ABSTRACT: The innate immune system utilizes many approaches for defense against invading microorganisms, including complement-mediated lysis, engulfment, formation of neutrophil extracellular traps (NETs), and release of antimicrobial peptides (AMPs). Recent evidence demonstrates that macrophages produce the AMP LL-37 in response to endogenously produced 1,25(OH)2D to enhance innate immunity. Additional evidence shows 1,25(OH)2D modulates the adaptive immune system as well through direct effects on T cell activation and on the phenotype and function of antigen-presenting cells (APCs), particularly of dendritic cells (DCs).

This paper hypothesizes that well-tolerated Vitamin D3 supplementation merits investigation in combating coronaviruses and their diseases, such as COVID-19.

DISCUSSION: The immune system defends the body from foreign, invading organisms, promoting protective immunity while maintaining tolerance to self. The implications of vitamin D deficiency on the immune system have become clearer in recent years and in the context of vitamin D deficiency, there appears to be an increased susceptibility to infection and a diathesis, in a genetically susceptible host to autoimmunity.

There are two major classes of amphipathic AMPs present in human respiratory lining fluids: defensins and cathelicidins. There is evidence that both of these classes of AMPs play a role during Influenza A Virus (IAV) infection. One representative of the class of cathelicidins is LL-37. Recent reviews have discussed the extraordinary range of activities of LL-37, which include direct antimicrobial and antiviral activities, chemotactic activities for various immune cells, modulation of macrophage responses to inflammatory stimuli, and modulation of dendritic cell responses.

Deaths caused by IAV infection mostly result from acute lung injury, systemic inflammation or bacterial superinfection, suggesting that new treatments with anti-viral, anti-bacterial and anti-inflammation effects would be ideal. AMPs are antimicrobial peptides that not only play important roles as host defense against pathogens but also modulate inflammatory responses, and thus they are potential candidates for IAV treatment.

Previous studies have reported that 1,25(OH)2D3, the hormonal form of vitamin D, is a negative endocrine regulator of the RAS and inhibits renin biosynthesis. The results of the present study demonstrated that vitamin D inhibited renin, ACE and Ang II expression, and induced ACE2 levels in LPS-induced ALI. Therefore, vitamin D may attenuate LPS-induced ALI by, at least partially, inducing ACE2/Ang-(1–7) axis activity and inhibiting renin and the ACE/Ang II/AT1R cascade.

Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for severe acute respiratory syndrome-coronavirus (SARS-CoV) and the new coronavirus (SARS-CoV-2) that is causing the serious coronavirus disease 2019 (COVID-19) epidemic.

Observational studies report consistent independent associations between low serum concentrations of 25-hydroxyvitamin D (the major circulating vitamin D metabolite) and susceptibility to acute respiratory tract infection. 25-hydroxyvitamin D supports induction of antimicrobial peptides in response to both viral and bacterial stimuli, suggesting a potential mechanism by which vitamin D inducible protection against respiratory pathogens might be mediated.

The recent discovery that vitamin D induces antimicrobial peptide gene expression explains, in part, the ‘antibiotic’ effect of vitamin D and has greatly renewed interest in the ability of vitamin D to improve immune function. Subsequent work indicates that this regulation is biologically important for the response of the innate immune system to wounds and infection and that deficiency may lead to suboptimal responses toward bacterial and viral infections.

To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, and to identify factors modifying this effect, 25 eligible randomised controlled trials (total 11 321 participants, aged 0 to 95 years) were identified. Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.

CONCLUSION: Whereas, in consideration, it is reasonable to investigate the role of Vitamin D deficiency in COVID-19 (SARS-CoV-2) disease (via ACE2 receptor entry) and reducing the innate immune system’s effective defense. Further, exogenous Vitamin D supplementation may reasonably lessen susceptibility to the disease progression and complications, via AMP promotion and immune system modulation, specifically related to inflammatory response mechanisms.
COVID-19 and Vitamin D3

Why Vitamin D3 is the KEY to fighting Coronavirus like COVID-19!

The innate immune system is the best protector - when supported.

...vitamin D induces antimicrobial peptide gene expression."²
- kills virus
-kills bacteria
-blocks ARDS
(Immunover reaction)

CATHELICIDIN C206H340N69O92
“AMPs (anti-microbial peptides Cathelicidin and Defensin) are endogenous proteins playing important roles in host defense through direct antimicrobial and antiviral activities and through immunomodulatory effects.”³

¹Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS)
Rachel C.A Dancer, Chunw Parekh, [...], and David R Thickett, Thorax, 2015.

²The vitamin D-antimicrobial peptide pathway and its role in protection against infection
Adrian F Gombart, Future Microbio. 2009.

³Calcitriol-modulated human antibiotics: New pathophysiologcal aspects of vitamin D
Mechanism of COVID-19 and Vitamin D3

"COVID-19 Hijacks ACE2"

Scientists demonstrate how COVID-19 infects human cells
Researchers have used cryogenic electron microscopy to show that coronaviruses enter human cells through an interaction with angiotensin-converting enzyme 2 (ACE2).¹

Drug Target Review, 3/5/20, H. Balfour.

How does Vitamin D3 Block the Coronavirus?
(Answer: by upregulating ACE2 receptors, blocking virus hijacking.)

*upregulation is where a cell increases its sensitivity to a hormone by increasing the number of available receptors.

ACE2 receptor

Human Cell

Angiotensin I

Angiotensin II

RAS

The renin-angiotensin system (RAS) is a central regulator of renal and cardiovascular functions.

Liver

Renin

Renin-angiotensin-aldosterone system

Vitamin D suppresses renin gene expression at least in part by blocking the formation of CRE-CREB-CBP complex.²

1,25(OH)2D(3)

Hypertension

Vasconstriction

Na and H2O retention

Angiotensin

Angiotensinogen

Angiotensin-II

Angiotensin-converting enzyme

Spike Glycoprotein

Stability of brain

Anterior pituitary hormone

Fasting signal

ACTH

Renin

Vasconstriction of blood vessels

Increased circulating volume

Extra cellular fluid volume

Blood pressure

The main role of ACE2 (angiotensin-converting enzyme) is the degradation of Ang II resulting in the formation of angiotensin 1–7 (Ang 1–7) which opposes the actions of Ang II. Increased Ang II levels are thought to upregulate ACE2 activity, thus, ACE2 plays a crucial role in the RAS because it opposes the actions of Ang II. Consequently, it has a beneficial role in many diseases such as hypertension, diabetes, and cardiovascular disease.³


²Wehua Yuan, Wei Pan, Juan Kong, Wei Zhang, Frances L. Saxon, Karl E. Weng, Ronald Cohen, Anna Klepet, Zhongyi Zhang and Yan Chun Li

³Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease Chris Tiekstra and M. C. Thomas

JCCollier, 415 20 v1.4

Mechanism of Vitamin D3 and ARDS* (*Acute Respiratory Distress Syndrome)

How Does COVID-19 Kill?

"VITAMIN D DEFICIENCY IS NEARLY UNIVERSAL IN THE DEVELOPMENT OF ARDS." ¹

How Does Vitamin D3 Protect Lungs From COVID-19?

Answer: Engaging Endogenous Anti-Viral/Bacterial Defenses.

"VITAMIN D INDUCES ANTIMICROBIAL PEPTIDE GENE EXPRESSION." ²

"STUDIES TO DATE WOULD ARGUE IMPORTANCE OF INDIVIDUALS TO HAVE SUFFICIENT SERUM LEVELS OF 25(OH)D TO SYNTHESIZE CATHELICIDIN." ²

ARDs

CATHELICIDIN (antimicrobial peptide)
Mechanism through which vitamin D modulates the secretion of cathelicidin and beta-2-defensin. Binding of some microbial antigens (Ag) to toll-like receptors (TLRs) activates 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1), so that, depending on intracellular concentrations of 25-hydroxyvitamin D, local synthesis of 1,25-dihydroxyvitamin D is enhanced. The latter in turn binds to its receptor (VDR), and the intranuclear hormone-receptor complex activates the transcription of the cathelicidin and beta-2-defensin genes. Intracellular concentrations of 25-hydroxyvitamin D depend on plasma concentrations of this molecule, which is the most reliable marker of the nutritional status of this vitamin. ³

¹ Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS) Rachel C A Dancer, Dhiru Farokh, […], and David R Thickett. Thorax, 2015.

² The vitamin D-antimicrobial peptide pathway and its role in protection against infection Adrian F Gombart, Future Microbio. 2000.

“Cytokines are inflammatory immunologic proteins that are there to fight off infections and ward off cancers,” said Randy Cron MD PhD, a UAB professor of pediatrics and medicine. But when they are out of control, they can make you very ill. A cytokine storm is the result of an immune system out of control resulting in increased production of inflammatory proteins that can lead to organ failure and death. 1


*CRS Acute Respiratory Distress Syndrome. Respiratory failure precipitating death or permanent lung disability.

Mechanism of D3 Deficiency: Latitude, Season, & Skin Pigment

**January**
- UNLIKELY
- 0 1 2 3 4 5 6 7 8 9 10 11
- LIKELY

Vitamin D Synthesis

Via VDR, vitamin D modulates the activity of both the innate and adaptive immune system.

**February**
- Pigment Matters!

**March**
- Latitude Matters!

**April**

**May**

**June**

**July**

**August**

**September**

**October**

**November**

**December**

**Little or No Vitamin D in the Winter Months**

"Melanin, which causes skin pigmentation, lowers the skin's ability to make vitamin D in response to sunlight exposure."

**Root Problem?**

"Insufficient exogenous vitamin D to support immune system."

**Solution:**

D3 (Calcidiol)

**Cathelicidin**

\[ \text{Cathelicidin: } \text{C}_{205}\text{H}_{340}\text{N}_{30}\text{O}_{63} \]

"AMPs (anti-microbial peptides Cathelicidin and Defensin) are endogenous proteins playing important roles in host defense through direct antimicrobial and antiviral activities and through immunomodulatory effects."

"...an estimated number of more than a billion individuals are vitamin D deficient."

---

1. Nutrigenomics of Vitamin D Carsten Carlberg
   School of Medicine, Institute of Biomedicine, University of Eastern Finland, FI-70211 Kuopio, Finland; carsten.carlberg@uef.fi


3. The Role of Antimicrobial Peptides in Influenza Virus Infection and Their Potential as Antiviral and Immunomodulatory Therapy. Heij JNT, Hartschuh KL.

---

Copyright © James D. Collier, 2020.