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Highlights

- This article firstly reviewed the effects of vitamin D on drugs from the aspects of efficacy and pharmacokinetics
- The article suggests a general phenomenon that vitamin D improves the efficacy of drugs and reduces the adverse effects of drugs
- This article reviewed the effects of vitamin D through drug metabolizing enzymes and drug transporters.

Narrative Review

Effects of Vitamin D on drugs: response and disposal

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Abstract: Vitamin D supplementation and vitamin D deficiency are common in clinical and daily life. Vitamin D not only promotes calcium absorption and immune regulation but also changes drug effects (pharmacodynamics and adverse reactions) and drug disposal in vivo when combined with various commonly used clinical drugs. The extensive physiological effects of vitamin D itself may be the cause of synergism effects or alleviation of adverse reactions, and vitamin D affecting drug in vivo disposal through drug transporters and/or metabolic enzymes may also lead to changes in drug effects. In this paper, the effects of vitamin D combined with commonly used drugs were reviewed from the perspective of drug efficacy and adverse reactions. The effects of vitamin D on drug transport and metabolism were summarized and analyzed. It is hoped that more attention will be paid to vitamin D supplementation and vitamin D deficiency in clinical treatment and drug research and development.

Keywords: Vitamin D; Drug; effect; adverse reactions; pharmacokinetic

1. Introduction

Vitamin D (VD) is used worldwide as a calcium absorption promoter[1]. The guidelines for diagnosis and treatment of osteoporosis in various countries recommend daily use of VD to prevent the occurrence and development of osteoporosis[2, 3]. Moreover, VD deficiency (25[OH]D < 20 ng/ml [50 nmol/L])[4] is widespread. The degree of VD deficiency is affected by age, sex, nutritional status, and amount of sun exposure. Elderly individuals, children, and pregnant women are more likely to suffer from VD deficiency[5-7]. Thus, the difference in VD level among individuals is widespread(Table 1).

VD is a class of steroid derivatives that includes vitamin D_2 (ergotcalcitol) and vitamin D_3 (cholecalcitol). It is converted into 25-hydroxyvitamin D (25(OH)D) in the liver and then into an activated form 1,25-dihydroxyvitamin D (1,25(OH)2D, calcitriol) in the kidney. Activation of the VD system can activate vitamin D receptor (VDR) in the muscle and liver, which causes the VDR and retinoid x receptors (RXR) to form a heterodimer, regulate gene transcription and biological function, and also carry on the plasma membrane of chromosome receptor (mVDR) effect[9]. VD deficiency often causes muscular and skeletal diseases[10] and is closely related to diseases of the immune, nervous, and cardiovascular systems[11-13]. At the same time, VD can affect drug disposal in vivo through cytochrome P450 enzyme (CYP450) and transporter[14-17], so as to change the efficacy or adverse reactions of the drug[18]. In this paper, the effects of VD on the pharmacodynamics and pharmacokinetics of commonly used clinical drugs are summarized, and the relationship between VD and drug

efficacy and adverse reactions is clarified, so as to provide a theoretical basis for rational clinical use of drug therapy in VD-deficient/supplement patients.

2. VD and drug efficacy

2.1 Neurological Drugs

VD can regulate the development and function of the nervous system by affecting the production and release of neurotrophic factors, synthesis of nerve mediators, intracellular calcium homeostasis, and oxidative damage of nerve tissue[19], thus synergizing with multiple drugs. When combined with lamotrigine, VD significantly enhanced its antiepileptic effect[20, 21]. The anti-migraine effect of amitriptyline was enhanced and the number of attacks decreased after VD was adequately supplemented[22]. Even though VD has no effect on depression[23], when combined with the antidepressants clozapine[24] and fluoxetine[25], the antidepressant effect was significantly better than with a single medication, showing the synergistic effect and enhanced benefits of combined medication. In addition, VD alone did not influence Alzheimer disease, but patients with Alzheimer disease who took memantine plus VD (6 months) had a statistically and clinically related improvement in cognitive ability[26]. This may be due to the reduction of cortical axon degeneration in neurons exposed to amyloid beta-peptide or glutamate by memantine combined with VD[27]. VD also promoted the transcriptional changes of dopamine-related genes in some areas of the brain, increasing the release of dopamine[28].We speculate that the synergism between VD and nervous system drugs is not a simple superposition of drug effects but a systematic interaction.

2.2 Antineoplastic Drugs

In recent years, many studies have reported that the anticancer treatment of VD combined with a variety of chemotherapy drugs has been carried out in phase II or phase III clinical trials, some of which have achieved good clinical effects and can alleviate adverse reactions of chemotherapeutic drugs[29-31]. Anticancer drugs with enhanced or synergistic effects of VD include DNA-damaging agents (cisplatin, carboplatin, and doxorubicin), antimetabolic drugs (5-fluorouracil, cytarabine, hydroxyquinoline, and gemcitabine), and microtubule-interfering agents (paclitaxel and docetaxel calcium) [32], as detailed in Table S1. The synergistic mechanisms of VD and these drugs are different; some function by activating the apoptosis-signaling pathways (e.g., As_2O_3[33], metformin[34, 35], gemcitabine[36, 37]) and others by regulating the expression of tumor-suppressor genes (e.g., 5-Fu[38]) or by enhancing the oncology oxidative damage effect (doxorubicin[39]) and immune adjustment (5-Fu[40]). VD may also increase the anticancer activity of gemcitabine or irinotecan by inhibiting the expression of efflux protein or CYP3A4[41, 42].

2.3 Cardiovascular drugs

VD has a wide range of roles in the cardiovascular system[43]. VD deficiency not only leads to the occurrence and progress of many cardiovascular diseases[44] but also may mask the effect of therapeutic drugs, resulting in the appearance of no significant effects [45]. Supplementation of VD not only improves the clinical symptoms caused by VD deficiency but also may have a synergistic effect with drugs, which is manifested as an enhanced drug effect.

Although the antihypertensive effect of VD has not yet been confirmed[46, 47], it can produce synergistic effects with a variety of antihypertensive drugs, possibly because of the

role of VD in regulating the renin-angiotensin system (RAS) and reducing oxidative stress and the inflammatory response. VD combined with RAS-related antihypertensive drugs, such as enalapril[48-51], irbesartan[52], and losartan[53], demonstrated more significant antihypertensive effects in a rat hypertension model. Rat experiments showed that VD and the beta-blocker propranolol have synergistic antihypertensive effects through two different antihypertensive mechanisms[54]. Human trials have shown that VD can be used as a calcium ion antagonist as an adjuvant therapy for nifedipine. The combined application of the two agents results in a better antihypertensive effect, especially for the control of hypertensive crisis[55, 56]. VD has no effect on human insulin secretion or sensitivity[57], but some studies have reported that VD combined with hypoglycemic drugs have a synergistic effect. Combined application of VD and metformin can improve insulin sensitivity in the skeletal muscle of rats with diabetes mellitus type 2[58] and synergistically protect the liver of rats[59]. A case report of occult autoimmune diabetes in adults found that VD analogues and DPP-4 inhibitor Sigliptin improved beta-cell function and maintained good glycemic control in diabetic patients[60]. In addition, VD supplementation has been found in clinical trials to reduce the concentration of saturated atorvastatin and active metabolites ($P < 0.001$) and has a synergistic effect on cholesterol lowering with atorvastatin ($P < 0.005$)[61].

2.4 Hormone

As a hormone, VD in combination with progesterone or glucocorticoid enhances their physiological effects. First, the role of VD in combination with glucocorticoid in the control of asthma has been verified by many clinical studies. Compared with budesonide alone or

budesonide combined with salbutamol/formoterol, nebulized budesonide and VD significantly improved lung function in children, reduced airway inflammation, improved asthma control[62], significantly improved forced expiratory volume for 1 second (FEV_1)[63], reduced episodes, and reduced hormone use[64-66].

Second, both progesterone and VD are natural hormones known to have neuroprotective effects[67]. VD can alleviate ischemic injury synergistically with progesterone by regulating nerve inflammation, oxidative damage, and growth factors, especially by triggering the BDNF/TrkB/erk1/2 signal[68]. Combined treatment of progesterone and VD hormone can also activate mitogen-activated protein kinase, which has a neuroprotective effect, making the protective effect of progesterone on spatial memory and reference memory in rats superior to that of progesterone alone[69, 70].

2.5 Immunosuppressant

Nuclear receptor VDR and VD metabolic enzymes are widely expressed in all cells of natural and adaptive immune systems[71]. VD deficiency is associated with an increased risk of various autoimmune diseases and infectious diseases[72], and the combination of VD and clinical immunosuppressants (such as tacrolimus, cyclosporine, and avermectin A) can produce synergistic effects. Clinical studies have proven that VD combined with tacrolimus is superior to tacrolimus alone in the treatment of children with vitiligo[73], and VD can improve the clinical effect of avermectin A in the treatment of psoriasis[74, 75]. Moreover, VD can also enhance the effect of cyclosporine on the expression of dectin-1 and proinflammatory cytokines in immortalized human corneal epithelial cells and resist the stimulation of *Aspergillus fumigatus* or curdlan on cells[76].

2.6 Anti–hepatitis C drugs

The most effective antiviral therapy is currently recognized as long-acting interferon polyethylene glycol (PEG) interferon alpha (PEG-IFN alpha) combined with ribavirin, followed by common IFN alpha or compound IFN combined with ribavirin. Clinical studies have found that VD level and VDR gene polymorphism in patients with chronic hepatitis C are closely related to the response of patients to PEG-IFN combined with ribavirin treatment[77-79], and VD supplementation can enhance the effect of PEG-IFN/ribavirin on patients with hepatitis C virus (HCV) infection [80]. A meta-analysis of randomized effects showed that VD combined with PEG-IFN-alpha injection and oral ribavirin could significantly improve the viral response rate of hepatitis C at 24 weeks after treatment, and the additional use of VD also had a positive effect on sustained the viral response rate[81]. However, a retrospective study also found that 25(OH)VD level did not affect the efficacy of antiviral therapy on naive genotype 1 HCV-infected patients[82].

2.7 Antiplatelet Drugs

Antiplatelet drugs can inhibit the growth of platelet cyclooxygenase. Platelet resistance is a common clinical application problem of antiplatelet drugs. VD level and VD binding protein in vivo are closely related to platelet resistance. A study involving 503 patients found that the incidence of high-residual platelet reactivity (HRPR) increased significantly with the decrease of VD concentration in patients treated with adenosine diphosphate antagonists (such as tiglilo and clopidogrel)[83]. VD-deficient patients who carry the VD binding protein (DBP) G allele, especially in homozygotes, can experience an increased incidence of HRPR [84]. López-Farré AJ et al. analyzed the plasma of 19 patients with acetylsalicylic acid (ASA)

sensitivity and 19 patients with ASA resistance and found that all three subtypes of DBP increased in patients with aspirin resistance, which showed that DBP may be a new regulatory factor for ASA to inhibit platelet action[85].

3. VD and Adverse Drug Reactions

3.1 Nervous System Drugs

VD improved the effects of antiepileptic agents, the Parkinson's drug levodopa, and morphine on the liver, immune system, and nervous system. It was found that VD supplementation had significant protective effects on the formation of hepatic nodules, antioxidant enzymes, and DNA damage induced in hepatocellular carcinoma rats[86]. It also improved the development and behavior of autism-like behaviors in rats induced by valproic acid[87]. This may be because antiepileptic drugs could lower VD levels in the body, and VD supplementation may help improve symptoms caused by VD deficiency[88, 89]. Furthermore, cell experiments have shown that calcitriol significantly reduced the activity and proliferation of levodopa, an anti-parkinson drug, on neural stem cells by activating the PI3K signaling pathway and reducing oxidative stress[90]. VD also reduced the apoptosis of T cells induced by morphine through the production of reactive oxygen species and prevented the adverse effect of morphine on the immune system[91], without affecting the analgesic effect of morphine[92].

3.2 Antitumor Drugs

The improvement of adverse reactions of VD to antineoplastic drugs was mainly in reducing the incidence of adverse reactions, reducing bone loss, protecting the kidney, and alleviating drug-induced pain. VD intervention inhibited the production of inducible nitric

oxide synthase induced by nitrogen mustard, thereby alleviating local skin damage, enhancing tissue repair, and preventing bone marrow depletion[93]. It also alleviated kidney damage caused by cisplatin and doxorubicin by inhibiting fibrosis, apoptosis, and proliferation factors[94, 95]. Finally, VD also protected rat chromosome damage caused by doxorubicin in a dose-dependent manner[96]. In clinical practice, supplementation of VD significantly improved the concentration of serum 25(OH)D and reduced joint pain caused by letrozole[97]. In addition, a second-stage study found that VD analogues could improve pain induced by mitoxantrone[30].

3.3 Cardiovascular Diseases Drugs

VD deficiency is a risk factor not only for cardiovascular disease but also for adverse reactions of cardiovascular drugs. Supplementary VD improved the incidence and extent of adverse reactions of cardiovascular drugs (such as statins and antihypertensives) (Table S2). Many recent studies have found that VD deficiency increased the risk of statin-related MRSE[98-105]. Therefore, supplementation of VD could improve or prevent the occurrence of statin-related MRSE[102-104, 106] and alleviate the cardiopulmonary dysfunction[107] and migraine caused by simvastatin[108]. Moreover, VD supplementation in patients with statin myopathy seems to be an effective strategy to improve drug compliance and prevent cardiovascular comorbidities and mortality[109].

Telmisartan combined with VD analogues was shown to moderately improve kidney injury in mice with adriamycin-induced nephropathy, to inhibit the expression of bax/bcl-2 in podocytes and the effect of apoptosis, and to be more effective than single therapy[49]. In

addition, calcitriol has a protective effect on captopril-induced keratinocyte detachment and apoptosis[110].

3.4 Immunosuppressor

Nephrotoxicity is an increasingly prominent clinical safety issue of immunosuppressants such as cyclosporine and tacrolimus. Renal protection is particularly important during drug administration[111, 112]. Compared with single-drug therapy, tacrolimus combined with VD could effectively alleviate renal tissue damage in IgAN rats through the immune response and NF-kappa B/TLR 4 pathway[113], and VD could reduce the expression of transforming growth factor–b1 and Smad signal transduction[114] and alleviate cyclosporin-induced nephropathy[115]. Moreover, VD can prevent cyclosporin-induced alveolar bone loss in rats and restore the production of relevant inflammatory mediators to normal levels [116].

In addition, VD could significantly reduce the degree of apoptosis of primary hippocampal cells induced by dexamethasone and the occurrence of cognitive impairment and severe depression induced by glucocorticoids in rats[70]. It could also improve the resistance of dendritic cells induced by glucocorticoids by influencing metabolic pathways such as lipid, glucose, and oxidative phosphorylation and responding to the production of reactive oxygen species [117]. It may also inhibit the cytotoxicity of dexamethasone and induced apoptosis[118].

3.5 Other drugs

Gentamicin (GM) is an aminoglycoside antibiotic widely used in the treatment of infected patients, but its associated oxidative stress and side effects of renal injury limit its

long-term clinical application[119-121]. Park JW et al.[122]found that VD analogues prevented GM-induced kidney injury by inhibiting inflammation and fibrosis of kidney tissue in rats. VD combined with GM resulted in decreased systolic blood pressure, increased urine volume, and increased glutathione in AKI rats[123].

Alendronate sodium combined with VD could reduce the side effects of kidney injury. Alendronate sodium/calcitriol complex enteric-coated tablet (Maxmarvil) could minimize the side effects of alendronate sodium, reduce the harm to the esophagus and gastrointestinal mucosa, and improve the tolerance of clinical medication[124]. Some studies showed that VD deficiency was a potential risk factor for nephrotoxicity induced by angiocontrast agent diatrizoate or gadoterate meglumine[125].

In conclusion, VD can synergize with 39 kinds of drugs and alleviate 21 kinds of adverse reactions. We tried to explore the reasons for this phenomenon. Except for the broad physiological role of VD itself, which is the main reason for increased drug efficacy and reduced adverse reactions, for example, the regulatory role of VD on the immune system and the inhibition of oxidative stress may also be important ways for VD to increase drug efficacy[126, 127]. In addition,by searching the database(https://db.yaozh.com/targets),we found that 31 of the 39 synergistic drugs (80%) were metabolized by CYP: CYP3A4 participated in the metabolism of 26 drugs, and 21 drugs had a protein binding rate of more than 90%. Of these 21 drugs, 18 (86%) were metabolized by CYP (Table S3). Therefore, we speculate that VD may affect the efficacy of drugs by altering their pharmacokinetic behavior.

3.6 Vitamin D supplementation during medication

In the process of drug development and marketing, healthy subjects and targeted patients are the main subjects and VD levels in this group of people are often normal. Current guidelines suggest that 400–800 IU/day of VD can meet the needs of most healthy people, with a maximum recommended intake of 4000 IU / day[128, 129]. However, when VD is used in combination with other drugs during clinic, the amount of VD may differ from the recommended dosage.

In the literatures we summarized (Table S4), there were 23 drugs (31 articles) reported on the combined use with VD in patients. Among them, 23/31 studies used VD(cholecalciferol), otherwise calcipotriol (topical), calcitriol or doxercalciferol. Seven studies found that the incidence or severity of adverse reactions decreased when four drugs were combined with VD (two studies 800 UI / day, two 2000IU / day, and one 3333IU / day, a topical calcipotriol); 16 studies found that VD could increase 13 drugs' clinical efficacy (four studies 200IU-1000IU / day, eight studies 1000-2000IU / day and two 5000IU / day);The dose of vast majority studies (14/19) was greater than the 400-800 UI / day which is recommended by the guidelines. What's more, six studies reported no change in efficacy of 6 drugs combined with VD, two studies used vitamin D3 (dose 2800UI / day and 4000UI / day), and other studies used calcitriol, calcifediol, and doxercalciferol, respectively. It can be seen that during clinical medication, drug interactions may also occur at the doses recommended by the guidelines, although they are less likely to occur. From another perspective, although VD can increase the efficacy of the drug or reduce adverse drug reactions, large doses do not ensure that VD can achieve this effect, but VD deficiency is likely to lead to treatment failure or increase adverse drug reactions, as drug development is based on groups with normal VD

levels. Therefore, VD supplementation to adjust the level of VD in the body to the normal level is very necessary for drug treatment, and if patients/doctors want to increase the efficacy of the drug through the combination of VD, they need to adjust the dose according to the situation of different drugs..

4. Effects of VD on Pharmacokinetics of Drugs

The field of pharmacokinetics mainly studies the dynamic changes of the body's drug disposition. This includes drug absorption, distribution, biochemical transformation (or metabolism), and excretion in the body. This process is affected by many factors. We found that VD could change the pharmacokinetic behavior of many drugs (Table 2). For example, cefdinir and cefadroxil[130], JBP 485[131], digoxin[132, 133], and adefovir dipivoxil drugs were affected by drug transporters[134]; midazolam[135] and mycophenolic acid[136] through metabolic enzymes; and simvastatin[137] by both drug transporters and metabolic enzymes(Figure 1).

4.1 Effects of VD on Drug Transport

Drug transporters are special proteins that transport endogenous or exogenous compounds across cell membranes, which mainly include the solute carrier family (SLCs; e.g., organic anion transporting polypeptides, OATPs; organic anion transporters, OATs; apical sodium-dependent bile acid transporter, ASBT; proton coupled transporter, PCFTlate, etc.) and the ATP-binding cassette (ABC) transporters (P-glycoprotein; multidrug resistance proteins, MRPs; breast cancer resistance protein, BCRP). They are widely distributed in the liver, small intestine, kidney, brain, and other tissues and organs and can regulate the

absorption, distribution, metabolism, and excretion (ADME) of substrates and endogenous substances and ultimately change their exposure in the circulatory system and the tissues[138]. VD could affect various drug transporter expression and activity[139], leading to changes in the pharmacokinetic behavior of drugs.

4.1.1 The Solute Carrier Family

VD could down-regulate the expression of organic anion transporters OAT1 and OAT3 in the kidney by activating protein kinase C(PKC)[140-144] and reduce their transport capacity and decrease the clearance of substrates (JBP 485, cefdinir, and cefalexin). Therefore, plasma concentration and AUC were significantly increased, and the exposure in vivo was increased[130, 131].

VD could up-regulate the expression of ASBT(SLC10A2) in the intestines and kidneys of rats by activating the VDR/RXR heterodimer, increase the absorption of cholylsarcosine[144, 145], and induce the FXR effect secondary to increasing the expression of FXR, SHP, Osta Bsep, and MRP 3 in rats[146].

Although studies have been conducted on the relationship between VD and organic anion transport polymorphic OATP, PCFT(SLC46A1), and peptide transport protein rPepT1 (SLC15A1), the regulatory role of VD remains unclear. For OATP, the expression of OATP1A2 in human small intestinal Caco-2 cells increased after incubation with VD[16]. However, the pharmacokinetic behavior of fexofenadine and the expression of OATP1A2 and OATP2B1 in duodenum did not change in healthy volunteers after oral VD[147]. VD also up-regulated PCFT expression in Caco-2 cells[16] and 3H-labeled folic acid cell uptake in a

dose-dependent manner[148], but not in VDR-/- mice and healthy volunteers[147, 149]. VD down-regulated the expression of rPepT1 in the kidney, duodenum, and proximal jejunum of rats[143, 144] but enhanced the transport activity or had no effect (transport substrate glycocreatine, cefdinir and cefadroxil)[130, 150].

4.1.2 The ATP-Binding Cassette Transporters

VD could significantly induce the expression and activity of p-gp (also known as multidrug resistance protein 1, MDR1; ATP-binding cassette sub-family B member 1, ABCB1; Table 3). VD induced the mRNA and protein expression of Mdr1a in rat brain, small intestine[144], liver[146], and kidney[143] by binding the VdR/RXR alpha heterodimer to multiple VD response elements (VDREs)[151]; increased the removal of P-gp substrates (NBD-CSA, the fluorescent P-gp substrate, and quinidine) in brain and kidney[152, 153]; and reduced the exposure of digoxin to blood and brain[132, 154]. In addition, VD induced the expression of MDR-1 and P-gp in various cell lines, increased the translocation of digoxin, and decreased the accumulation of 5 (and 6)-carboxy-20, 70-dichlorofluorescein[15, 17, 155].

Some studies have found that daily supplementation of vitamin D3 (1000 IU) in healthy subjects did not cause the p-gp–mediated interaction with digoxin; rather, it may have been caused by the basically unchanged plasma 25(OH)D_3 level (15.4±3.7 and 14.4±3.6 ng/mL, respectively)[133]; It may also may because of the difference in VDR expression in different species or tissues. For example, VD down-regulated the expression of P-GP in multidrug-resistant leukemia Jurkat/ADR and K562/ADR cell lines[156] and in rumen, jejunum, and liver of sheep[157] but had no effect on the expression and activity of P-gp in

the duodenum of rats[150]. The expression of P-gp in different cell lines is also different, leading to different effects of VD on P-gp in different cell lines. For example, the effect of VD on MDR1 mRNA in LS180 cells is more significant than that in Caco-2 cells[158] and is stronger in LS174T cells than in HepG2 cells[159].

VD could regulate MRP 2, 3, and 4. 1,25(OH)2D3 treatment promoted oral absorption of adefovir dipivoxil by inducing the function of MRP 4 in the basal side of the intestine of rats[134], which has been verified in in vitro cell experiments[150, 160]. VD or LCA (VDR agonist) up-regulated the expression of Mrp-3 in colon (not liver) and colorectal adenocarcinoma McA-38 cells in mice[161]. However, it has also been reported that 4 days of intraperitoneal injection of 1,25(OH)2D3 (0-2.56 nmol/kg/d) corn oil reduced MRP 2, MRP 3, and MRP 4 protein expression levels in duodenal and proximal jejunal tissues of rats, and the mRNA level and protein level of MRP 4 in renal tissues were also decreased in a dose-dependent manner[143]. Whether the effect of VD on MRP is tissue specific needs to be confirmed by further studies.

4.2 Effects of VD on Drug Metabolism

The drug's metabolic enzymes in the body require the participation of phase I metabolic enzymes (such as cytochrome P450; CYP450) and phase II metabolic enzymes (such as UDP-glucuronosyltransferase; UGT)[162]. The effect of VD on metabolic enzymes may also be an important factor affecting the pharmacokinetic behavior of drugs.

4.2.1 Cytochrome P450

In drug metabolism, P450 participates in 75% of drug metabolism, among which 1A2, 2C9, 2C19, 2D6, and 3A4 are involved in three-quarters of P450 enzyme metabolism, most of which is catalyzed by P450 3A enzyme[163]. Polymorphisms of human VDR BsmI G>A (Rs 1544410), ultraviolet sunlight, and VD levels were significantly correlated with CYP3A4 expression/activity and area under the substrate drug curve (AUC)[135]. VD could also up-regulate the expression of CYP3A in kidney in sheep[157] and jejunum and in rats[164], but VD had little substantial effect on the CYP3A4 activity in human liver[165]. VD regulates CYP3A4 in two ways: direct regulation and indirect regulation. On one hand, VD could directly activate VDR/RAR and induce the expression of CYP3A4 in small intestinal and colon cancer cells by combining VDRE (DR3 and ER6) in the promoter region of the CYP3A4 gene[166]. On the other hand, VD could activate mir-627 to indirectly inhibit the expression of CYP3A4 and reduce the metabolism of irinotecan in tumor cells, thus enhancing its growth inhibition and apoptosis induction[42].

VD also has extensive effects on other CYP enzymes. Studies on the upstream regulation sequences of the CYP24 gene in rats and humans showed that multiple VDREs are synergistically involved in the regulation of human CYP24 gene transcription by VD[167]. 1,25(OH)2D3 could induce a 20,000-fold increase of CYP24 mRNA transcription in fibroblasts[168], activate VDR to inhibit CYP 7A1 mRNA expression and bile acid synthesis in HepG 2 cells[168], and up-regulate the expression of CYP2B6 and CYP2C9 in normal differentiated primary human hepatocytes[14].

4.2.2 Phase II Metabolic Enzymes

Human UGT is Phase II Metabolic Enzymes and a superfamily of enzymes that

metabolize various endogenous substances (bilirubin and steroid hormones) and exogenous compounds (drugs and dietary substances). Wang X et al. found that the expression of UGT1A8 and UGT1A10 was highly correlated with the level of VDR mRNA in human large intestine tissue. VD could significantly increase the transcription level of the UGT gene in the human intestine and also significantly increase the oxidative level of Mycophenolic acid (MPA) glucuronic acid in cells, reduce the exposure of the human body to MPA, and increase the clearance rate[136]. VD also reduced mRNA and protein levels of UGT2B15 and UGT2B17 in LNCaP and 22Rv1 cells, possibly through a response region between UGT2B15 promoter-171 and -113 bp[170].

Bile salt sulfotransferase (SULT2A1) is a sulfonyl-bound phase II enzyme highly expressed in the liver, intestine, and steroid-producing adrenal tissue[171]. Both reporter gene analysis and endogenous induction results showed that hSULT2A1 gene expression was up-regulated after VDR activation[172]. 1,25(OH)2D3 induced Sult2A1 expression through the complex element of VDR/rxr-acting on the C/eBP site (9 bases downstream of VDRE) and the reverse repetitive DNA element (IR0) between –191 and –168 bits of Sult2A1[173-175].

5. Conclusion

The VD level in vivo is closely related to drug efficacy and drug in vivo disposal. Kim Robien summarized the effect of drugs on VD absorption and metabolism[176], but the level of VD in vivo is an important factor affecting the efficacy of drugs, and its influence on pharmacodynamics and pharmacokinetics is also of great clinical significance. This paper summarized the changes in drug effects when VD is used in combination with drugs.

Supplementation with VD may result in increased efficacy or decreased adverse reactions, while lack of VD may result in decreased efficacy and increased adverse reactions. This is related to the extensive physiological effects of VD itself, such as the regulation of the immune system by VD and the anti-inflammation and anti-oxidative stress; but changes in drug effects and adverse reactions may be also caused by the influence of VD on pharmacokinetics. The effect of VD on drug CYP metabolic enzymes has been reviewed[177], while we not only evaluated VD's role in drug transporter and drug metabolism processes (phase I metabolism and phase II metabolism) but also introduced the role of VD in drug pharmacokinetics and summarized the relationship between VD and pharmacodynamics, in the hope of providing theoretical support for clinical practice.

At present, although VD deficiency and supplementation are very common in clinical medication and daily life, the level of VD in clinical medications has not received the attention of industry, medical institutions, or clinicians. When the drug fails to meet the anticipated curative effect or is associated with adverse drug reactions, the role of the VD level in patients is seldom considered. In addition, the selection of subjects in drug clinical trials or the formulation of clinical medication schemes also do not take into account the possibility of VD deficiency or supplementation. The population of individuals with VD deficiency does not receive enough clinical attention. We hope that this paper will draw attention to the interaction between VD and drugs and lead to a more rigorous and comprehensive study on the effects and safety of drugs in this special group of people.

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Table 1. Epidemiological investigation of vitamin D deficiency/insufficiency

Region	Category	VD deficiency(25(OH)D<20ng/ml)	VD insufficiency (<30ng/ml)
USA	Elders	26%	72%[178]
	Pregnant (12 weeks' gestation)	35%	96%
	Pregnant (20 weeks' gestation)	44%	96%
	Pregnant (35 weeks' gestation)	16 %	75%[179]
	White newborn	10%-46%[180]	
China	Male	5.8%[181]	67.9%
	Female	10.9%	53.1%
	Children		65.3%[182]
	Pregnant		57.1%[183]
Europe	European population	40.4%[184]	
Italy	women	77.4%[5]	

Table 2. Effect of Vitamin D on Drugs' Pharmacokinetics

Drug	Object	Results	Mechanism	References
Mycophenolic acid (MPA)	Human small intestine cells	VD reduced AUC_{0-12} and C_{max} by 40% and total clearance of MPA increased by more than 70%	UGT1A	[136]
Cefdinir/cefadroxil	Rats	The area under the blood concentration-time curve (AUC) of cefdinir and cefadroxil increased significantly as the clearance rate (CL) decreased	OAT 1/OAT 3	[130]
JBP 485	Rats	1,25(OH)2D3 inhibits renal excretion of JBP 485.	OAT 1 and OAT 3	[131]
Adefovir/adefovir Dipivoxil	Rats	1,25(OH)2D3 treatment promotes oral absorption of adefovir dipivoxil but not adefovir	P-GP and/or MRP 4	[134]
Simvastatin	Rats	VD reduces the bioavailability of simvastatin and has a significant effect on the pharmacokinetics of simvastatin.	oatp/cyp3a4	[137]
Digoxin	FXR(-/-)mice	Blood (24%) and brain (29%) exposure decreased, kidney (74%) and systemic (34%) clearance increased	P-gp	[132]
Alendronate	Healthy menopausal women	No significant effect on pharmacokinetic parameters of isoflavones		[124]
Digoxin	Healthy participants	Does not affect the pharmacokinetic behavior of digoxin (probably because vitamin D levels have not changed)	P-gp	[133]
Midazolam	Healthy participants	VD affects the AUC and oral bioavailability of oral midazolam.	CYP3A4	[135]
Tenofovir disoproxil fumarate	Patients	Free 1,25(OH)2D concentration correlated with plasma tenofovir concentration		[185]
Isoflavones	Menopausal women	No significant differences in pharmacokinetic parameters of isoflavones.		[186]

Table 3. Effect of vitamin D on P-gp

Active substance	Objects	Results	References
1,25(OH)2D3	Caco-2 cell	Increase ABCB1 mRNA and multidrug resistance protein (MDR 1 or P-GP).	[15]
1,25(OH)2D3	Caco-2 cell	The expression of multidrug resistance genes P-gp, MDR1 and MRP2 increased, digoxin turnover increased, and intracellular accumulation of 5 (and 6)-carboxy-20, 70-dichlorofluorescein decreased.	[17]
1,25(OH)2D3	LS180/CaCo-2 cell	The expression of MDR1 mRNA increased slightly in LS180 cells and no effect in Caco-2 cells.	[158]
1,25(OH)2D3	LS174T cell	DHC increased P-gp expression by two times, and decreased the accumulation of Rh123(P-gp substrate) in LS174T cells.	[155]
1,25(OH)2D3 and LCA	LS174T/HepG2 cell	It was difficult to detect VDR mRNA in HepG2 cells, but VDR mRNA highly expressed in LS174T cells.1,25(OH)2D and LCA increased the level of ABCB1 mRNA in LS174T, intestinal P-gp was up-regulated;there is no effect on ABCB1 (HepG2).	[159]
Quercetin (VDR activator)	Caco-2 cell	Expression of CYP3A4 ,multidrug resistance protein 1 and TRPV6 receptor mRNA increased.	[187]
1,25(OH)2D3	Calu-3 cell	submicromolar concentrations of di-OH vit D3 stimulate P-gp expression in human airway epithalial cell line.	[188]
1,25(OH)2D3	Jurkat/ADR and K562/ADR cell lines	The surface P-glycoprotein content and intracellular glutathione content ,MDR1 mRNA,MRP1 mRNA all decreased.	[156]
1,25(OH)2D3	rat intestinal everted sac	P-gp are not induced,the A-to-B and B-to-A transport of digoxin (P-gp) in the ileum was unchanged.	[150]
1,25(OH)2D3	RBE4 and hCMEC/D3 cell lines	Increased expression of Mdr1b mRNA,P-gp protein and increased P-gp transport activity (special photoaccumulation of NBD-CSA, fluorescent substrate of P-gp).	[152]
1,25(OH)2D3	fxr(-/-) and fxr(+/+) mice	The expression of Mdr1 mRNA and P-gp protein in kidney and brain increased, Body	[132]

		exposure of digoxin decreased significantly, and fecal clearance increased. The level of digoxin in the brain is relatively low.	
1,25(OH)2D3	mice	Increase the expression of P-gp RNA in kidney by 1.5 times to twice.	[154]
1,25(OH)2D3	rat	The expression of Mdr1a mRNA and protein in kidney were significantly increased (2 - 20 times).	[143]
1,25(OH)2D3	rat	Liver multidrug resistance protein 1a (Mdr1a) mRNA and P-gp protein increased.	[146]
Doxercalciferol and calcitriol	rat	Increase the expression of P-gp protein in small intestine and kidney.	[144]
1,25(OH)2D3	rat	The expression of P-gp in brain increased 1.75 times and the concentration of quinidine in extracellular fluid decreased, which could affect the distribution of quinidine.	[153]
25(OH)D3 or 1,25(OH)2D3	sheep	25-OHD 3 decreased P-gp in rumen, jejunum and liver, but had no significant effect on renal P-GP. 1,25-(OH) 2D3 had no effect on P-gp.	[157]

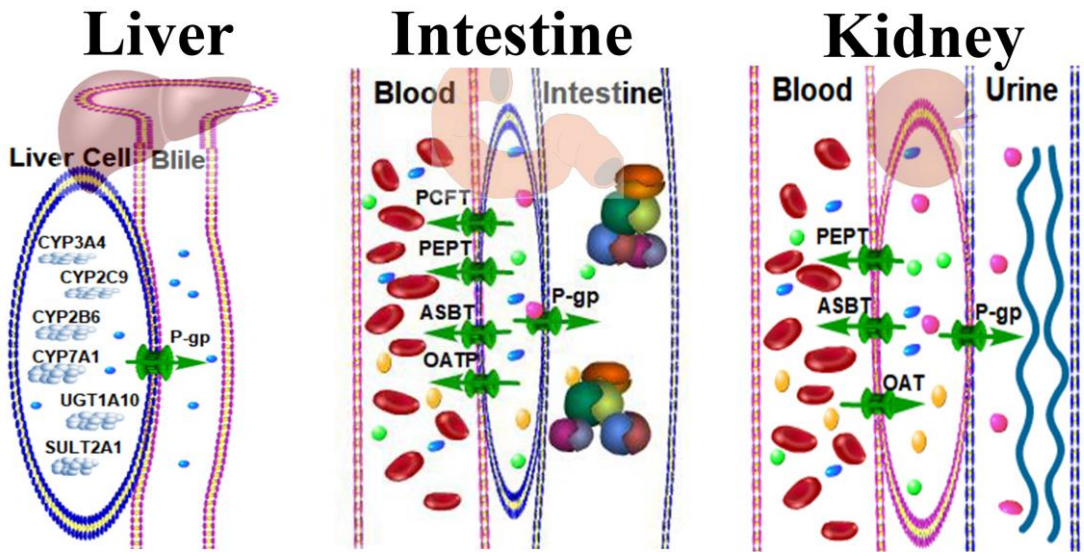

Figure 1. Transporters and metabolic enzymes affected by vitamin D