Journal of International Medical and Biological Sciences
International Peer Reviewed Open Access Journal
JIMBS
ISSN: 2362-1311 (Online)

C- Reactive Protein in Childhood Asthma

Muna Tawfik Al Jeborey [1*], Murad Fatooh [2] and Haider Jasim Kadhum [3]

1. M.B.Ch.B, D. Ped., Pediatric department Al Furat AlAwsat Teaching Hospital , Najaf, Republic of Iraq.
2. M.B.Ch.B, D. Ped., Pediatric department Al Furat AlAwsat Teaching Hospital , Najaf, Republic of Iraq.
3. FICMS-Ped.,Pediatric department Al Zahraa Teaching Hospital , Najaf, Republic of Iraq

ORIGINAL ARTICLE

Received: *02 March, 2021* , ***Reviewed***: *30 May,2021,* ***Accepted***: *8 June , 2021*

Vol. 7, No. 03, 2021

Abstract:

Background: Asthma is characterized by chronic inflammation of the airways in response to a wide variety of stimuli. C-reactive protein (CRP) is a highly sensitive systemic marker of inflammation and tissue damage, thus CRP could theoretically also be a useful tool for detecting systemic inflammation in asthma. Objective: To evaluate the relationship between peripheral blood CRP levels and asthma Patient and method: The study was carried out at Al-Zahraa Maternity and pediatric teaching hospital in Al- Najaf al-Ashraf province in Iraq, in 2008. CRP was measured in 75 asthmatic children and 50 almost matched healthy controls. Results then compared.

Results: there were 22 cases CRP positive (29.3%) of the total cases ,and 53 While only 5 controls were CRP positive (10%) . Of the 22 CRP positive asthmatic cases, 12 were retested again one week later when 9 showed significant elevation in CRP during acute exacerbation compared to only one case (14.3%) among the 7 cases at remission. While 3 cases during acute exacerbation 6 cases during remission had just positive CRP. Conclusion: Increased levels of CRP are significantly associated with respiratory symptoms in asthmatic children and it could be used as a marker of severity of asthmatic exacerbation , additionally it could be a useful index in the assessment of the response to treatment

Keywords: *Childhood asthma, pathogenesis, etiology, epidemiology, C-reactive protein, prediction*

Corresponding author:

Dr. Muna Tawfik Al Jeborey *Pediatric department Al Furat AlAwsat Teaching Hospital , Najaf, Republic of Iraq.*

Citation:

Al Jeborey M, Fatooh M, Kadhum H. . C- Reactive Protein in Childhood Asthma JIMBSR, 2021;7(3):75–87

Introduction

Asthma is a chronic disease of worldwide distribution that mainly affects the child population. It is a highly prevalent disease with global prevalence varies from country to country, fluctuating between 6 to 30% (1). According to the World Health Organization, nearly 300 million people suffer from asthma worldwide, being the most frequent chronic disease in the pediatric age. In children the prevalence of asthma in the age group of 6 to 7 years was 17.9% and in the group of 13 to 14 years is 15.5 %. At international level, it is estimated that 5% of all asthmatic patients present severe evolution, which is associated with a high morbidity and accounts for at least 50% of health costs due to this disease. The vast majority of these patients despite receiving adequate treatment have poor control of their symptoms with frequent exacerbations, consultations to emergency services, hospitalizations and sometimes decreased lung function, with a very poor quality of life (2-6). A combination of environmental exposures , inherent biological and genetic vulnerabilities are implicated in the etiology of childhood asthma. The risk factors for asthma show great variability around the world, some as the family history of asthma , allergic rhinitis, exposure to intra-familial tobacco , prematurity , obesity , introduction of other dairy products before 4 months of age and low socioeconomic status have been identified by their direct relationship with this disease. In addition, residing in an urban area may increase the risk of asthma and asthmatic symptoms in relation to rural areas, probably due to environmental contamination (1). Asthma is characterized by airway hyper responsiveness and inflammation ,in which various cells, cytokines and mediators play a role. Inflammatory cells (mast cells, eosinophils, T lymphocytes, neutrophils), chemical mediators (histamine, lcukotrienes, platelet-activating factor, bradykinin), and chemotactic factors (cytokines, eotaxin) result in the underlying inflammation found in asthmatic airways (7).

The pathologic changes linked to persistent airways inflammation and hyper responsiveness underlie the chronic basis of asthma . Inflammation contributes to airway hyper-responsiveness, which is the tendency for the airways to constrict in response to allergens, irritants, viral infections, and exercise. It also results in edema, increased mucus production in the lung, influx of inflammatory cells into the airway, and epithelial cell denudation. Chronic inflammation can lead to airway remodeling, which results from a proliferation of extracellular

matrix proteins and vascular hyperplasia and may lead to irreversible structural changes and a progressive loss of pulmonary function (8,9). Children with asthma have symptoms of coughing, shortness of breath or rapid breathing, and chest tightness. Exacerbating factors include viral infections, exposure to allergens and irritants (smoke, strong odors, fumes), exercise, emotions, and change in weather/humidity. Nighttime symptoms are common. Rhino-sinusitis, gastro-esophageal reflux, and sensitivity to non-steroidal anti-inflammatory drugs (especially aspirin) can aggravate asthma. Treatment of these conditions may lessen the frequency and severity of the asthma. Obtaining a family history of allergy and asthma is useful because allergic diseases occur in families (8,9). During acute episodes, the physical examination may reveal tachypnea, tachycardia, wheezing, and a prolonged expiratory' phase. Physical findings may be subtle, and classic wheezing may not be prominent if there is minimal air movement. As the attack progresses, cyanosis, diminished chest movement (tight chest), retractions, agitation, inability to speak, tripod sitting position, diaphoresis, and pulsus paradoxus (decrease in blood pressure with inspiration of >15 mm Hg) may be observed. Physical examination may show evidence of other atopic diseases, such as eczema or allergic rhinitis (8-10). There are different effective laboratory and imaging diagnostic tests available now a days that support clinical diagnosis ; Spirometry, chest radiography , allergy skin testing should be a part of the evaluation of all children with persistent asthma. In vitro serum tests, such as radio allergosorbent test (RAST) and enzyme-linked immunosorbent assay, are another option to measure levels of antigen-specific IgE (8,9).

Management of asthmatic child include regular assessment and monitoring , control of factors contributing to asthma severity and pharmacotherapy. Medications includes quick-relief medications including short-acting inhaled or oral beta2 agonists, short-course oral corticosteroids, are taken as needed for immediate relief of acute symptoms. Long-term control medications should be taken daily to maintain control these include inhaled corticosteroids which are the most effective long-term anti-inflammatory medications and long- acting $beta_2$ agonists (8 – 10).

C - reactive protein

C - reactive protein (CRP) is a member of the class of acute phase reactants as its levels rise dramatically during inflammatory processes occurring in the body. CRP considered as a highly

sensitive systemic marker of inflammation and tissue damage, thus CRP could theoretically also be a useful tool for detecting systemic inflammation in asthma; indeed, an association between serum CRP level and severity of asthma has been suggested (11). Recently, high sensitivity assays for CRP (hs-CRP) have become available in clinical laboratories. A population based study showed associations of increased levels of serum hs-CRP with a high frequency of airway hyper responsiveness and low forced expiratory volume in one second (FEV1) among subjects without heart disease suggesting that systemic inflammation may be associated with respiratory impairment. Another epidemiological study showed that elevated levels of hs-CRP correlate significantly with respiratory symptoms and with prevalence of non-allergic asthma (12-15).

Although the CRP response is nonspecific and cannot be used alone in differential diagnosis, it is a valuable test and has advantages over the ESR. It is a measure only of tissue damage and is not affected by immunoglobulin levels. Levels of CRP rise and fall more rapidly and over a broad range with changes in the clinical condition. Measurement of CRP is sensitive and reproducible. The level does not have diurnal variation, and it is not affected by age, sex, or hematocrit (16).

Therefore, the present study tried to assess the relationship between peripheral blood CRP levels and asthma as a highly sensitive systemic marker of inflammation and tissue damage and its value as a predictor for severity and response to treatment of asthma based on clinical evaluation among group of Iraqi child patients in Najaf city.

Patients and Methods:

The study was carried out at Al-Zahraa pediatric teaching hospital in al- Najaf al-ashraf govemorate between 10th of February and 15th of August 2008. CRP was measured in 75 asthmatic children ;47 male and 28 female; with age range from 2- 11.5 years , and also measured in 50 non asthmatic control (22 male and 28 female with age range from 1.5-8 years). Regarding the asthmatic pt. serum sample is sent for CRP immediately after arrival to the emergency unit ,before receiving any treatment. Diagnosis of asthma were made prior to the entry to the study on the basis of clinical and laboratory evaluation. Immediately at arrival to the emergency department ; 2ml of blood is aspirated before giving any treatment. The blood sample is centrifuged and the serum was used undiluted .The CRP reagent contains latex particles coated with anti-human CRP antibody. When the reagent is mixed with serum containing CRP at a level greater than 6 mg/1,particles will agglutinate,

this interpreted as positive sample. The reagent can be used for semi- quantification of CRP , for this purpose the sample is diluted over arrange of dilution each tested qualitatively . The CRP level can be estimated from the last dilution with visible agglutination. CRP kit is from RANDOX lab. UK with a lower detection limit is 6 mg/l. Data were collected by history from the mother or relative ,child ,physical examination , height, weight, SPO2 ,CXR and differential WBC count and the examination including that of tonsils, ear and for any focus of infection .The exclusion criteria include evidence of pneumonia by CXR ,fever or having other chronic or acute illness other than asthma . The patient have been categorized into four group according to the severity of asthma based on the clinical and historical bases as mild intermittent, mild persistent , moderate persistent and severe persistent. Additionally all patients are categorized as to have" sever" or " non-severe asthma . We defined severe asthma as cases that met one or more of the following criteria: more than 12 wheezing attacks in the lastl2 months; sleep disturbed by wheezing attacks more than 4 times per month; or wheezing attacks that limited speech, presence of confusion, anxiety, fatigue or silent chest, $Sp0_2$ <93% . Non-severe asthma (mild /moderate) was defined as meeting one or both of these criteria: less than 12 wheezing attacks in the last 12 months or sleep disturbed by wheezing attacks less than 4 time per month or there is nasal flare, tachycardia use of accessory respiratory muscles, head retraction, feeding difficulty and SpO_2(93-96%) (10, 17) . Out of the CRP positive cases, 12 are retested again during remission, acute exacerbation was defined when there was persistent coughing, tachypnea according to age, respiratory muscle retractions, and auscultatory findings of ronchi with prolonged expiration. Remission was defined when there is no persistent cough, the respiratory rate was normal for age , there were no respiratory muscle retractions and normal breath sounds were heard on auscultation. The results during acute exacerbation and during remission arc compared ,also for each class of severity mentioned above. Spirometry was performed in patients older than 5 years. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and categorized as underweight: when BMI percentile for age is < 5^{th} percentile, normal; BMI percentile for age is 5^{th} -84^{th} , overweight: BMI for age is > 95 percentile. *Statistical analysis* was performed using the statistical package for social sciences version 20, descriptive and analytic statistical procedures were applied accordingly Level of significance se at p. value <0.05 to be considered statistically significant.

Results

The study included 75 asthmatic patients and 50 non-asthmatic apparently healthy controls aged 2 – 11.5 year . Both groups were almost matched for age and gender, (P>0.05). (Table 1). Among the 75 asthmatic patients, 22 (29.3%) were CRP positive while among controls only 5 cases (10%) were CRP positive, with a statistically significant difference that CRP positive was more frequent in asthamatic than non-asthamtic group, (P<0.05), (Table 2)**.**

***Relationship between severity class and CRP level*:** CRP positive was reported in 9 (25%) cases with mild intermittent asthma; 6 (26.1%) of mild persistent , 5 (35.7%) of moderate persistent in both cases (100%) of sever persistent class, however, the differences were statistically insignificant, (P>0.05), (Table 3).

Severity of Symptom and CRP level: Severe asthma with positive CRP include 6/9 cases (66.6%) ,and non-severe (mild-moderate) with positive CRP were 16/66 (24.2%) with significant difference, (P<0.05), (Table 4)**.**

***Progress of asthma and CRP*:** Acute exacerbation was significantly associated with CRP positive status, 75% of cases with acute exacerbation vs. only 1/7 (14.3%) of those in remission were CRP positive , (P<0.05), moreover, out of the 22 CRP positive cases 12 were retested again one week later when 9/12 (75%) show significant elevation in CRP (>6mg/l) during acute exacerbation ,while 3(25%) were just positive (=6mg/l), compared with one case (8.3%)with significantly high CRP and 6 (50%) were just positive during remission (Table5).

Relationship between CRP and FEV1 Out of the 22 CRP positive patients eleven were over 5 years to whom spirometry is applicable, we took 10 of them and the mean FEV1 is compared with the mean CRP both during acute exacerbation and during remission, the mean CRP during acute exacerbation was 11.8 mg/l, compared with 6mg/l during remission and FEV1 was 86% during acute exacerbation and 96% during remission , (Table 6).

Relationship of CRP with demographic, allergic disease provocative factors and seasonal recurrence: Among the 22 CRP positive asthmatic patients 12 (54.5%) of rural origin , 17 cases (77.3%) with positive family history , 19 (86.4%) had personal or family history of other atopic disease or allergy including food allergy. Asthmatic attack were provoked by dusts, tobacco ,or drugs in 15(24%) patients, while those who are not provoked by these triggers or provoked by other triggers (exercise for e.g.) were seven(58.3%). Note : the study was carried out in almost dusty weather of the year in our country. Seasonal recurrence

found to be positive in 13(29%) of cases which, while 9 (30%) show no seasonal recurrence¸(Table 7)**.**

Relationship between body mass index and CRP : There were 6 over weight patient found to have positive test (40%) of the overweight cases in the study, while 13 has normal weight(30.2%), and 3 (17.6%) were under weight, (Table 8). However, BMT percentile were used as parameter for detection of obesity. From the ten cases (all >5 years) mean CRP (± SD), mean FEV1(±SD) were obtained both during exacerbation and remission. *P. value* is <0.05**.**

Table 1. Age and gender distribution of the studied group

Variable		Asthmatic patients (n = 75)		Control (n = 50)		P. value
		No.	%	No.	%	
Gender	Male	47	62.7	31	62.0	> 0.05
	Female	28	37.3	19	38.0	
Age (year)	≤ 5	41	54.7	27	54.0	> 0.05
	> 5	34	45.3	23	46.0	

Table 2. Results of CRP testing of the studied group

Group	CRP Positive		CRP Negative		Total
	No.	%	No.	%	
Asthmatic patients	22	29.3	53	70.7	75
Control	5	10.0	45	90.0	50
P. value = 0.018 significant					

Table 3. Relationship between severity class and CRP level

Severity class	CRP Positive		CRP Negative		Total
	No.	%	No.	%	
Mild intermittent	9	25.0	27	75.0	36
Mild persistent	6	26.1	17	73.9	23
Moderate persistent	5	35.7	9	64.3	14
Sever persistent	2	100.0	0	0.0	2
Total	22	29.3	53	70.7	75

P. value > 0.05

Table 4. Relationship between Symptom severity and CRP

Symptoms severity	CRP Positive		CRP Negative		Total
	No.	%	No.	%	
Severe asthma	6	66.7	3	33.3	9
Non - severe asthma (mild/moderate)	16	24.2	50	75.8	66
Total	22	29.3	53	70.7	75

P. value = 0.026 significant

Table 5. Progress of asthma and CRP levels

Disease progress	Significant elevation in CRP*		Just positive CRP**		Total
	No.	%	No.	%	
Acute exacerbation	9	75.0	3	25.0	12
Remission [#]	1	14.3	6	85.7	7
Total	10	52.6	9	47.4	19

*Significant elevation in CRP >6 mg/1, ** just positive =6 mg/1, # 5 cases became negative were subtracted from the remission cases

P. value = 0.037

Table 6. Comparison of CRP and FEV1 according to disease progress

Parameter	Acute exacerbation	Remission
CRP Mean(±SD)	11.8 ± 2.2	4 ± 2
FEV1 Mean(±SD)	86 ± 6.6	96 ±4

Table 7. Relationship of CRP with demographic, allergic disease provocative factors and seasonal recurrence

Variable		No.	%
Residence	Rural	12	54.5
	Urban	10	45.5
Family history	Positive	17	77.3
	Negative	5	22.7
Personal or family history of other atopic disease or allergy	Positive	19	86.4
	Negative	3	13.6
Asthmatic attack were provoked by dusts, tobacco ,or drugs	Yes	15	68.2
	No	7	31.8

Table 8. Relationship between body mass index (BMI) an CRP in asthmatic patients

BMI percentile	CRP Positive		CRP Negative		Total
	No.	%	No.	%	
Underweight.	3	17.6	14	82.4	17
Normal	13	30.2	30	69.8	43
Overweight	6	40.0	9	60.0	15
Total	22	29.3	53	70.7	75

P. value < 0.05

Discussion

The results of our study demonstrate that there is a significant association between CRP and asthma as shown by relatively high percentage of CRP we results among asthmatic vs. control (29.33% vs. 10%) *p*. *value* < 0.05. Although studies on the predictive values of cardiovascular events by HsCRP blood levels in adult populations had shown that age is another factor in the production of CRP[f131], however, we found no significant age and gender relation in *p. value* (>0.05). Also our study demonstrate that there is a significant association between the severity of asthma symptoms and CRP level which is shown by high percentage of positive test in severe vs. non severe (66.6% vs. 24.2%) , *p. value* < 0.05

The criteria that used in the classification of the severity were well studied by Al-Thamiri et al. (17) as a dependable criteria of severity and our result were consistent with a similar study by Takemura M and his associates in adult population in 2005 (18) no significant correlation in our study between the severity class and CRP *(P. value* >0.05).

In asthma, the importance of airway inflammation has been well established. Beside the airway inflammation, systemic inflammation may exist in asthma (17-9). Another significant correlation in our study is between peripheral blood levels of CRP and the clinical asthmatic state. This was shown by a significantly higher mean CRP level (11.8 mg/l) during acute exacerbations compared to the mean level (6 mg/1) during remission (*P.value* <0.05) . This finding is further supported by the positive correlation mentioned above between CRP and asthma severity in a form of clinical findings supported by the finding ofnegative correlation between CRP and FEV) as a mirror for respiratory symptoms(*P.value* <0.05). These results agreed with that of Ruth et al. in 2004 (15). The rise in CRP is driven by its rate of synthesis, which starts very rapidly after a stimulus, reaches a peak at around 48 h later, and falls rapidly when the pathological stimulus ceases, with a plasma half-life of approximately 19 h (20). A correlation of peripheral blood CRP levels with severity, extent, and progression of inflammatory pathologies has been well established. Recent publications suggested that CRP has a contributing role in the pathogenesis of diseases in addition to its being merely an inflammatory marker (21). There are no studies to date that have identified the role of CRP in the pathogenesis of asthma.

Our study show that the correlation between asthma and CRP were not significantly affected by the residence of patient (whether urban or rural) , similarly not affected by the presence or absence of family history of asthma or seasonal recurrence

, on the other hand its significantly affected by personal or family history of other atopic or allergic disease including eczema ,allergic rhinitis *p. value* is (<0.05),also significantly affected by the provocative factor which is mostly in our study is dust and to lesser extent tobacco, as our study carried out in almost dusty weather in our country, *P.value* <0.05 . We study the correlation between CRP in asthmatic and BMI percentile which is used as parameter for detection of obesity, high percentage of over wt. pt.(40%) have positive test compared with under wt. (17.6%) and normal wt. (30.2%), *P.value* <0.05. Several studies have recently reported a strong association between increasing asthma prevalence and increasing BMI, but the causality is unknown. Schachter et al (22) reported that obesity (BMI >30) in adult was a risk factor for self-reported asthma and wheeze. Many factors are associated with both asthma and obesity which complicates the picture. Firstly, obesity might be a consequence of asthma as these subjects have reduced exercise capacity and obesity is a known side effect of oral steroid treatments. Secondly, gastro-esophageal reflux and obstructive sleep apnea are both possible risk factors for asthma development and are related to obesity (23,24) Thirdly, obesity has detrimental effects on respiratory symptoms and lung function, and weight reduction in obese asthmatics has been associated with improvement in symptoms, lung function, and quality of life (25,26).

Conclusions:

The increased levels of CRP are significantly associated with respiratory symptoms in asthmatic children and it could be used as a marker of severity of asthmatic exacerbation , additionally it could be a useful index in the assessment of the response to the treatment. Hence CRP could be used as a helpful tool in the assessment of severity of asthma in conjunction with clinical and laboratory data, however, further studies are required in order to better express the clinical significance of the association of C-reactive protein and asthma, especially its responsiveness to treatment.

***Ethical Issues**: All official and child's parents/guards' agreement were obtained, collection of data and blood samples and examination were performed according to the standard ethical guidelines for medical and health researches including human being*

***Conflict of interest**: Authors declared that none*

References:

1. *Munayco V, Arana G, Torres-Chang J, Saravia L, Soto-Cabezas MG. Prevalence and factors associated with asthma in children from 5 to 14 years of age in a rural area of southern Peru. Journal of Experimental Medicine and Public Health 2009; 26 (3): 307-13.*
2. *Bousquet J, Bousquet PJ, Godard P, Daures JP. The public health implications of asthma. Bull World Health Organ. 2005; 83: 548-54*
3. *Forno E, Gogna M, Cepeda A, et al. Asthma in Latin America. Thorax 2015; 70: 898-905.*
4. *Mallol J, Aguirre V, Aguliar P, et al. Changes in the prevalence of asthma in Chilean schoolchildren between 1994 and 2002. Rev Med Chile 2007; 135: 580-6.*
5. *Valdivia G, Caussade S, Navarro H, et al. Influence of socioeconomic status on bronchial asthma and changes in its prevalence in school population over a period of 6 years. Rev Med Chile. 2009; 137: 215-25.*
6. *Fan Chung K, Wenzel SE, Brozek JL, et al. International ERS / ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014; 43: 343-73.*
7. *Umetsu DT , Mclntire JJ , Akbari O , Macaubas C , DeKruyff RH . Asthma: An epidemic of dysregulated immunity . Nat. Immunol. 2002 ; 3: 715 - 2 0*
8. *Andrew H. ,Liu,Ronina a. Covar, Joseph D. Spahn, and Donald Y. M. Leung Childhood Astluna. Tn: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson textbook of pediatrics, 18th ed. Philadelphia, WB Saunders Company, 2008: (953-970)-143.*
9. *Mary V. Lcsly, Asthma. In Behrman RE, Kliegman RM eds. Nelson essentials of pediatrics 5Th ed. Philadelphia, WB Saunders Company ,2007: (396-405)-14.*
10. *Peter H., John H. Asthma in Forfar & AmeiPs Textbook of Pediatrics 7th ed. Churchill Livingstone 2008:(689-697)-20*
11. *Sa'vykoski T, Haiju T, Paldanius M, et al. Chlamydia pneumoniae infection and inflammation in adults with asthma. Respiration 2004; 71: 120-125.*
12. *Wilkins J , Gallimore JR , Moore EG, Pepys MB . Rapid automated high sensitivity enzyme immunoassay of C-reactive protein . Clin. Chem . 1998 ; 44 : 1358-61 .*
13. *Danesh J , Muir J , Wong Y - K , Gallimore JR, Pepys MB. Risk factors for coronary heart disease and acute-phase proteins . Eur. Heart J .1999 ;20 : 954 - 9*
14. *Olafsdottir IS. Gislason T, Thjodleifsson B, et al. C reactive protein levels are increased in non-allergic but not allergic asthma: a*

multicentre epidemiological study. Thorax 2005;60: 451-454

15. *Ruth Soferman et al. HsCRP levels: Measurement of airway inflammation inasthmatic children. Pediatrics International (2008) 50, 12-16.*
16. *Pepys MB, Hirschfield GM (2003). "C-reactive protein: a critical update". J. Clin. Invest. 111 (12): 1805-12*
17. *Al-Thamiri D, W. Al-Kubaisy and S.H. Ali Asthma prevalence and severity among primary-school children in Baghdad Eastern Mediterranean Health Journal, Vol. 11, No. 1/2, 2005: 79-86*
18. *Takemura M, Matsumoto H, Niimi A, Ucda T et al. High sensitivity C- reactive protein in asthma Europian Respiratory Journal 2006; 27: 908-9122005*
19. *Jousilahti P, Salomaa V, Hakala K, Rasi V, Vahtera H, Palosuo T. The association of sensitive systemic inflammation markers with bronchial astluna. Ann .Allergy Astluna Immunol 2002; 89: 381-38.Wouters EF. The systemic face of airway diseases: the role of C-rcactive protein. Eur Respir J 2006;27:877-879.*
20. *Karen Scruggs, Michael T. Johnson Pediatric Treatment Guidelines new AAP Guidelines Current Clinical Strategies Publishing 2004.*
21. *Schachter LM, Salome CM, Peat JK, et al. Obesity is a risk for asthma and wheeze but not airway hyper responsiveness. Thorax 2001;56:4-8.*
22. *Gislason T, Janson C, Vermeire P, et al. Respiratory symptoms and nocturnal ?gastro esophageal reflux: a. population-based study of young adults in three European countries. Chest 2002;121:158-63.*
23. *Richter JE. Gastro esophageal reflux disease and asthma: the two are directly related. Am J Med 2000; 108(Suppl 4a): 153-8S.*
24. *Stenius-Aamiala B, Poussa T, Kvamstrom J, et al. Immediate and long term effects of weight reduction in obese people with asthma: randomized controlled study. BMJ 2000;320:827-32.*
25. *Hakala K, Stenius-Aamiala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. Chest 2000;118:1315-21.*