

The relationship between leptin and testosterone in infertile men

Wisam Suhail Najem*, Abdulla Aqeel A. Al-tayar**, Sajeda Saed Al-Chalaby***

Department of Medicine*, Physiology **, College of Medicine, Tikrit University, Iraq
***Departments Of Physiology, Medicine, College of Medicine, University of Mosul, Mosul, Iraq

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Abstract

The corresponding decrease in men fertility and fecundity may be explained in parallel to obesity, and obesity may be considered as an etiology of male infertility. Leptin, the adipocyte-derived hormone that plays a key role in body weight homeostasis, has recently emerged as a relevant neuroendocrine mediator in different systems, including the reproductive axis. A case-control study was carried out to examine the relationships between leptin and testosterone hormone in males. Eighty men their ages between 20 and 45 years; fertile normozoospermia as a control (n = 28) and infertile oligozoospermia (n = 52); were recruited in the study. There was a highly significant negative correlation between testosterone and leptin. This result is suggestive of a link between the adipocyte derived hormone, leptin and male reproduction. This study showed that obesity may represent an actual threat to male fertility causing a decrease of total testosterone with hyperleptinaemia.

العلاقة بين هرمون اللبتين و هرمون التستسترون في الرجال العقيمين

وسام سهيل نجم عبد الله عقيل علي ساجدة سعيد الجلي

الملخص

الزيادة المترابطة في عقم الرجال قد تفسر مع وجود السمنة ، وتعتبر السمنة كسبب مهم لعقم في الرجال . هرمون اللبتين هو هرمون يتكون من الخلايا الدهنية و التي تعمل بدور مهم في وزن الجسم . هرمون اللبتين وجد حديثا له دور اساسي كوسيط عصبي هرموني في مختلف أجهزة الجسم و منها الجهاز التكاثري الذكري . أجريت هذه الدراسة المقطعية لدراسة العلاقة بين هرمون اللبتين و هرمون التستسترون في الرجال . ثمانون رجل اشتركوا في الدراسة الحالية ، بأعمار تتراوح بين 20 الى 45 سنة: 28 من الرجال الخصيين كمجموعة سيطرة و 52 شخص من الرجال العقيمين تطوعوا في هذه الدراسة . هنالك علاقة معنوية عالية بين هرمون التستسترون و هرمون اللبتين . و الدراسة الحالية تقترح وجود علاقة و ارتباط بين هرمون اللبتين و وظيفة الجهاز التناسلي الذكري . هذه الدراسة بينت بان الرجال ذو السمنة المفرطة اكثر عرضة للعقم و فرط تركيز هرمون اللبتين.

Introduction

‘Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year’.⁽¹⁾ Obesity is the accumulation of excessive body fat negatively affecting health. Obesity is a chronic pathological condition and a risk factor for diabetes and cardiovascular disease.⁽²⁾ Obesity is associated with several metabolic disorders and its contribution to infertility in women has been studied for many years. Much less understood is whether obesity in male produces metabolic and hormonal changes that undermine their fertility, some evidence had suggested a link.⁽³⁾ Testosterone is formed by the interstitial cells of Leydig, which lie in the interstices between the seminiferous tubules and constitute about 20 per cent of the mass of the adult testes. Leydig cells are almost nonexistent in the testes during childhood when the testes secrete almost no testosterone, but they *are* numerous in the newborn male infant for the first few months of life and in the adult male any time after puberty; at both these times the testes secrete large quantities of testosterone.⁽⁴⁾ Leptin, a 16-kD adipocyte-derived cytokine, is synthesized and released from fat cells in response to changes in body fat. Leptin circulates in blood and acts on the brain to regulate food intake and energy expenditure. When fat mass decreases, plasma leptin concentrations decrease, which stimulates appetite and suppresses energy expenditure until fat mass is restored. When fat mass increases, leptin concentrations increase, which suppresses appetite until weight is lost. This system maintains homeostatic control of adipose tissue mass.⁽⁵⁾ The interaction between obesity and

fertility has received increased attention owing to the rapid increase in the prevalence of obesity in the developed world.⁽⁶⁾ Leptin seems to signal metabolic information to the reproductive system, as leptin treatment results in earlier onset of puberty in normal female mice and prompt return of fertility in congenitally infertile female ob/ob mice.⁽⁷⁾ *Isidori et al., 1999*⁽⁸⁾ investigated the relationship linking leptin and androgens in men. Their studies, indicate that excess of circulating leptin may be an important contributor to the development of reduced androgens in male obesity.⁽⁸⁾ *Luukkaa et al., 1998*⁽⁷⁾ studied the serum leptin concentrations in 269 elderly non diabetic men. They found that the serum leptin concentration correlated inversely with that of testosterone in elderly men.⁽⁷⁾ *Behre et al., 2003*⁽⁹⁾ demonstrated a close association between serum levels of testosterone and leptin in a total of 58 adult age-matched males in their cross-sectional analysis.⁽⁹⁾ Leptin levels were found to be linked with normal functioning in the reproductive system. Leptin receptors are present in testicular tissue and the discovery of leptin in semen has established a link between this protein hormone and male reproductive function.⁽¹⁰⁾ The aim of the present study was to determine the relationship between leptin hormone and testosterone level in infertile men

Patients, materials and methods

Eighty males, their age range from 20- 45 years, were recruited from infertility clinic in the Al-Batool Teaching Hospital in Mosul from

February 2011 to June 2011. They were grouped into normozoospermic fertile men (n =28) and infertile men (n = 52). Subjects completed a questionnaire including information about demographics, health and paternity status and life-style factors. Exclusion criteria were Venereal diseases, mumps, D.M, orchitis, alcohol consumption, DXT, genital tract infections, associated varicocele, chronic medical illness (cerebrovascular, hypertension, hereditary hyperlipidemia, and thromboembolic events), cryptorchidism, trauma and tumors. Each subject was investigated by measurement of serum Testosterone and Leptin. Subjects were invited to a quiet room. Using disposable syringes, blood sample of 5 ml in volume was obtained by antecubital venipuncture in the morning at 9.00 – 12.00 am. After centrifugation, serum samples were immediately stored at -20C° until later analysis. Thawing of the samples was allowed to take place at 40C° before conducting the assay. All the assay tubes were arranged and labeled in the assay racks. Serum total Testosterone was estimated by miniVIDAS™ (The Compact Automated Immunoanalyzer) using bioMérieux Testosterone 30418 kit. The serum was stored at -20C° and measured later by the enzyme linked immunesorbent assay (ELISA) method. Using ® Leptin (Sandwich) ELISA (EIA-2395) kit. The data obtained in the current study was analyzed by statistical analysis

system 2003 which was formerly called SAS.

1. Standard statistical methods were used to determine the mean, standard deviation and standard error.
2. Student's unpaired t test was used to compare the results of various parameters between control group and patient group.
3. Linear regression analysis [Pearson correlation coefficient (r)] was performed in the total patient group to identify the relationship between leptin and testosterone levels.
4. $p \leq 0.05$ was considered statistical significant limit in the current study.

Results

Table (1) shows that the age of patient was not significantly different in comparison with the control group ($p=0.37$). The testosterone level of patient was significantly lower in comparison with the control group ($p<0.0001$). The leptin level of patients was significantly higher in comparison with the control group ($p<0.0001$). Figure (1) shows the degree of correlation between Testosterone and leptin level in patients. r- value indicate a highly significant negative correlation between these two parameters. ($p= 0.0016$)

Table (1):- The mean & SE of testosterone & leptin of infertile patients & controls

Parameters	Control n=28	Patients n=53	P value
Age (years)	31.29 ± 1.37	31.85 ± 0.86	NS
Testosterone	5.67 ± 0.277	4.111 ± 0.240	0.001
Leptin	6.918 ± 0.609	15.262 ± 1.406	0.001

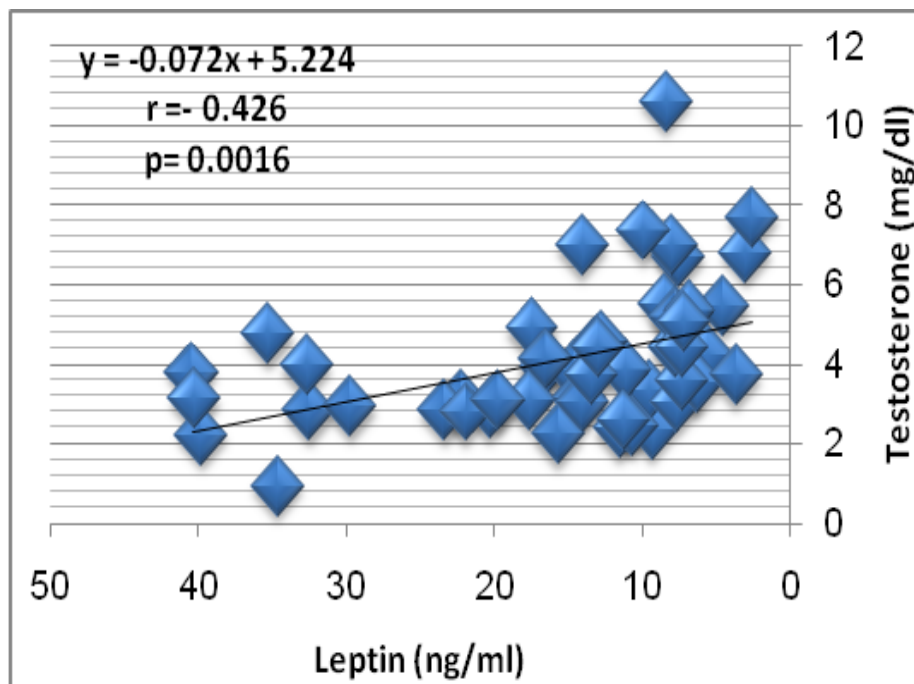


Figure (1):- The Pearson correlation between Leptin and testosterone level in infertile men.

Discussion

The present study showed a highly significant negative correlation between these two parameters ($p=0.0016$) as shown in (Figure 1). The result of this study agrees with Hanafy *et al.* 2007⁽¹¹⁾ who measured the serum leptin concentrations in 80 men (fertile normozoospermia as a control ($n = 30$) and infertile oligozoospermia ($n = 50$)). and studied its relationship with testosterone. They found that the serum leptin concentration correlated inversely with that of testosterone. Moreover, this result agrees with the result obtained by Isidori *et al.*, 1999⁽⁸⁾ who investigated the relationship linking leptin and androgens in men. This study showed that circulating leptin and fat mass (FM) were inversely related with total testosterone and free testosterone and concluded that excess circulating leptin may be an important contributor to the development of reduced androgens in male obesity. However, there is consistent enthusiasm in the literature, with considerable circumstantial support, for the hypothesis that alterations of sperm parameters associated with obesity can be attributed to inappropriate suppression of the hypothalamic-pituitary-gonadal axis by elevated estrogens derived from peripheral aromatization, and resulting decreased testosterone production reflected in low levels of circulating testosterone and intratesticular testosterone.⁽¹²⁾ The testosterone level was significantly decreased as leptin level increased. The result of this study agrees with Madah *et al.*, 2001⁽¹³⁾ who investigated the relationship of sex hormones, leptin and anthropometric indices in 186 adult

men and effect of average weight loss on these variances in obese individuals. Serum leptin levels were negatively related to serum level of testosterone. In multiple regression analysis serum leptin levels were the only determinant of serum testosterone, while leptin variations were explained both by leptin and testosterone. They Concluded that elevated serum leptin and low testosterone and SHBG levels were associated with high BMI in men. An inverse relation between serum leptin and testosterone shows the role of leptin in reducing serum testosterone in obese men.⁽¹³⁾ Also, leptin possibly has a direct inhibitory effect on testosterone production by binding to Leydig cells.⁽¹⁴⁾ It has been observed in obese men that the peripheral leptin receptors in the testis are directly exposed to high-leptin concentrations with possible negative effects on gonadal functions.⁽¹⁵⁾ Soyupek *et al.* 2005⁽¹⁶⁾ suggested that the effect of leptin on reproductive functions originates from a systemic effect related to central neuroendocrine system, androgen levels or spermatogenic existence rather than its direct effect on testicular tissue. Recently, Ishikawa *et al.* 2007⁽¹⁴⁾ showed that the dysfunction of spermatogenesis is associated with an increase in leptin and leptin receptor expression in the testis. It is now likely that, at least in males, communication between the hypothalamic-pituitary-gonadal axis and adipose tissue represents a complete, bidirectional feedback loop.⁽¹⁷⁾ In conclusion, the data of our study indicate that leptin is signal linking excess of adipose tissue to altered steroidogenic function of the testis. These studies

complement and add significant information to the knowledge of the interaction between leptin and male reproductive function whereas leptin excess as a result of obesity seem to have deleterious effects on the target steroidogenic cell. The testosterone level was significantly decreased as leptin level increased in infertile men. The present study recommend that the increasing prevalence of obesity and apparent simultaneous decrease in male reproductive potential calls for greater clinician awareness of the effects of obesity on fertility, better understanding of underlying mechanisms, and implementation of effective avenues of treatment.

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