

## Evaluation of the Relation between Asthma, Obesity and Leptin Level in Iraqi Asthmatic Patients and the Main Risk Factors that are Associated with Leptin Level<sup>#</sup>

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### Abstract

This study tries to clear the correlation and association between asthma, obesity and leptin levels. Also it will work to indicate the main risk factors which play role in the elevation of leptin level within asthmatic patients. This is a case control study conducted on (38) asthmatic patients and (20) healthy control who were closely similar by age, gender and BMI. The main statistical tests used were student *t* test, linear regression test and correlation test. Significance was set at  $P < 0.05$ . Sampling method used for this study was convenience sampling method. The main results of this study show a significant association and positive correlation between age (old age  $\geq 40$  years old), female gender, BMI (overweight and obese) and steroid utilization with leptin elevation in Iraqi asthmatic patients since  $P$  values  $< 0.05$ . This study concludes that there is a correlation between obesity, age, sex and utilization of steroid with leptin level and they were the main risk factors which play role in the mechanism of elevation of leptin in Iraqi asthmatic patients.

**Key words:** Leptin, Asthma, BMI.

### الخلاصة

تهدف هذه الدراسة على إيجاد العلاقة بين الربو و السمنة و مستوى اللبتين و تحديد عوامل الخطورة الاساسيه التي تلعب دوراً في ارتفاع مستوى اللبتين عند المرضى المصابين بالربو . تشمل هذه الدراسة على (38) مريضاً مصاباً بالربو و (20) من الأشخاص الأصحاء المتقاربين بكل من العمر و الجنس و كتله الجسم. التحليل الإحصائي المستخدم في هذه الدراسة هو اختبار *t*. اختبار الارتداد الخطي و اختبار العلاقة. إذا كانت  $p < 0,05$  تعتبر الزيادة معنوية. طريقه جمع العينات كانت بواسطة طريقه الاختيار المريح. كانت النتائج الاساسيه لهذه الدراسة هي علاقة معنوية  $p < 0,05$  بين العمر (كبير من او يساوي 40), الإناث, كتله الجسم (الوزن الزائد و البدين) و استهلاك الستيرويد مع مستوى اللبتين عند المرضى العراقيين المصابين بالربو. تستنتج هذه الدراسة بان هناك علاقة بين السمنة, العمر, الجنس, استهلاك الستيرويد و زيادة مستوى اللبتين عند المرضى المصابين بالربو و تعتبر من عوامل الخطورة الاساسيه التي تلعب دوراً في ميكانيزميه زيادة هرمون اللبتين عند المرضى العراقيين المصابين بالربو.

### Introduction

Leptin is a 16 kDa (kilo dalton) nonglycosylated circulating hormone, secreted mainly by the adipose tissue and its mRNA is mostly synthesized in mature adipocytes, although it is also found in other tissues<sup>(1)</sup>. It's major function is the regulation of fat mass by decreasing food intake (it decreases the content of neuropeptide Y at the hypothalamus) and increasing resting energy expenditure<sup>(2)</sup>. Therefore it is often considered as an anti-obesity hormone, though its primary function seems to be mediating adaptation to fasting<sup>(1)</sup>. There is scientific evidence showing that leptin is involved in the initiation of puberty, pregnancy, breast-feeding, immune system regulation, inflammatory processes, respiratory function, sex hormones, growth hormone, and thyroid hormones, in addition to bone tissue metabolism, septic processes, hematopoiesis, cachexia, and others<sup>(3-5)</sup>. In case of asthma leptin exerts its action through the leptin receptor (Ob-R) by activating both

phosphatidylinositol-3-OH kinase and mitogen-activated protein kinase signaling pathways. So leptin function as a regulatory link between the endocrine and immune systems and might represent a bridge between inflammation and tissue repair. It also contributes to regulation of the maturation of fetal lung cells and to homeostasis of the endothelium<sup>(6-8)</sup>. Leptin is increased during allergic reactions in the airways and might play a role in the relationship between obesity and asthma<sup>(9)</sup>. The specific role of the leptin/leptin receptor pathway in the bronchial epithelium from asthmatic patients is still largely unexplored<sup>(6)</sup>. In obese asthmatic patients, there is increasing evidence for an important role played by the epithelium in orchestrating the inflammatory responses and in producing a chronic wound scenario involving tissue injury and aberrant repair leading to airway remodeling<sup>(6)</sup>.

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Airway remodeling has been related to the severity of asthma, and consistently, major tissue changes have been observed in patients with asthma<sup>(10)</sup>. Asthma and obesity are both important current public health problems; but the underlying mechanisms have not yet been established<sup>(11)</sup>. For these reasons this presented study tries to clear the relation between asthma, obesity and leptin levels. Also it will work to indicate the main risk factors which play a role in the elevation of leptin level within asthmatic patients.

## Materials and Methods

### Subjects

This is a case control study conducted on (38) asthmatic patients and 20 healthy control who were closely similar by age, gender and BMI but the only difference that the control were not suffering from asthma. Those asthmatic patients were admitted to AL-KHADHIMEIA Teaching Hospital and AL-YARMOOK Teaching Hospital between 23<sup>th</sup> November 2010 to 30<sup>th</sup> December 2010. Clinical data that related with patients age, gender, BMI and waist to hip ratio were collected from patients' files by specific data sheet form designed for this study.

### Methods

Blood samples were drawn between 9:00 AM and 12:00 PM. All specimens were centrifuged at 4000 rpm within 2 hour of collection and serum stored at -20°C until analysis. After preparation of serum, the levels of leptin were measured with (ELIZA) method using DRG (DRG Instruments GmbH\ GERMANY) kit. All of the patients who were involved in this study fulfilled the inclusion criteria. The inclusion criteria include adult asthmatic patient  $\geq 18$  years old, male or female and were admitted for treatment of asthma. The exclusion criteria include smokers, alcoholism and chronic obstructive pulmonary disease (COPD). The following anthropometric measurements were obtained: weight, height, BMI (body mass index), and waist and hip circumferences. Weight was measured after calibration the scale before each weight measurement. Height was obtained with an aluminum cursor stadiometer graduated in millimeters. The subject was barefoot, with heels, back, and head in contact with the stadiometer in horizontal plane. Body mass index (BMI) had been estimated from person's weight & height, it was calculated by dividing weight (in kilograms) by height (in square meters).

BMI $\leq$ 18.5 (Underweight)

BMI=18.5-24.9(Normal weight)

BMI=25-29.9(Over weight)

BMI $\geq$  30(Obese)<sup>(12)</sup>

Waist and hip circumferences (WC and HC, respectively) were measured with a tape measure to the nearest 0.5 cm. The waist-to-hip ratio (WHR) was calculated by dividing waist measurement (in centimeters) by hip measurement (in centimeters). The cutoff points of risk for WHR were  $\geq 0.8$  for women and  $\geq 1.0$  for men; WC cut-off points were  $\geq 102$  cm for men and  $\geq 88$  cm for women<sup>(3)</sup>.

### Statistical analysis

Since the type of data collected were continues type, therefore the statistical tests used were Linear Correlation test and linear regression test the main reasons for selecting these two tests are the data were normally distributed and this linear correlation test will help us to detect the type of correlation depending on (*r*) (*r* value range +1 to -1) whether it is positive or negative correlation but these results will mean nothing only when *P* value  $< 0.05$  (significant result). While Student *t*-test was used to find if there is a differences between the measured leptin values and the control values, significance was set at *P*  $< 0.05$ . Sampling method used for this study was convenience sampling method which is a type of non probability sampling which involves the sample being drawn from that part of the population which is close to hand. That is, a sample population selected because it is readily available, convenient and within inclusion criteria. It may be through meeting the person<sup>(13)</sup>. The results were expressed as mean  $\pm$  standard deviations (SDs).

## Results

Clinical characteristics of asthmatic patients are summarized in Table 1. The mean values for age, weight, height, WHR and BMI did not show any difference between the groups of asthmatic patients and healthy control since all *P* values  $> 0.05$ . Leptin level for the total asthmatic patients is significantly higher than the healthy control, also leptin level for female asthmatic patients is significantly higher than healthy control since *P*  $< 0.05$ . But leptin for male asthmatic patients show no significant differences than control one. We notice also leptin level for female higher than for male. While in Table 2 the results show that the leptin level in postmenopausal asthmatic women is significantly higher than that which was found in premenopausal asthmatic women since (*P* =0.041). Risk factors that are associated with elevation of leptin levels in asthmatic patients will be shown in the Table 3. According to the results which are shown in Table 3 gender, age, BMI and cortisone

treatment are the main risk factors that play a role in increasing leptin level in asthmatic patients. Also as shown in the results the female gender is highly associated and correlated with increases in leptin level than male gender, the age above or equal to 40 years is strongly associated and correlated with elevation of leptin within asthmatic patients. While in case of BMI according to the results, obesity is highly correlated and associated with elevation of leptin level in asthmatic patients followed by overweight. Normal weight and underweight both show a very weak

correlation with leptin level. According to linear regression test, steroids treatment (prednisolone or dexamethasone) which have been received by 34 asthmatic patients and only 4 asthmatic patients did not receive it show a significant and strong positive correlation with elevation of leptin level among asthmatic patients. So according to the results of this study it had been shown that obesity and receiving cortisone treatments are the two parameters highly associated and play a role with elevation of leptin level among Iraqi asthmatic patients.

**Table1: Asthmatic Patients and Healthy Control Variables**

Variables	Asthmatic	Control	P value*
Demographic data			
n	38	20	
Gender, female/male	22/12	10/10	
Utilization of steroid, yes/no	34/4	-	
Age (years)	52.7±14.4	50.4±12.7	0.274
Weight (kg)	75.94± 21.53	73.7±19.83	0.649
High (cm)	158.92±9.78	159.77±9.48	0.359
Waist (WC) (cm)	107.29±19.74	106.73±17.45	0.802
Waist-Hip ratio (WHR)	0.97±0.14	0.95±0.13	0.074
BMI (kg/ m <sup>2</sup> )	30.48±8.89	28.79±6.92	0.182
Leptin total (ng/ml)	40.52±25.49	27.33±7.20	0.031
Female (ng/ml)	48.18±24.80	27.93±6.64	0.037
Male (ng/ml)	24.10±11.34	22.46±6.41	0.083

\*Student *t* test is used.

**Table2: Difference Between Leptin Level of Post menopausal Women With Pre menopausal**

Variables of Asthmatic Patients	n	Leptin Level	P value*
Leptin Menopausal status			
post menopausal status	15	47.29±13.09	0.041
pre menopausal status	7	29.73±17.52	

\*Student *t* test is used.

**Table3: Association and Correlation of Asthmatic Patients Variables With Leptin Levels**

Variables of Asthmatic Patients	P value*		Correlation (r)
Gender	0.044	Female (P = 0.001) Male (P= 0.117)	2.015 0.873
Age (years)	0.029	≥ 40 (P= 0.031) < 40 (P= 0.573)	1.127 0.941
BMI	0.001	Underweight (p= 0.114) Normal (p= 0.281) Overweight (p= 0.006) Obesity (p= 0.000)	0.116 0.629 1.924 3.052
Utilization of Steroid	0.000		3.004

\*Linear regression test

## Discussion

The aim of this study was to investigate serum leptin levels and its relationship with the main risk factors which play role in its elevation within Iraqi asthmatic patients. The results of student *t*-test show that there is a significant increase in leptin level among asthmatic patients than healthy control. Also serum leptin levels of asthmatic patients and especially of asthmatic female were higher than those of healthy controls in spite of no difference in age, weight, high, waist-hip ratio and BMI levels. The lack of difference in leptin levels between asthmatic and healthy males could be a result either of a true modifying effect of sex on leptin or a small sample size to detect a difference<sup>(14)</sup>. The results also show that leptin level in female is higher than in male. This can be explained by the effect of sex hormones on leptin expression, as testosterone can inhibit and ovarian sex steroids can increase the expression of leptin<sup>(11,15)</sup>. Serum leptin levels are relatively low in prepubertal ages, showing a gradual rise in both sexes before the onset of puberty, followed by a significant increase during puberty in girls and a decrease in boys<sup>(16,17)</sup>. This finding was in agreement with previous observations for higher serum leptin concentration in women than in men<sup>(15)</sup>. Also according to the results of our study it had been shown that the leptin level among postmenopausal women is higher than that found in premenopausal women, the reason may be due to that in postmenopausal woman who already obese the incidence of asthma attack is higher than the non obese woman because the concentration of storage endogenous estrogen in obese woman is higher than non obese one and this is what leads to high incidence of asthma attack. So both factors postmenopausal and obesity are the main two factors which play role with incidence of asthma attack<sup>(18)</sup>. This result was in agreement with this mentioned by Sood *et al*<sup>(15)</sup> for higher serum leptin concentrations association with current asthma in women and this association may be stronger in postmenopausal women. Findings of our study revealed that the age play role in the elevation of leptin level since it shows a significant association ( $P < 0.05$ ). The explanation for that in aging people there are several factors that will start to increase too like immunological factors and leptin that presuppose to hyperleptinemia. But the age factor will play a risk role within leptin level elevation when the patients are overweight women therefore age alone as an isolated factor is not so risky factor without BMI and gender<sup>(15)</sup>. These findings

are similar to those reported in other studies, which showed an increase of leptin with aging<sup>(19, 20)</sup> and an inverse to those found in other literatures which showed decrease of plasma leptin with aging<sup>(21)</sup>. Also our results show that BMI specifically obese and overweight is a strong risk factor which plays a role in the elevation of leptin level among asthmatic patients. This point also was mentioned by Mai and his colleague<sup>(11)</sup> that BMI (overweight or obese) is one of the main risk factor which play a role in the elevation of leptin level within asthmatic patients<sup>(6)</sup>. Also Sood and his colleague<sup>(15)</sup> indicated a high association of BMI in females than males because of high production of hormones in female than in male which lead to this point<sup>(9)</sup>. Moreover BMI and gender (specifically old women) considered as a main risk factors for elevation of leptin among asthmatic patients<sup>(3)</sup>. Since these two points i.e., BMI and gender (old women) are already found in our study so this can explain the strong association between BMI factor and leptin level. These observations have led some to conclude that leptin may be important in explaining the link between obesity and asthma, particularly in women. Our results is clear that utilization of steroids which had been used by the asthmatic patients also is considered as a one of the risk factor that play a role in the elevation of leptin level. Since the use of steroid by asthmatic patients is considered as one of the main factors which play a role in the elevation of leptin level<sup>(11)</sup>. The main explanation for this is that the use of dexamethasone by patients suffering from problems with their pulmonary system will leads to elevation of leptin level. The cortisone treatment will mainly effects on adipoinular and hypothalamic-pituitary-adrenal (HPA) axis in preterm in those patients. This adipoinular mainly responsible for regulation of energy and activity and since leptin is responsible for such things so this will leads to increases in leptin level. So administrated steroid will lead to elevation in leptin level through its' direct effect on adipoinular<sup>(22)</sup>. It has been assessed that synthetic dexamethasone stimulates both leptin synthesis in preadipocytes and adipocytes and increases leptin secretion and leptin receptor mRNA expression in choriocarcinoma cells<sup>(6, 23)</sup>.

## Conclusion

The results of our study suggest that asthma and obesity have a strong relation to leptin level. The risk factors which play a role in elevation of leptin level in Iraqi asthmatic patients are gender, age, BMI and utilization of steroids. To be more accurate [old women x

BMI (overweight or obese) x utilization of steroid] were considered as the main risk factors which cause elevation of leptin level within Iraqi asthmatic patients. Also our study proves that leptin level among post menopausal women is significantly higher than that of pre menopausal ones. Therefore these results clear the main factors that will cause the elevation of leptin within asthmatic patients and the relation between asthma, obesity and leptin. So this can help the Iraqi physicians and clinicians how leptin can play role within incidence and increases of asthma severity, and also it clear that the detection of leptin level is very important in order to control its level. In order to reduce or prevent the incidence of asthma attack.

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