

Relation of Serum Leptin with sex Hormones of obese Infertile Men and Women

Reshma Farooq¹, Sualiha Lutf Ullah² & Humera Ishaq^{3*}

¹University of King Abdul Aziz Hospital Al-Ahsa, Saudia

²Dr. HMI Institute of Pharmacology and Herbal Sciences, Hamdard University, Pakistan

³Faculty of Pharmacy, Hamdard University, Karachi, Pakistan

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ABSTRACT

The present study was designed to evaluate the relationship between serum leptin and sex hormones in obese infertile men and women. Sex hormones (LH, FSH and testosterone) and serum leptin of infertile obese men (n=66) and women (n=30) compared with control fertile men (n=60) and women (n=30) with same ages to find the relation and contribution of serum leptin and sex hormones in causation of fertility or infertility. The results revealed that Serum leptin level in obese (BMI>24) fertile and infertile male and female were significantly (p<0.01) higher than normal (BMI<24) fertile male but in infertile normal subjects it was significantly decreased. Values of LH, FSH and Testosterone were significantly (p<0.01) higher in obese (BMI<24) fertile and infertile men and women than normal (BMI<24) subjects. Serum leptin has strong negative correlation with LH, FSH and testosterone in fertile obese and normal male and female which were statistically significant at the level of p<0.05. This study has concluded that hyperleptinemia is associated with infertility in men and women. Sex hormonal imbalance may also be associated with BMI and serum leptin in infertility.

INTRODUCTION

Leptin is the protein released from the white adipose tissue and its blood level depends on fat stores as a regulator of food intake and energy expenditure (Priour *et al.*, 2008). The role of serum leptin in the maintenance of body weight, associated with several other regulatory functions in endocrine systems including the hypothalamo-pituitary gonadal axis is well documented. Recent works show that leptin is also involved in reproduction and responsible for the fertility of the humans and animals. Genetically studies illustrated that in *ob/ob* mice, treatment with leptin initiates fertility (Chehab *et al.*, 1996). In wild-type mice, leptin triggers the time of puberty (Ahima *et al.*, 1997). Administrations of leptin to food-deprived animals cause the drop of LH and FSH levels normally observed during starvation (Ahima *et al.*, 1996). Leptin has been shown to act both at the hypothalamic and pituitary levels to stimulate reproductive hormones, LHRH as well as LH and FSH

secretion (Yu *et al.*, 1997). In cross-sectional studies, it was observed that in healthy boys and girls, before and during puberty, the percentage of body fat rises resulting in an elevation of serum leptin levels and in FSH and LH as well as estradiol in girls (Blum *et al.*, 1997; Garcia-Mayor *et al.*, 1997). It has been suggested that there is a leptin threshold level for menarche (Matkovic *et al.*, 1997), and it has been hypothesized that the elevated leptin in early puberty might be a critical event for further pubertal development in boys (Garcia-Mayor *et al.*, 1997; Mantzoros *et al.*, 1997). In postmenstrual women, a critical leptin level is seemingly a prerequisite for menstruation (Laughlin and Yen, 1997; Tataranni *et al.*, 1997; Ko'pp *et al.*, 1997). Studies in female adolescents with eating disorders or under weights showed that low leptin levels predicted amenorrhea (Ko'pp *et al.*, 1997). In a recent study, female adolescents with secondary amenorrhea due to acute anorexia nervosa were followed up during weight gain. It was found that higher level of LH generally tracked the elevation of leptin level. There was a critical serum leptin level of 1.85 mg/L below which LH levels were insufficient to trigger menstruation (Ballauff *et al.*, 1999).

* Corresponding Author

Dr. Humera Ishaq

Assistant Professor, Faculty of Pharmacy, Hamdard University, Karachi

Tel: 092-021-6440214, 092-021-6440142. Fax: 092-021-6440171.

e-mail: h_73ishaq@yahoo.com

The discovery that human spermatozoa secrete leptin, the presence of both leptin receptors on human spermatozoa and soluble leptin receptors in the seminal plasma has opened a field of study in reproductive biology (Jope *et al.*, 2003; Aquila, *et al.*, 2005). Jensen *et al.* (2004) and Tena-Sempere *et al.*, (1999) showed that, among overweight men, 24.4% had a total sperm count of <20 millions/ml compared with 21.7% among men with normal weight. Tena-Sempere *et al.* (1999) suggested that effect of leptin on fertility may involve alterations in intracellular metabolism or its fuels at extra hypothalamic sites. In addition, Soyupek *et al.* (2005) suggested leptin's impact on the gonadal function in two pathways, indirectly by the central neuroendocrine system and directly through the peripheral tissue membrane receptors.

The suggestion that leptin plays a crucial role in pubertal development and that there is a critical level being necessary for onset of puberty, the regulatory system describes that a causal relationship between leptin and pubertal development is not always demonstrable. Some of the patients with congenital or acquired generalized lipodystrophy became infertile and delayed maturation, whereas others have normal pubertal development and are fertile showing that the very low leptin levels in these patients do not inhibit puberty and fertility (Seip and Trygstad, 1996; Garg 2000).

This study aimed to determine the changes in gonadotropic and sex hormones, and serum leptin in obese fertile and infertile men and women. We also hypothesize that leptin levels predict the function of the hypothalamic-pituitary-gonadal axis in male and female.

MATERIALS AND METHODS

Subjects

Male and female patients of infertility were taken from private hospitals of Karachi Pakistan. Written consent was obtained from all subjects included in this study irrespective of cause of infertility.

Protocol

It was a case control study, in which a group of infertile females and males with the age of 25-50 years were compared with a control group of fertile with same sex and age to find out the contribution of serum leptin level in causation of fertility.

Groups

First men and women were divided in to two groups viz. fertile and infertile which were further categorized in to two each groups on the basis of BMI, normal (BMI <24.0) and overweight or obese (BMI >24).

Method

Serum was obtained randomly from blood samples of these groups. LH, FSH and testosterone were quantitatively determined by EIA kits (Amgenix International. Inc, USA), while leptin levels were measured by DSL-10-23100 Active human leptin

ELISA kit (diagnostic system laboratory Inc; Webster, Texas, USA). Body mass index (BMI) of all subjects was calculated as weight in kg/height in m².

Statistical analysis

Data was analyzed on computer software statistical product selective solution (SPSS-17) version-17. Mean leptin values, BMI values among infertile and fertile were analyzed by paired t-test. $P \leq 0.05$ was taken as statistically significant. Correlation coefficient was calculated between serum leptin and LH, FSH and testosterone. Level of significance determined by paired tailed t- test. $P \leq 0.05$ was taken as statistically significant correlation.

RESULTS

Changes in serum leptin and values of correlation with sex hormones in fertile and infertile men and women are shown in figure 1, 2 and 3.

Serum leptin level in obese fertile (14.04±2.1ng/ml) and infertile (14.7±1.45ng/ml) male were significantly ($p < 0.01$) higher than normal (BMI <24) fertile (5.16±1.2ng/ml) male but in infertile normal (2.67± 0.87ng/ml) male it was significantly decreased. Similarly in female serum leptin concentration in obese fertile (20.4± 0.9ng/ml) and infertile (22.8± 1.9ng/ml) were significantly ($p < 0.01$) more than normal fertile women (16.5± 0.87ng/ml) but significantly lesser in normal infertile female (13.4± 0.85ng/ml).

Values of LH were higher in female than male. It was significantly ($p < 0.01$) decreased in obese fertile and infertile and also in infertile normal men and women. Values of LH in obese fertile and infertile men and women were 6.21±1.77ng/ml, 4.52±0.4 mIU/ml, 7.9±0.4 mIU/ml and 4.6± 0.54 mIU/ml. While in normal fertile and infertile males and females values were 7.26±0.97, mIU/ml 5.95±2.03 mIU/ml, 9.2±0.97 mIU/ml and 5.6± 0.54 mIU/ml.

Like LH, Follicle stimulating hormone (FSH) also decreased significantly ($p < 0.01$) in infertile obese, and normal males and females. In normal fertile and infertile males and females' values were 4.52± 1.0mIU/ml, 3.76± 0.9mIU/ml, 5.5±1.77mIU/ml and 2.1±1.5mIU/ml. But Values of FSH in obese fertile and infertile men and women were 4.3± 0.54mIU/ml, 3.76± 0.9mIU/ml, 4.85±0.7mIU/ml and 1.85±1.4mIU/ml.

Testosterone was significantly ($p < 0.01$) increased in fertile normal and obese males and females but decreased in infertile normal and obese men and women. Values were 2.85± 0.3ng/ml, 2.85± 0.3ng/ml, 2.1±0.8ng/ml and 1.2±0.1ng/ml in fertile normal and obese males and females while in infertile normal and obese men and women, it was 6.76± 0.9 ng/ml, 3.89± 0.52 ng/ml, 3.0±0.07 ng/ml and 0.21±0.04ng/ml

Figure 2 shows that serum leptin has strong positive correlation with LH, FSH and negative with testosterone in fertile obese and normal male and female which were statistically significant at the level of $p < 0.05$. While in infertile normal male and females values were statistically insignificant.

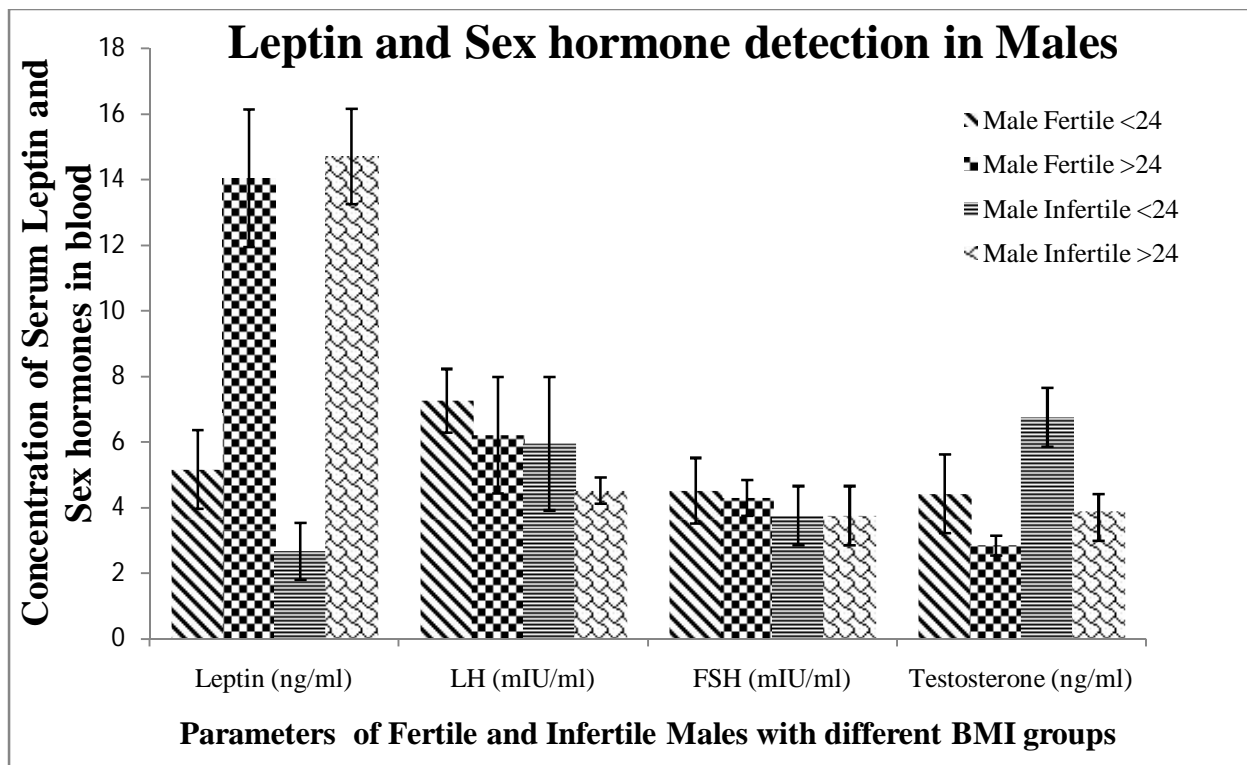


Fig. 1: Changes of Serum levels of Leptin, Testosterone and Gonadotropins in Fertile and infertile men related to BMI. Results are expressed in Average \pm sem $P < 0.05$.

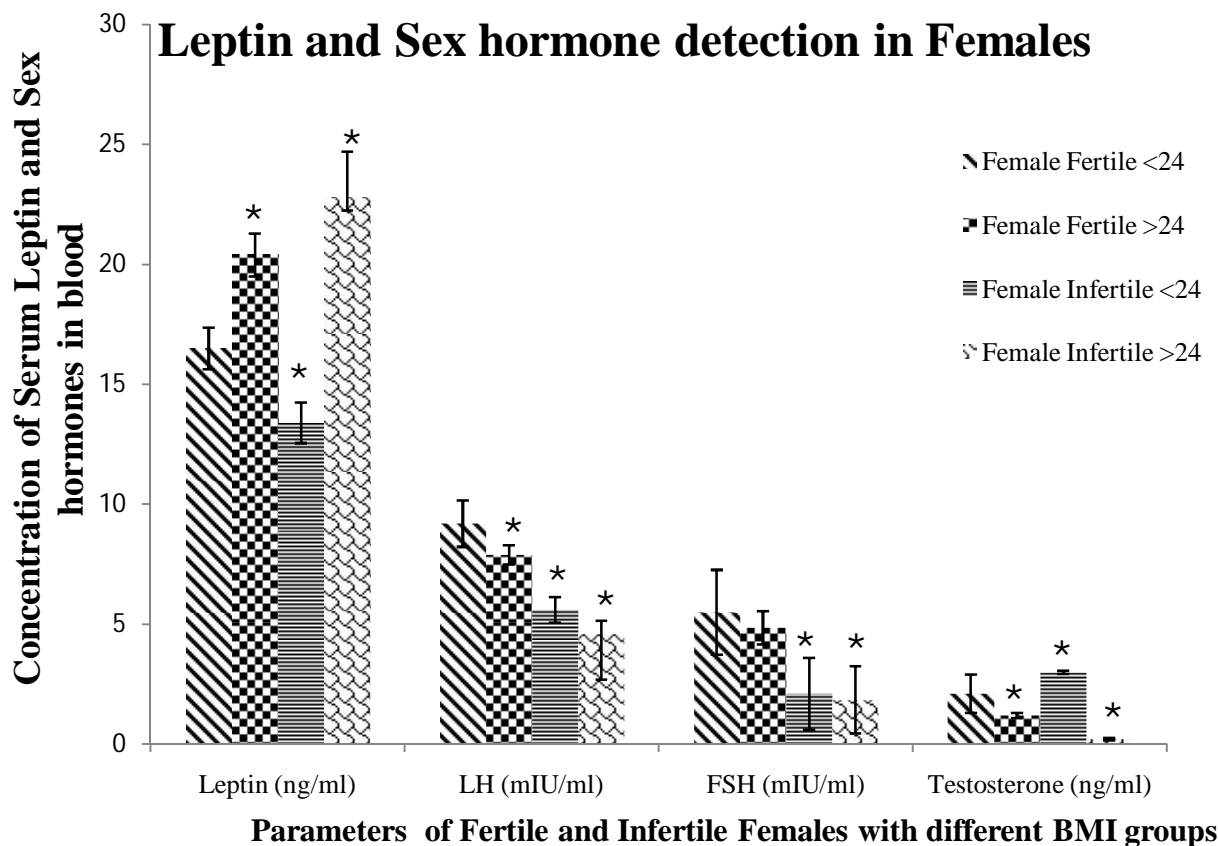


Fig. 2: Changes of Serum levels of Leptin, Testosterone and Gonadotropins in Fertile and infertile women related to BMI. Results are expressed in Average \pm sem. * $P < 0.05$

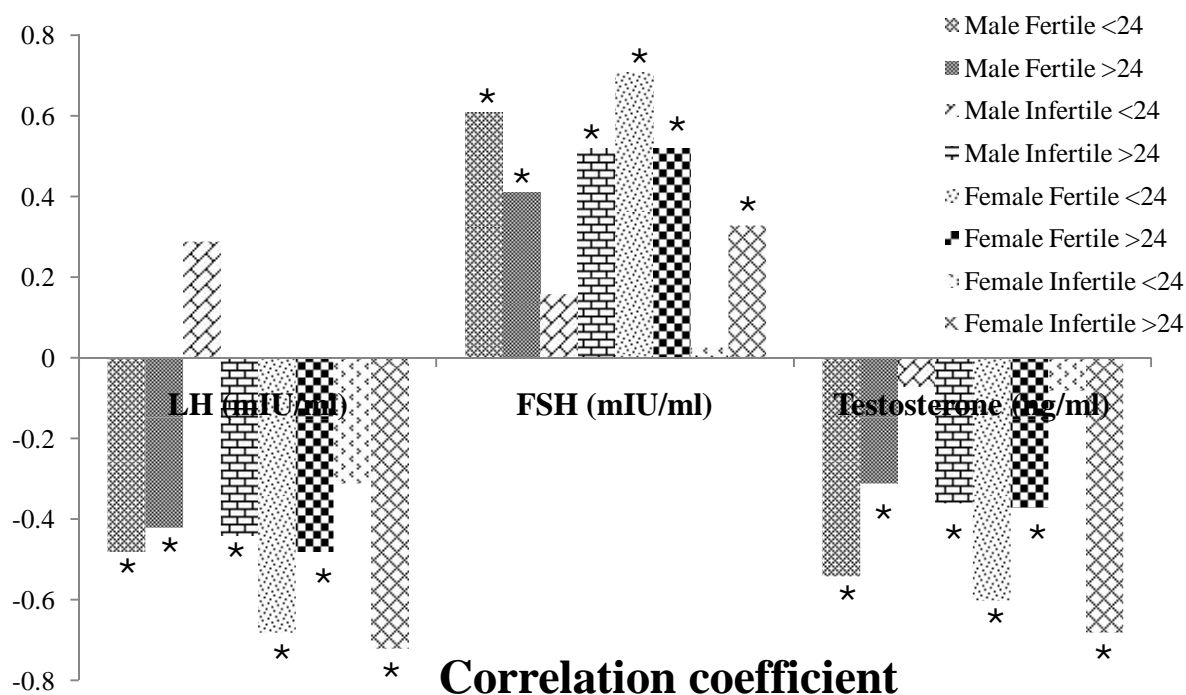


Fig. 3: Correlation between Serum leptin and other hormones. Results are expressed in Correlation coefficient. *P < 0.05.

DISCUSSION

In present study serum leptin level was found to be higher but values of testosterone was decreased in obese fertile and infertile subjects. These results are similar to several studies that relate the leptin and testosterone in young age infertile male and female (Zohdy *et al.*, 2007; Zorn *et al.*, 2007; Baltaci *et al.*, 2006; Cannady *et al.*, 2000; Wunder *et al.*, 2006). Some workers reported that obesity was associated with a significant disturbance in the hormonal milieu, which can affect the reproductive system. At the peripheral level, in the gonads, interaction between serum leptin and reproductive axis are bidirectional. This peptide has been suggested to exert a local paracrine/endocrine effect on regulation of reproductive functions. Reciprocally sexual steroids (17- β -estradiol, progesterone and testosterone) could modulate the leptin secretion at hypothalamic/pituitary level could be responsible for sexual dimorphism in circulating serum leptin (Tena-Sempere *et al.*, 1999; Zamorano *et al.*, 1997). Leptin, given in specific doses can fully restore the starvation induced changes of LH pulsatility and testosterone levels show the role of leptin in regulating neuroendocrine processes including reproduction (Chan *et al.*, 2002). Webstich *et al.* (2001) showed that Males with anorexia nervosa are characterized by low testosterone levels, causing decreased sexual drive and performance. The restoration of healthy weight is associated with an increased testosterone level and a normalization of gender-related behaviors.

It has been demonstrated that serum leptin levels are higher in women than men. Lower serum leptin levels in men has been attributed to higher testosterone level, given the fact that testosterone administration to hypogonadal men caused the

reduction of serum leptin (Luukkaa *et al.*, 1998; Baltaci *et al.*, 2006). In present study significant negative correlation was found between serum leptin and testosterone in infertile men and women. There are inconsistent results about relationship of serum leptin and testosterone; fewer reported no correlation (Thomas *et al.*, 2000; Al-Harithy *et al.*, 2006; Tupikowska *et al.*, 2006; Carraro-Ruiz-Torres, 2006) while others observed negative correlation (Bahre *et al.*, 1997; Luukkaa *et al.*, 1998; Baltaci *et al.*, 2006). Intramuscular testosterone treatment decreased plasma leptin levels in female to male transsexuals (Luukkaa *et al.*, 1998). Testosterone supplementation has been reported to normalize otherwise elevated plasma leptin levels in both young and old hypogonadal men without concomitant changes in body habitus, body fat content, or BMI, confirming a strong correlation between leptin and BMI, a gender difference in the levels of leptin. A recent population-based study reported an inverse correlation between leptin and testosterone that was independent of BMI (Luukkaa *et al.*, 1998). Our results also show that gonadotropin hormones (LH and FSH) decreased with the increase of serum leptin in obese both fertile and infertile men and women. These results are good in agreement with most of the studies, who explained that serum leptin in obese infertile patients was significantly higher than in obese fertile subjects. In many previous studies, the BMI was positively correlated with serum LH and leptin levels. Several reports showed that the accumulation of fatty tissue in men was associated with decreased total, free T, and increased E2 serum levels. Zohdy *et al.*, (2007) reported significant negative correlation between BMI and serum Testosterone. Zorn *et al.* demonstrated a link between leptin and testicular function, independent of FSH and LH, possibly involving Testosterone and

SHBG through a regulation of Leydig cell function. On the other hand, Jensen *et al.* (2007) reported that BMI had no effect on serum LH or FSH and inversely correlated with sperm concentration, sperm motility, sperm normal forms, and serum Testosterone. Tena-Sempere (2002) suggested that leptin acts as a direct inhibitory signal for testicular steroidogenesis, which may be relevant to explain the link between decreased T secretion and hyper-leptinemia in obese men. Yu *et al.* (1997) correlated serum leptin and pituitary hormones, having a potent effect on the anterior pituitary in vitro, stimulating FSH and LH. Eman and coworkers (2010) also reported that Serum leptin mediates a link between obesity and male infertility. Obese oligozoospermic patients had significant increase in mean BMI, serum FSH, LH, E2, PRL, when serum leptin compared with obese fertile controls. Studies in animals support our results. In rodents, most data have also been obtained with female animals since reproductive function in terms of amenorrhea or menstruation and fertility in terms of pregnancy are more readily measurable than in male animals. However, similar to *ob/ob* females, the sterility of *ob/ob* males was also corrected after leptin substitution (Cheheb *et al.*, 1996). Leptin treatment induced an elevation of testis weight and the mostly atrophied interstitial Leydig cells regained their usual morphology and clustering characteristic (Mounzih *et al.*, 1997) and resulted in a rise in LH but not in FSH secretion (Yu *et al.*, 1997). Our data also showed significant ($p < 0.01$) positive correlation co-efficient between serum leptin and LH, and serum leptin and FSH in infertile obese men and women. Significant positive correlation between leptin level and body weight was observed, and negative correlation was seen between FSH, LH and leptin respectively.

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