YKL-40 AS A NEW BIOMARKER IN ASTHMATIC CHILDREN AND ASTHMATIC EXACERBATION. ITS ROLE AND CORRELATIONS WITH EOSINOPHIL'S PERCENTAGE AND SERUM IGE LEVEL

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ABSTRACT

YKL-40 is a member of the mammalian chitinase like protein class of 40 Kda (kilo Dalton) heparin binding glycoprotein. Its name is derived from the protein's molecular weight and three N-terminus amino acids (tyrosine[*y*], lysine[*k*] and leucine[*l*]) (*Ober*; et al 2008).

YKL-40 is secreted by various cell-types including macrophages, chondrocytes, and some types of cancer cells. The exact physiological role of YKL-40 is not known, but it has been implicated in cell development, inflammatory disease such as asthma and cancer progression (*Francescone; et al 2011).*

The aim of this study was to investigate whether serum YKL-40 were increased in Asthmatic children and identify its correlation with acute exacerbation, total IgE, blood Eosinophil percentage (EO%) and Pulmonary Function (PF).We measured serum YKL-40 levels, EO%, and serum IgE in 30 children with Asthma as well as in 20 apparently healthy controls from the communities surrounding AL-Salama Hospital, EL-Khobar district, Saudi Arabia. Pulmonary Function (PF) of Asthmatic patients was also measured.

Our data showed that the serum YKL-40 was significantly elevated in patients with Asthma (77.66*ng/m*L) compared with control (*55.16ng/mL*) (*P=0.001*) and when Asthma patients were stratified, serumYKL-40 levels in exacerbation group were significantly higher (*83.72 ng/mL*) than those in stable Asthmatic group (*77.66ng/mL*) (*P=0.043*).

In addition, serum YKL-40 was correlated positively with the level of IgE (*with r =0.298 and p = 0.018*) and EO% (*with r = 0.272 and p =0.032*) but negatively correlated to pulmonary functions as Forced Expiratory Volume in 1st second (FEV1)(with *r =-0.044 and p=0.0001*).

Thus, we conclude that YKL-40 is found significantly high in the serum of asthmatic children and its level correlates with exacerbation attacks, indicating that high levels of serum YKL-40 may be biological characteristic of the asthma exacerbation.

INTRODUCTION

Airway Hyper responsiveness (AHR) and reversible airway obstruction (RAO) are characteristic features of Asthma. Many Studies and researches are designed to evaluate and determine mechanisms of Asthma and how airway inflammation causes the disease and how to contribute to Asthma severity *(Brannan JD, 2010).*

Recent studies focused on several mechanisms of airway inflammations, regulation of the immune responses by environmental factors , altered Allergens, injury-repair process (remodeling), inflammatory mediators as cytokines (INF γ) from Th1 and IL5 from Th2 cells regarding to the balance between Th1/Th2 cell clones. Studies explained the importance of chemokines, IgE synthesis / production and processes contribute in the pathogenesis of asthma *(Dougherty; et al 2014).*

YKL-40 is a member of the mammalian chitinase like protein class of 40 kDA (kilo Dalton) heparin binding glycoprotein. Its name is derived from the protein's molecular weight of three N-terminus amino acids (tyrosine[*Y*], lysine [*K*] and leucine [*L*]). The gene for YKL-40 has been identified on chromosome 1q31-q32). YKL-40 is also called [human cartilage glycoprotein 39 (HCgp39)] or chitinase-3 like1 (CH3L1) binds chitin but it is deficient in chitinase activity. It is produced at sites of inflammation in many cells and is secreted by smooth muscle and Macrophage (Mo). YKL-40 has been shown to be a potent growth factor for connective tissue cells and a potent migration factor for endothelial cells (Rathcke *et al., 2006*).

Researches have demonstrated substantial levels of YKL-40 in environments with inflammation or where remodeling of the extracellular matrix (ECM) occurs. Previous studies have demonstrated that the expression level of YKL-40 was increased during T-helper (Th1) inflammatory cells (*Lee. et al., 2008*). Furthermore, it is suggested that YKL-40 has a role in inflammation and tissue remolding in human diseases as joint injury, liver fibrosis, type2 DM and cancer (*Johansen et al., 2003*).

As current concepts of pathogenesis of Asthma, it is the result of exaggerated Th2 airway inflammation, airway remolding's role in the pathological features of asthma, and YKL-40 is believed to have a role in the pathogenesis of asthma and attracts the attention of

many collaborative groups. Recent study of *Chupp; et al 2007* established that YKL-40 level were increased in lung and circulation of patients suffered from severe Asthma.

YKL-40 level predominantly increased at the site of allergen deposition in response to allergen challenge. Whether, YKL-40 is stable or more increased during exacerbations of asthma (*Kupper et al., 2010*).

PATIENTS AND METHODS

Study design and subjects:

30 Asthmatic children aged 6-16 years were selected from AL-Salama hospital, Al-Khobar city over period between March and December, 2012. Asthmatic group was divided into two subgroups (15 for each stable and exacerbation). The diagnosis of Asthma was based on established guidelines (*GINA. 2011*). 20 apparently healthy children with the same age group without allergic manifestations were encountered as control group.

Exacerbation group:

15 Asthmatic patients who requested urgent medical care for an acute exacerbation of Asthma were recruited for the exacerbation group after presentation to a clinic or emergency room. Acute exacerbation of Asthma was defined as episodes of a rapidly progressive increase in a shortness of breath , cough , wheezing or chest tightness or a combination of these symptoms necessity a non-scheduled visit associated with a decrease in respiratory airflow quantified by measurements of (FEV1)(*GINA 2011*).

In our study, Asthmatic patients with exacerbation were enrolled only when (FEV1) was < 80% of the predicted value.

Exclusion criteria:

We excluded from this study patients who had concomitant diseases proved to be related to YKL-40 as DM, rheumatoid arthritis, hepatic fibrosis or had pneumonia within the preceding 4 weeks from the study. Blood samples from the exacerbation group were collected within 6 hour after the medical visit.

Stable group:

15 age matched patients with stable Asthma were recruited during their scheduled clinic visit. Their symptoms and (FEV1) were stable. The enrolled patients experienced no change in their treatment course for at least 4 weeks and had no evident asthma exacerbation during that time period.

Our study was approved by the human investigations committee at our institution at AL-Salama hospital. All groups gave written informed consent.

Blood sample of was collected from both asthmatic group and control group which divided into two tubes, one with EDTA for CBC and EO% and the other for serum IgE and serum YKL-40assay.

Measurement of serum IgE level and YKL-40

IgE assay:

1ml of clotted blood sample was collected for determination of Serum IgE. This fluorescent enzyme immunoassay (FEIA) measures total and allergen-specific immunoglobulin E (IgE) in human serum. The technique used for this test is (*ImmunoCAP, Phadia AB, Uppsala, Sweden*). Results of this procedure is rapidly available *(Holgate*; 2005).

Serum YKL-40 level: (*Quidel, San Diego, CA, USA*)

1ml of clotted blood samples was collected for the determination of YKL-40 level. ELISA (*enzyme-linked immunosorbent assay*) is a widely-used application for the detection of YKL-40 assay in a microwell format. This assay requires the use of an antibody labeled with a tag such as peroxidase or phosphatase, and an enzymatic substrate that produces a visible signal, indicating the presence of the Allergen. Signal levels are measured in a spectro-photometer. In a properly optimi-zed assay, the intensity of the signal generated is proportional to the amount of Allergen present (*Leung; et al 2005*).

Calculation of the result: the standard curve for the YKL-40 EIA Kit is generated using the A405 values for each Standard (on the *Y* axis) and the assigned concentration for each YKL-40 Standard (on the *X* axis).The data will be graphed manually and the values (*ng/mL*) of the test specimens will be read directly from the best-fit line of the Standard Curve.

* **Interquartile Range (IqR)** for children (male / female) was 60.25ng/mL while its Median range was (*45.75- 87.0*) and for control group (IqR) was 55.16 and its Median range was (*34.23 - 70.75* ng/mL). The minimum detection limit is 20ng/mL from

ELISA kits (*de Marco.et al. 2010*).

Analysis was performed using SPSS software, version 13.0 (*SPSS, Chicago IL., USA*). YKL-40 levels were not normally distributed and the values were compared among the study groups with the use of non-parametric tests, including the (Mann-Whitney U-test and the Kruskal-Wallis H-test). YKL-40 level were expressed as Median and interquartile range (IqR).

Simple association between YKL-40 levels and total IgE, EO% and pulmonary function (PLF) were assessed using Spearman's rank correlation analysis.

RESULTS

In our study, we measured the level of serum YKL-40 in 30 asthmatic children divided into two subgroups, stable [15 children, 8 boy / 7 girl] and exacerbation [15 children, 10 boy / 5 girl] and control group of non-asthmatic apparently normal children [20 children 12 boy / 8 girl] from the same community near to AL-Salama Hospital, EL-Khobar district, Saudi Arabia and compared the findings of the exacerbation group with those from the stable group and controls. Furthermore, the relationships between serum YKL-40, IgE, EO% and pulmonary function (PF) were investigated.

The characteristics of patients and controls are shown in (Tab1).

There were significant statistical differences between asthmatic and control groups as regard percentage of Eosinophils (EO %), serum IgE .Compared with patients in the stable group, those with exacerbation group had more severely compromised pulmonary function (PF) (Table 1).

There were significant statistical differences for percentage of Eosinophils between the control group (2.9±1.4) and patients with stable asthma (5.29 ± 4.33) and for exacerbation group (5.3±43) with a *p value* for control versus to all (*P=0.001*) and for stable versus exacerbation group was (*p=0.26*).

There were significant differences as regard IgE between the control group (131.5±0.87) and both patients groups (stable & Exacerbation) with Asthma .There were significant differences between stable group (420.5±255) versus exacerbation group (536.1±41.0) with a p value

(*p=0.484*). Statistical difference between control group versus both asthmatic groups was significant (*p=0.001*).

YKL-40 levels in patients with Asthma were higher than those in control. Interquartile range (IqR) for Asthma group was 60.25 with median (45.75- 87.0 ng/mL) versus control IqR was 55.16 with median (34.23 – 70.75 ng/mL) with a p value (*p=0.003*) (fig 1a).

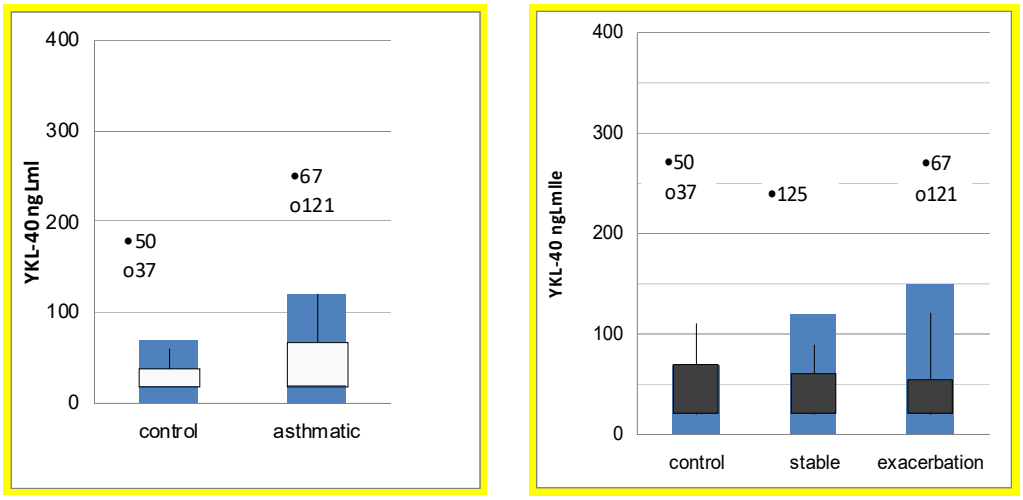
When the relationship between YKL-40 level of both asthmatic groups and those of control group were evaluated, we found that the YKL-40 level for patients in the exacerbation group were significantly higher than those in the control group with IqR 83.72 ng/mL and median (47.0- 97.25 ng/mL) versus IqR 55.16 ng/mL with median (34.23-70.75 ng/mL)and a p value (*p=0.001*), and those in the stable group, IqR was 83.72 with median (47.0 - 97.25 ng/mL) versus IqR 60.25 ng/mL with median (39.0 – 72.75 ng/mL) and a p value (*P=0.043*).

YKL-40 levels in patients in exacerbation group were significantly higher than those in stable group with IqR 83.72 ng/mL with median (47.0 – 97.25 ng/mL) versus those in stable patient group IqR was 60.25ng/mL with median (45.75-78.0 ng/mL) (fig 1b).

Table (1): **The characteristics of patients and control in the study**.

Characteristic	All	control	Stable	Exacerbation	Control vs. all patient (P value)	Stable vs. Exacerbation group. (P value)
Number of patients	50	20	15	15		
Age(Years)	10.1±4.2	9.8±6.3	7.4±4.6	8.1±3.6	0.41	0.06
Male to Female ratio	30/20(1.5:1)	12/8(1.5:1)	8/7(1.14 : 1)	10/5(2 : 1)	0.4	0.1
IgE (kU_a/L)	506.3±44.1	131.5±87	420.5±255	536.1±41.	<0.001	0.484
EO%	5.29±4.33	2.9±1.4	5.26±1.93	5.3±4.3	0.001	0.26
FEV1/FVC			0.96±0.05	0.68±0.1		<0.001

Data are represented as mean +/- SD unless otherwise stated IgE, EO% (eosinophil %), FEV1,FVC (forced expiratory volume in 1st second/ forced vital capacity).continuous data were compared using Kruskal-wall is and categorical data were compared using Pearson's on chi-squared test.



(a) **(b)**

Figure (1): *Serum YKL-40 levels in asthmatic patients and controls. The levels of circulating YKL-40 were assessed in patients with asthma and controls. a) The serum YKL-40 levels in patients with asthma were higher than those in controls. b) When patients were stratified according to exacerbation attacks, the serum YKL-40 levels in patients in the exacerbation group were higher than those in the control group and those in the stable group. Data are presented as median (horizontal line in each box), with 25th and 75th percentiles (top and bottom of each box) and 10th and 90th percentiles (top and bottom of each bar) and outliers (○: >3 quartile deviations; • :> 6 quartile deviations). #: p=0.003; ***: p=0.001; ¶: p=0.043.*

Fig. 2 Correlation of serum YKL-40 levels with several associated items ((IgE) levels and the percentage of peripheral blood eosinophils

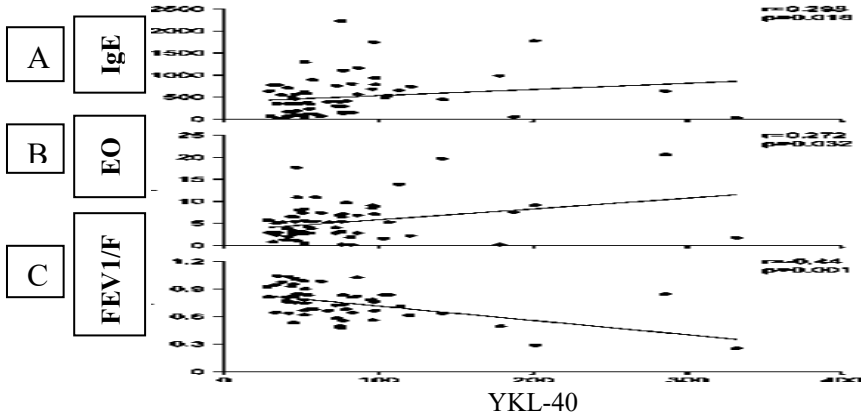


Figure (2): *Correlation of serum YKL-40 levels with several associated items. Spearman's rank correlation analysis showed a significant correlation between the serum YKL-40 levels. a) The total serum immunoglobulin E levels (IgE) (r=0.298, p=0.018); b) the percentage of*

peripheral blood eosinophils (r=0.272, p=0.032); c) forced expiratory volume in 1 s (FEV_1)/predicted value (r=-0.44, p=0.001).

In patients with asthma, the correlation between SerumYKL-40 levels, IgE, EO% and the ratio of prebronchodilator (FEV1) to the predicted value were investigated. The findings revealed that SerumYKL-40 levels correlated with IgE levels (*r=0.298, p=0.018*) (fig 2a), The EO% (*r=0.272, p=0.032*) (fig 2b) and the ratio of (FEV1) (*r=-0.044, p=0.0001*) (fig 2c).

DISCUSSION

Chitin, a polymer of N-acetyl glucosamine, is the second most abundant polysaccharide in nature. It is found in the walls of fungi ; the exoskeleton of crabs, shrimp and insects, the micro-filarial sheath of parasitic nematodes and the lining of digestive tracts of many insects (*Shebata. et al., 2010*).

Chitin accumulation is regulated by the balance of chitin synthase - mediated biosynthesis and degradation by chitinase (*Zhu et al., 2004*).

Elevated circulating YKL-40 levels were proved to be present in patients with meningitis, pneumonia, Rheumatoid arthritis and hepatic fibrosis (*johanson. ; et al 2007*).

Furthermore, *Chupp* have demonstrated that YKL-40 is strongly up-regulated in the airway epithelium & alveolar macrophages of patients with Asthma and serum YKL-40 levels are elevated in patient with Asthma. Circulating YKL-40 levels are correlated with Asthma severity. The thickness of the sub-epithelial basement membrane and pulmonary function suggesting that circulating YKL-40 levels are a biomarker for Asthma (*Chupp. et al., 2007*). Additionally, YKL-40 concentrations increased in response to Allergen challenge predominantly at the site of Allergen deposition (*Kuepper* et al., 2008).

Our study manifests that in children aging from 6-14 years, circulating levels of YKL-40 are increased in patients with asthma compared with healthy children. When the asthmatic patients were categorized, circulating levels of YKL-40 in the exacerbation group were higher than those in the stable and healthy children groups which suggest that serum YKL-40 levels correlate with asthma exacerbation attacks. In addition, the serum levels YKL-40 correlate positively with serum IgE levels

and EO% and correlate negatively with pulmonary function.

Our data showing the comparison of serum YKL-40 levels between asthma and healthy children, and the correlation between the protein levels and lung functions coincide with those from the study of (*Chupp.; et al 2007)*. Another study by (*Sohn et., al 2009*) suggested that in the East Asian children, there is no significant associations between YKL-40 single nucleotide polymorphism (SNPs) and asthma are observed, while a (SNPs) was found to be associated with atopy and serum YKL-40 levels. Although this study did not compare serum YKL-40 levels of asthmatic children with those of healthy control children directly, the basis for this potential discrepancy may be due to the differences in the mean ages of these children, since some children with atopy may develop asthma with increasing age.

In our Study, we showed that during exacerbation attacks, serumYKL-40 levels of patients with Asthma are higher than those of the stable group and healthy children, and illustrated the protein's correlations with IgE and EO% among asthmatic patients. However, perspective studies will be required in order to determine whether serum YKL-40 would decline when those exacerbations children are completely controlled after treatments; this is the aim of our further efforts. Although the pathogenic role of YKL-40 in Asthma remains unclear, our study indicates that the high levels of YKL-40 may be a biological characteristics of Asthma exacerbation.

CONCLUSION

In our study, we conclude that serum YKL-40 level are increased in asthmatic children patients and its level correlates with exacerbation attacks indicating that YKL-40 may be either a cause or a new biomarker for asthma and its disease severity.

RECOMMENDATIONS

Future researches are recommended to determine how airway inflammatory activity causes and contributes to disease severity. Furthermore, as molecules contributing to the regulation of airway inflammation are discovered, the role of cytokines and their balance in the development and evolution of disease will be important to understand asthma persistence and severity.

Also we recommend further studies to follow the levels of YKL-40 after improvement of exacerbation activity to confirm

the relation of YKL-40 with the disease activity.

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دور (YKL-40) كعلامة بيولوجية في الأطفال المصابين بالربو الشعبي وكذلك علاقته بالأزمات الربوية الشديدة بالإضافة الى دراسة ارتباطه بنسبة خلايا الايسينوفيل وكذلك الجلوبين المناعي E في الدم لدى هؤلاء المرضى

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(YKL-40) عبارة عن بروتين ثلاثي النهايات شبيه بالكيتينيز لدى الثدييات وتكمن اهميته في أنه إما أن يكون السبب أو أحد العلامات البيولوجية لمرض الربو الشعبى .

كان الهدف من هذه الدراسة هو دراسة الفرق بين ارتفاع مستوي (YKL-40) بالدم لمرضى اطفال الربو الشعبى المستقر والحالات الشديدة مع تحديد العلاقة بينها وبين نسبه خلايا (ايسينوفيل) وكذلك مع مستوي (الجلوبين المناعي E) بالاضافه الي وظائف الجهاز التنفسي.

وقد أجريت هذه الدراسة علي عدد(50) طفلا أعمارهم تتراوح بين 6-16 سنة كان عدد الأطفال الاصحاء منهم (20) كمجموعه ضابطه مقارنه والمصابون بالربو الشعبي (30) كمجموعه مرضي والتي تم تقسيمها الي مجموعتين فرعيتين كل منهما (15) لكل من الاطفال المصابون بالربو وبحاله مستقره و(15) للأطفال بحالات أزمات ربوية متكررة. وقد تمت هذه الدراسة بمستشفى السلامة بمدينة الخبر على مدى 9 اشهرفي الفترة مابين شهري مارس وديسمبر 2012.

وفي هذه الدراسة نقوم بقياس مستويات كل من (YKL-40) وتحديد نسبه خلايا ايسينوفيل للأطفال الذين يعانون من الربو وكذلك في الاطفال الاصحاء كمجموعه مقارنه ضابطه وذلك للمناطق السكنية المحيطه بمستشفي السلامة بالخبر بالمملكة العربية السعودية. كما نقوم كذلك بقياس وظائف الجهاز التنفسي لمجموعتي المرضى .

وأظهرت نتائج البحث أن هناك ارتفاع ذو دلالة إحصائية لمستوي (YKL-40) في الاطفال المرضي المصابون بالربو الشعبي معطيا مؤشرا (77,66 نانوغرام/مللي) مقارنة للمجموعة الضابطة المقارنة من الأطفال الاصحاء معطيا مؤشرا (55,16 نانوغرام/مللي) بمعامله إحصائية (P = 0،001) وبالنسبة لمجموعه حالات الاطفال المصابين بأزمات الربو الشعبي الحاده معطيا مؤشرا (83,72 نانوغرام /مللي) بمعاملة إحصائية (P = 0,001) كما لوحظ أن مستوي (YKL-40) لمجموعة حالات الأطفال الحادة اعلي من معدل حالات اطفال الربو الشعبي المستقرة بالإضافة الي ذلك فقد ارتبط مستوي (YKL-40) بمعاملة ذات دلالة إحصائية ايجابية مع كل من خلايا الايسينوفيل بالدم وكذلك لمستوي (الجلوبين المناعي E) وعكسيا مع وظائف الجهاز التنفسي .

وبالتالي فإننا نستنتج من هذه الدراسة أن مستوي (YKL-40) في زيادة مضطردة مع مجموعه مرضي الربو الشعبي مع أزمات المرض المتكررة مشيرا الي أن مستويات عاليه من (YKL-40) قد تكون من الخصائص البيولوجيه أو كسبب مباشر لمرض الربو الشعبي للأطفال .

كذلك توصي هذه الدراسة بعمل دراسات أخرى تعمل على متابعة مستويات (YKL-40) بعد استقرار حالة المرضى لدعم النتائج السابقة دراسة العلاقة الفعلية بين مستوى تلك المادة ونشاط الربو الشعبي.