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The Effect of Omega-3 in the Management of Clinical Symptoms and Quality of Life Deterioration in Iraqi Chronic Asthmatic Patients.

دور الاوميجا-3 في علاج الأعراض السريرية والتدهور في نوعية الحياة للمرضى العراقيين المصابين بداء الربو المزمن

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Abstract

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness.

In secondary care populations up to 50% of patients with asthma have been reported to have clinically significant depressive symptoms and over a third of asthmatic outpatients have been found to have a major depressive episode.

There is some evidence that omega-3 fatty acids are related to mental health, including that they may be useful as an add-on for the treatment of depression associated with bipolar disorder. However, significant benefits due to eicosapentaenoic acid (EPA) supplementation were only seen when treating depressive symptoms and not manic symptoms suggesting a link between omega-3 and depressive mood.

The aim of the present study was to investigate the effect of omega 3 on the management of moderate persistent asthmatic patient who are poorly responded on a combination of inhaled corticosteroids and long acting ß 2 agonists.

Forty five asthmatic patients were included in the study, 21 male and 24 female, who were uncontrolled adequately with inhaled combination of corticosteroids and long acting ß2 agonists. The effect of omega 3 was investigated after 1,2,3 and 4 weeks on symptom frequency, night symptoms and quality of life.

The result of the study evoked a positive effect on all studied parameters that might be agree with old studies and denied with others.

The study concluded that omega 3 might be play an important role in the management of clinical symptoms and quality of life of asthmatic patients.

Key words: omega-3; clinical symptoms; quality of life; asthma

الخلاصة

الربو من الأمراض الالتهابية المزمنة للمجاري التنفسية حيث تلعب العديد من الخلايا والعناصر الخلوية دورا في ذلك. يسبب هذا الالتهاب في الأشخاص ذو التحسس العالي نوبات راجعة من السعال خصوصا أثناء الليل أو في الصباح الباكر.وكذلك الازيز وعدم القدرة على التنفس وضيق الصدر.

في جمهرة العناية الثانوية ، 50% من مرضى الربو سجلت لديهم أعراض مكئبة مهمة سريريا ، وان اكثر من ثلث مرضى الربو الخارجيين وجد ان هنالك تراجعا كبيرا في النوبات المكئبة الرئيسية.

تشير بعض الدلائل إلى أن الاوميغا3 له علاقة بالحالة العقلية ,وبضمن ذلك ان له فائدة عند استخدامه كعلاج مضاف لحالات الكآبة والتي تصاحب الاضطراب ثنائي القطب . عموما، لوحظت فوائد مهمة لمضافات حامض الايكوسابنتاينوك في علاج أعراض الاكتئاب ولكن ليس لأعراض الهوس مما يدل على وجود رابط ما بين الاوميغا3 والمزاج الاكتئابي.

الدراسة الحالية قد اجريت للتحري عن فعالية الاوميغا 3 في علاج مرضى الربو المستديم المعتدل والذين يستجيبون بشكل ضعيف لتوليفة من الكورتيكوستيرويد المستنشق مع محفزات بيتا 2 مديدة المفعول.

شملت الدراسة 45 مريضا قسموا إلى 21 ذكر و24 أنثى والذين لم يسيطر عليهم بالشكل الكافي بعلاجات الستيرويدات الاستنشاقية ومحفزات بيتا 2 الطويلة الأمد. درس تأثير الاوميغا3 بعد 1، 2، 3 و 4 أسابيع على تكرار الأعراض والأعراض الليلية ونوعية الحياة.

أشارت النتائج التي توصلت إليها الدراسة إلى التأثير الايجابي في كل المعايير قيد الدراسة والتي توافقت مع دراسات سابقة واختلفت مع أخرى.

توصلت الدراسة إلى أن الاوميغا3 ربما يلعب دورا مهما في السيطرة على الاعراض السريرية ونوعية الحياة لمرضى الربو.

Introduction:

❖ **Asthma definition**

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness[1].

❖ **Sign and symptoms** :

Asthma is characterized by recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing[2]. Sputum may be produced from the lung by coughing but is often hard to bring up[3]. During recovery from an attack, it may appear pus-like due to high levels of white blood cells called eosinophils[4]. Symptoms are usually worse at night and in the early morning or in response to exercise or cold air[5]. Some people with asthma rarely experience symptoms, usually in response to triggers, whereas others may have marked and persistent symptoms[6].

❖ **Associated conditions:**

A number of other health conditions occur more frequently in those with asthma, including gastro-esophageal reflux disease (GERD), rhinosinusitis, and obstructive sleep apnea[7]. Psychological disorders are also more common[8], with anxiety disorders occurring in between 16–52% and mood disorders in 14–41%[9]. However, it is not known if asthma causes psychological problems or if psychological problems lead to asthma[10]. Those with asthma, especially if it is poorly controlled, are at high risk for radio-contrast reactions[11].

❖ **Etiology :**

Asthma is caused by a combination of complex and incompletely understood environmental and genetic interactions[12,13]. These factors influence both its severity and its responsiveness to treatment[14]. It is believed that the recent increased rates of asthma are due to changing epigenetics (heritable factors other than those related to the DNA sequence) and a changing living environment[15].

❖ **pathophysiology :**

Asthma is the result of chronic inflammation of the airways which subsequently results in increased contractability of the surrounding smooth muscles. This among other factors leads to bouts of narrowing of the airway and the classic symptoms of wheezing. The narrowing is typically reversible with or without treatment. Occasionally the airways themselves change[2]. Typical changes in the airways include an increase in eosinophils and thickening of the lamina reticularis. Chronically the airways' smooth muscle may increase in size along with an increase in the numbers of mucous glands. Other cell types involved include: T lymphocytes, macrophages, and neutrophils. There may also be involvement of other components of the immune system including: cytokines, chemokines, histamine, and leukotriens among others[16].

❖ **Classification :**

Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in one second (FEV_1), and peak expiratory flow rate[17]. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic), based on whether symptoms are precipitated by allergens (atopic) or not (non-atopic)[18]. While asthma is classified based on severity, at the moment there is no clear method for classifying different subgroups of asthma beyond this system[19]. Finding ways to identify subgroups that respond well to different types of treatments is a current critical goal of asthma research[19].

Although asthma is a chronic obstructive condition, it is not considered as a part of chronic obstructive pulmonary disease as this term refers specifically to combinations of disease that are irreversible such as bronchiectasis, chronic bronchitis, and emphysema[20]. Unlike these diseases, the airway obstruction in asthma is usually reversible; however, if left untreated, the chronic

inflammation from asthma can lead the lungs to become irreversibly obstructed due to airway remodeling[21]. In contrast to emphysema, asthma affects the bronchi, not the alveoli[22].

Table 1 : Clinical classification (≥ 12 years old)[17]

Severity	Symptom frequency	Night time symptoms	%FEV_1 of predicted	FEV_1Variability	SABA use
Intermittent	≤2/week	≤2/month	≥80%	<20%	≤2 days/week
Mild persistent	>2/week	3–4/month	≥80%	20–30%	>2 days/week
Moderate persistent	Daily	>1/week	60–80%	>30%	daily
Severe persistent	Continuously	Frequent (7×/week)	<60%	>30%	≥twice/day

❖ **Management**

Non pharmacological therapy

Although the mainstay of the management of asthma is pharmacologic therapy, it is likely to fail without attending to the non-pharmacologic therapy issues.

Important non-pharmacological measures include patient education, avoidance of triggers and smoking cessation[23].

Initial therapy for asthma needs to be combined with structured asthma education. Important components of education include informing patients of the chronic nature of asthma, the need for regular controller therapy, and a review of inhaler technique[24]. Avoidance of exposure to the offending allergen is the most important step in controlling allergen-induced asthma[25]. Smoking cessation studies have shown a significant improvement in the control of symptoms and lung function within weeks of stopping. Parents of children with asthma should stop or at least not smoke around their children[26]. Comorbid conditions, such as sinusitis or seasonal allergic rhinitis, should also be treated. Coexisting gastroesophageal reflux should be treated as well. Patients with aspirin sensitivity should avoid taking nonsteroidal anti-inflammatory drugs. In general, individuals with asthma should avoid taking beta blockers[25].

Pharmacological therapy

- **Inhalation route of drug delivery**

Inhalation therapy is the preferred route of administration of anti-asthmatic drugs to the airways due to its rapid, efficient and safe delivery.

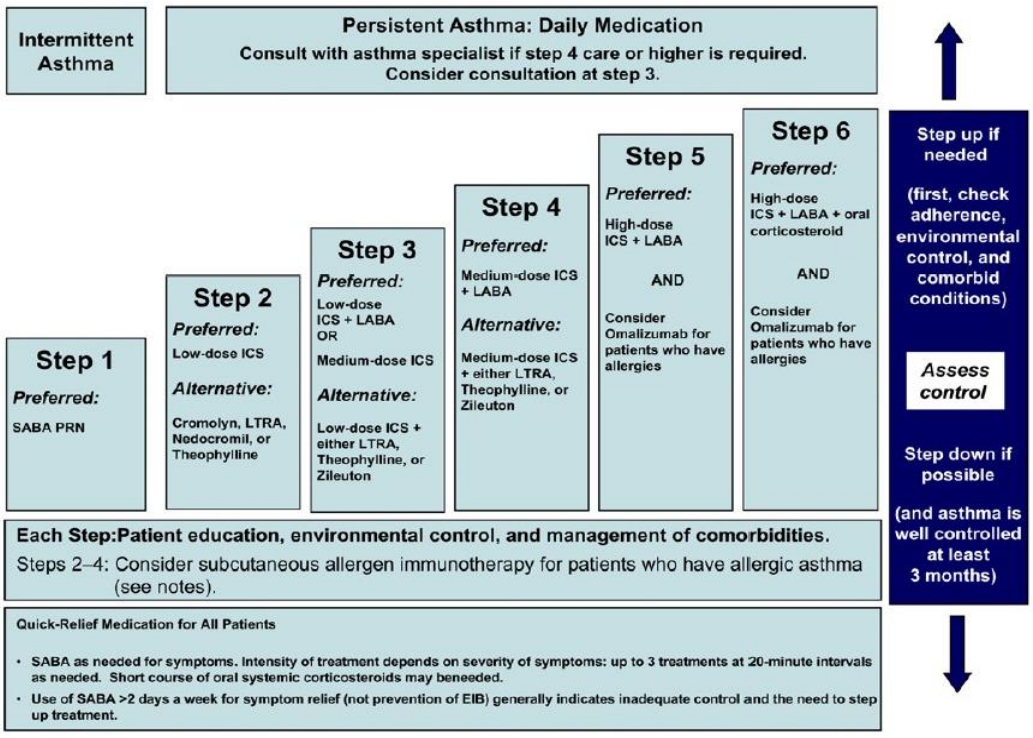
Inhalation therapy delivers therapeutic agents directly into the lungs of

patients with asthma, and is likely to remain the route of delivery of choice for the foreseeable future. Ideal inhaler includes delivery of an accurate and consistent dose, easy handling by the patient and feedback mechanisms which indicate successful inhalation. Currently available inhalers include :

(1) pressurized metered-dose inhalers (pMDIs)
(2) breath-actuated MDIs (BAIs)
(3) dry powder inhalers (DPIs).

▪ **Antiasthmatic drug classes:**

Drugs currently available to treat asthma are classified as quick-relief medications or relievers and long-term control medications or controllers on the basis of their principal pharmacodynamics and clinical effects. Thus, short-acting bronchodilators such as inhaled ß2- agonists or anticholinergics are considered quick-relief medications. Corticosteroids, long-acting ß2- agonists, leukotriene receptor antagonists, sustained-release theophylline products, cromolyn sodium, nedocromil sodium and omalizumab are considered long-term control medications, since they are used to achieve and maintain control of symptoms and are usually used daily on a long-term basis. Former nomenclature that classified drugs according to whether or not they had bronchodilator or anti-inflammatory properties is discouraged, since some medications have anti-inflammatory as well as bronchodilator properties[27]. The stepwise management of persistent asthma in youths 12 years and adults is summarized in figure 1-5[1].



*Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.

Fig. (1-5): Stepwise approach for managing asthma in youths 12 years of age and adults. From expert panel report 3: Guidelines for the diagnosis and management of asthma [1].

SABA: short acting beta agonists. PRN: as necessary.
ICS: inhaled corticosteroid. LTRA: leukotriene receptor antagonist.
LABA: long acting beta agonists.

❖ **Prognosis** :

The prognosis for asthma is generally good, especially for children with mild disease[28]. Mortality has decreased over the last few decades due to better recognition and improvement in care[29]. Globally it causes moderate or severe disability in 19.4 million people as of 2004 (16 million of which are in low and middle income countries). Of asthma diagnosed during childhood, half of cases will no longer carry the diagnosis after a decade[30]. Airway remodeling is observed, but it is unknown whether these represent harmful or beneficial changes[31]. Early treatment with corticosteroids seems to prevent or ameliorates a decline in lung function[32].

Relation between asthma and depression

In secondary care populations up to 50% of patients with asthma have been reported to have clinically significant depressive symptoms and over a third of asthmatic outpatients have been found to have a major depressive episode [33-38].

An increased mortality rate in patients with co-morbid asthma and depression has also been reported for asthma patients treated in tertiary care[33]. It has been hypothesized that concurrent depression leads to poor adherence with asthma treatments and hence to poorer outcomes[39]. Eisner/2005 reported that depressive symptoms were also associated with an increased risk of being hospitalized for asthma[40].

Omega 3

Are polyunsaturated fatty acids (PUFAs) with a double bond (C=C) at the third carbon atom from the end of the carbon chain[41].

Omega-3 fatty acids are believed to be related to mental health[42], including that they may tentatively be useful as an add-on for the treatment of depression associated with bipolar disorder[43]. However, significant benefits due to eicosapentaenoic acid (EPA) supplementation were only seen when treating depressive symptoms and not manic symptoms suggesting a link between omega-3 and depressive mood[43]. There is also preliminary evidence that EPA supplementation is helpful in cases of depression[44]. The link between omega-3 and depression has been attributed to the fact that many of the products of the omega-3 synthesis pathway play key roles in regulating inflammation such as prostaglandin E3 which have been linked to depression[45]. This link to inflammation regulation has been supported in both in vitro[46] and in vivo studies as well as in meta-analysis studies[47]. The exact mechanism in which omega-3 acts upon the inflammatory system is still controversial as it was commonly believed to have anti-inflammatory effects[48].

Aim of the study

The present study was done to investigate the effect of omega 3 on the management of moderate persistent asthmatic patient who are poorly controlled on a combination of inhaled corticosteroids and long acting ß 2 agonists.

Patients, materials and methods

❖ **Patients**

This study was conducted in the Respiratory Consultation Clinic, Baghdad Teaching Hospital-Medical City from February till April 2015. Forty five asthmatic patients were included in the study, all of them were diagnosed by internist to have moderate persistent asthma as defined by the Global Initiative for Asthma (GINA 2006)[17]. They were 21 male and 24 female, the age range was 18-40 year.

Patients were divided into two groups :

Group (1) study group : 22 patients, 10 male and 12 female

Group (2) control group : 23 patients, 11 male and 12 female

The Diagnosis of asthma for at least 1 year before the baseline (pretreatment) visit under supervision of respiratory specialist.

Inclusion criteria : patients with moderate persistent asthma who were uncontrolled adequately at the time of study by treatment with two divided puffs daily of a metered-dose symbicort inhaler/ AstraZeneca, France (budesonide 160 mcg and formoterol fumarate dehydrate 4.5 mcg per 1 puff).
Exclusion criteria : All patients with other co-morbidities were excluded from the study.
The studied group were treated by Omega-3 capsule (medellpharma Netherlands; batch No. F33169) 1000 mg daily in addition to their regular treatment. While a daily dose of placebo drug (starch-filled capsule) was added to the regular treatment of control group.
Included patients were assessed regarding the following case sheet information:

A- General

1) Name, age and gender.
2) Date of visit
3) Residency
4) Occupation

B- clinical presentation and respiratory parameters

1) Symptom frequency/week
2) Night time symptoms/week
3) Asthma quality of life (AQoL) score [49] (table 2.1).

Table 2.1: Asthma quality of life (AQoL) score[49].

	symptom	No/0	Yes/1
1	Dizziness		
2	Eye problems		
3	Impaired hearing		
4	Headache		
5	General fatigue		
6	Sleep disturbance		
7	Nervousness		
8	Sweating		
9	Breathlessness		
10	Chest pain		
11	Coughing		
12	Irritability		
13	Exhaustion		
14	Impaired concentration		
15	Restlessness		
16	Depression		
17	Cries easily		
18	Difficulty to relax		
19	Abdominal pain		
20	Nausea		
21	Diarrhea		
22	Constipation		
23	Loss of appetite		
24	Loss of weight		
25	Overweight		
26	Feeling cold		
27	Pain in the joint		
28	Back pain		
29	Pain in the legs		
30	Difficulty in passing urine		

❖ **Method**

All patients enrolled in the study were assessed by the following parameters; blood pressure, complete blood picture (CBP), renal function test (RFT), liver function test (LFT), fasting blood sugar (FBS), lipid profile, chest X-ray (CXR) and electrocardiography (ECG) to exclude any co-morbidity.

The study involve baseline assessment of the following parameters for all patients; symptom frequency, Night time symptoms and AQoL before treatment with the studied drug (Omega 3) for all patients of both groups. These parameters were assessed after starting treatment on weekly basis for four successive weeks.

Group 1 patients received Omega 3 tablets as an add-on therapy in addition to their concurrent treatment. While group 2 patients received placebo in addition to their concurrent treatment.

The statistical analysis was performed by Graph Pad Prism (Version 5.01) which includes:

1. Mean ± Standard error of Mean (Mean ±SD).
2. One way analysis of variance (ANOVA) was used to examine the difference of the individual data within the same group, if there are significant differences, unpaired T-test was used to determine the difference between the two variables, one before management and the second after 1, 2, 3 or 4 weeks of ongoing management. The results of analysis with P values < 0.05 was considered significant.

Results and Discussion

❖ **Effects of studied drugs on symptoms frequency**

Table 3-1 show the effect of treatment for group1 (omega-3 1000 mg daily) and group 2 (placebo starch capsule daily) on asthma symptoms frequency after 1,2,3 and 4 weeks. It is obvious that there is changes in the symptoms frequency mean value regarded to the type of the studied drug as compared to the control one, and also regarding to the investigated time intervals as compared to base line.

Group 1 symptoms frequency mean value for the base line was 5.31± 0.99, whereas it was 5.09± 0.86, 5.00± 0.69, 5.00± 0.75 and 3.36± 1.04 after 1,2,3 and 4 weeks respectively.

Group 2 symptoms frequency mean value for the base line was 5.60± 0.98, whereas it was 5.56± 0.76, 5.62± 0.85, 5.58± 0.91 and 5.57± 0.84 after 1,2,3 and 4 weeks respectively.

The results of present study showed there was significant decrement ($P \geq 0.05$) in the mean frequency of symptoms after the 3rd week of treatment of group 1 of patients enrolled in the study as compared with the baseline values. While there was no significant changes occurred with group 2 during all the study period as compared with the baseline values This indicates the role of omega 3 in the improvement in the symptom frequency for asthmatic patients.

This result agreed with old studies regarding the effect of omega 3 in the symptom frequency of asthmatic patients [50,51]. While other studies denied this finding [52] .

Table 3-1 : effect of treatment on symptom frequency

GROUP No.	MEAN SYMPTOM FREQUENCY/WEEK				
	B	**A1**	**A2**	**A3**	**A4**
1 (n=22)	5.31± 0.99	5.09± 0.86 a	5.00± 0.69 a	5.00± 0.75 b	3.36± 1.04 b
2 (n=23)	5.60± 0.98	5.56± 0.76 a	5.62± 0.85 a	5.58± 0.91 a	5.57± 0.84 a

values are presented as mean ± standard deviation of the mean(SD). **B** baseline values **A1** values after 1 week of treatment **A2** values after 2 week of treatment **A3** values after 3 week of treatment **A4** values after 4 week of treatment

a No Significant difference (P<0.05) as compared with baseline(before treatment)values (analyzed by unpaired T-test).

b Significant difference (P<0.05) as compared with control group values(analyzed by unpaired T-test).

❖ **Effects of studied drugs on night symptoms**

Table 3-2 show the effect of treatments for group1 (omega 3 1000 mg capsule daily) and group 2 (placebo starch capsule daily) on night symptoms after 1,2,3 and 4 weeks. It is obvious that there is changes in the night symptoms value referred to studied drug as compare to the control one, and also regarding to the investigated time intervals as compared to base line.

Group 1 night symptoms mean value for the base line was 5.18± 0.73, whereas it was 5.00± 0.87, 5.18± 0.73, 4.45± 0.80 and 3.22± 0.92 after 1,2,3 and 4 weeks respectively.

Group 2 night symptoms mean value for the base line was 5.00± 0.73, whereas it was 5.21± 0.45, 4.98± 0.66, 5.18± 0.75 and 5.09± 0.73 after 1,2,3 and 4 weeks respectively.

The study findings showed that omega 3 have a statistically significant (P≥ 0.05) effect on improving night symptoms after the 2nd week of treatment in comparison with the baseline in asthmatic patients of moderately persistent asthma who are under treatment with inhaled steroids and long acting ß agonists. While there was no significant changes occurred with group 2 during all the study period as compared with the baseline values This indicates the role of omega 3 in the improvement in the night symptom for asthmatic patients

The study finding are supported by the previous studies that points to the possibility for interaction between omega 3 and asthma medications that confer greater anti-inflammatory benefits than either intervention alone or at least similar anti-inflammatory effects with less toxicity[53].

Table 3-2 : effect of treatment on mean night symptoms

GROUP No.	MEAN NIGHT SYMPTOMS/WEEK				
	B	**A1**	**A2**	**A3**	**A4**
1 (n=22)	5.18± 0.73	5.00± 0.87 a	5.18± 0.73 a	4.45± 0.80 b	3.22± 0.92 b
2 (n=23)	5.00± 0.73	5.21± 0.45 a	4.98± 0.66 a	5.18± 0.75 a	5.09± 0.73 a

values are presented as mean ± standard deviation of the mean(SD). **B** baseline values **A1** values after 1 week of treatment **A2** values after 2 week of treatment

A3 values after 3 week of treatment **A4** values after 4 week of treatment

a No Significant difference (P<0.05) as compared with baseline(before treatment)values (analyzed by unpaired T-test).

b Significant difference (P<0.05) as compared with control group values(analyzed by unpaired T-test).

❖ **Effects of studied drugs on Asthma Quality of life (AQoL) score.**

Table 3-3 show the effect of treatments for group1 (omega 3 1000 mg capsule) and group 2 (placebo staech capsule) AQoL score as a baseline value and after 1,2,3 and 4 weeks. It is obvious that there is changes in the quality of life score value depending on the type of the studied drugs as compared to the control one, and also regarding to the investigated time intervals as compared to base line.

Group 1 AQoL score mean value for the base line was 21.36± 1.78, whereas it was 20.96± 1.44, 18.40± 1.41, 15.59± 1.56 and 13.68± 1.49 after 1,2,3 and 4 weeks respectively.

Group 2 AQoL score mean value for the base line was 20.47± 1.59, whereas it was 19.87± 1.11, 20.66± 1.24, 20.12± 0.97 and 20.23± 1.03 after 1,2,3 and 4 weeks respectively.

The study findings denotes that omega 3 has a statistically significant ($P \geq 0.05$) effect on improving quality of life in asthmatic patients after the 1st week of treatment in comparison with the baseline of moderately persistent asthma who are under treatment with inhaled steroids and long acting ß agonists. While there was no significant changes occurred with group 2 during all the study period as compared with the baseline values This indicates the role of omega 3 in the improvement in the quality of life for asthmatic patients.

The explanation behind this result is that asthma is frequently accompanied with depression[35], which is one of the main causes of deterioration of quality of life [54], since omega 3 has a potential effect for depression control [43,44], then it is expected that it have a positive role in improving asthmatic patients life quality.

Table 3-3 : effect of treatment on AQoL score

GROUP No.	AQoL score				
	B	**A1**	**A2**	**A3**	**A4**
1 (n=22)	21.36± 1.78	20.96± 1.44 a	18.40± 1.41 b	15.59± 1.56 b	13.68± 1.49 b
2 (n=23)	20.47± 1.59	19.87± 1.11 a	20.66± 1.24 a	20.12± 0.97 a	20.23± 1.03 a

values are presented as mean ± standard deviation of the mean(SD) **B** baseline values **A1** values after 1 week of treatment **A2** values after 2 week of treatment **A3** values after 3 week of treatment **A4** values after 4 week of treatment

a No Significant difference ($P<0.05$) as compared with baseline(before treatment)values (analyzed by unpaired T-test). **b** Significant difference ($P<0.05$) as compared with control group values(analyzed by unpaired T-test).

Conclusion and recommendations

1. It was concluded in this study that omega 3 could be useful adjuvant therapy to the asthma treatment regarding symptom frequency, night symptoms and quality of life.
2. Larger scale studies, different doses and longer duration are recommended to investigate the optimal schedule of management of asthmatic patients with omega 3.

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