CLINICAL TRIAL

Influence of Pharmaceutical Care Interventions on Clinical and Biochemical Markers of Asthmatic Patients at Baghdad Teaching Hospital, Baghdad, Iraq

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ABSTRACT

Background: Asthma is a significant cause of morbidity and mortality worldwide. Asthma, a chronic respiratory disease characterized by chronic airway inflammation, bronchial hyper-responsiveness, and reversible airflow obstruction, poses a substantial economic burden on patients and caregivers alike. Education is a critical component in the management of asthma.

Objective: This study is designed to assess the impact of pharmacist-led educational interventions on asthma control and serum levels of inflammatory and oxidative stress biomarkers.

Method: Patients in this study received conventional therapy for chronic bronchial asthma, in addition to pharmaceutical care and patient education by clinical pharmacists for three months. All patients enrolled in this study were assessed clinically for asthma control test (ACT) and biochemically; serum levels of Interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and SOD-3 at the baseline and after 3 months.

Result: At the end of the study, patients who received a pharmaceutical care plan significantly improved their asthma control by improving the asthma control test score and significant changes in IL-6, TNF-alpha, and SOD-3 levels ($p < 0.05$) after 3 months of follow up by a pharmacist.

Conclusion: The present study results provide supportive evidence concerning pharmacists' favorable effects on asthma patient care and support pharmacists as valuable health care team members.

Keywords: Asthma, Asthma control test, IL-6, Pharmaceutical care, TNF-α.

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which persistent inflammation is associated with airway hyper-responsiveness (exaggerated airway-narrowing response to specific triggers such as viruses, allergens, and exercise), and results in frequent episodes of wheezing, chest tightness, breathlessness and/or coughing that may vary in intensity over the years.[1] These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with a treat or through effective bronchial asthma treatment, including a fast-acting bronchodilator.[2,3]

It can cause a major disability for people who have asthma and significantly affect their quality of life.[4] The significant increase in the prevalence of asthma and other allergies (for example, eczema) over the past several decades cannot be explained by relying on genetic factors alone, leading to an increased focus on other risk factors such as environmental exposure. It is expected that cases will rise asthma to over 400 million cases globally in 2025.[5]

Many studies have shown that the prevalence of asthma varies between countries and within countries and is directly proportional to different allergies, where different lifestyles are adopted, and societies become civilized. However, this trend is expected to continue during the next two decades.[6]

Some factors contribute to causing asthma; respiratory infections, allergens, environmental changes, emotions, exercise, drugs/preservatives, and non-allergenic airborne irritants.[7] Many cells and cellular elements are involved in this inflammation, but mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells are especially important.[8] Oxidative stress plays a critical role in the pathophysiology

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of asthma due to its ability to chronically activate airway inflammatory cells such as macrophages and eosinophils that produce reactive oxygen species.[9]

The essential components of asthma management include avoiding allergens, using appropriate medications, regular monitoring of asthma control, using written asthma action plans, adherence to therapy, and regular review of inhaler device technique.[1] Numerical asthma control tools such as the asthma control questionnaire (ACQ) and ACT are sensitive tools for assessing symptom control. Furthermore, both peak expiratory flow rate and symptom monitoring are useful in asthma self-management. However, peak flow monitoring has no advantage over symptom monitoring as an asthma management strategy for older adults.[10,11]

Pharmacists have in an excellent position to play an active and positive role in the management of asthma. It is important to change the pharmacist's practice in healthcare to a more patient-centered approach through the provision of supports and focuses on optimizing the use of medicines and improving health outcomes. Recent meta-analyses have shown a positive impact of pharmacists when delivering clinical services for patients with chronic conditions such as diabetes or hypertension.[12] Similarly, a systematic review by Garcia-Cardenas *et al.* (2016) demonstrated that clinical pharmacists could effectively screen for poorly controlled asthma.[13] A narrative review revealed an expanding role of pharmacists in asthma care across different settings like medication adherence and clinical outcome.[14] The objective of this study was to evaluate the impact of pharmacists' interventions on clinical asthma outcomes in Iraqi adult patients.

METHOD

This interventional study was carried out over three months. Twenty-three patients with mild to moderate asthma were randomly selected at the respiratory unit of Baghdad Teaching Hospital. All patients diagnosed with symptomatic asthma. The enrolled patients were assigned to receive conventional therapy for chronic bronchial asthma according to disease stage and severity and pharmacist intervention, including patient care and education for three months.

Conventional therapy used in this study includes many drugs according to the severity of the disease and treatment prescribed by the physician. Patients on bronchodilator reliever medication such as short-acting β2- agonist (Salbutamol), methylxanthines (aminophylline), also inhaled preventer medication such as corticosteroid/long-acting β2-agonist combination. Some patients were on leukotriene antagonist (montelukast).

Patients data were collected at baseline, including age, gender, family history, comorbid diseases, and the onset of asthma symptoms. All patients enrolled in this study were assessed clinically for ACT and the serum levels of IL-6, TNF-alpha and SOD-3, total WBC, Monocyte, Granulocyte and Lymphocytes at the beginning of the study and after 3 months. The plasma levels of all parameters were measured using specific kits for enzyme-linked immunoassay (ELISA).

Asthma Control Test (ACT)

A validated number of questions was scheduled to all patients before and after treatment to calculate the asthma control score for the 4 past weeks. The total scores range from 5 to 25. Score of 25 means that asthma was under control for 4 past weeks, and a score 20 to 24 means the asthma is on target for the 4 past weeks. However, when the score is below 20, the asthma is not under control for the 4 past four weeks. Appendix 1 shows the ACT questionnaire used in this study to reflect an image of the frequency of asthma symptoms and asthma medications over the last 4 weeks period.[15]

Sample Collection

Ten milliliters (mL) of non-fasting venous blood were drawn using a disposable syringe of 10 mL capacity. Eight mL of the blood was collected in a disposable plain tube. Two-mL of blood was taken to measure white blood cell count, and lymphocytes and the rest were left to clot and separated by centrifuge at the speed of 4000 rounds per minute (rpm) for 10 minutes. The serum samples were stored at (-80ºC) to detect IL-6 and TNF-α levels until the examination time.

RESULT

The disease characteristics and demographic data of 23 asthmatic patients are explained in Table 1. Whereas the age of all patients contributed in this study was ≤ 50 years, the gender of patients was 13 (56.4%) male and 10 (43.6%) female. Patients with a family history of chronic bronchial asthma were only 2 patients (8.7%). Regarding to duration of disease, patients with a duration of (< 1 year) were 9 (39.1%), patients with a duration of 1 to 5 years were 9 (39.1%), while patients with chronic bronchial asthma duration > 5 years were 5 (21.7%). There were 15 (65.2%) patients in rural areas and 8 (34.8%) patients in urban areas. Concerning to education level, two patients (8.7%) presented with a primary level of education

Table 1: Patients demographic data and characteristics**.**

Demographic characters		*Value N (%)*
Gender	Male	13 (56.4)
	Female	10 (43.6)
Age group	≤ 50	23 (100)
	> 50	0 (0)
Family history	No	21 (91.3)
	Yes	2 (8.7)
Duration of disease	< 1 year	9 (39.1)
	1–5 years	9 (39.1)
	> 5 years	5 (21.7)
Residence	Rural	15 (65.2)
	Urban	8 (34.8)
Comorbid disease	No	23 (100)
	Yes	0 (0)
Education level	Primary	2 (8.7)
	Secondary	14 (60.9)
	College	3 (13.0)
	PG	4 (17.4)

Data presented as mean ± SD. No: number, %: Percentage, PG: Post graduate.

and 14 patients (60.9%) with a secondary level of education, while 4 patients (17.4%) were post-graduated from college, and all the patients had no comorbid disease.

As illustrated in Table 2 and Figure 1, patients in this study showed a significant ACT value improvement after 3 months of follow-up compared with baseline value ($p < 0.01$). This study also demonstrated that total white blood cell level decreased non-significantly after 3 months of follow-up regarding the baseline value ($p > 0.05$). However, using a pharmaceutical care program revealed a highly significant reduction in lymphocyte levels of all patients of this study after 3 months of follow-up compared with baseline value ($p < 0.01$), Table 3.

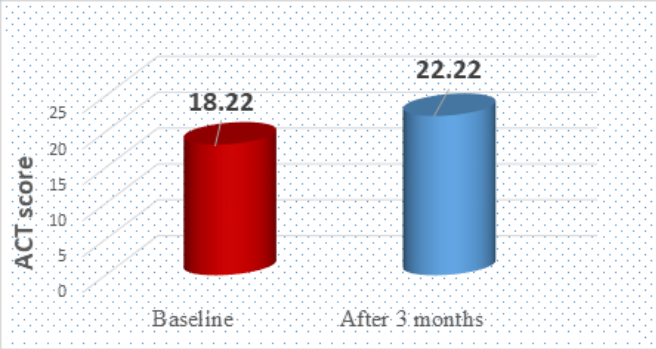

Figure 1: Effect of pharmacist intervention on the asthma control test

Table 2: Effect of pharmacist intervention on the asthma control test

Parameter		*Mean ± SD*
ACT	Baseline	18.22 ± 3.11
	After 3 months	22.22 ± 4.86
	p-value	0.004 **
	Percent of change	+ 21.9 %

Data presented as mean ± SD, were**:** paired t-test used for comparison between baseline and after 3 months, **: Highly Significant difference ($p < 0.01$).

Table 3: Effect of pharmacist intervention on Total WBC and lymphocytes

Parameter		*Mean ± SD*
T.WBC (10*3/uL)	Baseline	9.70 ± 3.71
	After 3 months	8.20 ± 1.48
	p-value	0.055^{NS}
Lymphocyte (%)	Baseline	33.94 ± 2.60
	After 3 months	27.51 ± 3.67
	p-value	0.003**

Data presented as mean ± SD, were paired t-test used for comparison between baseline and after 3 months NS: Not significant ($p > 0.05$), **: Highly significant difference ($p < 0.01$).

Table 4: Effect of pharmacist intervention on inflammatory markers

Biomarker		*Value (Mean ± SD)*
IL-6 (pg/mL)	Baseline	228.73 ± 98.80
	After 3 months	176.61 ± 45.57
	p-value	0.033*
TNF-α (pg/mL)	Baseline	160.539 ± 56.082
	After 3 months	126.022 ± 21.20
	p-value	0.022*

Data presented as Mean ± SD were IL-6: Interluken-6, TNF-α: Tumor necrosis factor alpha, Paired t-test used to compare baseline and after 3 months, *: Significant difference ($p < 0.05$).

The effects of 3 months of the pharmaceutical care plan are seen in Table 4. However, inflammatory markers IL-6 and TNF-α values were significantly reduced in asthmatic patients who participated in this study.

DISCUSSION

Despite the obtainable of many pharmacological treatments, about 50% of asthmatic patients in the United States experienced exacerbations in 2016, indicating the need for effective add-on therapy. Asthma control remains suboptimal due to low medication adherence, poor inhaler technique, and many patient-related factors. That is why, in the health care setting, pharmacists position allows them to play a vital role in providing long-term follow-up care for the effective management of chronic diseases, such as asthma.[12]

The major participants were male through data analysis, and these results contrast with most of the other studies. It showed that asthma occurs in females more than males with a ratio of about 3:1, and this ratio still until this ratio is around the time of menopause.[16,17] This may be due to the small sample size of the population used in this study. The age of participants was less than 50 years, and this agreed with other studies which reported that asthma occurs with an adult more than children.[18,19] Asthma that occurs in the first 30 years of life is strongly related to family history of asthma,[20,21] but this study presents that more than 90% of the participants have no family history due to a small sample size to compare with other studies. It has been reported that asthmatic patients with low socio-economic status have poor asthma control, which may be due to a low level of education or maybe due to low income, which leads to failure of treatment and poor compliance.[22,23]

Results of this research shown in Table 2 and Figure 1 agreed with another study by Vermeulen *et al.* (2013), which suggested that patients have uncontrolled asthma if the score of ACT is below 20, and patient's referral to the doctor is necessary.[24] In this study, pharmacist intervention revealed a significantly improvement in ACT score after 3 months of follow-up compared to the baseline score.

This improvement in the ACT result from the role of the pharmacist in enhancing patients educations about proper medication use as prescribed by a physician, increase knowledge of trigger factors that lead to deterioration of inflammation, also increase awareness about important side effects of asthmatic medications and other medications that may interfere with symptoms of asthma. The pharmaceutical care plan also comprises enhancing patients' compliance with their medications, and asthmatic patients should know that asthma is non-curable, and patients should take their medications chronically to improve ACT scores and enhance the quality of life. Otherwise, this may lead to the deterioration of symptoms that interfere with normal life activities and health. The findings of this study were consistent with the previous studies to explain the important role of pharmacists in asthma control.[25-28]

As declared earlier, asthma is an inflammatory disease and involves the mobilization of different types of white

blood cells into the lung and results in clinical symptoms of asthma.[29] Increased total white blood cells (WBC) and lymphocytes count was presented in asthma, inhuman, and animal studies compared to healthy controls.[30] In this research, as shown in table 3, three months of follow up with pharmacist interventions showed a slight reduction of total white blood cells and lymphocytes counts as a result of increased adherence of patients with its medications and enhance inhaler technique of the asthmatic patients, which is also demonstrated in other similar studies.[31,32]

The serum levels of IL-6 are raised in several inflammatory diseases.[33] As a result, IL-6 is regarded as one of the general markers of inflammation,[34] a marker on disease severity and progression.[35] In asthma, serum levels of IL-6 elevated in most patients and associated with lower lung function and more frequent asthma exacerbations and increased more in obese asthmatic patients.[36]

As shown in table 4 in the current study, the serum level of IL-6 decreased markedly in asthmatic patients receiving pharmaceutical care after 3 months of follow-up compared with baseline. Ilmarinen P *et al.* (2016) showed that the serum level of IL-6 in asthmatic patients increased as the inflammation increased, leading to an increased need for ICS.[37] However, due to the impact of pharmaceutical care, medication adherence improved, and patients complained of a decrease in asthmatic patients who participated in the present study. This effect is explained through ACT score, which increases,[22] and consequently considered an outcome for reducing IL-6 level in those patients.

Tumor necrosis factor-alpha (TNF-α), a potent pro-inflammatory cytokine with immune-regulatory properties released primarily by macrophages and mast cell, is thought to play a key role in asthma pathogenesis.[38] It has been reported that moderate-severe asthmatic patients present with elevated TNF-α levels associated with high utilization of healthcare services, poor symptom control, and more chance of airflow obstruction than patients with low TNF-α levels. However, such patients might get benefit from therapy with anti-TNF-α medications.[39] Although there is remarkable variation in response, previous studies have revealed an improvement in quality of life, pulmonary function, and airway hyper-responsiveness, in addition to lowering the exacerbation frequency in asthmatic patients treated with anti-TNF-alpha therapy.[40]

As explained in Table 4 in the present research, serum level of TNF-α significantly reduced after 3 months of follow-up. This change results from the effect of pharmacist interventions that enhance medication adherence and correct use of medications and enhance patient complaints.

CONCLUSION

This study provides further evidence for a role pharmaceutical care program that revealed a remarkable improvement in the asthma control represented by asthma control test (ACT) and some of the inflammatory markers in a sample of Iraqi patients. Further studies are essential to evaluate the pharmacist's role in other medical illnesses.

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