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SICKLE CELL ANAEMIA AND VITAMIN D DEFICIENCY

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Abstract

Sickle cell disease is a serious haematological disorder associated with significant morbidity and mortality. Therefore, it has been a disease of concern of many healthcare researchers; and despite the various advances in discovering the pathogenesis of the disease, many basic scientific processes are still not understood. Vitamin D association with sickle cell disease was one of the topics of recent interest. Vitamin D deficiency is known to be very common among patients with sickle cell anemia. Although the exact relationship between them remains elusive, some researchers postulated that the immunomodulatory role of vitamin D plays a role in reduction of the associated complications and the severity of sickle cell anemia symptoms. Over the last few decades, the association between vitamin D and sickle cell disease became clearer, and the understanding of this association led to a notable improvement in management of sickle cell disease and reducing its associated morbidity, complications, and mortality. This article will discuss the association between vitamin D deficiency and sickle cell anaemia and review how treating this deficiency state helped to improve the outcome of sickle cell disease.

Keywords: *Anaemia, vitamin D deficiency, sickle cell, sickle cell disease.*

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INTRODUCTION:

Sickle cell anaemia is one of the grave disorders associated with serious morbidity and mortality. Sickle cell disease is caused by a genetic mutation that results in increased proportion of haemoglobin S leading to anaemia, recurrent infection, or vaso-occlusive crisis e.g. cerebrovascular stroke, acute limb ischemia, or myocardial infarction [1]. Patients with sickle cell anaemia often experience chronic pain and they have a shorter life expectancy than their fellows [2]. Sickle cell anaemia has a considerable negative impact on quality of life. For instance, about 10% of patients with the disease develop disabling cerebrovascular stroke at young age and they live crippled [3]. The chronic pain experienced with the vast majority of patients increase the frequency of school or work absences and results in poor school performance and loss of career [4]. Long and frequent hospital admission disrupts the family and social life and results in considerable psychological disturbance[5].

Therefore, haematologists and scientists are endeavouring to find a curable treatment of sickle cell disease. Several researches have demonstrated and made great discoveries in the field of pathogenesis of sickle cell disease, its risk factors, and genetics, and some new treatment lines were proposed and proved to be effective [6-8]. However, a curable regimen is still lacking. Despite the major advances made in understanding the nature and pathophysiology of the disease, many basic scientific processes are still not completely understood. Each decade, new understanding of these basic scientific processes helps in treating the disease and preventing its complications.

Over the last few decades, the association between vitamin D and sickle cell disease was discovered and studied, and the understanding of this association led to a notable improvement in management of sickle cell disease and reducing its associated morbidity, complications, and mortality[9]. This article will discuss the association between vitamin D deficiency and sickle cell anaemia and review how treating this deficiency state helped to improve the outcome of sickle cell disease.

Vitamin D Physiology, Metabolism, And Relation To Immunity

Vitamin D gained much attention of the medical researchers during the past decade. It was found to be involved in many physiologic processes in the human body and to be associated with many pathological conditions when deficient. In human body, vitamin D exists in two forms: cholecalciferol (or vitamin D_3 form) and ergocalciferol (or vitamin D_2 form) [10]. Vitamin D_3 is the main form of vitamin D in the body and is rarely found in food. It is synthesized in the skin tissue with a simple non - enzymatic reaction when exposed to ultraviolet rays of sun light. Vitamin D2 is supplied by dietary intake of foods rich in vitamin D particularly mushrooms and fish oil, and it undergoes hydroxylation twice, first in liver forming a 25-hydroxy vitamin D, then in the kidney forming the active 1,25 dihydroxy vitamin D [11].

When activated, vitamin D binds to certain receptors called "vitamin D receptors" or VDRs that are widely spread in almost all body tissues [12]. The discovery of these VDRs was the pivot of identifying the various functions of vitamin D in human body. Vitamin D was known for its role in regulating calcium metabolism and bone integrity. It was well-established to be essential during management of bone diseases such as rickets and osteoporosis and in treatment of parathyroid gland dysfunction [13]. However, recent researches have depicted that it is also vital for the integrity of immune system; and consequently, it was shown to be important in pathogenesis and management of different autoimmune or immune mediated diseased such as rheumatoid arthritis, hyperproliferative disorders, multiple sclerosis, cancer, and infections [14]. Vitamin D plays a vital role in these diseases through modulating the immune system [12,14]. In recent years, immune dysfunction was found to be one of the pathophysiologic mechanisms of development of sickle cell disease, and therefore, vitamin D was studied in correlation with sickle cell disease as it will be discussed in the next sections.

The relationship between vitamin D and immune system was a topic of concern during the past few decades. Researchers reported that vitamin D is essential for the integrity and effective function of both innate and adaptive immunity [12]. Innate immunity implies the interaction between antigen presenting cells and foreign antigens. This interaction results in release of inflammatory mediators such as Catheliciden and reactive oxygen species (ROS) that destroy the foreign antigen [15]. Vitamin D enhances the release of Catheliciden promoting and accelerating antigen destruction. The antigen presenting cells have VDRs on their surface and those VDRs are expressed excessively during infection, for vitamin D to act and accelerate antigen elimination [15]. Furthermore, vitamin D role continues to the adaptive immunity through direct

activation of T helper cell and stimulating the release of different cytokines such as Il-2, IL-6, IL-12, and INF-γ [14,16]. The discovery of vitamin D role in modulation of both innate and adaptive immunity was the basis for using and studying it in management of many immune-mediated diseases including sickle cell disease.

Sickle Cell Anaemia And Immunity

Though sickle cell disease is known to result from genetic mutation of the DNA alleles responsible for proper haemoglobin synthesis, inflammation and immune-mediated reactions have a substantial role in the pathogenesis and progression of the disease [17]. Literature studies had demonstrated that patients with sickle cell anaemia show leucocytosis, dysfunction of different leucocytes (particularly monocytes and granulocytes), elevated cytokines and several inflammatory mediators, and endothelial cells dysfunction [18-20]. Therefore, scientists postulated that there may be an immune-mediated reaction playing a role in the pathogenesis of sickle cell disease, and many researches were subsequently held to study the effect of some immunomodulatory agents, including vitamin D, on the prognosis and outcome of sickle cell disease.

Vitamin D Deficiency And Sickle Cell Anaemia

Vitamin D is one of the most common vitamins to be deficient among patients with sickle cell anaemia. It is estimated that about 60% of patients with sickle cell disease have vitamin D deficiency [18]. This may be due to diminished intake with the debilitating state due poor appetite encountered among these patients, or due to reduced exposure to ultraviolet light. Patients with sickle cell anaemia are often less active and more often staying at home or hospitals with less exposure to sun light [21,22].

Vitamin D deficiency was reported to exacerbate symptoms of sickle cell anaemia and worsens the outcome[9]. As aforementioned, vitamin D is essential for immune integrity, and immune dysfunction is an established pathophysiologic process in sickle cell disease [18]. Additionally, vitamin D deficiency presents clinically with systemic manifestations closely similar to manifestations of sickle cell disease such as chronic pain, bone aches, generalized fatigue, and symptoms of chronic inflammation [23]. This makes patients experience exaggerated forms of these symptoms and make physicians unaware of a potential underlying vitamin D deficiency.

Though vitamin D deficiency and sickle cell anaemia are commonly associated, the exact relationship between them remains elusive. Many researchers tried to study this relationship. Unual et al studied the correlation between vitamin D levels in patients with sickle cell disease and the inflammation [18]. They studied vitamin D levels and bone health in correlation with inflammatory mediators including white blood cell count, cytokines (namely IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α and IFN-γ), and c-reactive protein levels. Results from their study revealed no correlation between vitamin D and white blood cells, c-reactive proteins, or bone health, but it was significantly correlated with certain cytokines such as IL-4, IL-6, IL-12, and TNF-α. They also reported that TNF-α, in their study, was associated with significantly higher vaso-occlusive episodes [18]. Therefore, they postulated that vitamin D deficiency was probably correlated with endothelial dysfunction and cytokine release, and resulted in higher frequency of vaso-occlusive crisis.

Management Of Vitamin D Deficiency In Patients With Sickle Cell Anaemia

Because vitamin D was known to posses an immunomodulatory function, many researchers studied its role in treatment of patients with sickle cell disease. Vitamin D supplements were administered to patients with sickle cell disease in a single oral dose of 300000 IU of cholecalciferol regularly for a three-month period to treat vitamin D deficiency states and to increase the 25-hydroxy vitamin D levels in blood to more than 75 mmol/L. Vitamin D supplement was found to significantly reduce the frequency of pain, improve the physical functioning scores, and enhance the quality of life [9,24]. Some studies are still under research to determine the impact of vitamin D supplement on vaso-occlusive events, bone parameters, systemic inflammation, and long-term outcome [25]. Therefore, vitamin D supplementation is currently considered an expensive additional treatment that can enhance the outcome and prevent complications of sickle cell disease.

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CONCLUSION:

Vitamin D deficiency is very common among patients with sickle cell anemia. Although the exact relationship between them remains elusive, some researchers postulated that the immunomodulatory role of vitamin D plays a role in diminution of the complications and reducing the severity of sickle cell anemia symptoms. Vitamin D supplementation to patients with sickle cell disease was found to improve the outcome and life quality of those patients.

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REFERENCES:

1. Centers for Disease Control and Prevention (CDC). CDC Sickle Cell Disease (SCD). CDC.

2. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. *N Engl J Med*. 2017;376(16):1561-1573. doi:10.1056/NEJMra1510865

3. Talahma M, Strbian D, Sundararajan S. Sickle cell disease and stroke. *Stroke*. 2014;45(6). doi:10.1161/STROKEAHA.114.005144

4. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. In: *The Lancet*. Vol 376. ; 2010:2018-2031. doi:10.1016/S0140-6736(10)61029-X

5. Hasan SP, Hashmi S, Alhassen M, Lawson W, Castro O. Depression in sickle cell disease. *J Natl Med Assoc*. 2003;95(7):533-537.

6. Malowany JI, Butany J. Pathology of sickle cell disease. *Semin Diagn Pathol*. 2012;29(1):49-55. doi:10.1053/j.semdp.2011.07.005

7. Centers for Disease Control and Prevention. Sickle Cell Disease: Data and Statistics. Sickle Cell Disease Homepage.

8. Ren J, Ding X, Trudel M, Greer JJ, MacLean JE. Cardiorespiratory pathogenesis of sickle cell disease in a mouse model. *Sci Rep*. 2017;7(1). doi:10.1038/s41598-017-08860-8

9. Soe HHK, Abas ABL, Than NN, et al. Vitamin D supplementation for sickle cell disease. *Cochrane Database Syst Rev*. 2017;2017(1). doi:10.1002/14651858.CD010858.pub2

10. Adams JS, Hewison M. Update in vitamin D. *J Clin Endocrinol Metab*. 2010;95(2):471-478. doi:10.1210/jc.2009-1773

11. Christakos S, Ajibade D V., Dhawan P, Fechner AJ, Mady LJ. Vitamin D: Metabolism. *Endocrinol Metab Clin North Am*. 2010;39(2):243-253. doi:10.1016/j.ecl.2010.02.002

12. Lucas R, Gorman S, Geldenhuys S, Hart P. Vitamin D and immunity. *F1000Prime Rep*. 2014;6. doi:10.12703/P6-118

13. Landry CS, Ruppe MD, Grubbs EG. Vitamin D receptors and parathyroid glands. *Endocr Pr*. 2011;17 Suppl 1:63-68. doi:10.4158/EP10325.RA

14. Hewison M. An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)*. 2012;76(3):315-325. doi:10.1111/j.1365-2265.2011.04261.x

15. Miller J, Gallo RL. Vitamin D and innate immunity. *Dermatol Ther*. 2010;23(1):13-22. doi:10.1111/j.1529-8019.2009.01287.x

16. Scacchetti AT, Cariani E, Manieri G, Vecchi C, Trenti T. Vitamin D, atopy, immunity. *Clin Chem Lab Med*. 2014;52(6). doi:10.1515/cclm-2013-0915

17. Pinheiro LT, Silva RK de S, Barbosa RPT, Moura RRL, Parente DM. The Genetics of Sickle Cell Anemia: A Literature Review. *Int J Eng Technol IJET-IJENS*. 2015;15(36):1510403-1511503.

18. S. U, Y. O, G. E, L.T. G. The association between vitamin d and inflammation in sickle cell disease. *Blood*. 2014;124(21).

19. Damanhouri GA, Jarullah J, Marouf S, Hindawi SI, Mushtaq G, Kamal MA. Clinical biomarkers in sickle cell disease. *Saudi J Biol Sci*. 2015;22(1):24-31. doi:10.1016/j.sjbs.2014.09.005

20. Rees DC, Gibson JS. Biomarkers in sickle cell disease. *Br J Haematol*. 2011. doi:10.1111/j.1365-2141.2011.08961.x [doi]

21. Han J, Zhang X, Saraf SL, et al. Risk factors for vitamin D deficiency in sickle cell disease. *Br J Haematol*. 2018. doi:10.1111/bjh.15270

22. Boettger PC, Knupp CL, Liles DK, Walker K. Vitamin D Deficiency in Adult Sickle Cell Patients. *J Natl Med Assoc*. 2016. doi:10.1016/j.jnma.2016.10.003

23. Ladhani S, Srinivasan L, Buchanan C, Allgrove J. Presentation of vitamin D deficiency. *Arch Dis Child*. 2004;89(8):781-784. doi:10.1136/adc.2003.031385

24. Soe Htoo Htoo K, Abas Adinegara BL, Than Nan N, et al. Vitamin D supplementation for sickle cell disease. *Cochrane Database Syst Rev*. 2013;(11). doi:10.1002/14651858.CD010858

25. Jena Simon. Vitamin D3 in Patients With Sickle Cell Disease - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03012555. Accessed August 3, 2018.