Section: Physiology

Original Research Article

RELATIONSHIP BETWEEN SERUM VITAMIN D LEVELS AND USE OF INHALATIONAL CORTICOSTEROIDS IN TREATMENT OF CHILDHOOD ASTHMA – A STUDY FROM CENTRAL KERALA

Harikrishnan R[1], Saraswathy L[2], Sajitha Nair[3], Sajitha Krishnan[4]

[1]Assistant Professor, Department of Physiology, Govt medical college, Kozhikode, Kerala, India (Former Student AIMS Kochi, Kerala, India)
[2]Professor Department of Physiology, AIMS, Kochi, Kerala, India
[3]Professor Department of Paediatrics, AIMS, Kochi, Kerala, India
[4]Professor Department of Biochemistry, AIMS, Kochi, Kerala, India

Received : *09/07/2025*
Received in revised form : *26/08/2025*
Accepted : *18/09/2025*

Keywords:
25(OH) D, ICS. Asthma

Corresponding Author:
Dr. Harikrishnan R
Email: hari1703aj@gmail.com

DOI: 10.47009/jamp.2025.7.5.173

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (5); 913-917

ABSTRACT

Background: This prospective case control study conducted at a reputed tertiary care centre in central Kerala was to find out any relationship that existed between the use of inhalational corticosteroids and serum levels vitamin D in the treatment of childhood asthma. **Materials and Methods:** The samples were collected from children of age group 5 to 15 yrs. Serum was then separated and stored in deep freezer. The quantitative estimation of total 25(OH)D is done using ARCHITECT 25(OH) D assay which is a chemiluminescent microparticle immunoassay (CMIA). Data collected in proforma sheets were entered into Microsoft excel sheets. Statistical analysis was done in the Department of Biostatistics. **Result:** A decreasing trend in 25-OH vitamin D level was noticed from low total daily steroids using group to higher total daily steroids using group. The p value was found to be 0.689. There was a male preponderance in our study. **Conclusion:** A large population based study is necessary for confirming the association between the use of inhalational corticosteroids (ICS) and serum 25(OH) D levels in the treatment of childhood asthma.

INTRODUCTION

Vitamin D is a prohormone and it is considered to be the oldest of all known hormone. It is also called sunshine vitamin since, it can be synthesized in skin on exposure to sun[1]. The most important role of vitamin D is in skeletal health i.e., calcium metabolism and bone mineralization.[1]The D vitamins are a group of fat-soluble secosteroids. Vitamin D_3 (Cholecalciferol) belongs to animal origin and and vitamin D_2 (Ergocalciferol) are of plant origin. The evolutionary importance of a sufficient vitamin D supply can be inferred from the ethnical and gender difference in skin pigmentation. Lighter skin coloration gives higher ability to produce vitamin D from sunlight. People living in high altitudes where there is less sunlight and also for females in all populations are lighter in skin pigmentation considered to be factors that can increase the efficacy of Vitamin D synthesis.[2] The hormone has got skeletal and extra skeletal actions. Apart from being important in mineralization of bones,Vitamin D is important in foetal brain maturation, lung maturation and is also involved in development and functioning of nervous system. Over the time, vitamin D has evolved into a hormone that is thought to be regulating up to an estimated 2000 genes[3].The name Vitamin D was coined by McCollum in 1922. Windaus and Hess discovered ergosterol and named its irradiation product as Vitamin D_2. In the year 1935 Windauss et al isolated 7 dehydrocholestrols and its irradiation product was named as Vitamin D_3 and also established its structure.[3,4]

Vitamin D enhances the innate immunity against various infections and is important in fighting infectious diseases, especially tuberculosis, influenza and viral upper respiratory tract infections. Monocytes and macrophages recognizes pathogens-e.g., tuberculosis by utilizing their toll-like receptors (TLRs) and this induces both VDR and CYP27B1, which increases the local production of $1,25(OH)_2D$ that is dependent on the serum 25(OH)D concentration [4,5]. $1,25(OH)_2D$ enhances the innate immune system by inducing the production of antimicrobial peptides like cathelicidin, reactive oxygen species by the (reduced) nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and potentially reactive nitrogen species by inducible nitric oxide synthase (iNOS), and by inducing autophagy.

Asthma is a common chronic inflammatory condition of lung airways resulting in episodic airway obstruction commonly triggered by environmental factors. This chronic inflammation increases airway hyper responsiveness to provocative exposures and causes considerable morbidity.[5]Asthma is a common cause for paediatric emergency department visits and the third leading cause for hospitalizations and school absenteeism. The prevalence of asthma worldwide is estimated to be 300 million.

It is estimated that asthma accounts for about 1 in every 250 deaths worldwide. Many of the deaths are preventable,mainly being due to suboptimal long-term medical care and delay in obtaining help during the acute attacks. The burden of asthma in many countries is of huge magnitude and resources need to be provided to counter preventable environmental factors such as air pollution.[610]Etiology of childhood asthma is a combination of environmental exposures and inherent biological and genetic vulnerability. Environmental factors include inhaled allergens, respiratory viral infections, chemical and biological air pollutants like tobacco smoke and automobile exhaust. Immune response to these common exposures can be a stimulus for prolonged pathological inflammation. This pathogenesis in developing lung during early life can have an adverse effect on growth and differentiation of lung. Once asthma has developed, ongoing exposure appears to worsen

Asthma management is aimed at reducing airway inflammation by minimizing pro-inflammatory environmental exposures using daily controller anti-inflammatory medications and controlling co-morbid conditions that can worsen asthma.

Asthma predictive index for children include parental asthma, eczema and inhalant allergen sensitization as major criteria and allergic rhinitis, wheezing apart from cold, eosinophil>/= 4% and food allergen sensitization as minor criteria.[9]

Table 1: Classification for asthma severity.[10,11]

Asthma Severity	Days with symptoms	Nights with symptoms
Severe persistent	Continual	Frequent
Moderate persistent	Daily	>1/ week
Mild persistent	>2/week but <1 time /day	>2/ month
Mild intermittent	</= 2 / week	<2/ month

Classification is based on symptoms before initiation of treatment and is based on patients' most severe symptoms.

Corticosteroids are the most potent and effective medication used in treatment of both acute and chronic asthma manifestation. Inhalational corticosteroids (ICS) therapy is the recommended therapy of choice in children with persistent type of asthma.ICS has shown to improve lung function, reduce airway hyper reactivity, and reduces rescue medication, emergency hospital visits and hospitalizations by 50%. It also reduces the risk of death due to asthma.

Studies published from different countries especially from western world have shown an association between vitamin D deficiency and asthma and have also shown association between vitamin D deficiency and asthma control and its exacerbations. Despite several studies worldwide on serum vitamin D levels and childhood asthma, there are hardly any studies from Kerala. Hence, in the present study, an attempt has been done to study the relation between the severity of asthma, effect of inhalational cortico steroid use in children aged 5 to 15 yrs.

MATERIALS AND METHODS

This is a prospective case control study conducted in the Department of Physiology and Department of Pediatrics at Amrita institute of Medical science (AIMS) Kochi, after obtaining approval from institutional ethics committee.

Cases were recruited from the Department of Pediatrics. Children aged 5yrs- 15yrs with asthma, attending outpatient department (OPD) were recruited. They were diagnosed as severe persistent or moderate persistent according to severity of symptoms.[7,8]The controls were children attending OPD not having asthma, and also children admitted for illness other than respiratory illness, who were not on steroids or vitamin D supplements. Children of either sex were recruited. Newly detected cases of less than 3 months duration were not included in the study. Total number of children recruited for study were 82, out of which 17 children were diagnosed with severe persistent asthma, 34 children were diagnosed with moderate persistent asthma and 31 children without asthma were recruited as controls.

Clinical data collected included presenting age, sex, duration of illness, symptoms of current illness and dose of medications. Data on variables like vitamin D rich food intake, effective sun exposure, school absenteeism and socioeconomic status were collected using proforma. The study group and control group sample size were designed after discussing with statistician.

Sample size: Based on the mean value of serum vitamin D in moderate and severe persistent asthma, and in those without asthma, from the existing literature with 95% confidence and 80% power,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

minimum sample size comes to be 20 for severe and 30 each for moderate and control groups.[12]

The cases and controls were matched with respect to age and sex. Consecutive cases and controls, satisfying the matching factors and exclusion and inclusion criteria, were included in the study.

Statistical Analysis

1) Mean and Standard deviation of vitamin D and all other measurable study variables were computed for all the 3 groups.

2) To test the statistical significance of the difference in the mean value, among the three groups, analysis of variance was applied.

3) To identify the statistically significant pair of groups, multiple comparison test was applied.

Study Design: The study is carried out as a case - control study.

The samples were collected from children attending pediatric OPD with the permission of the Professor in charge, three days a week. This process continued for a period of five months.

All the samples were taken under aseptic conditions after getting written informed consent from the parents.

5 ml of blood was collected in vials from peripheral vein under aseptic conditions for the estimation of vitamin D, calcium.The samples were taken to the biochemistry lab and centrifuged at 3000 rpm for period of 5min to separate the serum. The serum was then transferred to Eppendorf vial with name and identification number written on it. These containers were then stored at -20 degree Celsius in a deep freezer. Serum 25 (OH)D levels were estimated using ARCHITECT 25OH assay which is a chemiluminescent microparticle immunoassay (CMIA).

Method of vitamin D estimation

The quantitative estimation of total 25-OH D is done using ARCHITECT 25OH assay which is a chemiluminescent microparticle immunoassay (CMIA).

Vitamin D is a fat soluble steroid hormone majority of which is produced photo chemically in the skin from 7-dehydrocholestrols.Two forms of vitamin D are biologically relevant vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol).Both D2and D3 can be obtained from food, but only an estimated 10-20% of vitamin D is supplied through nutritional intake.The estimated vitamin D is a sum total of 25-OH derivative of both vitamin D2 and vitamin D3.

Biological principles and procedures

The ARCHITECT 25-OH is a delayed one step immunoassay, including a sample pretreatment for the quantitative estimation of vitamin D in human serum, using CIMA technology with flexible assay protocols, referred to as Chemiflex.

Sample and pretreatment reagents are combined. An aliquot of sample and pretreated reagent are combined with assay diluents and paramagnetic anti-vitamin D coated micro particles to create a reaction mixture. Vitamin D present in the sample binds to anti-vitamin D coated microparticles. After incubation, a biotinylated vitamin D and anti-Biotin acridinium-labelled conjugate complex is added to the reaction mixture and binds to uncoupled binding sites of anti-vitamin D microparticles. After washing, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). An indirect relationship exists between the amount of vitamin D in the sample and the RLUs detected by ARCITECT i System optics.

The reagents used include Micro particles, Conjugate, Assay diluents, Pre-treatment 1, Pretreatment 2, ARCHITECT i Pre-trigger solution, ARCHITECT i Trigger solution, and ARCHITECT I wash buffer.

The measuring interval of this method is from 8 ng/ml (20nmol/L) to 160ng/ml (400nmol/L). This method has high sensitivity and specificity,and the potential interference from hemoglobin, bilirubin, triglycerides, protein, rheumatoid factor and red blood cells is designed to be less than 10%.

Expected pediatric sufficiency range for serum vitamin D is 20-100ng/ml. The insufficiency range is 15-20ng/ml and deficiency is<15ng/ml.[13]

Data collected in proforma sheets were entered into Microsoftexcel sheets. Statistical analysis was done in the Department of Biostatistics.

RESULTS

The statistical study on steroid use was done among cases only. The asthma cases were divided in to two groups. One group with total daily ICS dose less than 500mcg/day and the second group with total daily ICS dose more than 500mcg/day.

Table 2: Association between total ICS dose/day among asthma cases and serum 25-OH vitamin D levels.

Total daily inhaled steroid use	25-OH vitamin D		Total n(%)	p value among group
	<15ng/ml (Deficient) n(%)	>15ng/ml (Insufficient +Sufficient) n(%)		
<500mcg/d	9 (52.9%)	8 (47.1%)	17(100%)	0.689
>500mcg/d	20 (58.8%)	14 (41.2%)	34(100%)	
Total	29 (56.9%)	22 (43.1%)	51(100%)	

Out of total 51 asthma cases, 17 (33.3%) were getting a total daily steroid dose of less than 500mcg/day, and 34 (66.6%) were getting a total daily dose of steroids more than 500mcg/day. Out of 17 cases with total daily steroid dose of less than 500mcg/day, 9 (52.9%) had 25-OH vitamin D levels <15ng/ml and rest 8 (47.1%) had 25-OH vitamin D levels >15ng/ml.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

In the group with total daily steroid dose of more than 500mcg/day, 20 (58.8%) had 25-OH vitamin D levels were <15ng/ml and 14 (41.2%) had 25-OH vitamin D levels >15ng/ml. Vitamin D deficiency was found to be higher in children on total daily steroids >500mcg/day.A decreasing trend in 25-OH vitamin D level was noticed from low total daily steroids using group to higher total daily steroids using group.But no statistically significant association was found between the two groups.The p value was found to be 0.689.There was a male preponderance in our study,as was the case in studies conducted at various places.

DISCUSSION

Brehm et al in his study on ICS and vitamin D levels found that children with insufficient vitamin D levels and who were on ICS had higher odds of having a severe asthma exacerbation6. The highest odds were in children who were vitamin D insufficient and who were not on ICS. These results suggest that having sufficient vitamin D levels confers additional benefit to use of ICS. He also suggested that since vitamin D sufficiency reduces the severity of viral infections, it in turn reduces severe exacerbations by preventing the severe sequelae, without affecting the incidence of viral infections. Interventional studies examining effect of vitamin D on asthma had showed a secondary outcome that vitamin D3 supplementation (1200 IU/day) in school children was associated with a significantly [83%] reduced risk for asthma exacerbations.[7]The levels of 25(OH)D correlate positively with asthma control and improved lung function in children with asthma.

Searing et al, in their study demonstrated that, for optimum pharmacological effect of glucocorticoids to come to effect, there has to be sufficient levels of vitamin D in blood. According to them, up regulation of MKP-1(mitogen activated protein kinase phosphatase-1) and IL-10 expression is essential for glucocorticoid mediated anti inflammatory and immunosuppressive effects. They found that vitamin D enhances steroid induction of MKP-1 and IL-10 in peripheral blood mononuclear cells. Also, they proposed an additional possibility that vitamin D has effects on glucocorticoid pathways and vitamin D insufficiency promotes the need for higher doses of glucocorticoids to achieve treatment effects.An inverse relation was noticed on levels of 25(OH)D in children who were on corticosteroid use.[8]

In the study by Searing et al, from Denver, significant association between ICS use and lower vitamin D levels was found. A significant inverse correlation was noticed with vitamin D levels and age ($p<0.0001$); high body mass index ($p=0.04$);FEV1 percent predicted ($p=0.004$) .Among the therapeutic modalities assessed, there was significant association between lower vitamin D levels and inhaled corticosteroid use ($p=0.045$); use of oral steroids (p-0.02); total steroid dose ($p=0.001$) and use of long acting beta-2 agonists ($p=0.0007$).[8]

In another study by Xystrakis and colleagues, on addition of vitamin D and dexamethasone to cultures of CD4+ regulatory T cells from steroid resistant asthmatics, there was enhanced IL-10 secretion from these cells, to levels comparable from cells of steroid sensitive subjects treated only with dexamethasone. The study demonstrated that vitamin D blocked the down regulation of steroid receptors, induced by dexamethasone.[9]

Our study group included 51 children diagnosed to have severe or moderate persistent asthma and who were on inhaled corticosteroids for more than three months. The severity of disease was assessed according to NAEPP and GINA guidelines.[10,11] Thirty one (31) children without asthma were recruited as controls. A decreasing trend in 25-OH vitamin D level was noticed from low total daily steroids using group to higher total daily steroids using group.But no statistically significant association was found between the two groups.The p value was found to be 0.689.There was a male preponderance in our study,as was the case in studies conducted at various places.

CONCLUSION

A large population based study is necessary for confirming the association between the use of inhalational corticosteroid and serum vitamin D levels in the treatment of childhood asthma, and if needed a National program for prevention of vitamin D deficiency can also be implemented.

REFERENCES

1. Wacker M, Holick MF. Vitamin D- Effects on skeletal and extraskeletal health and the need for supplementation. Nutrients. 2013;5:111–148.
2. Jablonski NG, Chaplin G. The evolution of human skin coloration. J. Hum. Evol. 2000;39:57–106.
3. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmun. Rev. 2012;12:127–136.
4. Wolf G. The Discovery of Vitamin D: The Contribution of Adolf Windaus. J. Nutr.June 2004; 134(6): 1299-1302.
5. Liu AH, Covar RA, Spahn JD, Leung DY. Childhood Asthma.In Kligman RM, Behrman RE, Jenson HB, Stanton BF,eds. Nelson Textbook of Pediatrics, 18th edn.Philadelphia:Saunders. 2008;953-970.
6. Brehm JM, Schuemann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, Weiss ST, Litonjua AA.Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program Study. J Allergy Clin Immunol. 2010;126 (1):52-58.
7. Brown SD, Calvert HH, Fitzpatrick AM. Vitamin D and asthma. Dermato-Endocrinol. 2012;4:137–145.
8. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. J. Allergy Clin. Immunol. 2010;125:995–1000.
9. Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF,AdikibiT, PridgeonC,DallmanM, Loke TK,Robinson DS, BarratFJ,O'GarraA, LavenderP, LeeTH,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

CorriganC, HawrylowiczCM. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. J Clin Invest 2006;116 (1):146-155.
10. Global Initiative for Asthma. Global strategy for asthma management and prevention. NIH publication;c2010. Revised 2014. Available from http://www.ginasthma.org.
11. National Asthma Education and Prevention Program: NAEPP guidelines for the diagnosis and management of asthma-update on selected topics, 2002. WashingtonDC,NIH,2002 (NIH publication no. 02-5075).
12. Gupta A, Sjoukes A, Richards D, Banya W, Hawrylowicz C, Bush A, Saglani S. Relationship between serum vitamin D, disease severity and airway remodeling in children with asthma. Am J Respir Crit Care Med. 2011.15;184(12):1342-1349.
13. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations. Pediatrics. 2008; 122: 398-417.

ISSN (O): 2687-5365; ISSN (P): 2753-6556