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Vitamin-D deficiency in Asthmatic children and adolescents from northern India - A hospital based prospective study

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ABSTRACT

Vitamin-D plays a key role in bronchial asthma due to its immune modulatory effect. It is known to be associated with airway hyper-responsiveness, decreased pulmonary function, impaired asthma control and steroid resistance. In asthmatic children, vitamin-D3 levels lower than 30□g/mL are shown to increase number of asthma exacerbations. To estimate serum vitamin-D levels in asthmatic children and to evaluate the effect of vitamin D deficiency on disease progression and response to therapy. This prospective observational study was carried in a tertiary level care hospital in one of the northern states of India over a period of 18 months.Inclusion criteria : All consecutive children aged between 1-18 years with bronchial asthma coming to pediatric inpatient and outpatient clinics were studied. Children with significant renal pathology, rickets, autoimmune diseases, chronic malabsorption, liver disease and those who refused consent were excluded. Ethical approval: Obtained from Institute Ethics committee [IEC/18/154]. These children were subjected to vitamin D estimation after written informed consent and clinical data monitoring. Out of 131 bronchial asthma patients, three fourths of children [75.6%] had Vitamin D deficiency and25% had positive family history. The Median (IQR) serum vitamin-D levels were 15.5 (8.8)□g/mL.Children in the vitamin-D deficient group had the largest proportion of partially controlled and uncontrolled asthma. The prevalence of Vitamin D deficiency in asthmatic children in our study was 75.6%.Vitamin D deficiency was associated with increasing severity of asthma and poor disease control.

INTRODUCTION

Bronchial asthma is a chronic airway inflammatory disease characterized by hyper responsiveness and episodic airflow obstruction. [1-3]The prevalence of bronchial asthma in children is increasing globally, as well as in India. This varies from 1-18%.[4-6]The airway inflammation causes acute broncho constriction followed by chronic mucus plug formation, airway remodelling and alveolar oedema and thus leading to airflow limitation. [7-9]The role of vitamin-D in allergic and respiratory illness is being reported more and more due to its immune modulatory effect.[10-13]Vitamin D deficiency is associated with increased airway hyper-responsiveness, reduced pulmonary function, poor asthma control and steroid resistance.[13-15]Vitamin-D deficiency is defined as 25[OH]D levels less than 20 □g/mL, levels between 2030 □g/mL suggest vitamin-D insufficiency and levels above 30 □g/mL indicate sufficiency. Serum levels of 25[OH] D>150 □g/mLsuggest toxicity. [12] Vitamin-D3 plays a key role in innate immunity as well as in adaptive immunity by altering the regulatory T-cells, TH1 and TH2 cells response and by the promotion of phagocytosis. [16] Vitamin-D3 is shown to influence chemokine expression from bronchial smooth muscles. [14] Vitamin-D receptor [VDR] activation enhances expression of IL-10 and inhibits expression of IgE in B-cells. [17-21] Because of its effect on T-regulator cells, TH1 and TH2 cells, vitamin-D3 aids in decreasing number of asthma exacerbations. In asthmatic children, vitamin-D3 levels<30□g/mLare

associated with impaired pulmonary function, increased exacerbations and need for frequent medications.[22]Vitamin-D supplementation can reduce the number of exacerbations and aid in better asthma control. [23-27]

This study aimed to estimate mean serum vitamin-D levels in children with bronchial asthma and to evaluate the effect of vitamin-D deficiency on disease progression and response to therapy.

MATERIAL AND METHODS

Study design : Hospital based prospective observational study

Setting : Pediatric outpatient, inpatient,asthma clinic of a tertiary care hospital in Northern India

Duration : 18 months [1st January 2018 to 30th June 2019].

Participants : All consecutive children aged between 1-18 years with bronchial asthma were included.This included all seasons.The subjects were selected according to eligibility criteria:

Inclusion criteria : All children and adolescents aged between 1-18 years presenting with features suggestive of asthma or on asthma treatment and patient/guardians giving consent for study.

Exclusion criteria : Children with renal disease, rickets, autoimmune diseases, chronic malabsorption, chronic liver disease, children <1 year and >18 years of age and those who refused consent were excluded.

Study measurements: Eligible children and adolescents were evaluated and baseline data [age, weight, height, BMI and sex] were recorded ina pre designed, pre tested performa after obtaining written informed consent from parents or guardians. 2 ml of peripheral venous blood was drawn from these children for the quantitative determination of total25[OH] vitamin D by Chemiluminescence Method on Siemens Advia Centaur XP [Siemens Diagnostics Tarry Town, NY, USA].

Sample Size and Technique: Assuming 18% prevalence of bronchial asthma in children and adolescents, with absolute precision of 7% and power of 80%, the estimated sample size was 120. To account for losses we have enrolled 131 children.

Ethical approval: was obtained from Institute ethics committee [protocol number: IEC/18/154]. The study was designed to confirm the Declaration of Helsinki and ICMR guidelines for ethical biomedical research on human subjects. Following Institutional Ethics Committee approval, a patient information document was presented to each patient fulfilling the above mentioned criteria. After explaining pertinent details of the study, a valid informed consent were obtained for assessment according to a pre-designed and pre-tested proforma.

On the basis of serum vitamin-D level all the participants are divided into 3 groups:

Sufficient group: Participants having serum vitamin-D levels > 30 g/mL,

Insufficient group: Participants having serum vitamin-D levels between 20-30 g/ml

Deficient group: Participants having serum vitamin-D levels <20 g/mL.

Similarly, based on type of asthma participants are categorized into 4 groups:

I. Intermittent asthma

II. Mild persistent asthma

III. Moderate persistent asthma and

IV. Severe persistent asthma.

Depending up on the asthma control participants are categorized into 3 groups :

- Well controlled asthma
- Partially controlled asthma
- Uncontrolled asthma

Statistical analysis: Data analysis was performed using Statistical Package for Social Sciences [SPSS] Version 23.0 [SPSS, Inc. Chicago III., USA] for Windows. Numerical data were analyzed using means and standard deviations or medians and ranges as appropriate. Categorical data were summarized as percentages. For categorical variables, differences were analyzed with 2 [chi square] test and Fisher's exact test when appropriate. Correlations were determined by using Pearson's test or spearman Rho as appropriate. Non-parametric tests [Wilcoxon Test] were used to make group comparisons, when the variables were not normally distributed in the 2 subgroups. Non-parametric tests [Kruskal Wallis Test] were used to make group comparisons, when the variables were not normally distributed in >2 subgroups.All p-values are two-sided. Pvalues < 0.05 were considered significant

RESULTS

Base line demographic details: A total of 131 bronchial asthma patients were enrolled after obtaining written informed consent.The mean [±SD; Standard Deviation] age of study participants was 9.55±3.97 years [range:2-18 years]. 70.2% of participants were males with a male to female ratio of 3:2.As per the geographical location, 4.6% of our participants belong to hilly area.The median [IQR:Inter quartile range] of body weight [kg] of study children was 26.4 [14-20]. The weight [kg] ranged from 10.7 - 87.8. The median [IQR] of height [cm] was 129.9 [30]. The height [cm]ranged from 89.5 - 179.3. The median (IQR) of BMI [kg/m^2]was 15.5 (3.4). The BMI [kg/m^2] ranged from 9.6 - 36.1.

Asthma Progression:

Type of asthma: Most of the participants [47.3%, n=62] were in mild persistent group followed by moderate persistent group [33.6%,n=44].12.2% [n=16] were having intermittent asthma and very few [6.9%, n=9] had severe persistent asthma.

Asthma control: In terms of level of asthma control, majority of the participants had [66.4%,n=87]partially controlled asthma followed by well controlled asthma [26.7%, n=35]. Very few [6.9%, n=9]had uncontrolled asthma.

Course of Asthma: The median [IQR] age of onset of disease was 4 [5].The age of onset [years] ranged from 1 - 14. The median [IQR] duration of illness in years was 4 [2.1].In terms of number of exacerbations in past one year, the median [IQR] number of exacerbations was 5[4]. In terms of ongoing treatment, majority [80.9%, n=106] of our participants were receiving MDI budesonide and levosalbutamol followed by MDI formeterol and levosalbutamol [7.6%, n=10].The median [IQR] duration of treatment [years] was 1 [0.5].With regard to family history,

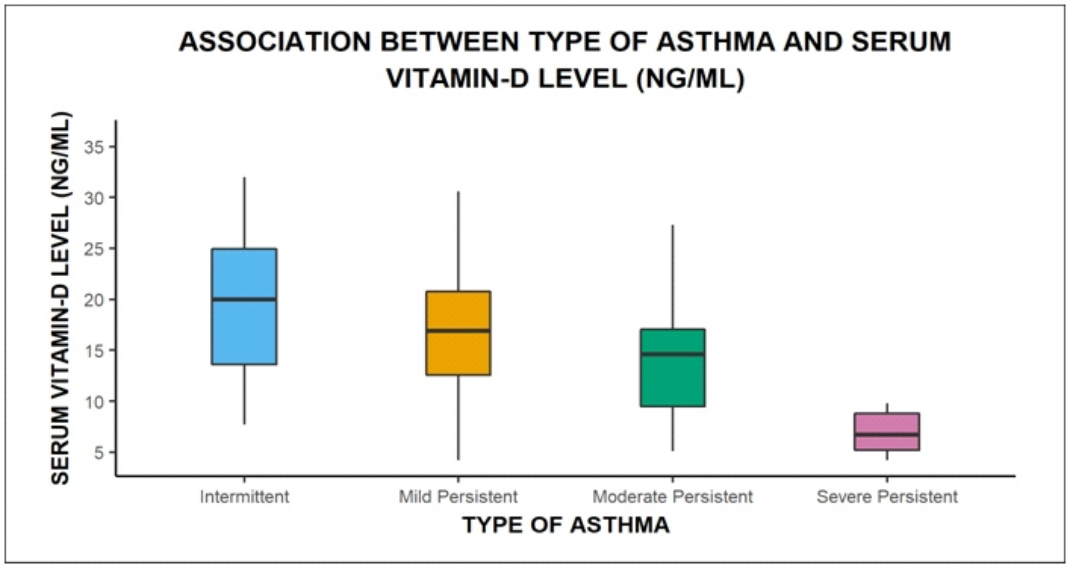

Fig. 1 : Association between type of asthma and serum Vitamin-D level (ng/mL)

Note: $X^{2:}$14.7, P value: <0.015

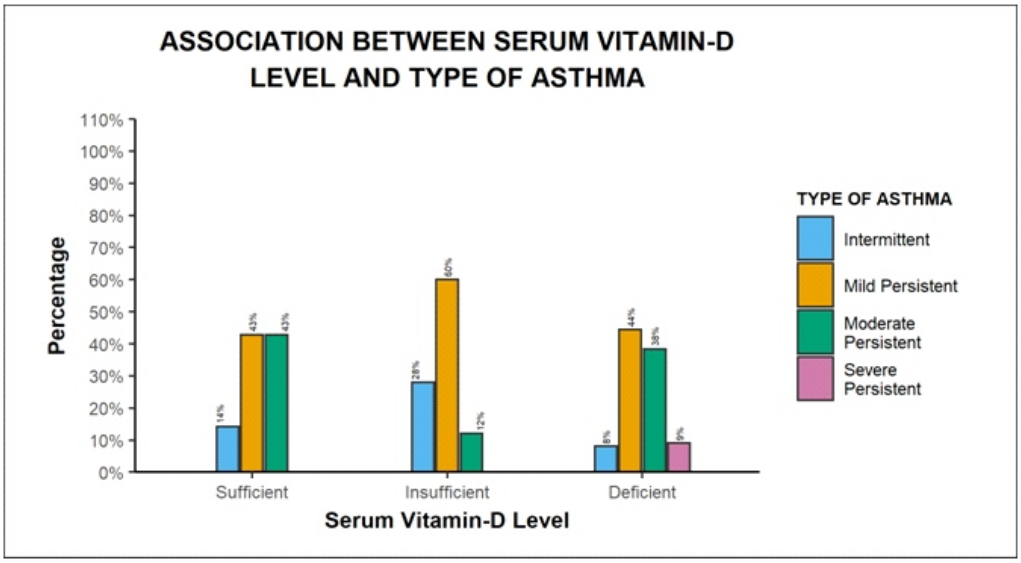

Fig. 2 : Association between serum Vitamin-D level and type of asthma.

nearlyone fourth [24.4%, n=32] of the participants had positive family history of asthma.

Vitamin D levels and its association with Asthma:

The Median [IQR] serum vitamin-D levels were 15.5 [8.8] g/mL, while the mean±SD serum vitamin-D levels were 16.2 ±7.1 g/mLwith a range of 4.2 36 g/mL.Three fourths [75.6%, n=99]of children with bronchial asthma had vitamin-D deficiency and 19.1%[n=25] had vitamin-D insufficiency. Only 5.3% [n=7] had sufficient levels of serum vitamin-D.

Vitamin D and Age: The median [IQR] age [years]in sufficient, insufficient and deficient group was 7 [3.5], 9 [6], 9 [7.5] respectively. There was no significant difference between vitamin D levels and age [years] [$X^2 = 1.4$, $p = 0.5$].

Vitamin D and gender: 85.7% of the participants in the sufficient group, 76% in insufficient group and 67.7% in deficient group were males.Thus, there was no significant difference between vitamin D levels and gender [$X^2 = 1.5$, $p = 0.53$].

Serum vitamin-D level and type of asthma: As shown in Table 1, Serum vitamin-D levels [g/mL] were not normally distributed in the 4 types of asthma. Thus, non-parametric test (Kruskal Wallis Test) was used to make group comparisons. The mean [SD] serum vitamin-D levels [g/mL] in intermittent, mild persistent, moderate persistent and severe persistent asthma groups were 19.67±6.95, 17.24 ± 6.54, 15.± 6.93 and 7.98 ± 4.53 respectively. There was a significant difference between the 4 groups in terms of serum vitamin-D levels [X^2 = 21.59, p = <0.001], with the median serum vitamin-D level being highest in intermittent asthma and lowest in severe persistent asthma. The Box-and-Whisker plot [Figure-I] depicts the distribution of serum vitamin-D level [g/mL]in the 4 groups. The middle horizontal line represents the median serum vitamin-D Level, the upper and

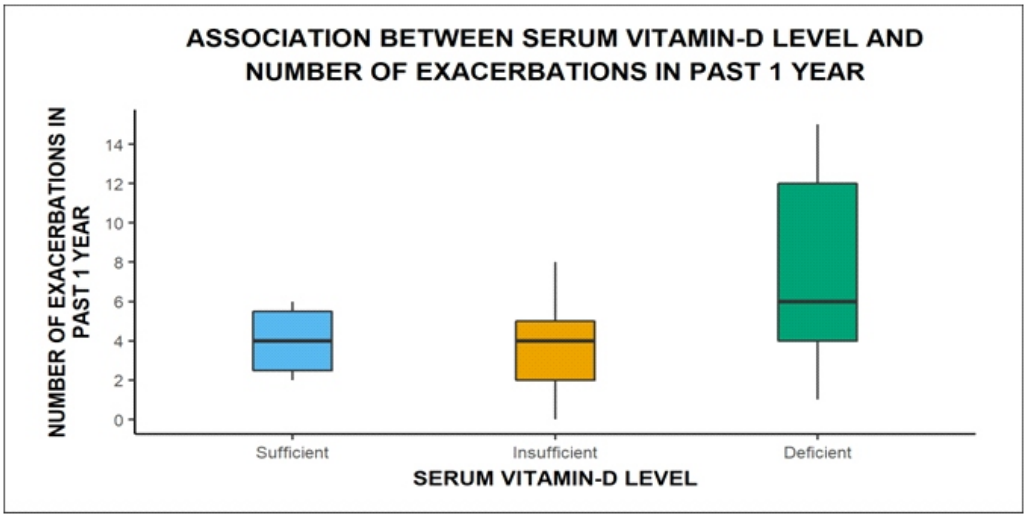

Fig. 3 : Association of the Vitamin-D status and of number of asthma exacerbations in past one year.

Table 1 : Comparison of the 4 subgroups of asthma in terms of serum Vitamin-D level (ng/mL) (N = 131)

Serum Vitamin-D Level (ng/ml)	Type of Asthma				Kruskal Wallis Test	
	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent	X^2	p value
Mean (SD)	19.67 (6.95)	17.24 (6.54)	15.00 (6.93)	7.98 (4.53)	21.586	<0.001
Median (IQR)	20 (11.32)	16.9 (8.16)	14.6 (7.58)	6.7 (3.6)		
Range	7.7 - 32	4.2 - 34	5.1 - 36	4.2 – 19		

lower bounds of the box represent the 75th and the 25th centile of serum vitamin-D level [□g/mL]respectively, and the upper and lower extent of the whiskers represent the maximum and the minimum serum vitamin-D level [□g/mL]in each of the groups. In the vitamin Dsufficient group, 42.9%had mild as well as moderate persistent asthma [Figure:II, Table:I]. Very few [14.3%] had intermittent asthma and none had severe persistent asthma. In vitamin Dinsufficient group, majority [60%] had mild persistent followed by intermittent [28%] and moderate persistent asthma [12%].In this group also, none of the participants had severe persistent asthma. Contrastingly, invitamin-D deficient group, majority had mild persistent [44.4%] followed by moderate persistent [38.4%] and severe persistent asthma [9.1%]. The least common type of asthma in vitamin-D deficient group was intermittent [8.1%]. And hence, there was a significant difference between vitamin-Dstatus and type of asthma [X^2 = 14.8, p < 0.015].

Similarly, there was a significant difference between vitamin-Dstatusand number of exacerbations in the past one year [X^2 = 15.6, p <0.001] [Figure-III], with median number of exacerbations being highest in the vitamin D deficient group. For every 1 unit increase in number of exacerbations in past 1 year, the serum vitamin-D level [□g/mL] decreases by 0.76 units.

Association between serum vitamin-D level and asthma control: Fisher's exact test was used to explore the association between serum vitamin-D level and asthma control [Table-II].

Majority [57.1%]of children with Vitamin-D sufficiency had well controlled asthma followed by [42.9%] partially controlled asthma and none had uncontrolled asthma. Similarly, most of the children [52%]with vitamin-Dinsufficiency had well controlled asthma followed by partially controlled asthma [48%] and none had uncontrolled asthma. Contrastingly, two thirds of children[72.7%] with vitamin-Ddeficiency had partially controlled asthma. 18.2% had well controlled asthma and 9.1% had uncontrolled asthma. And hence, there was a significant difference between the vitamin D status and asthma control [X^2 = 16.5, p <0.003]. In summary, children in the sufficient group had the largest proportion of well controlled asthma whereas the participants in deficient group had the largest proportion of partially controlled and uncontrolled asthma.

The median [IQR] number of exacerbations post vitamin D supplementation in insufficient and deficient group was 0 and 1[1.5] respectively which was statistically significant [X^2 = 31.4, p <0.001]. The serum vitamin-D level [□g/mL] in well controlled, partially controlled and uncontrolled asthma ranged

Table 2 : Association between serum Vitamin-D level and level of asthma control at presentation (N = 131)

Level of Asthma Control at Presentation	Serum Vitamin-D Level				Fisher's Exact Test	
	Sufficient	Insufficient	Deficient	Total	X^2	P Value
Well Controlled	4 (57.1%)	13 (52.0%)	18 (18.2%)	35 (26.7%)	16.471	0.003
Partially Controlled	3 (42.9%)	12 (48.0%)	72 (72.7%)	87 (66.4%)		
Uncontrolled	0 (0.0%)	0 (0.0%)	9 (9.1%)	9 (6.9%)		
Total	7 (100.0%)	25 (100.0%)	99 (100.0%)	131 (100.0%)		

from 7.334, 4.236 and 4.5-13.7 respectively. Vitamin D sufficient group had the largest proportion of well controlled asthma whereas vitamin D deficient group had the largest proportion of partially controlled and uncontrolled asthma.

DISCUSSION

This study included 131 children and adolescents with a male: female ratio of 2.3:1. This could be explained by the fact that more outdoor exposure to allergens, more physical work [exercise induced asthma] could have increased overall prevalence of asthma in male children. Farzad et al. found 3:2 male to female ratio in his 100 asthmatic patients cohort.[28]Geographical distribution: very few [4.6%] participants belonged to hilly areas. Having less participants from hilly areas eliminates the confounding factor of higher Vitamin-D deficiency in hilly areas [due to less sunlight exposure and seasonal variation]. The mean age of onset of disease was 5.37 ± 3.2 years which was similar to the report by Farzad et al.[28]had slightly younger children in his study [mean age: 4.4 ± 1.2 years, range 38.5].The mean duration of illness [years] in our study population was 4.06 ±2.43 SD. Esfandiar et al.[29] reported a lower mean duration of disease [13.1□±□24.6 months]. The mean serum vitamin-D Level [□g/mL] was 16.15 [SD - 7.07] with a range of 4.2 36.Farzad et al.[28] reported slightly higher mean 25[OH]-D_3 levels [18.98□g/mL]. Karanam S et al.[30] found even higher mean±SD vitamin D levels in asthmatic children aged between 6-15 years [23.38±8.75]. Different life style factors [e.g., sunscreen use, increased time spent indoors, and clothing coverage] and inherited or intrinsic factors [e.g., skin melanin content, ethnicity, dark-skin, decreased cutaneous production of vitamin D3]. There was a higher prevalence of Vitamin D deficiency in male children. This can be explained by the high overall prevalence of bronchial asthma in male population.

75.6% of study children had vitamin-D deficiency and 19.1% had insufficiency. Farzad et al. reported a lesser proportion of Vitamin D deficiency [55%] and slightly higher proportion of insufficiency [30%].[28]Karanam S et al. showed 40% vitamin-Ddeficiency, 26.7% insufficiency. [30] KrishnanE et al**.** reported 83.3% prevalence of Vitamin D deficiency, which was higher than our study.[31] This difference in prevalence may be contributed by the factors like skin colour, sunlight exposure, socio-economic status, diet, serum calcium levels, nutritional status of the child.

A per group of asthma, 100% of children with severe persistent group had vitamin D deficiency followed by, 86.3% of children with moderate persistent group, 70.9% of mild persistent and 50% of intermittent group. Thus, vitamin D deficiency was associated with increasing severity of asthma in our study. Also, most common type of asthma was mild persistent in our study.

Maximum participants in our study had multiple number of exacerbations. 80.9% of our study participants were on MDI budesonide and levosal butamol treatment, Only, one fifth of our participants had well controlled bronchial asthma and majority had partially controlled asthma. Study by Karanam S et al. showed higher proportion of well controlled asthma.[30] Out of 99 vitamin-D deficient participants 72 had partially controlled asthma, 18 had well controlled asthma and 9 had uncontrolled asthma. All the 9 children with uncontrolled asthma were vitamin D deficient. None of vitamin-D insufficient or sufficient group had uncontrolled asthma. And hence, Vitamin D deficiency is associated with poor control of asthma. These findings were similar to study by Karanam S et al**.**[30]

Out of all participants, 91.6% of had History of some drug intake in the form of antibiotics, antihistaminic, anti-inflammatory and nebulisations but none of them had history of intake of drugs affecting serum vitamin-D levels. Some patients had history of anti-tubercular drug intake and those patients were excluded from the study. 8.4% of the participants had no history of any other drug intake. Farzad et al**.** found that 76% of their participants had history of intake of anti-inflammatory drugs.[28]A significant proportion [one fifth] of our participants had family history of asthma or atopy. Vitamin D deficient group had highest number of exacerbations in past one year. Other studies also, revealed that vitamin-D insufficiency or deficiency was associated with higher odds of severe exacerbation over a four year period. [32,33] The mean [SD] of number of exacerbations post Vitamin-D therapy [given to the patients who were having deficient or insufficient levels of vitamin-D] was 1.46 [1.7] and the median [IQR] was 1 [2]. Thus, there was decrease in number of exacerbations following vitamin D therapy.

Strengths: Our study had adequate sample size and all the

parameters pertaining to bronchial asthma including the effect of vitamin D supplementation were analyzed.

Limitations: As most of general population in India are deficient in Vitamin-D level, not taking a control group in this study was the major drawback. Also, other causes of vitamin D deficiency were not evaluated as it was beyond the scope of the present study.

CONCLUSION

To conclude there was a high prevalence of vitamin-D deficiency in children and adolescents with bronchial asthma with three fourth of them being vitamin-D deficient. It is associated with disease severity and poor asthma control. One fourth of study children had family history as a risk factor for asthma. Vitamin D supplementation has shown to reduce the number of asthma exacerbations. Vitamin D supplementation can be proposed as an adjunct therapy option for asthmatic patients if vitamin-D levels are in deficient or insufficient zone.

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