Impact of depression and anxiety disorders in asthma control

Impacto dos transtornos depressivo e de ansiedade no controle da asma

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ABSTRACT: Asthma is a prevalent disease in doctor offices and Pneumology outpatient clinics and it reaches different age groups. The control of the disease aims to improve the quality of life of the patient and to avoid complications. It is done using drugs with anti-inflammatory and bronchodilator properties and by the control of environmental factors, possible triggers of asthmatic crises. However, the influence of psychological conditions on this control is hardly mentioned. Anxiety and depressive disorders are very prevalent nowadays and there is a lot of evidence that they have a strong influence on asthma control. In order to assess the prevalence of depressive symptoms and anxiety in patients with asthma and to analyze the impact they have in asthma control, an observational, descriptive, and cross-sectional study was carried out from April 2019 to March 2020 with asthma patients treated at pneumology outpatient clinic of the Faculdade Ciências Médicas de Minas Gerais, in Belo Horizonte (MG). Forty patients participated in the study, who answered two validated questionnaires (HADS - Hospital Anxiety and Depression Scale and ACT - Asthma Control Test) and provided demographic and spirometric values. The results showed that there is an association between asthma control and psychiatric disorders. The prevalence of anxiety and/or depression disorders among the total sample was 75%, and anxiety was more prevalent. Among those considered to have uncontrolled asthma, the disorders were present in 92%, whereas among those with controlled asthma the prevalence was 47%. However, there was no significant association between age, sex, spirometric values, and asthma control. At the end of the study, it was not possible to clearly define a cause-consequence relation between asthma control and psychiatric disorders, despite the evident relationship found between them, and therefore further studies on the topic are necessary.

Keywords: Asthma; Anxiety disorders; Depressive disorder; Anxiety; Depression; Cross-sectional studies.

RESUMO: A asma é uma doença prevalente nos ambulatórios e consultórios de Pneumologia, atingindo faixas etárias variadas. O controle da doença visa melhorar a qualidade de vida do portador e evitar complicações, sendo feito através do uso de medicações anti-inflamatórias e broncodilatadoras e do controle de fatores ambientais, possíveis gatilhos das crises. No entanto, pouco se fala a respeito da influência das condições psicológicas sobre esse controle. O transtorno de ansiedade e o transtorno depressivo são muito prevalentes na atualidade e existem diversas evidências de que exercem forte influência no controle da asma. Com o objetivo de avaliar a prevalência de sintomas depressivos e de ansiedade em pacientes portadores de asma e analisar o impacto destes no controle da doença, foi realizado um estudo transversal, observacional, descritivo no período de abril de 2019 a março de 2020 envolvendo asmáticos atendidos no ambulatório de Pneumologia da Faculdade Ciências Médicas de Minas Gerais, em Belo Horizonte (MG). Participaram do estudo 40 pacientes, que responderam a dois questionários validados (HADS - Hospital Anxiety and Depression Scale e ACT - Asthma Control Test) e dos quais foram coletados dados demográficos e espirométricos. Os resultados mostraram a existência de associação entre o controle da asma e os transtornos psiquiátricos. A prevalência de transtornos de ansiedade e/ou depressão na totalidade da amostra foi de 75%, sendo o de ansiedade o mais prevalente. Entre os portadores de asma não controlada, os transtornos estavam presentes em 92%, ao passo que entre aqueles com asma controlada a prevalência foi de 47%. Não houve, no entanto, associação significativa entre idade, sexo, alterações espirométricas e o controle da asma. Ao final do estudo, não foi possível definir claramente a relação causa-consequência entre controle da asma e os transtornos psiquiátricos, apesar da evidente associação encontrada, sendo necessário, portanto, novos estudos para tal.

Descritores: Asma; Transtornos de ansiedade; Transtorno depressivo; Ansiedade; Depressão; Estudos transversais.

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INTRODUCTION

Asthma is a chronic inflammatory disease characterized by hyperresponsiveness of the lower airways and variable limitation to airflow, reversible spontaneously or with treatment, manifesting clinically by recurrent episodes of wheezing, dyspnea, tightness in the chest, and cough, especially at night and in the morning upon awakening. It results from an interaction between genetics, environmental exposure, and other specific factors that lead to the development and maintenance of symptoms[1,2].

The disease affects both children and adults, and it is a global health issue that affects about 300 million individuals. It is estimated that, in Brazil, there are approximately 20 million asthmatics, if a global prevalence of 10% is considered[2,3]. In 2013, there were 129,728 hospitalizations and 2,047 deaths from asthma in Brazil [1].

Hospitalizations and mortality from asthma are decreasing in many Brazilian regions, in parallel with greater access to treatments. However, the cost of uncontrolled asthma is still remarkably high for the health system and families. Cases of severe asthma are estimated to affect more than a quarter of the family income among users of the *Sistema Único de Saúde* (SUS), but this high cost can be significantly reduced with adequate disease control. However, a national survey found only 12.3% of asthmatics with well-controlled asthma[1].

Disease control refers to the extent to which asthma manifestations are suppressed, either spontaneously or by treatment, and comprises two distinct domains: the control of current clinical limitations and the reduction of future risks (reduction of asthma instability, exacerbations, accelerated loss of lung function and adverse treatment effects). This control should preferably be evaluated concerning the last four weeks, and it includes symptoms, needs for relief medication, limitation of physical activities, and intensity of limitation to airflow. Currently, in addition to the Global Initiative for Asthma (GINA)[3] asthma control questionnaire, other tools are available, which have already been culturally adapted for Brazil, including the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT). From these questionnaires, asthma can be classified into three distinct groups: controlled asthma, partially controlled asthma, and uncontrolled asthma. When not controlled, however, asthma can seriously limit daily activities and it can even be fatal[1,2].

To improve control, it is important to identify and try to reduce factors capable of intensifying symptoms or precipitating exacerbations of asthma, among which we can mention the lack of treatment adherence; the incorrect use of medication and/or inhalation devices; the use of drugs that can decrease the response to treatment (non-steroidal anti-inflammatory drugs and β-blockers); home exposure (for example, dust or smoke); occupational exposure; smoking; and other comorbidities[1].

Evidence indicates that emotional disorders can induce an inadequate control of asthmatic disease, influencing, for example, the reduction of quality of life, the increase in hospitalizations, the worsening of symptoms, the need for higher doses of inhaled corticosteroids, the difficulty adherence to treatment and even the precipitation of lethal crises[4,5].

Depression, along with anxiety, presents itself as an important cause of disability in the world, limiting physical, personal, and social functioning. In primary care clinics, the prevalence of depression was estimated at 5% to 10% of all patients, and only one in a hundred mentions the disease as the reason for the consultation. Up to 50% of the time, the problem is not detected by professionals. Studies have established a correlation between a depressive and anxious state with the worsening of several clinical conditions, such as asthma[6].

Although the relationship between asthma and psychological suffering is still not well understood, there is a study that shows[4] the existence of such a correlation. There has already been suggested a hypothesis that chronic psychological stress leads to the development of a pro-inflammatory state, with increased production of superoxide and pro-inflammatory cytokines[4]. However, the evidence-based guidelines for asthma do not yet provide a detailed outline for a good approach, screening, and diagnosis of anxiety and depression. For this to change, further studies and research on the topic need to be carried out to corroborate and elucidate the relationship between mood disorders, especially depression and anxiety, with uncontrolled asthma.

In this context, the present study was carried out to corroborate the idea that a multidimensional approach, including assessment of mental status, should be considered for asthmatic patients to improve that patient's quality of life.

CASUISTICS AND METHODS

This is a descriptive, observational, cross-sectional epidemiological study, conducted from April 2019 to March 2020 at the *Ambulatório de Pneumologia da Faculdade de Ciências Médicas de Minas Gerais* (FCM-MG), in Belo Horizonte (MG), Brazil. The research protocol was approved by the local ethics committee under the number CAAE 06386818000005134 and all study participants signed an informed consent form.

Overall, the study involved the participation of 40 patients, who were allocated according to the following eligibility criteria: age equal to or greater than 18 years;

asthmatic patients previously diagnosed at least one year ago through spirometry available at the time of assessment; patients who were followed up at the Pulmonology of the Outpatient Clinic of FCM-MG for at least three months. The study did not include patients who refused to participate or who were unable to answer the questionnaires; carriers of other pulmonary disorders (Chronic Obstructive Pulmonary Disease, sequelae of tuberculosis, pulmonary hypertension, or pulmonary fibrosis); patients with severe comorbidities (neoplasms, chronic renal failure, liver failure, autoimmune diseases, heart failure) and patients with known neuropsychic disorders, except for anxiety disorder and depressive disorder.

Eligible patients answered two validated questionnaires, the first of which was the ACT (Asthma Control Test) — a self-administered questionnaire with satisfactory reproducibility, useful for quantifying and evaluating asthma control and which was validated for this purpose. It consists of 5 questions, related to the four weeks preceding the assessment, addressing multiple dimensions of control, including episodes of shortness of breath, nighttime awakenings, limitations in daily activities, self-assessment of asthma control, and need for relief medication. Each question is scored on a 6-point scale - from 0 (good control) to 5 (bad control) - and, therefore, the total score ranges from 5 to 25. A score ≥ 20 on the ACT is defined as controlled asthma[7].

The second questionnaire applied was the HADS (Hospital Anxiety and Depression Scale), widely used in the screening of psychiatric morbidity, which consists of 14 questions — 7 for anxiety and 7 for depression, each scored from 0 to 3. The maximum score for anxiety or depression, therefore, is 21. Higher scores indicate more symptoms. An anxiety score ≥ 8 in HADS was considered a diagnosis of anxiety, while a depression score ≥ 9 in HADS was considered a diagnosis of depression[4,13].

Finally, demographic data (age and sex) and spirometric data (FEV%, FVC%, FEV1, FVC, and FEV1 / FVC ratio were collected before and after the use of a short-acting inhaled β2-agonist), provided by the participants, was made, and analyzed according to the normal recommended by the *Sociedade Brasileira de Pneumologia e Tisiologia*[15].

The data obtained were digitized in a Microsoft Excel 2010 spreadsheet and imported for statistical analysis in software R version 3.4.3. The numerical variables were presented as mean ± standard deviation and the categorical variables as absolute and relative frequencies ("n (%)"). To compare means between numerical variables, the Mann-Whitney test was used and associations between categorical variables were assessed using the Chi-square test or Fisher's exact test. The level of significance in all tests was 0.05.

RESULTS

Of the 40 study participants, 25 were females (62.5%) and 15 males (37.5%). Regarding age, the mean was 52.5 (± 15.9). 15 participants (37.5%) had controlled asthma and 25 (62.5%) had uncontrolled asthma, according to the ACT classification. The demographic and clinical characteristics of the sample are shown in Table 1.

Regarding the spirometry data, the average value found for the Final Expiratory Volume in relation to the predicted value (FEV1%) was 66.5 (± 19.4) and for the Tiffenau index (TIF) 0.7 (± 0 ,1). The complete spirometric data of the patients are shown in Table 2.

Table 1 - Clinical and demographic characteristics of the sample

	Asthma Control			
	Total (n=40)	**Controlled** (n=15)	**Uncontrolled** (n=25)	**P-value**
Age	52,5 ± 15,9	51,4 ± 18,6	53,1 ± 14,5	0,944 [M]
Sex				
Female	25 (62,5)	9 (60,0)	16 (64,0)	> 0,999 [Q]
Male	15 (37,5)	6 (40,0)	9 (36,0)	
ACT Score	16,6 ± 5,2	22,0 ± 1,9	13,4 ± 3,5	< 0,001 [M]

[M] Mann-Whitney Test; [Q] Qui-square Test. Data are presented as mean ± standard deviation or absolute number (percentage).
Source: prepared by the authors.

Table 2 - Sample spirometric data

| | Asthma control | | | |
	Total (n=40)	Controlled (n=15)	Uncontrolled (n=25)	P-value [M]
Pre-BD				
FEV1	2,1 ± 1,0	2,2 ± 1,0	2,0 ± 1,0	0,530
FEV1 (% of predicted)	66,5 ± 19,4	67,8 ± 15,5	65,8 ± 21,6	0,675
CVF	3,0 ± 1,2	3,2 ± 1,4	2,9 ± 1,1	0,494
FVC (% of predicted)	74,7 ± 17,9	75,5 ± 18,6	74,2 ± 17,8	0,716
TIF	0,7 ± 0,1	0,7 ± 0,1	0,7 ± 0,1	0,900
Post-BD				
FEV1	2,3 ± 1,0	2,4 ± 1,0	2,2 ± 1,0	0,557
CVF	3,2 ± 1,2	3,3 ± 1,3	3,1 ± 1,2	0,485
TIF	0,7 ± 0,1	0,7 ± 0,1	0,7 ± 0,1	0,566

[M]Mann-Whitney test. Data are presented as mean ± standard deviation. Caption: BD: Bronchodilator; FEV1: Forced Expiratory Volume in the first second, FVC: Forced Vital Capacity, TIF: Tiffenau index. **Source**: prepared by the authors.

It should be noted that there was no significant association between sex, age, and spirometry measures with asthma control classified according to the ACT (p> 0.05).

Of the 40 patients in the sample, 10 had none of the two mood disorders assessed according to the HADS score, 17 had anxiety, 7 depression, and 6 the binomial anxiety/depression.

There was a significant association (p <0.05) between asthma control and symptoms of anxiety and/or depression. The prevalence of mood disorders among the 40 patients in the sample was 75%, and isolated anxiety disorder was the most common. Of the 15 controlled asthmatic patients (ACT 20), 8 (53%) did not present a mood disorder. Among the 25 patients with uncontrolled asthma (ACT <20), only 2 (8%) were considered to have no anxiety and/or depression. Among the group of patients with uncontrolled asthma and patients with mood disorders, 12 (48%) had anxiety, 6 depression (24%) and 5 had binomial anxiety and depression (30%). The correlation between mood disorders and asthma control is shown in Table 3 and Graphs 1 and 2.
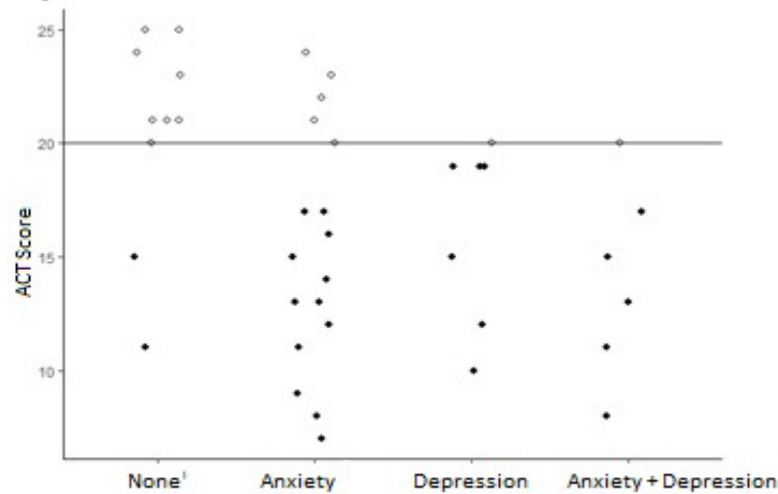
Table 3 - Correlation between asthma control and mood disorders

| | Asthma Control | | | |
	Total (n=40)	Controlled (n=15)	Uncontrolled (n=25)	P-value [F]
Symptoms of anxiety and depression				0,014
None	10 (25,0)	8 (53,3)	2 (8,0)	
Anxiety	17 (42,5)	5 (33,3)	12 (48,0)	
Depression	7 (17,5)	1 (6,7)	6 (24,0)	
Anxiety and Depression	6 (15,0)	1 (6,7)	5 (20,0)	

[F] Fisher's exact test. Data are presented as mean ± standard deviation or absolute number (percentage). **Source:** prepared by the authors

Graph 1 - Correlation between asthma control and mood disorders
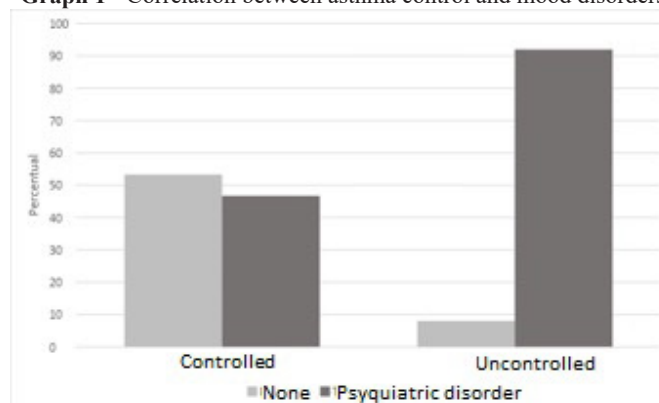
Source: prepared by the authors

Graph 2 - Correlation between asthma control and mood disorders

DISCUSSION

Supporting the epidemiological statistics that point out that the prevalence of asthma is higher in females among adults[6], the women in the study constitute most of the sample (62.5%). As asthma is a multifactorial disease, in which genetic, environmental, pathophysiological, and immunological factors are involved, the reasons for gender-specific differences can also be multiple, such as differences in airway physiology and pathology and behavioral differences between both sexes. However, the hormonal factor seems to be a fundamental component to understand this dissimilarity. Approximately 20-40% of asthmatic women report worsening of respiratory symptoms during the premenstrual and menstrual periods. The mechanism of worsening asthma in the menstrual cycle is still unknown, but it has been suggested to reduce serum progesterone levels, increase mucous secretions, increase the synthesis of prostaglandins in the premenstrual period, and alter the regulation of the receptor β2-adrenergic[9].

Several studies show a preponderance of asthma in childhood, with a decline in young adults and a second increase in those over 60 years of age[8]. The study was conducted with adult participants (> 18 years), with an average age of 52.5 (± 15.9), according to the statistics.

As previously noted in the results, there was no significant association between sex, age, and asthma control. However, a study published in 2014 counters this finding[9]. It shows that women's perception of asthma is different from men's perception and the results suggest that women with asthma experience greater impact and frequency in their respiratory symptoms and more commonly experience limitations in daily life caused by asthma than men. Following this line of reasoning, it was expected that uncontrolled asthma would be more prevalent in the women in the study, since the classification of asthma by the ACT takes into consideration the self-perception of symptoms, activity limitations, and disease control, which did not occur, however.

The GINA (Global Initiative for Asthma)[3], considered the main global guideline for asthma management, takes into consideration daytime symptoms, nocturnal awakenings, frequency of rescue medication use, and activity limitation to classify asthma control. However, the document does not consider FEV% as a control parameter, although it is deemed a risk factor for future exacerbations when <60%. Therefore, it is assumed that asthma control is closely related to the patient's perception of the impact of the disease on his or her daily life; thus, psychological factors, such as anxiety and depression, can have a strong influence on asthma control. The results of the present study corroborate this since no significant association ($p > 0.05$) was found between spirometric data and asthma control.

Several studies have shown the high prevalence of psychiatric disorders, especially anxiety and depression, as well as post-traumatic stress disorder, in asthma patients[10]. The findings of the present study confirm this fact. Of the 40 participating asthmatic patients, 30 had anxiety and/or depression, which represents 75% of the sample. The isolated anxiety disorder was the most prevalent (57%), followed by the isolated depressive disorder. The anxiety/depression binomial was found in a smaller number of participants.

As previously elucidated, there was a significant association ($p < 0.05$) between asthma control and symptoms of anxiety and/or depression, showing that the presence of mood disorders influences asthma disease control. Regarding this as the focus of the study, hypotheses

for such an association are raised.

The first is that psychiatric disorders intensify the inflammation inherent in asthma. Although there is little documented data on how this occurs, it is hypothesized that psychological stress causes a cholinergically mediated increase in airway reactivity, as well as stimulating the release of pro-inflammatory cytokines such as the interleukins IL-2, IL-4, IL-8, and IL-33 and transforming growth factor (TGF-β), which are involved in the inflammatory response in asthma, as was shown in a study conducted in 2017[14]. The systemic inflammatory process generated by chronic psychic disorders may also be able to cause alterations in the small pulmonary airways, at the level of bronchioles, alveoli, and perivascular spaces, whose chronic affection is responsible for severe and difficult-to-manage asthma[17].

A second hypothesis would be that mood disorders alter asthma patients' awareness of their disease, increasing the perception of symptoms and reducing the perception of the level of control[10]. This would justify low ACT scores, increasing the number of asthma patients considered to be uncontrolled. Moreover, respiratory symptoms secondary to mood disorders — in the case of anxiety, a feeling of breathlessness, and increased heart rate, and in the case of depression, insomnia, and fatigue — may overlap with those of asthma[4], underestimating asthma control. Anxiety and depression in asthma patients can also be responsible for reducing their adherence to asthma treatment since they often present clinically with demotivation, pseudodementia, and memory lapses. A patient who is less adherent to regular treatment has consequently less control of the disease.

Another point to consider is the fact that dyspnea is one of the most limiting symptoms in patients with asthma and it can also be seen as one of the most important factors in determining the severity and quality of life of patients with the disease. There are several factors related to the origin of asthma dyspnea, including hypoxemia, hypercapnia, and increased respiratory effort. In this sense, the hypothesis raised is that the hyperventilation which occurs in anxiety attacks may lead to systemic hypoxemia and pulmonary hypoxia and, consequently, to the symptom of dyspnea reported by the patient. Therefore, perhaps,

it was observed in the present study that uncontrolled asthmatics had a higher prevalence of anxiety symptoms[16].

On the other hand, it has also been postulated that poorly controlled asthma leads to an increase in anxiety and depression symptoms for reasons that have not yet been elucidated in the literature. It is worth mentioning that since this is a cross-sectional study it is difficult to define whether anxiety and depression disorders are the cause or the consequence of uncontrolled asthma, despite the clear association between them.

Another limitation of the study was the small sample size due to the difficulty in finding participants who met all the eligibility criteria. Thus, the results of this study may limit the external validity of the result obtained.

Despite the limitations, the main hypothesis of the study that there is a correlation between asthma uncontrol and the concomitant presence of anxiety disorder and/or depression was corroborated.

CONCLUSION

The results of the present study suggest the existence of an association between depressive and anxiety disorders and asthma control. Therefore, the professionals who monitor patients with asthma must be aware of this fact to improve the management of these patients, directing them, when necessary, to psychiatric and/or psychological monitoring concomitantly with the conventional clinical monitoring of asthma.

Because of the evidence shown, we infer that it is important to consider screening for depressive disorder and anxiety disorder in the approach to asthma in adults. With this, it is possible to minimize the unfavorable evolutions and outcomes for patients with the disease, such as limitation of daily activities, exacerbations, and hospitalizations to improve their quality of life and reduce the burden and expenses of the public health system and the private system with avoidable hospitalizations. Finally, we conclude that it is important that the theme discussed here is addressed and studied by more researchers to expand and consolidate information and data on the subject.

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