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Correlation between gastroesophageal reflux disease lung volumes and exacerbation of bronchial asthma: Italian pilot observational retrospective study GERDAS

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Abstract

Reflux asthma is an entity characterized by typical symptoms and, in some cases, is "silent"; it is more dangerous when associated with obesity and sleep apnea syndrome. Numerous studies demonstrate its high prevalence in the general population, particularly in the pediatric population, where, despite medical specialists' treatment, asthma symptoms remain poorly controlled with a high risk of acute exacerbations. This clinical study aims to show how the addition of a particular type of alginate (Deflux Plus sachets) containing hyaluronic acid and melatonin at low doses administered over a prolonged period of 6 months causes a reduction in vagal reflex stimulation of the esophagus and pulmonary microaspiration reflexes by regulating lower esophageal sphincter motility in asthmatic patients, improving the asthma control test (ATC) score. In the reported statistical analysis, receiver operating characteristic curves were performed for sensitivity and specificity for the analyzed parameters, including the ACT score, with statistically significant data $p<0.0001$. We conclude that combining conventional therapy for reflux asthma with alginates may improve the risk of acute asthma exacerbations and dynamic lung volumes.

Introduction

Over the past 40 years, the literature on the correlation between asthma and reflux disease has yielded much information on this topic. The close relationship between mechanisms regulated by the autonomic nervous system, obesity, lifestyle, dietary habits and gastroesophageal reflux disease has been described by many authors. The classic clinical symptoms described by almost all the existing literature on the subject concerning reflux disease include chronic coughing, dysphonia, retrosternal burning, regurgitation, dysphagia, odynophagia, nausea, vomiting, a sense of abdominal bloating, dyspnea, vocal cord nodules, laryngospasm, Reinke's edema, *etc*. It has also been debated in recent years whether there are "silent" forms of reflux disease that occur without or with few symptoms. It is known that at least three-quarters of the bronchial asthma population who use bronchodilators or not on a regular basis are affected by gastroesophageal reflux disease (GERD). It would appear from numerous studies and reviews in the literature that there is a bi-directional relationship between GERD and asthma, determined by the continuous amount of hydrochloric acid that is aspirated into the airways, and that would result in chronic inflammatory damage, stimulating the vagal nerve fibers, and generating bronchoconstriction.

This mechanism has been extensively studied in children, in particular by Kim *et al*. [1], who evaluated these effects through two

longitudinal cohort studies in children, which demonstrated the above-mentioned bi-directional relationship. Furthermore, the presence of atypical reflux symptoms such as non-cardiac chest pain, hoarseness, chronic hiccups, and loss of dental enamel, some of which are sometimes difficult to detect and manage, was described by Mujica *et al*. [2]. Other studies carried out by Althoff *et al*. have shown, on the other hand, a colinear relationship with two other diseases, which are obesity and sleep apnea syndrome [obstructive sleep apnea (OSA)] [3]. In particular, all three entities would play a key role in generating pro-inflammatory stimuli for each other through cytokine activation mechanisms determined by the predisposing state of obesity, generating eosinophil-mediated T helper (Th)2-type inflammation. However, there are also forms of non-Th2-mediated asthma or non-atopic asthma that, in obese asthmatic patients, would cause difficult management by physicians. In particular, in the aforementioned study, it was seen that a 5-10% weight loss in body mass would lead to a reduction in asthma symptoms and an increased quality of life. Furthermore, scientific evidence has shown that manipulating the gut microbiome can potentially improve the management of obese asthmatic patients by reducing dietary intake of fatty acids and increasing fiber intake, which would affect asthma control. In OSA patients, intermittent hypoxia would lead to increased obstruction of airflow in the lungs, increased air remodeling and pro-fibrosing markers, increased Th1-type inflammation and neutrophil levels, as well as interleukin (IL)-8 and metalloproteinase-9. The same authors also state from studies and evidence in the literature that regular use of continuous positive airway pressure (CPAP) would lead to an improvement in quality of life and spirometric values in asthmatic and obese patients, as well as reducing the degree of systemic inflammation and extrapulmonary symptoms, as Cazzola *et al*. state in their clinical study [4]. The authors also point out that increased vagal tone with airway hyper-responsiveness, associated with repeated episodes of oxidative stress on the bronchi, brought about by hypoxia stimuli and consequent intermittent hyper-oxygenation, could contribute to bronchoconstriction.

On the other hand, in their study, Shigemitsu *et al*. demonstrated a high prevalence (60%) of nocturnal symptoms in asthma patients, who are very often undiagnosed, with an associated comorbidity of OSA, and a higher frequency of the glycine 16 polymorphism of β-2 agonist receptors found in patients with nocturnal asthma symptoms [5]. Moreover, these subjects have significant changes in the daytime percentage of the predicted value of forced expiratory volume in the first second (FEV_1%), even more than 15%, with increased bronchial hyperresponsiveness and systemic inflammation. In this study, it was also shown that nocturnal asthma patients have elevated melatonin levels in comparison to non-night asthma patients and the healthy control group. This is because melatonin regulates circadian homeostasis, hormone levels, and systemic cytokines, in particular IL-1, IL-6, and tumor necrosis factor α.

Other authors state that the association of asthma, obesity, and OSA would represent a triangle of inflammation, corroborating the above hypotheses and the hypothesis that GERD and sleep disorders together feed systemic inflammation, as stated by Gupta *et al*. [6]. In their study, they demonstrated how treatment with anti-reflux therapy combined with the use of CPAP results in an increase in lung volumes on respiratory function tests, in particular peak expiratory flow.

A study carried out by Theodoropoulos *et al*. demonstrated a strong correlation between chronic cough and GERD [7]; in particular, the chronic cough symptom would be present in 96.2% of these three conditions: post-nasal drip, asthma, and GERD. Furthermore, GERD would lead to cough in 4-24% of patients with chronic cough. The pathophysiological mechanism underlying the cough is determined by receptors located in the upper and lower airways, which are located throughout the bronchial tree, tympanic membrane, and external auditory canal, as well as in the tracheobronchial-esophageal mucosa. Stimuli to C-type nociceptive fibers located in the bronchi caused by acid reflux would generate episodes of apnea, coughing, bronchoconstriction, hypotension, and bradycardia.

Another study carried out by Field *et al*. showed that GERD causes asthmatic symptoms but has little effect on lung function, stating that this "paradoxical effect" would lead to increased ventilation/minute and dyspnea [8]. Anti-reflux therapy, according to the authors, would have a strong benefit for patients who report respiratory symptoms related to and secondary to GERD. According to Sontag *et al*. [9], physiological studies on asthma and GERD suggest two neuro-mechanical physiological mechanisms underlying the event: i) a pathway regulated by the vagus "reflex theory"; ii) the mechanism of microaspiration of small amounts of acid reflux into the bronchial tree "reflux theory". According to the first hypothesis, there would be a GERD-induced vagus reflex mechanism from the esophagus to the lung that would lead to bronchoconstriction through increased flow resistance, which would be proportionally reversed after taking antacid therapy. The second hypothesis would be determined by the mechanism of microaspiration of hydrochloric acid doses on the mucous membrane of the bronchial epithelium, leading to exudative edema with subsequent bronchoconstriction.

In a review by Sopo *et al*. (2009) [10], therapy with proton pump inhibitors would only be valid in patients with reflux asthma if two conditions are present and fulfilled: asthma is not responsive to standard therapy in the first instance, and finally, the presence of an instrumental parameter that highlights the severity of GERD, represented by the reflux index, which must be greater than 10. Another study by a US multidisciplinary team, led by McCallister *et al*. [11], demonstrated a strong relationship between GERD and asthma, stating that hyperinflation of the lungs is present in asthmatic patients, which would lead to increased work of breathing, altered diaphragmatic dynamics, and a change in thoracoabdominal pressures, which would promote herniation of the lower esophageal sphincter (LES) in the thorax, with increased LES tone and acid reflux in the airways.

Another interesting study by Kilic *et al*. described the impact of laryngopharyngeal and gastroesophageal reflux in children, correlating it with asthma symptom control employing a score [12].

In the study, it was also shown that there was a high prevalence of laryngopharyngeal reflux (70%) *versus* gastroesophageal reflux (46%) in children. Other important studies in the literature by Alexander *et al*. demonstrated the importance of looking for extraesophageal reflux symptoms in the so-called "silent reflux", defining it as increased exposure to acid reflux by the esophageal mucosa without typical GERD symptoms, indicating that it is present in between 35% and 50% of asthmatic patients and that it makes the management of these patients difficult, and stating that this mechanism was still unclear [13]. A plausible explanation for this is provided by Naik *et al*. [14], who attempted to uncover the interrelationship between the two pathologies, showing that there is a direct correlation between GERD and direct laryngeal-pharyngeal acid damage with microaspirations that would lead to pro-inflammatory mechanisms on the bronchial mucosa and tussigenic stimuli. Finally, according to Mallah *et al*. [15], these continuous insults to the airways would lead to an increased risk of asthmatic exacerbations, some of which involved the use of corticosteroids, with a particular incidence in children. The study we are going to present is a retrospective observational cohort study, in which we decided to examine a total of 80 patients who reported typical GERD symptoms and who were diagnosed with bronchial asthma by simple spirometry

and bronchus reversibility tests. They were then subjected to a course of inhaled corticosteroid/long-acting β-agonist (ICS/LABA), proton pump inhibitors, and Deflux Plus sachets twice a day for about 6 months, evaluating at serial spirometric-clinical controls whether the FEV_1%, percentage of predicted value of forced vital capacity (FVC%), and asthma control test (ACT) score values changed, with surprising results as will be illustrated later in the paper.

Materials and Methods

We examined a cohort of the Italian Caucasian population of 80 people, aged between 20 and 60 years, with a male predominance (62.50% men and 37.50% women) (Figure 1) who visited the Outpatient Clinic "La Madonnina" from January to July 2022 for reported asthmatic symptoms associated with typical gastroesophageal reflux symptoms. The inclusion criteria were: i) diagnosis of bronchial asthma according to the Global Initiative for Asthma 2022 guidelines [16]; ii) diagnosis of GERD made by esophageal pH-metry. Exclusion criteria were represented by i) the presence of comorbidities in history (OSA, obesity, *etc*.); ii) the presence of "silent reflux" or extraesophageal reflux symptoms. As can be seen from the exploded pie chart, the prevalence of symptoms described by the cohort was coughing and retrosternal burning (36% and 23%, respectively).

Patients underwent simple spirometry with a bronchus reversibility test and an ACT score at baseline (baseline T0), then were observed and re-tested with clinical spirometry plus an ACT score at T1 (1 month), T3 (3 months), and T6 (6 months). After the first diagnosis of asthma at time 0, they were placed on fixed therapy with ICS/LABA, proton pump inhibitors at a dosage of 20 or 40 mg/day as well as Deflux Plus 1 sachet twice a day, 20 minutes after main meals, and reassessed at regular intervals. Data on FEV_1%, FVC%, and ACT score were collected at time 0, 1 month, 3 months, and 6 months (Figures 2 and 3). All test patients were first asked for written informed consent by the outpatient facility, complying with the regulations on the processing of personal data. Statistical analysis was performed with Graphpad Prism 8 by measuring the mean of the percentage of the predicted FEV_1 value, FVC, and the increase of the ACT score over time.

Receiver operating characteristic (ROC) curves were performed for FEV_1%, FVC%, and ACT score at baseline and 6 months, comparing the values to compare the sensitivity and specificity of the parameters in relation to GERD asthma. It would appear that the effect obtained is due to the concomitance of ICS/LABA therapy and therapy with i) antacids, and ii) alginates containing hyaluronic acid and melatonin as in Deflux Plus sachets, which would regulate the motility of LES by adjusting its tone, consequently reducing the microaspiration and pro-inflammatory pulmonary mechanisms given by GERD, also favoring an improvement in reflux symptoms and implementing FEV_1% and FVC% values. The other evidence from the study was an increase in the ACT score and a reduction in the risk of asthma exacerbations over the 6 months analyzed. However, further prospective randomized controlled clinical trials will be necessary to demonstrate the long-term effectiveness of this therapy.

Results

The results obtained (Figures 2 and 3) show strong statistical significance for the mean FEV_1% and FVC% achieved from T0 to T6 ($p<0.001$). In particular, we report that for the ROC curves of FEV_1% and FVC%, $p<0.001$ was obtained with a high confidence interval (CI) (95% CI 0.74 to 0.87 for FEV_1%, and 95% CI 0.65 to 0.81 for FVC%). It should be noted that, for the ACT score compared at T0 and T6, there is a constant and more significant $p<0.001$ with a CI for the ROC curve of 100% (95% CI 1.00 to 1.00) and an error of approximately 0. This indicates that these three parameters have a very high sensitivity and specificity in the pathology under investigation and represent important data for any prospective randomized controlled trials in the near future.

Discussion

As pointed out in the work of Griffiths *et al.* [17], respiratory diseases associated with GERD develop as a result of reflex neural mechanisms restricted to the lower esophageal sphincter or as a direct effect of gastric contents causing aspiration, upper airway irritation, and lung disease. GERD has been proposed as a contributing factor in the pathogenesis of interstitial lung disease, in particular idiopathic pulmonary fibrosis and scleroderma. Microaspiration

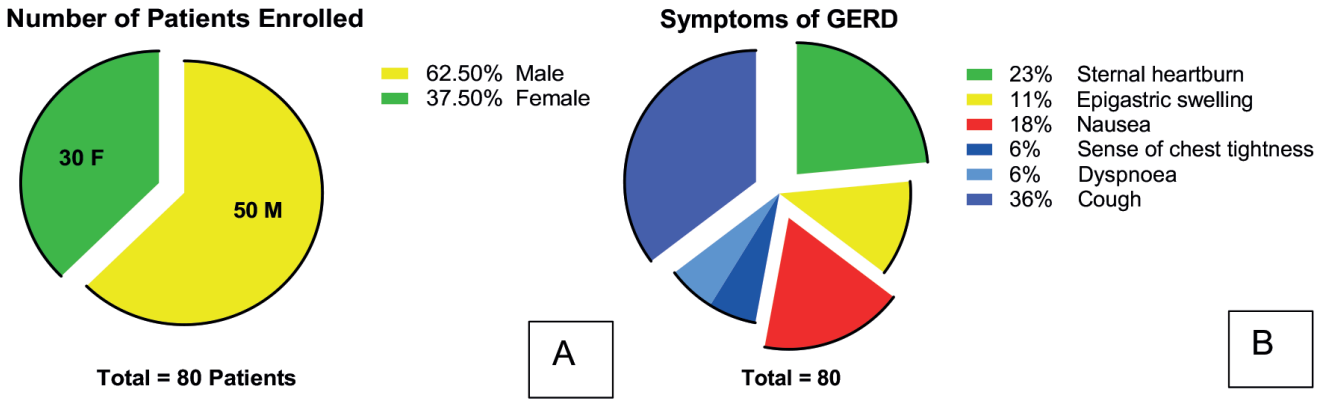

Figure 1. A) Number of patients enrolled in the study (total of 80 patients) with evidence of a greater presence of men than women (62.5% versus 37.5%); B) description of gastroesophageal reflux symptoms reported by patients at baseline (highest percentage represented by the symptom cough: 36%).

over time can lead to pneumonia, increased epithelial permeability, stimulation of fibrotic cell proliferation, and finally pulmonary fibrosis.

This shows that GERD is a possible cause of inflammatory stimuli in all lung diseases (obstructive and restrictive). It would appear that the most conspicuous, albeit limited, data comes from the study by Rogers [18], who states that there are several potential mechanisms suggesting a relationship between OSA and asthma, but the cause-effect relationship was not very clear. Limited data suggests that OSA treatment may improve asthma but with little evidence of clinical outcomes. As hypothesized by Kasasbeh *et al.* [19], OSA and asthma may coexist, and asthma would play a major role in fueling OSA as a disease of varying degrees in terms of airflow obstruction, bronchial hyperresponsiveness, and airway inflammation. Pathophysiologically, the two conditions appear to overlap significantly, as airway obstruction, inflammation, and obesity are key aspects of both disorders. The authors suggest that the treatment of the individual patient suffering from both asthma and OSA should be multidisciplinary and comprehensive. However, Alexander *et al.* [13], in another paper in the Mayo Clinic Proceedings, state that the evidence on the effectiveness of anti-reflux therapy on lung function is still weak. The debate is related to the role of therapy in the pathophysiological mechanisms underly-

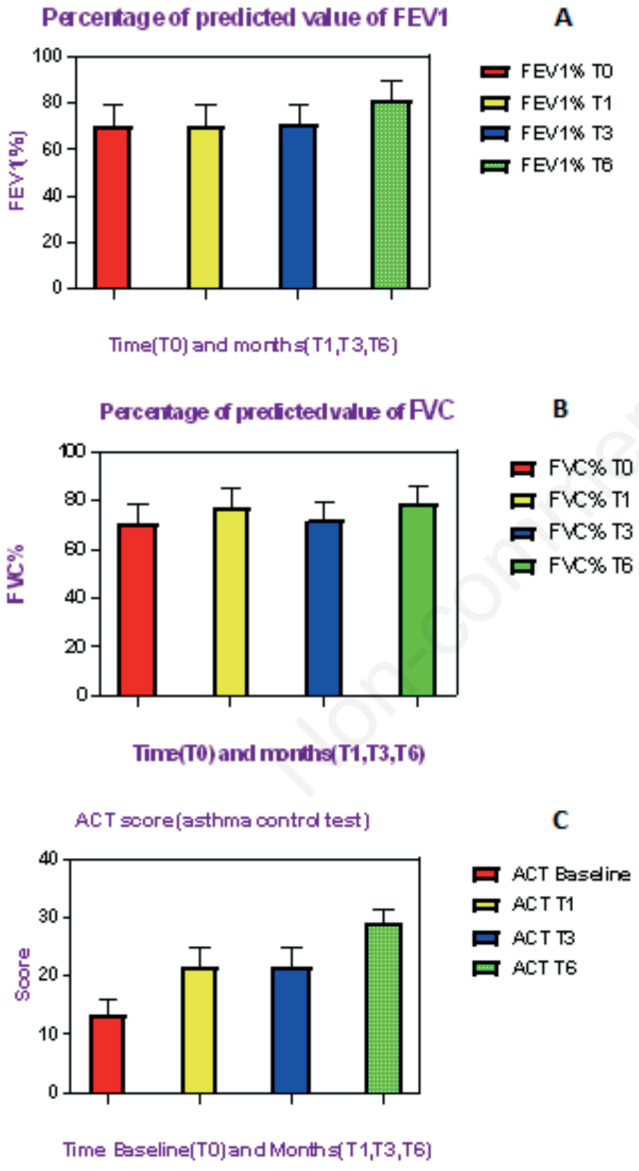

Figure 2. Percentage of predicted value of forced expiratory volume at first second (FEV1) (A), percentage of forced volume capacity (FVC) (B), and asthma control test (C) at time 0 (T0), 1 (T1), 3 (T3), 6 (T6) months. Note that statistical significance is reached in the graphs for the values examined p<0.0001.

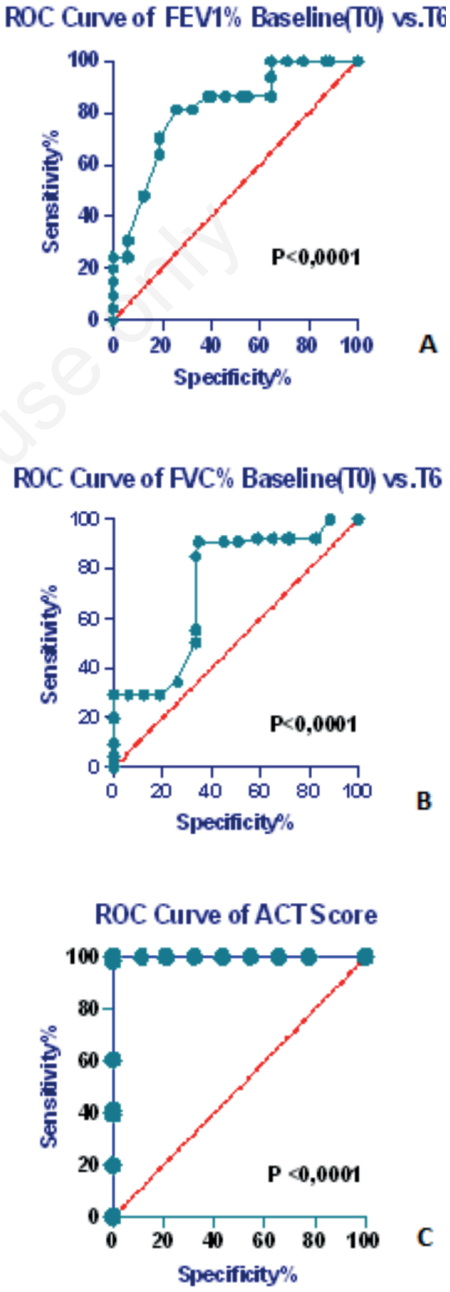

Figure 3. Receiver operating characteristic (ROC) curves of predicted value of forced expiratory volume at first second (FEV1%) (A), percentage of forced volume capacity (FVC%) (B), and asthma control test (ACT) score (C). In the visible ROC curves, statistical significance is reached for the values examined p<0.0001. T0, baseline; T6, 6 months.

ing the association between asthma and GERD. In a retrospective clinical study by a more recent multidisciplinary group than Mahdavinia *et al.* [20], a strong correlation is demonstrated in children between GERD, allergic rhinitis, recurrent sinusitis, and atopic bronchial asthma. It seems that the factors leading to recurrent asthma in patients with GERD are due to an altered autonomic regulation induced by the reflux itself, which would lead to a pressure variation between the abdomen and the thorax that alters the effectiveness of diaphragmatic dynamics and the efficacy of asthma treatment, as demonstrated by the work of Harding [21]. This would explain why there is such a high prevalence of GERD in obstructive lung disease, in particular, in asthma, from 30% to 90%, compared to an average of 24% in controls, and in chronic obstructive pulmonary disease (COPD) patients, from 19% to 78%, compared to an average of 18% in controls, as indicated by a recent review by Broers *et al.* [22]. The authors of this study state that there is an increased risk of exacerbation of obstructive disease in patients with GERD. It is therefore important to emphasize, as has been done by Benich 3rd *et al.* [23], how crucial it is to return to the initial semeiological assessment of the patient with a chronic cough (*i.e.*, lasting more than 8 weeks), which must include an accurate history assessing the patient's medication intake, a targeted physical examination, and, in most patients, a chest X-ray. In fact, Szentivanyi *et al.* have taken up in an editorial the concept formulated in the past by Eppinger and Hess of "vagotonia" as the constitutional basis of allergic disease (the "allergic diathesis"), which may be appropriate to take the opportunity to re-examine this topic from the perspective of GERD-related asthmatic pathology [24]. Researchers in this editorial suggested that airway epithelial damage with sensitization of bronchial nerve endings causes exaggerated cough and bronchomotor responses, stating that bronchial hyperresponsiveness is associated with a decreased cough threshold. A Japanese real-world study conducted by Shirai *et al.* demonstrated how GERD impacts the quality of life, resulting in greater cough-related impairment, poor asthma control, and COPD-related symptoms [25]. A US study by Parsons *et al.* showed that there is a very high prevalence of "silent GERD" in the general population with symptoms that cannot be well controlled even with common antacid therapy [26]. Furthermore, it was explicitly stated that this form of GERD does not affect the control of asthmatic symptoms. According to a systematic review by Theodoropoulos *et al.* [27], an important role in the genesis of reflux asthma is played by the non-adrenergic, non-cholinergic autonomic system, as the afferent and efferent pathways are stimulated by the vagus nerve, the production of substance P and vasoactive intestinal polypeptide, which have been found in lung and gastric tissue. According to the authors, the only solution to the disease is to change lifestyle habits by leading an active, healthy, and regular lifestyle, avoiding red meat, fat, fruit juice, fizzy drinks, coffee, chocolate, and tea, and using more pillows in bed to reduce the mechanism of acid microaspiration into the trachea.

Finally, as stated by two clinical studies carried out on children by Blake *et al.* and Thakkar *et al.* in their respective reviews [28,29], there is a correlation between asthma and GERD in children who are less responsive to antacid therapy than adults. The clinical study we conducted challenges some of the hypotheses made by some of the authoritative authors cited above, highlighting the presence of good control of GERD symptoms in asthmatic patients without other comorbidities. Probably the absence of OSA and obesity among the other pathologies in the cohort examined plays a fundamental role in the control of asthmatic symptoms and the increase of the ACT score at serious controls. It will be necessary to examine pediatric population groups and those with other comorbidities in prospective randomized controlled clinical trials to have a better statistical definition of the picture described. However, the hypothesis remains that one of the drugs prescribed, in particular Deflux Plus sachets, may act to inhibit, with the "barrier" effect of hyaluronic acid and alginates, vagal stimulation on the esophagus, and through low-dose melatonin, it would appear to act on the tone of the esophageal sphincter as well as minimally at a central level.

Conclusions

The study's evidence is encouraging and positive because it shows that the action of certain drugs routinely used on GERD appears to be able to increase lung volumes on respiratory function tests, reduce reflux and asthma symptoms, as well as promote a better stability of the inflammatory picture in the bronchial mucosa, leading to an increase in the ACT score. It has also been demonstrated, by analyzing the ROC curves of the FEV_1%, FVC%, and ACT score parameters, that in patients with gastroesophageal reflux asthma, it is essential to correlate these parameters for high sensitivity and pathology-related specificity in the management of the patient's risk of flare-ups, and it is possible to see how, for all three parameters, there is a high CI with an error percentage of the ACT score of approximately 0. The other evidence is represented by the fact that this type of alginates, containing hyaluronic acid and melatonin, perform a double protective action, on the esophagus and the lung through two effects: i) the "barrier" effect brought about largely by the hyaluronic acid and alginates, which would limit damage to the esophageal mucosa and avoid vagal stimulation "reflex theory"; ii) the effect of reducing the motility of the LES caused in part by the melatonin in a reduced dose in the drug, which would reduce the "lung microaspiration" or "reflux theory" mechanism. Prospective, randomized, controlled clinical trials will be needed to further demonstrate these results.

The limitations of this study are related to the fact that the population sample is small in number (total number: 80 patients), subjects with so-called "silent reflux" or extraesophageal reflux symptoms were not examined, nor were those with other important comorbidities frequently associated with asthma, such as obesity and OSA.

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