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Effect of alfacalcidol on the pulmonary function of adult asthmatic patients: A randomized trial

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ABSTRACT

Background: Despite the use of alfacalcidol in the management of corticosteroid-induced osteoporosis, it has never been considered an adjunct treatment for asthma management. It can target vitamin D deficiency, a possible risk factor for asthma, and, hence, improve pulmonary function of patients with asthma.
Objective: To explore the effect of alfacalcidol administration on pulmonary function and study the pattern of vitamin D deficiency in adults with asthma in Egypt.
Methods: Serum 25-hydroxyvitamin D was measured in 115 adults: 33 healthy subjects and 82 patients with asthma. Then, patients with asthma were randomized to receive standard asthma treatment only (n = 39) or receive it in addition to 1 μg of alfacalcidol daily for 4 months (n = 43). Randomization was stratified by the stage of asthma severity. Spirometry and measurement of 25-hydroxyvitamin were performed at baseline and end of follow-up.
Results: Vitamin D deficiency was more common in patients with asthma (57.3%) than in healthy subjects (21.2%; $P < .001$). In patients with asthma, alfacalcidol significantly improved forced expiratory volume in the first second and forced vital capacity ($P < .001$ for the 2 tests). Moreover, more patients in the intervention arm showed improvement in asthma severity stage ($P = .04$). A nonsignificant difference was observed in improvement of forced expiratory volume in the first second between patients with vitamin D deficiency and those without deficiency in the intervention group ($P > .05$).
Conclusion: Alfacalcidol supplementation improved the pulmonary function and severity stage of adult patients with asthma regardless of deficiency.
Trial Registration: ClinicalTrials.gov Identifier: NCT02747381.

Introduction

Bronchial asthma is a widespread pulmonary inflammatory disorder that is manifested in patients by variable restraint of airflow.[1]

The T-cell population is considered the main player in asthma pathophysiology. In addition to the classic role of T-helper cell type 2 (T_H2) in asthma, other subsidiary groups such as T_H17 and T_H9 were discovered to play particular roles in certain phenotypes of asthma.[2] T cells control the incidence of airway inflammation and, hence, remodeling, bronchoconstriction, and hyperresponsiveness.[3] In contrast, T-regulatory cells suppress the T_H2 response, providing more tolerance in the airways through the production of interleukin-10.[4]

Vitamin D has been shown to control many underlying mechanisms that contribute to asthma pathophysiology. It has an important role in lung structural development, control of inflammatory and proliferative responses in airway smooth muscle cells, and modulating immune responses in asthma.[5] Its action is mediated through the interaction of the pharmacologically active form of vitamin D-1,25-dihydroxy cholecalciferol ($1,25[OH]_2D$) and the vitamin D receptor.[6] The vitamin D receptor is found on many cells of the immune system, namely T cells, B cells, macrophages, and dendritic cells, and is present in airway smooth muscles.[5,7]

Alfacalcidol (1α-hydroxy cholecalciferol) is a vitamin D hormone analog that requires hydroxylation at position 25 to be converted to $1,25(OH)_2D$.[8] This process takes place in the liver and bones with unlimited activity.[9] Conversely, the process of 1α-hydroxylation in the kidneys is under tight control through a feedback mechanism with calcium and phosphate levels.[10] Accordingly, the use of the 1α-hydroxylated form of vitamin D in patients with normal calcium, phosphate, or vitamin D levels is preferred, especially in the management of inflammatory and respiratory conditions.[9] In general, a higher level of 25-hydroxyvitamin D_3 (25-OHD) is required

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to attain better clinical outcomes in asthma compared with musculoskeletal conditions.[11] In addition to the reported effects of $1,25(OH)_2D$, alfacalcidol has been shown to possess direct immunomodulatory and anti-inflammatory functions without the need to be activated by 25-hydroxylation.[12]

To date, only a few trials have studied the effect of vitamin D supplementation in adult asthma and none have used alfacalcidol as a form of vitamin D for treatment. This study examined the clinical effects associated with the usage of alfacalcidol supplementation for 4 months as adjunct therapy to the standard of care and investigated the pattern of vitamin D deficiency in patients with asthma in Egypt.

Methods

Study Design

The study was carried out at the Imbaba Chest and Allergy Research Institute (Cairo, Egypt) from August 2014 to February 2016 as an open-label prospective randomized controlled trial. The study was performed in accordance with the Declaration of Helsinki. This human study was approved by the ethics committee of the Faculty of Pharmacy, Cairo University (approval number CL1122). All adult participants provided written informed consent to participate in this study. The trial was registered on ClinicalTrials.gov (identifier number NCT02747381). The study was funded by the Faculty of Pharmacy, Cairo University.

Subjects

To be eligible for enrollment, patients needed to be nonsmokers, adults (18 to 65 years old), have asthma, and diagnosed according to the National Asthma Education and Prevention Program (NAEPP) asthma guidelines.[13] Exclusion criteria were asthma exacerbation, hypercalcemia, hyperphosphatemia, pregnancy and breast-feeding, and being on nutritional supplements with a potential effect on 25-OHD serum concentrations. Patients with a history of stones in the urinary tract or diseases of calcium or bone metabolism in addition to renal or liver impairment also were excluded from the study. In addition, serum 25-OHD was measured for healthy subjects selected to be comparable to the patients in age, sex, and season of sample collection.

The recruited patients were categorized into 4 groups based on their asthma severity stage[13] and then randomized to the intervention or control group by the first author (Fig 1). Randomization was done by numbering patients chronologically and then assigning patients with odd numbers to the intervention group and those with even numbers to the control group. Because all patients were recruited from the same hospital, all were treated from within the same formulary. The selected treatment regimen was unified for patients in the 2 groups. Patients with intermittent asthma were treated with Ventalinhaler (The Arab Drug Company, Cairo, Egypt; each actuation contains 100 μg of salbutamol) as needed. In addition to Ventalin, patients with mild asthma were prescribed Ventalin Compositum at 2 puffs every 12 hours (each puff contains 50 μg of beclomethasone dipropionate plus 100 μg of salbutamol). In addition to Ventalin and Ventalin Compositum, patients with moderate asthma were prescribed Foradil Aerolizer (formoterol fumarate; each inhalation capsule contains 12 μg of eformoterol fumarate dihydrate; Novartis Pharma AG, Basel, Switzerland) at 1 capsule twice daily or Uniphyllin (theophylline; each tablet contains 400 mg of theophylline; The Nile Company for Pharmaceuticals, Cairo, Egypt [under license of Mundipharm AG, Basel, Switzerland]) at a half-tablet twice daily. Patients with severe asthma had their beclomethasone inhaler dose increased to high or had oral prednisolone added to their treatment regimen. Treatment for each patient was stepped up or down to the minimum treatment step to achieve symptom control according to the NAEPP guidelines.[13] Patients in the intervention group received an adjunct alfacalcidol capsule (1 μg/d; Leo Pharma Product, Copenhagen, Denmark) for 4 months.

Patients' demographic data, family history, concurrent atopic conditions, and current medications data were obtained. Patients were interviewed monthly for 4 months and were assessed for their compliance by counting the remaining capsules in the medication box. In addition, 25-OHD and total immunoglobulin E (IgE) were measured at baseline and at 4 months.

Total calcium also was measured at baseline and at 4 months for the intervention group only to monitor the possible incidence of hypercalcemia associated with alfacalcidol therapy.

Spirometry

Spirometric maneuvers were performed using the Contec SP10 spirometer (Contec Medical System Co, Qinhuangdao, China) according to the American Thoracic Society guidelines for the standardization of spirometry.[14] Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, peak expiratory flow, and forced expiratory flow at 25% to 75% of FVC ($FEF_{25\%–75\%}$) and the percentage of predicted values of each of these parameters were recorded for each patient at baseline, 2 months, and 4 months. Patients were educated about the spirometric technique verbally and through demonstration. During each spirometric maneuver, the patient was encouraged to inhale maximally and exhale as maximally and forcibly as possible for a minimum of 3 times or until the results were reproducible with a maximum of 8 times. In addition to baseline spirometry in the first interview and to confirm the diagnosis of asthma after already being diagnosed by the physician in the clinic, a post-bronchodilator reversibility test was performed, during recruitment only, through inhalation of 200 to 400 μg of salbutamol in the form of 2 to 4 puffs of Ventalin. An increase in the FEV_1 of 12% or 200 mL from the baseline reading was considered consistent with the asthma diagnosis. The reversibility was detected through repeating the spirometry 15 minutes after the administration of the inhaler. During each follow-up, the spirometric maneuver was carried out at the same time in the morning and the patients were asked to cease using their asthma medication, especially the reliever, before coming to the clinic until the spirometry was completed to avoid falsely improved results.

Sample Collection

Blood samples were collected from all patients at baseline and at 4 months. Serum samples were separated from whole blood and stored at $-20^{\circ}C$ to be assayed in batches. The analysis of 25-OHD was performed using an Euroimmun enzyme-linked immunosorbent assay kit (Luebeck, Germany). All sample analyses were performed by the Chemical Pathology Department Laboratories at Kasr El-Aini Hospital of Cairo University. For analysis, patients with 25-OHD levels lower than 20 ng/mL were considered to be "deficient," those with levels of 20 to 30 ng/mL were considered "insufficient," and those with levels of at least 30 ng/mL were considered "sufficient."[15]

Study Outcomes

The primary outcome of the present study was the change in patients' FEV_1 percentage of predicted values at 4 months (end of follow-up) compared with baseline.

The secondary outcomes included changes in other spirometric parameters, namely FVC, FEV_1/FVC ratio, $FEF_{25\%–75\%}$, and peak expiratory flow; changes in serum 25-OHD and IgE levels after 4 months; and the comparison of vitamin D levels between patients with asthma and healthy controls.