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ORIGINAL ARTICLE

Correlation of vitamin D serum level and quality of life in asthma patients

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ABSTRACT

Aim Moderate to severe asthma patients with sufficient and insufficient vitamin D serum level, respectively, were assessed with quality of life questionnaires before and after treatment with vitamin D added to their standard asthma treatment.

Methods Patients with moderate to severe asthma have been divided into two groups based on a serum level of vitamin D as sufficient or insufficient level of vitamin D, respectively. During 12 months, a total of 120 patients with sufficient level of vitamin D as well as 120 patients with insufficient level were given treatment with 2000 IU vitamin D for a three-month period. Quality of life of all patients was assessed by Asthma Control Test (ACT), Asthma Quality of Life (AQOL) and the physician's assessment expressed through the Global Evaluation of Treatment Effectiveness (GETE), which were performed before and after the treatment with Vitamin D.

Results Values of ACT and AQOL were higher after the treatment with vitamin D in both groups of patients. Values of GETE were lower after the treatment with vitamin D in both groups. All assessed components, psychological, physical, as well as the subjective feeling of control of the disease assessed by treating physicians, showed improvement after treatment.

Conclusion Adding vitamin D in the treatment regimen of moderate to severe asthma patients improves quality of life and general asthma treatment effectiveness.

Keywords: ACT, AQOL, GETE, obstructive disease, vitamin D deficiency

INTRODUCTION

Asthma is a chronic airway condition characterized by inflammation, which presents with a variety of causes and fluctuating symptoms. Key features of asthma include airway blockage, inflammation, and increased bronchial sensitivity, all contributing to the distinct clinical signs. These often include coughing, difficulty breathing (dyspnoea), chest tightness, and wheezing, particularly noticeable during exhalation. Globally, approximately 300 million individuals are affected by asthma, with this number anticipated to rise to 400 million by 2025 (1). The condition's onset and response to treatments are influenced by both environmental and genetic factors. However, the precise interaction between these elements remains uncertain, prompting ongoing research (2). Asthma can be viewed as the outcome of external triggers acting on a genetically susceptible person. Risk factors include environmental allergens (such as dust, pet dander, mold, and pollen), respiratory viral infections, family history, air pollutants, tobacco smoke, stress, and obesity (3,4). Airway obstruction in asthma occurs due to changes like swelling, increased mucus production, thickened airway walls, and bronchoconstriction (5).

Asthma is frequently categorized by its severity, symptom recurrence, and lung function metrics (FEV1 and PEF), classifying cases as mild, moderate, or severe. Patients can transition between these categories due to the dynamic nature of asthma (6). Another classification approach focuses on the level of asthma control: controlled, partially controlled, and uncontrolled (6,7).

The primary aim of asthma treatment is to achieve optimal disease control, which involves preventing symptoms, maximizing lung function, reducing exacerbations, enhancing quality of life, lowering the risk of morbidity and mortality, and protecting against permanent lung damage. Severe asthma, a challenging form of the disease, remains uncontrolled even with high-dose inhaled corticosteroids (ICS) combined with long-acting bronchodilators (LABA), despite addressing contributing factors or worsening when reducing therapy. The treatment focuses on preventing exacerbations, minimizing chronic symptoms, maintaining normal lung capacity, promoting regular physical activity, and avoiding side effects from treatment (7). Oral corticosteroids

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(OCS) are the leading cause of side effects in conventional asthma therapies. Although asthma cannot be completely cured, well-managed control allows patients to lead a near-normal life. Recurring exacerbations, requiring short-term oral or injectable corticosteroids more than twice per year, suggest inadequate symptom management with the current therapy (6).

Vitamin D plays a crucial role in regulating immune responses and respiratory infections (8). Serum 25-hydroxy vitamin D (25OHD) levels indicate total vitamin D derived from diet and sun exposure and reflect the body's stored vitamin D (9–11). Research shows that vitamin D enhances the response to glucocorticoids in severe asthma, potentially helping manage exacerbations and symptom intensity (12). Respiratory syncytial virus (RSV) is linked to both the development and worsening of asthma, and vitamin D may influence these processes (9,13).

In 2022, Rosser et al. (14) emphasized that vitamin D boosts regulatory T-cells, suppresses Th2 and Th17 immune responses, and increases IL-10 production. This could lead to lower immunoglobulin E levels, reduced bronchial hyperreactivity, decreased pro-inflammatory cytokines, and improved response to steroids, thereby enhancing asthma control and quality of life. While there is no universally accepted optimal vitamin D level, deficiency is defined as serum 25OHD below 50 nmol/L, insufficiency between 50 and 75 nmol/L, sufficiency between 75 and 100 nmol/L, and level above 150 nmol/L suggest toxicity (15). The European Food Safety Agency advises a daily intake limit of 4000 IU of vitamin D (16). Lower 25(OH)D levels are associated with increased asthma incidence, hospitalization rates, emergency visits, reduced lung function, and heightened airway sensitivity, especially in children with asthma (17). Vitamin D's protective role is evident, with maternal intake during pregnancy influencing asthma development in childhood and adulthood (18).

There is limited and inconsistent data on how vitamin D impacts the quality of life in adult patients with moderate to severe asthma (19). Despite full asthma treatment, these individuals often report occasional breathlessness, dry cough, and fatigue that do not qualify as exacerbations. In clinical practice, these residual symptoms are often treated with additional inhaled therapies, commonly a combination of short-acting bronchodilators (SABA) and inhaled corticosteroids, either self-administered or through emergency care (20).

There remains an unmet need for treatments beyond corticosteroids for these patients (21).

In our daily clinical practice, we use the guidelines of the European Respiratory Society, GINA (6) for the treatment of all forms of asthma. The availability of biological therapy for moderate to severe asthma is currently uncertain in Bosnia and Herzegovina. Therefore, alternative types of supportive treatment should be researched.

The aim of our study was to assess the quality of life and asthma control in moderate to severe asthma patients after adding vitamin D to the treatment regime. Similar studies have not been conducted in Bosnia and Herzegovina so far.

PATIENTS AND METHODS

Patients and study design

At the Clinic for Pulmonary Diseases, University Clinical Centre, Tuzla (Bosnia and Herzegovina) a one-year prospective study was conducted from July 2021 to July 2022 involving 240 patients divided into two groups. One group consisted of 120 patients with sufficient vitamin D concentration (76-100 nmol/L) (I) and the other group of 120 patients with insufficient vitamin D concentration (50-75 nmol/L) in the blood (II).

All patients were diagnosed with moderate to severe asthma according to GINA guidelines (6). According to the same guidelines, the patients were treated with therapy corresponding to the severity of their symptoms. After determining the value of vitamin D in the blood, a three-month treatment of all patients with vitamin D in a daily dose of 2000 IU (half of maximum daily recommended dose) was chosen for our study to be assessed for both groups of patients. Patients with malignant, psychiatric, rheumatological disease, patients on biological, immune and oral corticosteroids therapy, and chronic diseases that may affect the examined subjective and objective parameters in asthma monitoring were excluded from the study.

An informed consent was obtained from all patients.

This study was approved by the University Clinical Centre Tuzla review board.

Methods

The assessment of treatment effectiveness on the patients quality of life was done with questionnaires based on subjective criteria (ACT, AQOL) and physician assessment (GETE) before and after the three-month prescription of the therapy.

The Asthma Control Test (ACT) (22) is a questionnaire made up of five questions related to previous four weeks to which each patient answers. A short questionnaire assesses daytime and nighttime asthma symptoms, usage of short-acting beta agonists, and the impact of asthma on the patient's performance of daily activities. The total score represents the sum of the values corresponding to each answered question and ranges from 5 (poorly controlled asthma) to 25 (complete asthma control). Minimum significant difference refers to values of 3 or more.

The Global Evaluation of Treatment Effectiveness (GETE) (23) questionnaire is a scale of five values that is filled out by a physician for each patient: 1 = complete asthma control, 2 = significant improvement in control, 3 = moderate but limited improvement in asthma control, 4 = very poor asthma control, and 5 = a sign of worsening. GETE values 4 and 5 correspond to "lack of effectiveness of asthma therapy" and values 1 and 2 correspond to "clinically effective asthma therapy".

The mini asthma quality of life questionnaire (MiniAQLQ) (24) was used to assess the quality of life of patients. This questionnaire consists of 15 questions distributed in four domains: symptoms (five questions), daily activities (four questions), feelings (three questions), and environment (three questions). A change in total questionnaire value of p=0.5 was considered clinically significant.

Statistical analysis

The Kolmogorov-Smirnov test was used to test the null hypothesis that a set of normal distribution data (ACT, GETE, miniAQLQ). Mann-Whitney U test was used to test the null hypothesis that the medians of the two samples (divided based on serum level of Vitamin D as sufficient or insufficient level of Vitamin D) were identical. The changes in quality of life between the two

measurements (before and after vitamin D therapy) were analysed using the Wilcoxon Signed-Rank Test, which tested the null hypothesis that there was no difference between the measurements against the alternative hypothesis that there were differences. The shortcut to the hypothesis testing of the Wilcoxon signed rank-test was the critical z-value for a 95% CI (confidence interval) or a 5% level of significance which was z=1.96 for a two-tailed test. If z was < -1.96, or >1.96, the null hypothesis was rejected, the p=0.05 was set for all statistical tests.

RESULTS

In patients with insufficient concentration of vitamin D, median value of quality of life for ACT was statistically significantly higher after the treatment with vitamin D than before the treatment with vitamin D, 22 and 17, respectively (z= -9.550; p <0.005).

Median value of quality of life for GETE was statistically significantly lower after the treatment with vitamin D than before treatment with vitamin D, 3 and 4, respectively (z= -10.016, p<0.005);

Median value of quality of life for miniAQLQ was statistically significantly higher after the treatment with vitamin D than before the treatment with vitamin D, 4.6 and 3,9, respectively (z = -9.516; p<0.005).

Median value of quality of life for ACT was statistically significantly higher after the treatment with vitamin D than before the treatment with vitamin D, 20 to 17, respectively (z = -9.015; p<0.005);

Median value of quality of life for GETE was statistically significantly lower after the treatment with vitamin D than before the treatment with vitamin D, 2 to 4, respectively (z = -9.494; p<0.005);

Median value of quality of life for miniAQLQ was statistically significantly higher after the treatment with vitamin D than before the treatment with vitamin D, 4.9 to 4.5, respectively (z = -7.217; p <0.005) (Table 1, 2).

A statistically significant difference in median values of ACT after the treatment with vitamin D (ACT_POST) (z=-7.266; p=0.000), GETE after the treatment (GETE_POST) (z=-6.471; p=0.000), miniAQOL before treatment with (miniAQLQ_PRE) (z=-8.414; p=0.000), and mini AQOL after the treatment with vitamin D (AQLQ_POST) (z=-3.420; p=0.000) was found depending on the patient group (Table 3).

Table 2. Pre/post median value of quality of life based on subjective criteria and physician's assessment

Parameter	Median value of patients with	
	Insufficient concentration of vitamin D	Sufficient concentration of vitamin D
ACT_POST	22	20
ACT_PRE	17	17
ACT_POST-ACT_PRE	5	3
GETE_POST	3	2
GETE_PRE	4	4
GETE_POST-GETE_PRE	-1	-2
miniAQLQ_POST	4.6	4.9
miniAQLQ_PRE	3.9	4.5
miniAQLQ_POST - miniAQLQ_PRE	0.7	0.4

ACT, Asthma Control Test;, GETE, Global Evaluation of Treatment Effectiveness; MiniAQLQ, Mini asthma Quality of Life Questionnaire; PRE, before treatment with Vitamin D, POST, after treatment with Vitamin D

DISCUSSION

The World Health Organization describes human health as "a state of complete physical, mental, and social well-being, not merely the absence of disease" and has recently broadened this definition to include the ability to lead a "socially and economically productive life" (25). Kharaba Z et al. (24) demonstrated that asthma affects the quality of life of patients, impacting them physically, emotionally, professionally, and socially. There is growing awareness of patients' quality of life, with comprehensive questionnaires now assessing physical, social, and emotional well-being (24).

Despite regular therapy, asthma patients may still experience occasional breathing difficulties. Moderate to severe asthma is often linked to poorer disease control and more frequent complaints, which diminish quality of life. Commonly, clinical and physiological variables are used to assess asthma, which may not be enough to assess the patient's interpretation of their state of health. Thus, quality of life (QoL) is a significant endpoint as it reflects the impact of the disease from the patient's perception (26).

Table 1. Comparison of main parameters between two patient groups before and after the treatment with vitamin D

Group of patients	Statistical significance	ACT_POST-ACT_PRE	GETE_POST-GETE_PRE	miniAQLQ_POST- miniAQLQ_PRE
With insufficient concentration of vitamin D	z*	-9.550	-10.016	-9.516
	p	0.000	0.000	0.000
With sufficient concentration of vitamin D	z*	-9.015	-9.494	-7.217
	p	0.000	0.000	0.000

*the critical z-value (for a 95% confidence interval - CI and 5% level of significance) was z=1.96 for a two-tailed test; if z was z< -1.96, or >1.96, the null hypothesis was rejected;
ACT, Asthma Control Test;, GETE, Global Evaluation of Treatment Effectiveness; MiniAQLQ, Mini asthma Quality of Life Questionnaire; PRE, before treatment with Vitamin D, POST, after treatment with Vitamin D

Table 3. Difference in the median of the quality of life assessment before and after the treatment with vitamin D

Statistical significance	Pre and post quality of life assessment*					
	ACT		GETE		miniAQLQ	
	PRE	POST	PRE	POST	PRE	POST
z†	-1.160	-7.266	-1.695	-6.471	-8.414	-3.420
p	0.246	0.000	0.090	0.000	0.000	0.001

*Grouping variable: created based on serum level of vitamin D as sufficient or insufficient level of vitamin D
†the critical z-value (for a 95% confidence interval - CI and 5% level of significance) was z=1.96 for a two-tailed test: if z was z< -1.96, or >1.96, the null hypothesis was rejected;
ACT, Asthma Control Test;, GETE, Global Evaluation of Treatment Effectiveness; MiniAQLQ, Mini Asthma Quality of Life Questionnaire; PRE, before treatment with vitamin D, POST, after treatment with vitamin D

In our study we aimed to assess the role of vitamin D in asthma control by assessing quality of life of our patients. Patients with moderate to severe asthma and vitamin D deficiency, who received three months of vitamin D therapy, showed improvements in quality of life in terms of psychological, physical, and disease control aspects. This indicates that adding vitamin D to the standard asthma treatment can be beneficial.

Lower vitamin D level was significantly associated with increased asthma severity and poorer asthma control; controlled asthma was linked with higher vitamin D level compared to partially controlled and uncontrolled asthma (22).

Although, the VIDA randomized clinical trial from 2014 (27) found that administering vitamin D to adults with persistent asthma and low vitamin D levels did not reduce the risk of initial treatment failure or exacerbation. Reportedly, vitamin D administration reduced the likelihood of asthma exacerbations requiring systemic corticosteroids by 36% (28). Several study groups (29) showed inverse associations between vitamin D levels and markers of asthma severity and asthma control.

Some studies (30,31) found no improvement in quality of life with vitamin D supplementation, potentially due to the small sample size of 112 patients divided into two groups.

Our study involved a larger patient cohort and although they had a shorter three-month therapy period compared to the six months in the VIDA study, both studies reported improvements in symptoms, physical activity, and emotional well-being with vitamin D supplementation (27).

Some reviews noted that insufficient vitamin D supplementation dose may cause the treatment to fail and not affect the exacerbation rates as expected (32). Our patients were administered a dose of 2000 IU of Vitamin D, which has demonstrated benefits. However, it is crucial to consider a range of dosing options based on individual serum level of vitamin D, and further research is needed to explore this variability. In the era of biological treatment for moderate to severe asthma as corticosteroid sparing agents (22), there is urgent need in many low income countries such as Bosnia and Herzegovina for additional asthma treatment beyond OCS.

Our study suggests that vitamin D treatment can positively impact asthma control and therefore quality of life for moderate to severe asthma patients.

Future research with larger sample size, extended treatment durations, diversity in Vitamin D dose is necessary to definitely assess the role of vitamin D in asthma management.

AUTHOR CONTRIBUTIONS

Conceptualization, Dž.H. and J.N.; methodology, S.T.; software, M.N.; validation, J.N., S.T. and E.H.; formal analysis, E.M.; investigation, Dž.H.; resources, Dž.H.; data curation, J.N.; writing—original draft preparation, Dž.H.; writing—review and editing, Dž.H.; visualization, J.N.; supervision, S.T.; project administration, E.M. All authors have read and agreed to the published version of the manuscript.

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TRANSPARENCY DECLARATION

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