Original Research Paper Medical Science

Correlation of Bone Mineral Density (BMD) With Bronchial Asthma

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KEYWORDS :

Introduction

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a significant role. A worldwide increase in the prevalence of asthma has been reported in recent years, particularly in developing countries such as India (International study of Bronchial Asthma and allergies in childhood (ISAAC), 1998; Morbidity and Health Care International Institute for Population Sciences (IIPS) and Macro International; National Family Health Survey (NFHS-3), 2007). With an increase in prevalence comes an increased burden of disease in terms of morbidity, mortality and compromised quality of life.

Corticosteroids (CS) have been used for the treatment of asthma for over 50 years, long before a rationale was developed to explain their actions, Much of the early enthusiasm regarding oral corticosteroid therapy in asthma was undermined with the realization that their use resulted in a number of unpleasant side effects such as peptic ulcer disease, hypertension, osteoporosis, adrenal and immunologic suppression, Cushing's syndrome, and cataracts. Therefore, research was directed toward reducing the side-effect profile by delivering them directly into the airway. The first inhaled corticosteroid (ICS) to offer superior topical to systemic potency was developed in the early 1970s with the delivery of beclomethasone dipropionate (BDP) via a pressurized metered dose inhaler (MDI) (Brown et al, 1972; Clark, 1972). In the following years, numerous studies established inhaled BDP to have potent oral corticosteroid-sparing effects in patients with steroid dependent asthma along with improvements in lung function, decreased diurnal variability in peak flow rates, less need for supplemental bronchodilator use and an overall improvement in quality o f life. In the ensuing 20-25 years, several other potent topical steroids such as triamcinolone acetonide (TAA), flunisolide (FLU), budesonide (BUD) and fluticasone propionate (FP) with different physicochemical properties were developed for use in asthma. The key features for the development of these drugs included a high binding affinity to the glucocorticoid receptor, an extensive uptake into the lung, metabolic stability at the target, and rapid systemic inactivation, all of which were achieved, albeit to varying degrees, through structural modifications to the basic steroid molecule (Brattsand et al, 1982). Inhaled steroids are now widely regarded as the first-line choice of anti-inflammatory treatment for asthma.

Vitamin D is a potent immune system regulator having a potential role in various allergic diseases. A potential role of vitamin D in metabolic syndrome, colorectal cancer, breast cancer, multiple sclerosis, tuberculosis, pneumonia, influenza, respiratory distress (Tiwari S et al, 2013), depression has been proposed. Supplementation with oral vitamin D has led to significant improvement in patients with pneumonia (Manaseki-Holland et al, 2010; Khadilkar et al, 2013) and atopic dermatitis (Amestejani et al, 2012).

The role of vitamin D in asthma is not yet clear. Few studies have proposed a possible link between asthma and polymorphisms in other genes involved in vitamin D synthesis, bioavailability and metabolism (Wjst et al, 2006; Pillai et al, 2011). Lower Serum 25(OH) vitamin D have been correlated with a higher prevalence, hospitalization and emergency visits along with decreased lung function and increased airway hyperresponsiveness with exercise in various studies conducted in asthmatic children (Chinellato et al, 2011; Ozaydın et al, 2013). A protective effect of higher maternal vitamin D intake on asthma in children and adults has been demonstrated (Camargo et al, 2007; Morales et al, 2012). A few studies conducted in the recent past to evaluate the efficacy of vitamin D supplementation in patients of asthma have also shown promising results (Urashima et al, 2010; Majak et al, 2011).

Yadav et al (2014) concluded that Vitamin D has a definite role in the management of moderate to severe persistent bronchial asthma as an adjunct to standard treatment. M. Brehm et al (2009) demonstrated that lower vitamin D levels are associated with increased markers of allergy and asthma severity. Sutherland et al (2010) demonstrated reduced vitamin D levels are associated with impaired lung function, increased airway hyper responsiveness, and reduced corticosteroid response. Samrah S et al (2014) demonstrated the severity of vitamin D deficiency correlated with poor asthma control and a need for more medications to control asthma.

Therefore, in the light of above mentioned conflicting results we performed a study to correlate serum vitamin D level and bronchial asthma.

Methods

The present study was conducted in the Department of Tuberculosis and Respiratory Diseases, Institute of Medical Sciences, Banaras Hindu University, Varanasi. The study was conducted on 100 patients with the diagnosis of bronchial asthma who attended outpatient department of Tuberculosis and Respiratory Diseases, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi from June 2014 to July 2015. Patients below 18 years of age were excluded from the study.

A baseline data of cases is to be recorded including history, general examination, systemic examination, chest examination, and investigations.

The patients were subjected to routine investigations, Chest X-ray, DEXA-scan of lumbar spine and Pulmonary Function Test in Department of Tuberculosis and Respiratory Diseases, Institute of Medical Sciences, Banaras Hindu University, Varanasi.

After obtaining written informed consent, the participating patients were subjected to a structured questionnaire, which requested demographic data (age, gender, and residence), smoking, personal and family history of atopy, and clinical features of asthma (frequency and severity of the symptoms, exacerbations, duration of the disease).

Pulmonary Function Test was done in Department of Tuberculosis and Respiratory Diseases, Institute of Medical Sciences, Banaras Hindu University, Varanasi. Spirometry with post-bronchodilator response

was obtained as the primary test to establish the asthma diagnosis. The forced expiratory volume in one second (FEV_1) and Peak Expiratory Flow (PEF) and PEF variability were measured.

Optimally, the initial spirometry should also include measurements before and after inhalation of a short-acting bronchodilator in all patients in whom the diagnosis of asthma is considered. Reversibility is demonstrated by an increase of 12% and 200 mL after the administration of a short-acting inhaled bronchodilator (400 mcg of salbutamol).

Spirometry had a major role in our study as it was the basis to see if the patient had Bronchial Asthma or not.

Vitamin D status is best determined by measurment of 25 Hydroxy vitamin D, as it is the major circulating form and has longer half life(2-3 weeks) than 1,25 Dihydroxy vitamin D (5-8 hours). The recommended test for evaluation of Serum 25 (OH) vitamin D is LC-MS/MS (Liquid Chromatography Tandem-Mass Spectometry). The LC-MS/MS method provides a rapid, accurate, and sensitive alternative to other methods for determination of 25 hydroxy vitamin D. The assay measures both D2 (Ergocalciferol) and D3 (Cholecalciferol) metabolites of vitamin D. In our study according to reference ranges of Serum 25(OH) vitamin D level for LC-MS/MS test patients were divided in to:

- Deficient: Serum 25(OH) vitamin D level = < 50 nmol/L
- Insufficient: Serum 25(OH) vitamin D level = 50-74 nmol/L
- Sufficient: Serum 25(OH) vitamin D level = 75-250 nmol/L

Statistical Analysis

Statistical analysis was done using SPSS 16. Student's t test, Mann Whitney U test and One way analysis of variance was used to compare the significant difference in mean. For categorical variables Chi square test and Fisher's – exact test were used. Pearson correlation coefficient was used to test for correlations between various parameters. P-value <0.05 is considered as statistically significance.

Results:

A total of 100 cases of bronchial asthma were included in the study. Most of the cases were in the age group of 21-30 years (69%). Insufficient amount of serum 25(OH) vitamin D level was found in 46 cases. Insufficient amount of serum 25(OH) vitamin D level was found more in Medium-dose ICS (18) and High-dose ICS (22) group than Low-dose ICS (4) and Control group (2) (Table 1).

Low-dose ICS vs. Medium-dose ICS group (p=0.003); Low-dose ICS vs. High-dose ICS group (p<0.001); Low-dose ICS vs. Control group (p=0.888); Medium-dose ICS vs. High-dose ICS group (p=0.001); Medium-dose ICS vs. Control group (p=0.001); High-dose ICS vs. Control group (p<0.001). The mean of serum 25(OH) vitamin D was lower in Medium-dose (80.70±24.34) and High-dose ICS (65.12±14.96) group than Low-dose ICS (99.72±17.83) and Control group (98.77±13.86), and was lowest in High-dose ICS group (Table 2).

In Medium-dose ICS group significant correlation was found between BMD T-score and serum 25(OH) vitamin D level (p=0.009). In Medium-dose ICS group duration of inhaled corticosteroids was significantly correlated with the BMD T-score (p<0.001) and serum 25(OH) vitamin D level (p<0.001) (Table 3).

In High-dose ICS group significant correlation was found between BMD T-score and serum 25(OH) vitamin D level (p<0.001). In High-dose ICS group duration of inhaled corticosteroids was significantly correlated with the BMD T-score ((p<0.001) and Serum 25(OH) vitamin D level (p<0.001) (Table 4).

Table1: Group vs. Serum 25(OH) vitamin D level

Group	Deficient		Insufficient		Sufficient	
	No.	%	No.	%	No.	%
Low-dose ICS	0	0	4	8.70	8	16
Medium-dose ICS	2	50	18	39.13	12	24
High-dose ICS	2	50	22	47.83	11	22
No ICS(Control)	0	0	2	4.35	19	38
Total	4	100	46	100	50	100

χ^2=22.280; p=0.001

Table 2: Group vs. Mean of Serum 25(OH) vitamin D

Group	Serum 25(OH) vitamin D (Mean±SD)	f-value	p-value
Low-dose ICS	99.72±17.83	18.872	<0.001
Medium-dose ICS	80.70±24.34		
High-dose ICS	65.12±14.96		
No ICS(Control)	98.77±13.86		

Table 3: Correlations in Medium-dose ICS group.

Variables		BMD T-score	Serum 25(OH) vitamin D
Age	R	0.135	0.039
	P	0.460	0.830
Duration	R	-0.603**	-0.642**
	P	<0.001	<0.001
BMD T-score	R	1	0.455**
	P		0.009
Serum 25(OH) vitamin D	R	0.455**	1
	P	0.009	

Table 4: Correlations in High-dose ICS group.

Variables		BMD T-score	Serum 25(OH) vitamin D
Age	R	0.117	-0.102
	P	0.503	0.561
Duration	R	-0.667**	-0.558**
	P	<0.001	<0.001
BMD T-score	R	1	0.583**
	P		<0.001
Serum 25(OH) vitamin D	R	0.583**	1
	P	<0.001	

Discussion

The study was conducted on 100 patients who attended outpatient department of Tuberculosis and Respiratory Diseases, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi from June 2014 to July 2015.

In our study patients below 18 years of age were excluded from the study which was similar to a study by Kaun et al, 2012. majority of the patients were females (56%) and 44% were males which was similar to a study by Ip M et al, 1994. majority of the patients were in the age group of 21-30 years (69%). Ten percent were below 20 years of age and 21% in the age group of 31-40 years. Patients were divided in to four groups, 12% of the patents were in the Low-dose ICS group, 32% in the Medium-dose ICS group, 35% in the High-dose ICS group and 21% were in the Control (No ICS) group.

In our study number of patients having insufficient level of Serum 25(OH) vitamin D were higher among Medium-dose ICS (39.13%) and High-dose ICS group (47.83%) than Low-dose ICS (8.70%) and Control group (4.35%). The mean of serum 25(OH) vitamin D was lower in Medium-dose (80.70±24.34) and High-dose ICS (65.12±14.96) group than Low-dose ICS (99.72±17.83) and Control group (98.77±13.86). The mean was lowest in High-dose ICS group. When the mean of serum 25(OH) vitamin D was compared, it was statistically significant between Low-dose ICS and High-dose ICS group (p<0.001), Medium-dose ICS and High-dose ICS group (p=0.001), Medium-dose ICS and Control group (p =0.001) and between High-dose ICS and Control group (p<0001). We found that there was a positive association between insufficient level of Serum 25(OH) vitamin D and use of inhaled corticosteroids in higher doses. Our finding correlates with finding in a study by M. Brehm *et al* (2009), they studied the serum vitamin D levels and markers of severity of childhood asthma and demonstrated that lower vitamin D levels are associated with increased markers of allergy and asthma severity. Our finding also correlates with finding

in a study by Sutherland et al (2010), they studied vitamin D levels, lung function, and steroid response in adult asthma and demonstrated that reduced vitamin D levels are associated with impaired lung function, increased airway hyper-responsiveness, and reduced corticosteroid response. Higher vitamin D levels were associated with greater lung function, with a 22.7 (±9.3) ml (mean ± SE) increase in FEV_1 for each nanogram per milliliter increase in vitamin D (P = 0.02). Our finding was similar to finding in a study by Arias F et al (2013), they studied Vitamin D insufficiency and asthma severity in adults and demonstrated that vitamin D insufficiency was associated with a higher risk of severe asthma (odds ratio [OR], 5.04; 95% Confidence interval [CI], 1.23-20.72; P=0.02). Our finding was also similar to finding in a study by Korn S et al (2013), they studied severe and uncontrolled adult asthma is associated with vitamin D insufficiency and deficiency and demonstrated that serum 25(OH) vitamin D levels were related to asthma severity (intermittent: 31.1±13.0 ng/ml, mild: 27.3±11.9 ng/ml, moderate: 26.5±12.0 ng/ml, severe: 24.0±11.8 ng/ml, p=0.046) and control (controlled: 29.5±12.5 ng/ml, partly controlled 25.9±10.8 ng/ml, uncontrolled: 24.2±11.8 ng/ml, p=0.030). Our finding also correlates with finding in a study by Yadav M et al (2014), they studied effect of vitamin D supplementation on moderate to severe bronchial asthma and demonstrated that Vitamin D significantly reduced the level of severity of asthma patients over 6 month of treatment (p=0.016). Our finding also correlates with finding in a study by Salas NM et al (2014), they studied vitamin D deficiency and adult asthma exacerbations and demonstrated that vitamin D sufficiency was significantly associated with a decreased total number of asthma exacerbations (incidence rate ratio [IRR]: 0.61, 95% confidence interval [CI]: 0.44-0.84, p=0.002), decreased total severe asthma exacerbations (IRR: 0.41, 95% CI: 0.24-0.72, p=0.002) and decreased emergency room visits (IRR: 0.42, 95% CI: 0.20-0.88, p=0.023). Our finding was also similar to finding in a study by Samrah S et al (2014), they studied vitamin D deficiency and level of asthma control in women and demonstrated that the severity of vitamin D deficiency correlated with poor asthma control and a need for more medications to control asthma. The severity of vitamin D deficiency correlated with the number of asthma medications (p = 0.020). Serum 25(OH) vitamin D levels directly correlated with asthma control level using ACT score (p = 0.012) and GINA classification (p = 0.046).

In our study the number of patients having reduced bone mineral density were more in Medium-dose (41.1%) and High-dose ICS (53.6%) group than Low-dose ICS (0%) and Control group (5.4%). The mean of BMD T-score in High-dose ICS (-1.54±0.57) and Medium-dose ICS (-1.15±0.72) group were lower than Low-dose ICS (-0.56±0.16) and Control group (-0.63±0.28). The mean was within the normal range in Low-dose ICS and Control group and was lowest in High-dose ICS group. When the mean of BMD T-score was compared, it was statistically significant between Low-dose ICS and Medium-dose ICS group (p=0.002), Low-dose ICS and High-dose ICS group (p<0.001), Medium-dose ICS and High-dose ICS group (p=0.004), Medium-dose ICS and Control group (p=0.001) and between High-dose ICS and Control group (p<0.001). We concluded that as the dose of inhaled corticosteroids increases there was reduction in the bone mineral density of lumbar spine of the patients which was supported by a study by Hanania et al (1995), they demonstrated that the regular use of conventional doses of inhaled corticosteroids by patients with asthma can suppress adrenal function and decrease bone density in a dose-related fashion. Our finding also correlates with finding in a study by Packe et al (1992).

Finally, we conclude that there was a positive association between insufficient level of Serum 25(OH) vitamin D and use of inhaled corticosteroids in higher doses. Age was not significantly correlated with bone mineral density and Serum 25(OH) vitamin D level in young adults. Bone mineral density was not significantly reduced in patients using low dose inhaled corticosteroids and in Control group patients. When inhaled corticosteroids were used in medium and high doses for longer duration, there was reduction in bone mineral density of lumbar spine of patients, which was reduced more in females than males.

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