

Effect of Curcumin Supplement on Pulmonary Functions, Total and Differential White Blood Cell Count, Serum Level of Leptin and Body Mass Index in a Sample of Iraqi Patients with Chronic Bronchial Asthma

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Abstract:

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation together with increased oxidative stress that lead to clinical symptoms of asthma.

Obesity is a known risk factor of asthma

as the obesity is correlated with systemic inflammation and airway restriction. Curcumin, a natural product derived from the rhizomes of *Curcuma longa* (Turmeric), has a wide range of beneficial properties including anti-inflammatory and weight reducing agent. This study was designed to evaluate the effect of curcumin as supplement therapy on the pulmonary function, total and differential white blood cell count and metabolic status of chronic bronchial asthmatic patients. It is a prospective randomized controlled interventional study carried out on 40 patients visiting Al-Yarmouk teaching hospital and conducted from October 2017 to April 2018. The patients were allocated into group1; include 17 asthmatic patients assigned to receive conventional therapy for asthma alone, and group 2; include 23 asthmatic patients assigned to receive conventional therapy for asthma plus 750 mg curcumin capsule twice daily for two months. Results revealed significant improvement in forced expiratory volume in one second (FEV1) and the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) in group 2 patients after two months ($P < 0.01$). The total white blood cell count didn't show any difference after treatment except decrease in neutrophil count after curcumin supplement ($p < 0.05$). The leptin level and body mass index present with no significant difference in both groups after two months ($p > 0.05$).

Key words: chronic bronchial asthma, pulmonary function, leptin, curcumin supplement.

تأثير الكركم كمكمل غذائي على وظائف الرئة ، العد الكامل والتفصيلي لكريات الدم البيض، مستوى اللبوتين في مصل الدم و مؤشر كتلة الجسم في عينة من المرضى العراقيين المصابين بمرض الربو القصبي المزمن

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الخلاصة:

الربو هو مرض غير متجانس يتميز عادة بوجود التهاب مزمن في الشعب الهوائية الذي يكون السبب الرئيس في تكرار اعاقه تدفق الهواء و زيادة الجهد التأكسدي مؤديا الى الاعراض السريرية لمرض الربو. السمنة هي احد عوامل الخطورة

المعروفة لمرض الربو لارتباطها بالالتهاب العام وتحدد تدفق الهواء الى الرئتين. الكركم هو منتج طبيعي مشتق من جذور نبات و معروف بفوائده المضادة للالتهابات و المقللة للوزن. *Curcuma Longa* صممت هذه الدراسة لتقييم تأثير الكركم كمكمل غذائي على وظائف الرئة، العد التفصيلي والكامل لكريات الدم البيض والحالة الأيضية لعينة من المرضى العراقيين المصابين بمرض الربو القصبي. اجريت هذه الدراسة التداخلية العشوائية المحتملة المسيطر عليها على 40 مريضا خلال الفترة من تشرين الاول 2017 الى نيسان 2018. تم تقسيم المرضى الى مجموعتين، المجموعة الاولى ضمت 17 مريضا تم تحديدهم لتلقي العلاج التقليدي لمرض الربو والمجموعة الثانية تضمنت 23 مريضا تم تحديدهم لتلقي علاج الربو التقليدي بالإضافة الى 750 ملغرام من كبسول الكركم مرتين يوميا لمدة شهرين. بعد شهرين من العلاج اظهرت الدراسة زيادة ملحوظة في وظائف الرئة. التعداد الكامل والتفصيلي لكريات الدم البيض ومستوى هورمون اللبتين ومؤشر كتلة الجسم لم يشهدوا اي تغيير ملحوظ.

الكلمات المفتاحية: الربو، الكركم كمكمل غذائي

Introduction:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells^[1]. History of respiratory symptoms is present which include wheeze, shortness of breath, chest tightness and cough that vary over time and intensity with variable air flow limitation^[2].

Obese individuals have an increased prevalence of asthma and its persistence, as well as the need for increased treatment, also appears to be greater with obesity^(3,4). This relationship is explained by numerous mechanisms that include; first, the dietary lifestyle that predisposes to obesity may be important in the etiology of asthma^[5]. Second, the mechanical effect of obesity on the chest and abdominal wall affects respiratory function, and may increase the work of breathing, particularly with exercise. Alternatively, smaller tidal volumes and increased breathing frequency may cause an increase in airway smooth muscle shortening with enhanced airway hyperresponsiveness (AHR)^[6]. The last explanation is that adipose tissue secretes a number of adipokines, which have important role in the persistence of low-grade systemic inflammation that exist in obesity, such as leptin^[6].

Curcumin, a bright yellow spice, derived from the rhizome of *Curcuma longa* Linn, a perennial herb of the Zingiberaceae family^[7]. It is a lipophilic polyphenol which is nearly insoluble in water, but

quite stable at acidic pH of stomach^[8]. Curcumin is widely used in herbal medicine because it possesses many pharmacological properties^[9]. Curcumin may have a role in the treatment of different pulmonary diseases such as COPD, asthma, pulmonary fibrosis, cystic fibrosis, acute lung injury, and lung cancer being the most important. While several pathways are involved, the effects of curcumin seem to be mediated by the modulation of the same mediators such as nuclear factor-k (NF- kB) and activating protein-1 (AP-1) in the different diseases^[10]. Previous data from various studies have demonstrated the efficacy of curcumin in animal models of asthma^[11,12,13], but there are very few human trials which explored the efficacy of oral curcumin in asthma, hence, the present study was undertaken to clinically evaluate whether or not oral curcumin supplement can improve pulmonary function and disease control in asthmatic patients concomitantly with its effect on the body mass index and leptin level in those patients.

Patients and Method:

This is a prospective randomized controlled open-label interventional study conducted from October 2017 to April 2018. A total of 50 candidate patients with chronic bronchial asthma were recruited in the study during their visit to Al-Yarmouk teaching hospital. The patients were under the supervision of pulmonary specialist and were treated according to clinical

practice guideline and disease severity. Only 40 patients continue the study intervention. Approval of institutional ethical committee was obtained and written informed consent was taken from all patients. Those patients were allocated into two groups; group1; include 17 asthmatic patients assigned to receive conventional therapy for asthma alone , and group 2; include 23 asthmatic patients assigned to receive conventional therapy for asthma plus 750 mg curcumin capsule(combined with 5 mg piperine) supplied by(amazing nutrition USA) twice daily for two months. Conventional therapy used in this study includes many drugs according to the severity of the disease. Patients on bronchodilator reliever medication such as β 2-agonist (Salbutamol), methylxanthines (aminophylline), also, inhaled preventer medication such as corticosteroid/long acting β 2- agonist combination. Some patients were on leukotriene antagonist (montelukast) or systemic corticosteroid (Prednisolone) for short duration on acute exacerbation.

Pulmonary function was tested using Spiro Air (Volumetric P.F.T) in which forced expiratory volume in one second (FEV1) and the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) were measured in both groups before and after two months of treatment. Serum leptin (LEP) level was estimated using enzyme-linked immunosorbent assay (ELISA) kit (Elabscience Biotechnology/China). Total and differential white blood cell count were measured using Hematology analyzer (CELL-DYN RUBY/Abbott / USA). The

body mass index is calculated for each patient in both groups by dividing the weight of the patient in kilograms on the square of his height in meter.

Statistical Analysis:

The data were analyzed using the following software, Microsoft excel, (minitab v17, IBM SPSS v24). The results reported in this study were expressed as mean \pm SD. Chi square test was utilized to detect significant differences among demographic variables while paired t-test was used to compare between pre- and post-treatment results; two-sample t-test was used to compare pre- or post-treatment between Groups 1 and 2. The probability values of less than 0.05 were considered significantly different.

Results:

Patients Demographic Data and Characteristics:

Table (1) presents demographic data and disease characteristics of 40 asthmatic patients. Patients enrolled in this study were 14 male (35%) and 26 females (65%). The mean age for group 1 patients was (44.94 ± 12.24) while for group 2 patients was (44.83 ± 12.57) and the age range in group 1 was (20-64) years while in group 2 was (23-67). Patients with family history of chronic bronchial asthma were 9 (52.9%) patients in group 1, and 9 (39.1%) patients in group 2 have positive family history. There was no statistically significant difference in the mean values of gender, age, BMI, family history, comorbid disease and asthma symptoms onset($p > 0.05$).

Table (1) Demographic Data and Disease Characteristics

Variable	Study groups		p-value
	Group 1 (n=17)	Group 2 (n=23)	
Gender	n (%)	n (%)	0.481 ^{NS}
Female	10(58.8)	16(69.60)	
Male	7(41.2)	7(30.40)	
Total	17(100)	23(100)	
Age(years)	44.94±12.24	44.83±12.57	0.991 ^{NS}
Age range (years)	(20-64)	(23-67)	1.00 ^{NS}
BMI (kg/m²)	29.66±6.68	30.46±6.07	0.698 ^{NS}
Underweight (< 18.5)	-----	-----	0.118
normal weight (18.5-24.9)	5(29.41)	3(13.04)	
Over weight (25-29.9)	3(17.65)	12(47.83)	
Obese (≥ 30)	9(52.94)	9(39.13)	
Family history			0.385 ^{NS}
Positive	9(52.9)	9(39.1)	
Negative	8 (47.1)	14(60.9)	
Comorbid disease such as DM and HT			0.169 ^{NS}
Positive	8(47.1)	6(26.1)	
Negative	9(52.9)	17(73.9)	
Asthma symptoms onset			0.481 ^{N.S}
Childhood onset	10(58.8)	16(69.6)	
Adult onset	7(41.2)	7(30.4)	

Data presented as mean ±SD, (n) is number of patients and (%) is percentage. Chi- Square test for numerical values to compare between group 1 and group 2. Two-sample t-test is used to statistically analyze BMI where, NS: not significant (p>0.05). DM, diabetes mellitus and HT, Hypertention.

Effect of Conventional Therapy Alone and in Combination with Curcumin Supplement on Pulmonary Function test (PFT) After Two Months

The mean values of both measured and percentage of predicted value of forced expiratory volume in one second (FEV1) showed no significant difference at baseline and after two months of treatment ($p < 0.05$) between study groups. There is significant increase in post-treatment value of FEV1 compared to pre-treatment value in group 1 patients ($p < 0.05$),

Nevertheless, the increase in FEV1 in group 2 patients was highly significant ($p < 0.01$) after two months duration. Regarding forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio, Group 2 patients have shown highly significant increase in (FEV1/FVC) ratio after two months treatment as compared to pre-treatment values ($p < 0.01$). However, there is no significant difference in mean value of (FEV1/FVC) ratio at baseline and after two months from starting the intervention between study groups ($p > 0.05$), table (2).

Table (2): Effect of Conventional Therapy Alone and in Combination with Curcumin Supplement on Pulmonary Function test (PFT) After two Months

Variable	Study groups		
	Group1 (n=17)	Group2(n=23)	p-value
FEV1 (L)(meas.)			
Pre-treatment	1.66 ± 0.56	1.45 ± 0.59	0.272 ^{NS}
Post treatment	2.03 ± 0.91	1.90 ± 0.67	0.595 ^{NS}
p-value	0.023*	0.004**	-----
Percent of change	+ 18 %	+ 23.6 %	-----
FEV1(L) (% pred.)			
Pre-treatment	55.35 ± 18.80	50.00 ± 15.72	0.334 ^{NS}
Post treatment	66.00 ± 21.75	65.22 ± 16.65	0.898 ^{NS}
p-value	0.011*	0.001**	-----
Percent of change	+ 16 %	+ 23.3 %	-----
FEV1/FVC %			
Pre-treatment	70.9 ± 10.0	65.90 ± 8.42	0.095 ^{NS}
Post treatment	75.3 ± 13.2	75.5 ± 12.3	0.952 ^{NS}
p-value	0.060	0.002**	-----
Percent of change	+ 5.8 %	+ 12.7 %	-----

Data presented as mean ± SD, FEV1(L): forced expiratory volume in one second in liter, FVC (L): forced vital capacity in liter, FEV1/FVC % : forced expiratory volume in one second/ forced vital capacity ratio, PEF(L/S): peak expiratory flow in liter per second, % Pred.: Percentage of predicted value, Meas.: measured value. Paired t-test is statistically used to compare within group (pre- and post-treatment values) for each group. Two-sample t-test is used to compare pre or post treatment between group 1 and group 2 patients. FEV1/FVC % :75-80% (1), NS: No significant differences ($P > 0.05$), (*) Significant difference ($P < 0.05$), (**) Highly Significant difference ($P < 0.01$).

Effect of Conventional Therapy Alone and in Combination with Curcumin Supplement on total white blood cell and Differential White Blood Cell Count After Two Months.

The mean values of total WBC count, eosinophil, and lymphocyte count showed no significant difference between group 1 and group 2 at baseline and after two months of treatment with no significant

difference in post-treatment value within each group compared to pre-treatment value in both groups ($p > 0.05$). The mean count of neutrophil cells showed no significant difference at base line and after two months between study groups ($p > 0.05$) but significant decrease in post treatment count resulted in group 2 only compared to pre-treatment ($p < 0.05$), table (3).

Table (3): Effect of Conventional Therapy Alone and in Combination with Curcumin Supplement on Total White Blood Cell and Differential White Blood Cell Count After Two Months.

Variable	Study groups		
	Group 1 (n=17)	Group 2 (n=23)	P-value
Total WBC ($10^3/\mu\text{l}$)			
Pre treatment	9.48 ± 3.06	9.54 ± 2.92	0.951 ^{NS}
Post treatment	8.73 ± 1.86	8.57 ± 2.12	0.797 ^{NS}
P value	0.373 ^{NS}	0.133 ^{NS}	-----
Percent of change	- 8.5 %	- 11.3 %	-----
Neutrophil ($10^3/\mu\text{l}$)			
Pre treatment	6.13 ± 3.17	6.18 ± 2.52	0.951 ^{NS}
Post treatment	5.13 ± 1.78	5.15 ± 1.80	0.971 ^{NS}
p-value	0.260 ^{NS}	0.026*	-----
Percent of change	- 19.4 %	- 20 %	-----
Eosinophil ($10^3/\mu\text{l}$)			
Pre treatment	0.359 ± 0.30	0.359 ± 0.29	0.884 ^{NS}
Post treatment	0.410 ± 0.41	0.383 ± 0.51	0.783 ^{NS}
P value	0.467 ^{NS}	0.854 ^{NS}	-----
Percent of change	+ 12.4 %	+6.2 %	-----
lymphocyte ($10^3/\mu\text{l}$)			
Pre treatment	2.37 ± 0.93	2.50 ± 0.83	0.661 ^{NS}
Post treatment	2.55 ± 0.78	2.56 ± 0.78	0.958 ^{NS}
P- value	0.501 ^{NS}	0.765 ^{NS}	-----
Percent of change	+ 7.05 %	+ 2.3 %	-----

Data presented as mean ±SD. Paired *t*-test is statistically used to compare between pre- and post-treatment results within the same group. Two-sample *t*-test is used to compare pre or post treatment between group 1 and group 2 patients. WBC count $3.2-9.8 \times 10^9/L$ ^[1], Eosinophils: 1% to 3% of WBC^[1], Neutrophils: 54% to 62% of WBC^[1]. Lymphocytes: 25% to 33% of WBC^[1]. NS: No significant differences ($P > 0.05$), (*) Significant difference ($P < 0.05$).

Effect of Conventional Therapy Alone and in Combination with Curcumin Supplement on Serum Level of Leptin and Body Mass Index (BMI) After 2 Months.

There is no significant difference in the mean value of serum leptin at base line and after two months between study groups ($p > 0.05$). Post treatment, mild increase in leptin level was noticed in both group 1

and 2, though non-significant ($p > 0.05$). The mean value of BMI showed no significant difference at base line and after two months between study groups ($p >$

0.05). No significant difference in post treatment value compared to pre- treatment value in both groups ($p > 0.05$), table (4).

Table (4): Effect of conventional therapy alone and in combination with curcumin supplement on serum level of leptin and body mass index after 2 months.

Variable	Study groups		
	Group 1 (n=17)	Group 2 (n=23)	P -value
Leptin (ng/ml)			
Pre -treatment	29.5 ± 10.2	31.92 ± 6.89	0.375 ^{NS}
Post treatment	32.10 ± 8.76	33.82 ± 5.15	0.440 ^{NS}
P- value	0.116 ^{NS}	0.069 ^{NS}	-----
Percent of change	+ 8 %	+ 5.6 %	-----
Body mass index (kg/m ²)			
Pre treatment	29.68 ± 6.67	30.44 ± 6.10	0.712 ^{NS}
Post treatment	29.51 ± 6.67	30.35 ± 5.83	0.675 ^{NS}
P value	0.196 ^{NS}	0.610 ^{NS}	-----
Percent change	-0.57 %	-0.29%	-----

Data presented as mean ±SD. Paired *t*-test is statistically used to compare between pre- and post-treatment results within the same group. Two-sample *t*-test is used to compare pre or post treatment between group 1 and group 2 patients. the detection range of leptin is (0.156-10 ng/ml) [14].

BMI <18.5 consider as underweight, while a BMI ≥ 25 considered overweight and >30 is considered obese [15]. NS: No significant differences ($P > 0.05$).

Discussion:

Throughout the data analysis of the present study, the findings showed that the majority (65%) of the study participants were females and, these results agreed with the finding of other studies [16,17,18]. The reasons for the gender difference are unknown but have been linked to immunological and hormonal factors, and/or to differences in gender-specific responses to environmental or occupational exposures [16]. Also, all asthmatic patients in this study were aged between 20-67 years old and were matched in the study groups.

More than 80 % of patients in the present study is overweight (BMI ≥ 25 kg/m²) or obese (BMI ≥ 30 kg/m²). Most prospective studies including large number of patients showed that obesity is a risk factor for asthma and found a positive correlation between baseline body mass index and the subsequent development of asthma [4,19,20,21]. In general, the more BMI increases, the more the incidence of asthma rises, and this effect is generally stronger among women than among men and this may be related to the degree of adiposity in women, although this effect appears to be modest and depends on

factors such as age and gender^[22]. There are many theories that involve mediating factors linking obese state include abnormal circulating inflammation and oxidant stress, chest restriction with airway-narrowing, obesity-related comorbidities, and the obesity-related systemic inflammation triggers exaggerated lung responses to environmental factors, leading to asthma-like symptoms^[23]. More than (50%) of patients in both study groups had negative family history and this come in contrast with many studies that provide evidence that the incidence of asthma during the first 27 years of life is strongly related to family history of asthma^[24] and the risk of personal asthma increased in relation to both parents' asthma and siblings' asthma^[25]. However, the sample size in this study is small to compare.

With reference to the results in the present study showed that high percentage of asthmatic patients (65 %) were diagnosed as asthmatic in childhood period. This finding was close to that done by Mirabelli et al. in (2013) were 42% of adults with asthma reported the onset of asthma as occurring before the age of 16^[26]. This finding reflects the highest percentage of asthma among children as appeared in a study done by Al samarai et al. who demonstrated that 16 % of children from 25 different Iraqi primary school aged between 11-14 years were diagnosed with asthma^[27].

Effect of Curcumin Supplement on Pulmonary Function Test (PFT)

In the present study, curcumin supplementation produces significant increase in measured and predicted value of FEV1 with a percent of change of (+ 23.3%) for the predicted value ($p < 0.01$) compared to values in patients receiving standard bronchial asthma therapy. And the ratio of FEV1/FVC was also increased by 12.7% in patients on curcumin supplementation. A comparable result was noticed in Abidi et al. (2014) study, where the effect of

addition of curcumin doses of 500 mg twice daily for 1 month in 30 patients receiving standard bronchial asthma therapy resulted in highly significant increase in FEV1 ($p < 0.05$)^[28].

In another study done by Jusufovic et al. (2017), curcumin at doses of 500 mg twice daily in combination with medium dose inhaled corticosteroid to 50 non-smoker patients with moderate partially controlled asthma for two months and compared it to a parallel number of patients receive only medium dose inhaled corticosteroid. There was highly significant increase in the percentage of predicted FEV1% in curcumin group (increased by 7 % v 2 %) ^[29].

In contrast, early study by Kim et al. (2011) found that supplementation of nine asthmatic patients with 1000 mg curcumin twice daily for 6 months did not result in significant improvement in mean FEV1 value ($p = 0.0562$)^[30].

Effect of Curcumin Supplement on Total White Blood Cell and The Differential Count

asthma is an inflammatory disease and involve recruitment of different types of white blood cells into the lung and resulted in clinical symptoms of asthma^[2]. Increased total WBC and eosinophil count was shown in asthmatics, both in animal and human studies compared to healthy controls^[11].

Curcumin has been found to modulate the growth and cellular response of various cell types of the immune system^[31]. In the present study, the curcumin supplement produced comparable decrease in total WBC count to that of conventional treatment, except for marked decrease in neutrophil count after curcumin supplementation. These findings are close to that of Kim et al. in which curcumin supplement didn't produce significant effect on total WBC count after 6 months in 9 asthmatic patients despite relatively high dose 2000 mg of curcumin per day^[30]. Nevertheless, in a recent study,

curcumin supplement in asthmatic patients produced a decrease in total WBC count ($p=0.01$), eosinophil count ($p=0.000$), lymphocyte ($p=0.04$), and neutrophils ($p=0.04$)^[28]. Also, in another recent study curcumin supplement in asthmatic patient decrease eosinophil count ($p < 0.05$)^[29]. Experimentally, curcumin extract produced a significant decrease in total WBC count in blood in a rat model of asthma ($p < 0.01$)^[11]. In similar study in a rat model of asthma, curcumin extract significantly decreased total and differential WBC count ($p < 0.01$) in broncho alveolar lavage fluid (BALF) during both short term (15 days) and long term (60 days)^[32]. These findings suggested that curcumin may be having an anti-inflammatory, immuno-modulatory or may be effective in reducing the specific pathways of inflammation, which can lead to elevated WBC count^[32].

Effect of Curcumin Supplement on Leptin Level and Body Mass Index (BMI)

The hormone leptin, derived from adipocytes, is integrally involved in metabolic status and is a peripheral signal that has a central effect on the brain affecting appetite^[33,34]. Leptin, together with other adipokines, is responsible for the inflammatory state found in obesity and with both direct and indirect effects that lead to type 2 diabetes, metabolic syndrome, cardiovascular disease, autoimmune, and allergic diseases^[35]. There are data suggesting that curcumin may have an effect on leptin level directly by its effect on adipokine release from adipocytes^[36,37] with the suggestion that it may induce lipolysis and regulate leptin in animals^[38] and also it effect leptin receptor gene expression^[39] leading to a fall in leptin levels.

In the current study curcumin supplement didn't show any significant effect on leptin level, the possible reason is that not all the patient enrolled in this study were obese, and also they are not fasting since the leptin level affected by food, moreover, the

supplement used in this study contain only curcumin combined with 5 mg piperine. Leptin level was potently reduced when curcumin supplement is in a combination of three curcuminoids (curcumin, demethoxycurcumin and bisdemethoxycurcumin)^[37], or as phospholipid complex^[39] in obese patients.

Recently, scientists have suggested that curcumin can reduce obesity by inhibition of inflammatory mediator production^[40], and via reducing adipose tissue differentiation in vitro studies^[41]. In the current study, there was no change in the BMI in patients on both treatment regimen, the results matched to many other studies in which either curcumin doses were low, or the two months duration of intervention was short, or the use a less bioavailable form of curcumin^[12,42,43]. Nevertheless, other studies used a more bioavailable form of curcumin, or higher doses up to 2.8 g/day, and for longer periods such as six months, produced significant decrease in BMI of patients with different clinical settings^[44,45].

Conclusion:

In the current study the addition of curcumin supplement to the conventional therapy of asthma produce significant improvement in the pulmonary function in patients with chronic bronchial asthma but the curcumin supplement had no significant effect on total white blood cell count, leptin level and body mass index.

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