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Peer Review Report for "Association Between Low Serum Vitamin D Levels and Sepsis: A Single-Center Study in Tehran, Iran"

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Submit Date: 1 Apr 2020
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Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) — 25 Jan 2021

Dear AE,
I have read this article several times, according to me, it is suitabe to publish only as a letter to the editor because there is no novel result.
regards

REFEREE: Associate Editor | **Revision** (0) — 7 Feb 2021

Dear EIC,
The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.
Kind regards,

REFEREE: EIC | **Revision** (0) — 7 Feb 2021

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above

carefully according to reviewers' request.

Thanks.

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Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Abstract

Introduction: Vitamin D insufficiency is common in critically ill patients. It is hypothesized that deficiency in vitamin D would be associated with sepsis in the critically ill. Thus the present study was aimed to evaluate the relationship between vitamin D serum levels and sepsis severity.

Methods: This cross-sectional study was performed on patients over 18 years of age with sepsis presenting to a university hospital in Tehran, Iran, from February 2018 to March 2019. Plasma concentrations of vitamin D in critically ill subjects admitted were assessed. Data were analyzed using SPSS Version 20.0. A difference of $P<0.05$ was regarded as statistically significant.

Results: The mean serum level of vitamin D3 in the studied patients was 19.03 ±13.08 ng/ml. The prevalence of vitamin D insufficiency in critically ill subjects with sepsis was 100% (150/150). Only sex ($p=0.01$) showed a significant association with mean serum vitamin D level. Patients with sepsis had higher levels of vitamin D compared to the patients suffering from severe sepsis ($p=0.07$).

Conclusions: Our study showed that all critically ill patients we studied had vitamin D insufficiency. In concert with the biological evidence, our study suggests vitamin D deficiency may predispose patients to sepsis and be harmful to those with sepsis. Further studies are required to confirm our findings and establish causation and mechanisms underlying these observations.

Keywords: Sepsis, Vitamin D deficiency, Iran

Introduction:

Sepsis is common among critically ill patients and is associated with considerable morbidity and mortality[1, 2]. Despite advances in care and clinical outcomes, existing epidemiologic studies suggest that sepsis remains a major health problem worldwide [3, 4].In 2017, an estimated 48 million incident cases of sepsis were recorded worldwide and 11 million sepsis-related deaths were reported, representing 19·7% of all global deaths[5].Sepsis is treatable and infection-prevention efforts, can reduce sepsis incidence and improves outcomes[6-8].Recently, it has been found that vitamin D supplementation can improve prognosis in patients with sepsis[9, 10].Vitamin D plays an essential role in both the innate and the adaptive immune system for optimal function of antimicrobial activity[11-13]. Thus, it is a contributing factor to decreased sepsis incidence and severity[13]. However, patients with severe infections such as those with sepsis usually have a high prevalence of vitamin D deficiency [14-16]. Furthermore, several studies among patients with sepsis, have shown strong associations between decreased vitamin D levels and adverse outcomes (i.e. increased length of stay, acute kidney injury, and mortality) [17-19].Although role of Vitamin D is vital in sepsis as suggested by many studies, the correlation between vitamin D and decrease in mortality has not been yet confirmed [20-22]. In Iran, a high percentage of vitamin D deficiency was observed in the general population[23]. There are also an increasing number of patients with sepsis in health care settings [24]. Thus, this study was aimed to find out whether vitamin D levels can be correlated with outcome of the patients in the form of mortality and discharge in Tehran, Iran.

Methods:

Settings and patients

This cross-sectional study was conducted at auniversity hospital (Imam Hossein Hospital) in Tehran, Iran, from February 1, 2018, to March 5, 2019.Patients aged 18 years or older were considered for enrollment if they met the following criteria for sepsis: 1) confirmed or suspected source of infection determined by the treating clinician, and 2) with two or more criteria for the systemic inflammatory response syndrome (SIRS) [25]. Patients were excluded if they experienced shock due to reasons other than sepsis, neuroendocrine diseases, cardiac arrest on arrival, mental disorders, under constant use of vitamin D, or were pregnant.Patient data were obtained at enrollment, including demographics, comorbidities, and laboratories including cultures, and the suspected source of infection. This study was approved by our institutional human subjects committee and informed consent was obtained (IR.SBMU.MSP.REC.1397.126).

Vitamin D status measurements

Whole blood was collected after enrollment by venipuncture into collection tubes containing ethylenediaminetetraacetic acid as an anticoagulant. Within 1 hour of collection, each sample was centrifuged at 1500 rpmfor 10 minutes. The plasma was immediately aliquoted into 1 mL cryovials and stored at -20°C until the time of evaluation.After completion of samples, the concentration of serum 25-hydroxy vitamin D3 was measured by enzyme-linked radioimmunoassay (ELISA) using kits from DIA source Immunoassays S. A, (Belgium) according to the manufacturer's protocol. Vitamin D insufficiency was defined as baseline serum 25-hydroxyvitamin D (25OHD) levels <30 ng/mL [26].

Statistical analysis

Data were analyzed using SPSS Version 20.0 (IBM Corp., Armonk, NY, USA) and are expressed as mean ± standard deviation or median as appropriate. Categorical variables were compared using the Chi-square test, whichever is applicable. Continuous variables were compared using t-test and ANOVA as applicable. P <0.05 was considered statistically significant.

Results:

A total of 150 patients with a mean age of 70.8±13.3 years were studied (64.0% male).There were 96 (64.0%) males and 54 (36.0%) females. The mean serum level of vitamin D3 in the studied patients was 19.03 ±13.08 ng/ml. Vitamin D deficiency was considered to be present when serum levels were <30 ng/mL. Thus, the prevalence of vitamin D insufficiency in critically ill subjects with sepsis was 100% (150/150). Table 1 shows the association between the mean serum level of vitamin D and different variables. Only sex (p=0.01) showed a significant association with mean serum vitamin D level.

The cases included 56 patients with sepsis, 26 with severe sepsis, and 68 with septic shock. The mean age of patients with septic shock was not statistically different fromthe other two groups. Likewise, the number of patients with underlying disease in the septic shock group was similar to those in the other two groups. Patients with sepsis had higher levels of vitamin D compared to the patients suffering from severe septic (p=0.07).

Discussion:

Our study showed a high prevalence of low vitamin D levels in critically ill patients. Although patients with severe sepsis had more vitamin D deficiency, there

was no significant difference in the prevalence of low concentrations of vitamin D between the patients. Despite the different cut-off points for the definition of vitamin D deficiency, most studies showed a high prevalence of vitamin D deficiency in patients with sepsis.In 2015, Alves and others reported that 98% of patients with sepsis had severe vitamin D deficiency [27]. Likewise, a subsequent investigation by Shojaeiet al. found that the median concentrations of vitamin D levels in the patients with sepsis were 19ng/mL, similar to the concentrations found in our study [24]. Jeng and colleagues found significant differences in vitamin D concentrations in patients in the intensive care unit with sepsis compared with healthy individuals [13].

The results of previous studies showed that vitamin D deficiency in patients with sepsis was significantly associated with increased mortality [28, 29]. The potential mechanisms for an increased risk of sepsis in critically ill patients with vitamin D deficiency may be related to 1) the stimulatory effects on innate immunity, 2) the suppression of immune reactivity observed with vitamin D, 3) regulates control pathways that serve to reduce potential inflammatory damage from disproportionate activation of the immune response, and 4) induction of antimicrobial peptides[26, 30-32].

The correlation between sufficient vitamin D and reduced bacterial/viral infections has also been reported by some studies. According to a randomized, placebo-controlled trial study, the addition of vitamin D in the therapy of patients with pulmonary tuberculosis had been proven to show a significant difference in sputum conversion compared with placebo[33]. The evidence also suggested that vitamin D may have activity against influenza and invasive pneumococcal disease [34, 35].

Since vitamin D status is an important factor in the management of sepsis and other critical illness, few treatment guidelines exist to address vitamin D status.The American Society for Parenteral and Enteral Nutrition recommends 200 IU of

vitamin D daily for hospitalized patients [36]. However, further investigations estimate that doses of 400 or 500 IU daily remained in the insufficient range for most hospitalized patients [14, 37]. Thus, these studies suggest that higher recommended doses of vitamin D are likely needed to be used in patients with sepsis tocorrect vitamin D insufficiency.

There is some limitation to the current study. Due to data limitations, we are unable to provide details on premorbid health status, acute or chronic liver failure, use of vitamin D supplements, the type of infection, and detailed data on the outcomes.Larger studies are needed to assess the effects of other potential confounders, such as season, obesity, and medical comorbidities.

In conclusion, we have shown that all critically ill patients we studied had vitamin D insufficiency. In concert with the biological evidence, our study suggests vitamin D deficiency may predispose patients to sepsis and be harmful to those with sepsis. It seems that the consumption of vitamin D supplements might help decrease the prevalence of sepsis. Further studies are required to confirm our findings and establish causation and mechanisms underlying these observations.

Acknowledgment:

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Conflict of interest:

None.

Authors contributions:

All authors contributed equally to this work.

References:

1. Vincent, J.-L., et al., *Sepsis definitions: time for change.* Lancet (London, England), 2013. **381**(9868): p. 774.
2. Rudd, K.E., et al., *The global burden of sepsis: barriers and potential solutions.* Critical Care, 2018. **22**(1): p. 1-11.
3. Seymour, C.W., et al., *Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome.* American journal of respiratory and critical care medicine, 2012. **186**(12): p. 1264-1271.
4. Fleischmann, C., et al., *Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations.* American journal of respiratory and critical care medicine, 2016. **193**(3): p. 259-272.
5. Rudd, K.E., et al., *Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study.* The Lancet, 2020. **395**(10219): p. 200-211.
6. Rhodes, A., et al., *Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016.* Intensive care medicine, 2017. **43**(3): p. 304-377.
7. Seymour, C.W., et al., *Time to treatment and mortality during mandated emergency care for sepsis.* New England Journal of Medicine, 2017. **376**(23): p. 2235-2244.
8. Liu, V.X., et al., *The timing of early antibiotics and hospital mortality in sepsis.* American journal of respiratory and critical care medicine, 2017. **196**(7): p. 856-863.
9. Bikle, D., *Nonclassic actions of vitamin D.* The Journal of Clinical Endocrinology & Metabolism, 2009. **94**(1): p. 26-34.
10. Holick, M.F., *Vitamin D status: measurement, interpretation, and clinical application.* Annals of epidemiology, 2009. **19**(2): p. 73-78.
11. Hewison, M., *Vitamin D and innate and adaptive immunity*, in *Vitamins & hormones*. 2011, Elsevier. p. 23-62.
12. Hewison, M., *Antibacterial effects of vitamin D.* Nature Reviews Endocrinology, 2011. **7**(6): p. 337.
13. Jeng, L., et al., *Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis.* Journal of translational Medicine, 2009. **7**(1): p. 28.
14. Van den Berghe, G., et al., *Bone turnover in prolonged critical illness: effect of vitamin D.* The Journal of Clinical Endocrinology & Metabolism, 2003. **88**(10): p. 4623-4632.

15. Lee, P., J.A. Eisman, and J.R. Center, *Vitamin D deficiency in critically ill patients.* New England Journal of Medicine, 2009. **360**(18): p. 1912-1914.
16. Lucidarme, O., et al., *Incidence and risk factors of vitamin D deficiency in critically ill patients: results from a prospective observational study.* Intensive care medicine, 2010. **36**(9): p. 1609-1611.
17. Matthews, L.R., et al., *Worsening severity of vitamin D deficiency is associated with increased length of stay, surgical intensive care unit cost, and mortality rate in surgical intensive care unit patients.* The American journal of surgery, 2012. **204**(1): p. 37-43.
18. Braun, A.B., et al., *Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill.* Critical care medicine, 2012. **40**(12): p. 3170-3179.
19. Braun, A., et al., *Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill.* Critical care medicine, 2011. **39**(4): p. 671.
20. Autier, P. and S. Gandini, *Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials.* Archives of internal medicine, 2007. **167**(16): p. 1730-1737.
21. Higgins, D.M., et al., *Relationship of vitamin D deficiency to clinical outcomes in critically ill patients.* Journal of Parenteral and Enteral Nutrition, 2012. **36**(6): p. 713-720.
22. Flynn, L., et al., *Effects of vitamin D deficiency in critically ill surgical patients.* The American journal of surgery, 2012. **203**(3): p. 379-382.
23. Hashemipour, S., et al., *Vitamin D deficiency and causative factors in the population of Tehran.* BMC Public health, 2004. **4**(1): p. 38.
24. Shojaei, M., et al., *The Correlation between serum level of Vitamin D and outcome of sepsis patients; a cross-sectional study.* Archives of academic emergency medicine, 2019. **7**(1).
25. Nguyen, H.B., et al., *Serum 1, 25-dihydroxyvitamin D: an outcome prognosticator in human sepsis.* PloS one, 2013. **8**(5).
26. Moromizato, T., et al., *Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill.* Critical care medicine, 2014. **42**(1): p. 97-107.
27. Alves, F.S., et al., *Serum concentrations of vitamin D and organ dysfunction in patients with severe sepsis and septic shock.* Revista Brasileira de terapia intensiva, 2015. **27**(4): p. 376.
28. Rech, M.A., T. Hunsaker, and J. Rodriguez, *Deficiency in 25-hydroxyvitamin D and 30-day mortality in patients with severe sepsis and septic shock.* American Journal of Critical Care, 2014. **23**(5): p. e72-e79.
29. Arnson, Y., et al., *Vitamin D deficiency is associated with poor outcomes and increased mortality in severely ill patients.* QJM: An International Journal of Medicine, 2012. **105**(7): p. 633-639.

30. Deluca, H.F. and M.T. Cantorna, *Vitamin D: its role and uses in immunology.* The FASEB Journal, 2001. **15**(14): p. 2579-2585.
31. Gysemans, C.A., et al., *1, 25-Dihydroxyvitamin D3 modulates expression of chemokines and cytokines in pancreatic islets: implications for prevention of diabetes in nonobese diabetic mice.* Endocrinology, 2005. **146**(4): p. 1956-1964.
32. Mora, J.R., M. Iwata, and U.H. Von Andrian, *Vitamin effects on the immune system: vitamins A and D take centre stage.* Nature Reviews Immunology, 2008. **8**(9): p. 685-698.
33. Nursyam, E.W., Z. Amin, and C.M. Rumende, *The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion.* Hemoglobin, 2006. **1500**: p. 1500.
34. Cannell, J., et al., *Epidemic influenza and vitamin D.* Epidemiology & Infection, 2006. **134**(6): p. 1129-1140.
35. White, A.N., et al., *Let the sun shine in: effects of ultraviolet radiation on invasive pneumococcal disease risk in Philadelphia, Pennsylvania.* BMC infectious diseases, 2009. **9**(1): p. 196.
36. Board, A., *Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients.* Journal of Parenteral and Enteral Nutrition, 1993. **17**: p. 1SA-52SA.
37. Heaney, R.P., et al., *Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol.* The American journal of clinical nutrition, 2003. **77**(1): p. 204-210.

Table 1. Relationship between mean serum vitamin D3 level and different variables.

Variable	No. (%)	Vitamin D3	*P*-value
Sex			
Male	96 (64.0)	18	0.01
Female	54 (36.0)	19	
Age (year)			
< 65	76 (50.6)	14	0.12
≥ 65	74 (50.3)	20	
Source of infection			
Pneumonia	48 (32.0)	20	0.14
Soft tissue infection	41 (27.3)	14	
Bacteremia	22 (14.7)	16	
Urinary tract infection	20 (13.3)	11	
Central nervous infection	4 (2.6)	22	
Gastrointestinal infection	2 (1.3)	7.6	
Others	13 (8.7)	11	
Type of sepsis			
Sepsis	56 (37.3)	18	0.07
Severe Sepsis	26 (16.7)	9	
Septic Shock	68 (46.0)	13	

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision (1)** 11 Apr 2021

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.