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Serum Vitamin D Levels in a Population of Adult Asthmatics in Kinshasa, Democratic Republic of Congo

B Kabengele[a]*, P Akilimali[b], D Kaba[c], P Kayembe[d], Z Kashongwe[e], JM Kayembe[f]

[a,e,f]*Department of Pneumology, University Clinics of Kinshasa, School of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of Congo*

[b,c,d]*Kinshasa School of Public Health, University of Kinshasa, Kinshasa, Democratic Republic of Congo*

[a]*Email: benoit.kabengele@unikin.ac.cd*, [b]*Email: pierretulanefp@gmail.com*, [c]*Email: didine.kaba@unikin.ac.cd*, [d]*Email: patkayembe@gmail.com*, [e]*Email: zacharie.kashongwe@unikin.ac.cd*

[f]*Email: jm.kayembe@unikin.ac.cd*

Abstract

Background: Vitamin D deficiency is common in general population and is thought to be involved in the natural history of several chronic lung diseases such as asthma. However, the magnitude of the association has not yet been reported in asthmatic adults in Sub-Saharan Africa. The aim of this study was to determine serum vitamin D levels in adult patients with asthma living in Kinshasa. **Methods**: A sample of 216 subjects reporting asthma were recruited from the University Clinics of Kinshasa and some parishes in Kinshasa. Socio-demographic data were recorded, nutritional status assessed via body mass index (BMI) calculation, FEV1 values obtained, and serum vitamin D levels measured. Serum vitamin D levels were analyzed according to the time spent outdoors in the sun and their correlation with BMI and FEV1. **Results**: Participants were on average 45.23 years old (SD 17.56) and predominately female (74%). Serum vitamin D levels ranged from 5 to 42 ng/ml, with an average of 20.8 ng/ml (SD 6.1). Vitamin D levels were normal (≥30 ng/ml) in ten subjects (4.8%; 95% CI: 1.9-7.7) and abnormal (<30 ng/ml) in 197 subjects (95.2%; 95% CI: 92.0-98.0); of this latter group, 89% (95% CI: 84.6-93.2) were vitamin D insufficient (10-29 ng/ml) and 6% (95% CI: 3.0-9.6) vitamin D deficient (<10 ng/ml).

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* Corresponding author.

Mean serum vitamin D levels did not differ based on the time spent outdoors in the sun (p = 0.714), and there was no correlation between serum vitamin D and FEV1 (r = 0.018) or BMI (r = 0.033). **Conclusions**: Vitamin D insufficiency is common in adult asthmatics in Kinshasa but does not appear to be correlated with FEV1 or BMI. Additional population-based surveys are needed to fully assess associations between asthma and vitamin D concentrations for targeted interventions.

Keywords: Asthma; BMI; Democratic Republic of Congo; FEV_1; Sub-Saharan African; Vitamin D.

1. Introduction

Asthma is a major public health problem, with an estimated global prevalence of nearly 334 million people and 50 million affected individuals in Africa [1, 2, 3]. Four hundred million people worldwide are expected to suffer from asthma by 2025, with urbanization and the adoption of a westernized lifestyle in many communities exacerbating the problem [4]. In Kinshasa, the capital of the Democratic Republic of Congo (DRC), the reported prevalence of asthma among adults over 18 years of age is 6.9; 9.3% of whom suffer from severe asthma [5]. Asthma deteriorates a patient’s quality of life and increases hospitalizations and medication use [3, 6]. Health disparities are common in rural and urban areas and between high and low- and middle-income countries, suggesting the influence of environmental factors and others disease modifiers [2, 6-12]. For instance, some recent epidemiological studies suggest that vitamin D deficiency may be associated with an increased risk of infectious and chronic respiratory diseases including asthma, cancers, cardiorespiratory disorders, and autoimmune diseases [13-15]. Many observational studies have shown a significant association between vitamin D deficiency and over mortality rate, mainly due to cancers and cardiovascular diseases [16]. Vitamin D deficiency appeared more common in childhood asthma through two observational studies [17, 18], the latter showing an increased use of corticosteroids in asthmatic children. Columbo and al [19] reported vitamin D deficiency in elderly asthmatics with symptoms improvement after a 12 weeks’ supplementation treatment in Philadelphia, USA. The biological active form of vitamin D, 1.25-diyhdroxyvitamin D3, is predominantly synthesized through the action of solar UV-B on 7-dehydrocholesterol, an epidermal precursor, which subsequently undergoes hepatic and then renal transformation into calcitriol [15, 20-25]. The vitamin is contained in small doses in foods such as egg yolk, liver, offal, enriched milk, margarine, butter, and processed meats and at higher concentrations in fatty marine fish such as cod, halibut, and salmon [26]. Serum concentrations could therefore be influenced by the time of exposure to sunlight (seasonal variability), darker skin pigmentation, use of sunscreen, cloths completely covering the skin, ageing, and lesser by diet through malabsorption or inappropriate food intake, or some medications such as steroids [27]. Vitamin D has a broad range of systemic effects particularly on the skeleton, cellular differentiation and proliferation, inflammation, and regulation of the renin-angiotensin system [15, 20-25]. Its immunomodulatory properties are supported by the presence of vitamin D receptors on multiple cells of the immune system such as macrophages, dendritic cells, monocytes; and T-cells. These receptors play an important role in the transcription of various genes involved in inflammation and immune responses of the respiratory epithelium [28]. Airway epithelium is believed to contain high levels of the enzyme that helps the transformation of metabolite in active form of the hormone. The later has effects on inflammation and anti-infectious properties [29]. Hypovitaminosis D could there for be associated to increased production of pro-inflammatory mediators such as TNF-alpha, IL-6, potential physio pathological pathway of asthma inflammation. Vitamin D has immunomodulatory effects also by promoting the differentiation of naïve T cells into IL-10 -secreting regulatory T and increased serum levels of cytokines such as TGF-beta [30]. The hormone has properties to shift the TH1/TH2 balance, to reduce inflammation through the induction of IL-10, an anti-inflammatory cytokine, and to reduce airway remodeling through inhibition of TGF-beta production. Song and his colleagues [31] have shown that pretreatment of human airway smooth muscle with Vitamin D3 has preventive effect on the airway narrowing, through the downregulation of matrix metalloproteinase. Inflammation, bronchial hyper responsiveness, and airway obstruction are hallmark features of asthma, suggesting a potential link with response modifiers, including various biomarkers and hormones such as 1.25-diyhdroxyvitamin D3. Vitamin D has been shown to inhibit the release of IL-12 by dendritic cells, affecting thus the T lymphocyte differentiation and deregulating the TH1/TH2 balance, as mentioned above. Its deficiency then favors the overexpression of TH1 cytokines and inhibits the production of anti-inflammatory cytokines such as IL-10. Therefore, vitamin D deficiency could have potentially harmful health effects and might in part explain the increased prevalence of chronic and allergic diseases worldwide. It is estimated that one billion people, of all ethnicities and age groups, have vitamin D deficiency globally [32]. This deficiency has been documented in many countries, even, paradoxically, in the sunniest regions of Asia and sub-Saharan Africa [4, 33]. Nevertheless, questions remain about the role of vitamin D in asthma and the possible impact of its deficiency on the severity and poor control of asthma in both children and adults [15, 20, 33-35]. An analysis of National Health and Nutrition Examination Survey (NHANES) data in the USA on the general population since 1988 illustrated the impact of serum vitamin D levels on lung function [36]. High serum vitamin D concentrations were associated with improved lung function, while the negative effects of hypovitaminosis D on lung function in patients with obstructive airways disease appeared to be more dependent on serum vitamin levels than on worsening of the underlying condition [15, 19, 21, 23]. A later study further described an association between hypovitaminosis D and impaired respiratory function, wheezing, and poor asthma control [37]. However, the relationship between asthma and vitamin D levels has yet to be described in the adult sub-Saharan African population. Therefore, the main objective of this study was to determine serum vitamin D levels in adult asthmatics living in Kinshasa, DRC.

2. Materials and Methods

2.1. Patients, inclusion and exclusion criteria, and study questionnaire

This study was conducted between June 14, 2017 and February 27, 2018 on male and female adult asthmatics aged 18 years and older. Given the lack of asthma registers in health facilities in Kinshasa, the decision was made to perform convenience sampling and recruit asthmatics attending the University Clinics of Kinshasa and asthmatics in some parishes and churches in Kinshasa. Participants freely consented to answer questions and donate a 10 ml venous blood sample for vitamin D determination. Any person who claimed to have asthma and who was taking asthma medication or any person recognized as asthmatic by a health professional was included in the study. Pregnant asthmatics, individuals reported to have chronic renal failure, and those reporting taking vitamin D were excluded from the study. Several variables were collected from each participant using a structured questionnaire. Socio-demographic characteristics including age, sex, marital status, education level, household size, and socio-economic level were recorded. Asthmatics with less than a high school education were considered to have a "low" level of education, those who had completed high school or vocational training as having a "medium" level of education, and those who had completed higher education or university as having a "high" level of education. Socio-economic level was determined by a wealth index constructed from information on the possession (or not) of certain durable assets of the participant and on certain housing characteristics. Participants were classified into wealth index quintiles from the lowest (first quintile) to the highest (fifth quintile), where the higher quintiles indicated a higher socio-economic level. Environmental data such as time spent outdoors, tobacco exposure, co-morbidities, nutritional status, and respiratory function were also collected. Nutritional status was assessed by calculating the body mass index (BMI; weight (in kg) by height (in meters) squared). A participant with a BMI <20 kg/m^2 was considered "lean", 20-24.9 kg/m^2 "normal", 25-29.9 kg/m^2 "overweight", and ≥30 kg/m^2 "obese".

2.2. Spirometry and vitamin D measurement

Respiratory function was assessed by spirometry using a portable MiniSpir spirometer/oxymeter type device (Medical International Research; New Berlin, WI). Several parameters were measured including the forced expiratory volume in one second (FEV_1). A respondent with an FEV_1 >80% of the predicted value was considered to have "normal" lung function and one with an FEV_1 ≤80% of the predicted value was considered to have "abnormal" lung function. A total 25-hydroxyvitamin D (25-OH vitamin D) radio immunological assay was performed on a Wallac Wizard 1470 automatic gamma counter calibrated for iodine 125 at the Kinshasa Regional Center for Nuclear Studies on frozen serum at -20°C/-40°C using reagents from Demeditec Diagnostics GmbH (Kiel, Germany). Reagents included standards with concentrations ranging from 0 to 100 ng/ml, control serum, tracer (iodine 125 total vitamin D), tubes coated with 25-OH vitamin D total antibodies, incubation buffer, and wash solution. Results were derived from the standard curve by interpolation. The curve was used to determine the total vitamin D level of all samples measured at the same time as the standards. Serum vitamin D levels ≥30 ng/ml were considered "normal" or "sufficient" and serum levels <30 ng/ml were considered "abnormal": serum levels between 10 and 29 ng/ml were interpreted as "vitamin D insufficiency" and those <10 ng/ml as "vitamin D deficiency".

2.3. Data analysis

Data were entered into EpiData 3.1. After quality control and consistency checks, data were exported into SPSS 23.0 (IBM Statistics, Chicago, IL) and Stata 13 (StataCorp, College Station, TX) for analysis. Descriptive statistics were used to describe the basic study characteristics presented in tabular and graphical form. The means and their standard deviations were calculated for normally distributed continuous variables, while proportions with 95% confidence intervals (CI) were calculated for categorical variables. Analysis of variance (ANOVA) was used to compare serum vitamin D levels between asthmatic groups according to the time spent outdoors. Pearson's correlation coefficients were used to correlate serum vitamin D levels and BMI or FEV_1. A threshold of $\alpha = 0.05$ was used for all tests.

2.4. Ethical statement

The Ethics Committee of the School of Public Health of the University of Kinshasa approved the study protocol

(ESP/CE/030/2017). The informed consent form was read aloud to each participant and verbal consent witnessed by a third party was obtained from each participant. Data were collected and analyzed anonymously. No personal identifiers of participants were noted on the survey questionnaire. Respondents were informed that participation was voluntary. They were free to accept, to refuse to participate or to withdraw at any time without any penalty.

3. Results

Table 1: Socio-demographic characteristics of respondents

Characteristics		n	%
Age			
-	≤ 24 years	32	14.9
-	25 - 49 years	85	39.4
-	50 years and over	98	45.6
Gender			
-	Male	56	25.9
-	Female	160	74.1
Marital Status			
-	Single	83	38.4
-	Married	96	44.5
-	Divorced/separated/widowed	37	17.1
Educational level			
-	Low	90	41.7
-	Medium	72	33.3
-	High	54	25.0
Household size			
-	≤ 6 persons	98	45.6
-	> 6 persons	117	54.4
Socio-economic level			
-	Low	86	40.0
-	Medium	43	20.0
-	High	86	40.0
Smoking			
-	No, or ex-smoker of >6 months	187	86.6
-	Yes, or ex-smoker of <6 months	29	13.4

*Asthmatics who had not completed high school were considered to have a "low" level of education, those who had completed high school or vocational training as having a "medium" level of education, and those who had completed higher education or university as having a "high" level of education.

**Participants were classified according to the wealth index divided into quintiles from lowest (first quintile) to highest (fifth quintile), where the first and second quintiles indicated a "low" socio-economic level, the third as a "medium" socio-economic level, and the fourth and fifth as "high" socio-economic level. The study recruited and included 216 adult asthmatics, all of whom voluntarily agreed to participate in the survey and gave informed consent. Participants were aged between 18 and 88 years with an average age of 45.23 years (SD 17.56). About 15% of participants were under 25 years of age and 46% were under 50 years of age. Three-quarters (74%) were female and 45% were in a union. About four out of ten participants had a low level of education (42%) and a low socio-economic level (40%). Over half of households of the participants (54%) contained at least six individuals. Thirteen percent of participants were active or ex-smokers within the last six months (Table 1). About 73% of participants also had allergic rhinitis, 60% heartburn, 37% sleep disorders, 28% hypertension, 27% sinusitis, and 21% allergic dermatosis.

Table 2: Clinical, Para clinical, and Environmental data of the study population

Characteristics		n	%
Comorbidities			
-	Allergic rhinitis	156	72.6
-	Pyrosis (heartburn)	130	60.2
-	Sleep disorders	79	36.7
-	Hypertension	60	28.2
-	Sinusitis	57	26.9
-	Allergic dermatitis	44	20.5
Nutritional status*			
-	Lean	31	14.4
-	Normal	94	43.7
-	Overweight	56	26.0
-	Obese	34	15.8
FEV1 (%)**			
-	Normal	75	34.9
-	Abnormal	140	65.1
Time spent outdoors			
-	Less than one hour	18	8.4
-	One to five hours	82	38.1
-	Six to ten hours	49	22.8
-	Over ten hours	66	30.7

*Nutritional status was assessed by calculating the body mass index (BMI). A participant with a BMI <20 kg/m^2 was considered "lean", 20-24.9 kg/m^2 "normal", 25-29.9 kg/m^2 "overweight" and 30 kg/m^2 "obese".

**A respondent with a maximum FEV1 >80% of the predicted value was considered to have "normal" lung function and one with an FEV1 ≤80% of the predicted value was considered to have "abnormal" lung function.

In terms of nutritional status, 26% were overweight, 16% obese, and 14% lean. Almost three in ten asthmatics (31%) reported spending between one and five hours away from home every day and four in ten (38%) spent over 10 hours away from home each day. Sixty-five percent of asthmatics had an abnormal FEV_1 less than or equal to 80% of the predicted value (**Table 2**). Serum vitamin D levels were measured in 207 asthmatics (95.8% of respondents). Values ranged from 5 to 42.5 ng/ml with an average of 20.8 ± 6.1 ng/ml. Ten asthmatics (4.8%) overall (95% CI: 1.9 - 7.7) had normal serum vitamin D levels and 197 subjects had abnormal serum vitamin D levels (95.2%; 95% CI: 92.0 - 98.0). Eighty-nine percent (CI 95%: 84.6 - 93.2) of the latter group were vitamin D insufficient and 6% (95% CI: 3.0 - 9.6) were deficient.

There was no correlation between serum vitamin D levels and FEV_1 ($r = 0.018$) or BMI ($r = 0.033$) (**Figure 1**).

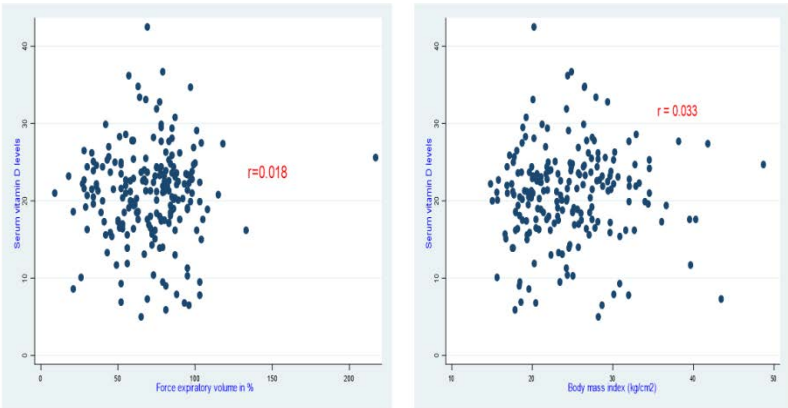

Figure 1: Serum vitamin D levels in asthmatics by FEV1 and BMI

Furthermore, the mean serum vitamin D level was not significantly different between respondents according to the amount of time they were exposed to the sun outdoors ($p = 0.714$; **Figure 2**).

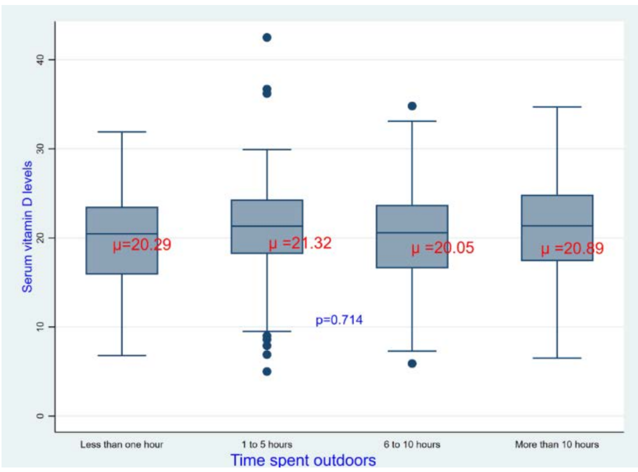

Figure 2: Mean serum vitamin D levels in asthmatics by time spent outdoors

4. Discussion

Here we present a cross-sectional study of 216 adults with asthma, 95.8% of whom were tested for serum vitamin D levels. Overall, serum vitamin D levels were below the normal threshold of 30 ng/ml in 95.2% of subjects, with 89% insufficient and 6% deficient. There were no correlations between serum vitamin D concentration and BMI, FEV_1, or time spent outdoors. With respect to the socio-demographic characteristics of the respondents, 54.6% were under 50 years of age, in line with other published data [5, 38, 39]. Participants' households contained at least six members in about half of cases. Such populated households increase the risk of exposition to respiratory nuisances such as flour and charcoals kept in confined spaces. Three out of four subjects had allergic rhinitis, consistent with other studies reporting this common association in atopic subjects [40, 41]. For example, Nyembue and his colleagues reported an allergic rhinitis frequency of 13.9% even in the overall Kinshasa population in a survey conducted in 2012 [42]. The vast majority of our subjects were either insufficient or deficient in vitamin D (89% and 6%, respectively). This is in concordance with the observation from Ingala and his colleagues who have reported a high proportion of women with hypovitaminosis D comparing normal to subjects with uterin leiomyoma (64.4 vs 57,7%). The later have use local immunoradiometric assay (IRMA) method different from ours [43]. However, the average concentration of vitamin D reported here (20.8 ±6.1 ng/ml) was much higher than African and Middle Eastern averages in the general population (13.9 ng/ml) [35]. However, it was lower than 28.7 ng/ml in North America, 27.2 ng/ml in the Asia/Pacific are, and 21 ng/ml in Europe [44]. The way serum vitamin D was measured could have impacted on the values reported, not relaying on standardized tools in different studies. We didn't find a consensus in the literature on the threshold defining vitamin D deficiency in the general population, and these inter-individual and intercontinental differences constitute a real limitation in the interpretation of data observed in different environments. Vitamin D insufficiency affects almost 50% of subjects worldwide. The condition is mainly due to lifestyle including outdoors activities, sunlight exposure, and environmental pollution more than to diet; only few aliments can provide vitamin D in the body. Reduced sunlight exposure acts through impairment of Ultraviolet-B induced production of the vitamin from the skin. The low serum levels reported here may initially seem paradoxical, the country being in tropical region, with two main seasons and almost permanent sunlight exposure. Dark skin in melanodermic subjects is known to absorb more UVB in the melanin of their skin than white people and then, leading the requirement of longer sun exposure period to produce the same amount of vitamin D [26, 33-35, 45]. However, Binkley and his colleagues [33] showed that low serum vitamin D concentrations were common in a general population of young adults in Honolulu, regardless of the degree of sunlight exposure, and were never greater than 60 ng/ml [26, 33]. The large proportion of vitamin D insufficient or deficient individuals reported in our study highlights the need for additional research addressing the real prevalence of hypovitaminosis D and the impact of supplementation strategies in overall health. Nutritional deficit could contribute to the prevalence observed; indeed, the basic diet in DRC often contains more vegetables, with access to meat and milk limited by the often low household incomes. The impact of the vegetarian diet and the absence of nutritional vitamin D supplementation programs in developing countries is well documented [46]. We did not investigate the eating habits of participants so could not establish a possible cause and effect relationship between dietary intake and vitamin D levels. Nevertheless, a connection has been considered between vitamin D status and increased asthma prevalence in various previous reports [47]. The study period from June to February includes both dry and rainy seasons characterized by different periods of sunshine and therefore solar UV-B exposure. As in a previous study by Columbo and his colleagues [19] on older asthmatics (age 65 or older), our study did not find a link between serum vitamin D levels and BMI. However, this contradicts the survey by Korn and his colleagues [48], who reported an inverse correlation between serum vitamin D levels and BMI ($r = -0.278$, $p < 0.001$). Patients with vitamin D deficiency had significantly higher BMI (28.3 ± 6.2 vs. 25.1 ± 3.9, $p < 0.001$), with the decrease in vitamin D bioavailability believed to result from hormone sequestration by hyperplastic fat cells in obese patients [26]. Parikh and al [49] reported an inverse relationship between BMI and serum vitamin D levels in healthy adults. To address this peculiar point, there is a need for additional studies including more participants with different BMI measures. Our reported lack of correlation between vitamin D and FEV_1 is consistent with the study by Columbo and his colleagues [19], who did not identify a difference in serum vitamin D levels in subjects with an average FEV_1 either above or below 70%, nor did they find normalization of FEV_1 after 12 weeks of vitamin D supplementation. However, Korn and his colleagues reported a positive association between vitamin D deficiency and low FEV_1 in asthmatic subjects [48]. This observation is supported by previous reports elsewhere in children, such as the study of Italian children by Chinellato and his colleagues [50], showing an inverse correlation with the impairment in lung function and increased bronchoconstriction with low vitamin D level, and in adults, in a survey conducted in china [51], as well as in the report from Sutherland and his colleagues [52] describing a link between reduced vitamin D levels and alteration of lung function, increased airway hyper responsiveness and reduced steroid response in some asthmatics. Our observation is also in concordance with data from the American National Health and National Examination Survey (NHANES III) cohort conducted from 1988 to 1994 and including 13,432 people in two age groups (20-49 years and >50 years) [36]. This nutritional surveillance study also revealed an association between vitamin D deficiency and decreased spirometry values, suggesting that the latter was not related to obstructive pulmonary disease but rather the nutritional deficiency [15, 19, 21, 23, 48]. Data on the association between asthma and vitamin D are, however, far from being consensually established. Some authors didn't find the association, such as Devereux and his colleagues through a case-control study in Scottish adults 18-50 years old [53], as well as Hughes and his colleagues, in a retrospective cohort of Australian adults. However, Brehm and his colleagues [54] revealed that vitamin D deficiency was frequent (28%) in asthmatic children in Costa Rica. Korn and his colleagues [48] also showed an average serum vitamin D concentration of 25.6 ± 11.8 ng/ml in a population of adult asthmatics (mean age 45.0 ± 13.8 years) in Germany, with 67% of participants in hypovitaminosis D. The role of this vitamin in asthma is also strongly suggested by previous basic research demonstrating expression of nuclear vitamin D receptor variants in Th2 phenotype lymphocytes known to be important in asthma and allergic diseases [15 ,21]. Finally, several authors have also shown that low vitamin D levels lead to proliferation of bronchial smooth muscle cells, release of pro-inflammatory cytokines, airway remodeling, and bronchial hyper-responsiveness that can decrease respiratory function [15, 19, 21, 23]. There are some limitations to this study. The small sample size may have missed some associations. The recruitment of patients based on reported asthma may have led to selection bias. The choice of sites chosen for convenience does not allow the results to be generalized. The lack of precision of the sampling season did not make it possible to formally study the association between vitamin D levels and season. However, the study does report the prevalence of hypovitaminosis in adult asthmatics and describes possible correlations between the epidemiological and clinical aspects of asthma with vitamin D deficiency. These are preliminary observations that will allow the development of more extensive study protocols across the country.

5. Conclusion

This study reports a significant prevalence of vitamin D insufficiency in a population of adult asthmatics. It does not appear to be correlated with FEV1 or BMI. The survey reinforces the interest of continuing research in the general population on the one hand, and pathological situation on the other hand. It justifies carrying out larger studies that include more subjects in different environmental conditions.

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