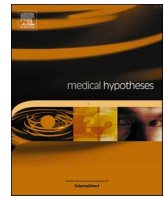




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Letter to Editors

Vitamin D may prevent COVID-19 induced pregnancy complication



ARTICLE INFO

Keywords

COVID-19
ACE2
Vitamin D
Preeclampsia
Pregnancy

ABSTRACT

SARS-CoV-2 enters target cells via the ACE2 receptor and downregulates it. ACE2 exhibits high catalytic activity to produce Angiotensin 1–7 (Ang-1–7), which has a vasodilator effect and also inactivates the vasoconstrictor Angiotensin II. In normal pregnancy ACE2 expression is raising in the uterus and placenta. Ang-1–7 levels in plasma are significantly higher in third-trimester pregnant women when compared to non-pregnant women. This may be contributing to systemic vasodilation and reduced blood pressure and modulating hemodynamics during pregnancy. Interestingly, Ang-1–7 plasma levels are lower in pregnancies complicated by pre-eclampsia than normal pregnancies. COVID-19 infection increased the inflammatory cytokines and reduced ACE2 level. This may lead to pre-eclampsia or hypertensive pregnancies, then increasing the perinatal and maternal mortality and morbidity. Vitamin D increased ACE2 expression and Ang-1–7 plasma levels and also decreased Ang II level in plasma. Moreover, Vitamin D reduced the inflammatory cytokine storm. So, Vitamin D supplementation can prevent the risk of preeclampsia or hypertension in pregnant women with COVID-19.

To the editor;

The pregnancy is considered a physiological condition, that accompanied by hypervolemia, increased cardiac output, and a diminished total peripheral resistance, still, the pregnant are normotensive, and blood pressure even tends to decrease in the second trimester. Estrogen and progesterone raise angiotensinogen and renin levels, which in turn leads to increased angiotensin II levels, the increased concentration of angiotensinogen, angiotensin II, indicate the increased activity of RAAS, but instead, there is a decrease in systemic vascular resistance characterizes the hemodynamics of the normal pregnancy [1]. The mechanism behind this response instructed to the accompanied increment in the ACE2 during pregnancy, ACE2 is producing Ang-1–7 which may reach 20-fold higher compared with non-pregnant women [1], contributing to the systemic vasodilation, reduced blood pressure and modulating hemodynamics during pregnancy.

Di Mascio et al. stated that the high miscarriage rate, preterm delivery, pre-eclampsia, cesarean section and perinatal mortality were associated with COVID-19 [2]. Most of these complications could be resulted from increased maternal vascular resistance and increase arterial blood pressure. Neves et al. [3] demonstrated that in the late pregnancy, Ang I and Ang II levels are increased [3], this may lead to a compromise in the quantity of the active ACE2 and could cause an increase in the activity of RAAS, and eventually increase maternal vascular resistance.

It has been known that SARS-CoV-2 binds angiotensin-converting enzyme 2 (ACE2) receptor. ACE is a part of the renin-angiotensin system (RAS), which converts the angiotensin I (Ang I) to the vasoconstrictor Ang II. ACE2 converts the Ang II to vasodilator Ang-1–7. COVID-19 infection downregulates ACE2, leading to increased accumulation of Ang II [4]. Moreover, Ang-1–7 plasma levels are shown to be higher in normal pregnancies than pregnancies complicated by pre-eclampsia [5]. In the case of COVID-19 pregnant women, complex formation of virus-

ACE2 can lead to more inactivation of ACE2. ACE2 reduction leads to an inevitable decrease in Ang 1–7 level results in pre-eclampsia.

Lin et al. [6] showed that the administration of Vit.D increased the ACE2 levels, decreased the ACE, and reduced the ACE1/ACE2 ratio and provides a renoprotective effect [6]. In an experimental study, Vit.D supplementation prevents acute lung injury by increased ACE2 level expression and inhibiting renin, ACE, and Ang II level [7]. It can prevent the development of preeclampsia and protect maternal and fetal health by increasing the ACE2 level in pregnant women infected with COVID-19 (Fig. 1).

Preeclampsia is associated with the immune system [8,9]. Failure of the immune system in pregnant women causes insufficiency of blood supply to the fetus and result in preeclampsia. Todros et al. indicated that preeclampsia is also concerned with the exaggerated inflammation that causes endothelial damage [9]. This immune response is a favorable scenario for predisposing COVID-19 infection, and increases the susceptibility to develop preeclampsia or increase arterial resistance in pregnant women, then may increase the maternal and fetal complications.

Vit D has been exhibits as an anti-inflammatory effect, as it reduces the T cells, so inflammation progression can be repressed indirectly by reducing inflammatory cytokines (IL-2, IL-6, IL-8, IL-12, IL-17, TNF α), and directly inhibits IFN- γ [4]. A meta-analysis and systematic reviews reported that Vit.D deficiency is an increased risk of the preeclampsia in nearly all pregnancies. Pregnant women with a Vit.D deficiency at a level lower than 20 ng/ml are more at the risk of preeclampsia [10]. Vit. D could have some protective properties against COVID-19 infection by enhancing cellular innate immunity through inducing the production of antimicrobial peptides, including defensins and cathelicidin, which reduce the survival and replication of viruses [4].

<https://doi.org/10.1016/j.mehy.2021.110733>

Received 24 June 2021; Received in revised form 8 October 2021; Accepted 28 October 2021

Available online 9 November 2021

0306-9877/© 2021 Elsevier Ltd. All rights reserved.

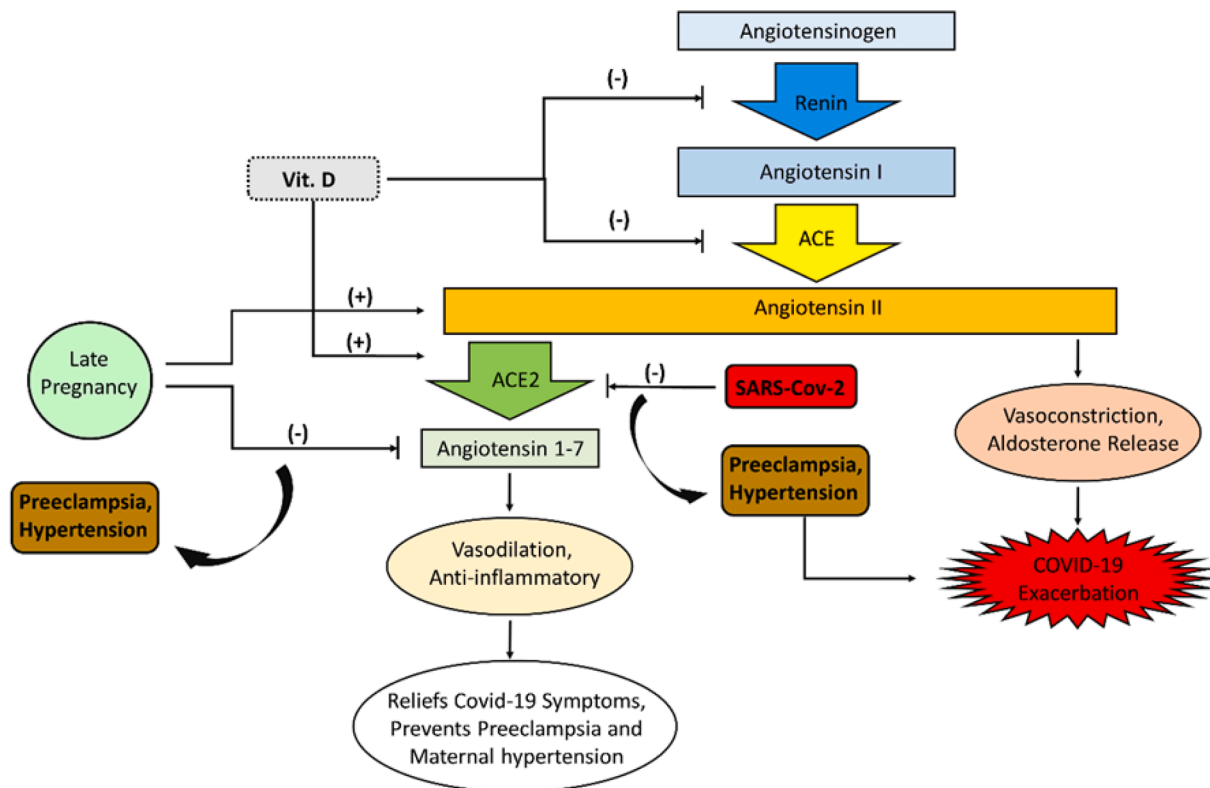


Fig. 1. The effect of Vit.D on RAAS and ACE2 levels. The inflammatory cytokines storm induced by the immune response to COVID-19 can cause severe organ damage and compromise the patient life, and in the pregnant patient could be a predisposing factor to develop preeclampsia, Vit.D supplement can decrease cytokines storm and prevent preeclampsia. Vit.D supplement can increase ACE2 levels and restore ACE2 levels in the late pregnancy, then prevent the concomitant complications of preeclampsia or increased maternal blood pressure caused by decreased ACE2 in late pregnancy and accompanied COVID-19 infection. Consequently, decrease fetal and maternal morbidity and mortality.

Funding

Not applicable.

Ethics approval

Not required.

Consent to participate

Not required.

Consent for publication

Not required.

Availability of data and material

All data were generated in-house and that no paper mill was used.

Code availability

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Merrill DC, Karoly M, Chen K, Ferrario CM, Brosnihan KB. Angiotensin-(1-7) in normal and preeclamptic pregnancy. *Endocrine* 2002;18(3):239-46.
- [2] Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* 2020;2(2): 100107.
- [3] Neves LAA, Stovall K, Joyner JaNae, Valdés G, Gallagher PE, Ferrario CM, et al. ACE2 and ANG-(1-7) in the rat uterus during early and late gestation. *Am J Physiol Regul Integr Comp Physiol* 2008;294(1):R151-61.
- [4] Aygun H. Vitamin D can prevent COVID-19 infection-induced multiple organ damage. *Naunyn Schmiedebergs Arch Pharmacol* 2020;393(7):1157-60.
- [5] Velloso EP, Vieira R, Cabral AC, Kalapothakis E, Santos RAS. Reduced plasma levels of angiotensin-(1-7) and renin activity in preeclamptic patients are associated with the angiotensin I-converting enzyme deletion/deletion genotype. *Brazilian J Med Biol Res* 2007;2007(40):583-90.
- [6] Lin M, Gao P, Zhao T, He L, Li M, Li Y, et al. Calcitriol regulates angiotensin-converting enzyme and angiotensin converting-enzyme 2 in diabetic kidney disease. *Mol Biol Rep* 2016;43(5):397-406.
- [7] Xu Jun, Yang J, Chen J, Luo Q, Zhang Q, Zhang H. Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Mol Med Rep* 2017;16(5):7432-8.

- [8] Kim J, Lee K-S, Kim J-H, Lee D-K, Park M, Choi S, et al. Aspirin prevents TNF- α -induced endothelial cell dysfunction by regulating the NF- κ B-dependent miR-155/eNOS pathway: Role of a miR-155/eNOS axis in preeclampsia. *Free Radic Biol Med* 2017;104:185–98.
- [9] Todros T, Masturzo B, De Francia S. COVID-19 infection: ACE2, pregnancy and preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 2020;253:330. <https://doi.org/10.1016/j.ejogrb.2020.08.007>.
- [10] Akbari S, Khodadadi B, Ahmadi SAY, Abbaszadeh S, Shahsavari F. Association of vitamin D level and vitamin D deficiency with risk of preeclampsia: A systematic review and updated meta-analysis. *Taiwan J Obstet Gynecol* 2018;57(2):241–7.

Ali Al-Kaleel^{a,*}, Lubna Al-Gailani^b, Mustafa Demir^c, Hatice Aygün^d
^a Faculty of Medicine, Cyprus International University, Cyprus

^b Cyprus International University, Cyprus
^c Department of Nephrology, Tokat State Hospital, Tokat, Turkey
^d Department of Physiology, Tokat Gaziosmanpaşa University, Faculty of Medicine, Tokat, Turkey

* Corresponding author at: 99258 Nicosia, Cyprus.
E-mail addresses: dr.alizaher@gmail.com, aalkaleel@ciu.edu.tr (A. Al-Kaleel), lalgailani@ciu.edu.tr (L. Al-Gailani).