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REVIEW

Therapeutic targets of vitamin D receptor ligands and their pharmacokinetic effects by modulation of transporters and metabolic enzymes

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Abstract
Vitamin D is involved in retaining the balance of several minerals in the body, such as calcium and phosphate, which are crucial for the bone formation and development. These physiological effects of vitamin D are mediated by activation of the transcription factor vitamin D receptor (VDR). Moreover, vitamin D is closely related to several pathological conditions including osteoporosis, secondary hyperparathyroidism, cancer, psoriasis and autoimmune diseases, which is not only due to calcemic but also non-calcemic effects of vitamin D such as cell proliferation, differentiation, and immunomodulation. These various abilities of vitamin D have made VDR an attractive therapeutic target. Already, numerous vitamin D analogs have been developed and studied in in vitro disease models or animal models, and some have been in clinical trials or approved for the treatment of certain diseases. In addition, the transcriptional and/or post-transcriptional regulation by VDR activation also affects the genes involved in drug metabolism and disposition, possibly leading to pharmacokinetic changes of several drugs in clinical use. This review provides a detailed summary of therapeutic targets of VDR ligands, and their effects on the transporters and metabolic enzymes, causing in vitro and in vivo pharmacokinetic changes of several drugs. The clinical research is further required for the confirming the clinical relevance of pharmacokinetic drug interactions by VDR ligands.

Keywords Vitamin D · Vitamin D receptor (VDR) · Therapeutic target · Transporters · Metabolic enzymes · Pharmacokinetics

Introduction

Vitamin D receptor (VDR) is a nuclear receptor that binds 1,25-dihydroxyvitamin D_3 (Calcitriol, $1,25(OH)_2D_3$), the active form of vitamin D_3 (cholecalcitriol), and mediates its various important biological effects. VDR has been known to be involved in calcemic effects, calcium and phosphorus homeostasis and maintenance of bone content. On the other hands, additional non-calcemic effects such as cell proliferation, differentiation, and immunomodulation have been reported to be mediated by VDR. It has generated the interest in targeting the VDR as various therapeutic targets. The huge amount of vitamin D analogs have been synthesized for the purpose of treating the several diseases such as osteoporosis, secondary hyperparathyroidism, cancer, psoriasis and autoimmune diseases. In the first part of this review, we extensively summarized and discussed the vitamin D related disease and the vitamin D analogs which have been clinically approved or investigated so far (Fig. 1).

It has been reported that VDR regulates metabolic enzymes and transporters via VDR transcriptional and/or post-transcriptional regulation *in vitro* and in vivo (Thummel et al. 2001; Fan et al. 2009; Eloranta et al. 2012; Chow et al. 2010, 2013; Maeng et al. 2012). Since treatment with VDR ligands modulate the expressional levels of the metabolizing enzymes and transporters, these VDR-mediated regulation could generate the impact on pharmacokinetic

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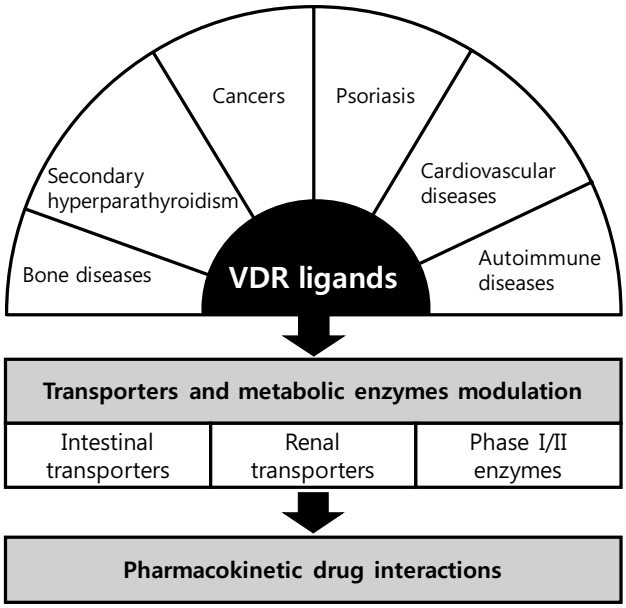

Fig. 1 Graphical summary of this review. It shows the specific diseases where VDR ligands can be effective (upper semicircle) and the modulation of transporters/enzymes by VDR ligands, resulting in pharmacokinetic drug interactions (lower parts)

changes of the drugs metabolized and/or transported by specific enzymes or transporters affected. Indeed, several studies have reported the pharmacokinetic changes of the drugs by VDR ligands treatment in vitro and in vivo. In the second and third part of this review, we summarized and discussed the modulation of drug transporters and metabolic enzymes in the important absorption and elimination organs by VDR activation in the previous literatures, and further discussed the pharmacokinetic relevance in terms of drug–drug interactions (DDIs) in vitro and in vivo (Fig. 1). It seems that VDR ligand drugs are more used as a second therapy rather than first line therapy. In addition, the diseases treated with VDR ligand drugs are mostly chronic disease, so the patients usually are likely to take other medicines with vitamin D analogs or VDR ligand drugs. Therefore, possible drug interactions should be considered when the VDR ligand drugs are used for the purpose of prevention or treatment of diseases.

VDR as a therapeutic target

A large number of vitamin D analogs (i.e., VDR ligand drugs) have been synthesized by numerous research groups. These analogs have been tested for the purpose of treating or preventing various diseases of the human body, including osteoporosis, secondary hyperparathyroidism, cancer, psoriasis and autoimmune diseases. By looking at the function and the role of vitamin D analogs in these diseases, the potential of VDR as a therapeutic target will be explored.

Bone diseases

A primary role of VDR is to maintain calcium and phosphate homeostasis during bone formation and resorption. Nutritional vitamin D deficiency, altered vitamin D responsiveness due to VDR mutations (hereditary vitamin D-resistant rickets), and impaired production of $1,25(OH)_2D_3$ consequent to CYP27B1 mutations (pseudo-vitamin D deficiency) all have rickets as their major phenotype, showing that vitamin D and $1,25(OH)_2D_3$ are significantly important to bone formation. Vitamin D deficiency may result in lower bone mineral density and increased risk of osteoporosis or bone fracture because a lack of vitamin D alters mineral metabolism in the whole body (Adami et al. 2009; Bell et al. 2010; Holick 2004; LeBoff et al. 1999). Accordingly, VDR ligands have been suggested to be useful for the prevention or the treatment of bone disease such as osteomalacia, osteoporosis, and rickets. A number of reports have demonstrated the prevention or the decrease of vertebral fractures and the increase of mineral density in total body and spine bone in post-menopausal women with $1,25(OH)_2D_3$ treatment (Sunyecz 2008; Papadimitropoulos et al. 2002). $1,25(OH)_2D_3$ has also been shown to treat secondary osteoporosis, especially corticosteroid-induced osteoporosis and post-transplantation bone loss in a clinical trial (Richy et al. 2004; El-Agroudy et al. 2003; Torres et al. 2004). However, the use of $1,25(OH)_2D_3$ in the treatment of osteoporosis is restricted by hypercalcemia, a serious side effect. Hence, attempts have been made to apply less calcemic analogs of vitamin D_3 to the treatment of osteoporosis. Alfacalcidol, 1α-hydroxyvitamin D_3, a precursor of $1,25(OH)_2D_3$, is an approved drug for the treatment of osteoporosis. Because alfacalcidol does not induce an immediate increase in calcium absorption from gut, it appears to be a safer treatment compared to $1,25(OH)_2D_3$. Alfacalcidol treatment showed therapeutic advantages in vertebral fracture incidence and spinal bone mass in several clinical studies (Fujita et al. 2007; Felsenberg et al. 2011; Francis et al. 1996). 2-(3-hydroxypropoxy)-$1,25(OH)_2D_3$ (ED-71) have been shown to be an efficient treatment for osteoporosis, providing higher restoration of mineral density than alfacalcidol in ovariectomized rats (Kubodera et al. 2003). ED71 is also efficient to osteoporosis patients in clinical trials. Lumbar bone mineral density has increased in a dose-dependent manner without producing hypercalcemia and hypercalciuria (Kubodera et al. 2003). 2-methylene-19-nor-(20S)-$1,25(OH)_2D_3$ (2MD), a highly potent analog of $1,25(OH)_2D_3$ promoted osteoclast formation and mineralization in human osteoblast cultures in vitro. 2MD also caused an increase

in bone mass in ovariectomized rats in vivo (Shevde et al. 2002; Ke et al. 2005). Though the markers for bone formation were increased by 2MD in postmenopausal women, bone mineral density (BMD) was not increased because bone resorption was also stimulated (DeLuca et al. 2011). Ro-26-9228 (1α-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol), a secosteroidal vitamin D derivative bearing a fluoro group at 1α position decreased bone resorption and increased the number of differentiated osteoblasts in a rat model of osteoporosis (Peleg et al. 2002).

Secondary hyperparathyroidism

Secondary hyperparathyroidism is a parathyroid glands disease characterized by high parathyroid hormone (PTH) levels and low blood calcium concentration. It is an early emerging and a major complication of chronic kidney disease (CKD). Decreased renal function induces the accumulation of serum phosphate level because the kidney is the organ performing the elimination of phosphate from the body. High phosphate level results in the decrease of ionized calcium level, which causes the stimulation of PTH secretion and downregulation of VDR in the parathyroid gland (Goto et al. 2008; DeLuca 2008; Bricker 1972). Defective renal function also induces the decreased production of $1,25(OH)_2D_3$. Vitamin D deficiency results in the enhanced synthesis of PTH and the increased proliferation of the parathyroid cells leading to the excessive secretion of PTH. (DeLuca 2008). Vitamin D deficiency is considered to play a crucial role during the initiation and the maintenance of hyperparathyroidism. Various vitamin D analogs, for example, maxacalcitol, paricalcitol, doxercalciferol, and falecalcitriol have been approved for the treatment of hyperparathyroidism. (Bikle 2014). Therapeutic effects with vitamin D and analogues are closely related to the reduced mortality in CKD patients, particularly in those having secondary hyperparathyroidism. (Duranton et al. 2013). 22-oxacalcitriol (OCT; Maxacalcitol) was shown to be highly potent to suppress PTH in vitro and in vivo (Brown et al. 1989). In the animal models of CKD, 22-oxacalcitriol was slightly less active than $1,25(OH)_2D_3$ in suppressing PTH, but 22-oxacalcitriol's much smaller calcemic activity has generated a wider therapeutic window (Brown et al. 1990; Hirata et al. 2002; Monier-Faugere et al. 1999; Naveh-Many and Silver 1993). Clinical trial studies for hemodialysis patients have confirmed that 22-oxacalcitriol was effective to suppress PTH levels (Akizawa et al. 2002, 2004; Hayashi et al. 2004; Tamura et al. 2005; Yasuda et al. 2003). Other preclinical studies have shown that 19-norD_2 (Paricalcitol) was about 10 times less calcemic and phosphatemic, while only about 3 times less active in suppressing PTH (Slatopolsky et al. 1995). Control of secondary hyperparathyroidism in uremic rats by 19-norD_2 could prevent or reverse the high turnover bone disease mediate by PTH (Slatopolsky et al. 2003). Several clinical studies have demonstrated that 19-norD_2 effectively reduced PTH with very few hypercalcemic events (Martin et al. 1998a, b). $1\alpha(OH)D_2$ (doxercalciferol) was also effective in decreasing PTH in predialysis patients (Coburn et al. 2004). Intravenous $1\alpha(OH)D_2$ showed comparable PTH suppression to that observed with oral $1\alpha(OH)D_2$. 26,27-F6-$1,25(OH)_2D_3$ (falecalcitriol) is more effective than calcitriol in vivo due to its slower metabolism. 23-hydroxylated metabolite of falecalcitriol is resistant to further metabolism and maintains higher activity (Imanishi et al. 1999). In dialysis patient treated with falecalcitriol, PTH was decreased by 25% with minimal change of serum calcium level (Nishizawa et al. 1991).

Cancers

Previous studies have suggest that calcitriol or its analogs have anti-proliferative effect in a wide range of tumor models including those of leukemia (Pepper et al. 2003), bladder (Ma et al. 2010), breast (Colston et al. 1992; Welsh et al. 2003), colon (Cross et al. 1991), kidney (Fujioka et al. 1998), lung (Nakagawa et al. 2005), pancreas (Colston et al. 1997), prostate (Getzenberg et al. 1997), bone (Hara et al. 2001), glioma (Naveilhan et al. 1994), and melanoma (Colston et al. 1981). Several reports have outlined the proposed mechanisms of antitumor activity of vitamin D (Beer and Myrthue 2004; Trump et al. 2010). It includes the inhibition of proliferation and the induction of differentiation (Pálmer et al. 2003; Jiang et al. 2003; Li et al. 2004; Muto et al. 1999; Wang et al. 1996; Zhang et al. 2006; Aguilera et al. 2007; Zhuang and Burnstein 1998; Campbell and Koeffler 1997), apoptosis (Chung et al. 2009; Bernardi et al. 2002; Pendás-Franco et al. 2008; McGuire et al. 2001; Guzey et al. 2002; Pepper et al. 2003), the prevention of invasiveness (Schwartz et al. 1997; Yudoh et al. 1999; Sung and Feldman 2000), and angiogenesis (Majewski et al. 1996; Mantell et al. 2000). Vitamin D and its several analogs such as seocalcitol (22,24-diene-24,26,27-trishomo-$1,25(OH)_2D_3$) (Bhatia et al. 2009; Ghous et al. 2008), inecalcitol (19-nor-14-epi-23-yne-$1,25(OH)_2D_3$), TX527 (19-nor-14,20-bi-sepi-23-yne-$1,25(OH)_2D_3$) (Ma et al. 2013; Okamoto et al. 2012), paricalcitol (19-nor-$1,25(OH)_2D_3$) (Kumagai et al. 2003; Park et al. 2012; Schwartz et al. 2008), doxercalciferol ($1\alpha(OH)D_2$) (van Ginkel et al. 2007; Albert et al. 2004; Grostern et al. 2002), maxacalcitol (22oxa-$1,25(OH)_2D_3$) (Seubwai et al. 2010; Kawa et al. 1996), BGP-13 (1R, 3S, 5Z)-5-((8E)-2-((3R)-3-((2R,3S)-3-(5-cyclopropyl-3H-1,2-dioxol-3-yl)-2-ethyl-3-methylcyclohexylidene) ethylidene)-4-methylenecyclohexane-1,3-diol), BXL0124 (20R-21(3-hydroxy-3-deuteromethyl-4,4,4-trideuterobutyl)-

23-yne-26,27-hexafluoro-1,25$(OH)_2D_3$) (So et al. 2011; Lee et al. 2010), MART-10 (19-nor-2α-(3-hydroxypropyl)-1,25$(OH)_2D_3$) (Chiang et al. 2013), and 1,25$(OH)_2D_3$-3-bromoacetate have been evaluated in rodent models to assess their anticancer activity and safety in vivo, and they have demonstrated the inhibition of tumor growth in various models of tumor types. Based on their promising results of anticancer activity, some analogs have been tested in cancer patients. Unfortunately, however, they did not lead to conclusive results for the beneficial effects (Leyssens et al. 2014; Trump et al. 2010; Hargrove et al. 2014; Narvaez et al. 2014; Marchwicka et al. 2014). Further studies are needed to fully understand the molecular mechanisms of action and the optimal applications of vitamin D analogue in cancer.

Psoriasis

Psoriasis is a chronic autoimmune disease characterized by red, itchy and scaly patches of skin because of the rapid growth of skin cells. It has been reported that vitamin D may play an important role in the skin diseases (Soleymani et al. 2015; Reichrath 2007). Vitamin D controls the proliferation and differentiation of keratinocytes, modulates immune systems and selectively induces apoptosis in the skin (Soleymani et al. 2015; Lehmann et al. 2004; Bollag 2007; Milde et al. 1991). Though the mechanisms mediating the effects of Vitamin D are not fully understood, it is very well-known that those effects are mediated via VDR at least in part (Lehmann et al. 2004; Trémezaygues and Reichrath 2011). VDR is expressed in keratinocytes, fibroblasts, Langerhans cells, sebaceous gland cells, and endothelial cells, which are related to the immune system of skin (Milde et al. 1991). VDR knockout mice show the suppressed level of epidermal differentiation marker and do not respond to the antiproliferative effects of vitamin D analogs in vitro (Bikle et al. 2004; Sakai and Demay 2000). A number of clinical studies have demonstrated that vitamin D and its analogs are effective and safe for treatment of psoriasis (Soleymani et al. 2015; Holick et al. 1996; Pérez et al. 1996; Kragballe et al. 1988, 1991; van de Kerkhof et al. 1989, 2002; Barker et al. 1999; Durakovic et al. 2001; Miyachi et al. 2002; Katayama et al. 2002). Topical application of calcipotriol was shown to be more effective for the treatment of psoriasis than that of bethamethasone 17-valerate (Kragballe et al. 1991). Maxacalcitol has been shown to be a more effective in reducing erythema and scaling than calcipotriol (Barker et al. 1999). Tacalcitol was also effective and safe for the treatment of not only refractory psoriasis having low responsiveness to topical corticosteroids, but also psoriasis vulgaris and plaque psoriasis (Katayama et al. 2002; Miyachi et al. 2002; van de Kerkho et al. 2002).

Cardiovascular diseases

A few studies have demonstrated the relationship between cardiovascular homeostasis and vitamin D (Weishaar et al. 1990; Weishaar and Simpson 1987a, b). Those studies suggested that vitamin D plays a role in retaining cardiovascular homeostasis through not only the direct actions of 1,25$(OH)_2D_3$ on VDR in cardiomyocytes but also the indirect actions on circulating calcium and hormones. Vitamin D receptors are expressed in various cells, such as cardiomyocytes, vascular smooth muscle cells and endothelial cells. Through the interaction with the vitamin D receptors on the cardiomyocyte, 1,25$(OH)_2D_3$ controls (1) calcium influx into the cell, (2) the amount of free cytosolic calcium available thus modifying contractility of the heart, and (3) cell growth and proliferation (Nibbelink et al. 2007; Walters et al. 1987). The direct effects of vitamin D on the VDR have been examined using VDR knockout mice (Simpson et al. 2007; Xiang et al. 2005; Rahman et al. 2007). In those studies, the data have demonstrated the profound cardiac hypertrophy, the overstimulation of the renin-angiotensin system (RAS), and the increase of both fibrotic lesions and heart weight-to-body weight ratio in VDR knockout mice. A number of studies in human have indicated the association of vitamin D deficiency with cardiovascular disease (Rostand and Drüeke 1999; Wang et al. 2008; Pilz et al. 2008a, b). These data have raised the possibility that supplementation of vitamin D or its analogs could be useful treatments or preventions for cardiovascular diseases. However, only a few studies have suggested that the increment of 25(OH)D levels may provide benefit to patients with heart failure or hypertension (Nemerovski et al. 2009; Schleithoff et al. 2006; Shedeed 2012). Further clinical studies should be needed to confirm that vitamin D supplementation can prevent or treat cardiovascular diseases.

Autoimmune diseases

Both vitamin D metabolizing enzymes and VDRs are also present in a variety of immune cells including antigen-presenting-cells, T cells, B cells and monocytes. These cells can convert 25(OH)D to 1,25$(OH)_2D_3$ through CYP27B1 and provide sufficient amount of 1,25$(OH)_2D_3$ for its local function (Morán-Auth et al. 2013). It is well known that vitamin D plays an important role in the management of immune functions (Prietl et al. 2013; Wöbke et al. 2014; Zhang et al. 2013). Therefore, impaired or insufficient levels of vitamin D result in the dysregulation of immune responses. It has been reported that several inflammatory

autoimmune disease including asthma (Li et al. 2011; Bener et al. 2012), inflammatory bowel diseases such as ulcerative colitis and Crohn's disease (Ananthakrishnan et al. 2012; Levin et al. 2011), multiple sclerosis (Martinelli et al. 2014; Pierrot-Deseilligny et al. 2012), rheumatic disorder (Shapira et al. 2010), and systemic lupus erythematosus (Abou-Raya et al. 2013) are all related to vitamin D deficiency. Consequently, vitamin D supplementation has been proposed as a hopeful and safe way for the prevention and the treatment of immune diseases (Prietl et al. 2013). Vitamin D seems to present a positive effect on autoimmune disease through the suppression of immune system (Daniel et al. 2008). $1,25(OH)_2D_3$ inhibited the differentiation and maturation of dendritic cells, leading to the suppression of dendritic cell-dependent T cell activation (van Etten and Mathieu 2005). $1,25(OH)_2D_3$ also blocked the secretion of both interleukin (IL)-2 and interferon (IFN)-gamma by T helper (Th) 1 and suppressed the secretion of pro-Th1 cytokine IL-12 by antigen-presenting cells (Lemire 2000). Th17 effector cells also can be affected by immunosuppressive effect of $1,25(OH)_2D_3$ (Daniel et al. 2008). Though a few studies indicated the effectiveness of vitamin D supplementation in autoimmune disease including atopic dermatitis and multiple sclerosis (Åivo et al. 2015; Di Filippo et al. 2015), further and long-term clinical trials are required to determine whether vitamin D supplementation has beneficial effect in immune diseases.

Modulation of drug transporters and metabolic enzymes

VDR is the well-known nuclear receptor, which has significant homology with other xenobiotic nuclear receptors such as the pregnane X receptor (PXR) and the constitutive androstane receptor (CAR). Like PXR and CAR, the VDR could regulate drug transporters and metabolic enzymes. In this section, regulations of drug transporters and metabolic enzymes in the important absorption/elimination organ are summarized in terms of expressional change by VDR ligand drugs in vitro and in vivo.

Drug transporters

Intestine

The regulation of transporters by $1,25(OH)_2D_3$ was first reported for the apical sodium dependent bile acid transporter (Asbt) in the rat intestine (Chen et al. 2006). The treatment of 0.64 nmol/kg/day of $1,25(OH)_2D_3$ for 4 continuous days led to the increased level of Asbt by 2–3 fold in the ileum segment. Consistently, Chow et al. (2009) reported that ileum Asbt was significantly increased in the rat for 2.56 nmol/kg/day of $1,25(OH)_2D_3$. Similarly, an important bile acid transporter, the mRNA of organic solute transporter (Ostα and Ostβ), localized mostly in the ileum, was modestly induced by the low doses (Chow et al. 2009).

The representative observation for the intestinal transporters' regulation by VDR activation are summarized in Tables 1 and 2. Primary active transporters have been extensively investigated by VDR activation in the intestine. To the best of our knowledge, the first observation for the intestinal efflux transporters by VDR dependent regulation was the colon multidrug resistance-associated protein 3 (Mrp3) in mice, with identified VDR response element (VDRE) for the Mrp3 promoter (McCarthy et al. 2005). In vitro Caco-2 cells, several studies to report expressional change of intestine efflux transporters exist (Fan et al. 2009; Maeng et al. 2012). The ATP-dependent efflux transporter, P-glycoprotein (P-gp), encoded by the multidrug resistance 1 gene (MDR1), and the multidrug resistance-associated proteins (MRPs) such as MRP2 and MRP4 was investigated in the 100 nM VDR ligands ($1,25(OH)_2D_3$, 1α-hydroxyvitamin D_3, 1α-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3) (Fan et al. 2009). The treatment of VDR ligands led to higher protein expression of P-gp, MRP2 and MRP4. The increased mRNA levels of P-gp and MRP2 were observed in the VDR ligand treated Caco-2 cells. Interestingly, only the increased change in the protein, not mRNA level of MRP4 was constituently found with $1,25(OH)_2D_3$ in Caoo-2 cells (Fan et al. 2009; Maeng et al. 2012). Moreover, in the rat intestine, protein levels of Mrp2, Mrp3 and Mrp4 were induced with no change of mRNA levels after $1,25(OH)_2D_3$ treatment, whereas P-gp remained unchanged for protein/mRNA levels (Chow et al. 2010). On the other hands, $1\alpha(OH)D_2$, a synthetic vitamin D_2 analog with 1.28 nmol/kg day every other day for 8 days showed a moderate increase in P-gp protein in the ileum of rats (Chow et al. 2011a, b). However, in the ileum segment of $1,25(OH)_2D_3$-treated mice, there was no demonstrable change in the P-gp, Mrp3 and Mrp4 (Chow et al. 2013).

Secondary active transporters including organic anion transporters and the oligopeptide transporter have rarely been investigated so far. PepT1 protein levels in the upper small intestine were significantly increased at the 2.56 nmol/kg/day of $1,25(OH)_2D_3$ (Chow et al. 2010). In addition, organic anion transporter 1 (Oat1) and organic anion transporter (Oat3) in the rat intestine were investigated. Namely, small increase in Oat1 mRNA in the duodenum and significant increase in Oat3 mRNA in the colon were observed with $1,25(OH)_2D_3$ treatment (Chow et al. 2010). However, in the ileum, levels of mRNA for Oat1 and Oat3 were markedly decreased in the $1,25(OH)_2D_3$-treated rats (Chow et al. 2010). Among the organic anion-transporting polypeptides

Table 1 Effects of VDR ligands on the specific diseases including bone disease, secondary hyperparathyroidism, cancers, psoriasis, cardiovascular diseases, and autoimmune diseases

Diseases	VDR ligand treated	Species	References
Bone diseases	$1,25(OH)_2D_3$	Human (vertebral fractures, osteoporosis)	Sunyecz (2008); Richy et al. (2004)
	$1\alpha(OH)D_3$	Human (vertebral fractures, osteoporosis)	Fujita et al. (2007); Felsenberg et al. (2011)
	ED-71	Wistar-Imamichi rat, human (osteoporosis)	Kubodera et al. (2003)
	Ro-26-9228	Sprague–Dawley (SD) rat (osteoporosis)	Peleg et al. (2002)
Secondary hyperparathyroidism	Maxacalcitol	Human	Bikle (2014)
	Paricalcitol		
	Doxercalciferol		
	Falecalcitriol		
Cancers	Seocalcitol	Human (prostate/hepatocellular cancer cell)	Bhatia et al. (2009); Ghous et al. (2008)
	Inecalcitol, TX527	C3H Mouse (squamous cell carcinoma, prostate cancer cell)	Ma et al. (2013); Okamoto et al. (2012)
	Paricalcitol	Human (leukemia, myeloma, colon/gastric/pancreatic cancer cell)	Kumagai et al. (2003); Park et al. (2012)
	Doxercalciferol	Human (neuroblastoma, retinoblastoma)	van Ginkel et al. (2007); Albert et al. (2004)
	Maxacalcitol	Human (bile duct carcinoma, pancreatic cancer cell)	Seubwai et al. (2010); Kawa et al. (1996)
	BXL0124, BGP-13	Human (breast cancer cell)	So et al. (2011)
	MART-10	Human (breast/pancreatic/head and neck cancer cell)	Chiang et al. (2013)
Psoriasis	Calcipotriol	Human	Kragballe et al. (1991)
	Maxacalcitol	Human	Barker et al. (1999)
	Tacalcitol	Human	Katayama et al. (2002); Miyachi et al. (2002)
Cardiovascular diseases	$1,25(OH)_2D_3$	Holtzman Rat (myocytes)	Nibbelink et al. (2007); Walters et al. (1987)
Autoimmune diseases	$1,25(OH)_2D_3$	Institute of Cancer Research (ICR) Mouse	van Etten and Mathieu (2005); Lemire (2000)

Table 2 Representative expressional changes of intestinal transporters by VDR modulation

Transporters	VDR ligand treated	Expressional change	Species	Refs.
Asbt	$1,25(OH)_2D_3$	↑ Protein ↔ mRNA, ↑ Protein	SD Rat	Chen et al. (2006) Chow et al. (2009)
P-gp	$1,25(OH)_2D_3$, $1\alpha(OH)D_3$ $1\alpha(OH)D_2$, $25(OH)D_3$	↑ mRNA, ↑ Protein	Human (Caco-2)	Fan et al. (2009) Chow et al. (2010)
	$1,25(OH)_2D_3$	↔ mRNA, ↔ Protein	SD Rat C57BL/6 Mouse	Chow et al. (2013) Chow et al. (2011b)
	$1\alpha(OH)D_2$	↑ Protein (ileum)	SD Rat	
MRP2 (Mrp2)	$1,25(OH)_2D_3$	mRNA, Protein ↔ mRNA, ↑ Protein	Human (Caco-2) SD Rat	Fan et al. (2009) Chow et al. (2010)
Mrp3	$1,25(OH)_2D_3$	↑ mRNA (colon) ↔ mRNA, ↑ Protein	C57BL/6 Mouse SD Rat	McCarthy et al. (2005) Chow et al. (2010)
MRP4 (Mrp4)	$1,25(OH)_2D_3$	↔ mRNA, ↑ Protein ↔ mRNA, ↑ Protein	Human (Caco-2) SD Rat	Fan et al. (2009) Maeng et al. (2012) Chow et al. (2010)
PepT1	$1,25(OH)_2D_3$	↑Protein	SD Rat	Chow et al. (2010)
Oat1/Oat3	$1,25(OH)_2D_3$	↑ mRNA (duodenum or colon) ↓ mRNA (ileum)	SD Rat	Chow et al. (2010)
OATP1A2	Vitamin D_3	↑ mRNA	Human (Caco-2)	Eloranta et al. (2012)

(OATPs), OATP1A2 gene and protein greatly increased in the Caco-2 cells with 500 nM vitamin D_3, suggesting that OATP1A2 gene is induced by vitamin D_3 at the transcriptional level through VDR (Eloranta et al. 2012).

Kidney

Because the kidney has the highest expressional levels of VDR compared with other organs and play an important role on the excretion of xenobiotics from body, VDR ligands can regulate significant influx and efflux transporters in the kidney. The representative examples for the kidney transporters' regulation by VDR activation are summarized in Table 3. In terms of efflux transporters, upregulation of mRNA/protein levels of renal P-gp localized in the apical membrane of kidney epithelial cells was reported in the $1,25(OH)_2D_3$-treated rats (Chow et al. 2010). Among the renal Mrps, only Mrp4 mRNA levels were decreased, whereas Mrp2 and Mrp3 remained unchanged in the $1,25(OH)_2D_3$-treated rats (Chow et al. 2010). The treatment of $1\alpha(OH)D_2$, a synthetic vitamin D_2 analog with 1.28 nmol/kg day every other day for 8 days led to increased mRNA levels of P-gp, Mrp2 and Mrp3 in the rats. Only levels of P-gp protein was significantly enhanced $1\alpha(OH)D_2$-treated kidney (Chow et al. 2011b). In contrast, $1,25(OH)_2D_3$ or $1\alpha(OH)D_3$ treatment increased P-gp and Mrp4 in the mice kidney (Chow et al. 2013).

In the renal solute carrier (SLC) transporters, levels of Oat1 and Oat3 mRNA and/or protein expression was significantly reduced in the rat kidney pretreated with $1,25(OH)_2D_3$ (Chow et al. 2010; Kim et al. 2014). In addition, renal PepT1 and Pept2 expression levels were markedly decreased in the $1,25(OH)_2D_3$-treated rats (Chow et al. 2010). In comparison, renal PepT1 mRNA expression was also decreased in the $1\alpha(OH)D_2$-treated rats (Chow et al. 2011b). More recently, the vitamin D-deficiency resulted in the down-regulation of renal Oat3 in the C57BL/6 mouse (Quach et al. 2018).

Liver

It is known that the level of VDR in the rat hepatocytes exist in the very low levels. Therefore, although less effects on the regulation of hepatic transporters by VDR activation is likely to be expected, $1,25(OH)_2D_3$-treatment may exert indirect or secondary effects on the hepatic transporters likely due to the activation or inhibition of other nuclear receptors such as FXR in the liver. It is known that there is little change on the sinusoidal uptake and efflux transporters in the rat liver with $1,25(OH)_2D_3$-treatment (Chow et al. 2009). For examples, for the hepatic uptake transporters, levels of mRNA/protein expression of Oatp1a1, Oatp1a4 and Oatp1b2 remained unaltered in the rat liver with $1,25(OH)_2D_3$-treatment. The sinusoidal efflux transporters, Mrp3 and Mrp4, showed insignificant increase on the protein levels. $1\alpha(OH)D_2$-treatment also demonstrated hepatic Mrp3 mRNA was induced by two-fold in rats (Chow et al. 2011b). However, for the hepatic canalicular transporters, the mRNA levels of Bsep and Mdr1a were found to be increased significantly. The levels of P-gp protein were significantly increased by about 2.5-fold in the rat liver with $1,25(OH)_2D_3$-treatment. Consistently, $1,25(OH)_2D_3$ or $1,25(OH)_2D_3$ showed no significant changes on the expression levels of hepatic transporters in the mice (Chow et al. 2013).

Table 3 Representative expressional changes of renal transporters by VDR modulation

Transporters	VDR ligand treated	Expressional change	Species	References
P-gp	$1,25(OH)_2D_3$	↑ mRNA, ↑ Protein	SD Rat	Chow et al. (2010)
	$1\alpha(OH)D_2$	↑ mRNA, ↑ Protein	SD Rat	Chow et al. (2011b)
	$1,25(OH)_2D_3$	↑ mRNA, ↑ Protein	C57BL/6 Mouse	Chow et al. (2013)
	$1\alpha(OH)D_3$			
Mrp2	$1,25(OH)_2D_3$	↔ mRNA, ↔ Protein	SD Rat	Chow et al. (2010)
	$1\alpha(OH)D_2$	↑ mRNA, ↔ Protein		Chow et al. (2011b)
Mrp3	$1,25(OH)_2D_3$	↔ mRNA, ↔ Protein	SD Rat	Chow et al. (2010)
	$1\alpha(OH)D_2$	↑ mRNA, ↔ Protein		Chow et al. (2011b)
Mrp4	$1,25(OH)_2D_3$	↓ mRNA, ↔ Protein	SD Rat	Chow et al. (2010)
	$1,25(OH)_2D_3$	↔ mRNA, ↑ Protein	C57BL/6 Mouse	Chow et al. (2013)
	$1\alpha(OH)D_3$			
PepT1/PepT2	$1,25(OH)_2D_3$	↓ mRNA	SD Rat	Chow et al. (2010)
	$1\alpha(OH)D_2$	↓ Protein (PepT1)		Chow et al. (2011b)
		↓ mRNA		
Oat1/Oat3	$1,25(OH)_2D_3$	↓ mRNA	SD Rat	Chow et al. (2010)
		↓ Protein (Oat1)		Kim et al. (2014)

Metabolic enzymes

Phase I enzymes

With respect to cytochrome P450 monooxygenases (CYPs), CYP3A4, the most abundant CYP isoform, was first found to be increased by the levels of mRNA and protein in human intestinal model, Caco-2 cells with $1,25(OH)_2D_3$-treatment (Schmiedlin-Ren et al. 1997). Furthermore, Thummel et al. (2001) demonstrated VDR induces expression of intestinal CYP3A by binding of the activated VDR-RXR heterodimer to the CYP3A PXR response element to induce CYP3A4 transcription. Also, VDRE sequence for human CYP3A4 gene has been identified (Thompson et al. 2002). It is known that the classical VDREs consist of a direct repeat of nuclear receptor half-sites separated by 3 nucleotides (DR3) (Carlberg 1995). In human ileum and liver, $1,25(OH)_2D_3$ induced CYP3A4 expression (Khan et al. 2009). Rat Cyp3a9 (Zierold et al. 2006) and Cyp3a1 (Khan et al. 2009; Chow et al. 2009; Xu et al. 2006) in the intestine consistently have been reported to be induced by VDR ligands (Chow et al. 2009). However, in the rat liver, the mRNA of hepatic Cyp3a1 and Cyp3a9 remained unchanged whereas Cyp3a2 in the cholangiocyte was slightly increased (Chow et al. 2009). The secondary bile acid lithocholic acid (LCA) was reported to induce CYP3A4 expression, which involves detoxification of LCA in human (Makishima et al. 2002) and mice (Cheng et al. 2014). On the other hands, other CYP isoforms by VDR activation has been rarely investigated so far. For examples, in the primary human hepatocytes, CYP2B6 and CYP2C9 could be induced by the $1,25(OH)_2D_3$-treatment (Drocourt et al. 2002). The possibility of regulation for other CYP subfamilies is further required to investigate by VDR activation.

Phase II enzymes

Among the Phase II enzymes, dehydroepiandrosterone sulfotransferase (SULT2A1), abundantly expressed in the liver and intestine, was first reported to be a target of transcription of activation of VDR (Echchgadda et al. 2004). In LS180 colorectal adenocarcinoma cells, the treatment with $1,25(OH)_2D_3$ selectively upregulated human cytosolic SULT1C2 protein levels (Rondini et al. 2014). Moreover, it has been demonstrated that Vit D_3-inducible SULT1C2 transcription is mediated through a vitamin D response element (VDRE) in exon 1 (Barrett et al. 2016). Similarly, the regulation of UDP-glucuronosyltransferase (UGT) by VDR activation was reported in a few literatures. UGT1A gene expression is significantly induced by $1,25(OH)_2D_3$ treatment in LS180 cells (Meyer et al. 2012). Two intestinal UGT1A8 and UGT1A10 also have a correlation with transcription levels of VDR and $1,25(OH)_2D_3$ treatment significantly increased transcription of both UGT genes (Wang et al. 2016).

Pharmacokinetic drug interactions with VDR ligands

Pharmacokinetic drug interactions describe how the medication can affect the absorption, distribution, metabolism, or excretion of another medication. VDR ligands are likely to be administered simultaneously with other drugs as adjunctive treatment and nutritional supplements in patients with various diseases because they have various pharmacological and biological activities. Thus, VDR ligands could cause drug interactions by modulation of transporters and metabolic enzymes involved in drug disposition described in the previous section, leading to undesirable effects such as inefficiency and adverse effects. This section summarizes the pharmacokinetic drug interactions by VDR ligands reported in the literature.

Drug interactions via transporter modulations

Digoxin

Recently, drug–drug interaction (DDI) caused by modulation of transporters have been reported to have clinical relevance. In particular, there are several in vitro and in vivo studies demonstrating the clinical significance of P-gp in oral bioavailability of drugs.

Digoxin, the P-gp probe substrate, has been used to evaluate P-gp function from in vitro study or to investigate the in vivo DDI effect. The effect of VDR ligand on the expression and function of P-gp was also studied using digoxin as mentioned above. The apparent basal (B)-to-apical (A) permeability (P_{app}) of [^{3}H]digoxin was significantly increased in Caco-2 cell treated with $1,25(OH)_2D_3$ for 3 days compared to control group (15.1×10^{-6} versus 11.8×10^{-6} cm/s) without changes of the P_{app} in the A-to-B direction, resulting in increased efflux ratio (from 5.8 to 8.0) (Fan et al. 2009). These results were probably due to increase of P-gp expression by VDR activation. However, the P_{app} of digoxin in both A-to-B and B-to-A directions was not significantly changed by $1,25(OH)_2D_3$ when the transport was investigated in the rat everted ileac sac, suggesting that functional activity of P-gp had remained unchanged by VDR activation (Maeng et al. 2011). The effect of vitamin D_3 on digoxin pharmacokinetics has also been investigated in a clinical setting

(Kota et al. 2012). The plasma concentration of digoxin was not significantly changed by coadministration of vitamin D_3, which was consistent with the no changes in the A-to-B and B-to-A permeability of digoxin in the above transport study using rat everted ileac sac, suggesting that there was no clinically significant P-gp-mediated drug interaction between digoxin and vitamin D_3 (Kota et al. 2012).

However, in in vivo drug–drug interaction study in mice, the area under the concentration–time curve (AUC) of digoxin based on plasma and brain concentration was decreased (24% and 23%, respectively) in $1,25(OH)_2D_3$-treated group, which is caused by increased renal (74%) and total body (34%) clearances of digoxin (Chow et al. 2011a, b). The results suggest the regulation of P-gp by VDR ligand could affect the renal and brain disposition of P-gp substrates, resulting in changes in plasma concentration of digoxin. The reason for interspecies difference in pharmacokinetic changes of digoxin by VDR ligands needs to be clarified for the predictive accuracy of drug–drug interactions.

Adefovir dipivoxil

Effects of $1,25(OH)_2D_3$ on the in vtiro permeability of adefovir dipivoxil (P-gp substrate) and its metabolites, mono(POM)-PMEA and adefovir (MRP4 substrate), were also investigated in Caco-2 cells (Maeng et al. 2012). Basolateral (B) to apical (A) (B-to-A) transport of adefovir dipivoxil, the prodrug of adeforvir, in Caco-2 cells was increased (from 1.97 to 3.19) by $1,25(OH)_2D_3$ treatment, resulting in elevation of efflux ratio (ER) from 1.97 to 3.19. The ER value in $1,25(OH)_2D_3$-treated groups were reduced to 1.57 by verapamil treatment indicating the increased efflux of the drug could be due to upregulation of P-gp by $1,25(OH)_2D_3$. However, the ER ratio of adeforvir dipivoxil was not changed compared with control group because both A to B and B to A permeability of adefovir dipivoxil was increased by $1,25(OH)_2D_3$. The apical efflux of adeforvir, the active metabolite of adefovir dipivoxil, was also increased by $1,25(OH)_2D_3$, which was possibly due to increased MRP4 by $1,25(OH)_2D_3$. The metabolism of adefovir dipivoxil to form an adefovir was unaffected by $1,25(OH)_2D_3$ in this study, but the interpretation of the result should be careful because activity and expression of metabolic enzyme, an esterase, for hydrolysis of adefovir dipivoxil in Caco-2 cells are different from those in vivo (Maeng et al. 2012).

The effect of $1,25(OH)_2D_3$ on the oral absorption and disposition of adefovir dipivoxil was also investigated in rats (Yoon et al. 2015). After intravenous administration of adefovir dipivoxil, there was no significant difference in pharmacokinetic parameters such as AUC, CL, V_{ss}, MRT, and $t_{1/2}$ of adefovir between control and $1,25(OH)_2D_3$-treated rats suggesting that renal excretion was not affected by $1,25(OH)_2D_3$ because adefovir is eliminated primarily by renal excretion. In addition, in the in situ closed loop study, no significant difference was observed in the remaining fraction of adefovir dipivoxil in the all regions of the intestinal loop between the two groups. However, the AUC and maximum plasma concentration (C_{max}) of adefovir were significantly ($p < 0.05$) increased in $1,25(OH)_2D_3$-treated rats compared with control rats by 64.5 and 109.9%, respectively, resulting in increased bioavailability (21.5% increase). Based on all the results above, the enhanced bioavailability seemed to be due to increased permeability of adefovir across the basolateral membrane via the induction of MRP4 (Yoon et al. 2015).

Cefdinir and cefadroxil

Cefdinir and cefadroxil, the cephalosporin antibiotics, are eliminated via renal OAT1/OAT3. The AUC of cefdinir or cefadroxil after intravenous and oral administration was significantly increased in the $1,25(OH)_2D_3$ treatment group compared with the control group because of decreased CL and CL_R caused by significantly decreased kidney uptake and cumulative urinary recovery (Kim et al. 2014). Tissue distribution study also showed the reduced the tissue partition coefficient (K_p) in the kidney. These results suggested that decreased renal elimination of cefdinir and cefadroxil was attributed to downregulation of rOat1/3 by $1,25(OH)_2D_3$ treatment (Kim et al. 2014).

JPB485

JBP485 (cyclo-trans-4-L-hydroxyprolyl-L-serine), a dipeptide compound having liver and gastrointestinal protective effects, has also been reported to be primarily excreted by Oat1 and Oat3 in rat kidney (Guo et al. 2012). The AUC of JBP485 after intravenous administration were significantly increased by 2.6-fold in the$1,25(OH)_2D_3$ treatment group. In contrast, the renal clearance of JBP485 and uptake of JBP485 into kidney slices were significantly decreased after $1,25(OH)_2D_3$ treatment. The interaction between JBP485 and $1,25(OH)_2D_3$ could also be due to inhibitory effect of $1,25(OH)_2D_3$ on expression of Oats in rat kidney (Miao et al. 2013).

Drug interactions via metabolic enzymes modulations

Midazolam

Midazolam is a widely used probe substrate for CYP3A4 to investigate drug–drug interaction by modulation of CYP3A4. Treatment of Caco-2 cells with vitamin D

analogs led to increased midazolam hydroxylation activity due to enhancement of CYP3A4 mRNA and protein levels in Caco-2 cells (Schmiedlin-Ren et al. 1997). Likewise, dose-dependent increase in midazolam 1′-hydroxylation activity was observed with an increase in CYP3A4 protein in Caco-2 cells treated with $1,25(OH)_2D_3$ for 2 weeks (Thummel et al. 2001). Although midazolam was used to confirm the functional change of CYP3A4 modulation by VDR ligands, the above results suggest a potential of VDR ligand-mediated drug interaction, resulting in concentration change of CYP3A4 substrate.

Atorvastatin

The effect of vitamin D supplementation on pharmacokinetics of atorvastatin, an another CYP3A4 probe substrate, has been investigated (Schwartz 2009). The plasma concentration of atorvastatin and its active metabolites (2-hydroxy-atorvastatin acid and 4-hydroxy-atorvastatin acid) were significantly decreased in patient during vitamin D supplementation. In addition, there was a tendency of negative correlation between total active atorvastatin and $1,25(OH)_2D_3$ concentration. These results could be predicted because increase in CYP3A4 expression by VDR ligands have been previously reported. However, LDL-cholesterol and total-cholesterol was decreased in those patients indicating drug effects was enhanced by unknown mechanism.

Table 4 Effects of VDR ligands on *in vivo* pharmacokinetics of drugs mediated by modulation of transporter and metabolic enzyme

Drugs(Victim)	VDR ligand treatment (perpetrator)	Enzyme/transporter involved in drug disposition	Species	Route	Pharmacokinetic changes compared with control (% increase)	References
Digoxin	Cholecalciferol$1,25(OH)_2D_3$	P-gp	Human C57BL/6 Mouse	PO IV	No changes ↓ Blood AUC (24%) ↓ Brain AUC (23%) ↑ CL_{tot} (34%) ↑ CL_R (74%)	Kota et al. (2012) Chow et al. (2011a)
Adefovir dipivoxil	$1,25(OH)_2D_3$	P-gp, MRP4	SD Rat	IV PO	No changes ↑ Adefovir AUC (64.5%) ↑ Adefovir C_{max} (109.9%) ↑ F (21.5%)	Yoon et al. (2015)
Cefnidir	$1,25(OH)_2D_3$	OAT1/3	SD Rat	IV PO	↑ AUC (100%) ↓ CL_{tot} (49.1%) ↓ CL_R (86.7%) ↓ A_e (80.0%) ↑ AUC (117%) ↑ C_{max} (100%) ↓ CL_R (81.1%) ↓ A_e (59.2%)	Kim et al. (2014)
Cefadroxil	$1,25(OH)_2D_3$	OAT1/3	SD Rat	IVPO	↑ AUC (74.5%) ↓ CL_{tot} (47.1%) ↓ CL_R (75.0%) ↓ A_e (51.6%) ↑ AUC (33.3%) ↑ C_{max} (74.9%) ↓ CL_R (73.7%) ↓ A_e (59.2%)	Kim et al. (2014)
JBP485	$1,25(OH)_2D_3$	OAT1/3	SD Rat	IV	↑ AUC (156%) ↓ CL_{tot} (57.2%) ↓ CL_R (69.4%) ↓ A_e (29.0%)	Guo et al. (2012)
Atorvastatin	Ergocalciferol and Cholecalciferol	CYP3A4	Human	PO	↓ AUC Atorvastatin (37.4%),2-hydroxy atorvastatin acid (52.0%) 4-hydroxy atorvastatin acid (54.5%)	Schwartz (2009)

AUC Area under the concentration–time curve, C_{max} maximum plasma concentration, A_e cumulative urinary excretion of drug, CL_{tot} total body clearance, CL_R renal clearance

The mechanism of this controversial results remains to be elucidated.

As reviewed above, the VDR ligands have a potential to elicit drug interaction effects via the regulation of transporters and metabolic enzymes. The *in vivo* drug interaction effect from various non-clinical and clinical studies are summarized in Table 4.

Conclusion

In summary, this review summarizes the vitamin D related clinically relevant diseases and the vitamin D analogs which have been clinically approved or investigated so far. Importantly, the VDR ligand (i.e, VDR activation) modulates various drug transporters and metabolic enzymes such as CYP3A in vitro and in vivo. Indeed, the VDR ligands have a potential to elicit drug interaction effects via the regulation of transporters and metabolic enzymes. Thus, the development of new VDR ligand drugs may require considering of the potential for drug interactions by modulation of drug transporters and enzymes via VDR activation.

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Compliance with ethical standards

Conflict of the interest These authors declare that they have no conflict of interest.

Human and animal rights participants All institutional and national guidelines for the care and use of laboratory animals were followed.

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