Vitamin D supplementation improves pathophysiology in a rat model of preeclampsia

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Faulkner JL, Cornelius DC, Amaral LM, Harmon AC, Cunningham MW, Jr, Darby MM, Ibrahim T, Thomas DS, Herse F, Wallukat G, Dechend R, LaMarca B. Vitamin D supplementation improves pathophysiology in a rat model of preeclampsia. Am J Physiol Regul Integr Comp Physiol 310: R346–R354, 2016. First published December 16, 2015; doi:10.1152/ajpregu.00388.2015.—Deficiency of vitamin D (VD) is associated with preeclampsia (PE), a hypertensive disorder of pregnancy characterized by proinflammatory immune activation. We sought to determine whether VD supplementation would reduce the pathophysiology and hypertension associated with the reduced uterine perfusion pressure (RUPP) rat model of PE. Normal pregnant (NP) and RUPP rats were supplemented with VD2 or VD3 (270 IU and 15 IU/day, respectively) on gestation days 14–18 and mean arterial pressures (MAPs) measured on day 19. MAP increased in RUPP to 123 ± 2 mmHg compared with 102 ± 3 mmHg in NP and decreased to 113 ± 3 mmHg with VD2 and 115 ± 3 mmHg with VD3 in RUPP rats. Circulating CD4+ T cells increased in RUPP rats to 7.90 ± 1.36% lymphocytes compared with 2.04 ± 0.67% in NP but was lowered to 0.90 ± 0.19% with VD2 and 4.26 ± 1.55% with VD3 in RUPP rats. AT1-AA, measured by chronotropic assay, decreased from 19.5 ± 0.4 bpm in RUPPs to 8.3 ± 0.5 bpm with VD2 and to 15.4 ± 0.7 bpm with VD3. Renal cortex endothelin-1 (ET-1) expression was increased in RUPP rats (116.0 ± 2.1-fold change from NP) and decreased with both VD2 (3.3 ± 1.1-fold) and VD3 (3.1 ± 0.6-fold) supplementation in RUPP rats. Plasma-soluble FMS-like tyrosine kinase-1 (sFlt-1) was also reduced to 74.2 ± 6.6 pg/ml in VD2-treated and 91.0 ± 16.1 pg/ml in VD3-treated RUPP rats compared with 132.7 ± 19.9 pg/ml in RUPP rats. VD treatment reduced CD4+ T cells, AT1-AA, ET-1, sFlt-1, and blood pressure in the RUPP rat model of PE and could be an avenue to improve treatment of hypertension in response to placental ischemia.

hypertension; immune activation; preeclampsia; vitamin D

PREECLAMPSIA (PE) IS A CLINICAL condition occurring in up to 7% of pregnancies in the United States commonly manifesting in late gestation (>20 wk gestation) with hypertension, placental ischemia, and low birth weight (5, 27, 47, 48, 58). Current treatment strategies for preeclampsia are targeted at safely lowering blood pressure and alleviating maternal complications (5, 48).

PE pregnancies are characterized by an abnormal immune profile compared with that seen in normal pregnancies. PE women exhibit an altered immune balance favoring proinflammatory factors, such as CD4+ T cells, B cells, inflammatory cytokines, and autoantibodies to the angiotensin type 1 receptor (AT1-AA), which are known to stimulate production of antiangiogenic protein-soluble FMS-like tyrosine kinase-1 (sFlt-1) (18, 33, 34, 56, 57). In contrast, anti-inflammatory T regulatory cells (TREGs) are decreased in PE (22, 53, 56). These immune alterations are recapitulated in the established experimental model of PE, the reduced uterine perfusion pressure (RUPP) rat (1, 20, 21). Adoptive transfer of CD4+ T cells from RUPP rats induces hypertension, AT1-AA, inflammatory cytokines and sFlt-1, and endothelin-1 (ET-1) in normal pregnant rats, indicating the significant role these cells play in the pathogenesis of this disease (63). Furthermore, AT1-AA and sFlt-1 play a significant role in the development of endothelial dysfunction and hypertension in PE and have been found to correlate with PE severity in patients (15, 25, 30, 43, 60, 64, 65, 67, 69, 71, 72). AT1-AA infusion induces many pathophysiological characteristics of PE, including increased blood pressure, vascular resistance, ET-1, and sFlt-1 (8, 35). Although the contribution of immune factors in the pathogenesis of preeclampsia is well established, immune therapy in preeclamptic women is limited by the potential for teratogenic effects of many anti-inflammatory and antihypertensive drugs.

The steroid hormone vitamin D (VD) is well established as a necessary factor for healthy calcium homeostasis; however, emerging findings of nonclassical effects of VD signaling have encouraged studies examining its potential in many disease states. VD has recently been recognized for its role as a potent factor in immune regulation in human physiology (6, 29, 31, 41, 44). Vitamin D receptor activation on immune cells inhibits proliferation of CD4+ T cells, B-cell activation, and also increases transcription of FoxP3+ TREGs (10, 29, 31, 39). Studies in clinical populations vary with regard to the potential benefit of the anti-inflammatory effects of VD in disorders in which immune activity is known to play a role, such as hypertension and PE. However, it has been suggested that VD deficiency (<50 nmol/l) in both mid-term and late-term gestation is associated with PE in pregnant women (4, 7, 66). Importantly, VD supplementation has been shown to reduce incidences of PE and improve fetal growth in some clinical studies; however, there remains a need for large-scale, standardized clinical trials to confirm these findings (23, 24, 28). There is little experimental data investigating the role of VD in placental ischemia and the immunoregulatory effects of VD in rodent models of PE have not been fully evaluated. To examine
this, we utilized both forms of VD that are metabolized in humans and animals, vitamin D2 (VD2) and vitamin D3 (VD3), for supplementation to the RUPP rat model of PE. We recently demonstrated that supplementation of VD2 or VD3 decreased circulating CD4+ T cells and lowered blood pressure in the RUPP rat model of PE (14). However, hypertensive mechanisms associated with T-cell activation, such as AT1-AA, ET-1, inflammatory cytokines, and sFlt-1 in response to placental ischemia were not determined. Moreover, the effect of vitamin D supplementation on fetal growth and survival was not examined. Therefore, we hypothesized that vitamin D administration to the RUPP rat model of placental ischemia would reduce inflammatory T cells, leading to a decrease in AT1-AA, ET-1, sFlt-1, and ultimately blood pressure during pregnancy.

MATERIALS AND METHODS

All procedures involving animals in this study were performed in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals and were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center. Animal experiments were conducted on timed-pregnant Sprague Dawley rats (Harlan, Indianapolis, IN) that were housed under a 12:12-h light-dark cycle and fed a standard laboratory chow diet.

Vitamin D administration to RUPP rats. For our studies, we used an established model of placental ischemia, the reduced uterine perfusion pressure (RUPP) rat. The RUPP procedure in Sprague-Dawley rats has been shown to induce many of the pathological characteristics of preeclampsia (1, 20, 21). Six groups of rats were used for this study: Normal Pregnant (NP) (n = 15), Normal Pregnant + Vitamin D2 (NP+VD2) (n = 6) (County Line Pharmaceuticals, Brookfield, WI), Normal Pregnant + Vitamin D3 (NP+VD3) (n = 6) (Enfamil, Glenview, IL), RUPP (n = 19), RUPP + Vitamin D2 (RUPP+VD2) (n = 11), and RUPP + Vitamin D3 (RUPP+VD3) (n = 13). The RUPP procedure was performed in pregnant rats under isoflurane anesthesia on gestational day 14 (GD14) by placing a constrictive silver clip on the abdominal aorta superior to the bifurcation (0.203 mm) and on both bilateral uterine arteries at the ovarian end (0.100 mm), as described previously (1, 20, 21). VD2 (ergocalciferol) and VD3 (cholecalciferol) were administered to NP and RUPP rats on GD14–GD18 at a dose of 270 IU and 15 IU, respectively, by daily gavage. Doses were determined on the basis of a concentration:effect mathematical formula for $2^{-\Delta\Delta Ct}$ (2$^{-\Delta\Delta Ct}$ gene of interest – avg Ct B-actin), which has been previously recommended by Applied Biosystems (Applied Biosystems User Bulletin, no. 2, 1997).

Measurement of circulating 25(OH)VD. Plasma isolated by centrifugation of whole blood on day of death was analyzed for 25(OH)VD via LC/MS analysis. Ten microliters of 0.2 ng/ml 25(OH) vitamin D$_3$ internal control was added to 200 ll rat plasma followed by acetonitrile (500 ll). Samples were then centrifuged at 10,000 g, and the organic phase extracted from solution by drying with nitrogen gas. Samples were reconstituted with water and reextracted with solid-phase extraction column (Waters Corp, Milford MA), washed with methanol, and eluted with ethyl acetate prior to analysis. All samples were analyzed using an autosampler on a Dionex Ultimate 3000 High-Performance Liquid Chromatography System (Dionex, Bannockburn, IL) prior to analysis on an ABSciex 4000 Q trap tandem mass spectrometer with electrospray ionization (ABSciei, Foster City, CA).

Determination of circulating sFlt-1, nitrate/nitrite, TNF-α, and IL-6. Commercially available ELISA from R&D Systems were used to measure sFlt-1, TNF-α, and IL-6 in rat plasma (Minneapolis, MN). ELISA to measure plasma nitrate/nitrite for determination of circulating nitric oxide was obtained from Cayman Chemicals (Ann Arbor, MI).

Statistical analysis. All data were expressed as means ± SE. Statistical analysis was performed in GraphPad Prism (La Jolla, CA) software using standard Student’s $t$-test and/or one-way ANOVA comparing the control and treated groups. $P$ value $<0.05$ was considered significant.

RESULTS

VD treatment improved blood pressure in RUPP rats. MAP in NP rats was 102.2 ± 3.2 mmHg and was not significantly changed in NP+VD2 (92.5 ± 4.4 mmHg, $P = 0.11$) or NP+VD3 rats (93.3 ± 4.4 mmHg, $P = 0.14$) (Fig. 1A). MAP increased significantly to 122.5 ± 2.0 mmHg ($P < 0.0001$) in RUPP rats compared with NP rats. VD2 and VD3 treatment significantly reduced MAP in RUPP rats to 113.4 ± 3.4 ($P < 0.05$) and 115.4 ± 2.7 mmHg ($P < 0.05$), respectively.

VD reduced fetal death in RUPP rats and did not cause adverse fetal effects in NP rats. Intraperitoneal growth restriction as measured by average pup weight on GD19 decreased to 1.84 ± 0.05 g ($P < 0.01$) in RUPP rats compared with 2.28 ± 0.12 g in NP and was unaltered in RUPP+VD2
Mean Arterial Pressure

Fetal Death

Pup weight

Placental Weight

Placenta:Fetal Weight

Fig. 1. A: vitamin D$_2$ and D$_3$ (VD2 and VD3) treatment in reduced uterine perfusion pressure (RUPP) rats reduced blood pressure compared with RUPP rats. RUPP rats had higher blood pressure compared with normal pregnant (NP) rats. B: pup weights were not altered in NP rats with VD2 or VD3 treatment and were decreased in RUPP rat groups. C: RUPP significantly increased fetal death compared with NP rats that was reduced with both VD2 and VD3 treatment, although only significantly with VD3. D: placental weights did not change with VD2 or VD3 treatment in either RUPP or NP. E: placental efficiency, evaluated as placenta/fetal weight ratio, did not change with vitamin D treatment in either RUPP or NP groups. One-way ANOVA and Student’s t-test, *$P < 0.05$.

(1.95 ± 0.09 g) or RUPP+VD3 (1.89 ± 0.10 g) groups (Fig. 1B). In addition, we observed no differences in pup weight in NP+VD2 (2.37 ± 0.05 g) or NP+VD3 (2.20 ± 0.10 g) rats compared with NP, indicating that VD did not adversely affect pup growth. Reabsorptions were found much more frequently in RUPP rats than NP (4.62 ± 1.29 vs. 0.07 ± 0.02 reabsorbed/live pups, respectively, *$P < 0.001$) (Fig. 1C). NP rats treated with VD2 or VD3 did not have altered reabsorption rates compared with NP (0.06 ± 0.05 vs. 0.06 ± 0.03 reabsorbed/live pups, respectively). Importantly, VD2 treatment reduced fetal death to 1.57 ± 0.57 reabsorbed/live pups (*$P = 0.05$) and VD3 treatment to 1.79 ± 0.46 reabsorbed/live pups (*$P < 0.05$) in RUPP rats, demonstrating that VD treatment was able to improve fetal survival in the presence of placental ischemia. Placental weights did not change from NP rats (0.62 ± 0.05 g) in either NP+VD2 (0.58 ± 0.01 g) or NP+VD3 (0.54 ± 0.02 g). RUPP rats had significantly reduced placental weight (0.50 ± 0.03 g, *$P < 0.05$) compared with NP (Fig. 1D). Neither VD2 (0.51 ± 0.03 g) nor VD3 (0.54 ± 0.03 g) supplementation in RUPP rats altered placental weight. Placental efficiency as defined by placenta/fetal weight ratio was not altered in RUPP rats (0.27 ± 0.01) compared with NP rats (0.28 ± 0.02) (Fig. 1E). Neither NP+VD2 (0.24 ± 0.01) nor NP+VD3 rats (0.25 ± 0.01) had altered placental efficiency compared with NP rats and VD2 (0.26 ± 0.01), and VD3 administration (0.29 ± 0.02) to RUPP rats did not alter this ratio either.
increased FoxP3+ TREG cell differentiation. RUPP rats had significantly less TREGs at 0.65 ± 0.42% CD4+/CD25+ lymphocytes (*P = 0.05) compared with NP rats. In the presence of placental ischemia, VD modestly increased TREGs to 1.76 ± 1.03% CD4+/CD25+ lymphocytes (P = 0.26) in RUPP+VD2 rats and 4.54 ± 2.82% CD4+/CD25+ lymphocytes (P = 0.086) in RUPP+VD3 rats, although these changes did not reach significance.

Proinflammatory cytokines were reduced with vitamin D treatment in RUPP rats. We assessed circulating TNF-α and IL-6 levels in our RUPP rats treated with VD. Although TNF-α increased five-fold in RUPP rats (103.5 ± 38.05 pg/ml) compared with NP rats (22.7 ± 9.2 pg/ml, P = 0.07), the variation in the RUPP rat group was greater than observed in previous studies and, therefore, did not reach statistical significance (Fig. 3A). However, a lowering of TNF-α levels in RUPP+VD2 (12.6 ± 5.3 pg/ml, P = 0.09) and RUPP+VD3 (52.7 ± 25.7 pg/ml, P = 0.29) was observed. Circulating IL-6 levels were significantly increased in RUPP rats (253.3 ± 60.6 pg/ml, *P < 0.05) compared with NP (93.3 ± 15.1 pg/ml) (Fig. 3B). Importantly, VD2- (62.6 ± 11.4 pg/ml, *P < 0.05) and VD3- (98.2 ± 17.5 pg/ml, *P = 0.05) treated RUPP rats had significantly lower plasma IL-6 levels compared with untreated RUPP rats.
sFlt-1 levels were significantly increased in RUPP rats. Plasma sFlt-1 levels were assessed with ELISA assay. VD treatment (8.1 pg/ml) (Fig. 5). VD2 and VD3 treatment in RUPP rats reduced PPET mRNA expression as fold change, respectively (*P < 0.05) and 3.1 ± 0.6-fold change, respectively (*P < 0.05).

Fig. 5. sFlt-1 was significantly increased in RUPP rats above levels of NP rats. sFlt-1 levels were significantly reduced in VD2-treated RUPP rats and modestly reduced in VD3-treated RUPP rats. One-way ANOVA and Student’s t-test.*P < 0.05.

DISCUSSION

In this study, we present evidence that vitamin D supplementation reduces immune pathogenesis and improves blood pressure and fetal survival in response to placental ischemia-induced hypertension during pregnancy. At present, safe therapeutics for immune activation in PE patients are restricted by potential teratogenic effects of immunosuppressive drugs. While PE has a complex etiology that at this time is not fully elucidated, immune mechanisms are suggested to play a significant role in the currently accepted two-stage theory of the pathogenesis of PE (54). VD is a safe supplement in pregnant women with no known adverse effects to either mother or neonate and may reduce the incidence of PE and improve fetal growth (23, 24, 28, 55).

Insufficient placental perfusion in the RUPP model induces a cascade of events, including immune activation, AT1-AA, ET-1, and sFlt-1 production, ultimately leading to hypertension and decreased fetal weight (1, 20, 21). The potential of VD supplementation to reduce immune activation and other pathological factors that are associated with placental ischemia has
not been previously evaluated prior to the current study. Therefore, we sought to test the hypothesis that VD improves immune activation, production of AT1-AA, ET-1, sFlt-1, and subsequently, blood pressure in the RUPP model of PE. Furthermore, we administered VD to NP rats to evaluate potential adverse fetal effects with VD administration during pregnancy.

Many proinflammatory cell types, including CD4+ cells, natural killer (NK) cells, and TH17 cells, have been found to play a role in the pathogenesis of placental ischemia. In particular, the role of CD4+ T cells has been well established. Adoptive transfer studies have confirmed that CD4+ T-cell function in RUPP rats is altered to promote the production of AT1-AA, ET-1, and sFlt-1 in otherwise healthy pregnant rats, as mechanisms of increasing blood pressure during pregnancy (12, 49, 50). CD4+ T-cell population was increased in RUPP compared with NP rats, and TREGs were decreased, consistent with what has been published previously (3, 11, 14, 49, 63). Data in the literature have shown that VD reduces proinflammatory CD4+ T cells and increases proliferation of TREGs in nonpregnant animals (10, 29, 31, 39). As predicted by these previous findings, VD treatment to NP rats did increase both CD4+ T cells and TREGs. In this report, we recapitulate a previous study in that VD2 and VD3 supplementation in RUPP rats reduced total CD4+ T cells (14). Although we did see a decrease in the total CD4+ T-cell number, there was no increase in the TREG subpopulation of CD4+ T cells with VD treatment in RUPP rats. Therefore, VD was ineffective in the presence of placental ischemia-associated CD4+ T-cell dysregulation, but under normal conditions, it was able to stimulate the percentage of CD4+ TREG cells in NP rats, which did not lead to adverse effects in the mother or fetus. The effect of VD treatment in the proliferation of other proinflammatory cell types known to contribute to the pathogenesis of PE, such as NK and TH17 cells, was not evaluated in this study and may be assessed in future experiments. A classical marker of proinflammatory T-cell activation is the production of inflammatory cytokines. We found that VD supplementation into RUPP rats significantly reduced IL-6 levels and lowered TNF-α. Our laboratory has shown that TNF-α or IL-6 infusion into pregnant rats induces AT1-AA and sFlt-1 production (36, 38, 51). Therefore, VD treatment in rats with placental ischemia altered activation of CD4+ T cells, thereby, possibly causing a reduction in proinflammatory cytokines, and a decrease in both AT1-AA and sFlt-1.

Many studies have confirmed that AT1-AA and sFlt-1 are central mediators of hypertension in PE women (15, 43, 60, 64). Clinical data have confirmed that severe PE in patients is associated with higher circulating AT1-AA and sFlt-1 levels, demonstrating a link between these mediators and pathogenesis of the disease (59, 60). This study is the first to measure changes in the production of AT1-AA and sFlt-1 in response to VD supplementation. AT1-AA production is a fairly unique factor to PE patients and is not found in measurable levels in normal pregnancy. In the absence of placental ischemia, AT1-AA infusion into pregnant rats induces hypertension, endothelial dysfunction, and sFlt-1 production (8, 51). The cascade of pathological events in PE that induce AT1-AAs remain under investigation; however, it is known that AT1-AAs are induced by CD4+ T cells derived from RUPP rats and that they are produced by B cells (37, 50). Therefore, we evaluated B-cell populations in response to VD supplementation in NP and RUPP rats and found that B cells were not significantly reduced. However, B-cell production of AT1-AA was reduced in RUPP rats with VD2 and VD3, which was also associated with decreases in plasma sFlt-1 levels. SFlt-1 is an anti-angiogenic peptide that acts as a soluble scavenger, sequestering vascular endothelial growth factor (VEGF). SFlt-1 infusion into pregnant rats increases blood pressure and intrauterine growth restriction (9, 45). Importantly, there is a strong mechanistic tie between AT1-AA and SFlt-1, as studies have confirmed that AT1-AA stimulates sFlt-1 production, which is associated with reduction of blood pressure in pregnant rats (8, 51, 71). In this study, we observed a similar link as decreased AT1-AA in RUPP rats were paralleled by a SFlt-1 reduction. Therefore, VD reduction of AT1-AA likely led to a decrease in SFlt-1 production and ultimately, a reduction in blood pressure.

VD has been shown to improve endothelial dysfunction and VDR signaling in vascular cells (46, 68). Endothelial dysfunction is an observed pathological event in the RUPP model, evident by vascular impairment, reductions in nitric oxide (NO) bioavailability, and production of ET-1 (3, 13, 32, 37, 40). Interestingly, we did not observe a change in circulating nitric oxide (NO) levels in RUPP rats treated with VD. ET-1 is a potent vasoconstrictor and is emerging as an important player in the vascular dysfunction observed in PE (19). VD supplementation significantly reduced renal production of ET-1 in RUPP rats in correlation with reduction of AT1-AA. ET-1 has been shown to mediate, at least in part, the hypertensive responses of RUPP and AT1-AA-infused, SFlt-1-treated, and to
RUPP CD4+ T cells in pregnant rats, (19, 52, 62). The observed improvement of ET-1 levels suggests improved function and endothelial activation with VD supplementation, which likely resulted from reduced CD4+ T cells, sFlt-1 secretion, and AT1-AA-mediated signaling, all of which could play a role in the observed reduction of blood pressure.

A significant concern in clinical studies of PE therapeutics is that maternal symptoms of PE are to be improved without causing adverse effects to the growing fetus. NP rats treated with VD had a slight decrease in blood pressure, although this did not reach significance. However, we have demonstrated that VD administration reduced blood pressure and fetal death in RUPP rats but did not negatively affect fetal weight, demise, or placental efficiency in NP or RUPP rats. Therefore, the present study suggests that VD supplementation in NP rats is not associated with reduced placental blood flow or fetal growth restriction.

We did not observe that circulating 25(OH) VD levels, the metabolite of VD measured in clinical assessment, were changed with VD2 or VD3 treatment in RUPP rats. We believe this could be due to the short duration of supplementation, as clinical studies have shown that it takes several weeks for lower doses of VD to be observed as increased circulating 25(OH) VD levels (2, 70). However, as there were no adverse effects on NP rats and there were beneficial fetal and maternal improvements in RUPP rats, we believe that a lack of increasing plasma VD levels demonstrates that VD supplementation is promising even for patients that do not have a VD deficiency. Although VD2 and VD3 are commercially available as supplements, clinical data have implicated that VD3 may be a better therapeutic for humans (42, 61). In contrast, VD2 may be more efficiently metabolized in rats (26). In accordance with these reports, our data showed that VD2 lowered blood pressure, AT1-AA, and sFlt-1 to a greater extent than VD3 in RUPP rats. Importantly, the reductions of AT1-AA, sFlt-1, and blood pressure were all in consistent proportion with regard to VD2 vs. VD3, further indicating that AT1-AA and sFlt-1 reduction led to the observed attenuation of blood pressure in RUPP rats.

Our data demonstrate that VD reduces proinflammatory CD4+ T-cell population, inflammatory cytokines, AT1-AA, sFlt-1, ET-1, blood pressure, and fetal demise in RUPP rats, without adversely affecting maternal physiology or fetal development in NP rats. Therefore, we conclude even in the absence of VD deficiency, VD supplementation should be considered further as a safe preventative for preeclampsia in pregnant women.

Perspectives and Significance

The present study demonstrates that VD could be a potential therapeutic to improve pathological characteristics and hypertension associated with preeclampsia without adverse fetal effects. Currently, clinical studies investigating the potential of VD supplementation to improve PE have yielded inconsistent results. However, as VD supplementation is a low-risk therapeutic, it could provide an adjunct therapy for the pathogenesis associated with placental ischemia. Further studies investigating VD supplementation in a large and diverse population are needed. This study provides evidence that VD may reduce pathological markers of PE, which will aid future trials seeking to comprehensively evaluate its therapeutic potential.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES

VIT D IMPROVES PATHOPHYSIOLOGY IN PREECLAMPTIC RAT MODEL


