D $<$ 30 ng/ml] have a 3.2-fold higher risk of developing hypertension than persons with a good vitamin D status. A recently published systematic review and meta-analysis came to the conclusion that vitamin D produces a fall in systolic blood pressure of -6.18 mmHg and a nonsignificant fall in diastolic blood pressure of -2.56 mmHg in hypertensive patients.[61]

Animal studies have shown that vitamin D deficiency increases blood pressure through an interaction with the renin-angiotensin system. In genetically altered mice (so-called vitamin D receptor null mice), which cannot synthesize vitamin D, it was observed that renin expression, the activity of the renin-angiotensin system, and the production of angiotensin II were drastically increased. The mice developed hypertension, cardiac hypertrophy, and edema. These observations correlate with those made in normal mice, in which inhibition of vitamin D biosynthesis led to a rise in renin expression, whereas the injection of $1,25(OH)_2D$ suppressed renin expression.[62,63]

Other mechanisms contributing to the antihypertensive effect of vitamin D are the direct effects of $1,25(OH)_2D$ on endothelial function, parathyroid hormone secretion and insulin sensitivity (**Fig. 2**). Vitamin D and magnesium have a mutually enhancing effect on endothelial function and vascular reactivity and on many metabolic processes (e.g., insulin metabolism). The antihypertensive effect of magnesium has been demonstrated in numerous interventional studies. Although administration of vitamin D and magnesium alone to patients with hypertension (severity II or III) is not likely to normalize blood pressure according to the WHO criteria, supplementation of vitamin D and magnesium monitored by laboratory-diagnostic tests may nevertheless allow attempts to reduce the dosage of other antihypertensive substances (e.g., diuretics and ACE inhibitors). This could certainly reduce many side effects of the antihypertensive drugs used (e.g., disturbances of glucose tolerance).

HMG-CoA-Reductase Inhibitors (Statins)

The enzyme, 3-hydro-3-methylglutaryl coenzyme A (HMG-CoA) reductase, plays a key role regulating the synthesis of cholesterol. In-vitro studies have indicated that the activity of the enzymes responsible for cholesterol synthesis, 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase (HMG-CoA-reductase) and lanosterin-14α-demethylase and thus cholesterol synthesis, is inhibited by vitamin D and some of its hydroxylated metabolites [e.g., 25(OH)D]. A vitamin D deficiency therefore appears to be associated with increased activity of these enzymes.[64,65]

A pilot study with 63 patients investigated the effect of the serum 25(OH)D level on the lipid-modulating effect of atorvastatin. The study included 40 men and 23 women, who were hospitalized due to acute myocardial infarction and in whom therapy with atorvastatin (10–80 mg/day) was started, depending on their cholesterol and triglyceride levels. The effect of atorvastatin on cholesterol and triglyceride levels was significantly greater in patients with a 25(OH)D level between 30 and 50 nmol/L and in patients with 25(OH)D $>$ 50 nmol/L than in patients with a severe vitamin D deficiency (calcidiol $<$ 30 nmol/L).[65] The results of this study suggest that, in patients with acute myocardial infarction, cholesterol and triglyceride levels can only be adequately reduced by atorvastatin in the presence of a 25(OH)D level $>$ 30 nmol/L. The informative value of this study is, however, limited by the small number of participants.

Furthermore a vitamin D deficiency may be associated with myalgia in statin-treated patients.

In one study with 82 vitamin-D-deficient, myalgic patients, under statin therapy, 38 were given vitamin D (50,000 units/week for 12 weeks), with a resultant increase in serum 25(OH)D from 20.4 +/− 7.3 to 48.2 +/− 17.9 ng/mL ($p < 0.0001$) and resolution of myalgia in 35 (92%).[66,67] Further studies are required to investigate whether any association exists between vitamin D deficiency and statin associated myositis-myalgia. As vitamin D also influences cardiovascular risk through other mechanisms (e.g., reduced activation of the renin-angiotensin system), vitamin D status should also be monitored in high-risk patients undergoing treatment with lipid-lowering drugs, antihypertensive drugs, and cardiac drugs, irrespective of any potential influence on statin activity (preferably also taking parathyroid hormone levels into account) and any deficiency should be corrected by targeted supplementation, as required.

Antituberculotic Drugs

In 1924, in his novel "The Magic Mountain," Thomas Mann described the curative effect of sunlight on tuberculosis. He was inspired to write this work while his wife, Katia, was staying in a lung sanatorium in Davos in 1912. Prior to the discovery of antibiotics, periods spent in sun sanatoriums in high alpine regions were considered the standard therapy of tuberculosis. In so-called heliotherapy, the production of vitamin D is stimulated by UV light (UVB: 290–315 nm); 25(OH)D is transformed into $1,25(OH)_2D$ by the immune cells (e.g., macrophages, B- and T-lymphocytes). In addition to other effects on the immune system, $1,25(OH)_2D$ induces the synthesis of antimicrobial peptides, the so-called cathelicidins, which in turn kills the Mycobacterium tuberculosis.[3]

In a recent, multicenter, double-blind, randomized study, in addition to a standard therapy with antituberculotic drugs, 146 patients with newly diagnosed open tuberculosis of the lung received either 100,000 IU vitamin D_3 four times at 14-d intervals or placebo. The primary endpoint was the time from the beginning of the tuberculostatic therapy to the time when no further bacteria were detectable in the sputum. In patients in the vitamin D group, this took on average 36.0 d, in the placebo group 43.5 d; the difference was not significant, however ($p = 0.41$). In addition, the patients were genotyped with regard to certain variants of the vitamin D receptor (TaqI-variants tt, Tt, TT) and the effect of the vitamin D receptor genotype on the success of the vitamin D administration was investigated. This analysis showed that only patients with the tt genotype of the vitamin D receptor had derived any benefit from the vitamin D supplementation; this genotype occurs in less than 10% of the population. After 56 d, the mean serum calcidiol level in the drug group was 101.4 nmol/L and 22.8 nmol/L in the placebo group. It was notable that 97% of the subjects had a vitamin D deficiency at the beginning of the study.[11] Determination of vitamin D status and targeted vitamin D supplementation therefore appears generally advisable in patients with tuberculosis.

Conclusion

The efficacy and side effect rate of several drugs can be improved by vitamin D. With regard to pharmacokinetic interactions, mediated by the pregnane X receptor, it can be assumed that the active substances described in this paper are not the only ones that interact with the PXR-VDR system and can lead to vitamin D deficiency. During long-term medication, therefore, vitamin D status [serum 25(OH)D level] should generally be monitored and any deficiency corrected.[7] Measurement of vitamin D status and subsequently targeted, individual vitamin D supplementation is advisable for preventative and supportive reasons in many diseases and drug therapies.

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