

Inhibitory Effects of Synthetic glucocorticoids drugs on hypothalamus – pituitary – adrenal gonads axes and differential white blood cells in Asthmatic patients

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Abstract

The present study focused on the different effects of synthetic glucocorticoids therapies on different hormones and white blood cells of asthmatic patients of both sexes. The present study included 80 asthmatic patients (40 males and 40 females) and sub divided into two categories : first group involved asthmatic patients treated with glucocorticoid therapies (20 males and 20 females) and second group included asthmatic patients treated without glucocorticoids therapies (20 males and 20 females). A thirty healthy subjects were involved in this study to perform comparison (control group) of both sexes (15 males and 15 females). All ages of the subjects ranged between 30 – 60 years old. Result of cortisol , testosterone , estradiol hormones showed significant decrease ($P < 0.01$) in first group (treated with glucocorticoids) and showed insignificant changes in the second group when compared with healthy control group. Concerning values of total white blood cells pointed out significant increase ($P < 0.05$) in both patients group when compared with control group. Differential white blood cells of first asthmatic patients group, explained significant increase in the levels of monocytes, neutrophils and insignificant increase in the levels of eosinophils and of lymphocytes when compared with control group. Moreover , results of differential white blood cells of second patients group (without glucocorticoids therapies) recorded a significant increase ($P < 0.05$) in the levels of monocytes , eosinophils, neutrophils , and insignificant changes of lymphocytes in a comparison with control group. In conclusion , changes mentioned above may be attributed mainly to inhibitory effects of synthetic glucocorticoids on axes of hypothalamus – pituitary – adrenal axes, and of reproduction , growth , maturation , and migration of white blood cells.

Key words: Asthma, Gluco corticoids

الخلاصة

تضمنت الدراسة الحالية التركيز على التأثيرات المختلفة للعلاجات القشرانية السكرية (Glucocorticoids) والمستخدمه في علاج بعض مرضى الربو على بعض الهرمونات (الكورتيزول و الهرمون الخصوي والاستراديول) والعد الكلي والتفريقي لكريات الدم البيض. شملت الدراسة الحالية اختبار 80 مريضا مصابا بالربو من كلا الجنسين (40 ذكرا و 40 أنثى) وقد قسموا إلى مجموعتين : المجموعة الأولى : تضمنت 40 مريضا (20 ذكرا و 20 أنثى) يعالجون باستخدام العلاجات القشرانية السكرية ، والمجموعة الثانية تضمنت اختبار 40 مريضا ايضا (20 ذكرا و 20 أنثى) يعالجون بدون استخدام العلاجات القشرانية السكرية . وقد اختبر 30 شخصا سليما (15 ذكرا و 15 أنثى) كمجموعة سيطرة لغرض اجراء المقارنات الاحصائية . تراوحت جميع اعمار اشخاص الدراسة (المرضى والاصحاء) بين 30-60 سنة .حققت نتائج هرمون الكورتيزول والهرمون الخصوي وهرمون الاستراديول انخفاضا معنويا ($P < 0.01$) في المجموعة الأولى من المرضى ولم تلاحظ تغيرات معنوية لدى المجموعة الثانية عند مقارنتها مع مجموعة السيطرة كما بينت نتائج العدد الكلي لكريات الدم البيض ارتفاعا معنويا ($P < 0.05$) في كلا المجموعتين من المرضى المصابين بالربو عند مقارنتهم مع الاشخاص الاصحاء . وبخصوص العدد التفريقي لكريات الدم البيض فقد بينت نتائج المجموعة الأولى ارتفاعا معنويا ($P < 0.05$) في قيم كل من الخلايا الاحادية والمتعادلة وانخفاض معنوي ($P < 0.05$) في قيم الخلايا اللمفاوية والحاوية عند مقارنتها مع الاشخاص الاصحاء . أما فيما يخص العدد التفريقي للكريات البيض في المجموعة الثانية من المرضى فقد لوحظ ارتفاع معنوي ($P < 0.05$) في قيم الخلايا الاحادية والمتعادلة والحاوية وتغيرات غير معنوية في قيم الخلايا اللمفاوية عند المقارنة مع مجموعة السيطرة أن التغيرات المستنتجة من هذه الدراسة يمكن عزؤها إلى التأثيرات المثبطة للقشرانيات السكرية على كل من محاور التكاثر والمهاد والنخامية والكظرية وتطور وهجرة كريات الدم البيض.

الكلمات الدالة: الربو، القشرانيات السكرية.

Introduction

Asthma is one of the most chronic diseases which affects the respiratory system and constitutes worldwide health problem (Drosdzol *et al.*, 2007). Asthma affects most ages, but periods it is widely prevalence in advanced age periods more than early ages. Also, its prevalence is more in females than males. It is found that sex hormones exert principle role in this variations (Canguven and Albayrak, 2011)

Asthma is resulted from hypersensitivity of bronchial passages and bronchial obstructions. Hypersensitivity of bronchi is produced by many specific and nonspecific stimuli affect bronchial epithelium, and suggested that the genetic factors are implicated in the etiology of asthma (Osman, 2003). Cellular and non – cellular components are also implicated in the developing inflammatory process of asthma especially leukocytes (eosinophils and lymphocytes), and these cells become activated and infiltrated into bronchial epithelium by cytokines and chemical attractants (Diamant *et al.*, 1999, Bateman *et al.*, 2008).

Medical strategies to treat of asthma are achieved by many glucocorticoid drugs which administrated to patients through orally, inhalation, and parenteral routs. These medications act directly on their specific receptors located on respirapory passages. Glucocorticoids prevent inflammation processes which are mediated by inhibition of genes responsible for encoding of inflammatory proteins (Keresmar, *et al* 2008)

Materials and Methods

1- Subjects of the study

The present study involved 80 asthmatic patients (40 female and 40 males), and sub – divided into two groups: first group included asthmatic patients treated with glucocorticoids (20 females and 20 males). 30 healthy subjects (15 females and 15 males) were involved as control group. All ages of the subjects ranged between

30 – 60 years old. The blood samples were taken from asthmatic patients attending to Marjan teaching hospital and allergy center in Babylon province. All subjects of the study (patients and control) were free from other chronic diseases such as thyroid disorders, cardiovascular diseases, bone diseases and diabetes. The blood samples of women taken at follicular phase of menstrual cycle for determination of estradiol.

2- Determination of cortisol hormone, testosterone hormone, and estradiol hormone:- The level of these hormones measured by using kits supplied from Biomerieux company. VIDAS apparatus was used, and the principal of this method based on competition binding with specific enzyme. The samples were read at wave length 450nm.

3- Determination of total and differential white blood cells:-

These parameters were achieved by using coulter system (Beckman Coulter Diff 5, Franch). The results were recorded directly from this instrument.

4- Statistical analysis.

Factorial experiments with completely randomized design and least significant difference was used at a level $P < 0.05$ for showing results significant (Daniel, 1999).

Results

1- Result of cortisol, testosterone, estradiol hormones were illustrated in table 1 showed significant decrease in ($p < 0.01$) asthmatic patients of both sexes (group 1) treated with glucocorticoids therapy in a comparison with healthy group. As for, values of these hormones were insignificantly different in asthmatic patients (group 2) of both sexes when compared with healthy subjects.

2- Results of total white blood cells which are explained in table 2, pointed out a significant increase ($p<0.05$) in both groups of asthmatic patients (group 1 and 2) of both sexes in a comparison with control group.

3- Values of differential white blood cells (table 2) explained the following changes :- the first patient group (treated with glucocorticoids) had been showed significant increase ($p<0.05$) in the levels of monocytes, neutrophils, and insignificant increase in the levels of eosinophils and of lymphocytes in a comparison with control group. The second patients group (without glucocorticoids) pointed out a significant increase ($p<0.05$) in the levels of monocytes, eosinophils, neutrophils, and insignificant changes in the values of lymphocytes when compared with healthy control group.

Table (1): means of estradiol, testosterone and cortisol hormones in asthmatic patients with glucocorticoids therapy (first group) and without glucocorticoids therapy (second group).

Groups	Cortisol hormone (ng/ml) female	Cortisol hormone male (ng/mL)	testosterone hormone (ng/L)	Estradiol hormone (Pg/L)
Control subjects	8.09±178.76	7.39±191.99	0.33±5.5	9.37±129.07
First group	8.17±83.68**	6.40±86.50**	0.30±4.0**	8.35±80.0**
Second group	10.45±160.23	8.52±176.25	0.39±5.4	11.33±129.93
L.S.D _(0.05)	19.535	19.535	0.826	23.25

-Values are means±SE

Values with astriske(**) are significantly different at $p<0.01$

Table (2):- Means of total and differential white blood cells (WBCs) in asthmatic patients with glucocorticoids therapies (first group) and without glucocorticoids therapies (second group).

sex	group	WBCs (cell/mm ³)	Mono(%)	Lymph(%)	Neutro(%)	Eosino(%)	Baso(%)
male	Control	0.12±4.23	0.43±3.86	2.15±30.1	1.44±56.73	0.55±2.46	0.18±1.06
	First group	0.17±5.41*	0.45±8.93**	1.38±23.13*	1.53±68.13**	0.23±3.13*	0.18±0.93
	Second group	0.13±4.84*	0.46±7.53**	2.07±29.86	1.67±60.66*	0.28±6.66**	0.19±0.86
female	Control	0.13±4.52*	0.49±5.66	1.63±29.00	1.96±57.26	0.40±2.86	0.19±1.00
	First group	0.19±5.21*	0.59±7.80**	1.72±21.86*	2.00±63.40*	0.43±3.22*	0.18±1.06
	Second group	0.15±4.73*	0.53±7.06**	1.50±28.06	2.83±63.06*	0.28±5.93**	0.18±1.26
L.S.D _(0.05)		0.368	1.181	4.181	4.641	0.714	N.S

-values are means±SE

-Values with one astrisk (*) are significantly different at $p<0.05$

- Values with two astrisk (**) are significantly different at $p<0.01$

Discussion

Concerning results of cortisol hormone which are obtained from this study and illustrated in table 1 showed a significant decrease ($p < 0.01$) in the levels of cortisol in asthmatic patients treated with glucocorticoids therapies. Many previous studies indicated that cortisol and its synthetic derivatives exert negative feedback mechanism on anterior pituitary and hypothalamus causing inhibition of adrenocortical trophic hormone (ACTH) and lead to inhibition of cortisol secretion (Rao *et al.*, 1999; Guyton and Hall, 2006).

Study of Beyleroglu (2011) explained that cortisol is affected by many stressful factors such as muscular activities, temperature, psychogenic state, age, and high altitudes. Additionally, cortisol and (ACTH) have falls with aging and this decrease remains with normal range but tend to rise into peak levels during midnight (Ferrari *et al.*, 2001, Kudielka and Kirschbaum, 2003). Previous experimental studies indicated that dexamethasone therapy has inhibitory effects on hypothalamus – pituitary axis (HPA) and this inhibitory effects are more in young than aging humans (Raskin *et al.*, 1994; Seeman and Wasserman, 2005).

Also, it had been found that using of dexamethasone for five consecutive days led to inhibition of both (CRH and ACTH) (Rabin *et al.*, 1990). Previous study of Gagliardo *et al.*, (2001) indicated that glucocorticoids therapies bind with natural glucocorticoids receptors which in turn cause deactivation to genes encoding inflammatory factors. In this context, inhaled glucocorticoids such as Beclomethason propionate affect cortisol production (Rao *et al.*, 1999).

Result of sexual hormones (estradiol and testosterone) showed a significant decrease ($p < 0.01$) in the first asthmatic patients group (treated with glucocorticoids). The inhibitory effects of synthetic glucocorticoids on reproductive function of both sexes and their effects in delay of reproductive were explained by many researches. These studies suggested that glucocorticoids act to prevent binding of sex hormones with their specific receptors at target tissues (MacAdam *et al.*, 1987). Previous study established by Bernier *et al.*, (1984) involved propagated Leydig cells in special conditioning media and these media were treated with natural glucocorticoids (cortisol and cortisone) and synthetic glucocorticoids (dexamethasone, betamethasone, and triamcinolon), these therapies led to attenuate testosterone secretion by cultured Leydig cells.

Schaison *et al.* (1990) used dexamethasone of his experimental study and concluded that this drug caused inhibition of testosterone and androstendione secretion, but on the other hand, the levels of luteal hormone (LH) remained unchanged because of inhibitory effects of dexamethasone on Leydig responsiveness. It should be stressed that androgens and estrogens are involved in bone remodeling mechanism and are implicated in the incidence of osteoporosis and of infertility during course of glucocorticoids therapy (Howland and Mycek, 2004).

It had been found that glucocorticoids therapies have inhibition of uterine and thymus growth. These effects are mediated by decreasing cytoplasmic and nuclear receptors which have specialized affinity to estrogen hormone, moreover, these changes are unrelated with receptors specialized with progesterone hormone (Rabin *et al.*, 1990). Previous experimental study which involved injection of glucocorticoids led to inhibition of reproductive axis through decrease of follicle stimulating hormone (FSH) and luteal hormone (LH) and gonadotrophic releasing hormone (GnRH). These effects are mediated by blocking of estradiol receptors at target tissues or by inhibition of HPA (Douglas *et al.*, 1990).

Study of Almeida *et al.*(1998) showed decrease of sperm concentrations in semen of animals treated with glucocorticoids and concluded that these effects resulted from inhibitory effects glucocorticoids on Gn RH which in turn lead to decrease of testosterone and sex hormone binding globulin

Results of total and differential white blood cells (table 2) showed significant increase (p.0.05) of total white blood cells in two asthmatic patients group of both sexes. About differential white blood cells, results of first group showed significant increase of monocytes , neutrophils , and insignificant increase of eosinophils and of lymphocytes .

The second patients group showed a significant increase in the levels of monocytes, eosinophils and insignificant changes of lymphocytes when compared with healthy control group. Concerning results obtained from asthmatic patients (group 1). The study of Schleimer and Bochner(1994) indicated that leukocytes such as eosinophils, in particular , are affected with glucocorticoids therapy. These drugs mediate inhibitory effects of cytokines network engaged with differentiation and maturation of inflammatory cells. The inhibitory mechanisms originate from several interactions among signal transduction or among membrane receptors and of transcription of ribonucleic acid (RNA)

Previous experimental study included using of synthetic glucocorticoids (dexamethasone) indicated significant increase of total white blood cells and these data were attributed to inhibitory effects of glucocorticoids on diapediasis of leukocytes or inhibition of phagocytes activities . As a result of these effects , neutrophils in particular retained within blood circulation (Corrigan *et al.*, 1991). Additionally , many previous researches involved using glucocorticoids showed significant increase of total white blood cells. These changes are associated with inhibition of leukocytes attraction and retention of lymphocytes within lymphatics. Also it had been found that glucocorticoids have inhibitory effects on activities and ratios of eosinophils (Baxter and Forsham , *et al.*, 1972 ; Cronstein *et al.* ,1992). Lamas *et al.* ,(1991) showed that injection of dexamethasone lead to deactivate of cytokines involved in growth and development of eosinophils.

In fact , dexamethasone has principle role in suppression of T – lymphocytes proliferation . Phospholipase A2 is inhibitory protein and become active by using glucocorticoids therapy (Hirata *et al.* ,1990; Corrigan *et al.*, 1991) .About results of total and differential white blood cells (table 2) in second group explained significant increase of total white blood cells and increase of monocytes, eosinophils and neutrophils.Lymphocytes showed nonsignificant changes when compared with healthy control group. Zietkowsky *et al.*(2010) explained that the asthma is chronic inflammatory diseases of respiratory airways. White blood cells, in particularly eosinophils have essential roles in developing of own pathogenesis . The inflammatory processes have production of many cytokines , for example, Granulocyte – monocyte – colony stimulating factor (GMSF), eotoxin , interleukin – 3 , and interleukin – 5 . The sources of these cytokines are eosinophils and T – lymphocytes .Of these, eotoxin is a potent chemo attractant and has activities to prolong life span of inflammatory cells and recruited white blood progenitors in bone marrow. The cytokine (IL – 5)is produced by several cells of the body and responsible for release and maturation of eosinophils. In human , this cytokine has high selective affinity , in fact , its receptors located at basophils and eosinophils. Eosinophils are characteristic feature of allergic pulmonary inflammations and these disease treated with inhibition of IL – 5 (Greenfeder *et al.*,2001).Previous studies of Hirari *et al.*,(1990) indicated that the eosinophils originate from myeloid precursors as

a response of active cytokine (IL-5). In animals , experimental researches had been found that blocking of IL-5 by monoclonal – antibodies led to decrease of leukocytes particularly eosinophils within bronchi and alveoli (Mauser *et al.*, 1995) . It should be stressed , that free oxygen radicals and toxic proteins produced by eosinophil are implicated in damage respiratory epithelial cells , through destruction of cellular junctions of epithelium. In fact , it had been found there is infiltrations of inflammatory cells within airways and as a result of chemotactic activity (Gleich , 1990). Other studies established increase the number of inflammatory cells is directly proportionated with severity of asthma. In this context, eosinophils mediate to secret several inflammatory mediators as a response to several stimuli especially peptide – leukotriene C4 (Laviolette *et al.* ,1995).In fact , T – lymphocytes exert essential role involve coordination of immune response in asthmatic patients . This coordination process is mediated by secretion of several specific cytokines which inturn act to migrate of eosinophils, neutrophils , and mast cells into respiratory passages. In this context ,immunological researches involved broncho-alveolar lavage and bronchial asthma indicated that mast cells, lymphocytes and eosinophils constitute principal components to allergic inflammatory processes of asthma. Also these studies indicated increase neutrophils in a moderate and serve asthma. Simultaneously increase activity of T- lymphocytes and mast cells to produce IL3 , IL4 , IL5 , IL 10 , and GM – CSF (Spallarossa *et al.*, 1990 Montenseirin, 2002). Our conclusion suggested that glucocorticoids therapies may be act to exert inhibitory effects on HPA axis and reproduction as well as affects on maturation and diapediasis of leukocytes.

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