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# Correlation of Prostaglandin-D2 with disease severity of adult asthma

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**Abstract:**

**Background**: Prostaglandin D2 (PGD2) is a lipid mediator appeared as a powerful activator that regulates the T-helper2 (TH2) and Type-2 innate lymphoid cells (ILC2), and functions as diagnostic marker and it has probable therapeutic targets for asthma.

**Objectives**: To define the role of Prostaglandin D2 biomarkers in disease severity, and to forecast disease risk and progression.

**Patients and methods:** A case control study was conducted on Forty four Iraqi asthmatic patients and 44 apparently healthy controls who were age and sex matched. Four ml of blood samples was taken from the study groups for the detection PGD2 using ELISA.

**Results:** The serum level of PGD2 was almost convergent between cases and control group (median= 36.5pg/ml and 35.1 pg/ml respectively). The high median serum concentration of PGD2 showed a strong statistically significant association with the severity of asthmatic patients (39.8 pg/ml) in severe cases compared to (30.84 pg/ml) in moderate cases (P value =0.005). The median concentration of serum PGD2 revealed a higher level in abnormal eosinophil, monocytes and total IgE (42 pg/ml), (48.9 pg/ml) and (38.5 pg/ml) respectively than the median concentration of normal counts.

**Conclusions:** Measuring serum PGD2 in asthmatics is crucial to predict disease susceptibility, severity and disease control.

**KeywordS:** Asthma, PGD2, Eosinophil, Asthma biomarkers, Asthma Severity.

## Introduction:

Asthma is a long-term and serious disease which affects different age groups. It was clearly documented that in Iraq, the levels of asthma control fall far below the goals of current international guidelines (1). About two thirds of uncontrolled asthmatic patients in Iraq are drug misusers (2). The presences of environmental, psycho-social and genetic predisposing factors play a major role in asthma development and disease exacerbations (3).

Prostaglandins (PGs) are products of arachidonic acid through two pathways of the cyclooxygenase (COX)-1/2 via two intermediates; which are PG-G2 and PG-H2. Type 2 inflammations are driven by PG-D2; so that an increased level of PG-D2 can be detected in the bronchial airways of asthmatic patients and allergic rhinitis during acute attacks (4). The biological properties of PG-D2 are controlled by a receptor classified in two different forms: the DP1, and the chemo-attractant receptor expressed on Th2 cells (CRTH2), or DP2 (4). A number of biological effects allied with clinical presentations of asthma are activated by PG-D2 and mediated by CRTH2 and DP1. CRTH2 is responsible for chemotaxis and activation of Th2 lymphocytes, eosinophils, and basophils while bronchoconstriction; vasodilatation; and suppression of cytokine production by dendritic cells are mediated through DP1 (5). The PGD2 receptor CRTH2 (DP2) is expressed strictly by type 2 inflammatory cells as Th2 cells, eosinophils and basophils. Notably, human ILC2 were identified according to expression of CRTH2, (5). PG-D2 triggers the secretion of other pro-inflammatory cytokines like (IL- 3, IL-8, IL-9, IL-21, GM-CSF and CSF-1) . Besides, the provoking role of PGD2 was simulated again by IgE activated mast cell resident in skin ILC2 via a CRTH2-reliant approach (6). Thus, PG-D2 plays a crucial role in the activation of ILC2, orchestrating both innate and adaptive immunity.

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**Patients and methods:**

This case control study was conducted in Microbiology Department /Collage of Medicine /University of Baghdad and the Respiratory and Allergic Diseases Center/Ministry of health/Iraq. Sampling, laboratory tests and study analysis were extended from February 2018 to April 2019.

Forty four asthmatic patients were randomly included in this study; they attended the Respiratory and Allergic Diseases Center/Ministry of health/Iraq. Their ages were determined from 18 years and above. Their Pulmonary Function Test results were classified according to The Global Initiative for Asthma (GINA) guidelines (FEV ≥ 80% is mild, from 60%-80% is moderate and ≤ 60% is severe asthma). Patients were compared to 44 apparently healthy individuals of medical and paramedical staff who were non-smokers and clear from any allergic and/or autoimmune disease so as their families. Their ages and sexes were matched with cases.

Any of the cases who proved to have a previous history of respiratory diseases as chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, pneumonia, or bronchitis, or any other co-morbid illness that need treatment like Aspirin (2-Acetoxybenzoic acid), non-steroidal anti-inflammatory drugs (NSAIDs) and Aspegic (DL-Lysine Acetylsalicylate) or anyone with past medical history of autoimmune diseases was excluded from the study.

**Ethical considerations:**

Ethical approval for the study was obtained from the ethical committee in the Department of microbiology and Dept. of Medicine as well as from the Council of the Collage of Medicine / University of Baghdad.

All patients and controls received a written and verbal information sheet explaining the aims of our study. A signed written consent was taken for each individual participating in this study.

**Sample collection:** From each individual a 4 ml of venous blood was drawn from, of which 2 ml were put in EDTA tube, then complete blood count test was done by blood auto analyzer laboratory machine. The remaining 2 ml of blood was centrifuged under 1000 x g for 15 minutes then 0.5 ml of serum was stored in Epindroff tube at -20°C until used for ELISA detection technique of Periostin.

The used Kit was *Human PG-D2* for the quantitative determination of endogenic human prostaglandin-D2 (PG-D2) concentrations in serum, plasma, tissue homogenates ELISA Kit (Cusabio Catalog Number CSB-E13898h) China.

**Assay's principle:** The quantitative sandwich enzyme immunoassay technique was used for this assay. Micro plate was pre-coated by antibody specific for PG-D2. The wells were pipetted by standards and samples and every PG-D2 there, was bound by the immobilized antibody. After discarding any boundless reagents, biotin-conjugated antibodies which are PG-D2 specific were added to the wells. Following washing, avidin conjugated Horseradish Peroxidase (HRP) was added to the wells. After a wash to get rid of any unbound avidin-enzyme substance, substrate solutions were added to the wells and color develops up to the amount of PG-D2 bound in the first step. The colors developments were faded away and their intensity were specified.

**Calculation of results:** According to professional soft "Curve Expert 1.4" which used to plot a standard curve created by Cusabio website. The figures may be expressed by plotting the concentrations log of ***PG-D2*** against the log of the optical density (O.D.) and the best fit line can be generated by regression analysis.

**Statistical methods:**

The results were calculated by the use of Statistical-Package for the Social Sciences (SPSS) package for Windows version 24.0 software (IBM Corporation, Armonk, NY, USA).

The median with interquartile range (IQR) (Mann-Whitney U test) for comparison of two non-normally distributed data of PG-D2 serum concentrations and Kruskal-Wallis H test for comparison of more than two of non normally distributed data were used to estimate the significant differences.

PG-D2 performance characteristics variables were determined by receiver operating characteristic curves (ROC) to establish the concentrations which are best to distinguish the diagnosis accuracy of the test of asthma in order to provide optimal cutoff values of the studied biomarker.

**Results:**

**Serum PG-D2 concentration between study groups**

Table -1 shows that the median IQR concentration of serum PG-D2 was (36.5 pg/ml) for the cases and (35.1 pg/ml) or the controls, with no statistically significant difference was observed (P=0.628). the wide range between minimum and maximum values of PG-D2 concentration in controls compared to cases was (1.06- 280.8 pg/ml) and (16.18-135.1pg/ml) respectively, and both figures -1 and -2 show skewed to the left curve distribution with more cases with serum concentration below 60 (pg/ml) of PG-D2, justifying the use of the Mann-Whitney test.

**Table -1: The difference in median concentration of serum PG-D2 level between study groups**

| Prostaglandin D2 (pg/ml) | Study group | | P – Value |
|---|---|---|---|
| | Cases (n= 44) | Controls (n= 44) | |
| **Mean ± SD** | 41.8 ± 22.4 | 45.0 ± 42.95 | |
| **Range** | (16.2-135.1) | (1.1 - 280.8) | |
| **Median** | 36.5 | 35.1 | **0.628** |
| **IQR (Q3-Q1)** | (27.7 - 49.1) | (23.14 –56.0) | |
| **Mean Rank** | 45.8 | 43.2 | |

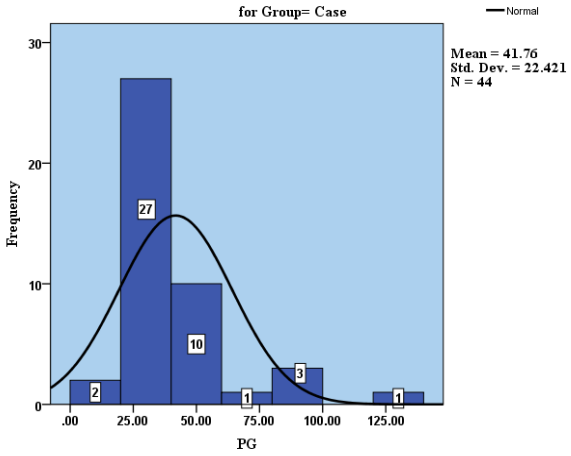


**Figure -1 Distribution of PGD2 concentration in asthmatics**

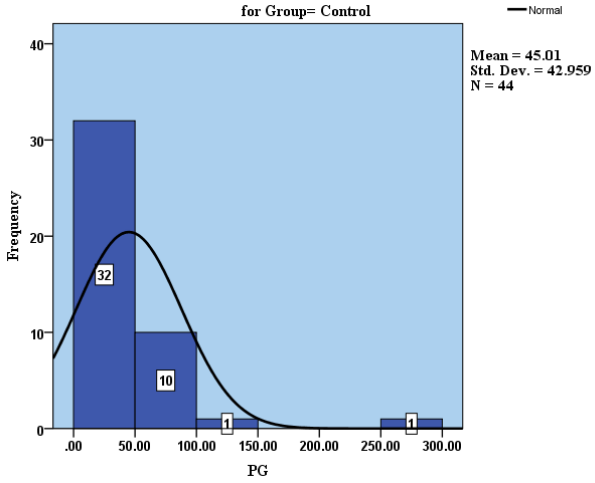


**Figure -2: Distribution of PGD2 concentration in contols**

**Clinical sensitivity of PG-D2 level by (ROC) curves to identify patients with Asthma:** ROC curves were generated by plotting sensitivity against (1-specificity) for the performance of serum PG-D2 marker in the diagnosis of asthma its efficiency was calculated among study groups as displayed in figure -3.There was no statistical difference in serum level of PG-D2 between asthmatics and controls (p=0.628) in the prediction of bronchial asthma and the area under curve AUC= 0.530; i.e. mid away from 1 (optimum Sensitivity and Specificity).

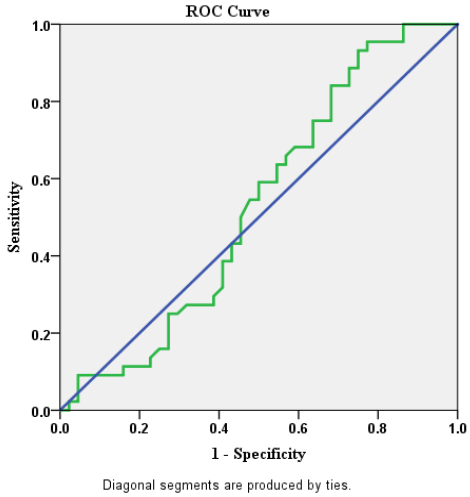


**Figure -3: Summary of ROC characteristics for serum PG-D2 among the study groups.**

**Association of serum PGD2 concentrations with clinical information of asthmatic patients:**

The differences between the clinical informations of cases and the serum concentration of PG-D2 are shown in Table -2. Regarding the severity of disease, asthmatic patients were further categorized into (mild, moderate and severe), the differences of serum concentration of PG-D2 in relation to disease severity are of a statistical significance (P value o= 0.019). There was a highly significance difference in the median concentration of PG-D2 between moderate and severe groups of (30.84 and 39.8) pg/ml respectively (P value = 0.005).

Regarding disease control, cases were also sub-grouped into (well, partly and poorly controlled) asthma. Median serum concentration of PGD2 showed a statistical non-significant difference (P value >0.05.

**Table -2: Duration and disease severity in relation to PGD2**

| Variables | Serum Conc. | | | P – Value |
|---|---|---|---|---|
| | Mean ± SD | Range | Median (IQR) | |
| Duration of Asthma (Years) | | | | |
| < 5(12) | 48.5± 24.2 | (16.2-91.6) | 41 (28.7- 57.5) | 0. 126 |
| ≥ 5(32) | 39.5± 21.7 | (16.8- 135.1) | 35 (27.2- 42.3) | |
| *Severity of Asthma | | | | |
| Mild (1) | 28.7 | 28.7 | 28.7 | 0.019 |
| Moderate (12) | 23.4±18.7 | (16.2-36.8) | 30.8 (25.9-42.1) | |
| Severe (31) | 46.8±24.9 | (16.2-135.1) | 39.8 (28.5-53.3) | |
| Level of asthma Control | | | | |
| Well (17) | 35.9± 15.9 | 16.2-84.4 | 32.6 (25.6- 39.8) | 0.275 |
| partly (9) | 52±37.6 | 16.2-135.1 | 42.7 (26-68.9) | |
| Poorly (18) | 42.1± 16.7 | 24.8- 91.6 | 37.6 (28.5-51.1) | |

***Mann Whitney (Moderate vs Severe) P- Value= 0.005**

**PGD2 in relations to other allergic investigations:** Table -3 shows the significant differences between serum concentrations of PG-D2 with different eosinophil counts, monocytes count, total IgE and specific Inhaled IgE levels. The median concentration of serum PG-D2 revealed a higher level of (42 pg/ml) in higher eosinophil count than the median concentration of normal count (28.7 pg/ml) (P value =0.0001).The same is true for the median concentration of PGD2 being higher (48.9 pg/ml) in high monocytes counts compared to normal monocytes counts (30.84 pg/ml) (P value = 0.0004). A high level of total IgE was observed in higher median concentration of PG-D2 (38.5 pg/ml) which was significantly different from the median concentration of the normal total IgE (27.7 pg/ml)(P value= 0.007). On the other hand, the PG-D2 level in asthmatic patients with positive test for specific inhaled IgE had a significant difference between its median concentration (39.8 pg/ml) compared to those with negative test for specific inhaled IgE with median concentration of (30.9 pg/ml)(P = 0.027).

**Table-3:Serum concentration of PG-D2 in relations to other allergy investigations**

| Variables | Serum Conc. | | | P – Value |
|---|---|---|---|---|
| | Mean ± SD | Range | Median (IQR) | |
| Eosinophil | | | | |
| Normal (19) | 31.93±13.9 | (16.2- 84.35) | 28.7 (24.8- 35.03) | 0.0001 |
| High (25) | 49.2±24.94 | (16.2- 135.1) | 42.0 (36.5- 55.00) | |
| Monocytes | | | | |
| Normal (28) | 33.13±13.2 | (16.2- 84.4) | 30.84 (25.00- 36.8) | 0.0004 |
| High (16) | 56.84±27.4 | (27.5- 135.1) | 48.9 (39.8- 62.44) | |
| Total IgE | | | | |
| Normal (10) | 28.5±10.1 | (16.2- 49.3) | 27.7 (19.8- 35.5) | 0.007 |
| High (34) | 45.7±23.6 | (23.8- 135.1) | 38.5 (30.9- 53.1) | |
| Specific Inhaled IgE | | | | |
| Yes (23) | 45.1±19.6 | (16.2- 91.6) | 39.8 (32.8- 53.0) | 0.027 |
| No (21) | 38.1±25.1 | (16.2- 135.1) | 30.9 (25.2- 38.2) | |

**Discussion:**

The present study has revealed insignificance differences between the PG-D2 serum levels among the cases compared with control subject. To the best of our knowledge, no study has made a direct comparison of serum PG-D2 level measured by ELISA between adult asthma patients and healthy controls, which might be explained by the quick release of PG-D2 after allergen sensitization, with a 150-fold spark in Bronchio Alveolar Lavage (BAL) within 9 minutes and their possibly return to normal levels within a short period of time (7,8). The current study agreed in some aspects with earlier work on expression of CRTH2 by Th2 lymphocytes among asthmatics using flow cytometry which reported a low PGD2 level in both blood and BAL (9). The count of CRTH2 blood lymphocytes were similar in healthy and asthmatics subjects, but there was a significant increase in the number of BAL CRTH2 T-cells in patients with asthma. In both blood and BAL, Furthermore; IL-4 or IL-13 produced by TH2 cells showed a greater expression of CRTH2 (10). The insignificant in differences of the serum level of PG-D2 in this study might be attributed to the rapid metabolism of PG-D2, with a short half-life in the circulation of about 30 minutes (11). Moreover, this might due to the measurement of PG-D2 in the serum by ELISA technique. Accordingly and based on previous research which showed that the PG-D2 gets rapidly metabolized followed by and excreted by the kidneys. So that, the level of PG-D2 and its metabolites were frequently measured in asthmatic patients and had been often performed in the urine (11), bronchoaveloar lavage fluids , and recently in induced sputum (12,13). The available data on PG-D2 levels in human serum was an inadequate. Bochenek et al., (2004) revealed that 9a,11b-PGF2, which is the primary metabolite of PG-D2, elevated remarkably in plasma in early asthmatic response (EAR) following to exposure to allergens (14).Furthermore, the role of dietary resource of omega 3 and omega 6 may be one of the explanations of non- correspondence of serum PG-D2 in asthmatics. In our study, as omega 6 rich diets may lead to increase the chance of suffering from asthma and / or asthma severity and vice versa of omega 3 diets that may lead to decrease the possibility of getting asthma and / or associated with decrease asthma severity (15). The plausible biological connection between the exposure to arachidonic acid and further risk for the existence of asthma cannot be fully understood yet. The production of cys-LT from arachidonic acid generate effects that are distinctive of asthma, like powerful bronchial constriction, enhanced the permeability across the endothelial membrane leading to airway edema, increased in the secretions of thick and viscous mucus, so far, recent trials for using their receptor antagonists as a target for treating asthma (15). The Clara cell may have a role in the non-significance of serum PGD2 in this study, as many proteins secreted by Clara cell (also known as CCSP, CC10, CC16, Clara cell antigen, secretoglobin, and uteroglobin) which are present in abundance of the surface fluid in bronchial airways . Uteroglobin play a fundamental

role in homeostasis and repair, and act as an impending biomarker of lung damage or disease. Clara cells, the most active producers of uteroglobin in lung, are found in bronchiolar epithelium and respiratory bronchioles. As a result Uteroglobin may influence the serum PG-D2 level, it has been reported that a decline in PG-D2 synthesis, triggered by uteroglobin, an anti-inflammatory protein, was reduced allergic inflammation (5,16).

*Association of PG-D2 with Severity of Asthma*

In the current study, a clear relationship was found between the severity of asthma and serum level of PG-D2 with a statstically significant differences when compared with moderate . this finding agrees those of other studies which found that PG-D2 has an effect on asthmatic patients as a proinflammatory as other research indicates (7). Our results coincide with those of Fajt et al., (2013) who revealed an increased in the expression of CRTH2 levels in BAL cells in severe asthmatics, using genetic expression and immune cyto-chemical studies (4).There was a strong relationship in the expressions PG-D2 and CRTH2 with bad clinical consequences related to asthma crisis and disease control (17). Other researchers who reported a higher counts of immuno-inflammatory cells like CRTH2 cells among severe forms of asthma cases compared to non-asthmatic.They also showed that the total number of CRTH2 epithelial cells decreased with the disease severity and that the reduction in this cell expression was specially observed in the epithelium areas with metaplasia obtained from biopsies of those patients. It is uncertain so far if this metaplasia in severe asthmatic cases is caused by PG-D2 otherwise if this activation leads to a decline in expression of CRTH2, as activation of PG-D2 in many other cell types, like TH2 cells down- regulates the expression of CRTH2 (18). The significant increase of serum PG-D2 among the severe asthmatic group in this study was similar to a study done by (Balzar et al.,2011) who demonstrated that an increased in the levels of PG-D2 is clearly associated with the highest disease severity in contrast to mild and moderate disease and especially among those who are on high-dose of inhaled corticosteroids in spite of the identified effects of inhaled corticosteroids on the reduction in the numbers of PGD2-producing mast cells in bronchial epithelium. It's not clear if PG-D2 levels in bronchoalveolar lavage are higher in patients with mild asthma compared to non-asthmatic subjects as study results are contradictory (20). An agreement was found with the results of this study regarding the significant relationship of PG-D2 with severe asthma. Bronchoconstriction is a feature of asthma; the inflammatory course is mediated by eosinophils through the release of cytotoxic granules and lipid mediators that damaging to tissues, inducing bronchial constriction. Moreover, PG-D2 may contribute to pathophysiology of asthma inducing increased mucus formation, vasodilation and capillary permeability (21).

*Relation of PG-D2 with EØ, Monocytes and IgE:* In the current study, a significant increase of serum PG-D2 in high eosinophilic patients was found and it agrees with the findings of by Honda et al. who showed that using nebulization of PG-D2 prior to aerosol Ag challenge enhanced TH2 inflammatory responses, like eosinophilia, which progressed to AHR (22). PG-D2 has been proved to chemo-attract eosinophils, basophils and Th2 lymphocytes. Eosinophilia whether in the blood or in tissue is a key element for atopic diseases including asthma and it correlates with the disease severity (4). Application of exogenous agonists of PG-D2 and DP2 in animal models provoke the infiltration of eosinophilia in peripheral blood , the conjunctiva, lung, nose, and skin , whereas blockage of DP2 receptors might improve atopic dermatitis, asthma, rhinitis, and conjunctivitis (23).

In hypersensitivity reactions mediated by allergen-specific IgE, numerous mediators are released by mast cells such as histamine, leukotriene C4, PG-D2 and TNFα (24). Mast cells also play a role during asthmatic attacks as the numbers of mast cells and the concentrations of PG-D2 are increased in the lower respiratory airways of asthmatics (17, 4). Serum levels of IgE are a predictive indicators with other biomarkers in bronchial asthma (25). There is a clear link between serum PG-D2 and IgE that also found in this study through the ability of PG-D2 to recruit, stimulate, and enhance leukotreines secretion from both TH2-like lymphocytes and type 2 innate cells (23). In fact, previous findings showed that haematopoetic PGD2 synthase (HPGD2S) was highly expressed which might be the efficient reaction that is solely up-regulated during mast cells activation (24). In general, PG-D2 pathway may affects directly and indirectly asthma biology. The serum PG-D2 level in our study had a significant relationship with monocytes. These results correspond with other studies that revealed the direct and indirect inflammatory role of Monocytes in immunopathogenesis of asthma. The occupant alveolar macrophages/monocytes fundamentally stock to preserve lung homeostasis by quelling inflammation, whereas immigrating monocytes primarily upholding allergic inflammation If lung macrophages come from stimulated monocytes are actually pathogenic, then blocking their mobilization could excess allergic inflammatory response (26). In addition; in this study the PGD2 had significant Positive relation with IgE. This coincides with the ability for antigens presentation that amplified by the expression of IgE -FCεRI receptors complex on the surface of DCs. Furthermore; it was verified that allergens were isolated by the effect of IgE, supporting their presentation to Th2 memory cells (27); and leading to a 1000-fold an increase in T cells activation (28).

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**Author's contributions:**
Mohammad A. Al-Karkhy, and Mustafa Nema conceived of the presented idea. Mohammad A. Al-Karkhy and Shatha F. Abdullah verified the analytical methods. All authors discussed the results and contributed to the final manuscript.

**Conflict of interest:**
The authors declare no conflict of interest.

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# أرتباط بروستوكلاندين د2 مع شدة المرض لمرض الربو عند الكبار

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**د. مصطفى نعمة**
**أ.د. شذى فاروق**

**خلفية البحث:** ظهر البروستاكلاندين دي 2 كواحد من الدهون الوسيطة ومنشط قوي ومنظم للخلايا اللمفية المساعدة 2 وللنوع الثاني من الخلايا اللمفية الفطرية, لتكون وظيفته كدلالة تشخيصية ومعالج مرتجى لمرض الربو.
**الاهداف:** لتحديد دور البروستاكلاندين دي 2 كمؤشر حيوي لشدة الربو وعوامل الخطورة وتقادم المرض.
**المرضى والطرق:** شملت هذه الدراسة المستقبلية بمقارنة 44 مريض عراقي مصاب بالربو القصبي بالمقارنة مع 44 شخصًا يبدو أنهم أصحاء وأعمارهم وجنسهم متطابقين مع المرضى وأعتبارهم كمجموعة تحكم (ضبط). وتم سحب 4 مليليتر من الدم الوريدي من جميع المشاركين بالدراسة ليتم كشف وقياس البروستاكلاندين دي 2.
**النتائج:** كان مستوى البروستاكلاندين في مصل مجموعة المرضى متقاربًا تقريبًا مع مجموعة التحكم حيث كان (الوسيط = 36.47 بيكوغرام / مل للمرضى و 35.13 بيكوغرام / مل لمجموعة التحكم). بينما كان التركيز العالي لوسيط البروستاكلاندين ذو علاقة احصائية منطقية في مرضى الربو الشديد (39.8 بيكوغرام / مل ) بالمقارنة مع مجموعة الربو متوسط الشدة (30.84 بيكوغرام / مل ) وبقوة مقدارها (0.005). كذلك اضهر تركيز الوسيط للبروستاكلاندين ارتفاعا في مجموعات الخلايا المرتفعة العدد الحمضية (42 بيكوغرام / مل) والأحادية (48.9بيكوغرام / مل) وارتفاعا ايضا في مجموعة المرضى المرتفعين الاي جي اي الكلي (38.5 بيكوغرام / مل) بالمقارنة مع مرضى الربو الذين لا يعانون من هذه الارتفاعات الثلاث السابقة.
**الأستنتاجات:** وبالتالي فإن قياس البروستاكلاندين دي 2 في مصل الدم في المصابين بالربو أمر بالغ الأهمية للتنبؤ بحساسية المرض وشدته والسيطرة على المرض.
**الكلمات المفتاحية:** الربو،البروستوكلاندين د 2، الخلايا الحامضية، شدة الربو.