"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF CHOLECALCIFEROL AS AN ADD ON THERAPY TO STANDARD TREATMENT IN ADULT PATIENTS WITH BRONCHIAL ASTHMA"

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DOCTOR OF MEDICINE

IN

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INSTITUTE OF PHARMACOLOGY
MADRAS MEDICAL COLLEGE
CHENNAI - 600 003

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CERTIFICATE

This is to certify that the dissertation entitled, **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF CHOLECALCIFEROL AS AN ADD ON THERAPY TO STANDARD TREATMENT IN ADULT PATIENTS WITH BRONCHIAL ASTHMA"** submitted by **Dr. V. VASANTH KUMAR,** in partial fulfilment for the award of the degree of Doctor of Medicine in Pharmacology by The Tamilnadu Dr.M.G.R.Medical University, Chennai is a bonafide record of the work done by him in the Institute of Pharmacology, Madras Medical College during the academic year 2016-2019.

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DECLARATION

I, **Dr. V. VASANTH KUMAR,** solemnly declare that the dissertation titled **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF CHOLECALCIFEROL AS AN ADD ON THERAPY TO STANDARD TREATMENT IN ADULT PATIENTS WITH BRONCHIAL ASTHMA"** has been prepared by me and submitted to Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in Pharmacology.

Date: **Dr. V. VASANTH KUMAR**

Place:

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Introduction

INTRODUCTION

Bronchial asthma is one of the most common diseases affecting nearly 300 million people globally (i.e.,) 8-10 % of the population. The rising prevalence of bronchial asthma in developing nations like India is attributed to various factors like urbanization, environmental pollution, industrialization, lifestyle changes.[1]

Bronchial asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness and airflow obstruction that is often reversible at least in the initial stages.[2] The pathogenesis of asthma is very complex and is not fully elucidated yet. A variety of cells and inflammatory mediators play a critical role in initiating, perpetuating and coordinating the repeated cycles of inflammation. The fundamental pathology in asthma is the exaggerated TH2 response to normally harmless environmental antigens resulting the release of TH2 cytokines mainly interleukins 4,5 and 13 of which IL4 and IL 13 are responsible for the production of antigen specific IgE by B lymphocytes. IL 5 is responsible for prolonging the survival of eosinophils.[2,3]

The repeated cycles of inflammation lead to infiltration of airways with eosinophils, lymphocytes and elaboration of various interleukins, chemokines and growth factors. These inflammatory agents cause various changes which are collectively termed as airway remodelling such as hypertrophy and hyperplasia of bronchial smooth muscle cells, epithelial injury, mucus gland hyperplasia, deposition of sub epithelial collagen, fibrosis and increased vascularity resulting in partly reversible or irreversible airflow obstruction. [2,3]

Treatment of bronchial asthma involves two major class of medications viz, bronchodilators and anti-inflammatory agents. Bronchodilators includes beta 2 agonists, anticholinergics and methylxanthines. These are mainly used as reliver(rescue) medications. These agents act principally by relaxation of bronchial smooth muscle and thereby reversing the airflow obstruction. Anti-inflammatory agents include corticosteroids, leukotriene antagonists and anti IgE therapy. These are mainly used as chronic controllers. These agents reduce airway inflammation and help to maintain control over asthma.[4,5] However, the chronic use of corticosteroids is associated with various adverse effects both locally and systemically like dysphonia, oral candidiasis, weight gain, osteoporosis, hypertension, etc and there is a variability in patient's response to corticosteroids[4] Given this situation there is a need for investigating the role of new drugs in the treatment of bronchial asthma. Of the various new therapies cholecalciferol has been found to have a role in the treatment of bronchial asthma.

Cholecalciferol or vitamin D, a fat-soluble vitamin is a prohormone with several active metabolites that act as hormones. Cholecalciferol is synthesized in our body from 7- dehydrocholesterol by the action of sunlight (UV B rays). Cholecalciferol so formed does not have significant biological activity, it must be converted to its metabolically active form 1,25 dihydroxycholecalciferol or calcitriol by series of hydroxylation reactions occurring sequentially in liver and kidney.[6]

1,25 dihydroxycholecalciferol acts by binding to its intracellular receptor, the vitamin D receptor resulting in the translocation of Vitamin D Receptor complex to nucleus and binding to specific sequences of DNA called Vitamin D Responsive Elements leading to changes in the transcription and subsequent translation of various proteins. The major roles of cholecalciferol in our body are promoting intestinal calcium and phosphate absorption, increasing renal reabsorption of calcium and phosphate and bone modelling and remodelling. Cholecalciferol is also found to have various effects in addition to calcium homeostasis like in immune system, skin, skeletal muscles, etc.[6]

Several studies have shown a relationship between serum vitamin D levels and bronchial asthma.[7,8] Low levels of Vitamin D are associated with reduced lung function, frequent exacerbations and severe disease. In addition, vitamin D deficiency is more common in asthmatics compared to general population as asthmatic patients tend to spend more time in doors, are less active physically and therefore their exposure to sunlight is less.[7]

Vitamin D is found to have anti-inflammatory activity in several in vitro studies. Vitamin D reduces inflammation by decreasing the levels of proinflammatory cytokines and increasing the levels of anti-inflammatory cytokines like interleukin 10.[9] Vitamin D also reduces bronchial smooth muscle cell hypertrophy and hyperplasia. In addition, vitamin D improves response to inhaled and oral corticosteroids.[10] Thus, Vitamin D by inhibiting the repeated

cycles of chronic inflammation reduces airway remodelling which is the major pathologic change seen in the lungs of asthmatic patients.[7]

Based on the anti-inflammatory and immunomodulatory effects of cholecalciferol, this study was taken up to evaluate the efficacy and safety of Cholecalciferol in patients with bronchial asthma in our community.

Review of Literature

REVIEW OF LITERATURE

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by airway obstruction, which is often reversible. Asthma is not a single disease but rather a clinical syndrome and a heterogenous disease. Asthma typically shows multiple endotypes with common manifestations but has distinct pathophysiologic mechanism and aetiology. This heterogeneity is seen as variability in pathologic, clinical and physiologic parameters between different patients.[2]

HISTORY OF ASTHMA

The term Asthma is derived from the Greek word *aazein*, which means to exhale with the open mouth.[11]

The earliest text where the word asthma is found is The *Corpus Hippocraticum*, by Hippocrates. Aretaeus (100 AD), a Greek physician, wrote the first clinical description of asthma. Galen (200 AD), another Greek physician, wrote several texts on asthma describing the clinical manifestations and treatment.[11]

Van Helmont (16th century), a Belgian physician and chemist, was the first one to propose that asthma originates in the lungs. Bernardino Ramazzini (17th century), an Italian clinician hypothesized a link between asthma and organic dust and exercise.[11]

Bronchodilators were used in the treatment of asthma as early as the beginning of 19th century. However, the role of inflammation in asthma was recognized only in the 1960s leading to the development and use of anti-inflammatory medications.[11]

EPIDEMIOLOGY

Bronchial asthma is one of the most common disease worldwide affecting nearly 300 million people (8-10% of population). The prevalence of asthma is increasing rapidly in developing countries such as India due to factors such as increasing urbanization, industrialization, air pollution.[1,12]

Peak age of presentations of asthma is 3 years although asthma can present at any age. In children, males are more affected than females. In adults, the sex difference is not significant. Usually the severity of asthma is constant and does not vary significantly in a patient. Usually patients who develop asthma at an early age become asymptomatic during adolescence, but asthma can return at a later age in these patients. However, patients who become asthmatic at a later age have a persistent disease and they rarely become asymptomatic.[1]

Bronchial asthma is a disease with severe morbidity however death due to asthma is uncommon. Risk factors for death are poorly controlled patients, lack or poor compliance to therapy, previous admission with near fatal asthmatic attack.[1]

RISK FACTORS

Asthma shows an interplay between various genetic and environmental factor.[1]

ENDOGENOUS FACTORS

1. ATOPY

This is the most significant risk factor. Atopy refers to the exaggerated IgE mediated immune response to various allergens.

Common allergens are house dust mites, cat and dog fur, cockroach, pollen and fungi. Asthmatic patients have significantly higher prevalence of other allergic diseases like allergic rhinitis, allergic conjunction and atopic dermatitis.[1]

2.GENETIC FACTORS

Several genes are implicated in the pathogenesis of asthma like genes involved in cytokine productions especially chromosome 5q containing genes for IL-4, IL-5, IL-9, IL-13. Other genes implicated in the pathogenesis are ADAM 33, DPP 10, HLA-G, ORMDL-3.[1]

3.AIRWAY HYPERRESPONSIVENESS

It is the characteristic physiologic abnormality seen in asthmatics. Airway hyperresponsiveness refers to the excess bronchoconstrictor response to various agents that normally would not have significant effect on airways. This antecedes the development of asthma. Presence of airway hyperresponsiveness increases the risk of developing asthma.[1]

ENVIRONMENTAL FACTORS

1. Infection

Viral infections like respiratory syncytial virus, rhino virus, atypical bacterial infections like chlamydia, mycoplasma increase the risk of asthma as well as they trigger acute attacks.

Hygiene hypothesis and asthma- Lack of infectious stimuli in early childhood preserves the T-Helper 2 response which predisposes to asthma whereas exposure to various infectious agents causes a shift to protective TH_1 response. This is called hygiene hypothesis which may also contribute to the development of asthma.[1]

2. Air pollution

Especially gases like ozone, sulphur dioxide, various components of motor vehicle exhaust increase the risk of developing asthma.[1]

3. Occupation

Occupational asthma is asthma occurring de novo as a consequence of exposure to specific agents in persons without previous history of asthma. It is of two types.

- Sensitizer induced asthma
- Irritant induced asthma [2]

Causes of Occupational Asthma

Sensitizing Agent-Induced Asthma [2]

Agent	Workers at Risk
Acrylate	Dental workers; adhesive handlers
Anhydrides	Workers using epoxy resin for plastics
Animal protein allergens	Veterinary workers; animal handlers
Dyes	Textile workers
Enzymes	Pharmaceutical workers; bakery workers; laboratory workers
Formaldehyde, glutaraldehyde	Hospital and healthcare workers
Isocyanates	Installers of insulation; manufacturers of plastics; rubbers and foam; spray painters
Latex	Healthcare workers; rubber workers
Persulfate	Hairdressers
Wood dusts	Forestry workers; sawmill workers; carpenters

Common Agents Responsible for Irritant-Induced Asthma[2]

- Acids (acetic, hydrochloric, sulfuric)
- Alkaline dust
- Ammonia
- Bleach
- Chlorine
- Diesel exhaust
- Formalin
- Mustard
- Oxide (calcium)
- Paints

Occupational asthma accounts for 10% of the asthmatics. Patient typically becomes symptomatic during working week and improves during weekend or vacation.

Early detection and avoidance of further exposure to etiologic agent is critical in occupational asthma.

4.Obesity

Obesity increases the risk of asthma by reducing tidal volume and functional residual capacity; increasing gastroesophageal reflux and increasing the expression of proinflammatory cytokines IL-6 and TNF-α by adipocytes.

5. Low birth weight

6. Prematurity

7. Duration of breast feeding

8. Diet[1]

PRECIPITANTS OF BRONCHIAL ASTHMA

These agents trigger bronchoconstriction and inflammation

1. Allergens such as pollen, animal fur cause activation of mast cells resulting in degranulation and release of inflammatory mediators.
2. Viral infections such as respiratory syncytial virus, rhino virus, corona virus.
3. Drugs such as beta blockers by increasing cholinergic mediated bronchoconstriction; aspirin by inhibiting cyclooxygenase it decreases the

level of prostaglandin E_2 which has a protective effect in asthma by increasing the synthesis of proinflammatory leukotriene B_4, C_4, D_4, E_4.[3]

4. Exercise leads to hyperventilation which increases the osmolality in bronchus triggering the release of inflammatory mediators.
5. Air pollution
6. Occupation – Exposure to fumes containing epoxy resins, plastics, organic dust such as cotton, wood, gases like toluene, chemicals such as formaldehyde, biological agents such as penicillin products.[3]
7. Physiological stress
8. Gastroesophageal reflux disease
9. Foods containing additives such as metabisulfite extrusion
10. Tobacco smoking[1]

Risk Factors and Triggers Involved in Asthma[2]

Endogenous Factors	Environmental Factors	Triggers
Atopy	Allergens–indoor	Allergens (especially house dust mite, animal dander, cockroach, fungi, seasonal pollens)
Airway hyperresponsiveness	Allergens– outdoor (fungi, pollens)	Changes in the weather (cold air)
Ethnicity	Obesity	Drugs (aspirin, β-blockers, NSAIDs)
Gender	Occupational sensitizers	Exercise and hyperventilation
Genetic predisposition	Parasitic infections	Extreme emotional expression (laughing, stress)
	Respiratory infections (viral)	Irritants (household sprays, paint fumes)
	Socioeconomic status	Respiratory infections
	Tobacco smoking (active and passive)	Sulfur dioxide and other pollutant gases Tobacco smoking

TYPES OF BRONCHIAL ASTHMA

1.Atopic

- Most common type.
- Due to IgE mediated type I hypersensitivity reaction.
- Usually begins in childhood.
- Asthmatic attacks are triggered by inhalation of environmental allergens such as dust, pollen.
- Family history of atopy is present.
- Serum total IgE levels are increased.
- Skin test for allergens in positive.[3]

2.Non-Atopic

- No evidence of allergen sensitization.
- Seen in adults.
- Family history is usually negative.
- Air pollution and viral infection are the common precipitants.
- Triggers leading to asthmatic attacks.
- Skin tests for allergens is negative.[3]

PATHOGENESIS OF ASTHMA

The pathogenesis of asthma is very complex and is not fully understood. This involves a variety of cells and inflammatory mediators that are activated by several mechanisms. The resulting airway inflammation is central to the

pathophysiology of bronchial asthma and causes bronchial dysfunction partly through changes caused by the release of inflammatory mediators and partly by airway remodelling. The fundamental abnormality in asthma is exaggerated T-Helper 2(TH_2) response to normally harmless environmental antigens. Since the pathogenesis of asthma involves both acute and chronic inflammation it is prudent to discuss these in detail.[2,3,13]

EFFECT OF ACUTE INFLAMMATION

When an antigen enters the airway of a susceptible person for the first time, it is taken up by the dendritic cells which then travel to pulmonary lymph nodes where the antigen is presented to naïve CD4 T cells. Dendritic cells play a key role in determining the differentiation of CD4 T cell. Prior to this, dendritic cells are influenced by molecular signals from bronchial epithelial cells and other local cells.[2]

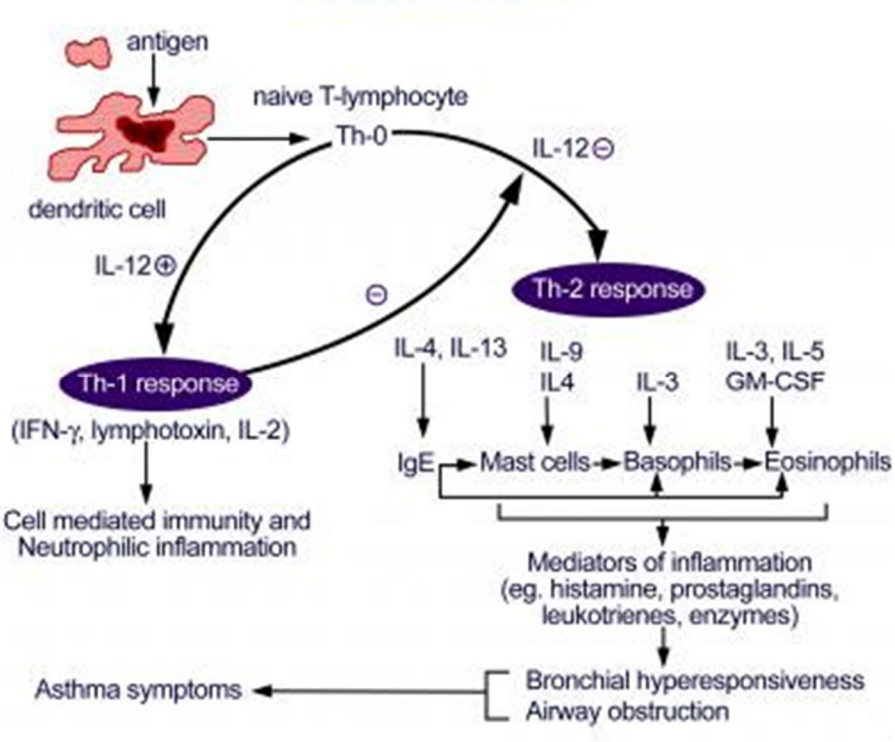
In genetically predisposed persons, TSLP (Thymic Stromal Lympho Protein) and GM-CSF (Granulocyte Monocyte Colony Stimulating Factor) produced by bronchial epithelium influence the dendritic cell to promote the differentiation of CD4 T cells to T-Helper2 lineage which eventually sets up the stage for allergic inflammation.[2]

These T-Helper$_2$ cells on reaching the airways secrete TH_2 chiefly IL-4, IL-15, IL-13 which play a key role in establishing the framework for further inflammation. These cytokines act on other inflammatory cells leading to self-fuelling cycles of inflammation and cellular injury. IL-4 promotes IgE production,

IL-5 causes activation of eosinophils and IL-13 causes mucus hypersecretion and also promotes IgE production.[2]

These antigen specific IgE binds to IgE receptor on the surface of mast cells. During subsequent exposure with sensitizing allergen, antigen-antibody reaction results in cross linking of IgE receptor on mast cells resulting in the release of variety of inflammatory mediators like histamine, leukotriene, prostaglandin, proteases which cause bronchoconstriction, plasma leakage, airway edema and increased mucous secretion. This is early phase of acute inflammation. Mast cells also release chemo attractants such as leukotrienes, chemokines, IL-5 which recruit a variety of inflammatory cells like eosinophils, basophils, neutrophils, lymphocytes. This forms the late phase of acute inflammation.[2]

PATHOGENESIS OF ASTHMA



INFLAMMATORY MEDIATORS

They initiate, perpetuate and coordinate the multiple processes seen in the inflammation. The major mediators implicated in the pathogenesis of asthma are;

1.Cytokines

Cytokines are small molecular weight glycosylated proteins. Cytokines is a broad term and it includes several mediators like interleukins, interferons and growth factors. Asthma shows the involvement of variety of cytokines like IL-1, IL-2, IL-3, IL-4, IL-5, IL-13, IL-18, TNF-α(Tumour Necrosis Factor-α), FGF(Fibroblast Growth Factor), PDGF(Platelet Derived Growth Factor), VEGF(Vascular Endothelial Growth Factor). These are responsible for recruitment and proliferation of leukocytes, airway hyperresponsiveness, mucus hypersecretion, increased vascular permeability, fibroblast activation.[2,3]

2.Chemokines

This family of small molecular weight proteins are classified into 4 types based on the arrangement of cysteine residues- XC, CC, CXC, CX_3C. Their major function in asthma is recruitment of other inflammatory cells by acting as chemoattractant.[2]

3.Leukotrienes

Leukotrienes are synthesized in eosinophils and mast cells from arachidonic acid. They are responsible for causing bronchoconstriction, increased mucus secretion and increased vascular permeability seen in asthmatics.[2]

4.Prostanoids

These are also derived from arachidonic acid. PGD_2, PGF_2, TXA_2 acts as bronchoconstrictors and also recruit other inflammatory cells of these PGD_2 plays a predominant role in asthma.

5.Nitric oxide

Increased expression of inducible nitric oxide synthase due to chronic inflammation results in increased production of nitric oxide in the airways. Nitric oxide causes cellular injury by promoting free radical formation.

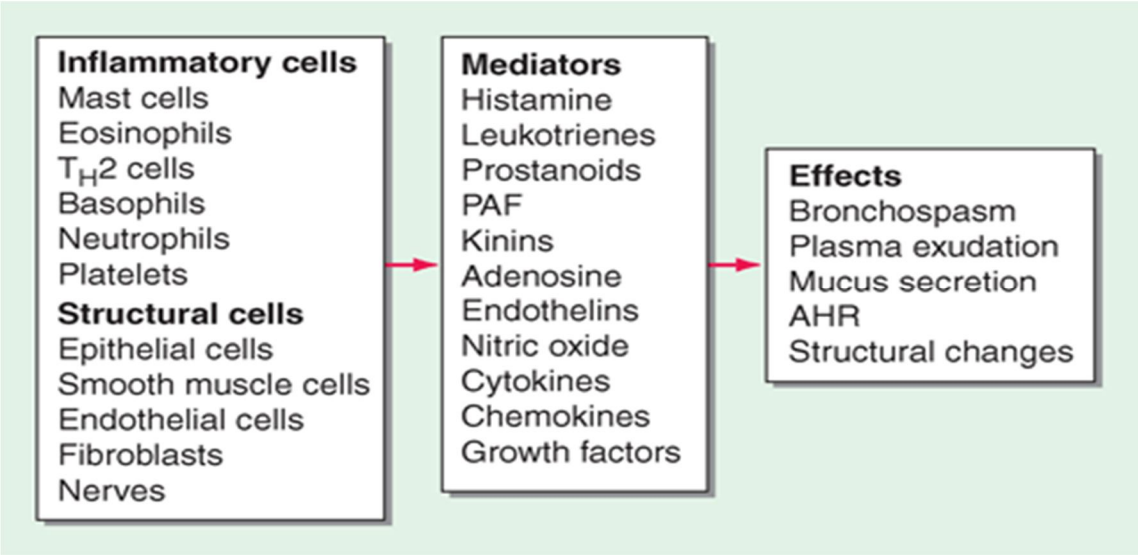
Other mediators involved are

1.Histamine

2.Platelet Activating Factor

3.Endothelin[2,13]

VARIOUS CELLS AND MEDIATORS INVOLVED IN ASTHMA



The repeated cycles of inflammation characterised by infiltration of eosinophils, mast cells, lymphocytes and elaboration of inflammatory mediators like interleukins, chemokines and growth factor leads to chronic inflammation of airway which is detrimental and injurious to airway.[2,3]

EFFECTS OF CHRONIC INFLAMMATION

Bronchial asthma shows continuous inflammation and repair simultaneously. This chronic inflammation causes characteristic changes which are collectively referred as airway remodelling.

Various changes seen in airway remodelling are

i. Airway epithelium

Chronic inflammation leads to epithelial damage which in turn leads to airway hyperresponsiveness due to loss of epithelial barrier function (leads to increased penetration of allergens), loss of enzymatic activity such as neutral endopeptidase which normally degrades various inflammatory mediators, exposure of sensory nerve endings leading to enhanced reflex neural effects on bronchomotor tone.[3]

ii. Fibrosis

Basement membrane of airways is thickened due to sub epithelial fibrosis with deposition of type III and V collagen due to release of profibrotic mediators such as Transforming Growth Factor β (TGFβ). This fibrosis results in irreversible narrowing of airways.[3]

iii. Airway smooth muscle

Bronchial smooth muscle cells show hypertrophy and hyperplasia due to simulation by growth factors such as platelet derived growth factor (PDGF). Inflammatory mediators may also modulate ion channels that regulate resting membrane potential of bronchial smooth muscle cells which alters the excitability of smooth muscle cells.[3]

iv. Blood vessels

There is increase of airway mucosal blood vessels due to stimulation of angiogenesis by vascular endothelial growth factor (VEGF). Chronic inflammation also results in microvascular leakage leading to airway edema and exudation.[3]

v. Mucosal glands

Chronic inflammation leads to hyperplasia of submucous glands and increase in number of goblet cells leading to mucous hypersecretion and formation of viscid mucous plugs.[3]

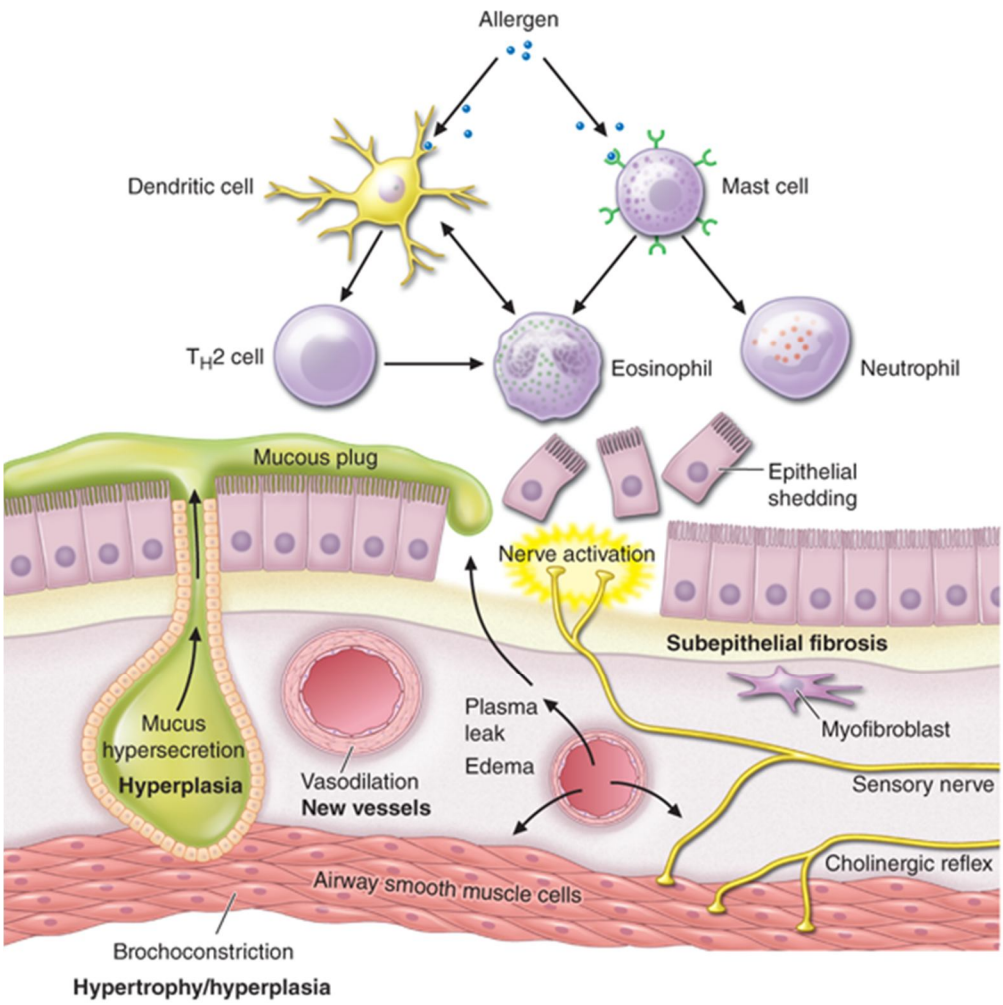
vi. Nerves

Inflammatory mediators may also activate sensory nerve fibres resulting in reflex cholinergic mediated bronchoconstriction and also increase the sensitivity of sensory nerve endings to external stimuli such as allergens. [3]

vii. Changes in pulmonary function

Limitation of airflow is due to bronchoconstriction, edema, congestion, exudation and airway remodelling leading to decrease in FEV_1, FVC, PEFR. [3]

AIRWAY REMODELLING



MORPHOLOGY OF LUNGS IN BRONCHIAL ASTHMA

Various features seen are

Occlusion of bronchi and bronchioles by thick tenacious mucous plugs.

Curshmann spirals are seen in sputum. These are formed due to extrusion of mucous plugs from sub epithelial mucosal gland ducts.

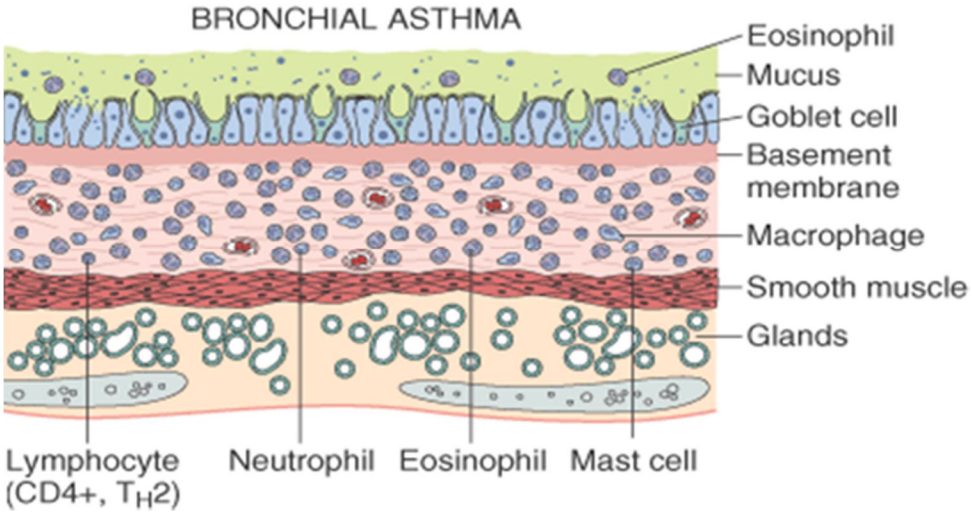
Charcot Layden Crystals are also seen in sputum. These are composed of eosinophilic protein called galectin 10.

Creola bodies are also seen in sputum. These are formed from shed epithelial cells.[3]

Microscopic features seen in chronic asthmatics are

a. Thickening of airway wall
b. Sub epithelial basement membrane fibrosis
c. Increased vascularity
d. Increase in submucosal glands
e. Hypertrophy and hyperplasia of bronchial smooth muscle cells[3]

MORPHOLOGIC FEATURES OF BRONCHIAL ASTHMA



CLINICAL FEATURES

SYMPTOMS

- Episodic wheezing
- Chest tightness
- Difficulty in breathing
- Cough with excess of sputum production

Seasonal variability of symptoms is seen. Family history of atopy may be present. The frequency of symptoms is highly variable. Usually asthma is worse at night due to circadian variation in bronchomotor tone between 3 to 4 am leading to increased occurrence of bronchoconstriction. Hence patients typically awake with symptoms in early morning.[5,14,15]

PHYSICAL EXAMINATION

Asthmatic patients are usually normal between exacerbation. Bilateral wheezing may be present. In severe cases decreased breath sounds, usage of accessory muscles is seen.

The severity and frequency of symptoms varies greatly between patients and also in the same patient.[5,14,15]

DIAGNOSIS

1.Lung Function Tests

Spirometry shows reduced forced expiratory volume in the first second (FEV_1), Forced Vital Capacity (FVC), FEV_1/FVC returns and Peak Expiratory Flow Rate (PEFR).

Reversibility of the lung volumes is diagnostic of bronchial asthma greater than 12% and 200ml increase in FEV_1 15 minutes after administration of inhaled short acting beta agonists shows the reversibility.

Airway hyperresponsiveness can be demonstrated by methacholine or histamine challenge where a decrease in FEV_1 by 20% is suggestive of airway hyperresponsiveness. However, this is rarely done.

Exercise testing can also be done.[1]

2.Chest X-Ray

Usually normal in patients with asthma. Chest X-ray is primarily used to exclude other causes of respiratory symptoms. In patients with severe disease hyperinflated lungs are seen.

3.Electrocardiogram

Normal in asthmatics. In acute severe asthma ECG may show sinus tachycardia, P-pulmonale, right axis deviation, right bundle branch block, arrythmias.

4. Haematologic tests

Eosinophilia may be seen in asthmatic patients. In patients taking corticosteroids eosinophil value may be normal.

Increased total serum IgE, increased IgE to inhaled allergens may be present in patients with atopic asthma.

5. Skin tests for allergens may be positive in patients with atopic asthma.

6. Exhaled nitric oxide

Non-invasive test to measure airway inflammation, as increased bronchial inflammation leads to increased exhaled nitric oxide. It is also used to test compliance (Inhaled corticosteroid decreases exhaled nitric oxide), to titrate dose of inhaled corticosteroids.[1,16]

MANAGEMENT OF BRONCHIAL ASTHMA

Treatment should be individualized for every patient and the patients should be monitored regularly with modification in treatment dose as and when required.

Aims of treatment are

a) Abolish symptoms
b) Reduce the risk of exacerbations
c) Restore lung function
d) Eliminate emergency visits
e) Maintain normal levels of physical activity
f) Minimize adverse effects[17]

Management of bronchial asthma involves

1.ASSESSING AND MONITORING ASTHMA SEVERITY AND ASTHMA CONTROL

Severity is the intrinsic intensity of the disease process. Control is the degree to which symptoms and limitations of physical activity are minimized by treatment. Control includes impairment and risk. Impairment is the frequency and intensity of symptoms and functional limitations. Risk is the likelihood of acute exacerbations or the chronic decline in lung functions.[5]

Classification of Asthma Severity[5]

Components of Severity	Intermittent	Mild	Moderate	Severe
Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
Night time awakenings	≤ 2x/month	3-4x/month	> 1 x/week but not nightly	Often 7x/week
Short-acting β2-agonist use for symptom control	≤ 2 days/week	> 2 days/week but not daily, and Daily not more than 1 x on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	• Normal FEV1 between exacerbations • FEV1 > 80% predicted • FEV1/FVC normal	• FEV1 > 80% • FEV1/FVC normal	• FEV1 > 60% but predicted < 80% predicted • FEV1/FVC reduced 5%	• FEV1 < 60% predicted • FEV1/FVC reduced > 5%
Recommended Step for Initiating Treatment	Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5 and consider short course of oral systemic corticosteroids

Classification of Asthma Control[5]

Components of Control	Well Controlled	Not Well Controlled	Very Poorly Controlled
Symptoms	≤ 2 days/week	> 2 days/week	Throughout the day
Night time awakenings	≤ 2x/month	1 -3x/week	≥ 4x/week
Interference with normal activity	None	Some limitation	Extremely limited
Short-acting beta-2-agonist use for symptom control	≤ 2 days/week	> 2 days/week	Several times/day
FEV1 or peak flow	> 80% predicted	60-80% predicted	< 60% predicted/
Validated Questionnaires ATAQ	0	1 -2	3-4
ACQ	≤ 0.75	≥ 1 .5	N/A
ACT	≥ 20	1 6-1 9	≤ 1 5
Recommended Action for Treatment	Maintain current step Regular follow-ups every 1 -6 months to maintain control. Consider step down if well controlled for at least 3 months.	Step up 1 step Re-evaluate in 2-6 weeks.	Consider short course of oral corticosteroids, Step up 1 -2 steps, and re-evaluate in 2 weeks.

2.PATIENT EDUCATION

It involves explaining the patient about asthma, its management, proper inhaler use and adverse effects of treatment.

It has many positive effects like reducing the need for emergency visits, reducing incidence of hospitalization, improving compliance and improving control. Patient should be taught to recognize symptoms of inadequate control, to use reliever medications. Patient should be asked to maintain a dairy listing exacerbations, triggers, use of reliever medications, PEFR values. Written personal action plan to be followed in case of increasing symptoms can be given for patients. This should be clear, simple and individualized. However, this can lead to overtreatment and increased adverse effects.[2,5]

3. CONTROL OF ENVIRONMENTAL FACTORS AND COMORBID ILLNESS THAT INFLUENCE BRONCHIAL ASTHMA

Significant reduction of exposure to allergens, irritants reduce the symptoms, improve control, reduce the need for medications.

Comorbid illness that may significantly influence the pathology of asthma like gastro oesophageal reflux disease, obesity, rhino sinusitis, obstructive sleep apnoea should be managed appropriately.[5]

4. PHARMACOLOGIC AGENTS

There are two major class of pharmacological agents viz, bronchodilators and anti-inflammatory agents. Bronchodilators are mainly used as reliver(rescue) medications. These agents act principally by relaxing of bronchial smooth muscle and thereby reversing the airflow obstruction. Anti-inflammatory agents especially corticosteroids are mainly used as chronic controllers. These agents

reduce airway inflammation and helps to maintain long term control over asthma.[5]

Various approaches to treatment are

1. Prevention of Antigen Antibody reaction—avoidance of antigen, desensitization.
2. Neutralization of IgE
3. Suppression of inflammation and bronchial hyperreactivity.
4. Prevention of release of mediators.
5. Antagonism of released mediators - leukotriene antagonists, antihistamines, PAF antagonists.
6. Blockade of bronchoconstrictor neurotransmitter.
7. Mimicking bronchodilator neurotransmitter.
8. Directly acting bronchodilators.[18]

CLASSIFICATION

I. Bronchodilators

A. β2 Sympathomimetics:

Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol.

B. Methylxanthines:

Theophylline (anhydrous), Aminophylline, Hydroxyethyl theophylline, Doxophylline.

C. Anticholinergics:

Ipratropium bromide, Tiotropium bromide.

II. Leukotriene antagonists

Montelukast, Zafirlukast.

III. Mast cell stabilizers

Sodium cromoglycate, Ketotifen.

IV. Corticosteroids

A. Systemic:

Hydrocortisone, Prednisolone, Betamethasone, Dexamethasone

B. Inhalational:

Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide.

V. Anti-IgE antibody

Omalizumab[18]

BRONCHODILATORS

Relax the bronchial smooth muscle and cause immediate reversal of airway obstruction.

Bronchodilators include 3 main class of drugs viz,

a) β2 agonists
b) Methylxanthines
c) Anticholinergic agents[4]

β2 AGONISTS

β2 agonists are the bronchodilator of choice in acute exacerbations and in chronic persistent asthma because they are most effective than other bronchodilators and have minimal adverse effects. Though other sympathomimetics are also effective in bronchial asthma selective β2 agonists are the preferred agents now because of minimal cardiac adverse effects. Because of minimal systemic adverse effects, rapid duration of action; inhalation is the preferred route of administration for β2 agonists; oral therapy is reserved for patients who cannot use inhalers properly and in cases of severe asthma.[4]

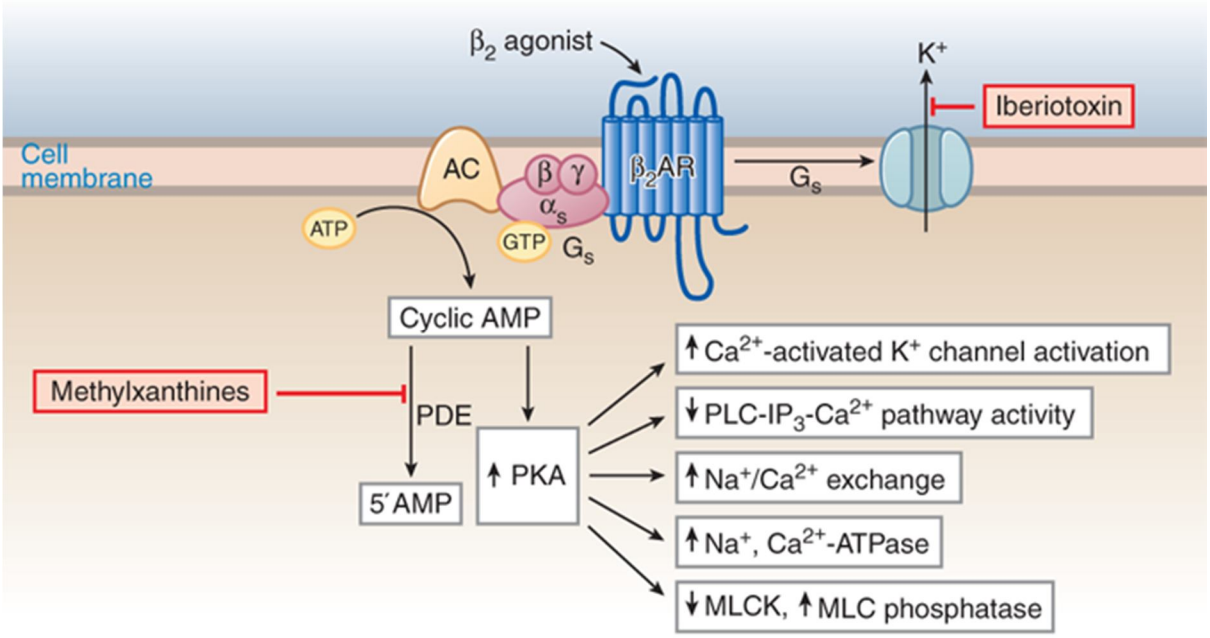
Mechanism of Action:

β2 agonists cause activation of β2 receptors (Gs subtype)-adenyl cyclase-cyclic AMP- Protein kinase A pathway resulting in bronchial smooth muscle relaxation.

Other effects include

- Inhibition of inflammatory mediator release.
- Reduction in microvascular leakage.
- Reduction in cholinergic mediated bronchoconstriction by acting on presynaptic B2 receptors leading to inhibition of acetylcholine release.[4,19-21]

MECHANISM OF ACTION OF β2 AGONISTS



CLASSIFICATION OF β2 AGONISTS

1.Short Acting Beta Agonist (SABA)

Acts for 3-4 hours

Includes Salbutamol, Terbutaline, Pirbutaline

2.Long Acting Beta Agonist (LABA)

Acts more than 12 hours

Includes Salmeterol, Formoterol

3.Very Long Acting Beta Agonist

Acts more than 24 hours

Includes Indacaterol, Vilanterol, Oladaterol[4,18]

LABA improves asthma control and reduces the risk of exacerbations. In asthmatic patients LABAs should never be used alone as they don't treat the underlying pathology i.e., chronic inflammation and this can lead to increased risk of near fatal asthma exacerbations. So LABAs should always be used in combination with inhaled corticosteroid as a fixed dose combination.

LABAs are an effective add-on therapy with the ICS and helps to achieve control without increasing the dose of ICS. Also, the combination of LABA with ICS is synergistic and helps to improve patient compliance.[4,22,23]

Adverse effects:

These are mainly due to stimulation of β2 receptors in extrapulmonary sites and includes

- Muscle tremor, most common adverse effect; due to the stimulation of skeletal muscle of β2 receptors.
- Tachycardia, palpitation due to stimulation of cardiac β2 receptors.
- Hypokalaemia, due to enhanced potassium entry into skeletal muscle mediated by β2 receptors.
- Increase in serum glucose, lactose, free fatty acid levels.[4,18]

TOLERENCE TO β2 AGONISTS

Seen with chronic treatment with beta 2 agonists because of down regulation of β2 receptors. However due to unknown reasons, tolerance doesn't develop bronchodilator action of β2 agonists, but tolerance develops to other actions of β2 agonists.[4]

ANTICHOLONERGIC AGENTS

Mechanism of Action:

Inhibit the bronchoconstrictor effect of acetylcholine by acting as antagonist at M_3 receptor in bronchial smooth muscle cell leading to bronchodilation. They also decrease the mucous secretion.[4,19]

Classification:

1.Short Acting Muscarinic Antagonists (SAMA)

Act for 6-8 hours

Include Ipratropium

2.Long Acting Muscarinic Antagonists (LAMA)

Act for more than 24 hours

Include Tiotropium, Umeclidinium, Aclidinium

Uses:

They are less effective bronchodilators. Anticholinergics are used mainly as an add-on bronchodilator in patients not controlled adequately on inhaled β2 agonists. The combination of anticholinergic agents with β2 agonists is additive and more beneficial than individual agents in patients with severe asthma.[4,18,22,23]

Adverse effects:

Includes bitter taste, dryness of mouth, urinary retention, anticholinergics may precipitate glaucoma in elderly.[4,18]

METHYLXANTHINES

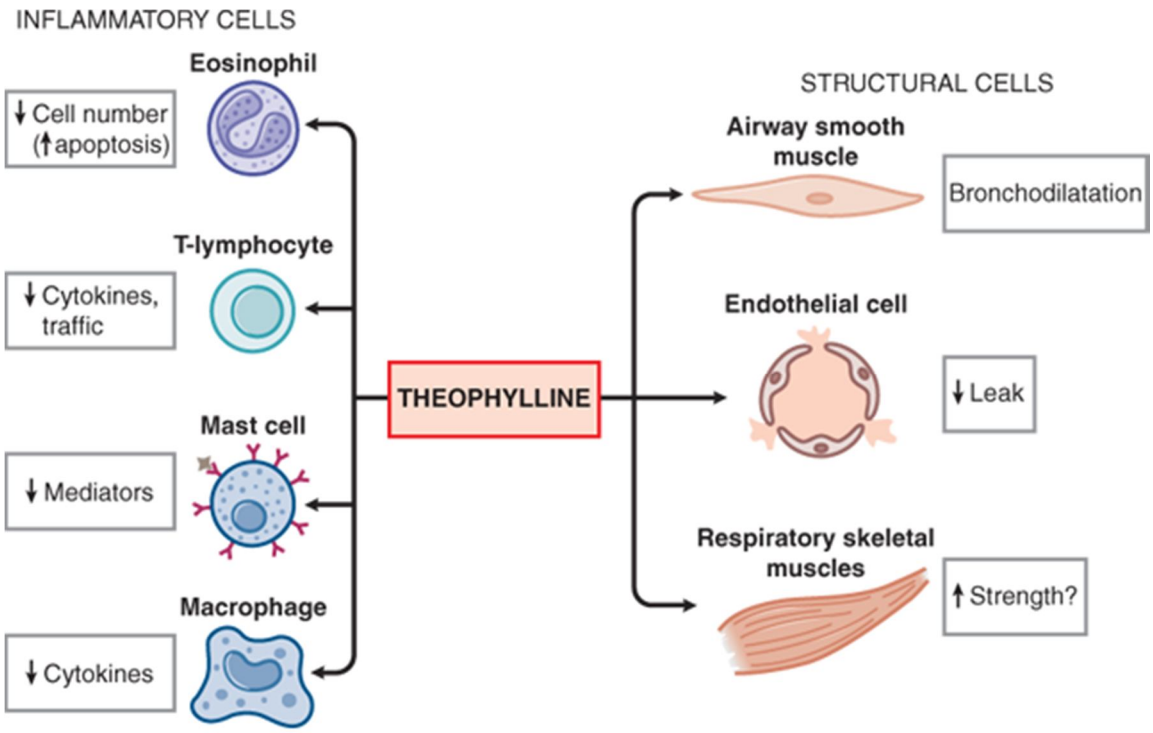
Methylxanthines are one of the earliest drugs used in asthma, in usage since 1930s. These are chemically related to caffeine.

Mechanism of Action:

Proposed mechanisms of action are

a. Nonselective inhibition of phosphodiesterase enzyme leading to increased intracellular levels of cyclic AMP which in turn leads to bronchodilatation.
b. Adenosine receptor antagonism. Adenosine acts as bronchoconstrictor in bronchial asthma by promoting the release of inflammatory mediators like leukotrienes and histamine.
c. Increasing the release of anti-inflammatory interleukin 10.
d. Reducing the expression of inflammatory genes by preventing the translocation of proinflammatory transcription factor Nuclear Factor kappa B(NFκB).
e. Promoting apoptosis of eosinophils and neutrophils by reducing the intracellular levels of anti-apoptotic protein BCl-2.[4,19,20,22]

ACTIONS OF METHYLXANTHINES



Uses:

Methylxanthines have narrow therapeutic index. Optimal therapeutic levels include 5-15 mg/L. The dose required to achieve this level varies among individuals because of difference in drug clearance and hence individualization of dosage and therapeutic drug monitoring are recommended.

They are less effective bronchodilators, so they are used mainly in patients who fail to respond or become intolerant to β2 agonists.

Oral methylxanthines- used as add-on agents. Sustained release formulations are preferred because immediate release preparation cause wide fluctuations in serum levels of methylxanthines and therefore have high frequency of adverse effects.

Intravenous- Aminophylline, a water-soluble ester of theophylline is used in acute exacerbations.[4,18,22,23]

Adverse effects:

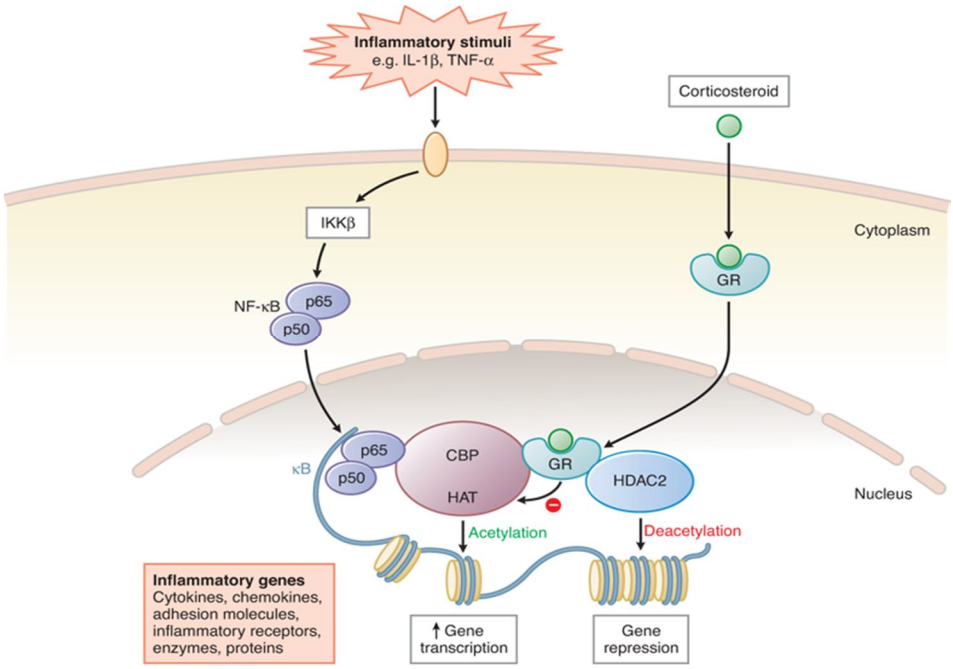
Include nausea, vomiting, headache, restlessness, abdominal discomfort, gastritis, diuresis. In toxic levels arrhythmias and seizure occur. Because of their low safety profile their use is currently declining.[4,18]

CORTICOSTEROIDS

Mechanism of Action

Corticosteroids bind to glucocorticoid receptor (GR) and this complex translocate to the nucleus, binds to specific sequences of DNA called Glucocorticoid Responsive Elements and modify transcription, leading to various effects.

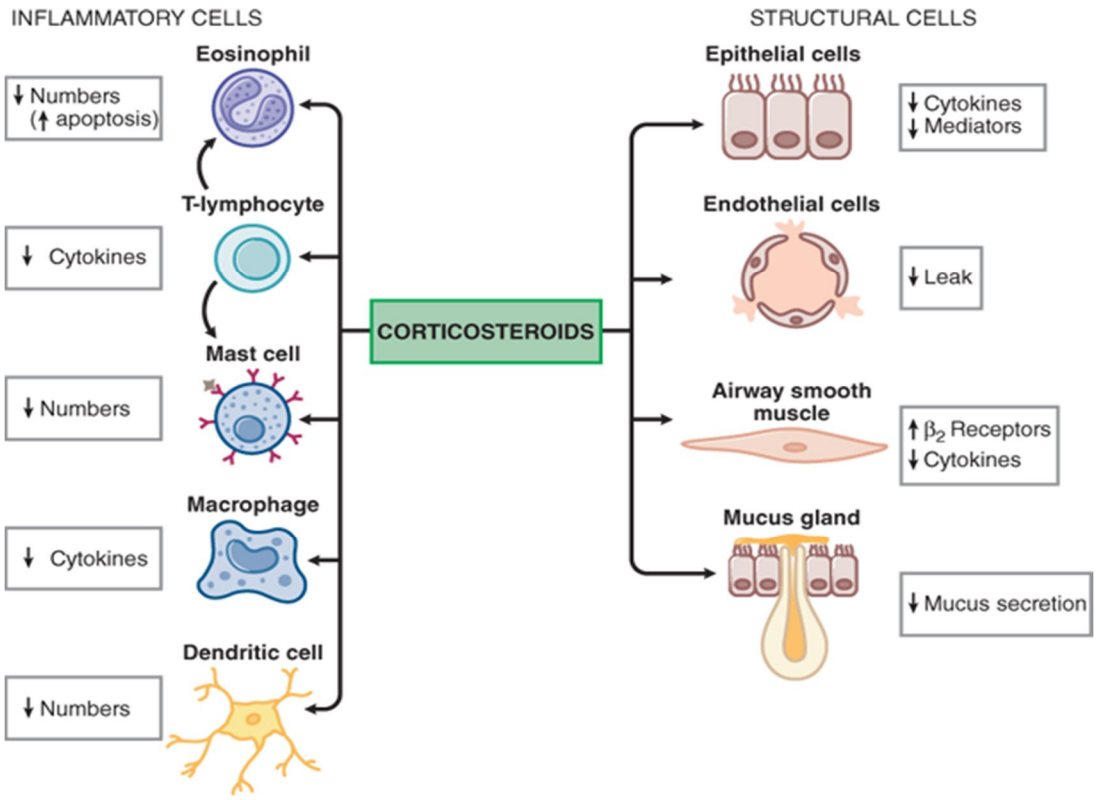
MECHANISM OF ACTION OF CORTICOSTEROIDS



Corticosteroids have profound anti-inflammatory action. This is due to its action on various processes involved in inflammation such as

a) Reduction in cytokine production
b) Inhibition of MAP kinase signalling pathway
c) Reducing eosinophil survival
d) Reduction in airway hyperresponsiveness
e) Reducing the number of T lymphocytes, mast cells in lungs
f) Improving vascular permeability thereby reducing exudation[4,18-19,22-23]

ACTIONS OF CORTICOSTEROIDS



CORTICOSTEROIDS AND β2 AGONISTS

Corticosteroids potentiate β2 agonists by

a) Preventing or reversing β receptor desensitization
b) Preventing or reversing β receptor uncoupling
c) Promoting the transcription of β receptor gene thereby increasing the availability of β receptors[4]

Available Inhaled Corticosteroids and Long Acting Beta 2 Agonists combinations are;

1. Beclomethasone - Formoterol
2. Budesonide - Formoterol
3. Fluticasone - Formoterol
4. Mometasone - Formoterol
5. Fluticasone – Salmeterol
6. Fluticasone – Vilanterol

Various routes used are

INHALED CORTICOSTEROIDS (ICS)

These are the first line agents in patients with chronic persistent asthma. Inhaled corticosteroids are used in any patient requiring the use of SABA more than 2 times per week. Usually Inhaled corticosteroids are started at minimal dose and titrated as per clinical response. Systemic absorption of ICS can occur from the particles deposited at oropharynx, airway and alveolus surface. This systemic

absorption can be minimized with the help of spacers and also by rinsing mouth after ICS usage.[4,18]

Comparative doses of inhaled corticosteroids[4,5]

Medication	Low Daily Dose	Medium Daily Dose	High Daily Dose
Beclomethasone 40 or 80 mcg/puff	80-240 mcg	240-480 mcg	> 480 mcg
Budesonide 90, 180, or 200 mcg/puff	180-600 mcg	600- 1200 mcg	> 1200 mcg
Flunisolide 250 mcg/puff	500- 1000 mcg	1000-2000 mcg	> 2000 mcg
Flunisolide 80 mcg/puff	320 mcg	320-640 mcg	> 640 mcg
Fluticasone 44, 110, or 220 mcg/puff	88-264 mcg	264-440 mcg	> 440 mcg
Mometasone 200 mcg/puff	200 mcg	400 mcg	> 400 mcg
Triamcinolone acetonide 75 mcg/puff	300-750 mcg	750-1500	mcg > 1500 mcg

ORAL CORTICOSTEROIDS

Prednisolone is the most commonly used oral corticosteroid and it is usually used as a short course during acute severe asthma and the dose is gradually tapered over 1 week after the exacerbation has resolved.

Prednisolone is given as a single dose in morning to minimize the risk of adrenal suppression as the morning dose coincides with the normal diurnal increase in plasma cortisol levels.[4,18]

PARENTAL CORTICOSTEROIDS (INTRAVENOUS)

Hydrocortisone is the preferred agent because of its rapid onset of action; intravenous corticosteroids are used in patients with acute severe asthma.[4,18]

Adverse Effects:

Local Adverse Effects of ICS

- Hoarseness of voice, dysphonia
- Oropharyngeal candidiasis
- Throat irritation, cough

These can be minimized using spacers or by rinsing mouth after ICS usage.

Systemic Adverse Effects

- Osteoporosis
- Hypertension
- Impaired glucose tolerance, Diabetes mellitus
- Cataract, Glaucoma
- Peptic ulcer
- Weight gain, fluid retention
- Hypothalamo-pituitary-adrenal axis suppression
- Psychosis
- Dermal thinning, capillary fragility
- Growth suppression in children[4,18,19]

ANTILEUKOTRIENES

Leukotrienes play an important role in the pathogenesis of bronchial asthma by causing increased vascular permeability, bronchoconstriction, exudation and mucous hypersecretion.

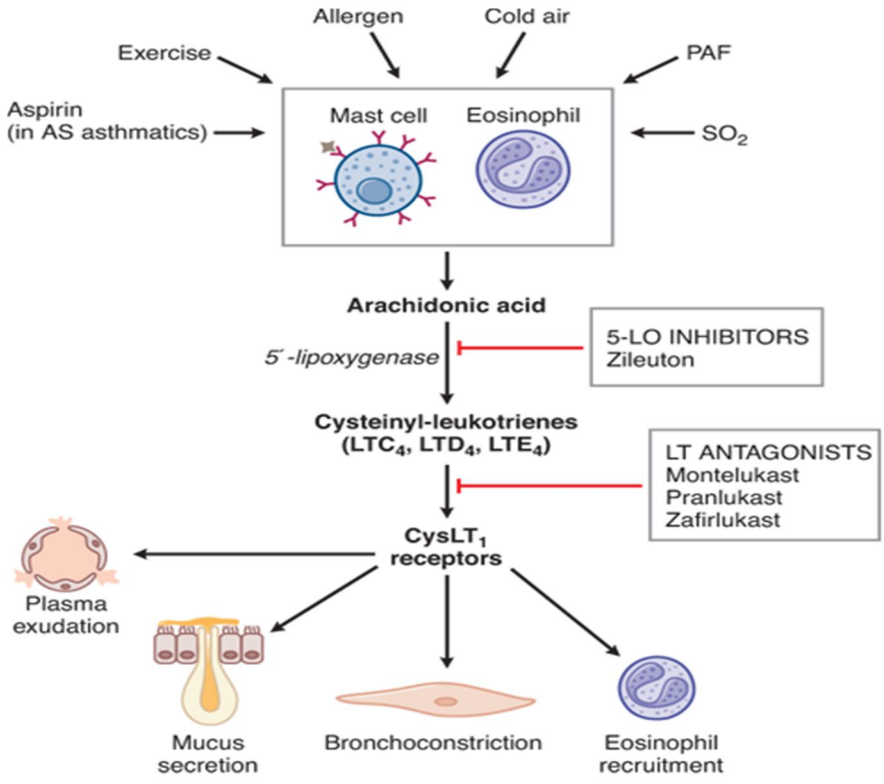
Hence inhibition of synthesis of leukotrienes by inhibitory 5-lipo oxygenase and antagonising the actions of leukotrienes at the level of cysteinyl leukotriene(cys-LT) receptor improves the control of bronchial asthma.

Antileukotrienes agents have anti-inflammatory property, but they are less effective anti-inflammatory agents than ICS. Hence, they are used mainly as an add-on agent.[4,18,19,24]

Classification:

1. Cys-LT receptor antagonist- Monteleukast, Zafirleukast.
2. 5-lipo oxygenase inhibitor- Zileuton.[18]

ACTIONS OF ANTILEUKOTRIENES



Adverse effects:

Hepatic dysfunction, nausea, headache, gastrointestinal distress.[4]

MAST CELL STABILIZERS

Includes the cromones - cromolyn sodium, nedocromil.

Mechanism of Action:

Cromones stabilize the mast cell membrane by preventing the influx of calcium ions provoked by antigen IgE reaction and hence prevent degranulation and the cascade of events leading to exacerbations. They also reduce leukocyte chemotaxis and activation.

Cromones are available as a metered dose inhaler, given 3-4 times daily.[4,18]

Adverse Effects:

Throat irritation, dryness of mouth, headache.

However, their use has declined with the advent of more effective inhaled corticosteroids.[4,18]

ANTI IgE THERAPY

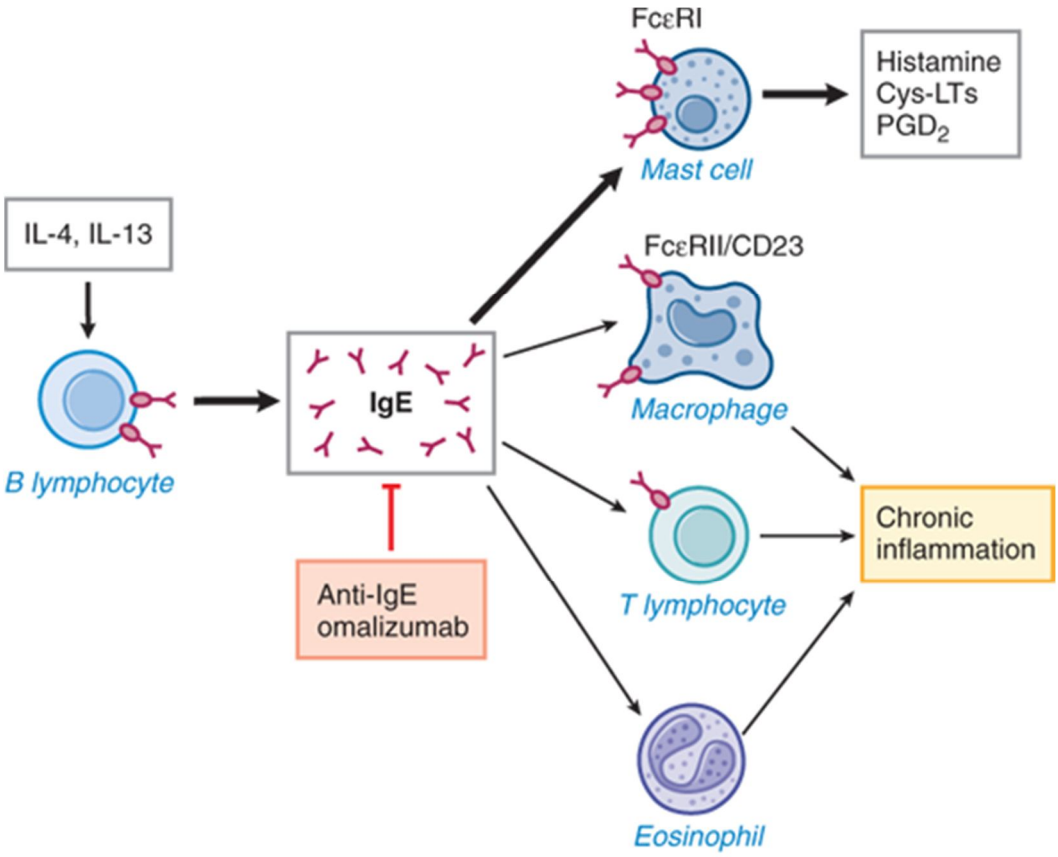
Omalizumab – Humanized monoclonal antibody to IgE.

Mechanism of Action:

Omalizumab blocks binding of IgE to its receptor on mast cells and thereby preventing their activation by allergens.

Omalizumab also decrease the levels of IgE in circulation and also reduce the need for oral and inhaled corticosteroids and the number of exacerbations.[4,18,19,24]

MECHANISM OF ACTION OF OMALIZUMAB



Omalizumab is used mainly in severe cases of bronchial asthma. It is given as subcutaneous injection every 2-4 weeks. However, it is very costly.

Adverse Effects:

Injection site reactions (pain, redness, swelling)

Anaphylaxis[4,18]

IMMUNOSUPPRESANTS:

Methotrexate, cyclophosphamide, intravenous immunoglobins are used when bronchial asthma is not adequately controlled with other agents or to as steroid sparing therapy.

Their disadvantages are

- Costly
- Less effective
- More adverse events[4,18)]

NEWER DRUGS IN DEVELOPMENT

NOVEL BRONCHODILATORS:

1.MAGNESIUM SULPHATE

Magnesium sulphate is used as nebulized form or intravenous injection in patients with acute severe asthma. It acts by decreasing cytosolic calcium levels in bronchial smooth muscle cells and thereby causing bronchodilatation. Adverse effects include flushing, nausea.

2.POTASSIUM CHANNEL OPENER – CROMAKALIM

Acts by opening K^+ ATPase in bronchial smooth muscle leading to hyperpolarization and thereby relaxation. Cardiovascular side effects especially postural hypotension limits the oral dose. Inhaled formulations are much effective.

3.VASOACTIVE INTESTINAL PEPTIDE ANALOGS

VIP is a bronchodilator; however, it cannot be used therapeutically because of its very short half-life of 2 minutes. Newer drugs acting as VIP analogs are under clinical trial.

Other newer class of drugs in development are

i. Rho kinase inhibitor
ii. Myosin light chain kinase inhibitors
iii. PAF (Platelet Activating Factor) antagonists
iv. Anti-IL-5 antibody (Mepolizumab)
v. Anti-IL-13 antibody
vi. Chemokine receptor antagonists
vii. MAP kinase inhibitor-Losmapimod
viii. NFκB inhibitor[4,18,19,22–24]

STEPWISE TREATMENT

Stepwise approach to asthma treatment is the description of levels of treatment required to achieve control. Various medications are adjusted up or down in a stepwise manner to achieve symptom control, minimise exacerbations and minimise adverse effects of medications. If patient has persistent symptoms or exacerbations in spite of treatment, consider the following before stepping up the treatment

- ❖ Poor compliance
- ❖ Persistent exposure to allergens, drugs, precipitants
- ❖ Incorrect inhaler technique
- ❖ Presence of comorbid illness that influence asthma management

Step 1: Occasional symptoms, less frequent than daily

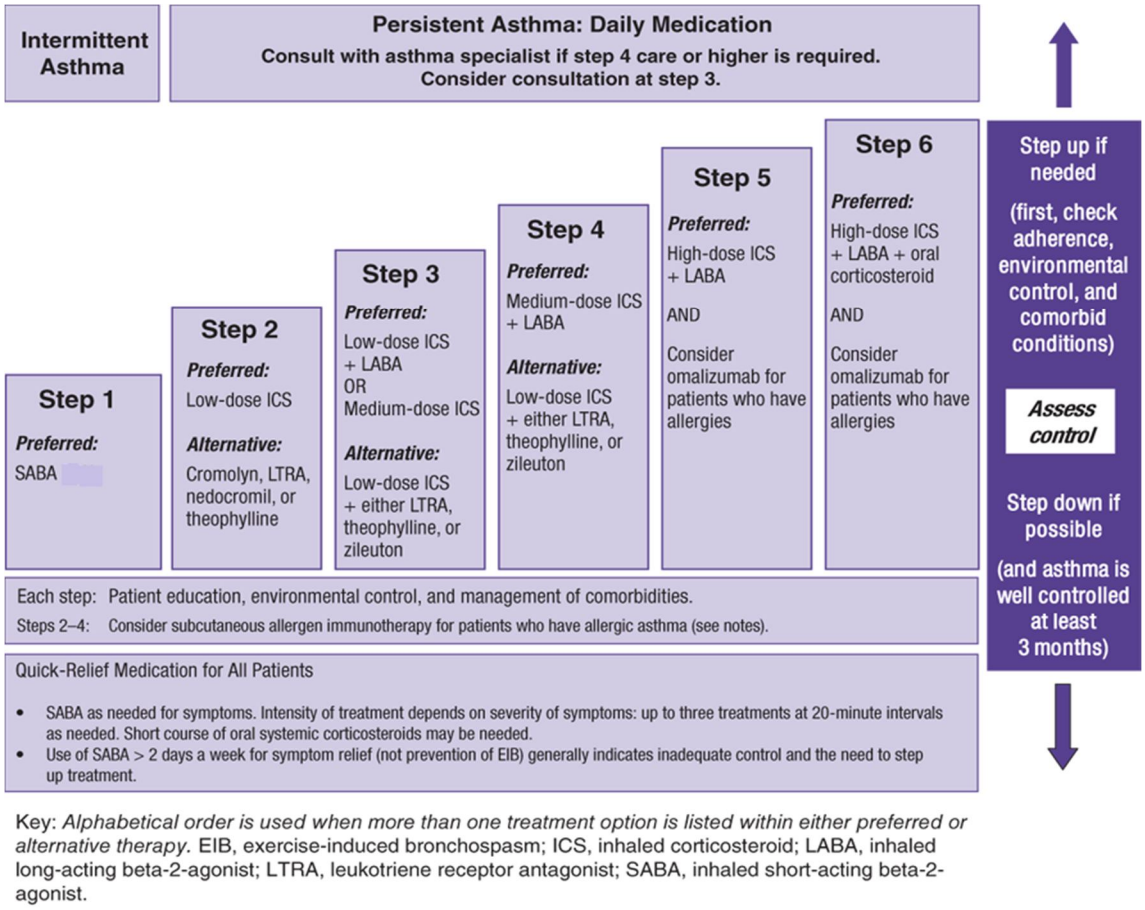
Step 2: Daily symptoms

Step 3: Severe symptoms

Step 4: Severe symptoms uncontrolled with high dose inhaled corticosteroids

Step 5: Severe symptoms and deteriorating [5,22,23]

STEP WISE TREATMENT OF BRONCHIAL ASTHMA



Key: *Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.* EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, inhaled long-acting beta-2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta-2-agonist.

STEP DOWN

Stepping down of treatment is done in patients with stable symptoms and stable peak flow meter readings. This is done by assessing the patient's control every 3 months. Stepping down therapy helps to reduce adverse events and cost of therapy.[1,5,22]

REFRACTORY ASTHMA

Refractory asthma is seen in 5% of patients. These patients remain symptomatic despite the use of maximal dose of inhaled corticosteroids. It is of two types;

- Corticosteroid dependent asthma – These patients require high dose of oral corticosteroids to achieve asthma control.
- Corticosteroid resistant asthma – These are the patients who fail to respond to high dose oral corticosteroids.

Management of these patients is difficult, and it involves checking compliance, inhaler technique, smoking cessation, appropriate treatment of comorbid disease that aggravate asthma, control of exposure to allergens or environmental triggers. Drugs like omalizumab, immunosuppressants can be used in these patients. However, the success of these therapies is not satisfactory.[1,2,22]

VITAMIN D

INTRODUCTION

Vitamin D or Cholecalciferol is a fat-soluble vitamin synthesized in the body from steroids by the action of ultraviolet rays on skin and also present in food. Vitamin D is a prohormone with several active metabolites that acts as hormones.[6]

HISTORY

The first scientific description of Rickets was written in the 17th century by Dr. Daniel Whistler and Prof. Francis Glisson.

Sir Edward Mellanby was the first are to conclude that rickets may be a dietary deficiency.

Prof. Elmer McCollum developed experimental rickets in dogs and cured rickets by treating them with cod liver oil in which vitamin A is removed by oxygenation. And he concluded that this is a new vitamin which he named as vitamin D.

Huldshinsky and Chick et al discovered that children with rickets could be cured by exposure to sunlight or UV light thereby hypothesizing that sunlight or UV light plays a role in vitamin D metabolism.

Vitamin D_2 was the first to be isolated in 1932 by Askew et al; later Windaus and Bock identified vitamin D_3 in 1937.

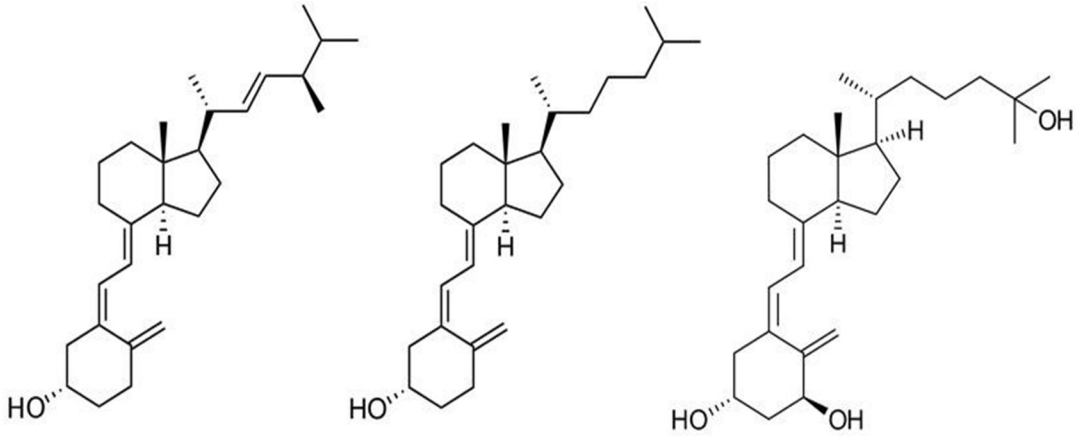
Nicolaysen discovered the role of vitamin D in intestinal calcium absorption. Carlsson and Bauer discovered the role of vitamin D in bones.

Fraser and Kodicek discovered 1, 25 OH D_3 and also conversion of 25 OH D_3 to 1, 25 OH D_3 in kidney.[25]

STRUCTURE

Vitamin D is a secosteroid. Secosteroids are those in which one of the rings are broken. The ring structure of vitamin D is derived from cyclo pentano perhydro phenanthrene ring of steroids.[6]

STRUCTURE OF VITAMIN D2, D3 AND CALCITRIOL



Vitamin D2 (Ergocalciferol) Vitamin D3 (Cholecalciferol) 1,25-dihydroxycholecalciferol (Calcitriol)

SOURCES

Vitamin D occurs in two forms - ergocalciferol (D_2) and cholecalciferol(D_3)

Ergocalciferol is chiefly found in plant sources and fungi.

Cholecalciferol is chiefly found in animal sources like fish liver oil, fish, egg yolk. Cholecalciferol is also synthesized in skin from sunlight.

Cholecalciferol has 10 times greater potency than ergocalciferol due to long half-life ($t_{1/2}$) of cholecalciferol and greater affinity of cholecalciferol for vitamin D receptor.[6,26]

BIOSYNTHESIS OF VITAMIN D

Vitamin D_3 is synthesized in the skin from 7–dehydrocholesterol by the action of ultraviolet rays specifically UVB – 290 to 310 nm.

The source of 7–dehydrocholesterol are the sebaceous glands which secrete 7–dehydrocholesterol uniformly onto the surface. The concentration of 7–dehydrocholesterol varies according to depth from surface with highest concentration in Malphigian layer of skin.

Determinants of vitamin D_3 synthesis in skin are

- Season
- Latitude
- Time spent outdoors
- Skin pigmentation
- Usage of sunscreens
- Skin thickness[6,26]

Vitamin D_3 as such does not have significant biological activity. It must be converted to its metabolically active form by hydroxylation to 1,25 dihydroxy cholecalciferol.[26–28]

This occurs in two steps

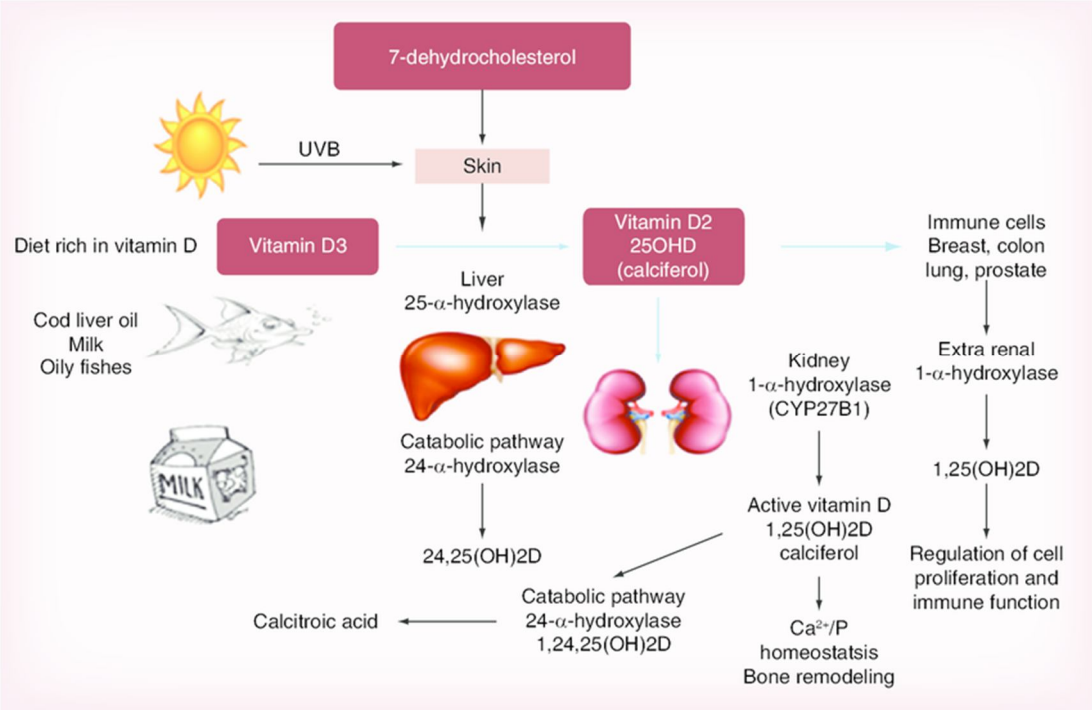
1. 25-Hydroxylation

   Occurs in liver by vitamin D 25 hydroxylase, a cytochrome P450 dependent mixed function oxidase. This $25OHD_3$ is secreted to the plasma. $25OHD_3$ is the major circulating form with $t_{1/2}$ of 19 days.[6,29]

2. 1-hydroxylation

   Occurs in kidney specifically in proximal tubular epithelial cells (mitochondria) with the help of 1 α hydroxylase. This step is highly regulated by negative feedback mechanism. $t_{1/2}$ of $1,25OHD_3$ is 3-5 days.[6,29]

BIOSYNTHESIS OF VITAMIN D

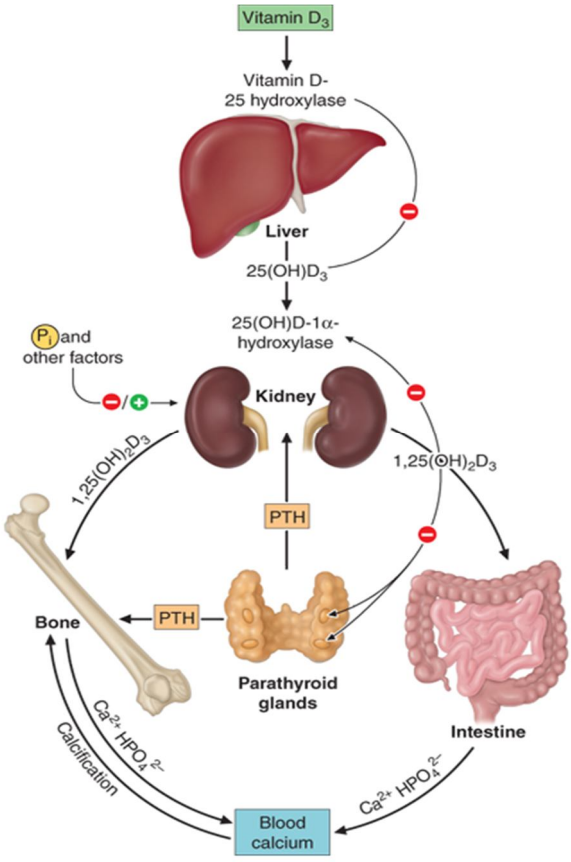


REGULATION OF VITAMIN D SYNTHESIS

Vitamin D synthesis is regulated at the level of 1 α hydroxylase in renal cells. Activity of 1 α hydroxylase is increased when the serum calcium is low, serum phosphate is low, vitamin D levels are low.

High circulating levels of $1,25OHD_3$ decreases the activity 1 α hydroxylase. The major hormone involved in regulating 1 α hydroxylase activity is parathyroid hormone(PTH) which simulates vitamin D synthesis when serum calcium levels are low and suppresses vitamin D synthesis when serum calcium levels are high.[6,27,30]

REGULATION OF VITAMIN D SYNTHESIS



MECHANISM OF ACTION OF CHOLECALCIFEROL

1, 25 OH D_3 is the functionally active form of vitamin D and this active form acts by binding to a specific intracellular receptor-the vitamin D receptor.[6,30]

VITAMIN D RECEPTOR(VDR)

Vitamin D receptor belongs to the steroid family of receptors and it is present in bone, kidney, intestine, as well as in various immune, endocrine, skin cells. This shows that the role of vitamin D is not only limited to calcium homeostasis.

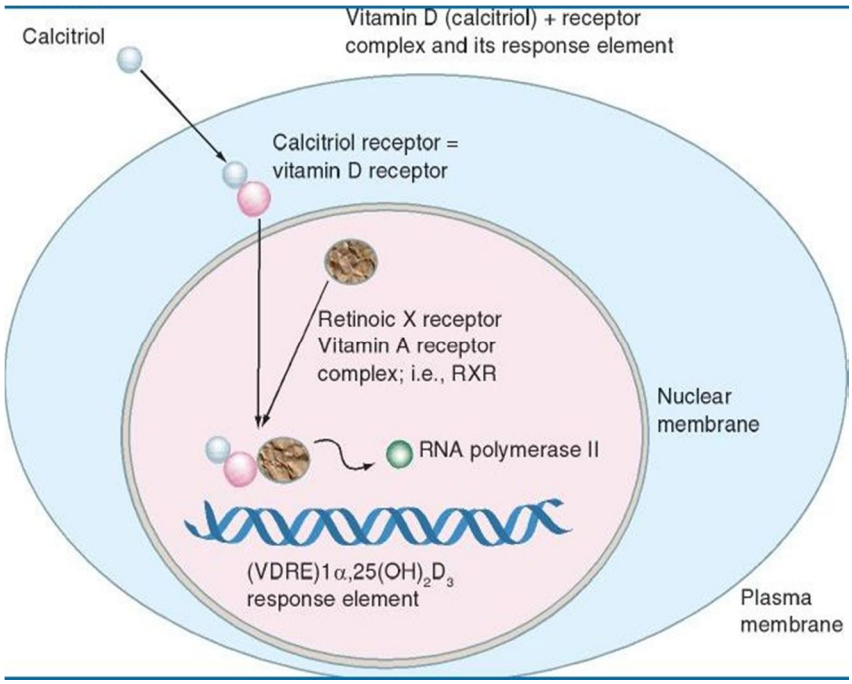
Binding of 1, 25 OHD_3 to VDR leads to its heterodimerization with another intracellular receptor called retinoid X receptor(RXR). This complex translocates to nucleus.

Inside the nucleus, vitamin D receptor complex binds to vitamin D response elements(VDRE) leading to changes in transcription of mRNA. Mostly vitamin D activates transcription however in some cases vitamin D suppresses transcription such as in IL-2(Interleukin-2), IFN(Interferon) gamma.

Various genes regulated by vitamin D are genes involved in mineral homeostasis, cellular metabolism, cell proliferation, cell differentiation, hormonal signalling, oncogenes, vitamin D metabolism.

There is also evidence for some non-genome mediated actions of vitamin D like rapid transport of calcium across intestine, PKC (Protein Kinase C) activation, MAPK (Mitogen Activated Protein Kinase) activation and calcium signalling.[6,27,28,30]

MECHANISM OF ACTION OF VITAMIN D



PHYSIOLOGICAL EFFECTS OF VITAMIN D

INTESTINE

Vitamin D increases the absorption of calcium and phosphate in small intestine by increasing

- Uptake of calcium from intestinal lumen to enterocytes by increasing the expression of calcium binding proteins such as calbindin and calmodulin.
- Translocation of calcium across cell to the basolateral membrane

- Active transport of calcium into circulation by Ca^{2+} ATPase
- Na^{+}/ phosphate cotransporter[6,26,27]

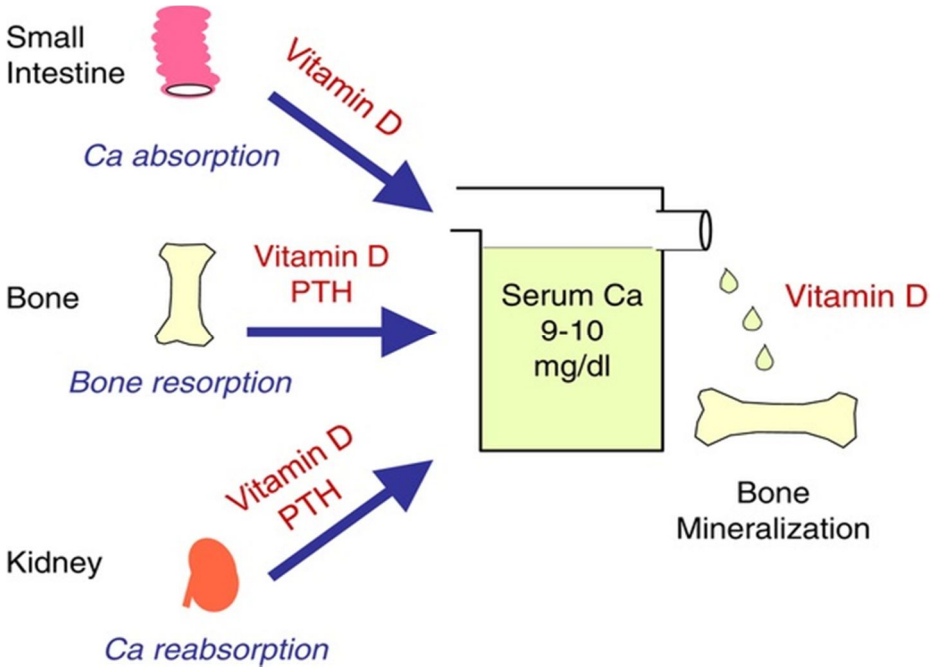
KIDNEY

Vitamin D increases reabsorption of calcium and phosphate by increasing the activity of calbindin, Na^{+}/ phosphate cotransporter[6,26]

BONES

It is the predominant target organ of vitamin D. Vitamin D regulates both bone formation(mineralization) and calcium metabolism(demineralization). Vitamin D acts predominantly on osteoblasts and osteoprogenitor cells. Absence of vitamin D leads to failure of mineralization and excess of demineralization thereby leading to soft and pliable bones.[6,26,27]

EFFECTS OF VITAMIN D



OTHER EFFECTS

PANCREAS-Vitamin D has a positive effect on insulin secretion and is essential for normal pancreatic function

SKIN-Vitamin D regulates keratinocyte proliferation and differentiation

IMMUNE SYSTEM-Vitamin D regulates cytokine production, promotes differentiation of T regulatory cells and promotes phagocytosis. Deficiency of vitamin D is associated with increased inflammation.

SKELETAL MUSCLE-Vitamin D is essential for control of intracellular calcium levels thus affecting the excitability and contractibility of skeletal muscles.

BRAIN-Vitamin D acts like a neurosteroid and plays a role in brain development.[6]

RECOMMENDED DAILY ALLOWANCE OF VITAMIN D[29]

AGE GROUP	VITAMIN D (IU/DAY)
Infants 0 to 12 months	400
Children aged >1 year- adults including pregnant and lactating women	600

No adverse events are seen with vitamin D_3 supplementation up to 10000 IU/day.[31] Most informative indicator of vitamin D status in body is serum $25OHD_3$ levels.

Reference range for serum Vitamin D levels are[6]

25-OH-D3 level ng/ml	Status
<20	Deficient
21-29	Insufficient
≥30	Adequate
>150	Excess

PHARMACOKINETICS

ABSORPTION

Vitamin D is absorbed by non-saturable passive diffusion that is dependent on the presence of bile salts. Absorbed predominantly (90%) into the lymphatic circulation from where it enters the blood.

TRANSPORT

Vitamin D_3 is transported in plasma by binding to vitamin D binding protein or transcalciferin. Vitamin D binding protein is an α-globulin produced by liver and binds 90% of circulating metabolites of vitamin D.

DISTRIBUTION

Vitamin D is distributed evenly among various tissues. Highest concentration is present in adipocytes.

METABOLISM

1, 25 OH D_3 is converted to inactive metabolites such as 1, 24, 25 OH D_3; 1, 26, 25 OH D_3; 1, 25 $(OH)_2$ D_3 23-26 lactone which are then conjugated with gluconic acid or sulfate.

EXCRETION

Inactive metabolites are excreted primarily through bile.[6,31]

FORMULATIONS OF VITAMIN D

Various available formulations of vitamin D are

1. Calciferol (Ergocalciferol, Vitamin D2)
2. Cholecalciferol (Vitamin D3)
3. Calcitriol (1,25 dihydroxy cholecalciferol)
4. Alfacalcidol

It is 1 α-OH cholecalciferol—a prodrug. Alfacalcidiol is rapidly hydroxylated in the liver to 1,25 (OH)2 D3. Therefore, it does not require 1α hydroxylation which takes place in the renal cells. Alfacalcidiol is used in renal bone disease, vitamin D resistant rickets, hypoparathyroidism.

5. Dihydrotachysterol

It is a synthetic analogue of ergocalciferol. However, it is less active than cholecalciferol formulations.[31]

DISEASE STATES

VITAMIN D DEFICIENCY

Deficiency of cholecalciferol leads to rickets in children and osteomalacia in adults.[6,26]

CAUSES OF DEFICIENCY

PRIMARY

Due to inadequate supply of vitamin D because of dietary deficiency or inadequate exposure to sunlight, prolonged exclusive breast feeding (breast milk is a poor source of vitamin D).

SECONDARY

Due to impairment in absorption, metabolism of vitamin D

- Gastro intestinal tract- malabsorption due to small bowel pathology, pancreatitis
- Liver- impaired 25 hydroxylation in patients with chronic liver disease, hepatitis
- Kidney- impaired 1 α hydroxylation in patients with renal failure
- Drugs such as phenobarbitone, phenytoin which induce vitamin D catabolism hypoparathyroidism[6]

Most prominent features of vitamin D deficiency are skeletal and neuromuscular.

RICKETS

Seen in children till the closure of epiphyseal growth plate. Deficiency of vitamin D causes impaired mineralization of bones leading to soft and pliable bones. Clinical features include bone pains, deformities of weight bearing bones like bow legs, knock knees, rickety rosary, pigeon chest, sabre tibia, delayed tooth eruption, muscle tenderness.[6,26]

OSTEOMALACIA

Seen in older children and adults. Deficiency of vitamin D leads to insufficient mineralization of bones which makes them more prone to fractures especially fractures of wrist, pelvis. Other features are muscle weakness, bone pain and tenderness.[6,26]

VITAMIN D TOXICITY

Also called hypervitaminosis

CAUSES: Usually due to overdosing on vitamin D supplements.

Hypervitaminosis leads to hypercalcemia and decrease in serum PTH levels.

Clinical features include anorexia, vomiting, headache, drowsiness, diarrhoea, polyuria, calcinosis, deposition of calcium and phosphate in soft tissues such as heart, kidney, blood vessels.[6,26]

DRUG INTERACTIONS

Bile salts binding resins such as cholestyramine and liquid paraffin decreases the intestinal absorption of vitamin D_3.

Antiepileptics- phenytoin and phenobarbitone increase the conversion of vitamin D_3 to inactive metabolites and also reduce the responsiveness of target tissues to vitamin D_3.[31]

ROLE OF VITAMIN D IN DISEASE STATES

1. IMMUNE SYSTEM

Vitamin D_3 plays a protective role in many auto immune disease such as psoriasis, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, graft rejection, diabetes mellitus.

2. Low serum vitamin D levels is a risk factor for cardiovascular disease
3. Cholecalciferol is also proposed to have anticancer effect especially in colonic, breast, prostate cancer.[6]

ROLE OF VITAMIN D IN BRONCHIAL ASTHMA

Vitamin D influences the course and treatment of bronchial asthma in multiple ways.[32] Vitamin D deficiency is more common in asthmatic patients compared to general population as asthmatic patients tend to spend more time in doors, are less active physically and therefore their exposure to sunlight is less.[33,34]

Multiple studies have shown that low levels of vitamin D are associated with frequent exacerbations, more symptomatic disease, increased airway hyperresponsiveness, increased serum total IgE levels, eosinophilia, requirement of higher doses of corticosteroids, reduced pulmonary function- reduced FEV1, FVC; suboptimal response to corticosteroids, increased exhaled nitric oxide levels and frequent emergency visits. This shows that vitamin D deficiency is associated with severe disease.[7,8,35–51]

Animal studies have shown that vitamin D reduces various features of airway inflammation like cellular infiltration, airway smooth muscle cell mass, goblet cell hyperplasia thereby reducing the features of airway remodelling seen in chronic asthma. Studies have also shown that vitamin D improves corticosteroid responsiveness in animal models of asthma.[38,46,52–54]

In vitro studies have shown that vitamin D inhibits the proliferation of human airway smooth muscle cell by inhibiting the translocation and binding of NFκB, a stimulatory transcription factor and increasing the stability of IκBα, an inhibitor of NFκB activity; vitamin D also reduces the production of interleukins like IL 17,9,5 and IgE.[33,38]

Several genes associated with bronchial asthma appear to be regulated by vitamin D.[33]

Various mechanisms by which vitamin D improves bronchial asthma are

1. Reducing inflammation

Vitamin D reduces airway inflammation by decreasing the production of proinflammatory cytokines like TNF alpha,[10,55] IL 17,5,22[9]; increasing the production of anti-inflammatory cytokines like interleukin 10[7]; inhibiting the activity of NFκB and increasing the activity of IκBα[9]; increasing T regulatory cell activity; inhibiting the differentiation and maturation of mast cells[35]; inhibiting the proliferation and differentiation of lymphocytes[56]. This leads to reduced proliferation of bronchial smooth muscle cells due to down regulation of genes like VEGF, IL 6, fibronectin 1, slowing down of cell cycle thereby leading to more organised structure[7,10], reduced sub epithelial collagen deposition and reduced goblet cell hyperplasia[33]. All these effects result in inhibition of airway remodelling, the key pathologic change seen in chronic asthma[35]. Vitamin D also modulates dendritic cell function by reducing the expression of major histocompatibility complex, costimulatory molecules leading to reduction in downstream lymphocyte responses[33].

2.Improving response to corticosteroids

Vitamin D has a synergistic activity with corticosteroids. Vitamin D also enhances the various effects of corticosteroids like corticosteroid mediated induction of mitogen-activated protein 1, an anti-inflammatory protein. Vitamin D also reduces the expression of FKN, a steroid resistance gene and upregulates the expression of glucocorticoid receptor in various target cells like lymphocytes, eosinophils, bronchial smooth muscle cells[7,10,57].

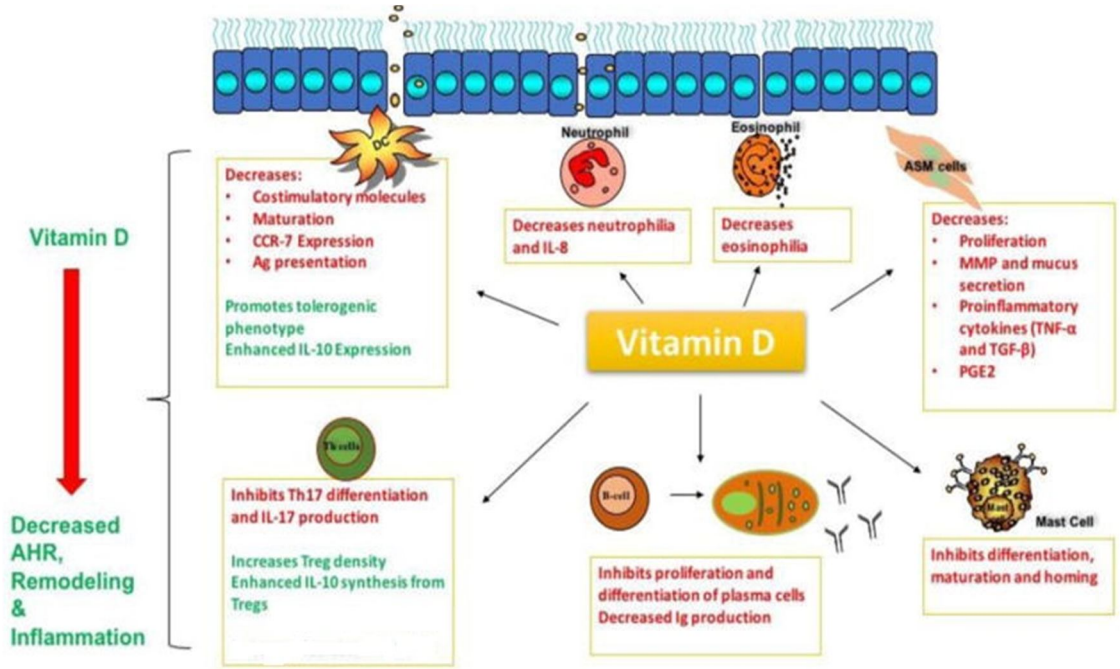
3.Enhancing pulmonary immunity

Vitamin D by improving pulmonary immunity reduces the risk of respiratory infection more specifically viral infections which are one of the most common precipitants of bronchial asthma. Vitamin D improves pulmonary immunity by increasing the levels of cathelicidin, defensin beta 2 which have antibacterial and antiviral activity. Vitamin D also modulates cytokine production in the event of respiratory infections resulting in enhanced pathogen clearance with limited inflammation[10,33].

4.Lung development

Vitamin D plays a role in the normal development of respiratory system. Vitamin D deficiency is associated with altered lung structure and impaired of pulmonary function leading to enhanced susceptibility to bronchial asthma[9].

EFFECTS OF VITAMIN D IN BRONCHIAL ASTHMA



Aim & Objectives

AIM & OBJECTIVES

AIM:

To evaluate the efficacy and tolerability of Cholecalciferol as an add on therapy to standard treatment in modifying disease severity in adult patients with bronchial asthma.

OBJECTIVES:

PRIMARY OBJECTIVES:

To observe the change in severity of bronchial asthma by FEV1 (forced expiratory volume), FVC (Forced Vital Capacity) and PEFR (peak expiratory flow rate).

SECONDARY OBJECTIVES:

- To assess the number of exacerbations
- To assess asthma control by asthma control questionnaire
- To observe for any adverse effect with study drug

Methodology

METHODOLOGY

METHODOLOGY

This prospective study was done to assess the therapeutic effect of Cholecalciferol in improving pulmonary function in bronchial asthma.

STUDY DESIGN:

This study was a randomized, open label, prospective, parallel group, comparative study.

STUDY CENTRE:

Institute of Pharmacology in collaboration with Institute of Thoracic Medicine, Rajiv Gandhi Government General Hospital, Chennai.

STUDY PERIOD:

The study was carried out from June 2017 to March 2018.

STUDY DURATION:

Treatment period of 12 weeks and Post treatment follow up period of 4 weeks per patient.

SAMPLE SIZE:

- N (No of participants in each group) = $2\sigma^2[Z(\alpha/2) + Z(\beta)]^2/\Delta^2$ [58]
- Taking α=0.05, β=80% we get $Z(\alpha/2)$ =1.96, $Z\beta$ =0.842
- σ (Standard deviation) =6.58, Δ (Difference between study groups) =5%
- We get N= 27.15, adding 10% loss to follow up we get N=30.
- Sample size=60 (Control group - 30, Study group - 30).

STUDY POPULATION:

Adult patients with bronchial asthma with mild to moderate severity attending Thoracic Medicine OPD, RGGGH, Chennai.

INCLUSION CRITERIA:

1) Both genders.
2) Age- 25 - 70 yrs.
3) Patients with bronchial asthma on inhaled corticosteroids with FEV1 >60%.
4) Patients willing to give written informed consent.

EXCLUSION CRITERIA:

1) Pregnant and lactating women.
2) Patients with evidence of clinically significant gastrointestinal, renal, respiratory, haematological, endocrinological, neurological, psychiatric or cardiovascular dysfunctions.
3) Current smokers
4) Patients already on vitamin D, calcium supplementations
5) H/o intolerance to cholecalciferol.
6) Patients taking drugs like beta blockers, non-steroidal anti-inflammatory drugs etc which are known to exacerbate bronchial asthma.
7) Patient enrolled in any other study.

STUDY PROCEDURE:

The study was conducted after obtaining the approval from the Institutional Ethics Committee, Madras Medical College and it is done in accordance with the Declaration of Helsinki & Good Clinical Practice (GCP) guidelines.

Patients diagnosed with mild to moderate bronchial asthma attending the Outpatient department of Thoracic medicine, Rajiv Gandhi Government General Hospital, were explained about the study purpose, procedure and benefits of the study. Information sheet and informed consent forms written in the regional language were provided to each patient. After obtaining written informed consent in patient's own language, the study was carried out.

SCREENING

The demographic details of the patients were recorded. The subjects were screened by complete medical history, clinical examination and laboratory investigations.

RECRUITMENT

After screening those who fulfilled the inclusion and exclusion criteria were enrolled in the study.

RANDOMIZATION:

The enrolled patients were randomized by simple randomization into either control group or study group and received the respective therapy.

TREATMENT PLAN

STANDARD TREATMENT

- MDI containing Budesonide 200 mcg and Formoterol 6 mcg bid

CONTROL GROUP

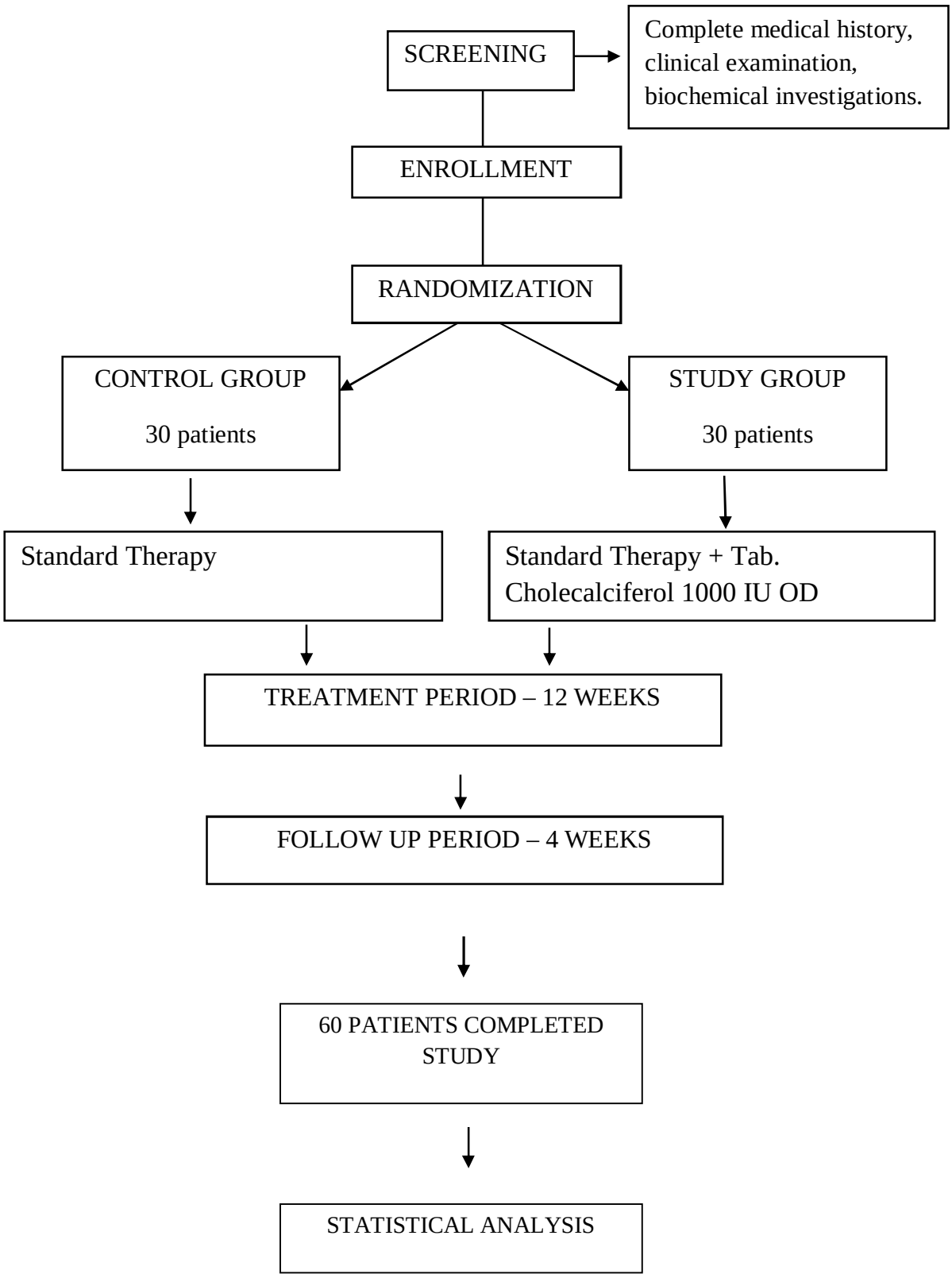
- Standard treatment

TEST GROUP

- Standard treatment + Tablet cholecalciferol 1000 IU/day for 12 weeks.

The study medication was issued for 2 weeks. After assessing the compliance at the end of 2 weeks, study medication was issued for the subsequent 2 weeks. The same procedure was followed till the completion of study.

STUDY FLOW CHART



INVESTIGATIONS:

Baseline investigations:

- Complete blood count- Hb, TC, DC, ESR, Eosinophil count
- Renal function test
- Random blood sugar
- Routine urine analysis
- Vitamin D levels

All the baseline investigations were done at screening and at the end of 12th week of the study.

Pulmonary function tests – FEV1, FVC, PEFR were done at baseline, 6th and 12thweek.

STUDY VISITS

SCREENING/ BASELINE VISIT:

- Written informed consent obtained.
- Demographic details obtained.
- Medical history taken and recorded.
- Vital signs recorded.
- General, Systemic examination done.
- Laboratory investigations
  - Complete blood count- Hb, TC, DC, ESR, Eosinophil count
  - Renal function test
  - Random blood sugar

- Routine urine analysis
- Vitamin D levels
- Pulmonary function tests – FEV1, FVC, PEFR done

VISIT 1 (Baseline):

- Investigation reports collected.
- Randomization done.
- Vital signs recorded.
- Pulmonary function tests done.
- Study drugs were issued for 2 weeks to respective groups.
- Instructed to return the empty strips during subsequent visit.
- Patients were instructed to report if any adverse events occur.

VISIT 2 (end of 2 weeks)

- Vital signs recorded.
- General, Systemic examination done.
- Patients were asked to return empty strips to check compliance.
- Adverse events monitored.
- Study medication issued for subsequent 2 weeks.

VISIT 3 (end of 4 weeks)

- Vital signs recorded.
- General, Systemic examination done.
- Patients were asked to return empty strips to check compliance.

- Adverse events monitored.
- Study medication issued for subsequent 2 weeks.

VISIT 4 (end of 6 weeks)

- Vital signs recorded.
- General, Systemic examination done.
- Pulmonary function tests done.
- Patients were asked to return empty strips to check compliance.
- Adverse events monitored.
- Study medication issued for subsequent 2 weeks.

VISIT 5 (end of 8 weeks)

- Vital signs recorded.
- General, Systemic examination done.
- Patients were asked to return empty strips to check compliance.
- Adverse events monitored.
- Study medication issued for subsequent 2 weeks.

VISIT 6 (end of 10 weeks)

- Vital signs recorded.
- General, Systemic examination done.
- Patients were asked to return empty strips to check compliance.
- Adverse events monitored.
- Study medication issued for subsequent 2 weeks.

VISIT 7 (end of 12 weeks)

- Vital signs recorded.
- General, Systemic examination done.
- Pulmonary function tests done.
- Patients were asked to return empty strips to check compliance.
- Adverse events monitored.

VISIT 8 (end of 16 weeks)

- Vital signs recorded.
- General, Systemic examination done.
- Adverse events monitored.

ASSESSMENT

Pulmonary function tests

- FEV1-
- FVC
- PEFR

INSTRUCTIONS TO PATIENTS

Patients were instructed clearly regarding the regular intake of the medicines. They were advised to report to the OPD for assessment and for receiving the drugs. They were counselled to report if any adverse reaction occurs.

COMPLIANCE

Patient compliance was monitored by daily drug reminder chart.

FOLLOW UP:

The patients were further followed up for a post treatment period of 4 weeks. After the completion of 16 weeks of study period, the patients were provided appropriate care at Institute of Thoracic medicine, Rajiv Gandhi Government General Hospital, Chennai.

ADVERSE EVENTS:

Any adverse event reported by the patient or observed by the investigator during the study was recorded. The onset of adverse event, causal relationship to the study drug and action taken was recorded. Appropriate medical care was provided.

WITHDRAWAL:

During the study period the subject was allowed to withdraw his/her voluntary consent and opt out of study. Similarly, at the discretion of the investigator, the subjects were withdrawn from the study if any serious adverse event was reported by the patient or observed by the investigator.

STATISTICAL ANALYSIS:

The obtained data was analysed statistically.

Distribution of age was analysed using student's t-test and sex distribution was analysed by Pearson chi- square test.

The biochemical investigations were performed at baseline and at the end of 12 weeks. The differences within the groups before and after treatment were analysed using student's paired t- test.

The difference within the groups in FEV 1, FVC, PEFR was analysed using students paired t-test. Similarly, the difference between the control and test groups was analysed using independent t test.

Statistical analysis was done by using SPSS software version 21. p value <0.05 was considered to be statistically significant.

Results

RESULTS

This study was conducted to evaluate the efficacy and safety of Cholecalciferol as an add on therapy to standard treatment in adult patients with bronchial asthma.

- 107 patients were screened.
- 41 patients were excluded from the study based on exclusion criteria.
- 6 patients who were eligible were not willing to participate in the study.
- 60 patients were enrolled in this study.
- All the enrolled patients completed the study.
- There were no drop outs.

TABLE 1: AGE DISTRIBUTION

AGE IN YEARS	CONTROL GROUP		STUDY GROUP	
	NO	PERCENTAGE	NO	PERCENTAGE
25-40	11	36.66%	10	33.33%
41-55	14	46.66%	15	50%
56-70	5	16.66%	5	16.66%
TOTAL	30	100%	30	100%

Table 1 shows age distribution of both the groups.

Age group 41-55 years had most number of patients in both the groups followed by age group 25-40 years.

FIGURE 1: AGE DISTRIBUTION

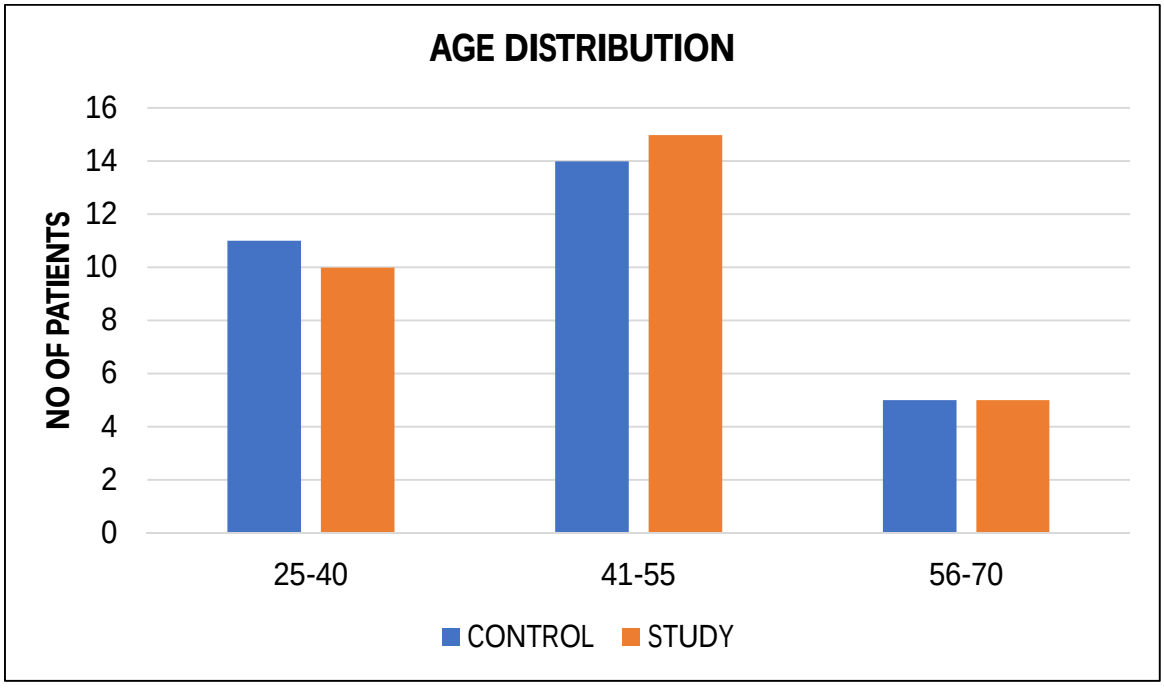


Figure 1 is the graphical representation of table 1.

TABLE 2: MEAN AGE DISTRIBUTION

GROUP	NO OF PATIENTS	MEAN AGE in years	SD
CONTROL	30	43.85	10.10
STUDY	30	44.96	9.32
p Value	0.6599		

Table 2 shows the mean age distribution of both the groups.

Mean age was similar in both the groups.

There were no statistically significant differences between the groups.

FIGURE 2: MEAN AGE DISTRIBUTION

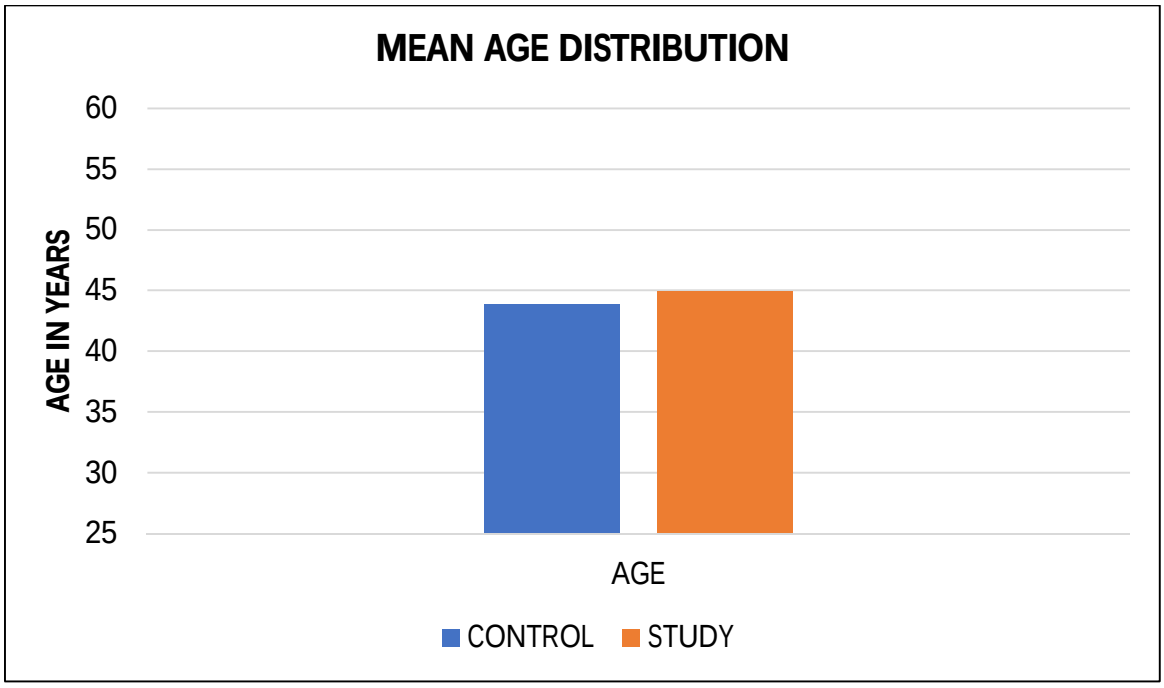


Figure 2 is the graphical representation of Table 2.

TABLE 3: SEX DISTRIBUTION

	CONTROL GROUP		STUDY GROUP	
	NO OF PATIENTS	PERCENTAGE	NO OF PATIENTS	PERCENTAGE
MALE	17	56.66	14	46.66
FEMALE	13	43.33	16	53.33
TOTAL	30	100	30	100
p VALUE	0.4383			

Table 3 shows the sex distribution in both the groups.

Control group had 56.6% males and 43.3% females while study group had 46.6% males and 53.3% females. There was no significant difference in male and female distribution in both the groups (p value=0.4383).

FIGURE 3: SEX DISTRIBUTION

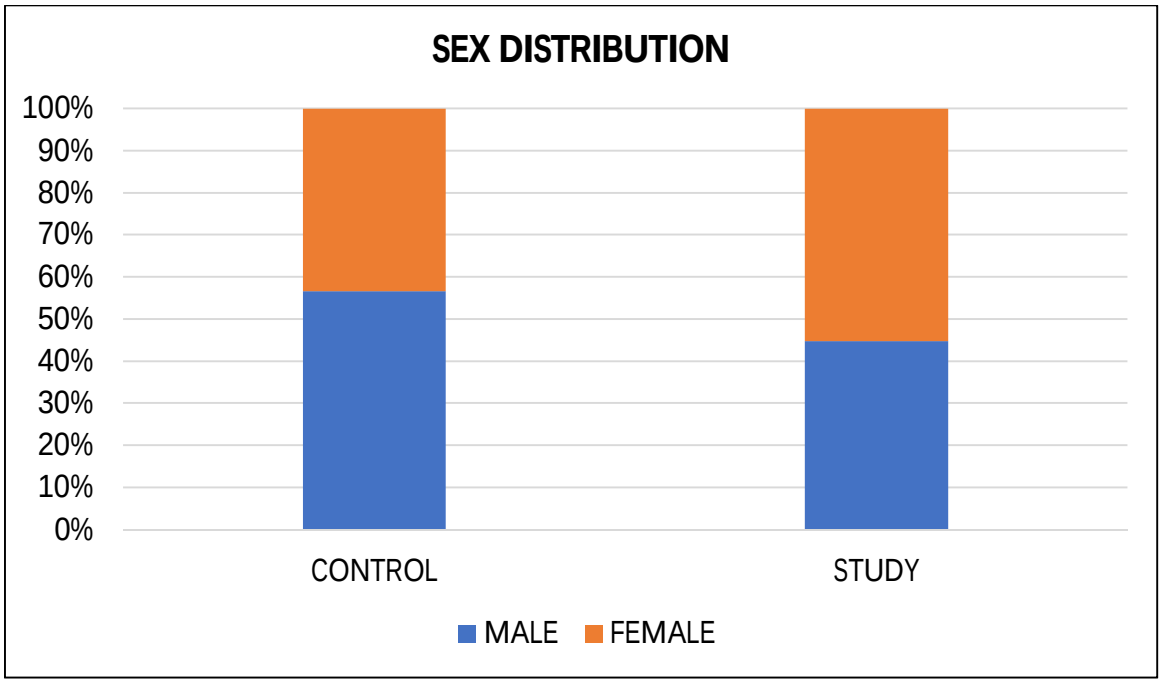


Figure 3 is the graphical representation of Table 3.

TABLE 4: MEAN DURATION OF ILLNESS

GROUP	MEAN DURATION OF ILLNESS (IN YEARS)
CONTROL	9
STUDY	8.33

Table 4 shows the mean duration of asthma in control and study group.

FIGURE 4: MEAN DURATION OF ILLNESS

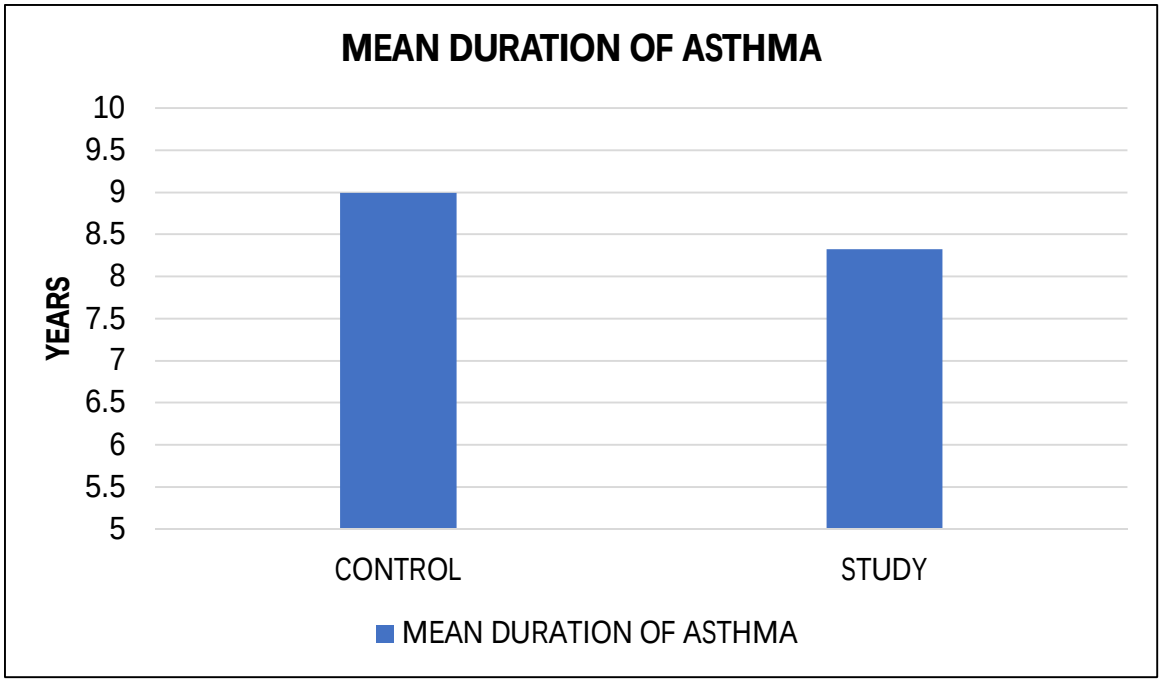


Figure 4 is the graphical representation of Table 4.

TABLE 5: Forced Expiratory Volume in 1 second (FEV 1)

GROUP	BASELINE MEAN±SD	6 WEEKS MEAN±SD	12 WEEKS MEAN±SD	p Value
CONTROL	62.94±1.66	66.05±2.67	70.25±2.24	0.0001
STUDY	63.60±2.05	67.17±2.75	72.44±1.97	0.0001
p Value	0.1815	0.1149	0.0109	

Table 5 shows the improvement in percentage predicted Forced Expiratory Volume in 1 second(FEV_1) in control and study group.

Within group analysis showed significant improvement in FEV_1 in both groups at 12 weeks compared to baseline (p value=0.0001).

Between the groups analysis showed a significant difference at the end of 12 weeks p value=0.0109.

FIGURE 5: Forced Expiratory Volume in 1 second (FEV 1)

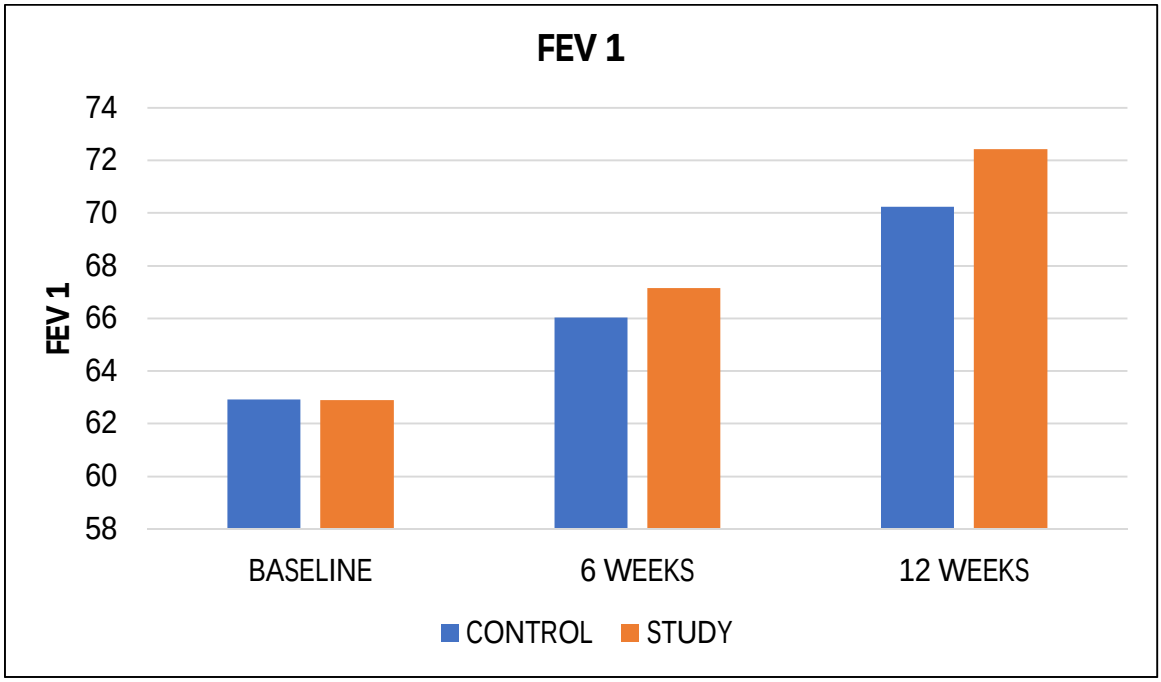


Figure 5 is the graphical representation of Table 5.

TABLE 6: Forced Vital Capacity (FVC)

GROUP	BASELINE MEAN±SD	6 WEEKS MEAN±SD	12 WEEKS MEAN±SD	p Value
CONTROL	63.87±1.68	67.16±1.96	69.27±1.83	0.0001
STUDY	64.35±2.04	68.11±2.22	71.34±3.97	0.0001
p value	0.3339	0.0842	0.0120	

Table 6 shows the improvement in percentage predicted Forced Vital Capacity(FVC) in control and study group.

Within group analysis showed significant improvement in FVC in both groups at 12 weeks compared to baseline (p value=0.0001).

Between the groups analysis showed a significant difference at the end of 12 weeks p value=0.0120.

FIGURE 6: Forced Vital Capacity (FVC)

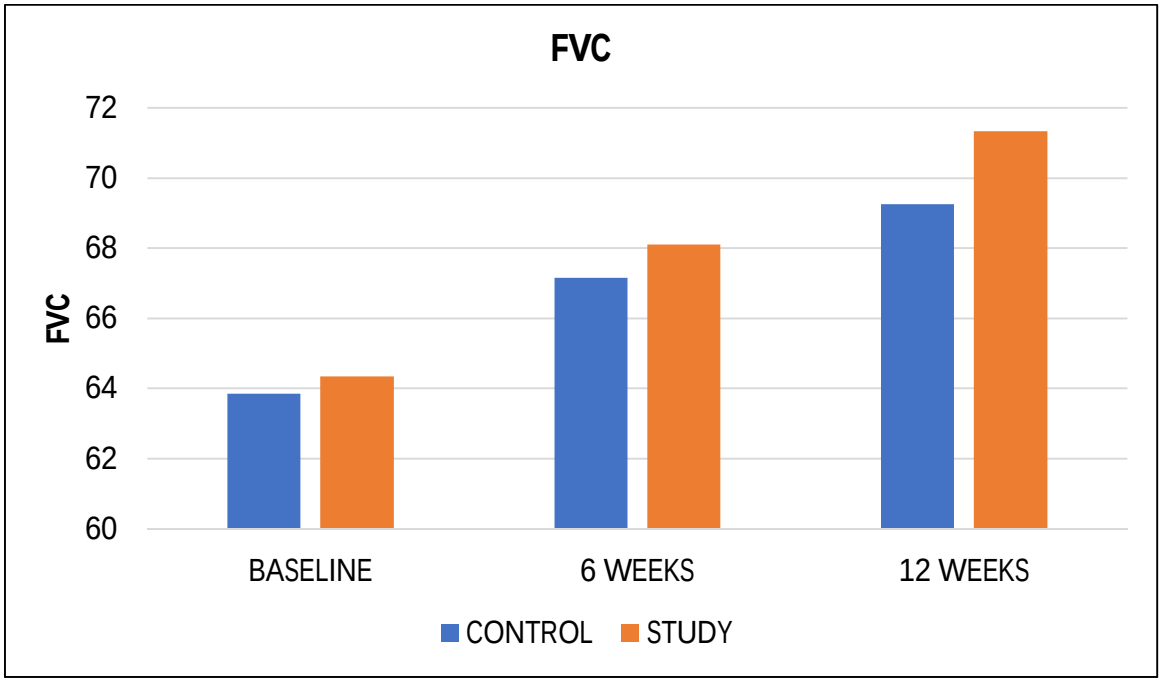


Figure 6 is the graphical representation of Table 6.

TABLE 7: Peak Expiratory Flow Rate (PEFR)

GROUP	BASELINE MEAN±SD	6 WEEKS MEAN±SD	12 WEEKS MEAN±SD	p Value
CONTROL	65.66±1.80	69.21±1.7	73.45±2.44	0.0001
STUDY	66.10±1.73	70.40±3.33	75.16±3.14	0.0001
p Value	0.3381	0.0866	0.0219	

Table 7 shows the improvement in percentage predicted Peak Expiratory Flow Rate(PEFR) in control and study group.

Within group analysis showed significant improvement in PEFR in both groups at 12 weeks compared to baseline (p value=0.0001).

Between the groups analysis showed a significant difference at the end of 12 weeks p value=0.0219.

FIGURE 7: Peak Expiratory Flow Rate (PEFR)

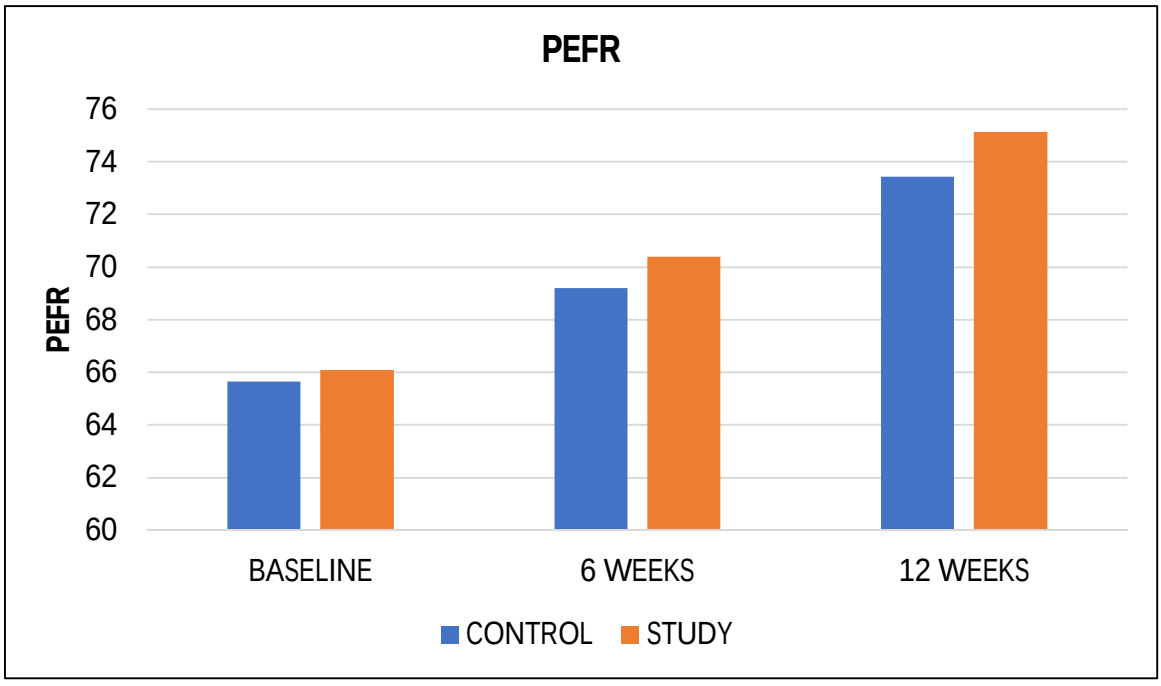


Figure 7 is the graphical representation of Table 7.

TABLE 8: Asthma Control Questionnaire Score

GROUP	BASELINE MEAN±SD	12 WEEKS MEAN±SD	p Value
CONTROL	2.25±1.21	4.99±1.29	0.0001
STUDY	2.48±1.23	5.24±1.01	0.0001
p Value	0.4812	0.3975	

Table 8 shows the Asthma Control Questionnaire score in control and study group.

FIGURE 8: ACQ

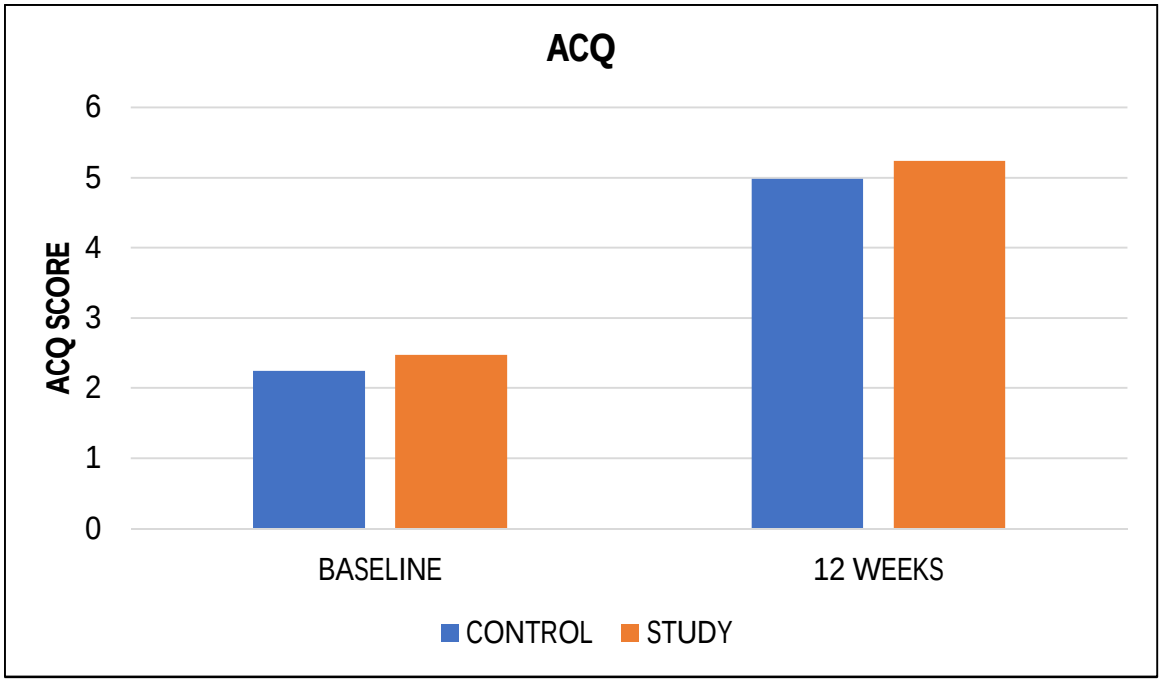


Figure 8 is the graphical representation of Table 8.

TABLE 9: NUMBER OF EXACERBATIONS

	CONTROL GROUP	STUDY GROUP
NO OF EXACERBATIONS	7(23.33%)	3(10%)

Table 9 shows the number of exacerbations in patients of both the groups.

7 patients had exacerbations in control group and 3 patients had exacerbations in study group.

FIGURE 9: NUMBER OF EXACERBATIONS

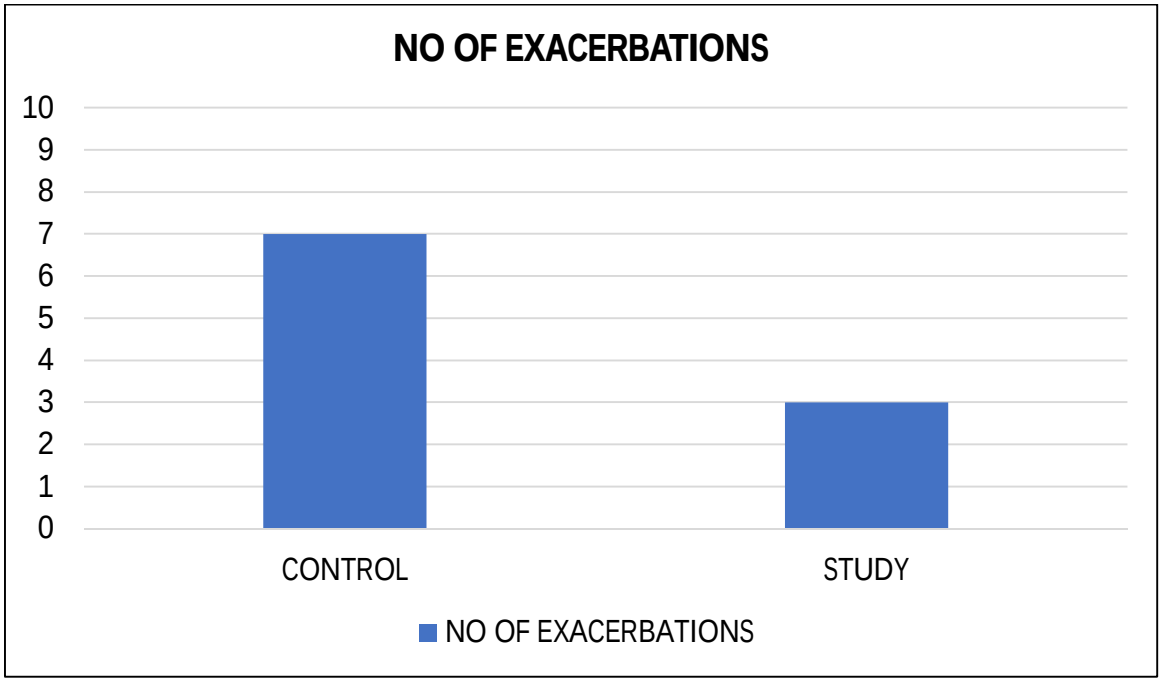


Figure 9 is the graphical representation of Table 9.

BIOCHEMICAL INVESTIGATIONS

TABLE 10: CONTROL GROUP

INVESTIGATION	BASELINE	12 WEEKS	p VALUE
RANDOM BLOOD SUGAR	98.87±9.68	96.67±9.94	0.7948
UREA	27.33±4.05	26.1±3.9	0.2602
CREATININE	0.89±0.2	0.92±0.21	0.5609
ABSOLUTE EOSINOPHIL COUNT	401±49.62	380.63±50.55	0.1226

Table 10 shows the biochemical parameters of control group.

Statistical analysis within the group did not show any significant difference in random blood sugar, urea, creatinine and absolute eosinophil count.

TABLE 11: STUDY GROUP

INVESTIGATION	BASELINE	12 WEEKS	p VALUE
RANDOM BLOOD SUGAR	97.03±9.81	98.83±9.91	0.5380
UREA	26.5±4.44	25.07±3.69	0.1586
CREATININE	0.94±0.3	0.85±0.25	0.2017
ABSOLUTE EOSINOPHIL COUNT	402.91±48.73	385.57±46.99	0.1631

Table 11 shows the biochemical parameters of study group.

Statistical analysis within the group did not show any significant difference in random blood sugar, urea, creatinine and absolute eosinophil count.

TABLE 12: SERUM VITAMIN D

GROUP	BASELINE	12 WEEKS	p Value
CONTROL	22.83±4.79	24.63±6.41	0.1563
STUDY	25.27±4.91	55.97±20.41	0.0001

Table 12 shows serum vitamin D levels in control and test group.

Study group showed a statistically significant improvement in serum vitamin D levels at 12 weeks compared to control group.

TABLE 13: INCIDENCE OF ADVERSE DRUG REACTIONS

	CONTROL GROUP	STUDY GROUP
NO OF ADRs	16(53.33%)	14(46.66%)

Table 13 shows the incidence of ADRs in patients of both the groups.

16 ADRs were reported in control group and 14 ADR were reported in study group.

FIGURE 10: INCIDENCE OF ADVERSE DRUG REACTIONS

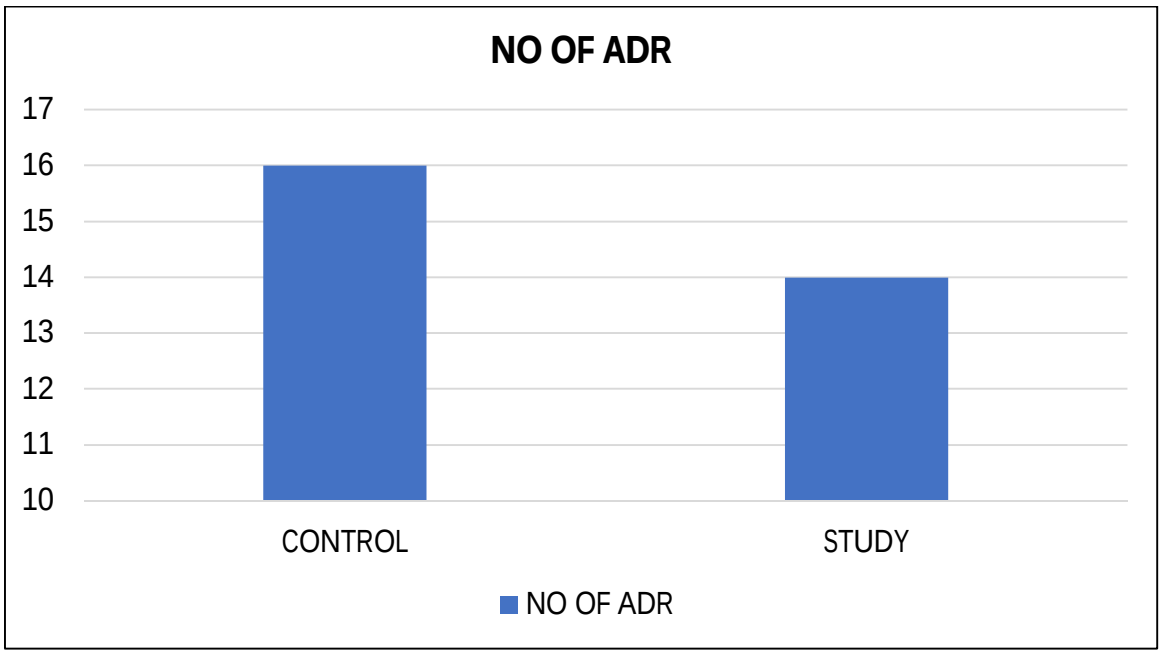


Figure 10 is the graphical representation of Table 13.

TABLE 14: ADVERSE DRUG REACTIONS MONITORING

ADR	CONTROL GROUP	STUDY GROUP
TREMOR	2	3
INSOMNIA	1	2
NAUSEA	-	2
GASTRITIS	4	1
PALPITATION	2	2
SLEEP DISTURBANCE	2	1
ORAL CANDIDIASIS	3	1
MYALGIA	2	2

Table 14 shows the adverse effect profile of both the groups.

Adverse effects were reported more in control group than in study group. Tremor and gastritis were the most common ADRs.

FIGURE 11: ADVERSE DRUG REACTIONS MONITORING

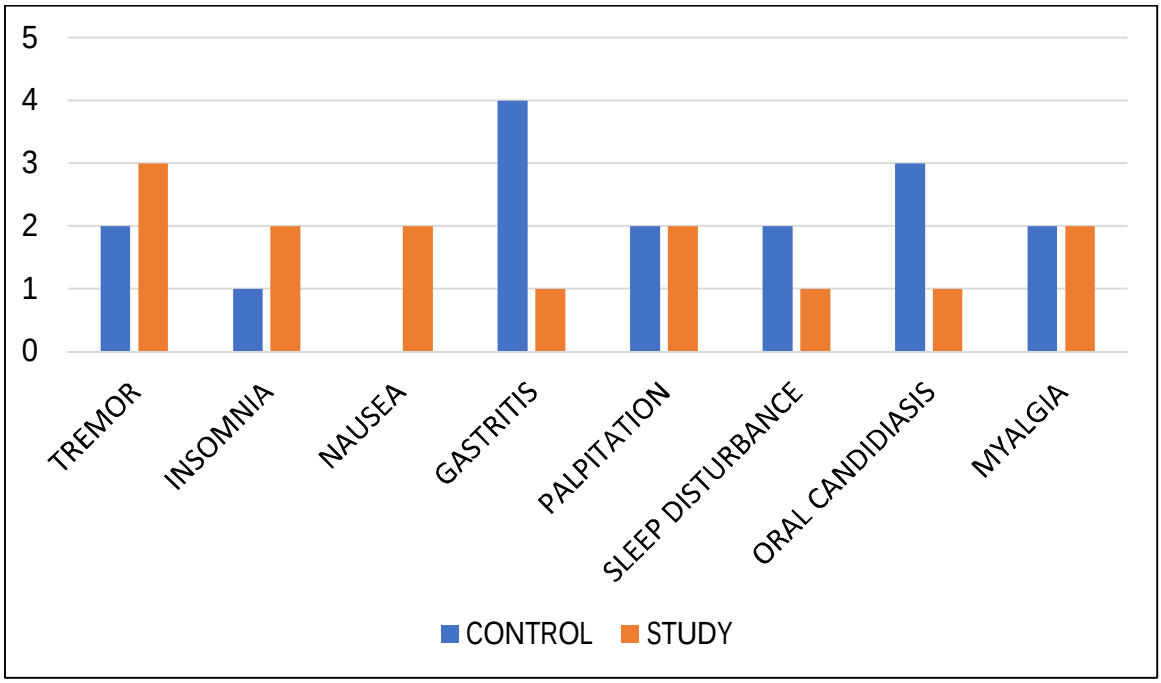


Figure 11 is the graphical representation of Table 14.

TABLE 15: CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS- CONTROL GROUP

ADR	Certain	Probable	Possible	Un-likely	Un-classified	Un-classifiable
TREMOR			2			
INSOMNIA			1			
NAUSEA			-			
GASTRITIS			4			
PALPITATION			2			
SLEEP DISTURBANCE			2			
ORAL CANDIDIASIS			3			
MYALGIA			2			

Table 15 shows causality assessment of individual ADR in control group.

Causality assessment was done using WHO-UMC causality assessment scale.

ADRs were categorized as possible.

TABLE 16: CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS-STUDY GROUP

ADR	Certain	Probable	Possible	Un-likely	Un-classified	Un-classifiable
TREMOR			3			
INSOMNIA			2			
NAUSEA			2			
GASTRITIS			1			
PALPITATION			2			
SLEEP DISTURBANCE			1			
ORAL CANDIDIASIS			1			
MYALGIA			2			

Table 16 shows causality assessment of individual ADR in control group.

Causality assessment was done using WHO-UMC causality assessment scale.

ADRs were categorized as possible.

TABLE 17: SEVERITY ASSESSMENT OF ADVERSE DRUG REACTIONS BY MODIFIED HARTWIG SIEGEL SCALE

SEVERITY	CONTROL GROUP	STUDY GROUP
MILD	16	14
MODERATE	-	-
SEVERE	-	-

Table 17 shows severity assessment of ADR by modified Hartwig Siegel scale.

All the ADR in control and study group were mild in severity.

Discussion

DISCUSSION

Bronchial asthma is a chronic inflammatory disease of the airways characterized by episodic airflow obstruction and airway hyperresponsiveness. Asthma is a heterogenous clinical syndrome with wide variability in pathologic, clinical and physiologic parameters among different patients.[2]

Asthma is a highly prevalent disease affecting nearly 300 million people worldwide. The recent rising trend in prevalence of asthma in India is attributed to various factors like industrialization, air pollution, life style changes, etc. Asthma is a disease with severe morbidity affecting the patient's day to day activities in multiple ways, however death due to asthma is rather uncommon.[1]

The pathogenesis of Bronchial asthma shows an interplay between various environmental and endogenous factors which act as risk factors, precipitants of asthma such as atopy, genetic predisposition, respiratory infections, airway irritants, drugs, smoking, etc.[1,2]

The pathogenesis of asthma is very complex and involves a variety of cells and numerous mediators such as cytokines, chemokines, leukotrienes, prostanoids, etc which serve to initiate, perpetuate and coordinate the multiple processes seen in the inflammation. Inflammation in the airways is the major pathologic abnormality seen in asthma and is also responsible for the airway dysfunction.[2,3]

The repeated cycles of inflammation lead to chronic inflammation of the airways characterized by epithelial damage, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, mucous gland hyperplasia which impair the normal respiratory function.[3]

Asthmatic patients commonly present with symptoms of breathlessness, chest tightness, cough, sputum production. Pulmonary function tests help in the diagnosis as well as monitoring patient's response to treatment.[5]

Management of bronchial asthma involves assessing and monitoring asthma severity and control, patient education, control of environmental factors that influence asthma and use of pharmacologic agents.[5]

Various pharmacological agents used to treat bronchial asthma are classified into two major types- bronchodilators and anti-inflammatory agents. Bronchodilators include beta 2 agonists, anticholinergics and methylxanthines. These are mainly used as reliever (rescue) medications. These agents act principally by relaxation of bronchial smooth muscle and thereby reversing the airflow obstruction. Anti-inflammatory agents include corticosteroids, leukotriene antagonists and anti IgE therapy. These are mainly used as chronic controllers. These agents reduce airway inflammation and helps to maintain control over asthma. However, the chronic use of corticosteroids which forms the backbone of asthma pharmacotherapy is associated with various adverse effects both locally and systemically like dysphonia, oral candidiasis, weight gain, osteoporosis, hypertension, etc and there is a variability in patient's response to

corticosteroids.[29] Therefore, there is a dire need for newer agents that reduce airway inflammation and improve long term control over asthma.

Cholecalciferol or vitamin D is a fat-soluble vitamin synthesized from 7-dehydrocholesterol in the skin by the action of UV-B rays from sun. However, cholecalciferol is not active as such and it is converted to its metabolically active form 1,25 dihydroxy cholecalciferol in kidney.[6]

In various target cells, 1,25 dihydroxy cholecalciferol binds to vitamin D receptor and the vitamin D receptor complex binds to specific DNA sequences resulting in changes in transcription of various genes and thereby leading to various changes in cellular function. In addition to its well-established role in calcium and phosphate homeostasis, bone modelling and remodelling, cholecalciferol also has a role in immune system, skin, skeletal muscles, etc.[6]

Several studies have shown a beneficial role of vitamin D in bronchial asthma. Vitamin D deficiency is more common in asthmatics compared to general population. Low level of vitamin D has multiple deleterious effects on bronchial asthma like frequent exacerbations; increased airway hyperresponsiveness; reduction FEV_1, FVC and increased requirement of corticosteroids.[7,8,35,38]

Vitamin D improves long term control over bronchial asthma by reducing the production of proinflammatory cytokines, increasing the production of anti-inflammatory cytokines, inhibiting proliferation and differentiation of various cells involved in asthma, inhibiting proliferation of airway smooth muscle cells,

enhancing the anti-inflammatory actions of corticosteroids, improving pulmonary immune function. Thus, vitamin D by its anti-inflammatory actions inhibits chronic inflammation and airway remodelling thereby resulting in improved control over bronchial asthma.[7,9-10,33,35-56]

In this study 107 patients were screened, and 60 patients who fulfilled the eligibility criteria were enrolled. They were randomised into control and study group of 30 patients each. The patients in the control group received standard treatment comprising formoterol and budesonide MDI and study group received tablet cholecalciferol 1000 IU/day in addition to standard treatment for 12 weeks.

The mean age in the control and study group was 43.85 years and 44.96 years respectively. There was no significant difference in the number of male and female participants between the groups.

At the end of 12 weeks FEV_1 showed a significant improvement in control group by 11.6% and in study group by 13.9%. On comparing both the groups there was a statistically significant improvement in the study group compared to the control group with p value of 0.0109.

FVC showed a significant improvement of 8.45% in control group and 10.86% in study group at the end of 12 weeks study period. On comparing there was a statistically significant improvement in the study group compared to the control group with p value of 0.0120.

At the end of 12 weeks PEFR showed a significant improvement by 11.86% in control group and 13.70% in study group. Between the groups analysis showed a statistically significant improvement in the study group compared to the control group with p value of 0.0219.

Number of exacerbations in the study period were 3 in study group compared to 7 in control group. Asthma Control Questionnaire scores showed a significant improvement of 2.74 points and 2.76 points at the end of 12 weeks in control and study group respectively.

Serum vitamin D levels showed a significant improvement in study group by 1.2 times compared to 0.08 times in control group. This is statistically significant improvement with p value of 0.001.

The is consistent with previous studies done by Yadav et al, Arshi et al, Nageswari et al.[35,50,51]

Assessment of asthma control using asthma control questionnaire showed a significant improvement at the end of 12 weeks in both the groups.

Addition of cholecalciferol did not affect blood pressure and other biochemical parameters like urea, creatinine, RBS.

The incidence of adverse effects was 46.6% in the study group and 53.3% in the control group. Tremor and headache were the commonest adverse event.

The number of adverse events were less in patients receiving cholecalciferol compared to patients receiving standard therapy. All the adverse drug reactions were categorized as possible under WHO-UMC causality assessment scale. According to modified Hartwig and Siegel severity assessment scale all the reactions reported were mild. This shows that cholecalciferol did not increase the occurrence of adverse events.

As evidenced by earlier studies, this study has also showed that addition of cholecalciferol to standard therapy significantly improved long term control over asthma.

Conclusion

CONCLUSION

From our study, we conclude that in patients with bronchial asthma

1. Cholecalciferol as an add on therapy is effective in improving FEV_1, FVC and PEFR thereby Cholecalciferol improves long term control over asthma.
2. Dose escalation of corticosteroids was not required.
3. Cholecalciferol was well tolerated.

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Appendices

APPENDIX-1

LIST OF ABBREVIATIONS

ACQ	-	Asthma Control Questionnaire
ACT	-	Asthma Control Test
AD	-	Anno Domini
ADR	-	Adverse Drug Reaction
AHR	-	Airway Hyper-responsiveness
AMP	-	Adenosine Mono Phosphate
ATAQ	-	Asthma Therapy Assessment Questionnaire
DC	-	Differential Count
DNA	-	Deoxyribo Nucleic Acid
ECG	-	Electrocardiogram
ESR	-	Erythrocyte Sedimentation Rate
FEV1	-	Forced Expiratory Volume in one second
FGF	-	Fibroblast Growth Factor
FVC	-	Forced Vital Capacity
GCP	-	Good Clinical Practise
GM-CSF	-	Granulocyte Monocyte Colony Stimulating Factor
HLA	-	Human Leukocyte Antigen
ICS	-	Inhaled Corticosteroid
IFN	-	Interferon
IgE	-	Immunoglobulin E

IL - Interleukin

IU - International Units

LABA - Long Acting Beta Agonist

LAMA- Long Acting Muscarinic Antagonist

LT- Leukotriene

MAP- Mitogen Activated Kinase

MDI- Metered Dose Inhaler

OD- Once Daily

OPD- Out Patient Department

PAF- Platelet Activating Factor

PDGF- Platelet Derived Growth Factor

PEFR- Peak Expiratory Flow Rate

PKA- Protein Kinase A

PKC- Protein Kinase C

PTH- Para Thyroid Hormone

RBS- Random Blood Sugar

RGGGH- Rajiv Gandhi Government General Hospital

RXR- Retinoid X Receptor

SABA- Short Acting Beta Agonists

SAMA- Short Acting Muscarinic Antagonists

SD- Standard Deviation

TC- Total Count

TH- T Helper

TNF- Tumour Necrosis Factor

TSLP- Thymic Stromal Lympho Protein

UMC- Uppsala Monitoring Centre

UV- Ultraviolet

VDR- Vitamin D Receptor

VDRE- Vitamin D Responsive Element

VEGF- Vascular Endothelial Growth Factor

VIP - Vasoactive Intestinal Peptide

WHO- World Health Organization

APPENDIX-2

CASE REPORT FORM

NAME: Mr/Mrs AGE/SEX:

OP No: DIAGNOSIS:

ADDRESS: CONTACT NO.:

VISIT 1 (DAY 1)

PAST HISTORY:

ALLERGIC TO:

PERSONAL HISTORY:

CLINICAL EXAMINATION:

Ht: Wt:

VITAL SIGNS

Pulse rate: BP:

SYSTEMIC EXAMINATION

RS -

CVS -

ABDOMEN –

CNS -

LAB INVESTIGATIONS:

Complete Blood Count:

Hb: TC: DC: P L E M B ESR:

Fasting Blood sugar: mg/dl. Blood urea: mg/dl. Serum Creatinine: mg/dl.

Liver function tests: SGOT: IU/L SGPT: IU/L

Routine urine analysis: sugar albumin deposits

Pulmonary function tests: FEV1: FVC:

PEFR:

TREATMENT:

VISIT 2 (6th week)

CLINICAL EXAMINATION:

VITAL SIGNS

Pulse rate: BP:

Adverse events:

VISIT 3 (12th week)

CLINICAL EXAMINATION:

VITAL SIGNS

Pulse rate: BP:

Adverse events:

VISIT 4 (16th week)

CLINICAL EXAMINATION:

VITAL SIGNS

Pulse rate: BP:

Adverse events:

Parameters	VISIT 1 (Day 1)	VISIT 2 (6^{th} week)	VISIT 3 (12^{th} week)	VISIT 4 (16^{th} week)
FEV1				
FVC				
PEFR				
Serum Vitamin D3				
Adverse events				
Date & Sign				

Name of the Doctor: Date:

Signature:

APPENDIX-3

INFORMED CONSENT FORM

Title: "A Prospective, Randomized, Open label, Comparative study of Cholecalciferol as an add on therapy to standard treatment in adult patients with bronchial asthma"

Name of the Participant:

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.
6. I hereby give permission to the investigators to release the information obtained from me as a result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC.
7. I understand that my identity will be kept confidential if my data are publicly presented.
8. I have had my questions answered to my satisfaction.
9. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form, I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

1. Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____Signature _____Date_____

2. Name and signature of impartial witness (required for illiterate patients)

Name _____Signature _____Date_____

Address and contact number of the impartial witness:

3. Name and signature of the investigator or his representative obtaining consent:

Name _____Signature _____Date_____

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு : ஆஸ்துமா நோய் சிகிச்சையில் வைட்டமின் டி யின் பங்கு வழக்கமான சிகிச்சை முறையுடன் ஓர் திறந்தநிலை ஒப்பிடுதல் ஆய்வு.

பெயர் : தேதி :
வயது : நோயாளி எண் :

..... என்பவராகிய நான் இந்த ஆய்வின் விவரங்களும் அதன் நோக்கங்களும் முறையாக அறிந்து கொண்டேன். எனது சந்தேகங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுய நினைவுடன் பங்கு கொள்ள சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் நன்கு புரிந்துகொண்டு எனது சம்மதத்தைத் தெரிவிக்கிறேன். இச்சுய ஒப்புதல் படிவத்தைப் பற்றி எனக்கு விளக்கப்பட்டது.

இந்த ஆய்வினை பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினைப் பற்றி அறிந்து கொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில்தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்த எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என்னிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்தினடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ளலாம் என சம்மதிக்கிறேன்.

இந்த ஆய்வின் முடிவுகளை வெளியிடும்போதே எனது பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன். இந்த ஆய்விற்காக இரத்தப் பரிசோதனை செய்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ள வேண்டும் என அறிந்து கொண்டேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைதது விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கறேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்றும் தெரிந்து கொண்டேன்.

ஆய்வாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

APPENDIX-4

INFORMATION TO PARTICIPANTS

Title: **"A Prospective, Randomized, Open label, Comparative study of Cholecalciferol as an add on therapy to standard treatment in adult patients with bronchial asthma**"

Principal Investigator:

Name of Participant:

This study is being conducted in Thoracic medicine OPD at Rajiv Gandhi Govt. General Hospital, Chennai. You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of this study?

Bronchial asthma is a chronic disease characterized by airway hyper responsiveness and reversible airflow obstruction leading to repeated episodes of wheezing, chest tightness and cough. This leads to airway remodeling resulting in irreversible airway obstruction. It is one of the most common chronic diseases globally. Its prevalence is raising in developing countries owing to factors like urbanization, industrialization, environmental pollution, changes in lifestyle, etc.

Vitamin D3 reduces airway hyper responsiveness and inhibits airway remodeling. Vitamin D3 improves the response to inhaled and oral corticosteroids. We want to test the efficacy and safety of treatment with Vitamin D3 in reducing severity of bronchial asthma.

We have obtained permission from the Institutional Ethics Committee.

The study design:

All patients in the study will be divided into 2 groups A & B. You will be assigned to either of the groups. Group A will receive standard treatment & Group B will receive standard treatment + Vitamin D3.

Study Procedures:

The study involves evaluation of severity of bronchial asthma. The planned scheduled visits involve visits at 6^{th}, 12^{th} ,16^{th} week after your initial visit. You will be required to visit the hospital 3 times during the study. At each visit, the study physician will examine you. Blood tests will be carried out twice during the study (at screening and at the end of study) and total of about 40 ml blood will be collected. These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any adverse events, you have to report it. You will be required to return unused study medicines when you report for your scheduled visits. This will enable correct assessment of the study results.

Possible benefits to you – Vitamin D3 along with standard treatment will cause reduction in severity of bronchial asthma.

Possible benefits to other people - The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, and Institutional Ethics Committee to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

The expenditure for the treatment and investigation for this study will not be collected from you.

Signature of Investigator Signature of Participant

Date Date

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு : ஆஸ்துமா நோய் சிகிச்சையில் வைட்டமின் டி யின் பங்கு வழக்கமான சிகிச்சை முறையுடன் ஓர் திறந்தநிலை ஒப்பிடுதல் ஆய்வு.

ஆய்வாளர் :

பங்கேற்பாளர் :

இந்த ஆய்வு சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனையில் நடைபெற உள்ளது. நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்களே முடிவு செய்து கொள்ளலாம். உங்களது சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளலாம்.

இந்த ஆய்வின் நோக்கம் :
ஆஸ்துமா முச்சுத்திணறல் மற்றும் இருமல் மீள் நிகழ்வுகளை வகைப்படுத்தும் ஒரு நாள்பட்ட நோய இது. உலகம் முழுவதும் பாதிக்கும் நாள்பட்ட நோய்களில் ஒன்றாகும். ஆஸ்துமா நகரமயமாக்கல், தொழில்மயமாக்கல், சுற்றுச்சூழல் மாசுபாடு, வாழ்க்கை முறை மாற்றங்கள் போன்ற காரணிகள் காரணமாக வளரும் நாடுகளில் அதிகமாக உள்ளது.

வைட்டமின் டி சுவாசப்பாதையில் வீக்கத்தைக் குறைக்கிறது. வைட்டமின் டி க்கு ஆஸ்துமா நோயை கட்டுப்படுத்தும் தன்மை உள்ளது.

இந்நோயின் சிகிச்சையில் வைட்டமின் டி யின் திறனை அறிவதே இந்த ஆய்வின் நோக்கம் ஆகும்.

இந்த ஆய்விற்கு இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டி சம்மதம் பெற்றிருக்கிறோம்.

இந்த ஆய்வில் கலந்து கொள்பவர்கள் அ மற்றும் ஆ என்று இரு குழுக்களாகப் பிரிக்கப்படுவர். அ குழுவில் இருப்பவர்கள் வழக்கமான சிகிச்சையும், ஆ குழுவில் இருப்பவர்கள் வழக்கமான சிக்சையுடன் வைட்டமின் டி மருந்தும் பெறுவர்.

இந்த ஆய்வில் நீங்கள் முதல்வாரத்தில் 6, 12 மற்றும் 16வது வாரங்களில் பரிசோதிக்கப்படுவீர்கள். நோயின் தன்மையில் ஏற்படும் முன்னேற்றத்தினை அறிந்து கொள்வோம். இரண்டு முறை இரத்தப் பரிசோதனை செய்யப்படும். அதற்காக எடுக்கப்படும் இரத்தத்தின் மொத்த அளவு 40 மி.லி. மட்டுமே. இந்த ஆய்வினில் ஏதேனும் பக்கவிளைவுகள் ஏற்பட்டால் உடனடியாக எங்களிடம் தெரிவிக்க வேண்டும்.

இந்த ஆய்வில் கலந்த கொள்வதன் மூலம் நீங்கள் நோயின் தன்மையில் முன்னேற்றம் பெறலாம். மேலும் வருங்காலத்தில் பிற நோயாளிகளும் பயன்பெற இந்த ஆய்வு உதவியாக அமையும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம். இந்த தகவல்தாளில் கையெழுத்திடுவதின் மூலம் உங்களைப்பற்றிய குறிப்புக்களையோ எடுத்துக்கொண்ட சிகிச்சை முறையை பற்றியோ, ஆய்வாளரோ, அல்லது இன்ஸ்ட்டியூசனல் எத்திக்ஸ் கமிட்யைச் சார்ந்தவர்களோ தேவை ஏற்பட்டால் அறிந்து கொள்ளலாம் என்று சம்மதிக்கிறீர்கள்.

இந்த ஆய்வில் பங்கேற்காவிட்டாலும், நீங்கள் வழக்கமான சிகிச்சையை தொடர்ந்து பெறலாம்.

இந்த ஆய்வில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆய்விலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆய்வின் போதோ அல்லது ஆய்வின் முடிவின் போதோ தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆய்வில் தாங்கள் கலந்து கொள்வதால் சிகிச்சைக்காகவோ, இரத்த பரிசோதனைகளுக்காகவோ தங்களிடமிருந்து எந்த கட்டணமும் வசூலிக்கப்படமாட்டாது.

ஆய்வாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

APPENDIX-5

ASTHMA CONTROL QUESTIONNAIRE

Please answer questions 1-6. Circle the number of the response that best describes how you have been in the past week.

1. On average during the past week, how often were you woken by your asthma during the night?
   a. Never
   b. Hardly ever
   c. A few times
   d. Several times
   e. Many times
   f. A great many times
   g. Unable to sleep because of asthma

2. On average, during the past week, how bad are your asthma symptoms when you wake up in the morning?
   a. No symptoms
   b. Very mild symptoms
   c. Mild symptoms
   d. Moderate symptoms
   e. Quite severe symptoms
   f. Severe symptoms
   g. Very severe symptoms

3. In general, during the past week, how limited were you in your activities because of your asthma?
   a. Not limited at all
   b. Very slightly limited
   c. Slightly limited
   d. Moderately limited
   e. Very limited
   f. Extremely limited
   g. Totally limited

4. In general, during the past week, how much shortness of breath did you experience of your asthma?
   a. None
   b. A very little

c. A little
d. A moderate amount
e. Quite a lot
f. A great deal
g. A very great deal

5. In general, during the past week, how much time did you wheeze?
    a. Not at all
    b. Hardly any of the time
    c. A little of the time
    d. A moderate amount of the time
    e. A lot of the time
    f. Most of the time
    g. All the time

6. On average, during the past week, how many puffs/inhalations of short-acting bronchodilator (eg. Ventolin) have you used each day?
    a. None
    b. 1-2 puffs/inhalations most days
    c. 3-4 puffs/inhalations most days
    d. 5-8 puffs/inhalations most days
    e. 9-12 puffs/inhalations most days
    f. 13-16 puffs/inhalations most days
    g. More than 16 puffs/inhalations most days

7. FEV1% predicted:
    a. >95% predicted
    b. 90-95% predicted
    c. 80-89% predicted
    d. 70-79% predicted
    e. 60-69% predicted
    f. 50-59% predicted
    g. <50% predicted

Scoring:

Sum points from all questions 1-7. Divide this sum by 7.

ACQ score = _____

APPENDIX-6

ETHICAL COMMITTEE APPROVAL

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.V.Vasanth Kumar
I Year PG in MD Pharmacology
Institute of Pharmacology
Madras Medical College
Chennai 600 003

Dear Dr.V.Vasanth Kumar ,

The Institutional Ethics Committee has considered your request and approved your study titled **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF CHOLECALCIFEROL AS AN ADD ON THERAPY TO STANDARD TREATMENT IN ADULT PATIENTS WITH BRONCHIAL ASTHMA" - NO.07042017**

The following members of Ethics Committee were present in the meeting hold on **04.04.2017** conducted at Madras Medical College, Chennai 3

1.Prof.Dr.C.Rajendran, MD.,	:Chairperson
2.Prof.K.Narayanasamy, MD.,DM.,Dean(FAC), MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	:Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
6.Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
7.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
8.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
9.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003