Abstract

Asthma is a chronic inflammatory lung disease characterized by inflammation of the airways, increased mucous production, and airway hyperresponsiveness. Airway inflammation and narrowing of airway passages lead to wheezing, coughing, chest tightness and shortness of breath. A hallmark feature of asthma is the presence and activation of inflammatory cells in the airways, notably eosinophils, basophils, mast cells, and T lymphocytes. The mast cells in the airways have the potential to release asthmatic mediators such as histamine, tryptases, chymases and various other enzymes, and cytokines. Current asthma treatments are based on inhaled corticosteroids, long and short acting β2-adrenoreceptor agonists as well as leukotriene antagonists. Inhaled corticosteroid has become first-line treatment for most of the patients. However; long term use of corticosteroid is known to induce various side effects like hyperglycemia, hypertension, cardiometabolic abnormalities, psychiatric adverse effects, weight gain and osteoporosis. Moreover, chronic use of corticosteroid induces vitamin D deficiency and low level of vitamin D contributes to increase in asthma severity.

Vitamin D is a seco-steroidal hormone which not only plays an important role in the metabolisms of calcium, phosphorus and bone but is also involved in regulation of immune system. Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (25(OH) vitamin D) which is further metabolized in the kidneys to its active form, 1,25-dihydroxyvitamin D (1,25(OH)2D3) which is also known as calcitriol. The biological responses to the calcitriol are mediated by vitamin D receptor (VDR); a member of the superfamily of nuclear hormone receptors. VDR is expressed by many cells of the immune system, including activated B and T cells, monocytes, and dendritic cells. Vitamin D inhibits Th1 (IFN-γ, TNF-α, and IL-2), Th2 (IL-4, IL-5, IL-9, and IL-13) and Th17 (IL-17, IL-21, IL-22 and IL-26) associated cytokines while some evidence shows that vitamin D may enhance Th2 responses. Regulatory T-cells (Tregs) are a subpopulation of T cells which modulate the immune system which exert their effect by inhibiting transcription of the inflammatory cytokine IL-2, expressing IL-10, and potentially converting effector T cells to hypo-responsive or regulatory forms. Vitamin D causes induction as well as proliferation of Tregs and increased IL-10-secretion and toll-like receptor (TLR)-9 expression. Both in vivo and in vitro studies have shown that vitamin D enhances the production of anti-inflammatory cytokine IL-10 by human T cells. Moreover, altered
vitamin D homeostasis is associated with increased risk of developing glucose intolerance, metabolic syndrome, cardiovascular events, psychiatric adverse effects, obesity and hypertension. There is disparity of Vitamin D doses which can be administered as daily dose or bolus dose (single high dose). So that present study was undertaken to evaluate efficacy of corticosteroids with vitamin D by using various animal models.

In preliminary study, we assessed the efficacy of different doses of vitamin D (50, 100 and 200 IU/kg) in asthma by using various animal models such as histamine/acetylcholine induced bronchoconstriction in guinea pigs, clonidine-induced mast cell degranulation, haloperidol induced catalepsy in mice. In our study we found that pre-treatment with vitamin D at all doses level (50, 100 and 200 IU/kg) were significantly attenuated histamine/acetylcholine induced bronchoconstriction in guinea pigs. Clonidine produced significant disruption of mast cells which was significantly inhibited by pre-treatment with the vitamin D. Haloperidol induces catalepsy by inhibiting dopamine D2 receptors and inhibits dopamine secretion. In our study we found that vitamin D (at all doses level; 50, 100 and 200 IU/kg) treated animals showed significant protection against haloperidol-induced catalepsy and comparable to standard drug chlorpheniramine maleate. Therefore, vitamin D has significant role in asthma.

Further, for chronic study we used ovalbumin induced airway model to confirmed antiasthmatic activity and adverse effects profile of corticosteroid-vitamin D combinations and monotherapies. For this study we have selected two different dosage schedule of vitamin D as 50 IU/kg given daily and bolus dose; 60,000 IU given only single dose. For this, 2 different doses of vitamin D (50 IU/kg, daily for 2 weeks, or and 60000 IU/kg, bolus dose, by intraperitoneal injection (i.p.)) were administered in combination with dexamethasone (2.5 mg/kg, i.p., for 2 weeks) prior to challenge with ovalbumin. At the end of the therapy, the asthmatic parameters such as differential white blood cell counts, serum and Broncho alveolar lavaged fluid (BALF) levels of immunoglobulin E (IgE), and interleukin-5, as well as serum levels of nitric oxide were significantly increased after allergen challenges in asthmatic rats as compared with the controls. Such increases were significantly attenuated by monotherapy with vitamin D and with combination therapy of vitamin D and dexamethasone, where the combination therapy was superior to the monotherapy. Dexamethasone-induced various side effects like hyperglycemia, hyperlipidemia, and behavioral abnormalities in the allergic rats were attenuated with
vitamin D. The daily dose was better for controlling serum levels of immunoglobulin E than the bolus dose, whereas the bolus was superior for reducing dexamethasone-induced psychotropic abnormalities. There were no significant changes in other parameters between the daily and the bolus dose.

In further study we aim to study the effect of vitamin D with corticosteroids antagonist; mifepristone; whether vitamin D could suppress inflammatory cell; independent from corticosteroid receptor or involved receptor other than corticosteroid for mechanism of action. We found that animals pre-treated with vitamin D, combination of vitamin D and dexamethasone significantly decreased the production of the inflammatory cells; eosinophils and neutrophils. However, animals pre-treated with mifepristone and received dexamethasone are unable to suppress inflammatory cells like eosinophils and neutrophils but those animal who were pre-treated with mifepristone and received vitamin D are able to suppress inflammatory cells like eosinophils and neutrophils. It is clear that vitamin D may act independently and does not involved glucocorticoids receptor. Further; we study the effect of vitamin D with PI3K inhibitors; wortmannin. We found that OVA-sensitized animals showed significant increase in eosinophils and neutrophils. Pre-treatment of animals with vitamin D, dexamethasone, wortmannin and combinations of vitamin D with dexamethasone and wortmannin significantly inhibited eosinophils and neutrophils in OVA model of asthma. Therefore, vitamin D, acts as synergistically with wortmannin.

In conclusion, vitamin D has significant antiasthmatic activity by inhibiting chemical mediator’s histamine, inflammatory cells, IgE, IL-5 and combination therapy with corticosteroid are more efficacies than monotherapy and helps to attenuates the corticosteroid induced adverse effects. Moreover, vitamin D significantly inhibited eosinophils and neutrophils; even in presence of corticosteroid receptor antagonist and acts synergistically with PI3K inhibitor. Therefore, vitamin D has significant role in asthma and should be given in combination with corticosteroid to enhance the efficacy and to improve adherence of treatments in asthma.