A Relationship between Asthma and Vitamin D

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg, 2025

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Declaration:

I, Alain Nzuzi Mvudi, do hereby declare that this research report is my unaided work.

It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine. This research report is submitted in the publishable format as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

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Signed on the 20th May 2025

Dedication:

To my parents, Papa Remy and Maman Annie; my wife, Henriette and my children, Matondo, Nkembo and Mwinda.

Publications and presentations arising from this research report:

The student intends to publish this research report in Wits Journal of Clinical Medicine (ISSN 2618-0189).

Ethical considerations:

Permission for this study was granted before data collection commenced by Dr. JML Tsitsi (Head of Department Internal Medicine, Chris Hani Baragwanath Academic Hospital), the Medical Advisory Committee (MAC) at this institution, as well as the Human Research Ethics Committee (Medical) at the University of the Witwatersrand HREC Ref No: M1911145. National Research Database Reference Number GP_202409_058. All participants signed informed consent.

Acknowledgments:

I hereby wish to acknowledge:

- The Chris Hani Baragwanath Academic Hospital management for allowing me to research at this institution, and the Pulmonology Department
- To all the asthma clinic participants who availed themselves
- To my supervisors Dr Van Blydenstein and Prof Omar for their guidance and support

Abbreviations

1α25vitD3	- One alpha, 25 dihydroxy cholecalciferol
AC	- Anticholinergic
BMI	- Body Mass Index
COPD	- Chronic Obstructive Pulmonary Disease
ICS	- Inhaled corticosteroid
IκBα	- Inhibitor of NF-Kb alpha
IL-10	- Interleukin 10
LABA	- Long acting beta agonist
LTA	- Leukotriene receptor antagonist
LPS	- Lipopolysaccharides
mRNA	- Messenger Ribonuclear acid
MKP – 1	- Mitogen-activated protein kinase 1
NF-ķB	- Nuclear factor kappa B
PPI	- Proton pump inhibitor
RSV	- Respiratory Syncytial Virus
SABA	- Short acting beta agonist
TLR	- Toll-like receptor
TNF	- Tumor Necrosis factor
UV	- Ultraviolet
Vit D	- Vitamin D
Vit D3	- Cholecalciferol
VDR	- Vitamin D nuclear Receptor

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Chapter 1: Extended Literature Review

Asthma is a disease characterized by inflammation and hyperresponsiveness of the airways. The hallmark of this condition is the reversible character of the airflow obstruction in the airways. There are many phenotypes of asthma including adult-onset asthma, allergic asthma, nonallergic asthma, asthma with fixed airflow limitation and asthma with obesity (1).
There are numerous risk factors for the development of asthma. They can be broadly divided into endogenous and exogenous factors. In the former category, the main factors are as follows: atopy, gender, obesity, and viral infections in infancy. In the latter group, the following factors can be found: exposure to allergens and smoking, the use of paracetamol or a non steroidal anti-inflammatory drug such as Ibuprofen, air pollution and diet (2,3). Low levels of vitamin D (vit D) have been associated with asthma occurrence (4).

Worldwide, Asthma is a major health problem with an estimated 262 million asthmatic patients in 2019 (5,6). The impact and burden of asthma in South Africa is significant. Indeed, the prevalence of asthma in all age groups was a staggering 8.1% in 2004 . Moreover, the fatality rate of asthma in South Africa was shown to be the fifth highest in the world, at 18.5 per 100000 asthmatics (7,8). The prevalence of childhood asthma in South Africa is rising especially in the teenage population and it is one of the highest in Africa (5,9). Studies have demonstrated that the exodus of the population from rural to urban areas in Africa in general, including South Africa; has resulted in a further increase in the prevalence of asthma, suggesting that there is something “asthmogenic” in African cities (9). Numerous factors have been shown to have a negative impact on asthma control notably: allergies, respiratory infections, and co-morbidities (10). Recently, studies have suggested that there might be a relationship between vit D level and asthma control (11,12).

Overview of vit D

Vit D3 is produced through ultraviolet (UV) light action on sun-exposed skin. One alpha, 25-dihydroxycholecalciferol (1α25vitD3) is the active metabolite of vit D. It acts on the transcription factor vit D receptor (13). Vit D is associated with calcium homeostasis; however, the distribution of vit D receptors in the body has shown that this molecule plays an important role in multiple areas of human physiology, including muscles, adipose tissues and immune modulation. Vit D is thought to impact the control of chronic inflammation through its action on immune regulatory cells (13). This has led to numerous studies looking at the role of vit D

in autoimmune disease as well as in asthma. In asthma, vit D levels are thought to play a role in the aetio-pathogenesis as well as in the asthma control (4,14).

The final activation of vit D takes place at the level of the kidney where 25 hydroxyvitamin D3 is converted to 1,25 dihydroxycholecalciferol by 1 alpha-hydroxylase (4). It has been shown that 1 alpha-hydroxylase enzymes are also produced locally by the epithelial respiratory cells. The active form of vit D3 from a biological point of view is 1, 25 dihydroxy-vit D3 (15). The physiological effect of calcitriol at the molecular level is mediated through the vit D nuclear receptor (VDR). VDRs are found in numerous organs in the human body including the lungs (16). As stated above, one of the physiological actions of vit D is decreasing inflammation through its interactions with immune regulatory cells. This also occurs in the airways where many immune regulatory cells are found. In this way, there is regulation of immunomodulation and inflammation that occur locally as a result of vit D activation (17).

There are clinical risk factors associated with vit D deficiency. These include age, decreased intake, sun exposure, certain comorbidities and medications (18,19). One risk factor of interest in patients with asthma is the use of chronic corticosteroids. It is worth noting that some studies have shown that steroids and vit D have synergistic effects in asthma management (20). Furthermore, increased chronic use of steroids in asthma leads to the following side effects: osteoporosis, adrenal insufficiency, cataracts, ischaemic heart disease and peptic ulcer diseases (21). Moreover, Skversky et al. established an association between vit D deficiency and the chronic use of corticosteroid use. Indeed, they have demonstrated that steroids lead to the upregulation of vit D-24 hydroxylase activity. This results in the degradation of 25(OH)vit D which is one of vit D metabolites (22,23) . According to the Endocrine Society guidelines, vit D deficiency is defined as level ≤ 20ng/mL, insufficiency: 21-29ng/mL, adequate: ≥30ng/mL (24). There is lack of standardization in vit D assays, which also adds to the variablity in the levels of patients being tested/reported (25).

Aside from steroids, another class of medication which has been shown to have an impact on vit D level is protein pump inhibitors (PPIs). Hypomagnesemia and the pH of gastric fluid are the two ways by which vit D level is influenced by chronic use of PPIs (26).The inhibition of H^+, K^+ ATPase enzyme in the intestinal lumen by PPIs results in increase pH. This in turn, causes a reduction of affinity between Mg^+ ion and its transporter, Transient Receptor Potential Melastatin 6/7 (TPRM 6/7). This, ultimately, leads to hypomagnesemia (26), Magnesium is one of the cofactor in vit D level (27). So low level of magnesium will result in vit D deficiency.

Furthermore, the bioavalability of vit D is affected by the acidity of the gastric environment (28). As mentioned previously, PPIs use has an impact on the pH of the intestinal lumen.

Vit D and chronic lung diseases

Many studies have shown how vit D deficiency plays a role in the pathophysiology of multiple lung diseases. For instance, surfactant synthesis is highly dependent upon the presence of vit D. Impairment in surfactant synthesis will result in pulmonary atelectasis and respiratory distress syndrome, especially in neonates (29). Concerning lung cancer, it has been shown that vit D has protective and curative effects (30). This anticancer effect can be explained by four mechanisms: inhibition of pathway Ras-Raf-Mek-ERK-MAPK and telomerase BCL2, as well as increased expression of IGF1 and Bax (30).

Bronchopulmonary dysplasia (BPD) is a disease affecting preterm infants. It is characterized by airway dysfunction and lung fibrosis. It is a very debilitating illness that can ultimately lead to respiratory failure and prolonged ventilation (31). BPD is strongly associated with vit D deficiency in neonates. At the molecular and cellular level, vit D deficiency leads to decreased production of type 2 alveolar cells and surfactant and activation of fibroblasts (31). This leads to airway remodeling, inflammation, and hyperresponsiveness. Furthermore, there is another important mechanism by which vit D deficiency mediates the aetiology of bronchopulmonary dysplasia, it has to do with endotoxin. Indeed, upon endotoxin exposure, there is a decreased production and expression of VDRs and enzymes, one alpha-hydroxylase, in the lungs, reduction of growth hormone, Vascular Endothelial Growth Factor (VEGF), coupled with increased production of a vit D regulatory enzyme, CYP24A1. The net effect is reduced angiogenesis and vasculo-genesis (31,32).

Chronic Obstructive Pulmonary Disease (COPD) is a disease characterized by airway inflammation with the destruction of lung parenchyma causing airflow limitation. Zhu *et al*. have shown a correlation between COPD development and/or severity and vit D insufficiency (33). Indeed, vit D inhibits the innate and adaptive immune response in the human body. This is done by activating different vit D receptors, with a low level of vit D having the opposite effect. There will be increased recruitment of monocytes and neutrophils, a switch towards a Th 2 and regulatory T cells mediated immunological response (33). The result will be lung destruction due to inflammation and structural changes which will make, in turn, the development of COPD more likely. However, the link between vit D deficiency and increased COPD exacerbation is not proven (33). In fact, a study conducted by Lehouk *et al.* showed

that supplementing high doses of vit D in COPD patients did not lead to a reduction of exacerbation (34).

A high level of vit D is associated with lower mortality in lung cancers. Furthermore, it has a protective effect with respect to the development of lung cancers. At the molecular level, those anti-tumour effects are mediated via the inhibition of the Ras-Raf-MEK-erk-MAPK pathway and the production of Telomerase BcL2, both involved in cell proliferation and survival (30).

Vit D and asthma

Cathelicidin and toll-like receptor (TLR) coreceptor CD14 play an important role in the immune system (35). Those two proteins are important for the detection of the microbial pattern in the respiratory tract. Activated vit D in the lungs leads to the increased gene expression of cathelicidin and TLR coreceptor CD14 (36). It is also important to take note of the fact that respiratory syncytial viruses can cause an increase of 1 alpha-hydroxylase expression in the respiratory tract (36). This in turn leads to an increase in the production of vit D which ultimately results in an enhanced immune system response. This is important especially because respiratory syncytial viral infection is an important cause of asthma exacerbation (35).

As shown above, there is a relationship between vit D level and reduced inflammation in respiratory syncytial virus (RSV) infected individuals. Nuclear factor kappa B (NF-ķB) is a protein complex which plays an important role in host defense against microorganisms in the lungs. Its effects are mediated by the induction, activation and secretion of antimicrobial peptides, cytokines and chemokines. Chemokines have been shown to contribute to the severity of RSV infections (37). This comes about mainly by having too strong an immune response mediated by chemokines. IκBα (Inhibitor of NF-Kb alpha) causes inhibition of NF-ķB, and the former is activated by vit D. In this way, vit D prevents excessive inflammation which leads to attenuation of the severity of respiratory syncytial viral infections (37).

Asthma control encompasses an assessment of symptoms and the future risk of adverse outcomes. The 2019 Global Initiative for Asthma (GINA) guideline categorizes patients' asthmatic control into three groups: well controlled, partially controlled, and uncontrolled (1). This is based on the frequency of daytime or nighttime symptoms in a week, the frequency of reliever use (Short Acting Beta Agonist – SABA), and the limitation of activity linked to asthma symptoms. In our study, the partially controlled and the uncontrolled were combined into a single group called uncontrolled asthma. The second part of the assessment of asthma looks at the future risk of adverse outcomes. This includes acute exacerbations, airflow

limitations and side-effects from medications (1). The classical predictors of exacerbations are previous exacerbations, high SABA use, exposure to smoking, allergens, uncontrolled comorbidities such as rhinosinusitis and gastroesophageal reflux. Other studies have shown eczema and obesity as other factors associated with poor asthma control (38–40). Recent observational data shows differences between asthma severity/ exacerbations and low vit D (1,41).

Hollams *et al*. have shown in a study conducted in Australia that in children with inadequate levels of vit D, there was an increased risk of atopy and asthma (42). Similar findings were found in a study in Qatar, where the majority of asthmatic children had vit D deficiency compared to the control group (43). This was mirrored in an adult study conducted on Chinese patients suffering from asthma, where 88.9 % had vit D deficiency (44).

Korn *et al.* have shown a correlation between low levels of vit D and severity as well as poor control of asthma (45). One possible explanation is the association between an increased level of a pro-inflammatory cytokine called tumour necrosis factor-alpha (TNF -alpha) and low level of vit D (46). An aggregate data of meta-analyses have demonstrated that, in patients who had received vit D supplementation, there was a decrease in acute exacerbations of asthma in patients requiring use of inhaled corticosteroids (47).

One mechanism by which vit D promotes better control of asthma is by inducing the upgrade of CD 200 in the respiratory tract. CD200 is a glycoprotein which, when bound to its receptor CD200R, leads to a series of events, notably deactivation of macrophages and mast cell degranulation, as well as suppression of basophil histamine release and pro-inflammatory cytokine secretion (48). CD200 is therefore an inhibitory ligand. Indeed, 1α25vitD3 leads to the upregulation of CD200 messenger ribonucleic acid (m-RNA). This occurs predominantly in airway resident T lymphocytes. The net effect is reduced inflammatory process in the respiratory tract (48). In addition, Urry *et al*. have demonstrated that there is an increased level of IL-10 and Foxp+3 Treg cells in the presence of 1α25vitD3 (49). In these Treg cells, there is an increased display of CTLA-4 and PD-1 receptors. Those are inhibitory receptors in nature. The overall effect is a decrease in inflammation (49).

Asthma control is one of the main targets of asthma management. In a Dutch study conducted by Kim Zomer-Kooijker in 654 children with asthma; it was shown that there is a strong relationship between respiratory tract infections and asthma control. The greater the frequency

of the respiratory tract infections; the poorer the level of asthma control (50). It has been shown that vit D deficiency is a contributory factor in the risk of paediatric tuberculosis, recurrent otitis media and severe bronchiolitis (51). In the same article, it was also shown that despite the lack of consensus, the level at which vit D(25(OH)D) needs to be for it to promote bone mineralization and calcium homeostasis is at least 10 ng/ml. Along the same line; the level of vit D that is optimal for it to have optimal immunomodulatory action is between 20-50 ng/ml (51).

Zhang *et al*. have shown that the production of cytokines by human monocytes and the induction of p38 by lipopolysaccharides (LPS) is inhibited by vit D provided their level is between 30-50 ng/ml. Moreover, they also have described that one mechanism by which vit D was achieving the abovementioned target was the upregulation of mitogen activated protein kinase 1(MKP-1) (52).

The presence of multiple vit D receptors in airway tissue combined with the anti-inflammatory effects of vit D are the two key elements to the understanding of the role of vit D in asthma pathogenesis (41).

There is no cure for asthma, therefore the main goal that is pursued in the management of asthma is the control of symptoms. Recent studies have shown that treatment of vit D deficiency is a promising avenue in achieving that goal. Due to the lack of data in Africa, we wanted to describe the relationship between vit D levels and the control of Asthma.

Is there a relationship between vit D levels and asthma control?

Numerous studies have investigated the relationship between vit D levels and asthma control. They have reached contradictory conclusions and shown conflicting results. For instance, Ogeyingbo *et al.* demonstrated a reduction of asthma exacerbations in adult asthmatic patients who had received vit D supplementation (12). Along the same line, Han *et al*. have shown an association between vit D insufficiency and asthma (53). The ACVID study demonstrated an improvement in the quality of life of asthmatic patients who had received calcifediol supplementation. This is hypothesized to result from the vit D related reduction of bronchial hyperresponsiveness, pro-inflammatory cytokine synthesis, and steroid resistance. The ultimate effect was better asthma control (54).

The main finding of a study conducted by Turkeli *et al.* in the paediatric population was as follows: poor asthma control and asthma severity were prevalent in asthmatic patients with

lower levels of vit D (55). This could be explained by the fact the biological impact of vit D on asthma phenotype is easily achieved in the paediatric population (34).

However, studies also have shown that vit D supplementation does not impact asthma control. Indeed, a systematic review and meta-analysis of randomized controlled trials released in 2022 showed that giving vit D to children with asthma did not reduce asthma attacks or exacerbations (56). Likewise, a study by Alkhatatbeh *et al*. in Jordania, showed that there was no association between the level of vit D and asthma control (57). Similarly in Norway, Brumpton *et al*. did not show a strong link between vit D deficiency and poorly controlled asthma (58). An English multi-cross sectional study arrived at the same conclusion (59). This could be explained by the fact that vit D deficiency is a widespread problem affecting a lot of adults irrespective of the fact that they have asthma or not and further complicated by the studies being conducted at differing latitudes, with differing exposures to sunlight. The studies mentioned above were conducted in populations of different ethnicity and in patients with asthma living at different latitudes with different sun exposure (51-55).

Due to the conflicting conclusions as to the relationship between vit D and asthma, we chose to investigate this question in a predominantly African population in Johannesburg, with a latitude of 26.2˚ south of the Equator.

Main objective

Determine the relationship between vit D levels and the level of control of asthma

Hypothesis

We hypothesize that low vit D levels is associated with a low level of asthma control.

Objectives

Primary:

Compare vit D levels between controlled and uncontrolled asthmatic patients

Secondary:

1. Determine the prevalence of vit D deficiency and insufficiency among asthma patients
2. Compare vit D levels in patients who are using inhaled steroids vs. oral steroids as maintenance therapy

3. Compare vit D levels in patients using low/moderate ICS vs. high dose ICS
4. Evaluate the relationship between low vit D levels and the following clinical parameters:
    a. Age
    b. Body Mass Index (BMI)
    c. Severity of asthma
    d. History of Atopy – atopic dermatitis, allergic rhinitis
    e. Inadequate Inhaler technique
    f. Number of acute exacerbations in the prior year

Chapter 2: Submissible article

Abstract

Background: Vit D is a micronutrient that plays numerous roles in terms of homeostasis, physiology and immunomodulation. The aim of this study was to investigate a relationship between vit D levels and asthma control.

Objectives: We describe the vit D level among an out-patient asthma population in Gauteng, South Africa. Our primary objective was to compare vit D levels between controlled and uncontrolled asthmatic patients and secondarily to estimate the prevalence of vit D deficiency and insufficiency among asthma patients, and to compare vit D levels amongst patients using different therapies (dose of steroid) for asthma.

Methods: A prospective, cross-sectional descriptive study using questionnaire, clinical record review and blood results was conducted at Chris Hani Baragwanath Academic Hospital from March 2020 to 30th June 2022. Vit D levels were measured using a double sandwich immunoassay using a chemiluminescent label.

Results: The sample was predominantly female, African, a median age of 52 years, and a mean vit D level was 24.2ng/ml. Only 19% of the cohort had controlled asthma. The prevalence of vit D insufficiency and deficiency were 41% and 35 % respectively, with no significant difference in mean vit D level between the controlled and uncontrolled asthma groups. There were 2 independent predictors of severe disease: the presence of eczema; and increasing waist circumference. There was no difference in terms of vit D levels among asthmatic patients using oral or inhaled corticosteroids in our study.

Conclusion: The main finding was the absence of significant difference in the median vit D levels between controlled and uncontrolled asthmatics.

Introduction

Asthma is a disease causing chronic airway inflammation, and is characterised by a positive history of respiratory symptoms such as wheezing, dyspnoea, cough, chest tightness, and expiratory airflow limitation (1). The characteristic airflow variation in asthma includes a rise in forced expiratory volume in one second (FEV1) of more than 12% and 200 ml from baseline value after bronchodilator use (1).

In 2019, it was estimated that there were 262 million people affected by asthma worldwide (5). Furthermore, between one-third to half of people suffering from asthma had symptoms not adequately controlled (5). In South Africa, there has been an overall decline in asthma-related deaths (5). However, South Africa has one of the highest rates of prevalence of childhood asthma, 8.1 % (9). Poor asthma control can lead to recurrent admissions and death, most of which happen in low- and middle-income countries, therefore achieving control is paramount (6,8,9) . A Moroccan study showed that the control of asthma was negatively impacted by allergies to animals, comorbidities, and respiratory infections (10). Many other factors are thought to impact on control of asthma for example environmental factors, and nutritional factors and one that has been investigated lately is vit D level (11,12).

Vit D is a micronutrient that plays numerous roles in terms of homeostasis and physiology in the human body. It is associated with calcium homeostasis, regulation of muscles and adipose tissue as well as immunomodulation. Vit D (1,25 dihydroxy-vit D) is the hormonally active form of vit D3 (13). The biological effect of calcitriol is mediated through the vit D nuclear receptor (VDR) (14). The locations of VDRs are widely spread in the human body including the lungs (16).

There is contradictory evidence with regards to the relationship between vit D levels and asthma control. Ogeyingbo *et al*. showed that vit D supplementation in adult asthmatic patients resulted in a reduction of rates of asthma exacerbations (12). In the same vein, a cross-sectional study conducted by Han *et al.* showed that there is a correlation between vit D insufficiency and asthma (53). The ACVID clinical trials demonstrated the positive effect of calcifediol on asthma control in patients with vit D deficiency (54). However, a review from Kumar *et al,* highlighted the fact that vit D supplementation might not have any beneficial effects on childhood asthma (56).

Given the conflicting conclusions on the impact of vit D on asthma, there was a need for a cross-sectional study to be conducted.

Methodology

A prospective, cross-sectional descriptive study was conducted at Chris Hani Baragwanath Academic Hospital from March 2020 to 30th June 2022. We considered all adult patients attending the respiratory outpatient clinic, with spirometry-confirmed asthma, for enrolment into the study. Patients with current active pulmonary tuberculosis, chronic pulmonary disease (COPD), active malignancy, malabsorption, or a history of pancreatic insufficiency, patients on vit D supplementation, and pregnant patients were excluded.

Data was abstracted from the file for each patient and a questionnaire was conducted. Data included demographics, anthropometric measurement, the control of asthma symptoms, the severity of asthma, evidence of atopy (eczema, allergic rhinitis), the suitability of inhaler technique (adequate or inadequate), the number of acute exacerbations in the past year, chronic medications and doses, the duration of sunlight exposure, and the smoking history.

Ten milliliters of blood were collected from the patient, centrifuged, and initially stored at 8 to 15°C. A double sandwich immunoassay using a chemiluminescent label was used to measure vit D levels. The instrument used was the Abbott © Architect, the assay was conducted at a South African National Accreditation System (ISO 15189) accredited laboratory.

The reference range for vit D levels used in this study was in line with the Endocrine Society: deficiency: ≤ 20ng/mL, insufficiency: 21-29ng/mL, adequate: ≥30ng/mL (24). The control of asthma was assessed based on the presence or absence of symptoms. Patients with no symptoms over the previous 4 weeks were classified as controlled. A patient was considered uncontrolled asthma if they had daytime symptoms more than twice a week, required short-acting beta agonist (SABA) use more than twice a week, had nocturnal awakening due to asthma, or whose activities were limited by asthma. Controlled asthmatics were patients who did not have any of the above-noted symptoms.

The severity of asthma can be categorized as mild, moderate, and severe. According to GINA 2019 guidelines (1), the severity of asthma is a retrospective assessment of the level of treatment required to control the patient's asthma symptoms.

An acute exacerbation was defined as any episode of acute worsening of asthma symptoms requiring a change in therapy. Inhaler technique was assessed by the treating clinician and documented as adequate or inadequate, according to the appropriate type of inhaler.

The data collected through the questionnaire and the blood results were then entered into Redcap (60,61) and analysed using Statistica v13.3. Histograms, the Shapiro-Wilk, and

Lilliefor's tests were used to determine the data distribution. Categorical variables were presented as counts and percentages and the Chi-square test was used to compare symptomatic and asymptomatic groups. The data summary of continuous variables was represented using means with standard deviations for normally distributed data and medians with interquartile ranges for non-standard distributed data. The independent variables of symptomatic and asymptomatic groups were compared using Mann Whitney U test for independent medians and Student's T-test for independent means.

Outcomes

The primary outcome was to compare vit D levels between controlled and uncontrolled asthmatic patients. The secondary outcomes were to estimate the prevalence of vit D deficiency among asthma patients, to compare vit D levels between patients managed with different treatment strategies, and to evaluate the relationship between vit D levels and severity (predictors of severity).

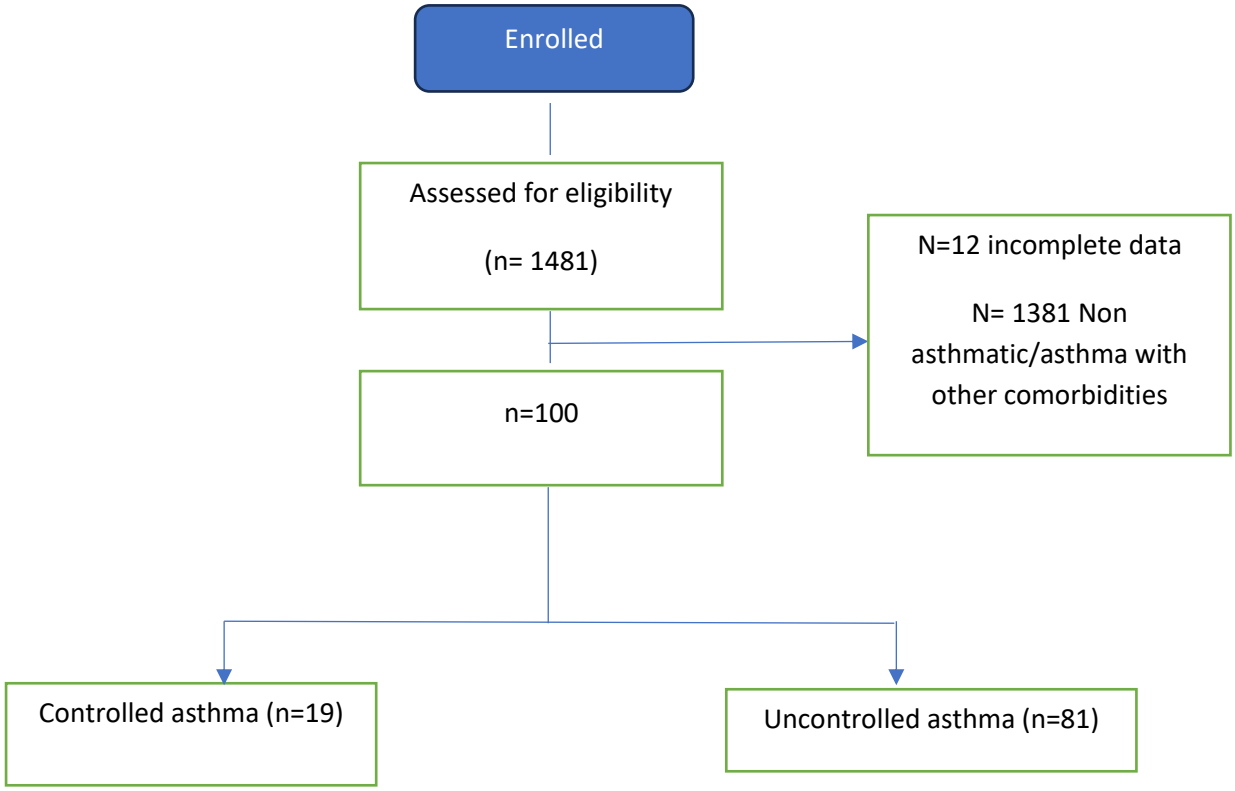
Due to the insignificant number of patients on oral steroids, we omitted the evaluation of this group.

Ethical considerations

Ethics approval was granted by the Human Research Ethics Committee of the University of the Witwatersrand (M1911145). Permission to conduct the study was given by the Head of the Respiratory Unit and the Head of Internal Medicine at Chris Hani Baragwanath Academic Hospital. All patients signed informed consent. NHRD number is GP_202409_058.

Patient flow is illustrated in Figure 1.

Figure 1:



Results

We recruited 100 patients from the respiratory OPD clinic during the study period. Baseline patient data is shown in Table 1.

Table 1: Baseline patient data

Variable	All (n=100)	Controlled asthma (n=19)	Uncontrolled asthma (n=81)	P
Age years, Median (IQR)	52.3 (39.6-61.3)	55.5 (36.1-64.5)	52.3 (39.6-61.3)	0.40
Female Gender n (%)	90 (90.0%)	16/19 (84%)	74/81 (91%)	0.35
Race				1.0
African	97/100 (97%)	19/19 (100%)	78/81 (91%)	
Non-African	3/100 (3%)	0/19 (0%)	3/81 (3%)	
Weight (Kg), Median (IQR)	81.5 (63-99)	72.5 (60-89)	84.2 (63.5-100)	0.30
BMI, Median (IQR)	31.7 (26-39)	31.0 (26-35.6)	32 (26-39.7)	0.28
Height (m), Median (IQR)	1.57 (1.53-1.63)	1.56 (1.52-1.59)	1.58 (1.54-1.64)	0.38
Waist circumference (cm) Median (IQR)	99 (88-111)	94 (81-104.0)	99 (89-112)	0.23

*N number, p pvalue, * statistically significant, IQR interquartile range, kg kilogram, BMI body mass index, m meter, cm centimeter*

The median age was 52 years. Majority (90%) of the patients were women and most patients were of African origin (97%). A small percentage (5%) were smokers. The table below shows the distribution of sunlight exposure.

Table 2: Sunlight exposure

Sunlight exposure hours/day	All	Controlled	Uncontrolled	*p
a. 0-3h (n%)	65/100 (65%)	52	13	0.72
b. 3-6h (n%)	24/100 (24%)	20	4	0.88
c. >6h (n%)	11/100 (11%)	9	2	0.73
All	100	81	19	

**X^2 test for differences amongst those with > 6 hours of sunlight exposure vs. <6 hours.*

There were 19 patients who were controlled and 81 uncontrolled, with no significant difference in the median vit D levels. Overall, the cohort displayed vit D insufficiency, with a mean vit D of 24.2ng/ml (SD: ±6.98) , and a median vit D level of 22.0ng/ml [IQR: 18-28]. A minority of patients (19%) were well-controlled. In the controlled group, the mean vit D level was 22.2ng/ml (SD: ±7.44) and the median was 22.0ng/ml [IQR: 13-28]. The mean vit D level amongst the uncontrolled group was 24.7ng/ml (SD: ±6.91) and the median was 23.0ng/ml [IQR: 19-28]. There was no statistical difference between the two groups, p=0.21.

Table 3: The prevalence of vit D deficiency and vit D insufficiency among Asthma patients attending the respiratory out-patients clinic

Vit D status	Prevalence (Confidence Interval)	n/ total for the group
Vit D deficiency (≤20ng/mL)	0.35 (0.30-0.40)	35/100
Vit D insufficiency (21-29ng/mL)	0.46 (0.41 -0.51)	46/100
Adequate Vit D levels (≥30ng/mL)	0.19 (0.15 -0.23)	19/100

Linear regression

We performed a regression analysis analysing the following factors as possible predictors of vit D levels: age, gender, body mass index (BMI), ethnicity (black vs. non-black) and sunlight exposure (<3 hours vs. ≥3 hours). In the final analysis only age and gender were selected based on initial p values <0.05. Female gender predicted a higher vit D level. See table 4 below.

Table 4: Regression model for predictors of vit D levels

Variable	Beta value	SE	P
Intercept 32.969			
Age	0.189	0.098	0.058
Gender	0.197	0.098	0.0495*

Table 5 Comparison of vit D levels (ng/ml) between patients managed with different strategies

Category	N	Median	IQR	*p
All	100	22.5	18-28	
Controlled	19	22.0	13-28	0,21
Uncontrolled	81	23.0	19-28	
Inhaled vs oral/inhaled				
Inhaled	92	22.5	18-28	0.5
Oral +Inhaled	8	23.0	21.5-32	
LTA/AC vs. No LTA/AC				
Leukotriene receptor antagonist	69	23.0	17-28	0.76
No Leukotriene receptor antagonist	31	22.0	19-28	
PPI vs. No PPI				
Proton pump inhibitors	44	22.0	17-25	0.08
No Proton pump inhibitors	56	23.0	19-29	

N number, LTA Leukotriene receptor antagonist, AC anticholinergic, PPI Proton pump inhibitors

Table 6 List of all medications

	Controlled N=19	**Uncontrolled N=81**	**ALL N=100**
SABA reliever use	16	79	95
ICS turbuhaler	3	5	8
LABA and ICS DPI	7	36	43
FABA and ICS turbuhaler	0	3	3
LABA and ICS PMI	6	29	35
ICS PMDI	4	14	18
Steroid nasal spray	11	40	51
LAMA	0	8	8
Antihistamine	8	50	58
LTA	2	20	22
PPI	10	34	44
Prednisone	0	8	8
Aspirin	0	2	2

**Short-Acting Beta2-agonist, Inhaled corticosteroids, Long-acting beta2-agonist, Inhaled corticosteroid dry powder inhalers, Fast-acting beta agonist, Inhaled corticosteroid Pressurized metered dose inhalers, Long-acting muscarinic antagonist, Leukotriene receptor antagonist, Proton pump inhibitors.*

Relationship between severity of asthma, vit D, and other characteristics

We used 10 variables for the model: vit D, age, height, weight, BMI, waist circumference, smoking history, inhaler technique, eczema, and aspirin use. The independent predictors for severity of asthma were having a history of eczema (OR 2.1 CI: 1.03-4.5), and waist circumference (OR 1.03 CI: 1.0-1.06). The median waist circumference (IQR) in severe disease was 106cm (98-117) compared to 95cm (87-108) in mild to moderate disease.

Discussion

The main finding of our study was that there was no significant difference in the median vit D levels among the two groups. Notably, a Jordanian case-control study was conducted between 2019 and 2020 at King Abdullah University with 150 participants and showed no association between the level of asthma control and that of vit D (57). A Norwegian study also showed that in adults with asthma, there is no correlation between low levels of vit D and the increased risk of uncontrolled asthma (58). Likewise, an identical conclusion was reached in an English multicentre cross-sectional study looking at the prevalence of vit D deficiency, environmental and social determinants in a group of adults with inhaled corticosteroid-treated asthma (59). Our finding is in keeping with these prior studies that were conducted in the northern hemisphere. A possible explanation is the fact that vit D deficiency is a global phenomenon affecting large parts of the population irrespective of whether they have asthma or not (18).

It is worth highlighting the fact that in the paediatric population, a series of studies have consistently shown that there is an association between lower levels of vit D and uncontrolled asthma (55). This finding could be explained by the fact that the impact of vit D on asthma phenotype, severe versus mild asthma, is thought to occur easily in the paediatric population. Indeed, vit D supplementation was shown to have a greater beneficial effect in terms of disease control among children with asthma compared to adults. (59). This was The link between asthma pathogenesis and vit D may be explained by a greater expression of vit D receptors in the paediatric airway tissue. This may facilitate anti-inflammatory effects, inhibition of pro-inflammatory factors, and the promotion of regulatory T cells secretion (41) .

In our study, the prevalence of vit D deficiency and insufficiency was 35% and 46% respectively. The median vit D was 22.5ng/ml (18.0-28.0). Other detailed characteristics of vit D levels in our population are shown in Table 4. In many previous studies in which the relationship between vit D and asthma was investigated, the same pattern was apparent: most of the asthmatics were either vit D deficient or insufficient. For instance, in a case-controlled study conducted by Mohammad *et al*. released in 2021, 77.3% of participants were vit D deficient and 20 % were vit D insufficient. In the same study, a great proportion of participants with asthma had vit D insufficiency (90.5%) whereas the rest had vit D deficiency (9.5%) (57).

In our population, the female gender predicted higher vit D levels. This finding is not in keeping with a review done by Norval *et al.* which demonstrated that vit D levels were lower

in women compared to men in South Africa (19). An explanation for this could be the fact that there was a predominance of females in our study. In addition, our sample was smaller.

Our study showed no difference between asthmatic patients using a combination of oral and inhaled steroid when compared to patients on inhaled steroids regarding vit D levels. Vit D in conjunction with steroids in asthma management has a complementary, synergistic, and beneficial effect (20). There is an increased risk of developing co-morbidities in asthmatic patients using steroids. According to Skov et al, the common co-morbidities associated with the use of steroids in asthmatics are as follows: osteoporosis, adrenal insufficiency, ischaemic heart diseases, peptic ulcer, and cataracts (21).

Our study showed a trend to a lower median vit D level among asthmatic patients taking PPIs compared to those not receiving any. This is in keeping with previous published study that has shown that vit D deficiency was prevalent in patients who were taking PPIs (26). There are two mechanisms which explain the impact of PPIs on vit D. The first one is the hypomagnesemia induced using PPIs. Indeed, magnesium is a cofactor in vit D metabolism. Magnesium deficiency leads to a low level of 1, 25(OH)2D despite adequate vit D intake (27). Chronic use of PPIs cause an increase the pH in the gastrointestinal lumen, this in turn leads to a decrease of affinity of the magnesium ion (Mg^{+}) and its transporter (26). The second mechanism is the fact that bioavailability of vit D is affected by the pH of the gastric fluid (28). This is directly affected by the use of PPIs whose mechanism of action is the inhibition of H^{+}, K^{+} ATPase located in gastric parietal cells (26).

Eczema and elevated body mass index (BMI)) are the two predictors of asthma severity in our study, speaking to two phenotypes with a propensity for higher severity in our setting: atopy and obese asthmatics. Those findings are in keeping with similar works conducted by other researchers. For instance, Jaun et al have shown in a prospective Swiss survey conducted between 2019 and 2022 that the variables associated with poor asthma control were as follows: higher BMI, oral steroids, exacerbation, and COPD (38).

Obesity leads to a biased inflammatory response CD4 Th1 driven. This is associated with a worse outcome regarding asthma severity and control (39). Furthermore, there is a decreased clinical response to inhaled corticosteroids in obese asthma patients. This is explained by the fact that the induction of mitogen-activated kinase phosphatase-1 by glucocorticosteroids is reduced by the inflammatory cytokines produced in obesity (39).

An Ecuadorian study reached the same conclusion as ours concerning eczema being associated with asthma severity. Especially virally induced asthma exacerbations are very common in asthmatic patients with atopy (40).

Some of the limitations of our study are the small size and female preponderance of our sample. These two elements make extrapolations difficult. As our cohort was skewed, we were unable to investigate further the association between female gender and higher levels of vit D. Another important point is that the assessment of the inhaler technique was not standardised and tested by the investigator and was noted in the files as assessed by the treating physician.

In conclusion, we conducted a prospective, cross-sectional, descriptive study of 100 patients with asthma who came for their follow-ups at the Chris Hani Baragwanath respiratory clinic between March 2020 and June 2022. 19 of those patients were well-controlled whereas 81 were not. The prevalence of vit D insufficiency and deficiency were 41% and 35 % respectively. Those trends are in keeping with previous studies. There was no difference in terms of vit D levels among asthmatic patients using oral and inhaled corticosteroids or inhaled corticosteroids in our study. The predictors of severity in our study were eczema and high BMI. This has implications in terms of management with an emphasis on weight loss programs being beneficial in optimizing asthma control. Although our study was limited to the impact of vit D in asthmatic patients, further areas of research should look at the relationship between vit D levels and other chronic lung pathologies including COVID-19.

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