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Vitamin D deficiency and Asthma Exacerbation in adult asthmatics: an epidemiological study

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ABBRIVIATION LIST

HAQ Index: Health care access and quality index.

SIGN: Scottish intercollegiate guidelines network.

BTS: The British thoracic society.

IgE: Immunoglobulin E.

IL-: Interleukin.

P21 and **p27:** cell cycle inhibitors.

VDR: Vitamin D receptors.

LC-MS: Liquid chromatography-mass spectrometry.

NHANES III: The third national health and nutrition examination survey.

ICS: Inhaled Corticosteroids.

OCS: Oral Corticosteroids.

LABAs: Long-Acting Beta Agonists.

SABASs: Short-Acting Beta Agonists.

LAMAs: Long-Acting Muscarinic Antagonists.

LTRA: Leukotriene Receptor Antagonists.

EMSA: Assessment of Asthma Control in Adult Asthma Population in the Middle East and North Africa.

INTRODUCTION

INTRODUCTION

Asthma is one of the omnipresent serious health problems known globally, affecting approximately 300 million people worldwide with an associated mortality rate of 1000 deaths per day [1].

Asthma is a common chronic disease that is complex and variable. It affects the respiratory system specifically the airways and the lung and presents a recuring symptoms and a consistent presence of inflammation, airflow obstruction, and bronchial hyperresponsiveness [2]. Treatment plans are determined depending on these characteristics, the intensity of asthma and its clinical manifestations [2].

In Algeria, asthma prevalence has reached 3.41% in 2019, and the estimated prevalence of asthma subgroups are rather varied, 18.6% for eosinophilic asthma, and 12.9% for severe asthma [3]. Algerian HAQ Index (health care access and quality index) has reached 63.7 in 2017 [3].

Asthma etiology is very diverse as a of the heterogenous nature of the disease [5], [29].

The major risk factors for asthma are of both genetic and environmental origins, and they are deemed as risk factors due to their important contribution in asthma onset [5], [29].

A variety of studies (case-control and genome wide linkage studies) identified about 18 genomic regions and more than 100 genes that are correlated to asthma and allergy across 11 different populations [29], [10]. Genome wide association studies identified an association between asthma inflammation and susceptibility locus for thymic stromal lymphopoietin (TSLP), these cytokines are present at high levels in the airways of asthmatics compared to healthy controls. Moreover, gene expression is a crucial process in asthma treatment response; the gene 3 beta-hydroxysteroid dehydrogenase/delta (5)-delta (4) isomerase type 1 (HSD3B1) is linked to the glucocorticoid resistance [29], [33], [32].

On the other hand, environmental exposure and interaction are another asthma risk factor that encompass a multitude of elements starting from the prenatal period, until adulthood, such as smoking and maternal smoking, prematurity, allergens and irritants exposure, and sensitivity to certain medications such as aspirin [5],[29],[10].

In the case of childhood onset asthma, the maternal diet plays a major role in the development of the foetal lung [34], [35] and researchers have proposed the role of vitamin D supplementation in early life wheezing and childhood asthma [36].

INTRODUCTION

Vitamin D is a secosteroid that can be synthesized endogenously in the skin or taken as supplements, it also exists in a couple of types of food especially animal based food [19].

Vitamin D encompasses two forms, the 25(OH) D circulating in the blood, and 1.25(OH) D which is the active form that interact with different tissues through the its receptor [18].

As reported through different studies, vitamin D is capable of regulating the function of lymphocytes, and mast cells along with antigen presenting cells, and more importantly, modulating the function of structural cells involved in the inflammatory response of heterogenous asthma endotypes [6], [37].

IL-17A is a proinflammatory cytokine that causes an aggravation in the allergic airway's response and it's produced at high quantities during asthma exacerbations. In a test to prove this association peripheral blood mononuclear cells (obtained from severe asthmatics) were exposed to vitamin D metabolites and it was observed that IL-17A secretion stopped, and the vitamin D metabolites reinforced antiviral responses in airway epithelial cells [6].

Asthma treatment usually follows a stepwise plan personalized for the patients depending on their clinical status [1]. The usual medication that are prescribed for the patient consists of inhaled corticosteroids to decrease the inflammation and the hyperresponsiveness in the airways; long and short acting beta agonists (LABAs and SABAs, respectively), which are bronchodilators that works on easing the bronchospasm of the airway smooth muscle, long and short acting muscarinic antagonists (LAMAs) which also work against bronchoconstriction and mucus secretion [8], [34].

Lastly, leukotriene receptor antagonists that have both an anti-inflammatory effect and a bronchodilation effect [8], [34], [30].

Vitamin D is considered by many studies as a possible therapy for asthma aggravation especially in patients with low circulating levels. However, data about the contribution of vitamin D in asthma and asthma exacerbation in Algeria are lacking. Thus, our research is based on investigating the association between vitamin D deficiency and asthma exacerbation in adult asthmatics, by conducting an epidemiological study with data collection from the patient's medical records. The collected data (survey and medical records) are compared to the literature sources to determine whether the correlation between vitamin D deficiency and asthma exacerbation exists in the studied population

LITERATURE REVIEW

CHAPTER I

ASTHMA

1 WHAT IS ASTHMA?

Asthma is a common chronic inflammatory disease that affects the respiratory system and lung function. Characterized by airflow limitation and persistent respiratory symptoms. It is tightly linked to bronchial hyper responsiveness which is an intense narrowing of the airway due to a variety of triggers such as allergens, viral infections, or exercising [7], [8], [9].

2 ASTHMA PHYSIOPATHOLOGY

When, for example, an allergen is inhaled, an immune response that is IgE dependant is activated, the IgE antibodies form a complex with mast cells to promote the secretion of the mast cell inflammatory mediators, histamine, prostaglandin and leukotriene after the cell's degranulation [39] and in the process, meanwhile, secreting cytokines to alert T-helper cells; when a T-helper cell gets activated, its interleukins are secreted IL-3, IL-4, IL-13 and IL-5, along with what's known as GM-CSF (granulocyte-macrophage colony stimulating factor to promote the activation of macrophages and the survival of dendritic cells, similarly, IL-3 and IL-4 are responsible for the survival of basophiles and neutrophiles and IL-13 [40] contributes in tissue remodelling fibrosis and hyperplasia [2], [38].

Later, within hours, and under the effect of mast cells [41], neutrophiles, basophiles, eosinophiles and lymphocyte T-helper & memory migrate towards the lung causing bronchospasm and inflammation.

In a healthy lung model, the presence of T-helper 1 cytokines in the airways is the norm, but in the case of asthma, T-helper 2 cytokines are more pronounced and that's due to either the Th2 overexpression or Th1 down regulation [2]. The imbalance towards Th2 type cytokines pattern would promote IgE in response to specific environmental agents, creating a gene-by-environment interaction and thus sensitization [2].

The progression of the disease partakes in the development of other factors involved in airway flow limitation such as edema and mucus hypersecretion and, as it was mentioned previously, hyperplasia and fibrosis [2], [38]

Moreover, the development of airways hyperresponsiveness due to the sensitization mentioned earlier, and the secretion of histamine at high levels [2].

Lastly, airway remodelling, in which epithelial cells turn into mesenchymal cells in which they lose their cell adhesion properties and tissue structure, a process that could be amplified

as a result of the TGF-B (transforming growth factor beta) and cytokines secreted by eosinophiles as a consequence of an interaction with mast cells; the remodelling leads to a loss in lung function, the dilation of vessels and proliferation, mucus gland hypersecretion, ASM hypertrophy and hyperplasia and subepithelial fibrosis [38].

3 ASTHMA SYMPTOMS

Includes wheezing, chest pain and tightness, shortness of breath, dizziness, coughing, and in cases bleu finger tips and /or bleu lips due to lack of oxygen [9].

It's important to mention that the assessment of asthma symptomology and their occurrence and frequency aids in asthma diagnosis [9].

4 ASTHMA RISK FACTORS

4.1 GENETICS

Asthma can be passed down the family line, a hereditary transition through generations. A wide genome study showed that about 18 genome regions and more than 100 genes are associated with asthma and allergy in 11 different populations [10].

4.2 PRENATAL RISK FACTORS

prenatal maternal smoking [44],[45], diet and nutritional pattern followed by the mother, stress, anti-biotic use, also delivering mode (natural or caesarean section) [10].

4.3 DURING CHILDHOOD

family structure, due to exposure to infections, where later born children are less susceptible to asthma for their acquired resistance because of their older, first born siblings infections [42],[43]. Also, exposure to animals, exposure to environmental tobacco smoke, socio-economic status [10].

Gene by environment interaction, which a modification in the gene of the child during growth depending on what surrounding aspects the child interacts with, their life style and exposure to chemicals [46].

4.4 ADULT-ONSET ASTHMA

occupational asthma, where the disease is triggered due to the nature of the job of the individual such as car painting, hairdressing, health care professionals, baking. Which means

a constant exposure to specific triggering substances for a long term (various chemicals, latex or even flour dust) [47]. Additional risk factors include: smoking tobacco or marijuana, air pollution and ATOPY (a genetic tendency that stimulates an immune system reaction to external allergens in an exaggerated and heightened manner) [10].

5 ASTHMA DIAGNOSIS

Asthma diagnosis follows guidelines that developed through the years [9]. The first published guidelines were provided by the thoracic society of Australia and New Zealand in 1989 [9].

These guidelines were established due to the very high price that was paid during the epidemic of asthma 1960s, where many lost their life for the simple reason of having no idea how to properly diagnose and treat asthma [9].

Diagnostic guidelines are undefined and constantly updated for asthma presents various underlying endotypes (a discrete disease with distinct mechanisms and pathway) and phenotypes (clinically diverse manifestations of asthma), and in some instants where the two function together [10].

As an example of these guidelines, the BTS/ SIGN British guidelines on the management of asthma, the BTS (British thoracic society) diagnostic algorithm that was updated in 2016 [9].

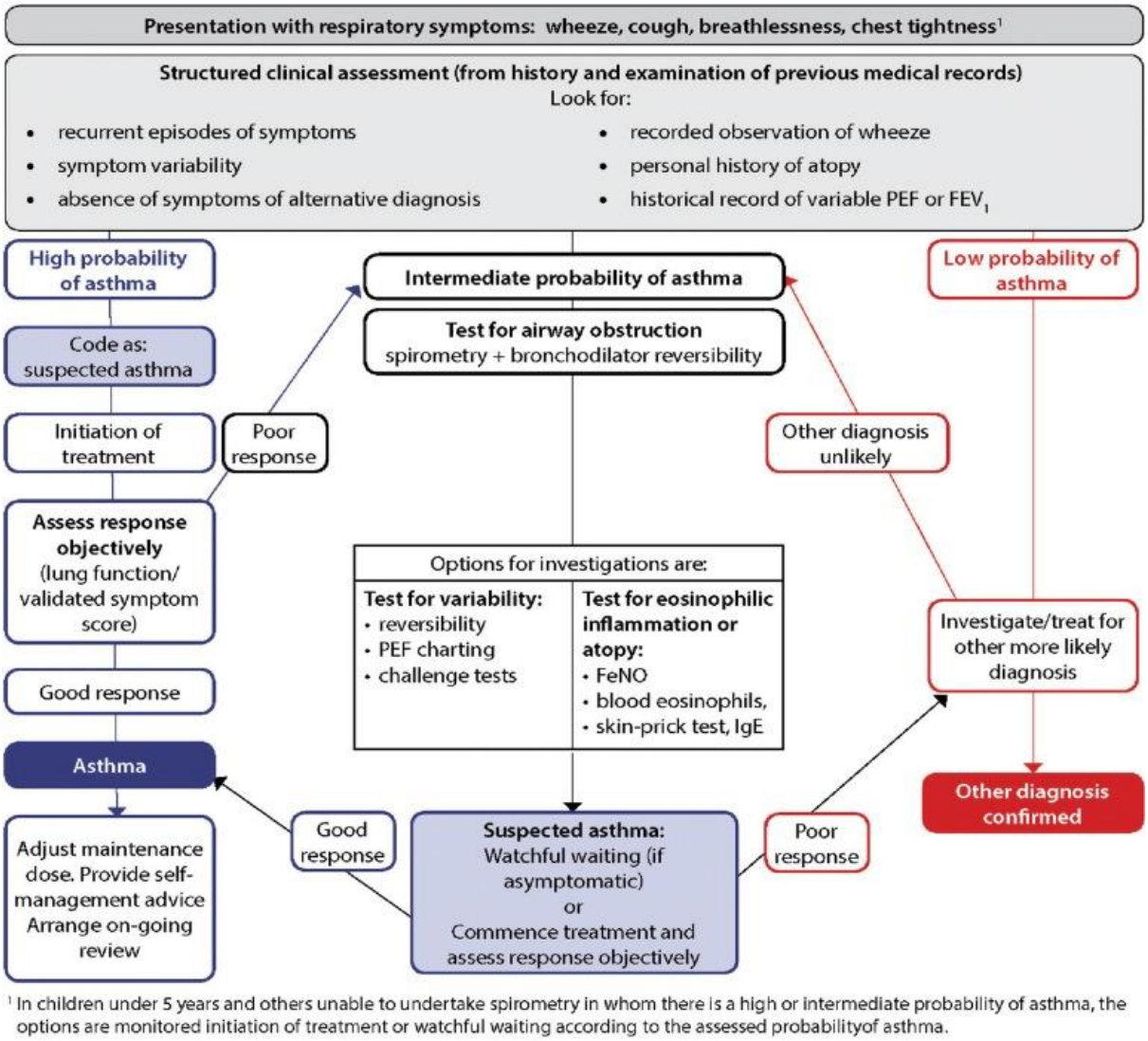

Figure 1. The British Thoracic Society asthma diagnosis algorithm [9]

And so, there are other radiological, biological, clinical, and functional parameters that assist in identifying and diagnosing asthma such as [9]:

- Bronchial provocation tests to evaluate the hyperresponsiveness (inhaled methacholine, histamine) [8].
- Allergy skin tests, to identify the phenotype of asthma and to be able to recognize the triggers of the disease [8].
- Imaging, especially for early prediction of childhood asthma [8].
- Blood tests such as eosinophils levels and IgE in a case of severe asthma and eosinophilic asthma [8].

6 ASTHMA TREATMENT

The treatment of an asthmatic patient is established on three fundamental elements that forms the cycle of asthma management (figure2) [4]

- Disease assessment.
- Treatment adjustment.
- Response (to the treatment) review (figure 2).

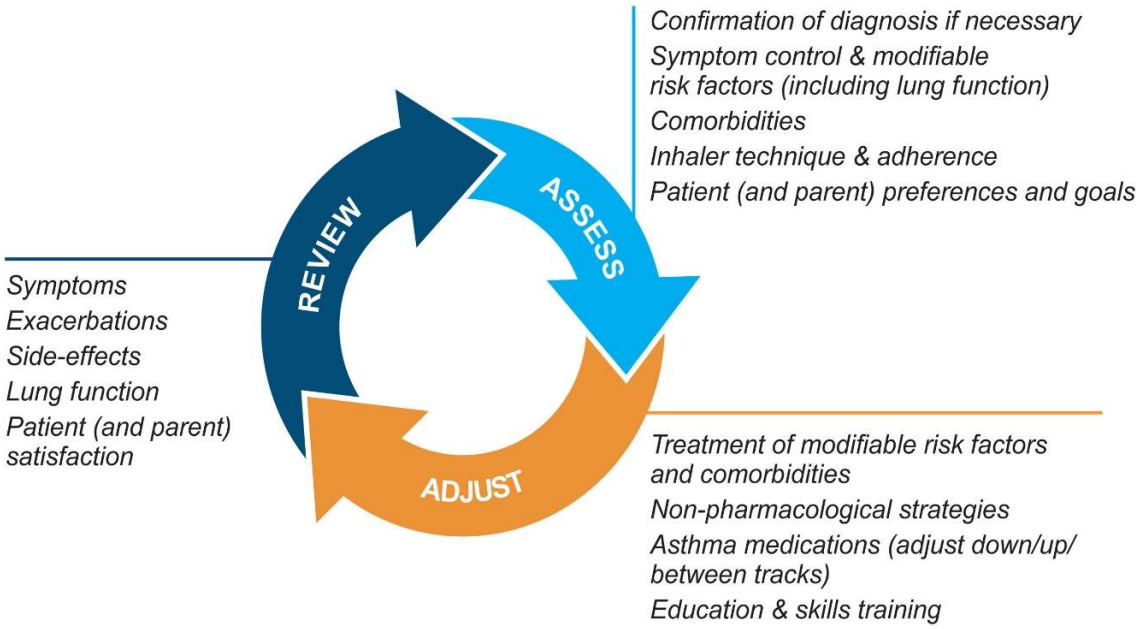

Figure 2. Asthma management cycle for personalized health care [1]

Asthma treatment splits into two types of interventions: pharmacological interventions [8] and no pharmacological interventions [1].

6.1 PHARMACOLOGICAL INTERVENTIONS

These interventions are set to decrease the severity of asthma symptoms rather than tackling the main source of the disease and they are categorized in two types [8]:

6.1.1 Controllers

First line treatment and the main stay in asthma management pharmacologically. They help in preventing and reducing asthma symptoms. Controllers are medications that are prescript to be taken daily for a long period of time and serve as their purpose an anti-inflammatory effect or/and a bronchodilation effect, such as include [8]: ICSs, LTRASs, LABAs in combination with ICS, LAMAs which are only prescript for adults, those of age 18 and plus.

Adding to that, other biological agents focused therapy:

- Anti- igE therapy, where igE is targeted for the purpose of inhibiting the allergic reaction and hypersensitivity with monoclonal anti-bodies, as an example: omalizumab [8], [11].
- Anti- IL-5 therapy, where IL-5 is targeted as a mean to block the eosinophilic pathway, usually is recommended for asthmatic patients with severe eosiphilic asthma, as an example to the monoclonal antibodies used: mepolizumab [8], [12].

6.1.2 Relivers

Englobe SABAs (bronchodilator) and inhaled anticholinergics (also a bronchodilator), prescript for acute symptoms and to be taken only in need [8].

Adding to that allergen specific immunotherapy and systemic corticosteroid therapy [8].

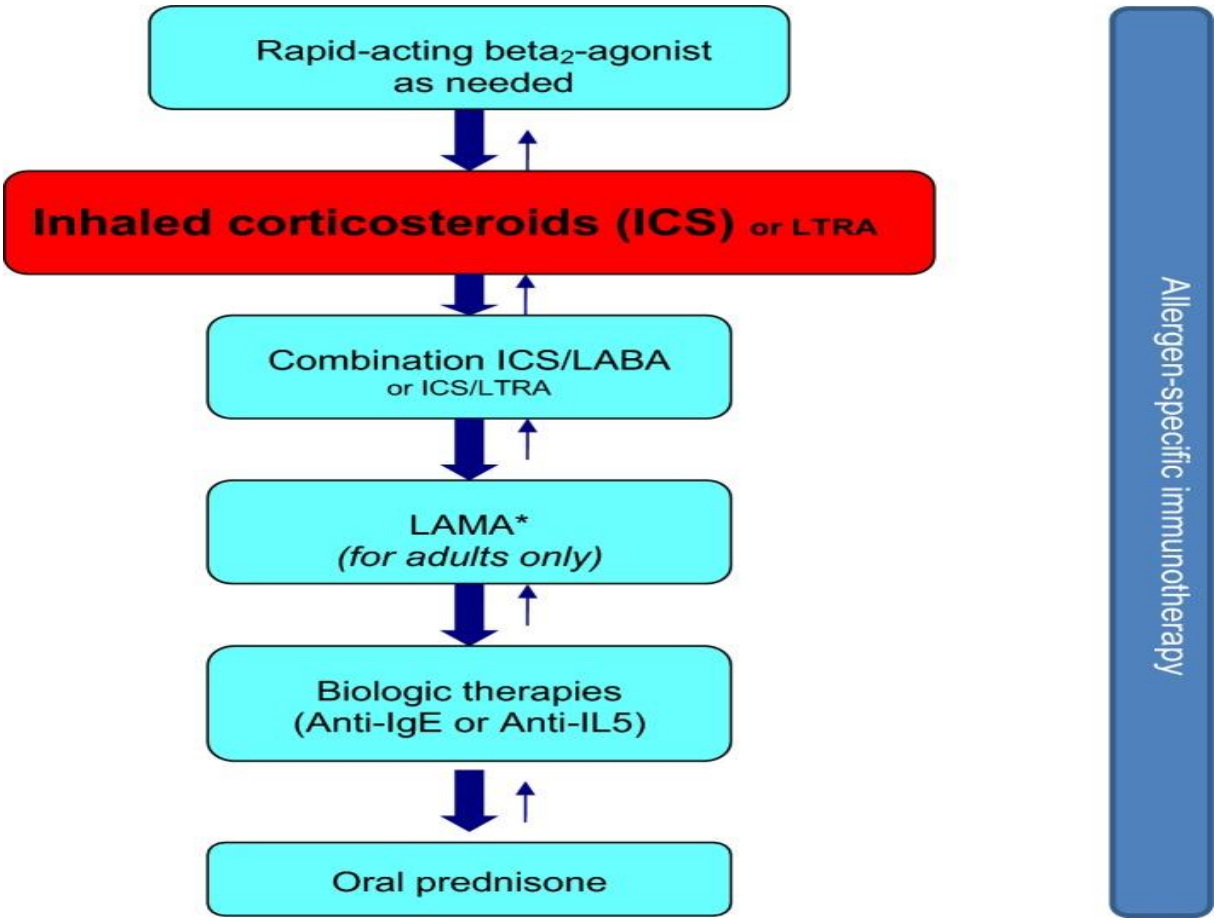

Figure 3. Asthma treatment stepwise algorithm

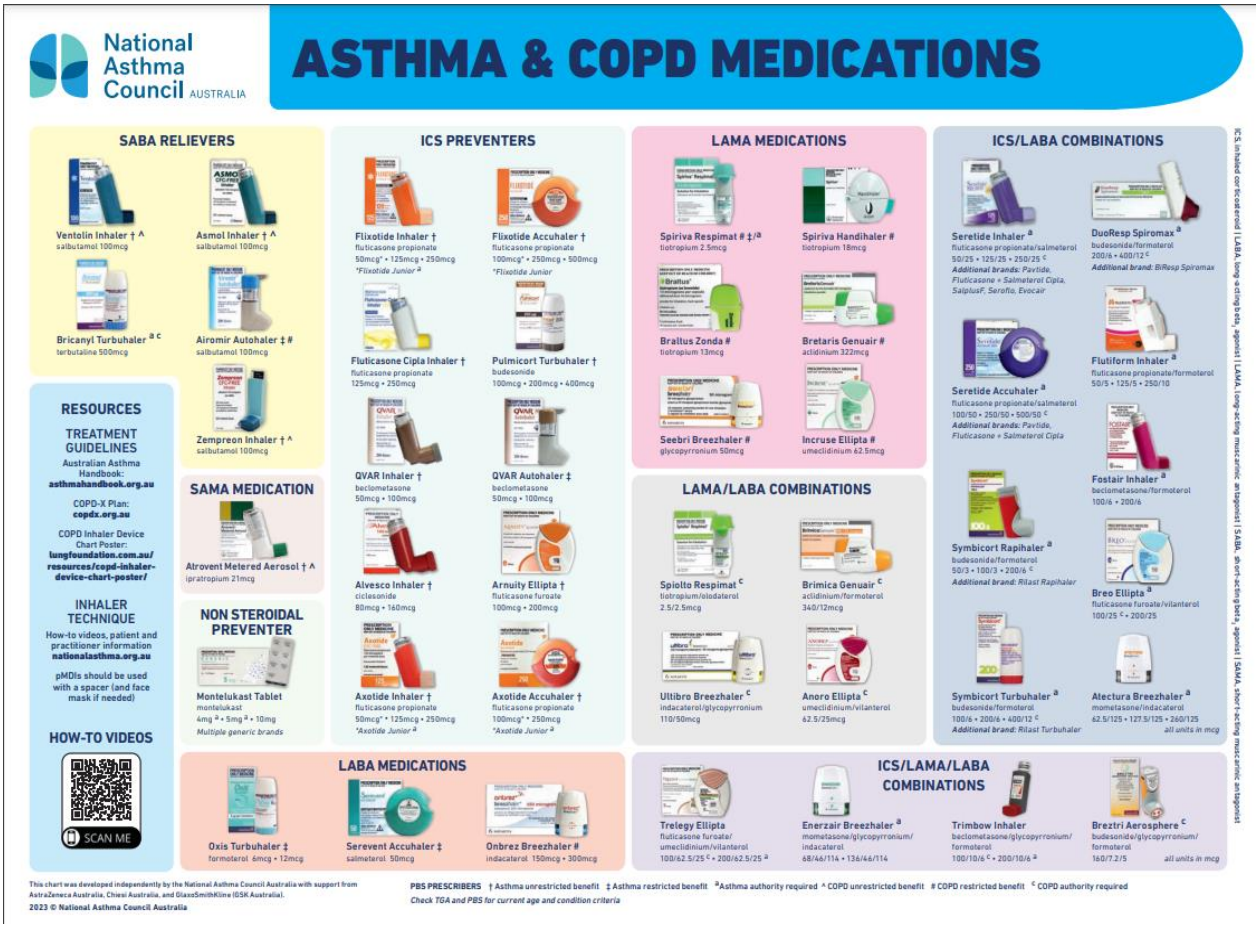

Figure 4. Asthma and COPD medication chart.

6.2 NON-PHARMACOLOGICAL STRATIGIES

In the purpose of improving asthma symptoms and reducing future complications and risk factors, health care providers strongly recommend and encourage to avoid smoking or vaping or cessing the act completely and avoiding smoking areas due to the toxic nature of the contents of a cigarette that are worse than nicotine and tart such as pesticide [48], [1]. Adding to that following a healthy and a nutritional diet, balanced for the general benefit of a good consumptions of nutriments and the benefit of losing weight for those whom struggle with obesity, and studies have indeed shown that weight loss helps improves asthma severity, and exacerbation and even lowers the rate of hospitalizations [49].

Exercising also is encouraged to improve cardiopulmonary fitness and aids in asthma control.

Also, managing stress and emotional turmoil such as depression and anxiety by seeking professional help and indulging in breathing exercises and relaxation activities helps in reducing asthma exacerbation [1], for studies have shown the contribution of stress in shifting

the balance of Th1 cytokines and Th2 cytokines, leaning to type 2 and causing a modulation that results in heightened reaction in asthmatic during times of stress [50].

Avoiding exposure to allergens and irritants indoors and outdoors is also a way to control and manage asthma such as avoiding turbulent weathers by shutting doors and windows and also seeking other means to for heating and cooking that are less polluting and offers an external discharge of said pollution; Signing into pulmonary rehabilitation programs is also advised [1].

7 ASTHMA PHENOTYPES AND ENDOTYPES

Asthma endotype (a discrete disease with distinct mechanisms and pathways) and asthma phenotypes (clinically divers manifestations of the disease) are diverse and many are still under study, understanding these phenotypes and endotypes provides an understanding of the illness expression and its mechanism of function, (table Ⅰ) [13].

Table Ⅰ: endotypes and phenotypes of asthma [13]

Endotype	Phenotype	Clinical characteristics	Molecular mechanism	Biomarkers	Natural history
T2 high	Atopic	Well defined, early onset, steroid sensitive	Allergic sensitization	Blood/sputum eosinophil count, serum specific allergen IgE, high FeNO, high total IgE	Identifiable and treatable, preserved lung function
	Late onset	± concomitant CRSwNP, steroid refractory	*Staphylococcus aureus* enterotoxin	Blood/sputum eosinophil count, high FeNO	Severe from onset, more frequent exacerbation
	AERD	Adult onset	Dysregulated arachidonic acid metabolism	Blood/sputum eosinophil count,	Severe from onset, more

Endotype	Phenotype	Clinical characteristics	Molecular mechanism	Biomarkers	Natural history
				urinary LTE4	frequent exacerbation
Non-T2	Non-atopic	Adult onset—paucigranulocytic or neutrophilic	NLRP3/1L-1 β, altered micro-RNA expression, Thl7	Induced sputum neutrophil count, MMP-9 in BAL	Variable course and lung function
	Smokers	Older adults	Oxidative stress, mixed Th2 high/Th2 low	Induced sputum neutrophil count	More frequent exacerbation, lower lung function
	Obesity related	Female sex	Oxidative stress, neutrophils, increased innate immune activation	Serum IL-6	Severe symptoms, preserved lung function
	Elderly	> 50 to > 65 years at onset	Immunosenescence, Thl/Thl7 inflammation	Induced sputum neutrophil count	Steroid resistant

8 SEVERE ASTHMA

severe asthma is defined as asthma that is so uncontrolled it cannot be stabilized high dose treatment, ICS or controllers, and if stabilized the reduction of treatment doses push it back to its unstable phase. According to WHO in 2010, severe asthma was classified as untreated asthma, difficult to treat as a result of other comorbidities or persistent triggers, and therapy resistant asthma that could only be stabilized with high concentration of medication or unaffected at all no matter how high is the dose [51].

8.1 PATIENT PERSPECTIVE

A patient with severe asthma is burdened with repetitive manifestations of the disease that interferes heavily with the patient's daily life, limiting their activity, affecting their mental health, disturbing their work and family life, and limiting their choices and preferences in

many aspects, not only that, but also the side effects caused by long term OCS also affect the patient severely, and finally the accumulating health care costs as a result of the constant hospitalization, doctor visits, and the need of medication [14].

8.2 SEVERE ASTHMA FACTORS

8.2.1 Genetics

- Mutation in promoter region of IL-4 gene and the coding region of their receptors which causes loss in lung function; moreover, non Th2 genes, transforming growth factor β1(TGF-β1), monocyte chemotactic protein1 are also related to the severity of the disease for they promote a fibrotic response and ADAM-33 genes polymorphisms result in a decreased lung function; in addition, β2 receptors polymorphisms, especially those in position 16 leading to arginine substitutions seemed to create a genetically determined response to standard medications, such as in studies based on regularly scheduled SABA use [15].

8.2.2 Environment

- Allergen exposure, especially a long-term allergen exposure [5], [15].

- Cigarette smoking, smokers express more frequent and severe exacerbations, And respiratory infections [15],[29],[30].

8.3 ASTHMA EXACERBATIONS

It’s an aggravation of the state of an asthmatic patient, representing an increase in asthma symptoms bordering on fatal caused by an increased airway obstruction, and in such state bronchodilator therapy seems inefficient [16].

8.3.1 Asthma exacerbations: triggers, risk factors and mechanisms

Several factors can trigger an exacerbation/asthma attack, like: rrespiratory infections, exposure to allergens and irritants, exercise, cold air or an amalgamate of these factors, by multiples mechanisms according to the trigger factor

8.3.1.1 Allergens

When an asthmatic individual faces a persistent allergen exposure, the response parts into two phases [6]: phase I being an immediate reaction by sneezing, eye and nose itchiness and rhinorrhoea and bronchospasm under the effect of histamine secretion, and Phase II which is estimated to happen about 6-8 hours later is mediated by eosinophils generating an

eosinophilic inflammatory response and is also characterized by a high T-cell levels in the airways.

8.3.1.2 Viral infection

In a normal viral infection the anti-viral response is mediated by interferons(IFN-α), proteins that alert the immune system of the virus, however in asthmatic patients levels of this proteins is rather low where eosinophilia and the secretion of IL-4 and igE are high, and it was discovered that igE molecules replace the IFN-α molecules on dendritic cells receptors which result in inhibiting their function leaving the respiratory system susceptible to rhinovirus induced wheezing and asthma exacerbations, in this case IFN-β are the suitable choice of treatment to reduce the viral infection and improves the symptoms [17].

8.3.1.3 Asthma exacerbation risk factors

Bacterial infection

Causes an increase of the mucus production in the lungs that leads to lower chronic airway inflammation [17].

Allergen exposure

Sensitization to allergens and irritants are the main causes of asthma exacerbations, especially indoor allergens [52].

- The secretion of histamine and other mast cell products causes bronchospasm due to the construction of airway smooth muscle ASM which in turn promotes the induction of mucus secretion [53].

Other risk factors

Pollutants, such as tobacco smoke, a main cause of persistent wheezing [54], and particulate matter a long with sulphur dioxide and nitrogen dioxide, diesel exhaust are also responsible factors of airway responsiveness and inflammation [53].

8.3.2 Asthma exacerbation prevention

As preventing measures to avoid a worsen state of an asthmatic patients, their state should be monitored regularly, and their treatment should be adjusted and controlled as needed and Another measure that should be taken seriously is patient education to increase their awareness and avert such crises [54].

CHAPTER II

Vitamin D the sunshine vitamin

1. DEFINITION

Also known as calciferol, a group of fat-soluble seco-sterols, vitamin D englobes two forms vitamin D2(ergocalciferol) and vitamin D3(cholecalciferol), vitamin D3 being the biologically synthesized form and vitamin D2 the manufactured form [18].

Vitamin D is naturally present in some types of food or added into some types of nutrients to form fortified food and is also endogenously synthesized as result of UV-B action on the epidermis, where 7-hydrocholesterol is converted to pre-vitamin D and through isomerization into vitamin D3 [56] [18].

It was mentioned that both forms of the vitamin, vitamin D3&vitamin D2 serves the same function and the only difference that they present is in their side chains [18].

2. VITAMIN D ORIGINS

2.1. NATUREL NUTRIMENTS

Vitamin D is naturally present in some types of food, mainly animal based food, fatty fish, trout, salmon, tuna, fish liver oil, also it exists in small quantities in beef, beef liver, chicken, egg yolk, turkey, cheese [18], [56].

2.2. FORTIFIED NUTRIMENTS

Vitamin D2 is embedded into milk in measured doses. i.e.,3mcg/cup equivalent to 120IU of vitamin D in the United States and 0.88-1.0 mcg/100mL equivalent to 35-40IU in Canada [18], [57].

Vitamin D is also embedded in vegetarian alternatives for milk such oat, almon, soy milk, moreover mushrooms are treated with UV-B radiation to increase their content in vitamin D [56], [58].

Baby formula in the United States of America contains 1-2.5 mcg/100Kcal(40-100IU), similarly 1-2 mcg/100Kcal(40-80IU) in Canada [18].

2.3. SUN EXPOSURE

Ultra violet radiations B (290-315 nm) penetrate the epidermis of the human body in which

7-dehydrocholesterol molecules reside to induce a conversion of these molecules into pre-vitamin D [18], [19].

This pre-vitamin D undergo isomerization (a heat induced, membrane enhanced reaction) to achieve the vitamin D3 classic form, The plasmic membrane of keratinocytes, where vitamin D3 resides, expulse the vitamin out of the cell where it binds to a vitamin D binding proteins DBP to be transferred towards the dermal capillary bed, where, and through blood circulation, is transferred to other tissues of the body, mainly the kidneys and the liver [18], [19], [59].

The moment vitamin D molecules reach the liver, vitamin D gets activated by a first hydroxylation converting it to 25-hydroxyvitamin D or D3[25(OH)D] (calcidiol) which is the circulating form of vitamin D and is considered as a biomarker of vitamin D serum levels [18].

On the other hand, when vitamin D reach the kidney, the molecules go through a second hydroxylation into 1α-25 dihydroxyvitamin D3 or [1.25$(OH)_2$ D] or calcitriol [18], [19], [59].

The 1.25$(OH)_2$ D form is considered a secosteroid hormone that function on different sites in different tissues [19].

The change of seasons, the latitude, weather conditions, skin melanin levels and sunscreen usage are all factors that affects directly the production of vitamin D in the epidermis [18], [19].

The best time estimated for a healthy sun exposure is from 10 a.m. to 4 p.m. for 5 to 30 min daily or twice a week to the individual limps or face is enough to trigger the vitamin D synthesize [18].

2.4. SUPPLEMENTS

Supplements usually contain both vitamin D2 and vitamin D3 [18].

Vitamin D2 in supplements comes from yeast's ergosterol that was treated by UV irradiation, and vitamin D3 comes from irradiated lanolin originating from sheep wool, also lichen is another source of vitamin D3 [18]. These vitamins (D2&D3) come in a single or multi-supplements that offers a range of dosage levels. i.e., 1000 to 5000 IU vitamin D per dose and 50000IU of vitamin D per dose [20].

Table Ⅱ: vitamin D content in selected group of food [18]

Food	Micrograms (mcg) per serving	International Units (IU) per serving	Percent DV*
Cod liver oil, 1 tablespoon	34.0	1,360	170
Trout (rainbow), farmed, cooked, 3 ounces	16.2	645	81
Salmon (sockeye), cooked, 3 ounces	14.2	570	71
Mushrooms, white, raw, sliced, exposed to UV light, ½ cup	9.2	366	46
Milk, 2% milkfat, vitamin D fortified, 1 cup	2.9	120	15
Soy, almond, and oat milks, vitamin D fortified, various brands, 1 cup	2.5–3.6	100–144	13–18
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 1 serving	2.0	80	10
Sardines (Atlantic), canned in oil, drained, 2 sardines	1.2	46	6
Egg, 1 large, scrambled	1.1	44	6
Liver, beef, braised, 3 ounces	1.0	42	5
Tuna fish (light), canned in water, drained, 3 ounces	1.0	40	5
Cheese, cheddar, 1.5 ounce	0.4	17	2
Mushrooms, portabella, raw, diced, ½ cup	0.1	4	1
Chicken breast, roasted, 3 ounces	0.1	4	1
Beef, ground, 90% lean, broiled, 3 ounces	0	1.7	0

DV: daily value.

3. VITAMIN D FUNCTIONS

In this part of the research, several functions of the vitamin D and its role in different tissue are covered.

3.1. GENE TRANSCRIPTION REGULATION

Through high affinity, the binding of $1.25(OH)_2$ D to its receptors VDR induces the binding of X receptors of retinoic acid to form a heterodimeric complex, this complex binds with specific nucleotide sequences in the DNA that are defined as vitamin D response elements, this binding triggers the attachment of a variety of transcription factors resulting in the up regulation and down regulation of gene's expression [19].

3.2. BONE HEALTH

1.25(OH)D3 binds to VDR in osteoprogenitor cells along with osteoblasts precursors generating a cell-to-cell contact that promote osteoclast formation with the purpose of bone resorption under the up regulation of osteoprotegerin ligand (RANKL) of the osteoblastic cells by 1.25(OH)D3, it also promotes the production of osteocalcin in osteoblastic cells which is involved in new bone formation [20].

3.3. INTESTINAL CALCIUM ABSORPTION

$1.25(OH)_2$ D3 stimulates calcium pumps PMCA-1 situated in the plasmic membrane of intestinal cells along with PMCA-1 mRNA, subsequently altering calcium extrusion from the cell and calcium absorption, adding to that, studies showed that $1.25(OH)_2$ D3 affects calcium diffusion indirectly through the induction of callbindin, calcium binding proteins [20], [60].

3.4. CELL DIFFERENTIATION AND PROLIFERATION

A study reported the role of $1.25(OH)_2$D3 in inhibiting cell proliferation and promoting cell differentiation along keratinocytes in leukaemia cells (Suda1989) [20].

Other studies showed its role in the inhibition of the proliferation of colon, breast, prostate cancer cells Krishnan et al., 2003) [20], [60].

p21 and p27 expression induction by $1.25(OH)_2$ D3 which are responsible of growth regulation [20], [61].

3.5. HORMONE SECRETION

$1.25(OH)_2$ D3 has an indirect effect on oestrogen synthesize by maintaining calcium homeostasis and it was suggested by kinuta et al.,2000 that $1.25(OH)_2$ D3 directly regulates the aromatase gene along with normalizing insulin secretion [20].

3.6. IMMUNITY

It was reported that $1.25(OH)_2$ D3 is able to inhibit the differentiation and survival of dendritic cells which accordingly causes an impaired alloreactive activation for T lymphocytes , and in another study $1.25(OH)_2$D3 was discovered to have an immunosuppression effect that was suggested to play a major role in supressing some autoimmune disorders along with drugs of the same function such as cyclosporin A. it was also reported that $1.25(OH)_2$ D3 is an inducer of antimicrobial peptides gene expression [20].

Past studies also showed the activity of $1.25(OH)_2$ D3 on T lymphocytes by suppressing their proliferation and regulating their cytokine production and in other in vitro studies a suppressing activity of $1.25(OH)_2$ D3 on Th17 and Th1 cytokine secretion was observed along an opposing activity of promoting Th2 cytokines secretion ; it was also confirmed that $1.25(OH)_2$ D3 possess a direct interaction with B lymphocytes by inhibiting cell differentiation of plasma cells and class-switched memory cells [21].

4. VITAMIN D DEFICIENCY

Due to constant emerging studies, vitamin D levels that correspond to vitamin D deficiency or insufficiency or sufficiency are yet to be defined precisely [21]. However, 25(OH) D was considered the biomarker of serum vitamin D levels due to the molecule's long half-life of 15 days [18], and so it was estimated that a level superior than 30 n/mL is considered a healthy level of serum vitamin D, and these levels are measured either by radioimmunoassay and competitive protein binding or by LC-MS for a quantitative measurement of 25(OH) D_2 and 25(OH) D3 [22].

4.1. VITAMIN D DEFICIENCY OUTCOMES

4.1.1. Musculosketal system

Low levels of $25(OH)_2$ D contribute to low bone mineral density, and increased risk of hip factor and nonvertebral and according to woman's health initiative, low levels of serum 25(OH) D of 10ng/mL present an increase in odds ratio of risk of hip factor moreover, in

another study, Low levels of circulating $25(OH)_2D$ contribute to persistent hyperparathyroidism and a higher osteoclastogenesis activity causing bone resorption at high levels [23].

4.1.2. Microbial disease

The intrusion of microbial agents into the body triggers an anti-microbial response, where pathogen associated patterns PAMPs triggers the toll like receptors TL12 pathway of monocyte-macrophage activating as a result the $CYP27B_1$-hydroxylase along with VDR gene expression in the cell to allow the binding of $1.25(OH)_2D3$ to its receptors to allow the expression of 1,25-(OH)2D-VDR-directed antimicrobial genes, low levels in vitamin 25(OH)D and subsequently, low levels of $1.25(OH)_2D3$ hinder the activation of these genes and its products, i.e., cathelicidin [23], [62].

Recent study by Ginde et al., about NHANES III population indicates that upper respiratory tract infection spread regardless of season, respectively follows the drop in 25(OH)D serum levels, which is obviously increase in winter time [63].

4.1.3. Cardiovascular disease

Following the same previously mentioned population, the prevalence of heart failure, coronary artery disease and peripheral artery disease increase with the decrease in 25(OH)D serum levels(<30-20ng/mL) [23].

4.2. VITAMIN D DEFICIENCY ETIOLOGY

A decline in vitamin D containing nutrients and supplements consumption is one of the many causes of vitamin D deficiency, along with the cut off on sun exposure periods, less than 20 min and less than 40% of the body exposed, is another cause; adding to that aging, melatonin levels (dark skin), consistent use of sunscreen are other risk factors, Plus other factors such as celiac disease and other malabsorption-causing diseases and some medications that promote the degradation of vitamin D. Refampin, and of course other hereditary diseases or genetic mutations that causes cells to develop resistance to vitamin D [24].

4.3. VITAMIN D DEFICIENCY & ASTHMA

A lot of studies have suggested the effects of low serum 25(OH)D on lung function. The main cause of asthma symptoms and their aggravation would be the narrowing of airways, and some studies hinted at the corelation between worsening narrowing of the airways and low serum levels of 25(OH)D [25].

Vitamin D possess an anti-proliferation affects that hinder the cell cycle and so inhibits hyperplasia of airway smooth muscle ASM [64]; also, under the effect of high vitamin D levels, airway remodelling could be improved by down regulating MMP-9 expression, that is usually secreted during an inflammatory response [65].

Down regulation of the ADAM33 metalloprotease expression that plays a major role in asthma and asthma severity by reducing the resulting outcomes of its activity (bronchial hyperresponsiveness, airway remodelling, etc.) [25], [65].

It was suggested by Banerjee et al., that vitamin D could aid in adjusting airway responsiveness by regulating ASM chemokines expression [66].

A cross study established by Turkeli et al., in children with asthma revealed that children with low vitamin D serum levels experience severe exacerbation that requires treatment and hospitalization. And from the group of children with low circulating vitamin D levels 72.2% of theme were deficient and showed clear signs of uncontrolled asthma [26].

PRACTICAL PART

METHODS

1. STUDY PROPERTIES

1.1. OBJECTIVES

i) to search for a correlation between vitamin D deficiency and asthma exacerbation in severe asthma patients.

ii) to find out from patient's medical records whether health care providers took in consideration the measurement of vitamin D serum levels during the follow-up visits.

1.2. TYPE OF THE STUDY

This is a cross-sectional epidemiological study based both on interviews with patients using a questionnaire that we drew up, and on a retrospective study of patients' medical records supplied by the pneumo-phtisiology department of the Nedir Mohamed University Hospital in Tizi-Ouzou.

1.3. PERIOD AND PLACE OF THE STUDY

The study was conducted at the pulmonology service of the Belloua hospital, affiliated to the university hospital centre Nedir Mohamed of Tizi-Ouzou. Interviews and data collection were performed from the beginning of June until the end of August.

1.4. TARGETED POPULATION

The study targeted the adult asthmatic patients attending the pneumo-phtisiology service that suffers from severe asthma (hospitalised or not). The total number of the selected patients is 20 patients, with an age range of 29 to 76 years old.

1.5. DATA COLLECTION

The data presented in this research was collected through patient medical files (patient history) and through interview (by a survey) where patients are questioned directly and the survey is filled in by us to maintain a homogenous pattern of answers and to avoid any embarrassment and time waste.

The patients were summoned by the service chef's secretary and the meeting took place at the Meeting room of day hospital.

1.6. STUDY CRITERIA

1.6.1. Inclusion criteria

The patients included in the study were adults suffering from severe asthma that consulted the service of pneumo-phtisiology and had their phone numbers in the medical records.

1.6.2. Exclusion criteria

Patients with mental problems, children, and those who don't have their phone number in the medical records are excluded from the study.

1.7. THE SURVEY

The collection of data by patient interview was achieved through the use of a survey that we prepared. The survey consists of an assembly of published questions about both asthma and vitamin D of other studies and articles that were adjusted as necessary to serve the purpose of our study.

1.7.1. Survey aspects

1.7.1.1. Socio-demographic factors

Gathering socio-demographical characteristics about the patient including their full name, address, age, sex, job statue and their IMC.

1.7.1.2. Asthma severity

Questions in the purpose of gathering information about the patient's asthma severity level and asthma triggers along with its effects on their life and their activity and they englobe the total of 14 questions followed by sub-questions.

These questions were followed lastly by Asthma Control Test (ACT), to assess the degree of asthma control, consists of 5 questions, each question have 5 answers on the scale from 1 to 5.

The results of test are presented as the sum of the scores of each question, and then compared to an official interval that indicates the level of control of asthma.

- From 7 to 14 asthma is considered non-controlled.

- From 15 to 19 asthma is considered partially controlled.

- From 20 to 25 asthma is considered well controlled.

1.7.1.3. Vitamin D deficiency

A set of 5 questions followed with sub-questions, to investigate the patient awareness of their vitamin levels and whether their deficiency was treated or not, and if so, what treatment plan did they follow.

1.8. PATIENT MEDICAL RECORDS

Specific informations were extracted including information about the patient personal data, asthma class and severity, diagnosis, blood tests, hospitalizations, treatments, and the provided health care during the hospitalization period.

1.9. STATISTICAL ANALYSIS

We conducted a descriptive analysis of quantitative and qualitative variables as a part of our statistical analysis. Moreover, the search of whether these numeric variables have a relation between them is conducted by using the bivariate Pearson correlation. Categorical variables are presented in percentage (%), correlation is researched using Chi-squared test of independence.

Statistical analysis was conducted using the software SPSS version 25.0 (Chicago, IL, USA).

RESULTS AND DISCUSSION

1. FINDINGS

1.1. POPULATION'S GENERAL CHARACTERISTICS

1.1.1. Sex & age

A total of 18 severe asthmatics were interviewed. Among them 55.6% were females (n=10), and 44.4% were males (n=8), (figure 5); with an age average of 61 years old (M=60.83).

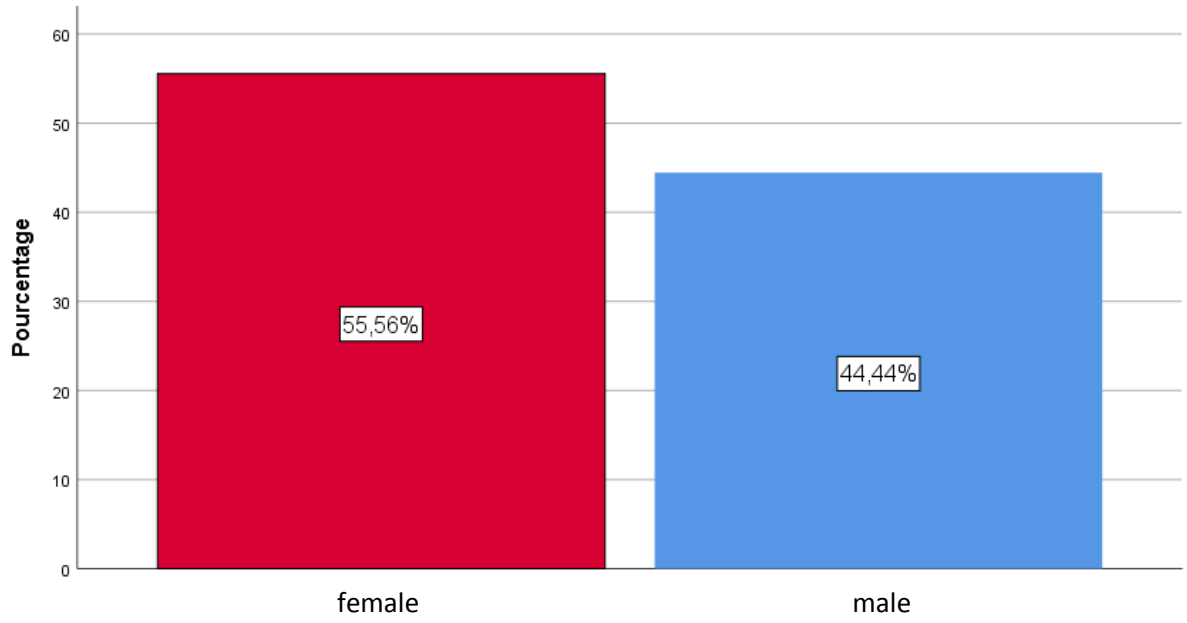

Figure 5. Sex distribution

1.1.2. BMI??(Body Mass Index)

With an average of 26.82, 50% of the patients present a normal body mass, while 33.3% are overweight. On the other hand, 5.6% were obese, 5.6% were extremely obese, and 5.5% were morbidly obese.

1.1.3. Living area, weather, presence of near asthma triggers

The studied population shows an even distribution, indeed, 50% were reported to live in urban areas (Tizi-Ouzou city) and the other 50% in rural areas (Redjaouna, Draa El Mizan, etc.).

Most of the patients (55.6%) were living in areas that are predominantly dry and sunny, whilst 44.4% were reportedly living in humid and cloudier areas. Moreover, 38.9% reported living close to forests, 11.1% having animals and 5.6% were living close to both dams and landfills. Similarly, 5.6% living close to forests & animals, and equivalently 5.6% close to dams &

animals, and 5.6% close to dams & forests & animals, also in a similar fashion, 5.6% having animals & factories & landfills close to their living area. However, 16.7 % did not report any close triggers to their living environment (figure 6).

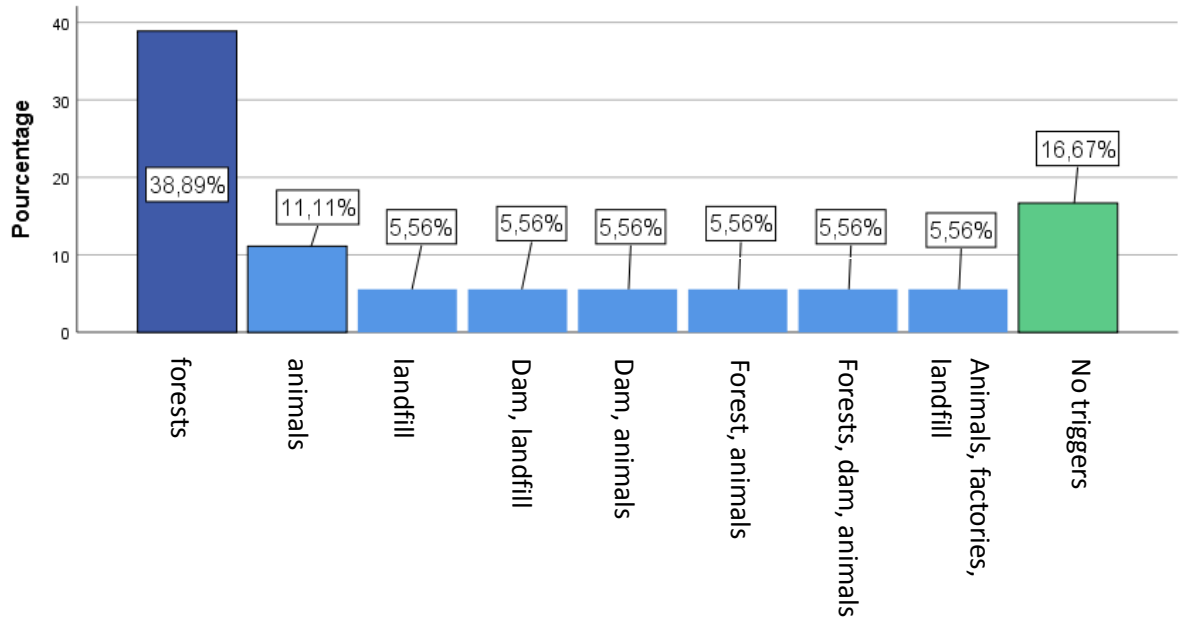

Figure 6. Frequency of asthma triggers

1.1.4. Patient activity and job status

Most of the patients (77.8%) claimed to have a sedentary life style and feeling constantly tired. In contrast, 5.6% were active, and 16.7% were moderately active.

On the other hand, 16.67% of the interviewed patients were employed, whereas 83.33% were either retired or staying at home.

- The absence (from work) average in a year is estimated to be 9 times/year (M= 8.3333).

1.2. ASTHMA SEVERITY

1.2.1. Asthma diagnosis

The mean age for asthma and severe asthma diagnosis were 39.83±14.65 and 53.27±17.12 respectively. Most of the patients (66.7%) have allergies (dust, cold, pollen, etc.) and 61.1% have medical history of asthma.

1.2.2. Hospitalization & physiotherapy

66.67% of the patients were hospitalized this year, and 77.78% were admitted to the ER (emergency room) only.

Within the patients: the mean of hospitalization was up to 1.44±2.04, and the mean of admittance to the emergency room was up to 5.33±5.66, similarly, the mean of asthma aggravation was also up to 5.33±5.71.

Moreover, stress was the main trigger for 27.78% of the patients, for 11.11% was the flu, for 22.22% no specific trigger.

94.9% of patients follow a routine check-up (figure 7), and 83.3% claim to be compliant to doctor orders.

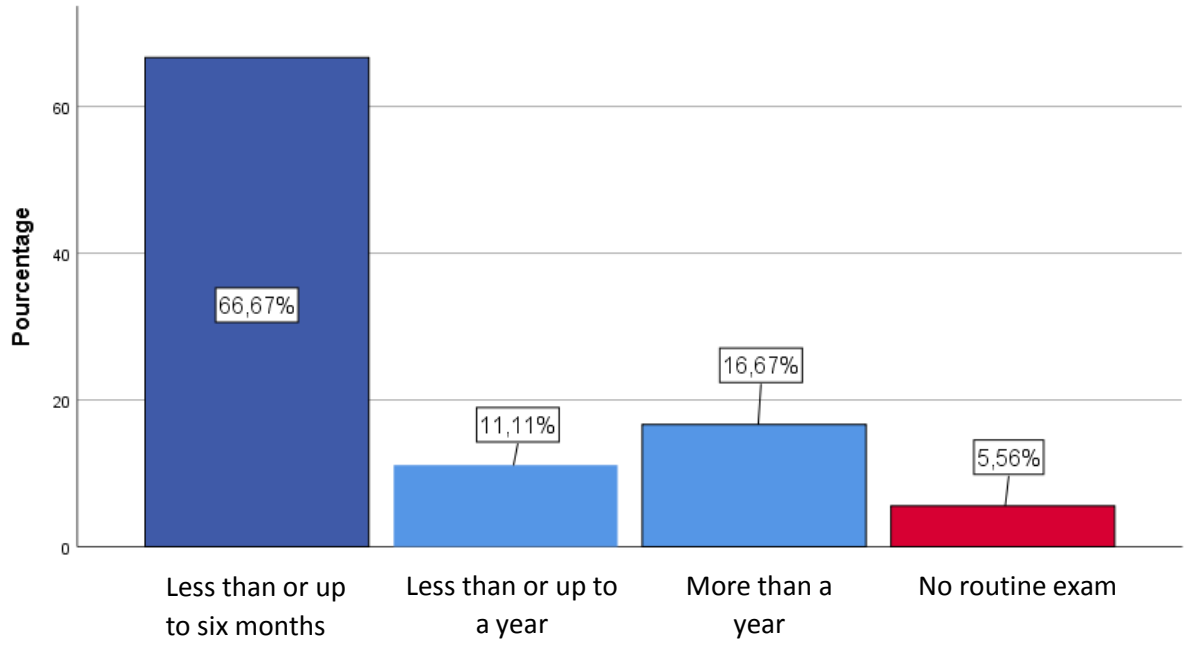

Figure 7. Patient's routine check-up.

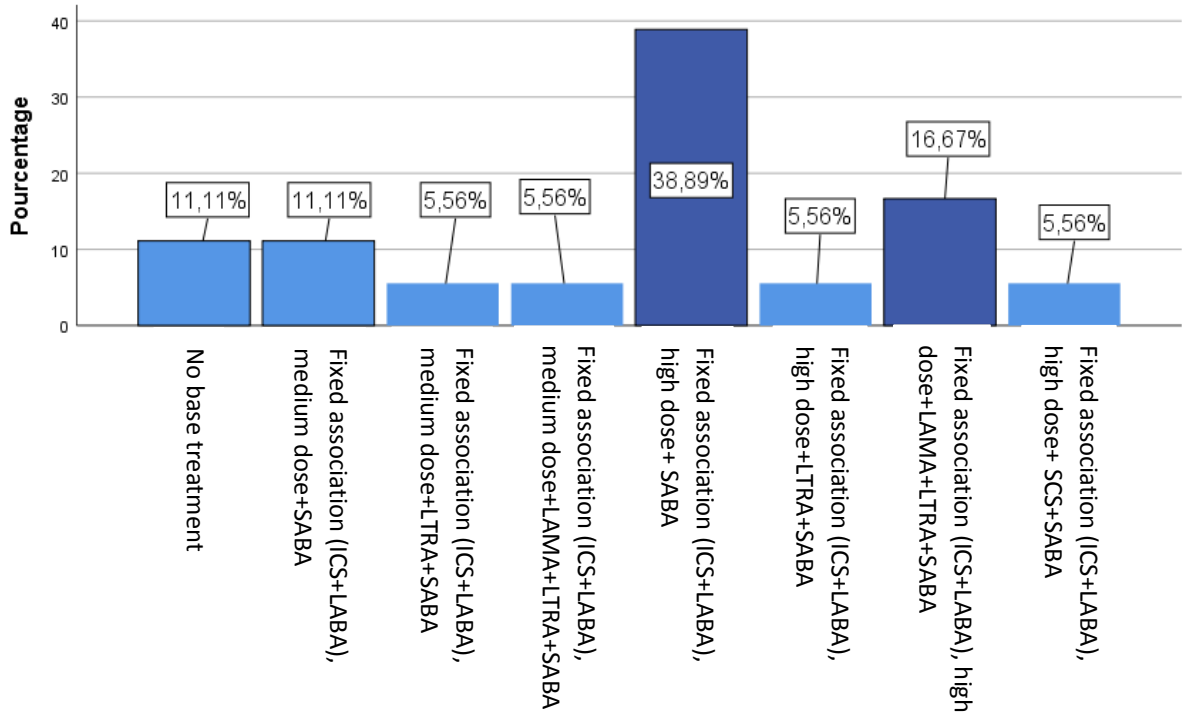

Figure 8. Patient's treatment.

1.2.3. Class of asthma

Majority of patient (88.9%) experience severe persistent asthma and 11.11% are unidentified. (Figure 9).

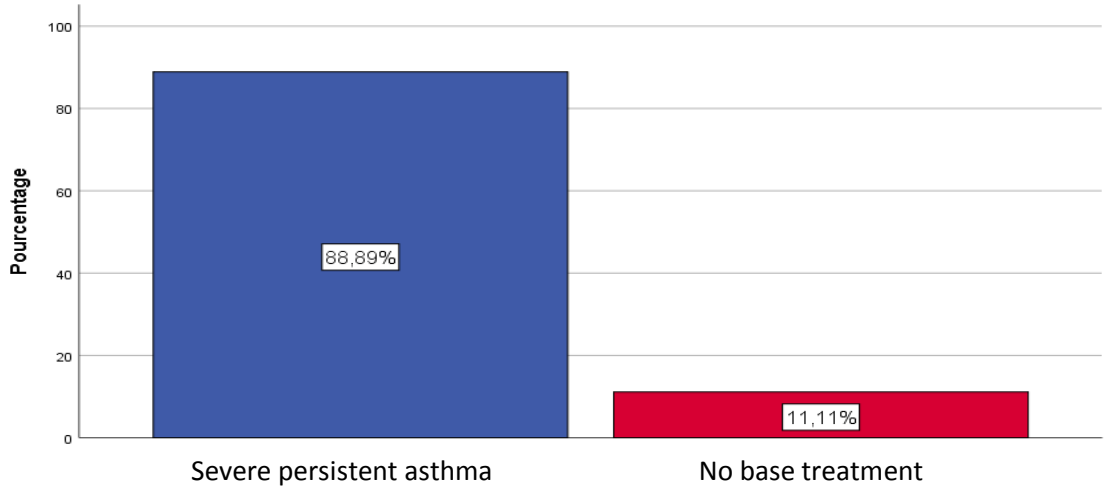

Figure 9. Asthma classes

1.2.4. Asthma symptoms

The most persistent type of symptoms were chest pain & whistling& trouble breathing& nocturnal awakenings for 16.67% of the patients (figure 10).

Asthma symptoms aggravation worsen especially in winter for 38.89% of the patients (figure11).

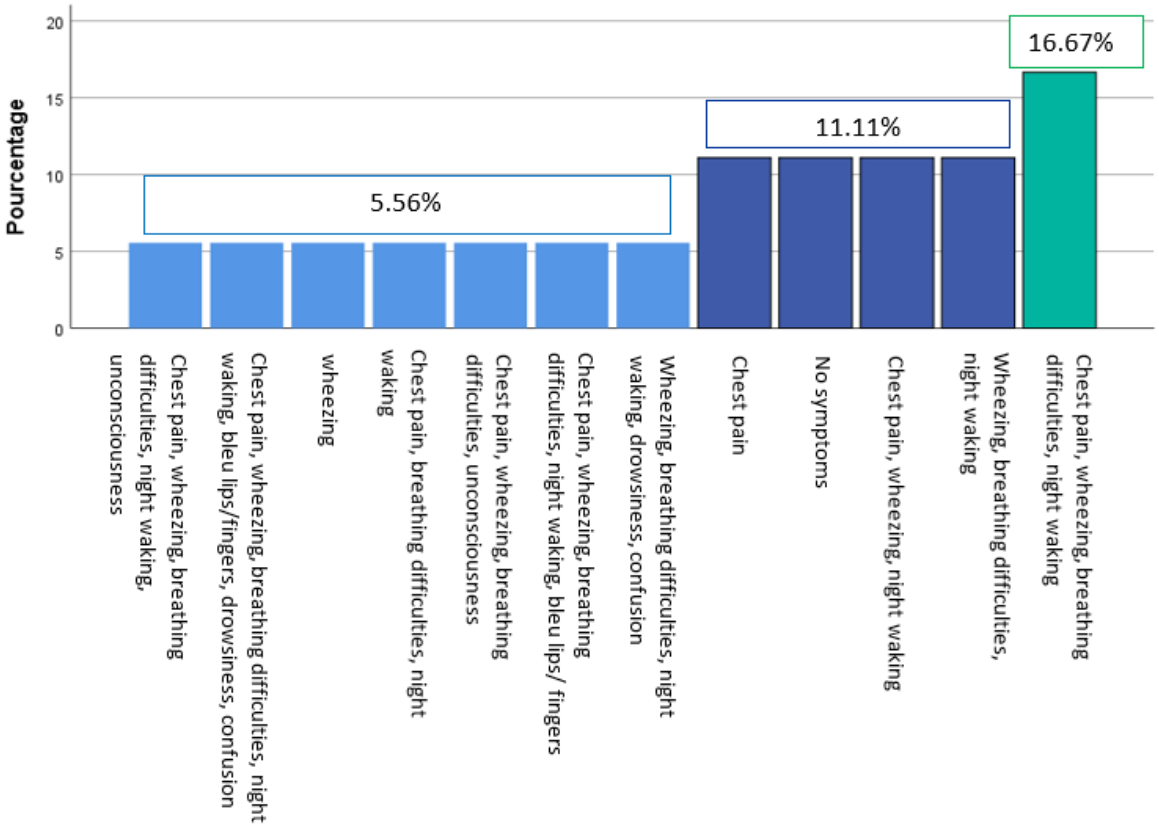

Figure 10. Asthma symptoms distribution

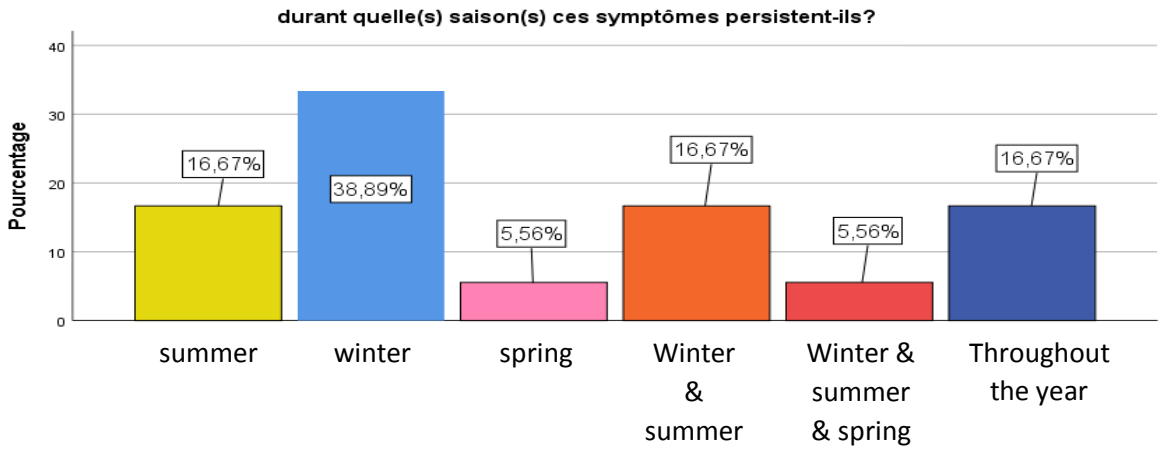

Figure 11. Season of asthma exacerbation.

1.3. VITAMIN D

1.3.1. Skin complexion/outdoor activity/sun exposure

66.7% of patients spend their time outdoor often, with an average of 2h a day. Also 38.89% of the patients display olive skin tone, and 61.11% of them display white/fair complexion.

1.3.2. Vitamin D deficiency

Up to 33.3% of the asthmatic patients suffer from vitamin D deficiency, and up to 33.3% had their deficiency treated, 27.8% with supplements and non with a vitamin D rich diet, however 33.33% of the patients have no vitamin D deficiency (figure 12).

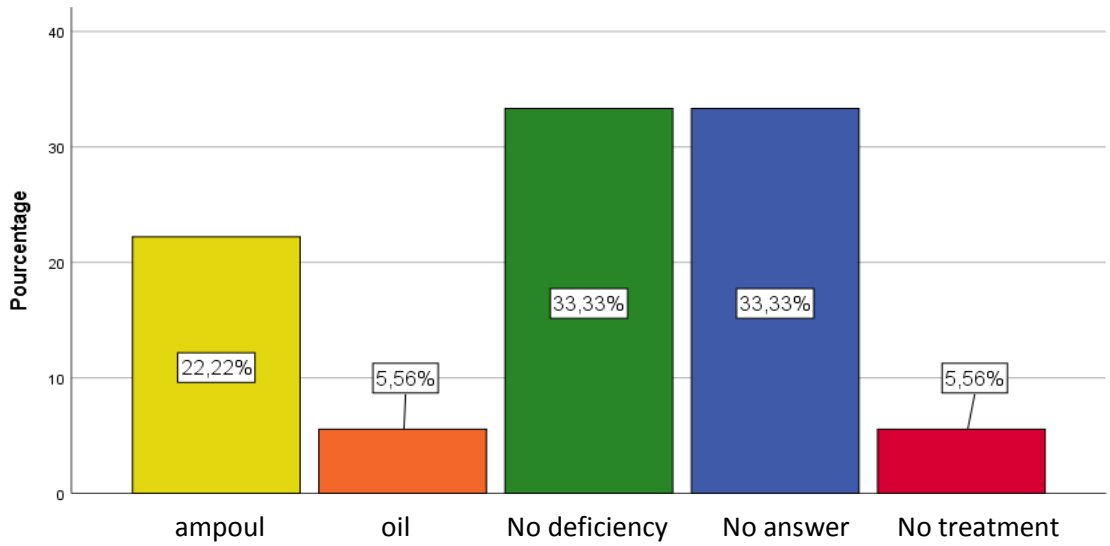

Figure 12. vitamin D deficiency and treatment.

1.4. DIGESTIVE PROBLEMS & OTHER MORBIDITIES AND DEFICIENCIES

27.8% of patients experience digestive issues, 22.22% diagnosed with IBS and 5.6% diagnosed with Ulcerative colitis (figure 13). Moreover, 11.1% of these individuals were diagnosed with anaemia and 5.6% were diagnosed with both anaemia and calcium insufficiency (figure 14).

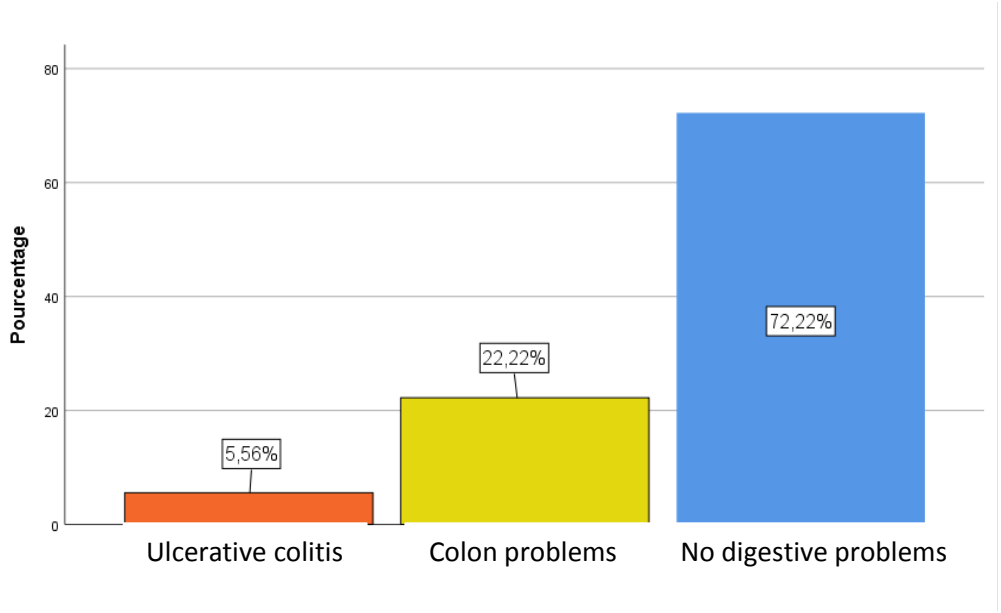

Figure 13. Digestive issues.

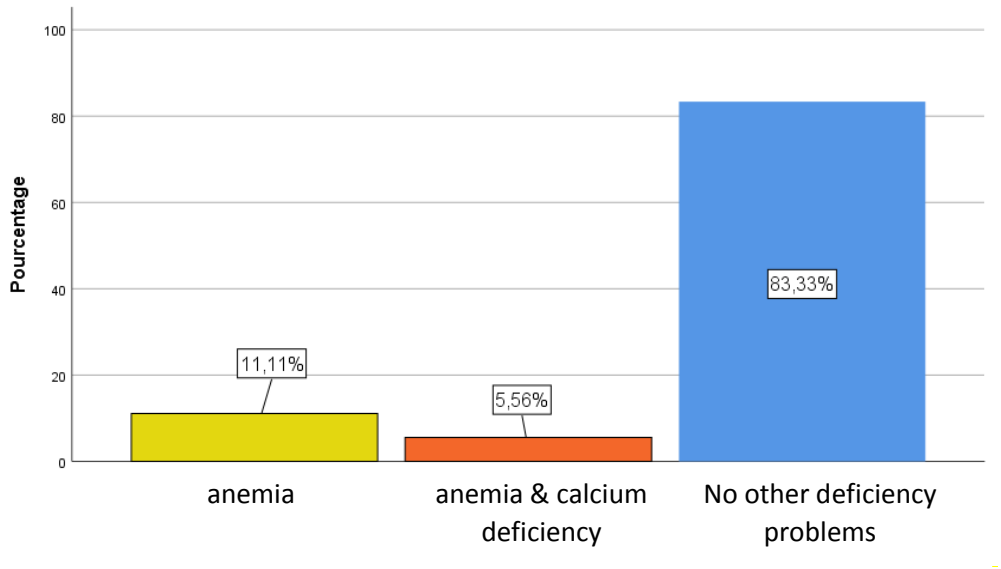

Figure 14. Other deficiencies.

55.6% of patients had other morbidities, such as heart problems, hypertension, diabetes, arthritis, etc., (figure 15).

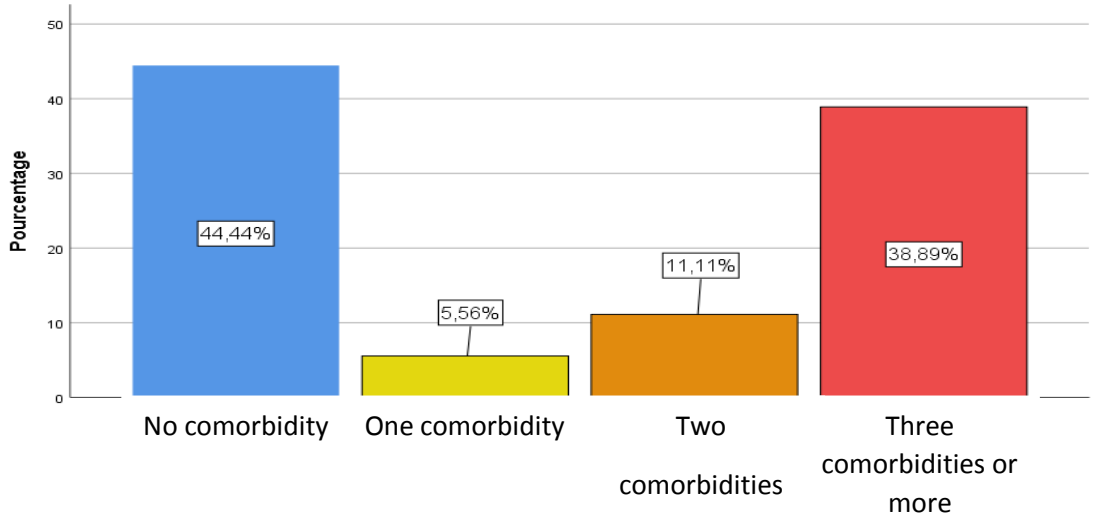

Figure 15. Comorbidities.

1.5. ASTHMA CONTROL TEST (ACT)

within the asthmatic patients:

27.78% of the interviewed patients had a well-controlled asthma, and 33.33% had a partially controlled asthma, similarly, 38.89% had a non-controlled asthma.

1.6. THE CORELATIONS BETWEEN ASTHMA AND VITAMIN D DEFICIENCY PARAMETERS

- To measure the linear correlation between two numeric variables, bivariate Pearson correlation is used.
- Similarly, in search for whether two categorical variables are independent or associated, Chi-squared test of independence is also used (table Ⅲ).

Table III: corelation between asthma and vitamin D deficiency.

		BMI score of the interviewed asthmatics	average annual absenteeism	What is your level of sun exposure (per hour)?	At what age were you diagnosed with asthma?	At what age did you discover that your asthma is severe?	What is the date of your last routine check-up (per year)?	If yes, how many times have you experienced an episode of respiratory distress?	If yes, how many times have you been admitted to the emergency room?	If yes, how many times have you been hospitalized?	Asthma Control Test score
BMI score of the interviewed asthmatics	Corelation de Pearson	1	-,450	-,337	-,302	-,273	-,188	-,093	-,085	-,070	,058
	Sig. (bilateral)		,703	,171	,224	,417	,454	,712	,738	,782	,820
	N	18	3	18	18	11	18	18	18	18	18
average annual absenteeism	Corelation de Pearson	-,450	1	1,000**	,286	1,000**	1,000**	-1,000**	-,945	-,866	,904
	Sig. (bilateral)	,703		,000	,815	.	,000	,000	,212	,333	,281
	N	3	3	3	3	2	3	3	3	3	3
What is your level of sun exposure (per hour)?	Corelation de Pearson	-,337	1,000**	1	-,114	,240	,436	-,547*	-,537*	-,369	,490*
	Sig. (bilateral)	,171	,000		,652	,477	,070	,019	,022	,132	,039
	N	18	3	18	18	11	18	18	18	18	18
At what age were you diagnosed with asthma?	Corelation de Pearson	-,302	,286	-,114	1	,723*	-,183	,246	,250	,378	-,169
	Sig. (bilateral)	,224	,815	,652		,012	,468	,326	,317	,122	,502
	N	18	3	18	18	11	18	18	18	18	18
At what age did you discover that your asthma is severe?	Corelation de Pearson	-,273	1,000**	,240	,723*	1	-,224	-,706*	-,707*	-,094	,143
	Sig. (bilateral)	,417	.	,477	,012		,507	,015	,015	,782	,676
	N	11	2	11	11	11	11	11	11	11	11
What is the date of your last routine check-up (per year)?	Corelation de Pearson	-,188	1,000**	,436	-,183	-,224	1	-,227	-,224	-,170	,056
	Sig. (bilateral)	,454	,000	,070	,468	,507		,365	,372	,501	,826
	N	18	3	18	18	11	18	18	18	18	18
If yes, how many times have you experienced an episode of respiratory distress?	Corelation de Pearson	-,093	-1,000**	-,547*	,246	-,706*	-,227	1	,988**	,549*	-,682**
	Sig. (bilateral)	,712	,000	,019	,326	,015	,365		,000	,018	,002
	N	18	3	18	18	11	18	18	18	18	18
If yes, how many times have you been admitted to the emergency room?	Corelation de Pearson	-,085	-,945	-,537*	,250	-,707*	-,224	,988**	1	,542*	-,676**
	Sig. (bilateral)	,738	,212	,022	,317	,015	,372	,000		,020	,002
	N	18	3	18	18	11	18	18	18	18	18
If yes, how many times have you been hospitalized?	Corelation de Pearson	-,070	-,866	-,369	,378	-,094	-,170	,549*	,542*	1	-,561*
	Sig. (bilateral)	,782	,333	,132	,122	,782	,501	,018	,020		,016
	N	18	3	18	18	11	18	18	18	18	18
Asthma Control Test score	Corelation de Pearson	,058	,904	,490*	-,169	,143	,056	-,682**	-,676**	-,561*	1
	Sig. (bilateral)	,820	,281	,039	,502	,676	,826	,002	,002	,016	
	N	18	3	18	18	11	18	18	18	18	18

** The correlation is statistically significant at the 0.01 level (bilateral)

* The correlation is statistically significant at the 0.05 level (bilateral)

According to the bivariate Pearson correlation, there is no corelation between asthma exacerbation and vitamin D deficiency, similarly, there is no corelation between asthma symptoms aggravation and vitamin D deficiency. (There is a significant negative correlation between sun exposure and ICU admission and exacerbation; a significant positive one between ACT score and sun exposure; the correlation between sun exposure and hospital admission was negative but not significant)

1.6.1. The relationship between vitamin D deficiency and asthma exacerbation

Depending on Chi-square test of independence (table IV), there is no association between asthma exacerbation and vitamin D deficiency, P-value > 0.05.

Table IV: Chi-square test of independence for vitamin D deficiency & asthma exacerbation.

Chi-squared tests			
	Value	df	Asymptotic significance (bilateral)
Pearson's chi-squared test	,643[a]	2	,725
Likelihood ratio	,618	2	,734
Number of valid observations	18		

a. 6 cells (100.0%) have an expected count less than 5. The minimum expected count is 1.33.

1.6.2. The relationship between vitamin D deficiency and asthma symptoms aggravation:

Depending on Chi-square test of independence (table V), there is no association between asthma symptoms aggravation and vitamin D deficiency, P-value > 0.05.

Table V: Chi-square test of independence for vitamin D deficiency & asthma symptoms aggravation.

Chi-squared tests			
	Value	df	Asymptotic significance (bilateral)
Pearson's chi-squared test	26,000[a]	22	,252
Likelihood ratio	30,186	22	,114
Number of valid observations	18		
a. 36 cells (100.0%) have an expected count less than 5. The minimum expected count is 0.33.			

1.6.3. The relationship between vitamin D deficiency and asthma control test (ACT)

Depending on Chi-square test of independence (table VI), there is no association between asthma control test score interpretation and vitamin D deficiency, P-value > 0.05.

Table VI: Chi-square test of independence for vitamin D deficiency & ACT score interpretation.

Chi-squared tests			
	value	df	Asymptotic significance (bilateral)
Pearson's chi-squared test	4,600[a]	4	,331
Likelihood ratio	4,531	4	,339
Number of valid observations	18		
a. 9 cells (100,0%) have an expected count less than 5. The minimum expected count is 1,67.			

1.7. PATIENT MEDICAL FILES STUDY

After an attentive through study of patient's medical files, the significant main results are presented in the table down below (table VII).

Table VII: patient's medical files analysis.

Patient general information	Clinical characteristics	Biological analysis
PATIENT 01	1-HOSPITALIZATION: 10 to17 Mars 2024. 2-DIAGNOSIS: Bronchial asthma exacerbation. Dyspnoea. 3- CATEGORY OF ASTHMA: Severe persistent asthma. 4- TREATMENT: Symbicort 400/12 (twice,2/j) +Ventolin 100mcg (twice, in case of dyspnoea). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5- DISEASE CONTROL: According to the patient's ACT score, the asthma is partially controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. URINE CYTOCOLOGY. HbA1c TEST. CREATININE TEST. CRP TEST. PT TEST. BLOOD UREA NITROGEN TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 02	1-HOSPITALIZATION: 11Sep 2011to 09 Jan 2012 11-15 Apr 2012 22 Jan to 03 Fab 2019 08-14 Apr 2019 10-19 Jan 2023 2-ASTHMA DIAGNOSIS: Bronchial asthma severe exacerbations. Aspirin- exacerbated respiratory disease. 3-CATEGORY OF ASTHMA: Severe persistent asthma. 4-TRAITMENT: symbicort 400/12 (1P,2/d) +montelukast 10mg (1/d) +donicort (2/j) (sinusitis treatment) Ventolin (in case). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is partially controlled. According to the patient medical files the exacerbation was controlled.	THE RECENT TESTS2023: HEMOGRAME. ELECTROLYTE TEST. URINE CYTOCOLOGY. HbA1c TEST. CREATININE TEST. CRP TEST. PT TEST. ALT TEST. AST TEST. ALP TEST. GGT TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 03	1-HOSPITALIZATION: 26 to 30 Dec 2019. 2-DIAGNOSIS: Flu-like syndrome. Dyspnoea. Moderate asthma exacerbations. 3- CATEGORY OF ASTHMA: Intermittent asthma. 4-TREATMENT: Bricoal 500mg (2/d). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is well controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. CRP TEST. PT TEST. BLOOD UREA NITROGEN TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 04	1-HOSPITALIZATION: 12 to15 Jan 2022. 2-DIAGNOSIS: Pulmonary infection. Bronchial asthma exacerbations. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TRAITMENT: Symbicort 400mg+ Ventolin. - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: The patient was not interviewed, thus, there is no associated ACT score, asthma control is undefined. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. PT TEST. aPPT TEST. FIBRINOGENE TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 05	1-HOSPITALIZATION: 13 to 16 Apr 2024. 2-DIAGNOSIS: Bronchial asthma exacerbations. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TRAITMENT: Spiriva (1/d) +Ventolin 100 mcg (in case). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is not controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 06	1-HOSPITALIZATION: 13 to 16 Jan 2022. 2-DIAGNOSIS: Bronchial asthma exacerbations. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: Seretide 400 (2P,2/d) +Ventolin (in case). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is well controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTES TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITOGEN. CRP TEST. PT TEST. aPPT TEST. FIBRINOGENE TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 07	1-HOSPITALIZATION: 01 to 16 Jan 2024. 2-DIAGNOSIS: Bronchial asthma exacerbation. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: symbicort 400mcg (2P,2/j) +montelain (1/night) +Ventolin (in case). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is partially controlled. According to the patient medical files the exacerbation was controlled after treating low cortisol levels.	HEMOGRAME. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 08	1-HOSPITALIZATION: 03 Jun 2024. 2-DIAGNOSIS: Moderate asthma exacerbation. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: symbicort 200mg (twice,2/d) +Biflor 5mg (1/d) +Nasacort (twice,2/d). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is partially controlled. According to the patient medical files the exacerbation was controlled	HEMO GRAME. ELECTROLYTE TEST. BLOOD UREA NITROGEN. CRP TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 09	1-HOSPITALIZATION: 15 to 21 May 2024. 2-DIAGNOSIS: Bronchial asthma exacerbations caused by AINS allergy (volterene). Dyspnoea. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: Ventolin 5mg (in case) +Seretide 5mg (twice/d). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is not controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYRE TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITROGEN. CRP TEST. PT TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 10	1-HOSPITALIZATION: 05 to 31 Oct 2019 2-DIAGNOSIS: Severe asthma exacerbation. Dyspnoea. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: Montelukast 10 mg (1/d) +Spiriva + Ventolin (in case) +Brequal 50/500 (2P/2d). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is uncontrolled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. BLOOD UREA NITROGEN TEST. CREATININE BLOOD TEST. CRP TEST. PT TEST. ALT TEST. AST TEST. ALP TEST. aPPT TEST. GLUC TEST. TCT TEST. BILIRUBIN TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 11	1-HOSPITALIZATION: 11 to 16 May 2024 2-DIAGNOSIS: Bronchial asthma exacerbation. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: Symbicort 200mg (2foie,2/j) + Ventolin (in case). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-ASTHMA CONTROL: According to the patient's ACT score, the asthma is uncontrolled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. GLYCOSILATED HIMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. ELECTROLYTE TEST. TCT TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 11	1-HOSPITALIZATION: 26 to 28 Apr 2024. 2-DIAGNOSIS: Moderate exacerbations of bronchial asthma. 3-CATEGORY OF ASTHMA: Persistent asthma. 4-TREATMENT: Symbicort 400mg (2P/d) +Montelaire + ventolin +anti-histamine + Nasal spray. - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: The patient was not interviewed, thus there is no associated ACT score. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITROGEN TEST. CREATININE BLOOD TEST. CRP TEST. TCT TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 13	1-HOSPITALIZATION: 11 to 19 Mar 2019. 2-DIAGNOSIS: Severe asthma exacerbation. Dyspnoea grade Ⅲ. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: symbicort 200mcg (1P,2/d) +Spiriva 18mcg (1/d) +Montelukast (1/d) +Nasonex (1/d) +Ventolin (2P/d), (in case of attack). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is well controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. PT TEST. aPPT TEST. GLU TEST. TCT TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 14	1-HOSPITALIZATION: 03 to 09 Jun 2024. 2-DIAGNOSIS: Bronchial asthma exacerbations. Dyspnoea. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: symbicort 400 (2P,2/d) +Ventolin (in case) +Solupred (6d). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient ACT score, the asthma is partially controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. ALT TEST. AST TEST. ALP TEST. GGT TEST. BiLiT TEST. BiLD TEST. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 15	1-HOSPITALIZATION: 26 Jun to 01Jul 2024 2-DOAGNOSIS: Severe bronchial asthma exacerbation. Dyspnoea. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: Seretide 500mg (2P/d) +Ventolin (in case). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is not controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. PT TEST. TUBERCOLOSIS NEGATIVE. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 16	1-HOSPITALIZATION: 16 to 22 Dec 2022 08 to 24 Jun 2024 2-DIAGNOSIS: Respectively, Severe asthma exacerbation. Bronchial asthma exacerbation. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: Ventolin 100mg (in case) +Seretide 250mg(twice/d). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is partially controlled. According to the patient medical files the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HIMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. PT TEST. TCT TEST. CALCIUM BLOOD TEST. TUBERCLOSIS NEGATIVE. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 17	1-HOSPITALIZATION: 11 Feb to 04 Mar 2024 2-DIAGNOSIS: Severe asthma exacerbation. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: Ventolin 100mg (in case) +Seretide 500mg (twice/d) + Montelair. - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, asthma is well controlled. According to the patient medical files the exacerbation was persistent before admittance, and during hospitalizing, they were controlled.	HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HIMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. PT TEST. ALT TEST. AST TEST. ALP TEST. GGT TEST. TCT TEST. TSH TEST. FT4 TEST. BiLiT TEST. BiLD TEST. BLOOD GAZ ANALYSIS. TUBERCLOSIS NEGATIVE. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 18	1-HOSPITALIZATION: 10 to 23 May 2023 2-DIAGNOSIS: Uncontrolled asthma. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: foster 100 (2P,3/d) + Spiriva (1/d) + Ventolin (in case) + Montelukast (1/d). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is well controlled. According to the patient's medical files, the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITOGEN. CREATININE BLOOD TEST. CRP TEST. TCT TEST. TUBERCLOSIS NEGATIVE. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 19	1-HOSPITALIZATION: 23Jun to 06 Aug 2023 10 – 17 Sep 2023 07 – 13 Mar 2024 23Apr to 19 Mar 2024 26Jun to 01 Jul 2024 2-DIAGNOSIS: Respectively, - Uncontrolled bronchial asthma exacerbation. - Uncontrolled bronchial asthma exacerbation. - moderate long term bronchial asthma exacerbation. - bronchial asthma exacerbation. - long term bronchial asthma exacerbation. 3-CATEGORY OF ASTHMA: Severe asthma. 4-TREATMENT: Montelukast 10 mg (1/d) +Duovent HFA 0,020 mg/0,050 mg (2,3/d) + symbicort 400mg (2P, twice/d) + Spiriva+ Ventolin (in case). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score the asthma is uncontrolled. According to the patient's medical files, the exacerbation was controlled.	HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. PT TEST. TCT TEST. BLOOD GAZ ANALYSIS. igE TEST. TUBERCLOSIS NEGATIVE. NO 25-HYDROXY VITAMIN D TEST.

PATIENT 20	1-HOSPITALIZATION: (01) 2019 (01) 2022 (06) 2022 (02) 2023 (03) 2024 2-DIAGNOSIS: Bronchial asthma exacerbation. 3-CATEGORY OF ASTHMA: Persistent severe asthma. 4-TREATMENT: Ventolin 100mg (in case) + brequal + aerosol (in case). - While hospitalization, no vitamin D supplements were incorporated in the treatment plan. 5-DISEASE CONTROL: According to the patient's ACT score, the asthma is uncontrolled. According to the patient's medical files, the asthma is persistent but the treatment controls the exacerbation.	THE RECENT TESTS 2024: HEMOGRAME. ELECTROLYTE TEST. GLYCOSILATED HEMOGLOBIN. BLOOD UREA NITROGEN. CREATININE BLOOD TEST. CRP TEST. PT TEST. ALT TEST. AST TEST. ALP TEST. GGT TEST. ALB TEST. BiLiT TEST. BiLD TEST. NO 25-HYDROXY VITAMIN D TEST.

Based on an analysis of the medical records of 20 asthmatic patients, it was found that there was no mention of a vitamin D deficiency check (no 25-hydroxyvitamin D test) in the collective patients' blood test results. In contrast, numerous studies and overviews have demonstrated a link between the management of asthma, aggravation of symptoms, and vitamin D deficiency.

2. DISCUSSION

The study interest is to find an association between vitamin D deficiency and asthma exacerbation in adults. It was carried for 3 months starting from the beginning of June until the end of august, the location of work is Belloua hospital, Tizi-Ouzou.

Within this research we found that:

Within our participants, with an age average of 61 years old, which shows a prevalence of asthma among the older individuals, a strong match to the study conducted in the US based on NHANES data, in which the highest prevalence of asthma was noticed in the patients aged 60 years and older [69]. 55.56% were females and 44.44% were males, similar to the same previous study based on NHANES, also recorded a higher asthma prevalence in females 64.0% and a lower prevalence within males 36.0%; the study emphasizes that females were 1.76 times more likely to have asthma then males [69]. and 66.7% of patients were allergic (dust, pollen, etc.) and 33.3 were non-allergic, moreover, 38.89% of patients presented uncontrolled asthma, similar to the conducted study by EMSA in 2018, in which less than one third of the patients achieved appropriate asthma control [67], and opposing the study by Eman Albataineh et al.in which, from 93 Jordan asthmatics, 45.2% were with controlled asthma and 36.6% were with uncontrolled asthma while 18.3% were uncontrolled [67].

27.78% proclaimed that the main trigger of their asthma exacerbation is stress and 22.22% didn't have any specific trigger to mention, furthermore, 88.9% of the studied population suffers from persistence asthma, the percentages of asthma severity and control support the results of Anna von Bulow et al. in their study in which low asthma control was more prevalent within severe asthmatic patients [68]. In addition, 33.3% of the patients had vitamin D deficiency and 33.3% don't, and 16.7% have other deficiencies (anaemia, calcium, iron), additionally, 27.8% of patients treated their vitamin D deficiency by supplement intake (Ampoule, oil).

Following up, 66.67% of the patients were hospitalized within this year, with a rate of hospitalization of 1 to 2 times a year (M=1.44), and the mean of asthma aggravation within patients is estimated to be up to 5.33±5.71.

The study unfortunately doesn't prove the association between vitamin D deficiency and asthma exacerbation, same with the correlation between vitamin D deficiency and asthma symptom aggravation and dyspnoea occurrence; even the medical records of the 20 asthmatic patients that were analysed showed that none of the patients had a vitamin D deficiency check (no mention of a 25-hydroxyvitamin D test). Although several studies associated low vitamin

D levels with asthma" flare-ups" and poor lung function along with asthma treatment ineffectiveness [26] and it was shown that it has a grand prevalence within chronic lung disease populations [27]. Similar studies that investigated the association between vitamin D and asthma control in adults, observed a more positive results; in which serum levels of 25-hydroxyvitamin D and lung function were measured, 60% of the patients were vitamin D deficient with a noticeable a lower ACT score meaning a higher prevalence of uncontrolled asthma in the sample and a reduced forced expiratory volume in 1 second [70]. Another comparable study, in which serum levels of 25-hydroxyvitamin D and lung function were also measured and the necessary data was collected through a questionnaire including asthma control test, it was recorded that 70% of the participants had insufficient 25(OH)D levels and low vitamin D was linked to poor asthma control, and those who are vitamin D deficient experience asthma exacerbations more frequently [71].

The role of vitamin D in the immunomodulatory of several diseases and it's over all function is quiet intriguing, and it is frustrating for researchers to face the same negative outcomes often, such as Bar Yosef et al. (2015) and Kerley et al. (2016) [26], when the outcomes of their separate studies didn't show any changes in the patient's lung function parameters [26].

In few other studies, conducted for the same purpose, it was reported that a relation exists between low levels of circulating vitamin D [25(OH)D] and acute respiratory infection susceptibility [26].

Another study also showed that the response to the standard corticosteroid therapy is reduced in vitamin D deficient patients [26].

In an example of contradicting outcomes in this subject of study, Brehm in his study linked low levels of circulating 25(OH)D with the risk of severe asthma exacerbation increase [28] and in the contrary Boonpiyatad et al. couldn't find this association although that he found that, indeed,

Patients with asthma present low serum levels of circulating 25(OH)D [28].

At last, a subgroups study showed the efficacity of vitamin D supplementation in reducing asthma exacerbation but these results were only valid for those who had low serum levels of 25(OH)D under 25nmol/L, excluding those with higher serum levels of 25(OH)D. However, the, interaction between subgroups, P-value was insignificant that means these observed results may vary across the different patient's subgroups [28].

To conclude, more studies should be conducted to investigate further in this subject. The short time of the study and the small size of the sample along with the lack of patient awareness and the search for willing collaborators were obstacles that effected this work heavily.

CONCLUSION

Conclusion

The present descriptive epidemiological study investigating the corelation between asthma exacerbations and vitamin D deficiency shows that deficiency in vitamin D was found in 33.3% of the patients, and only 27.8% of them treated it with supplements. The study didn't show relation between vitamin D deficiency and asthma exacerbation and none of the patients whose medical records were examined had a 25-hydroxyvitamin D test indicating a lack of routine investigation of this issue.

The conclusions of this study are subject to certain limitations, most notably the small sample size and the limited study period. Therefore, further research with larger cohorts, conducted over a longer duration, will be necessary to elucidate the relationship between vitamin D status and severe asthma.

ABSTRACT

Abstract

Context:

Vitamin D deficiency was reported to be associated with severe asthma exacerbations. However, numerous studies from developed countries remain contradictory and poorly designed, moreover, data are lacking in the developing countries including Algeria.

Objectives:

(i) Examine the association between vitamin D deficiency and severe asthma exacerbation in adults with asthma, and (ii) find out from patients' medical records whether healthcare providers took into account the measurement of serum vitamin D levels during follow-up visits.

Methodology:

The epidemiological study was conducted in the pneumo-phtisiology services of Belloua Hospital, in Tizi-Ouzou city. Twenty medical records of adult asthmatics were selected for data collection, and 18 of the 20 patients were interviewed during a survey using a semi-structured questionnaire in a professional setting. The data collected were analysed using SPSS v.25.

Results:

A total of 20 patients were interviewed, of whom 55.56% were women, and 88.89% were severe asthmatics with a mean age of 53.27±17.12. In addition, 66.7% of them were allergic (dust, pollen, etc.) and 33.3% had a vitamin D deficiency, while 33.33% had none. The average number of hospital admissions was estimated at 5 this year, and the average number of asthma exacerbations in this population was 5.44.

No correlation was found between severe asthma exacerbation, worsening of symptoms and interpretations of asthma control tests, respectively, and vitamin D deficiency (Σ p values > 0.05). Moreover, none of none of the patients had been tested for vitamin D deficiency.

Conclusion:

No association between vitamin D deficiency and severe asthma exacerbation was found, Further research with larger cohorts will be necessary to elucidate the relationship between vitamin D status and severe asthma.

Keywords: Asthma, severe asthma, exacerbations, vitamin D deficiency.

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