Role of vitamin D in diabetic retinopathy: Pathophysiological and clinical aspects

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Published online: 7 October 2020
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Abstract
Epidemiological data predict a dramatic increase in the prevalence of diabetes and of diabetic retinopathy (DR) – the most common complication of diabetes-for which however we do not have so far effective tools for prevention and treatment. Since hypovitaminosis D is very frequent in patients with diabetes and vitamin D (VD) has vascular protective properties, several studies have addressed the association of VD deficiency with DR and its severity and progression, whereas the effects of VD supplementation on its natural history are largely unknown. Here we review the available evidence that supports the possible protective role of VD in DR and suggests to determine the VD levels in DR patients calling for a definitive randomized clinical trial to ascertain whether VD supplementation could protect against DR.

Keywords Vitamin D · Diabetic retinopathy · Diabetes · Microvascular disease · Endothelium

Abbreviations

| Acronym | Definition |
|---------|------------|
| VD      | Vitamin D  |
| DR      | Diabetic retinopathy |
| PTH     | Parathyroid hormone |
| VDR     | Vitamin D receptor |
| mVDR    | membrane-located vitamin D receptor |
| nVDR    | nuclear-located vitamin D receptor |
| NHANES  | National Health and Nutrition Examination Survey |
| T2DM    | type 2 diabetes mellitus |
| BMI     | Body mass index |
| RCTs    | Randomized controlled trials |
| HbA1c   | glycated hemoglobin |
| T1DM    | Type 1 diabetes mellitus |
| DED     | diabetic eye disease |
| OR      | odds ratio |
| YKL-40  | tyrosine (Y), lysine (K) and leucine (L)-40 |
| MCP-1   | Monocyte chemoattractant protein-1 |
| IL-6    | Interleukin 6 |

| Acronym | Definition |
|---------|------------|
| HOMA-IR | Homeostatic Model Assessment of Insulin Resistance |
| RHI     | reactive hyperemia index |
| EC      | Endothelial cells |
| VSMC    | Vascular smooth muscle cells |
| eNOS    | Endothelial nitric oxide synthase |
| NO      | Nitric oxide |
| MAO     | Monoamine oxidases |
| VEGF    | Vascular endothelial growth factor |
| PGI2    | prostacyclin |
| PLCγ    | Phospholipase C-Gamma |
| PKC     | Phosphokinase C |
| ROS     | Reactive oxygen species |
| TXNIP   | Thioredoxin-Interacting Protein |
| NLRP3   | (NOD)-like receptor protein 3 |
| TNF-α   | Tumor necrosis factor α |
| IL-17A  | Interleukin 17A |
| CD3     | Cluster-Defined 3 |
| CD28    | Cluster-Defined 28 |
| LPS     | LipoPolySaccharide |
| C3      | Complement 3 |
| RAAS    | Renin-angiotensin aldosterone system |
| AGEs    | Advanced glycation end products |
| NFκB    | Nuclear factor-kappa B |
| RAGE    | Advanced glycation end product receptor |
| GLO1    | glyoxalase 1 enzyme |
| ICAM-1  | Intercellular adhesion molecule-1 |
| ER      | Endoplasmic reticulum |

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https://doi.org/10.1007/s11154-020-09575-4

Reviews in Endocrine and Metabolic Disorders (2021) 22:715–727

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1 Introduction

Vitamin D (VD) is actually a steroid hormone produced in the skin after exposure to sun irradiation in the form of cholecalciferol. Diet contribution to daily VD requirement does not exceed the 20% of total unless food is not systematically fortified with VD [1]. Hepatic and kidney hydroxylation in position 25 and 1 respectively are necessary to produce active VD. Kidney 1 alpha hydroxylase is under control of endogenous PTH [1] (Fig. 1). Activated vitamin D, acts through its cognate vitamin D receptor (VDR) that encompasses two subtypes: the membrane-located mVDR, and the nuclear-located nVDR which are expressed in the majority of mesenchymally derived cells; mVDR regulates the non-genomic effects of VD, which are exerted within seconds to minutes after its activation, and is mainly involved in secondary signaling mechanisms implicated in channel responses, adipocyte metabolism, insulinitropic effects, and antiapoptotic pathways. Conversely, nVDR regulates the genomic effects of VD, which are exerted within hours to days after its activation. Once phosphorylated/activated, nVDR forms a trimer with the retinoid X receptor; this complex then binds to the VDR response element, leading to changes in transcription and expression of target genes [1]. Recently, it has also emerged the role of circulating VD binding protein as a regulator of hormone bio-availability to target tissue with a clinically prevalent inhibitory effect on VD activity [3].

VD is crucial for the calcium and skeletal homeostasis in physiological and disease states [1, 4, 5]. It also has many systemic functions which are also known as extraskeletal effects [6] most of which are based on solid experimental evidences and positive observational studies, but less frequently on adequate randomized clinical trials [7]. Among the numerous extraskeletal actions VD has been proposed to play a pivotal role in the regulation of fundamental processes involved in cardiovascular homeostasis [8], as well as in the modulation of inflammation and tuning of the innate and adaptive immunity systems, which appear to be relevant in the response to respiratory viral infections [9–11]. Moreover, several studies have addressed, without reaching to date an univocal conclusion, the prevalence and role of hypovitaminosis D in diabetes, as well as the impact of VD supplementation on the natural history of diabetes, blood

Fig. 1 Metabolic pathways involved in the synthesis of VD, main external sources of VD and the potential mechanisms underlying widespread hypovitaminosis D (defined according to Sempos et al., 2018 [2])
glucose control, and prevalence and severity of its macro and microvascular complications [6, 12].

Assessment of total 25OHVD is widely accepted as a marker of the VD status [2, 12] and is used by several agencies to support vitamin D dietary requirements and thresholds for hypovitaminosis D in population surveillance [2, 13, 14]. In fact, definition of VD deficiency is still an open issue, as apparent from different recommendations from various scientific bodies [15]. However, there is quite a strong agreement among experts that 25OHVD levels below 12 ng/mL (30 nmol/L) represent deficiency and levels above 30 ng/mL (75 nmol/L) are clearly sufficient. Conversely, it is still unclear the clinical meaning of levels between 12 and 30 ng/mL (30 and 75 nmol/L) with thresholds of sufficiency at 20 ng/mL (50 nmol/L), [16] or ≥30 ng/mL (≥75 nmol/L) [17] according to different guidelines. These discrepancies are at least in part due to the lack of 25OHVD assay standardization [12].

In fact, due to progressive changes in lifestyle such as, indoor work extemized by confinement due to COVID-19 pandemic [10, 11], or sun avoidance, hypovitaminosis D is still widespread [17]. Implementing the <20 ng/ml (<50 nmol/L) threshold [16], approximately one third of the world population is deficient with figures increasing to 40% in Europe [18, 19]. Severe VD deficiency, defined as <30 nmol/l (or < 12 ng/ml), can be found in about 7% of the global population [17]. According to the NHANES, a large cross-sectional study on over 8000 subjects, 42% of the US population display insufficient VD levels African-Americans present the highest prevalence rate (82%), followed by Hispanic-Americans [20]. Interestingly, epidemiological data show that Italy is one of the Countries with the highest prevalence of VD deficiency in Europe [21]. A study from Isaia et al. on 700 women aged 60–80 years in Italy found values of 25OHVD lower than 5 ng/ml in 27% and lower than 12 ng/ml in up to 76% of enrolled subjects [22]. Moreover, another Italian study found a winter prevalence of hypovitaminosis D in as many as 32% of healthy postmenopausal women, and to 82% in patients engaged in long-term rehabilitation programs because of different neurological disorders [23].

As mentioned above, this widespread deficiency of circulating VD [24] besides its detrimental skeletal effects [25] has been linked to the development and progression of several diseases such as cancer [26], obesity [27], and healthy aging [28].

2 Vitamin D and diabetes

2.1 Hypovitaminosis D

In vivo studies have shown that T2DM rats display lower levels of 1,25OHVD as compared to controls [29], likely due to impaired hepatic and renal metabolism of VD [30]. Reduced 25OHVD levels have been hypothesized to be involved in the pathophysiology of skeletal fragility of patients with diabetes and in patients in whom diabetes may develop due to glucocorticoid treatment or endocrine diseases [4, 31–33]. In fact, it has been consistently reported that patients with T2DM had decreased circulating levels of 25OHVD [34, 35]. Interestingly, in an observational Italian study on 66 women with T2DM out of a sample of about 800 postmenopausal women the prevalence of severe VD deficiency was significantly higher in diabetic vs control subjects (39 vs. 25%, respectively) [35]. Recently, an association between low levels of circulating VD with poor glycemic control in patients with T2DM has also been reported [36]. Low levels of circulating 25OHVD are very frequently found also in obese non diabetic subjects, and are inversely correlated with BMI and adiposity [37]. The Copenhagen City Heart Study, a 29 year long prospective cohort study on nearly 10,000 patients, showed an association between low VD levels and increased risk of T2DM; in fact, the cumulative incidence of T2DM increased with decreasing VD concentrations at baseline, and when categorized by VD concentrations patients in the lowest quartile had an hazard ratio (HR) of 1.35 (95% CI 1.09–1.66) of developing T2DM [38]. Moreover, a historical prospective cohort study on over 100,000 subjects showed that patients with levels of VD <25 nmol/L had increased odds of transitioning from normal to impaired fasting glucose (OR 1.13, 95% 1.03–1.24), from normoglycemia to diabetes (OR 1.77, 95% 1.11–2.83), as well as from impaired fasting glucose to diabetes (OR 1.43, 95% 1.16–1.76) [39].

2.2 VD supplementation

2.2.1 Glycometabolic control

A recent study and a meta-analysis of RCTs showed that VD supplementation in T2DM patients can improve HbA1c, insulin resistance, and insulin secretion in short-term intervention [40, 41]. Another meta-analysis of RCTs showed, a favourable effect of VD administration on fasting glucose only in patients with poorly controlled diabetes [42]. In a recent meta-analysis of interventional studies in obese non diabetic patients no clear evidence for a beneficial effect of VD supplementation on weight loss or cardio-metabolic parameters was reported [43]. This may at least in part due to a VD “resistant state” which is consistently reported in obesity [44, 45].

2.2.2 Prevention of diabetes

In a recent multicenter, randomized, placebo-controlled trial involving more than 2.400 subjects at high risk for T2DM not necessarily VD deficient, VD3 supplementation did not
significantly lower the risk of diabetes when compared to placebo, after a median follow-up of 2.5 years [46]. However, in a post hoc analysis of the same study data from subjects with a baseline 25OHVD less vs greater than 12 ng/mL (30 nmol per liter) the hazard ratio favoured VD treatment [46]. In the Tromsø VD and T2DM Trial on 511 subjects with prediabetes a slightly but not significantly lower risk of progression to diabetes was observed in the VD vs placebo treated groups [47]. Both trials were not powered to detect the 10–15% observed reduction of diabetes risk among persons at risk for diabetes. Moreover, as many other VD trials the enrollment of large number of VD sufficient subjects likely heavily impacted on the conclusions [48].

### 2.2.3 Macrovascular complications

Data on the effects of VD on cardiovascular risk and complications of diabetes are controversial. A recent RCT on over 25,000 patients found that VD supplementation for five years had no cardiovascular protective effect (HR 0.97, 95% CI 0.85–1.12; \( p = 0.65 \)) [49]; however, these results may have been affected by selection bias of subjects without VD deficiency [7]. Indeed, other reports led to different results. In fact, meta-analyses show that hypovitaminosis D could reduce cardiovascular risk [50, 51]. Moreover, clinical studies showed that VD deficiency is linked to surrogate parameters of cardiovascular damage such as endothelial dysfunction, assessed as flow mediated dilation at the brachial artery [52], as well as with carotid intima-media thickness [53]. Mechanistic studies show that VD played a pivotal role in vascular protection and regeneration [54, 55], and that normalization of VD levels may significantly improve indexes of vascular function [56–58]. VD has also been reported to have protective roles against cerebrovascular complications [59].

### 2.2.4 Microvascular complications

Diabetic nephropathy is one of the most common causes of chronic kidney disease. Microalbuminuria and proteinuria are characteristic markers of this complication [60, 61]. In a meta-analysis of 9 RCTs a positive but not significant trend towards a VD mediated reduction in albuminuria and its possible role in slowing progression of diabetic nephropathy has been hypothesized [62]. A significant difference in 25OHVD levels in patients with painful diabetic peripheral neuropathy, has been recently consistently reported [63]. Treatment with VD in patients with painful diabetic neuropathy has also been associated with a significant decrease in the symptoms of the disease [64].

### 3 Diabetic retinopathy

A recent meta-analysis on 35 prevalence studies as well as on 4 incidence studies of diabetic eye disease (DED) among individuals with diabetes in Europe has recently been published [65]. Any diabetic retinopathy (DR) was prevalent in 25.7% (95% CI 22.8–28.8%) being significantly higher in persons with T1DM as compared to persons with T2DM (54.4% vs. 25.0%). The pooled mean annual incidence of any DR in patients with T2DM was 4.6% (95% CI 2.3–8.8%). Authors estimated that persons with diabetes affected by any DED in Europe will increase from the current 6.4 million to 8.6 million in 2050, of whom 30% require close monitoring and/or treatment. It is noteworthy that currently there are no widely effective interventions that can be used to prevent and/or to treat DR in addition to optimization of glucose control and blood pressure. Large epidemiological studies have shown that the threshold for the appearance of DR is at HbA1c levels of 6.5%, just above the upper limit of normal [66]. However, this biochemical target is not often reached despite intensive follow-up and residual hyperglycemia exposes to an increased risk of DR as well as of other serious complications [67]. Further intensification of treatment to maintain HbA1c below 6% with the modalities available today poses severe risks of hypoglycemia in T2DM patients with increased mortality [67]. In this perspective, local and systemic treatments with biological compounds as well as with the somatostatin analog octreotide [68–70] are promising additional tools.

### 4 Vitamin D in diabetic retinopathy

#### 4.1 Clinical aspects

##### 4.1.1 Hypovitaminosis D

In 2000, Aksoy et al. found an inverse relationship between presence and severity of DR, and VD concentrations, being the lowest in proliferative DR and the highest in diabetic patients without DR [71]. In 2011, a cross-sectional study on over 500 patients showed that VD deficiency was associated with increased prevalence of DR in T1DM patients; in this study, the prevalence of DR was double in VD deficient vs. VD sufficient patients (18% vs 9%, respectively; \( p = 0.02 \)); and in logistic regression, DR was associated with VD deficiency (OR 2.12 [95% CI 1.03–4.33]) [72]. Similarly, a retrospective cross sectional study on nearly 1000 patients from the NHANES showed that the prevalence of severe and mild DR were higher in poorly controlled patients with hypovitaminosis D vs. VD sufficient patients; in addition, a multivariate ordinal regression analysis on this database showed an association between VD deficiency and DR severity (OR 2.22, 95% CI: 1.36, 3.65) [73] (Table 1). These
data were confirmed by meta-analyses. One was performed on over 17,000 subjects from fifteen observational studies, and showed that T2DM patients with VD deficiency had an increased risk of DR (OR = 2.03, 95% CI: 1.07, 3.86); furthermore, patients with DR displayed a decrease in VD levels of 1.7 ng/mL (95% CI: −2.72, −0.66) [79]. Another was performed on over 10,000 participants from fourteen observational studies, and showed a significant association between DR and VD deficiency (OR = 1.27, 95% CI: 1.17, 1.37; \( P = 0.001 \)); furthermore, patients with DR displayed a decrease in VD of 1.32 ng/mL (95% CI: −2.50, −0.15) [80]. In addition, a multitude of cross-sectional studies also very recent [74] performed in different populations—such as Italian [75], japanese [76], chinese [77], and african-american [78]—reported consistent data (Table 1). The high reproducibility of the findings, and their cross-ethnicity, strengthened the hypothesis of an association of VD with DR, and attenuated the concerns raised by two studies in this regard. In fact, a prospective observational study showed that VD deficiency independently predicted all-cause mortality, but not the development of microvascular complications [81]. Moreover, a sub-analysis of the Veteran Affairs Trial reported that VD status had no impact on the incidence of vascular events in high-risk veterans with diabetes [82]. Noteworthy, a sub-analysis of the Field Study, a placebo-controlled trial on nearly 10,000 T2DM patients, showed that subjects with hypovitaminosis D had a higher cumulative incidence of microvascular events; in fact, a 50 nmol/L difference in VD levels was associated with a 18% (\( p = 0.007 \)) increase in risk of microvascular complications [83]. More recently, a sub-analysis of the Rotterdam Study, a prospective cohort study on over 5500 patients, showed that patients with hypovitaminosis D were at increased risk for DR, independently of the presence of cardiovascular risk factors [84].

### 4.1.2 Vitamin D supplementation

The active form of VD calcitriol supplementation has been shown to attenuate ex vivo and in vivo choroidal vasculature angiogenesis [85]. However, despite the reasonable rationale provided by the above discussed association data prospective studies on the effect of VD administration on DR in humans are lacking. In fact, although treatment of DR is often associated with the administration of dietary supplements [86] only very few studies specifically supplementing VD in patients with DR have been published so far [87–89]. These were short term studies mainly focusing on biochemical, immunological and inflammatory markers of vascular damage in patients with

| Author (Ref) | #Pts | VDD definition (ng/ml) | Main finding | OR (95% CI) |
|-------------|------|------------------------|--------------|-------------|
| Aksoy [71]  | 66 DM/20C | 1,25OHVD | VDD associated with DR/severity | NA |
| Kaur [72]   | 517T1DM | 25OHVD < 20 | DR 18% VDD vs 9% VDS | 2.12 (1.04–4.33) *1 |
| Long [73]   | 842 T2DM | 25OHVD < 20 | mDR/pDR > in uncontrolled VDD vs VDS | 2.26 (1.359–3.648) *2 |
| Afard [74]  | 60T2DM | 25OHVD < 20 | VD < in pts. with vs without DR | NA |
| Zoppini [75] | 715T2DM | 25OHVD < 30 | VD < in n DR vs mDR vs pDR | 0.758 (0.607–0.947) *3 |
| Shimo [76]  | 75T1DM | 25OHVD < 20 | VDD associated with DR | 3.45 (1.11–10.6)*4 |
| He [77]     | 1520T2DM | 25OHVD < 20 | DR/stDR > VDD vs VDS | DR 1.93 (1–23.2) stDR 2.42 (1.61–3.63) *5 |
| Millen [78] | 1339T2DM | 25OHVD <20, <30, >30, | VDD associated with DR | 0.77 (0.45–1.32) 0.64 (0.37–1.10) 0.39 (0.20–0.75) *6 |

*1 Multivariate analysis VDD with DR
*2 Ordinal regression in poorly controlled DM
*3 Multiple logistic regression analysis of association of serum 25OHD levels with composite microvascular end point, inclusive of diabetic retinopathy and/or nephropathy; OR for each SD increase in 25OHD level (ie, 13 ng/mL)
*4 Multivariate regression analysis of factors independently associated with DR
*5 Association of VDD with DR/stDR in a logistic non adjusted regression model
*6 Logistic regression for DR by categories of season-adjusted 25OHD trend for participants with 25OHD of 12- < 20, 20- < 30, and ≥ 30 ng/ml, respectively

VDD Vitamin D deficiency, VDS Vitamin D sufficiency
mDR mild diabetic retinopathy, pDR proliferative diabetic retinopathy
stDR sight threatening diabetic retinopathy
OR Odds ratio
CI Confidence intervals
NA not applicable
4.2 Pathophysiological aspects

4.2.1 General mechanisms of VD vascular protection in diabetes

VD protects vessels against diabetes via several intertwined mechanisms. Al Mheid et al. showed that VD status is independently associated with digital reactive hyperemia index (RHI), a marker of microvascular function, in healthy subjects; notably, the authors also found a significant increase in RHI in VD deficient patients after 6 months of VD oral supplementation [56]. Similarly, a study reported the association between VD and microvascular function, measured as RHI, in healthy women [92]. In addition, an association between VD and vascular function has been described in patients with diabetes [93]; moreover, a report described improved vascular function parameters in patients with diabetes, after VD oral supplementation [94]. Furthermore, in patients with diabetes and VD deficiency reduced endothelium-dependent microvascular function, assessed by iontophoresis of acetylcholine, when compared to patients with diabetes and non-deficient VD levels [95].

Experimental studies have shown that VD improves endothelial dysfunction and promotes vascular regeneration through the activation of VDR, that in turn regulates the expression of numerous genes involved in fundamental processes of potential relevance to cardiovascular function [96]; in fact, the suppression of VDR in endothelial cells (EC) alters vascular homeostasis [1, 97]. It is noteworthy that VDR is expressed in EC, pericytes, and vascular smooth muscle cells (VSMC).

4.2.2 Specific putative mechanisms of VD protection in DR

Here we will review a selection of the putative mechanisms possibly involved in specific VD protective effects against DR (Fig. 2).

VD increases eNOS-dependent NO production

VD promotes NO production in EC [93]; in addition, in endothelial-specific VDR−/− mice reduced endothelial NO synthase (eNOS) expression was reported [1]. In the presence of oxygen, NADPH and other co-factors, eNOS catalyzes the oxidation of L-arginine to form L-citrulline and NO. NO is a gas that easily diffuses across the cell membrane to the adjacent VSMC where it leads to a cascade of events, resulting in VSMC relaxation and thereby dilation of the vessel. In addition, NO is known to exert vasculo-protective activities, such as enhancement of endothelial cell survival [98] and inhibition of platelet aggregation. Finally, NO has key role in the pathogenesis of DR [99] and its modulation by VD may have protective effects in DR.

VD reduces oxidative stress

In diabetic mice VD mitigates oxidative stress through a multitude of intertwined mechanisms, such as enhancing the antioxidant defence systems [100], preserving mitochondrial function [100], restoring eNOS function (see above), and reducing the activation of monoamine oxidases (MAO) [101]. Interestingly, a recent study demonstrated that exposure to a high level of glucose caused upregulation of pro-inflammatory cytokines and a decrease in anti-oxidant enzyme expression both in vitro and in vivo. VD treatment increased cell viability, reduced reactive oxygen species production and caspase-3/7 activities in high-glucose-treated retinal pigmented epithelial cells suggesting that VD can protect the retina from high-glucose-induced oxidative damage and inflammation [102].

VD enhances vascular endothelial growth factor (VEGF) synthesis and release

VEGF has a key pathogenetic role in proliferative DR [103]. VD induces up-regulation of VEGF and of its receptors, by direct binding of VDR to two areas of the VEGF promoter [104]. VEGF primarily exerts its effect in DR through the production of vasodilatory mediators. In addition, VEGF signalling through its cognate receptor, increases eNOS – indirectly via calmodulin, directly via phosphorylation of eNOS, and via increase of eNOS levels – and thereby increases NO; moreover, VEGF promotes production of the vasodilatory prostanoctid prostacyclin (PGI2) through activation of phospholipase A2 via PLCγ/PKC, and plays a pivotal role in vascular regeneration [105]. Interestingly, VDR agonists were found to have significant and selective retinal anti-angiogenic properties modulating expression of VEGF in zebrafish [106] and in diabetic rats [107].

VD modulates inflammation and the immune system

Immune and inflammatory mechanisms also associated with diabetic gut microbiota dysbiosis [108–110] may play a role in the pathogenesis of DR. VD on the one hand reduces chronic inflammation [111] by inhibiting the activation of the ROS/TXNIP/NLRP3 inflammasome pathway [112], and by
suppressing the nuclear factor-kappaB (NF-κB) signalling pathway [113]. On the other hand, VD plays major role in the immune-system vascular activities: in fact (a) it increases the activity of myeloid angiogenic cells, by restoring their function and by enhancing their recruitment [54, 55]; (b) it modulates the immune system [114], by promoting the innate immune response and inhibiting the adaptive immune response [9], and by regulating regulatory T cells and immature dendritic cells, and thereby halting the progression of angiopathy [115]; and (c) it decreases the number and activation of macrophages and dendritic cells in the retina [116]. Interestingly, VD decreased diabetes-induced ROS and exerted protective effects against retinal vascular damage and cell apoptosis in association with inhibition of the ROS/TXNIP/NLRP3 inflammasome pathway in diabetic rat and in human retinal cells [116]. Furthermore, patients with proliferative DR were reported to have decreased serum level of 1,25OHVD and increased production of IFN-γ, TNF-α, IL-6, and IL-17A, by anti-CD3 and anti-CD28 antibodies activated PBMCs whereas 1,25OHVD significantly inhibited the proliferation of PBMCs, as well as the secretion of IFN-γ, TNF-α, IL-6, and IL-17A [117].

VD reduces transforming growth factor-β (TGF-β) production
Pre-treatment of mesothelial cells with VD inhibits high glucose and LPS-induced TGF-β production [118]. Accordingly, diabetic rats receiving VD showed lower levels of TGF-β in the retina, when compared to non-VD treated diabetic controls [107]. In addition, VD has been shown to reduce urinary TGF-β levels as well as albuminuria in diabetic patients in both a prospective clinical study [63], as well as in a randomized double-blind controlled study [119]. TGF-β plays a pivotal role in retinal microvascular homeostasis [120]. Indeed, TGF-β regulates the production of extracellular matrix, the replication and survival of EC, the interactions of EC and pericytes to ensure vessel stability, and the remodelling of vessels [121, 122]. When TGF-β signalling in vascular cells is increased vessels in the retina may show excess extracellular matrix, tortuosity, and aneurysms [123]. In fact, TGF-β has been suggested to be one of the possible biomarker of DR [124, 125].

VD regulates the activation of the complement cascade
VD reduces circulating C3 by modulating liver inflammation and by decreasing C3 secretion from adipocytes [126]. It is noteworthy that in diabetes complement dysregulation plays a role in the pathogenesis of diabetic retinopathy [127]; in fact, microvessels from animals and patients with short duration of diabetes display terminal products of complement activation, whereas healthy controls do not [128]. These alterations lead to increased presence and size of microthrombi, that are topographically associated with apoptotic cells, and that can contribute to capillary obliteration and retinal ischemia [129].

VD inhibits the renin-angiotensin aldosterone system (RAAS)
High blood pressure is known to be associated with DR [130] and upregulation of RAAS has been reported among the pathogenetic mechanisms of DR [131]. Several clinical studies have reported an inverse relationship between circulating VD levels and plasma renin activity [132]. In addition, VD
VD decreases the detrimental effects of advanced glycation end products (AGEs) VD supplementation in T2DM patients down-regulates the levels of AGEs and the gene expression of its cognate receptor (RAGE); these mechanisms appear to be at least in part mediated by glyoxalase I enzyme (GLO1) – an enzyme involved in the degradation and removal of AGEs – as VD supplementation tends to increase its expression [134]. In addition, VD modulates the vascular effects of AGEs by reducing the diabetes-induced increase of IL-6 and of NFkB-p65 DNA binding activity, both key mediators of AGEs signalling [135]. AGEs and RAGE are among the major pathways involved in the pathophysiology of diabetic complications and of DR [136], as their interaction induces the translocation of NF-κB, and the subsequent transcription of endothelial dysfunction biomarkers, such as intercellular adhesion molecule-1 (ICAM-1), endothelin-1, and E-selectin [137].

VD reduces endoplasmic reticulum (ER) stress VD decreases the expression of the classical ER stress pathway PERK-eIF2α-ATF4-CHOP, by modulating the activity of GRP78 – a master regulator of ER stress [138]. Moreover, VD-sufficient patients showed lower ER stress in monocytes as compared to VD deficient patients [139]; in addition, the deletion of the VDR in macrophages from T2DM patients activated ER stress, and induced a pro-adhesive phenotype in monocytes. Indeed, diabetes promotes the expression of endogenous biomarkers of ER stress, among which GRP78, a member of the heat shock protein family. Interestingly, also ER stress has been related to DR [140, 141].

VD regulates apoptosis of endothelial cells VD induces an overall pro-survival transcriptional program characterized by upregulated expression of anti-apoptotic genes and downregulated expression of pro-apoptotic genes [142]; in addition, VD determines the non-genomic activation of the PI3K-Akt survival kinase pathway [143], it also reduces apoptosis of EC by increasing NO production (see above).

Other possible mechanisms Based on the body of evidences presented above it is reasonable to hypothesize that VD could exert its vascular protective activities also by regulating diabetic leukostasis, and/or by improving the myogenic response of microvessels. Diabetic leukostasis is a phenomenon observed in diabetic retinal vessels, which has been proposed to be implicated in the pathogenesis of DR [144]. Even though there are currently no data on the effect of VD on leukostasis, it can be hypothesized that VD may co-orchestrate the response of immune cells to the stressed microvessels, thereby modulating neighbouring leukocytes, repairing cellular damage/alterations, and maintaining vascular homeostasis. In contrast, the myogenic response is the constriction of the afferent arterioles to increases in perfusion pressure, in order to dampen the transmission of pressure to capillaries and parenchyma. Thus, the impaired myogenic response induced by diabetes appears as a mechanism for accelerating microangiopathy [145]. To date, there are no evidences on the effect of VD on the impaired myogenic response in diabetes. However, the molecular actions described above, coupled with its activities on VSMC function [146, 147], suggest the hypothesis that VD could protect retinal microvessels against diabetes at least in part via restoring the myogenic response.

5 Conclusions

The above reviewed clinical and pathophysiological aspects suggest that VD deficiency may be implicated in the development and progression of DR. Since hypovitaminosis D is widespread and heavily impacts in the whole world [13], and is related also to development and natural history of T2DM, it can be suggested to determine the levels of VD in DR patients. Moreover, it can be suggested to integrate VD with cholecalciferol in patients with DR and severe VD deficiency, as well as in the general population [148].

Over the last years the quest for adjunct drugs for the prevention and treatment of DR has made little progress; in fact, so far prevention and treatment attempts of DR mainly consisted of drugs that target the pathways of glucose toxicity or discrete molecular abnormalities caused by diabetes [149]. The theoretical added value of VD could be to provide a broad protection to vascular cells enhancing vascular repair, reversing endothelial dysfunction, decreasing inflammation, and/or oxidative stress. All the above considerations provide a strong rationale for a well-designed, placebo-controlled, randomized clinical trial to learn whether VD supplementation protects against DR onset and/or progression. Knowing that VD protects retinal microvessels against diabetes and exerts beneficial effects on endothelial dysfunction may be of high clinical relevance. In fact, since VD deficiency is extremely common, particularly in patients at increased cardiovascular risk [7], and its supplementation is both safe and low-cost [148], it could have the potential to represent a new strategy for the prevention and treatment not only of DR but of other diabetic vascular diseases.

Acknowledgements The authors are grateful to Dr. Camillo Bechi Genzano and Dr. Erika Pedone for their help with the artwork. This work...
was supported by the Marie Skłodowska-Curie Actions 795877 to FT and by the Italian Ministry of University and Research to AMF and AG.

Compliance with ethical standards
Conflict of interest Authors have no conflicts of interest to declare.

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