

Research Article

Association between Exposure to Beta 2 Agonists and Corticosteroids and Acquiring Benign Joint Hypermobility Syndrome among Asthmatic Patients: a Case-Control Study

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Abstract

Background: Beta2 (β_2) agonists as relievers and corticosteroids as controllers are the mainstay drugs for asthma treatment. Benign Joint Hypermobility Syndrome (BJHS) is a connective tissue disorder with musculoskeletal symptoms. We had examined the possible association between the use of β_2 agonists and corticosteroids and acquiring BJHS in asthmatic patients. **Methods:** This was a case-control, hospital-based study including a group of asthmatics who had BJHS (cases), compared with a matched group of asthmatics without BJHS (controls) for the β_2 agonists and corticosteroids past and current pattern of use. Information was collected by face-to-face interview and clinical examination and from subjects' medical records using pre-structured questionnaire. BJHS diagnosis was based on the revised Brighton criteria. Asthma severity was reflected by a score, which was calculated from the asthma questionnaire. Comparison of exposure was done by Calculation of Odds Ratio. **Results:** Development of BJHS was found to be significantly associated with chronicity of asthma of average duration of 13.2 years, and hence to prolonged use of β_2 agonists and/or corticosteroids (OR 1.019; 95% CI 0.999 - 1.039, P=0.006). Exposure to β_2 agonist and corticosteroid (87 and 79 cases and controls respectively P=0.05) high asthma score (42.9 ± 9.8 and 40.4 ± 8.3 among cases and controls respectively, P=0.011) were significantly associated with the development of BJHS. **Conclusion:** Frequent and prolonged use of β_2 agonists and corticosteroids is significantly associated with acquiring BJHS. Implying a possibility of changing approach and handling in asthmatics follow up. Prospective and experimental studies are needed to support the evidence of association.

Keywords: Bronchial Asthma, Benign Joint Hypermobility Syndrome, Beta 2 agonists, Corticosteroids, Brighton criteria, Beighton score

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1. Introduction

Bronchial asthma is the most common reversible cause of airflow obstruction [1]. It is increasing in prevalence worldwide [1], standardized national prevalence data are not available in Sudan. Available data show 12% of children in Khartoum State report asthma symptoms [2, 3].

Asthmatic patients are treated in a stepwise manner according to the severity of the disease [4]. The cornerstones of the treatment are β 2 agonists as relievers and corticosteroids as controllers [5].

Benign joint hypermobility syndrome (BJHS) is a connective tissue disorder with joint hypermobility (JHM) in which musculoskeletal symptoms are not related to systemic rheumatologic disease [6]. BJHS is diagnosed based on the revised Brighton criteria [6, 7]. JHM or laxity and other extra joint manifestations in BJHS are due to qualitative or quantitative defects in collagen within the joint structure and in other tissues [6, 8, 9]. In contrast to its name, BJHS is not really benign, as it can lead to morbid complications like organ prolapse, heart valve lesions and recurrent joint dislocation [6, 10]; however, to our best of knowledge no prevalence estimations are available for it in Sudan.

BJHS has a genetic predisposition but the precise underlying genetic defect remains unknown [11]. An immunologic study proved that salbutamol is a potent suppressor of established collagen-induced arthritis [12]. Another study found that β 2 adrenergic stimulation triggers autophagy in cardiac fibroblasts [13]. Reduction of fibroblasts and hence the collagen production by asthma medications could be the underlying cause of BJHS among asthmatic patients, but this is not proved by studies. A study by Morgan et al. revealed increased frequency of airway disease among patients with Ehlers-Danlos Syndrome and BJHS and another published hypothesis had went in the track of assuming these connective tissue disorders as causes of asthma, but not the opposite [14, 15].

To the best of our knowledge, reviewing the English literature, no studies addressed the effect of asthma medications on joints or their relationship to BJHS. This study was based on our observation of asthmatic patients presented with recurrent joint dislocations and evidence of JHM.

The authors' main objective was to determine whether a significant association between exposure to medications of asthma and acquiring BJHS exists among asthmatic patients in Khartoum State, with particular emphasis on the patterns of use, dose, duration of treatment and medical conditions.

The hypothesis of this study had four pillars:

1. Use of β_2 agonist is associated with acquiring the BJHS.
2. Asthmatic patients using adjunct corticosteroids have more severe and rapid onset of the BJHS than asthmatic using β_2 agonists only.
3. The dosage and frequency of β_2 agonist use with or without corticosteroids are directly proportionate to speed of onset and severity of BJHS.
4. The duration of β_2 agonist use with or without corticosteroids is directly proportionate to the speed of onset and severity of BJHS.

2. Materials and Methods

Study Design This is an analytical, hospital based case-control study, which compared a group of asthmatic patients diagnosed with BJHS (cases) to a group of asthmatic patients without BJHS (controls) and assessed their exposure, dose, and chronicity of use of β_2 agonists and corticosteroids aiming to find out (if any) relationship.

Study setting and population: Study population included all asthmatic patients visited asthma emergency rooms in three central hospitals; Omdurman teaching hospital, Khartoum North teaching hospital and Alshaab teaching hospital, in Khartoum State, Sudan in the period from January 2013 through January 2014.

These hospitals chosen for being central in Khartoum state and serving a wide area. The reason for recruiting patients from emergency rooms was that these hospitals, as well as all hospitals in Khartoum State lack specialised asthma clinics.

Basic procedure of the study:

Selection of cases:

Definition of "case group": asthmatic patients diagnosed by physicians and confirmed by Spirometry, and who are on treatment for at least one year, and experienced BJHS symptoms and diagnosed to have it by the investigators by the revised Brighton criteria.

Inclusion criteria for cases:

1. Male and female asthmatic patients who visited asthma emergency rooms in the chosen hospitals, during the specified study period who were found to have BJHS in terms of revised Brighton criteria.
2. On asthma treatment for at least one year (as induction time for BJHS was unknown).
3. The absence of any systemic rheumatologic disease.

Exclusion criteria for cases:

1. Asthmatic patients affected by any chronic inflammatory joint conditions as these conditions are confounding factors in assessing hypermobility.
2. Asthmatic patients suffering from connective tissue disorders leading to hypermobility such as Marfan's Syndrome and Osteogenesis imperfecta.
3. Asthmatic patients on long term of corticosteroid for other disease

Selection of controls:**Definition of a "control":**

Known asthmatics diagnosed by physicians and confirmed by Spirometry, who are comparable to cases in every way except that they do not have BJHS, and visited the same asthma emergency rooms during the specified study duration.

Inclusion criteria for controls:

1. Male and female asthmatic patients who visited asthma emergency rooms in the chosen hospitals, during the specified study period
2. On asthma treatment for at least one year (as induction time for BJHS was unknown).
3. Matched cases according to specified matching criteria.

Exclusion criteria for control:

1. Asthmatic patients affected with any chronic inflammatory joint conditions.
2. Asthmatic patients suffering from any connective tissue disorder.
3. Asthmatic patients on long term of corticosteroid for other disease.

Matching to cases:

Gender, the age range of 5 years, and BMI category were used as matching criteria; one control per each case.

Measure of exposure:

In the light of literature that hypothesises connective tissue disorder as a cause of asthma, to exclude the possibility of confounding that the connective tissue disease leads to asthma, in this study the exposure status is not the use of β_2 agonists and/or corticosteroid per se, but the duration and pattern of use. It was established from historical records & ascertained from personal recall, using an interview. Exposure in cases and controls was compared to estimate disease risk associated with duration and pattern of use, as follows

1. Data were set in a 2 by 2 fourfold tables or other.
2. Results were expressed as odds ratio (Exposures between cases & controls are compared by calculation of Odds Ratio).
3. Test any differences for statistical significance by chi square tests and conditional logistic regression, to find out if the observed exposure among cases higher than the control group.

Sample size and sampling technique: The desired size of sample was calculated according to: formal mathematical equation that relates power of study (0.9), proportions exposed in control group and in case groups, ratio of cases vs. controls, and significance level.

$$n = \left(\frac{r+1}{r} \right) \left(\frac{(\bar{p})(1-\bar{p})(Z\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2} \right)$$

n = sample size in case group

r = ratio of control to cases (r = 1)

Zβ = desired power, for 80% power, Zβ = 0.84

Zα/2 = desired level of significance (typically = 1.96)

Proportion exposed in control group (p_o) = 20% ≡ p₁

Proportion exposed in case group (p_c) ≡ p₂ =

$$p_c = \frac{OR P_o}{P_o (OR - 1) + 1}$$

$$p_c = \frac{2(0.20)}{(0.20)(2 - 1) + 1} = \frac{0.40}{1.20} = 0.33$$

Average proportion exposed = $\frac{0.33+0.2}{2} = 0.265$

$$n = 2 \frac{(0.265)(1 - 0.265)(0.84 + 1.96)^2}{(0.33 - 1.0)^2} = 181$$

Total N= 362: (181 cases and 181 controls).

Sampling was by complete coverage during the study period:181 cases were recruited and frequency matching was used for controls selection, matching criteria: is in terms of age group, gender and body mass index (BMI) category, (at 1:1 ratio).

Data collection: Using personal approach with face-to-face structured interview, where questions on the survey were asked directly to the patients by the researchers. This strategy in data collection helped in reaching 100% response rate. The researchers interviewed all cases and controls on the basis of a detailed predefined Performa, with

their medical records reviewed and all respondents were clinically examined to detect the presence of Brighton diagnostic criteria for BJHS. A standard asthma questionnaire was filled to calculate asthma severity score for each participant.

Study Variables:

Gender, age, chronicity of asthma in years, types of asthma medications administered by the patient including the duration and the route of their use, any chronic disease/s, other long-term medications, patient's recognition of JHM, family history of JHM, time of recognition of JHM in relation to being asthmatic, history of joint dislocations, asthma score and present Brighton criteria were the variables of this study.

Asthma score: This score was structured by the investigators in order to categorise patients according to the severity of the disease, it was calculated from asthma questionnaire that covered detailed asthma history. The score was out of 90 with three categories, mild (up to 30), moderate (31-60) and severe (61-90).

Brighton criteria:

Patients were diagnosed as having BJHS based on the following revised Brighton criteria published by Grahame including Brighton score, which is a measure of JHM [7].

I. Major Criteria [7]

1. Brighton scores of four (Table 1).
2. Arthralgia for longer than 3 months in four or more joints.

II. Minor Criteria

1. Brighton scores of one, two, or three.
2. Arthralgia (3-month duration) in one to three joints or back pain (3-month duration) or spondylosis, spondylolysis/spondylolisthesis.
3. Dislocation or subluxation of more than one joint, or in one joint on more than one occasion.
4. Three or more soft tissue lesions (e.g. epicondylitis, tenosynovitis, bursitis).
5. Marfanoid habitus (tall, slim, span greater than the height (1.03 ratio), upper segment less than lower segment (<0.89 ratios), arachnodactyly).
6. Skin striae, hyperextensibility, thin skin, or abnormal scarring.
7. Ocular signs: drooping eyelids, myopia, antimongoloid slant.
8. Varicose veins, hernia, or uterine or rectal prolapse.

Test	Points
left little (fifth) finger passive dorsiflexion beyond 90°	1
right, little (fifth) finger passive dorsiflexion beyond 90°	1
left thumb passive dorsiflexion to the flexor aspect of the forearm	1
right thumb passive dorsiflexion to the flexor aspect of the forearm	1
left elbow hyperextends beyond 10°	1
right elbow hyperextends beyond 10°	1
left knee hyperextends beyond 10°	1
right knee hyperextends beyond 10°	1
forward flexion of the trunk with knees fully extended palms of hands can rest flat on the floor	1

TABLE 1: Tests for calculation of Beighton score.

9. Mitral valve prolapse.

Requirement for Diagnosis

Any one of the following:

1. Two major criteria
2. One major plus two minor criteria
3. Four minor criteria
4. Two minor criteria and unequivocally affected first-degree relative in family history [7].

Research bias: Selection bias was prevented by the clear definition of the study population, the controls were selected independently of the exposure status and a precise case definition and exposure definition were used by all investigators.

Measurement bias was prevented by using standard measurement instruments; questionnaires and performs to collect similar information from both cases and controls and every patient were clinically examined by two investigators to increase the accuracy of application of diagnostic criteria.

Recall bias prevented by using multiple sources of information for each subject such as records, follow up cards, inhaler cans to determine the dose.

Statistical Analysis:

1. Ascertain exposure rates among cases and controls:

2. Estimate disease risk associated with exposure: compare exposure in cases and controls (by Calculation of Odds Ratio)

3. Test any differences for statistical significance: Chi-square and student t-tests were used. 95% confidence interval was used and P value ≤ 0.05 was set as statistically significant.

Human and Animal Rights:

This research involved human subjects only, No experimental animals were involved. The protocol had been approved by the Research Department and Ethical Committee at Ministry of Health, Khartoum State.

Results Patients with BJHS (cases) were 181 matched to 181 patients without BJHS (controls). Females represented 68.5% of the study sample, the mean age (\pm SD) among both groups (34.9 ± 11.1), with 34.9 years (± 11) among cases and $34.9 (\pm 11.2)$ among controls.

The mean BMI (\pm SD) of the study sample was $24.9 (\pm 5.5)$ among cases, $25.2 (\pm 5.6)$ among controls and $25 (\pm 5.6)$ for both cases and controls.

Most of the patients (73.8%) were seen in Omdurman teaching hospital, followed by Khartoum North Teaching hospital 15.7%, and 10.5% from Al-Shaab Teaching hospital.

Exposure to salbutamol was approximate among both cases and controls, with 98.9% and 100%, respectively, whereas more than half of cases 51.4% and controls 55.2% were using it alone.

All participants were using reliever medications; the vast majority of cases via inhalational route 87.8 % (Table 2).

More than two-thirds (83.4%) of cases were falling within a spectrum of reliever inhaler consumption time ranging from less than a month to 3 months (Table 3). There was a significant statistical correlation between exposure to asthma medications with long period $\geq 1-2.5$ years (average induction time) ($p = 0.006$) and higher dose $\geq 4-5$ inhalers consumed per year ($p=0.05$) and acquiring BJHS.

Prednisolone /hydrocortisone bursts were received by 73.5% and 81.8% of cases and controls, respectively, during emergency room visits, but was not significantly associated with developing BJHS ($P=0.062$).

The family history of JHM was found to be positive in 16.5 % of cases and 5.5% of controls ($P= 0.001$), Odds ratio 3.4(95% CI 1.6-7.2).

Only 21.5% of cases had recognized their JHM and their ability to perform moves that cannot be performed by normal individuals; out of them, 74.5% reported this after being asthmatic. The rest of cases recognized their JHM at the time of interview when examined by the investigators.

Route of administration of reliever medication	Participant		Total
	Case%	Control%	
Inhalation by Inhaler	87.8	82.3	85.1
Inhalation by Nebulizer	3.3	2.8	3.0
Oral/ Syrup	0.0	1.7	0.8
Oral/ tablets	1.1	3.3	2.2
Oral Tablets and Nebulizer	0.6	0.6	0.6
Nebulizer & Inhaler	5.5	7.7	6.6
Oral tablets or syrup and Inhaler	0.6	1.7	1.1
Do not use reliever	1.1	0.0	0.6
Total	100.0	100.0	100.0

TABLE 2: Route of administration of -reliever medication- Salbutamol among Study Sample.

The single inhaler consumption duration	Participants		Total %
	Case %	Control %	
Less than a month	31.5	23.2	27.3
1-3 months	51.9	51.9	51.9
4-6 months	7.2	12.2	9.7
7-9 months	1.1	1.1	1.1
10 months- a year	1.7	3.3	2.5
More than a year	2.2	3.3	2.8
Have No Inhaler, Using Salbutamol tablets or syrup, or Nebulizer	4.4	5.0	4.7
Total	100	100	100

TABLE 3: Distribution of the Study Sample in Accordance with inhaler consumption duration.

The vast majority of cases (81.8 %) reported joint pain; of them 71.8% had pain for more than 3 months, 8.8% had joint pain for 3 months, 1.2% for less than 3 months and 18.2% had no joint pain at all. On the other hand, joint pain was reported by 33.7% of controls ($P=0.000$), Odds ratio 8.8 (95% CI 5.4-14.4).

Only 6.1% of cases and 3.3% of controls had a history of joint/s dislocation. Arthralgia for more than 3 months duration in 4 or more joints was reported in 48.6% of cases and 1.7% of controls ($P=0.000$), Odds ratio 56.143 (95% CI 17.3, 182.3).

Brighton criteria	Participants		Total %	P value	Odd Ratio	CI (Lower, Upper)
	Case %	Control%				
Ocular signs: dropping eyelids, myopia, antimongoloid slant.	56.4	11.6	34.0	0.000	9.8	5.7,16.9
Three or more soft tissue lesions	55.2	6.6	30.9	0.000	17.3	9.0,33.5
Arthralgia (3-months duration) in one to three joints or back pain (3-months duration) or spondylosis, spondylolysis.	34.8	23.8	29.3	0.021	1.71	1.1,2.7
Arthralgia for longer than 3months in 4 or more joints	48.6	1.7	25.1	0.000	56.143	17.3,182.3
Skin striae, hyperextensibility, thin skin, or abnormal scarring.	43.6	4.4	24.0	0.000	16.7	7.8,36.1
Varicose veins, hernia, or uterine or rectal prolapse.	21.0	5.0	13.0	0.000	5.07	2.4,10.9
Marfanoid habitus.	8.8	2.8	5.5	0.006	4.3	1.4,13.1
Dislocation or subluxation of more than one joint, or in one joint on more than one occasion.	5.5	1.7	3.6	0.048	3.4	0.94,12.8
Mitral valve prolapse.	0.6	0.0	0.3	0.317	-	-

TABLE 4: Brighton criteria among study sample.

The mean Brighton score (\pm SD) was 2.64 (\pm 1.62) among cases and 0.88 (\pm 1.20) among controls ($P=0.000$).

The most common Brighton criteria among cases were found to be the presence of dropping eyelid, myopia and/ or antimongoloid slant which represented 56.4% followed by the presence of 3 or more soft tissue lesions which were 55.2%. On the other hand, 11.6% of controls had a dropping eyelid, myopia and /or antimongoloid slant followed by the presence of 3 or more soft tissue lesions which were 6.6% (Table 4). This table also shows that asthmatics with most (7/9) of the Brighton criteria are significantly more likely to be (β) 2 Agonists and corticosteroids users.

Diagnosis by one major and two minors criteria was the commonest among cases (40.34%) while 66.86% of controls had sub-diagnostic criteria (Figure 1).

Development of BJHS was found to be significantly associated with chronicity of asthma of average duration of 13.2 years, and hence to prolonged use of β 2 agonists

Types of asthma medications	Duration of Medication Use in years	Beighton Score
Beta 2 agonists only	1.01 ± 0.1	1.7 ± 1.6
Beta 2 agonists and corticosteroid controller	2.6 ± 2.6	1.9 ± 1.8
P-value	0.000*	0.032*

TABLE 5: Means of the duration of asthma medication used in years and Beighton score.

and/or corticosteroids (OR 1.019; 95% CI 0.999 - 1.039, $P = 0.006$), with the frequency of consuming a 200 metered dose inhaler in a mean duration of 2.2 months, and with high asthma score (42.9 ± 9.8) ($P=0.011$).

No significant statistical correlation was found between developing BJHS and a certain type of medication per se, but it was significantly correlated with duration of salbutamol use in years ($P = 0.022$) and the number of salbutamol inhalers consumed per month ($P = 0.027$).

Acquiring BJHS correlated statistically with the duration of salbutamol alone or with corticosteroid used in years and Beighton score (Table 5).

*Statistically significant p- value.

Acquiring BJHS was not found to be correlated with added chronic diseases other than asthma ($P=0.083$) or their medications which had been used in the previous year before the interview ($P=0.91$).

3. Discussion

To the best of our knowledge, this is the first time in English literature to demonstrate an association of BJHS among Sudanese asthmatic patients compared with their matched controls.

Joint hypermobility (JHM) was observed in 68.5% of females among the cases in this study, justified by the fact that BJHS has a strong genetic constituent with an autosomal dominant pattern [6], and the likelihood of developing the disease seems to be higher in a female fetus [11, 20].

Compared to other populations, JHM showed lower prevalence figures in Nigerians (43%) [16], followed by 38.5% in females, and 25.4% in males among Iraqi students [17] and 6% in females, 2% in males among Caucasians [11]. Various environmental/acquired contributors, such as sex, age, sports habits, trauma, surgery, diet, and pain cognition [7, 11, 18, 19] need further exploration of their role in increasing the rate among Sudanese.

Patients with BJHS may have a family history of double-jointed relatives, recurrent dislocations or other presentations [6]. The significantly higher Beighton score among cases than controls while the majority of cases (83.4%) reported a negative family history of JHM and presence of sub-diagnostic criteria among 66.8% of controls suggest this form of BJHS may be acquired. That was supported by the fact that the onset of the disease took place after being asthmatic and using the medications in 74.6% of cases who recognized their JHM.

The average induction time was 1 year for regular β_2 agonists only, and 2.6 years for patients using combined β_2 agonists with corticosteroids as controllers, also the combination regimen increased the Beighton score more than β_2 agonist only ($p=0.032$). Thus, corticosteroids were not significantly associated with BJHS, but combination with β_2 agonist delayed the onset and increased the severity of the disease.

The vast majority (83.4%) of cases were falling within a spectrum of a single reliever inhaler consumption period ranging from less than a month to 3 months, fragmented to 31.5% in less than a month CI 95% (24.6% - 38.6%) and 51.9% during 1-3 months CI 95% (44.2%-59.2%). Therefore, exposure to asthma medication with long period 1-2.5 years (average induction time) or more ($p = .006$) and higher dose ≥ 4 -5 inhalers consumed/year ($p=0.05$) is associated with the development of BJHS.

Salbutamol has important effects on the immune inflammatory response and a significant therapeutic action in collagen-induced arthritis [12]. This effect was demonstrated by injection of 200 micrograms of Salbutamol every day for 10 days in mice, extending the effects of salbutamol in the human situation, however, would depend on the dosage [12].

The most commonly used type of reliever medications –among study sample- was salbutamol sulphate in a pressurized metered dose inhaler with valve, each depression of the valve delivers 100 mcg of salbutamol, with a total of 200 inhalations, giving a total dose of 20mg (20000 μ g) salbutamol per inhaler [21]. The majority of the case group in this study consumed four inhalers or more per year, therefore, they were exposed to ≥ 80 mg (80000 μ g) at least per year.

Increased duration of exposure to salbutamol in years and the number of salbutamol inhalers consumed per month were significantly associated with the development of BJHS. While corticosteroids had significant synergistic effect with salbutamol by increasing the severity of JHM, the duration of its use in years was not significantly correlated with BJHS because asthmatic patients are not treated with steroids alone, hence, their effect can be evaluated only in a group of non-asthmatic patient under treatment of steroid only.

Asthma per se has been excluded in this study as a cause of BJHS as well as other chronic diseases like hypertension, diabetes mellitus, and renal failure. Moreover, long-term medications such as antihypertensive and oral hypoglycemic were not significantly linked to acquiring BJHS (P-value = 0.05).

Regarding asthma score structured by the investigators to evaluate asthma severity; it was due to patient's ignorance and poor compliance, the questions made it easier for patients to tell as sure as possible, forced expiratory volume in the first second using a spirometer is the test for asthma attack severity, finances limited its use for us and our patients, all of our patients did not have an asthma diary as well

The vast majority of BJHS patients presented with joint pain, which is thought to be due to excessive joint laxity that leads to wear and tear on joint surfaces and strains [6]. It is noteworthy that joint pain was not due to any arthritic disease. In this study, 81.8% of cases had a history of joint pain, 71.8% of them had pain more than 3 months, which is comparable with 33.3% of (204) studied population of hypermobile participants with arthritic disorders in Nigeria [16]. This great difference is related to differences in pain threshold, attitudes to pain [22] and the effect of asthma medications.

A considerable higher prevalence of dropping eyelid 56.4% and soft tissue lesion (55.2%) among cases in this study compared to patients in London where dropping eyelids was present in 41% and soft tissue lesions in 10% of the studied group [23]. This significant difference might be related to salbutamol effect on collagen, as well as corticosteroids, in addition to ethnic and environmental factors.

4. Conclusion

High dosage, frequency and prolonged use of (β) 2 agonists and corticosteroids are significantly associated with acquiring BJHS. Corticosteroid controllers decrease the patient frequency of (β) 2 agonist use and lead to a more severe form of BJHS expressed in higher Beighton score, however, the symptoms take place over a longer duration, this may conclude that (β) 2 agonists have the primary role and corticosteroids have a synergistic role.

These important side effects of asthma medications could possibly change the approach and handling of asthmatics and their follow-up. Prospective and experimental studies are needed to support the evidence of association. In the future, the effect of these medications may be used in the restoration of lost joint function and movement span due to chronic inflammatory joint diseases.

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6. Conflict of Interest

The authors declare no conflict of interest.

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