RESEARCH ARTICLE

Frequency of hypovitaminosis D in patients with uveitis presenting at a tertiary care hospital in a low-middle-income country

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Abstract

Objective: To determine the frequency of hypovitaminosis D in patients with uveitis, and to analyse its association with gender and interferon-gamma release assay status.

Method: The retrospective, cross-sectional study was conducted in September 2021 at the Aga Khan University Hospital, Karachi, and comprised medical records and laboratory data of uveitis patients of either gender aged 18-75 years from January 2017 to September 2021. Vitamin D levels were analysed based on predefined criteria, and subgroups were assessed for gender and interferon-gamma release assay status. Data was analysed using SPSS 25.

Results: Of the 120 patients assessed, 63(52.5%) were included; 32(50.8%) females and 31(49.2%) males with median age 40 years (interquartile range: 31-49 years). The median vitamin D level was 14.8ng/ml (interquartile range: 8.2-22.1ng/ml). Hypovitaminosis D was observed in 51(80.9%) patients, with 45(71.4%) deficient and 6(9.5%) insufficient. Male gender and positive interferon-gamma release assay status had significant association with hypovitaminosis D (p<0.05).

Conclusion: Significantly high frequency of hypovitaminosis D was noted in uveitis patients, particularly in males.

Keywords: Vitamin D, Vitamin D deficiency, Tuberculosis, Uveitis, Interferon-gamma release assay.

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Introduction

Uveitis may be classified based on the anatomical location within the eye, the clinical course (acute versus chronic) or the causative factor (infectious versus non-infectious). In the developing world, infectious uveitis accounts for 30-50% of all cases of uveitis, whereas non-infectious uveitis is common in developed countries.[1,2] The prevalence of various types of uveitis exhibits significant geographical variations, which may be attributed to genetic, environmental, socioeconomic and nutritional factors. Micronutrients play an important role in immune modulation, and vitamin D's role in immune modulation is becoming increasingly clear. The vitamin D receptor (VDR) is expressed on immune cells (antigen-presenting cells, B cells and T cells) which is thought to play an important role in enhancing immunity.[3] Research in experimental model has shown that VDR agonists selectively inhibit type 1 T-helper cell pathway, halting aberrant activity in non-infectious autoimmune uveitis.[4] Similarly, high rates of non-infectious uveitis were associated with low vitamin D levels in a clinical study.[5] Conversely, normal levels of vitamin D combat systemic infections, such as coronavirusdisease-2019 (COVID-19), and are known to reduce the risk of influenza.[6]

In the human body, vitamin D exists in two forms: a metabolised inactive 25-hydroxvitamin D (25[OH]D), which is converted to its active form 1,25-dihydroxyvitamin D (1,25[OH]2D) in kidneys. This mechanism is strictly regulated by plasma parathyroid hormone levels and serum calcium and phosphorus levels.[6] Higher levels of 1,25(OH)2D are found in ocular sarcoidosis, which has led to an interest in the ratio between 1,25(OH)2D and 25(OH)D.[7] Additionally, some studies have reported that vitamin D induces anti-tuberculous activity in vitro in both monocytes and macrophages.[8] In one study, the odds ratio (OR) of developing uveitis was 4% lower for every 1ng/ml increase in 25(OH)D.[9] Interferon-gamma release assay (IGRA) is a diagnostic test for tuberculosis (TB) and TB-associated uveitis.[10]

The current study was planned to assess the frequency of hypovitaminosis D in patients with uveitis presenting at a tertiary care hospital, and its association with gender and IGRA status.

Materials and Methods

The retrospective, cross-sectional study was conducted in September 2021 at the Department of Ophthalmology, Aga Khan University Hospital (AKUH), Karachi, and

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comprised medical records and laboratory data of uveitis patients from January 2017 to September 2021. Data was collected from the medical records after getting approval from the institutional ethics review committee. The date of the first presentation to the clinic with the diagnosis was taken as the index date. The sample was raised using non-probability, consecutive sampling technique after the sample size was estimated using the World Health Organisation (WHO) calculator, taking the prevalence of hypovitaminosis D in uveitis as 33%, with 8.5% margin of error and 95% confidence interval (CI).[9] Those included were patients of either gender aged 18-75 years who had any type of clinically diagnosed uveitis, like anterior, intermediate, posterior, panuveitis, choroiditis or retinal vasculitis. Patients with incomplete blood workup or those who were taking vitamin D supplements, or medicines that interfered with vitamin D metabolism, such as bisphosphonates, cytostatics and statins, or those with systemic diseases, such as, renal failure, gastric bypass and parathyroid dysfunction which interfered with vitamin D levels, were excluded. The patients were categorised based on the anatomical classification of uveitis by the International Uveitis Study Group (IUSG).[11]

The serum levels of vitamin D were divided into four subgroups. Vitamin D deficient group had serum 25(OH)D level ≤20ng/ml, level 21-29ng/ml was taken as insufficient, levels of 30ng/ml was taken as sufficient, and level of 150ng/ml was considered vitamin D intoxication.[12] Hypovitaminosis D was defined as level <30ng/ml. Vitamin D levels of all uveitis patients measured within eight weeks of the index date were recorded. The primary outcome was the frequency of hypovitaminosis D. Subgroup analysis was done to evaluate hypovitaminosis D with gender, type of uveitis, vitamin D levels, and IGRA status.

Data was stored in an Excel sheet and analysed using SPSS 25. Data was expressed as frequencies and percentages or as median and interquartile range (IQR). Effect modifiers, including age, gender and type of uveitis, were stratified, and further subgroup analyses of vitamin D with gender and IGRA status were done using Fischer exact test. P<0.05 was considered significant.

Results

Of the 120 patients assessed, 63(52.5%) were included; 32(50.8%) females and 31(49.2%) males with median age 40 years (IQR: 31-49 years). The median vitamin D level was 14.8ng/ml (IQR: 8.2-22.1ng/ml). Hypovitaminosis D was observed in 51(80.9%) patients; with 45(71.4%) deficient and 6(9.5%) insufficient. Hypovitaminosis D was found in 29(45.9%) of the males and 22(34.8%) of the females (Figure 1). There were 12(19%) patients with normal vitamin D level (Figure 2), while no case of vitamin D intoxication was found.

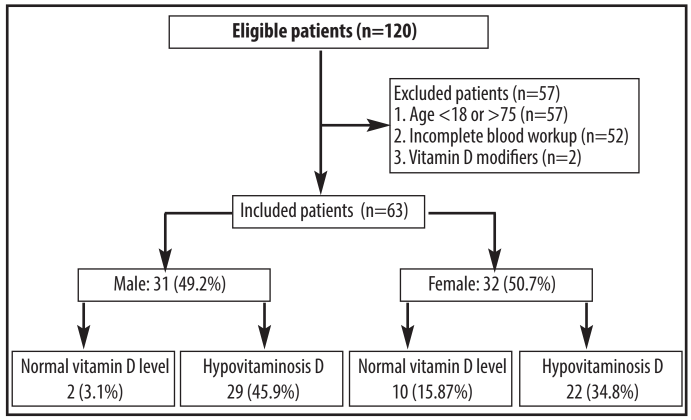

Figure-1: Proportion of hypovitaminosis D in male and female patients.

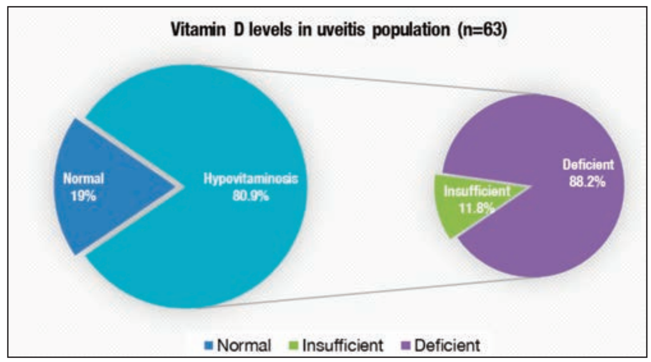

Figure-2: Vitamin D levels and sub-division of hypovitaminosis D.

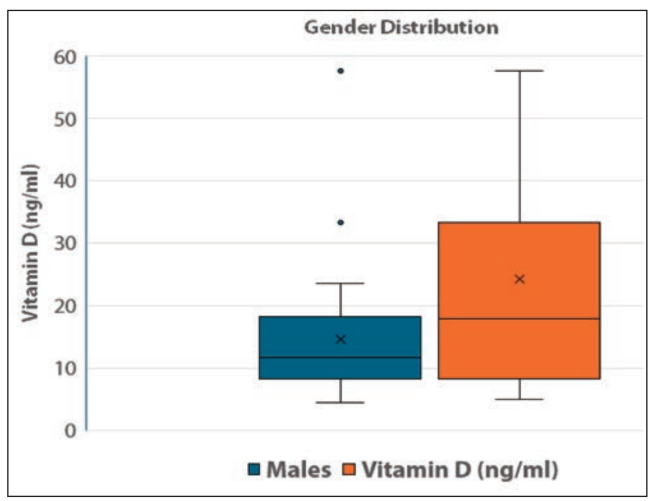

Figure-3: Median levels of vitamin D with respect to gender.

The most common anatomical type observed was retinal vasculitis 16(25.4%), followed by panuveitis 8(12.7%), anterior uveitis 7(11.1%), posterior uveitis 7(11.1%), and intermediate uveitis 3(4.8%), while 22(34.9%) cases remained uncategorised (Table 1).

Regarding laterality, 26(41.3%) patients presented with

Table-1: Patient characteristics.

Demographic characteristics	All Patients (n = 63)	Median Vitamin D Levels (ng/ml)
Male (n; %)	31 (49.2%)	
Age in years (median, IQR)	40 (IQR: 31.0-49.0)	
Median levels of vitamin D (ng/ml)		14.8 (IQR: 8.2-22.1)
Anatomical Classification:	Patients [n (%)]	Median Vitamin D Levels (ng/ml)
Bilateral disease	26 (41.3)	12.1 (IQR: 8.0-18.0)
Anterior uveitis	7 (11.1)	29.7 (IQR: 10.2-37.7)
Intermediate uveitis	3 (4.8)	7.54 (IQR: 6.0-12.1)
Posterior uveitis	7 (11.1)	12.6 (IQR: 10.5-18.4)
Panuveitis	8 (12.7)	14.1 (IQR: 11.4-19.3)
Retinal vasculitis	16 (25.4)	13.37 (IQR: 8.5-19.1)
Uncategorized	22 (34)	17.6 (IQR: 8.2-23.6)

IQR: Interquartile range.

Table-2: Relationship of vitamin D levels with gender and IGRA status.

Variables	Vitamin D Groups		Total	Median Level	IQR	*p*-value
	Hypovitaminosis D	Normal	(n = 63)	(ng/ml)		
Gender						
Male	29 (46.0%)	2 (3.1%)	31 (49.2%)	11.4	8.2-18.2	0.046*
Female	22 (34.9%)	10 (15.9%)	32 (50.7%)	17.85	8.2-33.3	
Total (Gender)	51 (80.9%)	12 (19%)	63 (100%)	14.8	8.2-22.1	
IGRA						
Negative	32 (50.7%)	4 (6.3%)	36 (57.1%)	11.6	8.2-20.8	0.031*
Positive	19 (30.1%)	8 (12.6%)	27 (42.8%)	17.7	8.2-31.1	
Total (IGRA)	51 (80.9%)	12 (19%)	63 (100%)	14.8	8.2-22.1	

*Fisher Exact test;IQR: Interquartile range, IGRA: Interferon-gamma release assay.

bilateral but asymmetric uveitis, and had a median vitamin D level of 12.1ng/ml. Patients with unilateral uveitis 19(30.1%) had a higher median vitamin D level of 18.1ng/ml.

The frequency of hypovitaminosis D was significantly higher in male patients (p=0.046). The median vitamin D level in males was 11.7ng/ml (IQR: 8.2-18.2ng/ml), which was significantly lower than the median level in females 17.85ng/ml (IQR: 8.2-33.3) (p=0.023) (Table 2, Figure 3).

IGRA status was positive in 27(42.8%) cases who had a median vitamin D level of 17.7ng/ml (IQR: 8.2-31.1ng/ml), which was significantly higher than the median level of 11.6ng/ml (IQR: 8.2-20.8ng/ml) in IGRA-negative participants (p=0.031) (Table 2).

Discussion

The current study found a significantly high frequency of hypovitaminosis D in the uveitis population. The role of vitamin D has been studied in experimental models and has shown inhibition of the T-helper 1 (Th1) pathway by VDR agonists, leading to reduced autoimmune activity in non-infectious autoimmune uveitis.[13] Hence, hypovitaminosis D is expected to be associated with a greater autoimmune response in the non-infectious uveitis population. Its role in uveitis with infectious aetiology is yet to be determined. The current study, to our knowledge, is the first to report 80.9% frequency of hypovitaminosis D in a uveitis population, and the first to report subgroup comparison of vitamin D levels with IGRA status.

Multiple studies have reported differing levels of vitamin D amongst uveitis patients. In a retrospective study of non-infectious uveitis patients conducted in the United States with 558 patients, normal vitamin D levels had 21% lower odds (protective effect) of having non-infectious uveitis compared to those with vitamin D levels <20ng/ml. However, the exact prevalence was not reported.[5] Another retrospective study in the US reported an OR of 2.53 for patients with non-infectious anterior uveitis to have hypovitaminosis D.[9] In a prospective case-control study in Australia, a prevalence of vitamin D deficiency in 74(54.1%) active uveitis patients and 77(23.4%) of inactive uveitis patients was reported, while the community it was 594(28.6%). These were again all non-infectious uveitis, with 75.7% classified as anterior uveitis, and 31% having an identifiable systemic disease.[14] A study in Turkiye evaluated vitamin D levels in acute anterior uveitis, and found an extremely low mean level of 5.75ng/ml compared to the control group with a mean level of 12.96ng/ml (p<0.05).[15] However, no data on the prevalence of vitamin D in uveitis patients in South Asia could be located.

The current finding of 80.9% prevalence of hypovitaminosis D in uveitis patients with median level 14.8ng/ml was comparable to the healthy population (84.3%) having a median level of 18.8ng/ml.[16] In neighbouring India, the prevalence was reported to range 30-91.2% in the adult population.[17] Other studies conducted in the US reported an overall prevalence of vitamin D deficiency 41.6% with the highest prevalence amongst Blacks (82.1%).[18] In Europe, it was reported to be <20% in northern Europe, and 30-60% in the other parts.[19]

Mycobacterium TB is unique in causing a primary ocular infection, or an autoimmune reaction secondary to an infectious aetiology. It is proposed that vitamin D enhances superoxide production in TB infection[20] and upregulates VDR on macrophages that aid in enhancing innate immune response by killing intracellular mycobacteria.[21] In the current study, the frequency of hypovitaminosis D in IGRA-positive patients was 42.8%. In the regional context, systemic TB is highly endemic in various parts of Pakistan, with a reported prevalence of 348 per 100,000 population per year[22] compared to high-income countries (HICs) having <10 per 100,000 population.[23] Hence, IGRA-positive patients were significantly high in the current uveitis population, and the number is expected to be high in the general population as well. A US study reported an overall prevalence of 5% IGRA positivity; 15.9% in foreign-born citizens, and 2.8% in US-born citizens.[24] Interestingly, a major proportion of the current patients had retinal vasculitis (25.4%) and panuveitis (12.7%), both of which are associated with TB uveitis.

Another significant finding of the current study was the higher frequency of hypo-vitaminosis D in the male population. Generally, in the South Asian culture, women experience relatively restricted outdoor exposure, use a headcover or veil when going outdoors which limits exposure to sunlight, receive a poorer diet compared to male members of the family, and have multiple pregnancies. However, another population-based study of vitamin D in healthy participants was conducted in a central region of Pakistan that reported similar findings of hypovitaminosis D in male and female participants (86.3% of males vs 84% of females).[25]

Along with its strengths, the current study has its limitations, including a high prevalence of vitamin D deficiency in the sample population, which was in line with a study of 4,380 patients showing that 53.3% of the Pakistani population had deficient and 31.2% had insufficient vitamin D levels.[25] Another limitation was the margin of error, which is 8.5%. Considering the retrospective design of the study, there were no control groups to make comparisons with. Despite the calculated sample size of 118, only 63 of 120 screened patients met the eligibility criteria. This limitation was due to the rarity of uveitis cases with complete laboratory data in the hospital records. Additionally, the limited sample size suggests that the results should be interpreted as preliminary data, warranting further investigation with larger sample sizes. Furthermore, the high level of hypovitaminosis D in the study participants may simply reflect hypovitaminosis D in the general population of our country. Another limitation is that the socioeconomic status (SES) of the patients presenting at AKUH, a private-sector hospital, is differ-ent from the general population that mostly presents to government-funded public hospitals.

All these limitations may have affected the generalizability of the current findings. Prospective research with broader population representation is warranted to validate the findings.

Conclusion

Significantly high frequency of hypovitaminosis D among uveitis patients was noted, emphasising its potential role in immune modulation. The observed high frequency aligns with regional trends and warrants attention in the context of uveitis. Subgroup analysis revealed a higher frequency in males, coupled with the intriguing correlation between vitamin D levels and IGRA positivity.

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References

1. Rathinam SR, Namperumalsamy P. Global variation and pattern changes in epidemiology of uveitis. Indian J Ophthalmol 2007;55:173-83. doi: 10.4103/0301-4738.31936.
2. Tsirouki T, Dastiridou A, Symeonidis C, Tounakaki O, Brazitikou I, Ka-logeropoulos C, et al. A Focus on the Epidemiology of Uveitis. Ocul Im-munol Inflamm 2018;26:2-16. doi: 10.1080/09273948.2016.1196713.
3. Aranow C. Vitamin D and the immune system. J Investig Med 2011;59:881-6. doi: 10.2310/JIM.0b013e31821b8755.
4. Tang J, Zhou R, Luger D, Zhu W, Silver PB, Grajewski RS, et al. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. J Immunol 2009;182:4624-32. doi: 10.4049/jimmunol.0801543.
5. Sobrin L, Stanwyck LK, Pan W, Hubbard RA, Kempen JH, VanderBeek BL. Association of Hypovitaminosis D With Increased Risk of Uveitis in a Large Health Care Claims Database. JAMA Ophthalmol 2018;136:548-52. doi: 10.1001/jamaophthalmol.2018.0642.
6. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical appli-cations. Chem Biol 2014;21:319-29. doi: 10.1016/j.chembiol.2013.12.016.
7. Rohmer J, Hadjadj J, Bouzerara A, Salah S, Paule R, Groh M, et al. Serum 1,25(OH)2 Vitamin D and 25(OH) Vitamin D Ratio for the Diagnosis of Sarcoidosis-Related Uveitis. Ocul Immunol Inflamm 2020;28:341-7. doi: 10.1080/09273948.2018.1537399.
8. Coussens AK, Martineau AR, Wilkinson RJ. Anti-Inflammatory and An-timicrobial Actions of Vitamin D in Combating TB/HIV. Scientifica (Cai-ro) 2014;2014:903680. doi: 10.1155/2014/903680.
9. Grotting LA, Davoudi S, Palenzuela D, Papaliodis GN, Sobrin L. Associa-tion of Low Vitamin D Levels With Noninfectious Anterior Uveitis. JAMA Ophthalmol 2017;135:150-3. doi: 10.1001/jamaoph thalmol.2016.4888
10. Rahman S, Irfan M, Siddiqui MAR. Role of interferon gamma release as-say in the diagnosis and management of Mycobacterium tuberculosis-associated uveitis: a review. BMJ Open Ophthalmol 2021;6:e000663. doi: 10.1136/bmjophth-2020-000663.
11. Deschenes J, Murray PI, Rao NA, Nussenblatt RB; International Uveitis Study Group. International Uveitis Study Group (IUSG): clinical classifi-cation of uveitis. Ocul Immunol Inflamm 2008;16:1-2. doi: 10.1080/09273940801899822.
12. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81. doi: 10.1056/NEJMra070553.
13. Amadi-Obi A, Yu CR, Liu X, Mahdi RM, Clarke GL, Nussenblatt RB, et al. TH17 cells contribute to uveitis and scleritis and are expanded by IL-2 and inhibited by IL-27/STAT1. Nat Med 2007;13:711-8. doi: 10.1038/nm1585.
14. Chiu ZK, Lim LL, Rogers SL, Hall AJ. Patterns of Vitamin D Levels and

Exposures in Active and Inactive Noninfectious Uveitis Patients. Ophthalmology 2020;127:230-7. doi: 10.1016/j.ophtha.2019.06.030.

15. Dadaci Z, Cetinkaya S, Oncel Acir N, Oncel M, Borazan M. Serum Vitamin D Levels in Patients with Acute Anterior Uveitis. Ocul Immunol In-flamm 2017;25:492-6. doi: 10.3109/09273948.2016.1139735.
16. Sheikh A, Saeed Z, Jafri SA, Yazdani I, Hussain SA. Vitamin D levels in asymptomatic adults--a population survey in Karachi, Pakistan. PLoS One 2012;7:e33452. doi: 10.1371/journal.pone.0033452.
17. Kamboj P, Dwivedi S, Toteja GS. Prevalence of hypovitaminosis D in In-dia & way forward. Indian J Med Res 2018;148:548-56. doi: 10.4103/ijmr.IJMR_1807_18.
18. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D defi-ciency in US adults. Nutr Res 2011;31:48-54. doi: 10.1016/j.nutres.2010.12.001.
19. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermay-er-Pietsch B, Bianchi ML, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. Eur J Endo-crinol 2019;180:P23-54. doi: 10.1530/EJE-18-0736.
20. Sly LM, Lopez M, Nauseef WM, Reiner NE. 1alpha,25-Dihydroxyvitamin D3-induced monocyte antimycobacterial activity is regulated by phospha-tidylinositol 3-kinase and mediated by the NADPH-dependent phagocyte oxidase. J Biol Chem 2001;276:35482-93. doi: 10.1074/jbc.M102876200.
21. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770-3. doi: 10.1126/science.1123933.
22. National Institutes of Health (NIH) Islamic Republic of Pakistan. National Tuberculosis (TB) Control Programme. [Online] 2020 [Cited 2022 April 06]. Available from URL: https://www.nih.org.pk/public/national-tb-control-program
23. Glaziou P, Sismanidis C, Floyd K, Raviglione M. Global epidemiology of tuberculosis. Cold Spring Harb Perspect Med 2014;5:a017798. doi: 10.1101/cshperspect.a017798.
24. Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, Castro KG, et al. Tuberculosis Infection in the United States: Prevalence Esti-mates from the National Health and Nutrition Examination Survey, 2011-2012. PLoS One 2015;10:e0140881. doi: 10.1371/journal.pone.0140881.
25. Riaz H, Finlayson AE, Bashir S, Hussain S, Mahmood S, Malik F, et al. Prevalence of Vitamin D deficiency in Pakistan and implications for the fu-ture. Expert Rev Clin Pharmacol 2016;9:329-38. doi: 10.1586/17512433.2016.1122519.

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SNAM: Concept, design, data collection, material preparations, analysis, study tables, figures, original draft, editing and final approval.
MBM: Concept, design, data collection, material preparations, analysis, study ta-bles, figures, editing and final approval.
HT, MI & MARS: Concept, design, data collection, material preparations, analy-sis, editing and final approval.