Upregulation of hnRNPC1/C2 expression in preeclampsia: a potential rationale for vitamin D insensitivity

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Drs Yuping Wang and David F. Lewis from Louisiana State University Health Sciences Center – Shreveport discuss hnRNPC1/C2 upregulation, a potential rationale for vitamin D insensitivity

Preeclampsia, a pregnancy-specific disorder in humans, is characterized by newly-onset maternal hypertension and proteinuria after 20 weeks of gestation. This pregnancy disorder complicates 5-8% of all pregnancies and is a leading cause of maternal and fetal morbidity and mortality worldwide. Preeclampsia is also a predisposing factor for cardiovascular and kidney diseases in women later in life. Although the etiology of preeclampsia is heterogenous, epidemiological studies revealed that vitamin D deficiency is a risk factor for preeclampsia development.

In fact, numerous clinical trials conducted around the world on vita- min D supplementation in prevention and reduction of preeclampsia showed that vitamin D supplementation in pregnancy not only reduces incidence of preeclampsia, recurrence of preeclampsia, preterm birth, and gestational diabetes, but also has beneficial effects on fetal growth and long-term child health outcomes [1-5]. However, some studies found no benefit having vitamin D supplementation in pregnancy [6, 7]. The inconsistent outcomes could be due to various reasons, such as different gestational age and different baseline of maternal vitamin D status at a trial entry; different doses of vitamin D supplementation intake; and different metabolic and cellular responses to vitamin D in individuals during pregnancy.

How does vitamin D elicit its biological actions

In humans, natural sources of vitamin D are either synthesized in the skin after exposure to sufficient sunlight or obtained from diet.

Following two hydroxylation steps, first in the liver by 25 hydroxylase and second in the kidneys by 1α-hydroxylase, bioactive vitamin D (1,25-dihy-droxyvitamin D, 1,25(OH)2D3) is then produced. As 25 hydroxylase and 1 α-hydroxylase are enriched in placental trophoblast cells, the placenta is also an important source of maternal and fetal bioactive vitamin D during pregnancy.

The actions of 1,25(OH)2D3 are mediated via binding to its receptor (vitamin D receptor, VDR), which is present in almost all cell types and organs in humans. In the nucleus, VDR forms receptor complex with retinoid-X receptor (RXR) and the receptor complex (VDR/RXR) then binds to vitamin D response elements (VDREs, the DNA sequences in the promoter region), and subsequently induces either activation or repression of the target genes. VDREs are present in many known genes that control mineral metabolism and regulate bone and muscle health. VDREs are also present in the promoter of VDR itself and in genes that control cell cycle, proliferation, modulate innate and adaptive immunity, etc. As a result, vitamin D not only regulates musculoskeletal system, but also strengthens functions in immune, endocrine, cardiovascular, and nerve systems, etc.

Aberrant hnRNPC1/C2 and VDR expression in placental trophoblasts and maternal vascular tissue in women with preeclampsia

Increased hnRNPC1/C2 expression and decreased VDR expression were found in placental trophoblasts from preeclamptic compared to those from uncomplicated pregnancies [8, 9]. Most recently, our group also found upregulation of hnRNPC1/C2 expression and downregulation of VDR expression in maternal systemic vessels from women with preeclampsia vs. uncomplicated pregnant controls [10]. In our in vitro study, we further demonstrated that inhibition of hnRNPC1/C2 expression in endothelial cells not only results in an increase in VDR expression, but also leads to an increase in endothelial response to 1,25(OH)2D3 [10]. These data clearly show that hnRNPC1/C2 negatively impacts vascular cell response to vitamin D.

Effects of hnRNPC1/C2: competing with VDR binding to VDRE

HnRNPC1/C2 was initially identified as a core component of 40S hnRNP particles and was later found to be able to modulate transcriptional responses to the active form of vitamin D by competing with VDR/RXR binding to VDREs [11]. Therefore, hnRNPC1/C2 is considered an endogenous repressor to VDR. HnRNPC1/C2 is overexpressed in patients with hereditary vitamin D resistant rickets (HVDRR) and hnRNPC1/C2 competes with VDR for occupation of VDRE in HVDRR cells [12]. For that reason, hnRNPC1/C2 is named as VDRE-binding protein (VDRE-BP) and increased VDRE-BP expression/activity is believed to be an underlying cause of 1,25(OH)2D3- insensitivity and a biomarker of "vitamin D resistance" or vitamin D insensitivity [13].

Although control of transcription of vitamin D-regulated genes may require additional recruitment of coregulators that affect VDR-mediated transcriptional activity, blocking accessibility of VDREs by hnRNPC1/C2 (VDRE-BP) is critical in limiting vitamin D-induced biological actions. As such, over-expression of hnRNPC1/C2 would produce a vitamin D insensitivity status, which provides, at least in part, a reasonable explanation for lack of vitamin D responses in those who take vitamin D supplementation in pregnancy.

Rationale of increased hnRNPC1/C2 expression- mediated vitamin D insensitivity in preeclampsia

Several potential mechanisms downstream from 1,25(OH)2D3/VDR complex formation could contribute to the impairment of 1,25(OH)2D3 action and produce vitamin D insensitivity or resistance in women with preeclampsia: 1) reduced maternal levels of vitamin D; 2) reduced VDR levels in the maternal vascular system and in placental trophoblasts (mater- nal-fetal interface); and 3) increased levels of hnRNPC1/C2 (VDRE-BP) expression. Reduced vitamin D and VDR levels impair formation of VDR/RXR complex. Increased hnRNPC1/C2 levels could block binding of VDR/RXR complex to VDRE, a critical step for 1,25(OH)2D3 – induced gene regulation. Therefore, enhanced hnRNPC1/C2 expression could play a key role in reducing vitamin D effects in preeclampsia. These results suggest that it is necessary to revisit the possible explanation for people who did not respond to vitamin D supplementation, not only pregnant women, but also other individuals as well.

Pregnancy is a critical time in the life- cycle of a woman. Adequate vitamin D status in pregnancy is needed for healthy pregnancy outcomes not only for the mother's well-being, but also for that of her developing fetus. Therefore, it is necessary to establish a recommendation for screening vitamin D deficiency in pregnant women and guidelines to monitoring maternal vitamin D status during pregnancy.

Large, well-designed prospective randomized clinical trials and personalized medicine are necessary to address these issues.

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