Serum leptin levels in obese infertile men and women

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Abstract: The present study was designed to evaluate the relationship between serum leptin and infertility in obese young and old men and women. The groups of infertile obese men (n=66) and women (n=30) compared with control obese fertile men (n=60) and women (n=30) with same ages to find the contribution of serum leptin level in causation of fertility. The results revealed that serum leptin were significantly raised in infertile male and female with $p<0.001$. BMI was also found to be significantly higher ($p<0.001$) in infertile men and women. Moreover a strong positive correlation was found between BMI and leptin level, and serum leptin and age in both fertile and infertile men and women. The values of correlation coefficients between serum leptin and BMI, and serum leptin and age are statistically significant ($r=0.3$-0.6, $p<0.01$-$p<0.05$). This study has concluded that obesity is associated with infertility in men and women. Sex hormonal imbalance may also be associated BMI and serum leptin in infertility. However further studies are required to determine the exact match by which enhanced BMI and serum leptin levels to female and male infertility

Keywords: Leptin, infertility, BMI and age.

INTRODUCTION

The word leptin is derived from leptose, meaning thin (Houscknecht *et al.*, 1998; Atiwerx and Siaels, 1998; Trayhurn *et al.*, 1999). It is secreted by the adipose tissue in proportion to adipose mass and therefore its circulating levels increase with weight gain and decrease with weight loss (Houscknecht *et al.*, 1998; Auwerx and Staels, 1998). A large amount of research has been conducted on leptin since its discovery in 1994 and it is now possible to evaluate the physiological significance of leptin (Houscknecht *et al.*, 1998; Auwerx and Staels, 1998; Chow and Phoon, 2003; Roberts *et al.*, 1997). Leptin is considered to play a wide range of functions in humans such as decreasing appetite and thereby food intake, stimulating and maintaining energy expenditure and acting as a metabolic hormone in a wide range of processes by binding to receptors in the brain (Trayhurn *et al.*, 1999). Leptin functions primarily as an anti-obesity hormone. Apart from its role in energy balance and the pathophysiology of bodyweight regulation, the role of leptin in neonatal physiology, puberty and reproduction has been addressed in recent years. The rise in leptin level at the onset of puberty and fall in post-menopausal women suggested that leptin may be associated with normal reproductive event (Frisch, 1980). Low leptin levels may also disrupt the reproductive system, as ovulation stop in starving women and testosterone level fall in men (Jensen *et al.*, 2004; Frisch, 1980).

Infertility is defined as years of unprotected coitus with conception and it is common problem among men and women of reproductive age (Considine *et al.*, 1996; Frisch, 1980). Little study has been carried out in male and female population to explore the status of serum leptin in patients of infertility. As a leptin plays a critical role in normal reproductive functions in particularly, ovulation, and spermatogenesis a change in the circulating leptin may prove to be an important link between body fat stores and status of fertility among men women of child bearing age. Establishment of such a link may provide new insight into causes of infertility and may lead to better treatment modalities in young women and man of child bearing age.

METHOD

It is a case control study, in which groups of infertile female and male with the age of 25-55 years were compared with a control group of fertile subjects with same sex and same age to find out the contribution of serum leptin level in causation of fertility. The male and female patients of infertility were taken from private Aziz Hospital of Karachi, Pakistan. Written consents were obtained from all subjects included in this study irrespective of cause of infertility. First men and women were categorized into fertile and infertile groups which were further divided on the basis of BMI, normal(BMI-18.5-24.5) and overweight or obese (BMI>25). These were further categorized according to the age into young (25years-35 years) and old (35-55 years). Serum obtain randomly from blood samples of these groups. Leptin level was measured by DSL-10-23100 Active human leptin ELISA kit by diagnostic system laboratory Inc; Webster, Texas, USA and body mass index (BMI) of all subjects was calculated as weight in kg/height in m^2.

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Data was analyzed on computer software statistical product selective solution (SPSS-17) version-17. Mean leptin values, BMI values among infertile and fertile with different age groups were analyzed by paired t-test. P≤ 0.05 were taken as statistically significant. Correlation coefficient was calculated between serum leptin and different age groups and serum leptin with different BMI groups. Levels of significance determined by paired tailed t-test. P≤0.05 was taken as statistically significant correlation.

RESULTS

Results are shown in tables 1 and 2. In present study 39.4% of total male were in young category (25-35 yrs) while 60.6% in old (36-60 yrs). In young males cases 50% were found to be fertile having normal BMI (18.5-24.5 kg/m^2) and remaining 50% were infertile and obese (25-40 kg/m^2). But in old ages male 46.8% were fertile having range of BMI 18.5- 24.5 kg/m^2 while 53.2% were obese and infertile. In total number of female (N=60) 50% were found to be young (25-35yrs) and 50% old (36-48 yrs). Similarly 50% of young and old both were fertile with normal BMI and remaining was infertile and obese. Results (table 1) show that BMI was significantly higher (p<0.001) in infertile than fertile male and female in both groups of ages. It was 32.5±1.12 kg/m^2 in infertile and 21.5±1.1 kg/m^2 in fertile young male (30±2.5 year). In older age (45±4.2 years) of male, value of BMI in fertile is 23.1±2 kg/m^2 and infertile 34±1.12 kg/m^2. Same pattern of BMI values were observed in female groups. Normal BMI (18.5-24.5 kg/m2), young (25-35 yrs) and old (36-48 yrs) female were fertile but obese (25-40 kg/m2) were infertile in both old and young ages.

In results (table 1) values of serum leptin level observed were more in female than male of both group of BMI, ages and fertility. In case of young (25-35 yrs) and old (36-60 yrs) male, level of serum leptin in obese infertile (11.8±1.91 ng/ml) was significantly higher (p<0.001) than fertile (7.0±1.12 ng/ml) normal male. Similarly in young and old female it was significantly increased in obese infertile (20.8±1.2 ng/ml, 18.8ng/ml) than normal fertile (19.01±1.0 ng/ml, 17.8±1.1ng/ml) groups. The value of serum leptin was increased significantly with the increase of age in both fertile and infertile of male and female shown in table 1.

Table 1: Changes in serum leptin levels of fertile and infertile males and females with different BMI and age groups

Sex	Age range (years)	% of ages	MBI means ± S.D. (range) (kg/m^2)	% of BMI	Fertility	Numbers (N)	Serum leptin (ng/ml)
Male	25-35 Young male	39.4	Normal 21.5±1.1 (18.5-24.5)	50	Fertile	16	7.0±1.12
			Obese 32.5±1.2* (25-40)	50	Infertile	16	11.8±1.9*
	36-60 Old male	60.6	Normal 23.1±2.1 (18.5-24.5)	46.8	Fertile	44	8.2.0±1.3
			Obese 34±1.1* (25-40)	53.2	Infertile	50	10.0±1.4*
Female	25-35 Young female	50	Normal 20.5±1.12 (18.5-24.5)	50	Fertile	15	19.01±1.0
			Obese 33±2.1* (25-40)	50	Infertile	15	20.8±0.2*
	36-48 Old female	50	Normal 22.2±1.2 (18.5-24.5)	50	Fertile	15	7.8±1.1
			Obese 36±2.2* (25-40)	50	Infertile	15	18.8±1.21*

Values are given as means±S.D. *p<0.001 when infertile groups of same sex, BMI and age are compared with fertile or control group by paired t-tailed test.

Table 2: Correlation between serum leptin and BMI, serum leptin and ages of fertile and infertile males and females

Sex	Age ranges (years)		BMI (kg/m^2)	
Male	Young 25-35	Old (36-60)	Normal 21.5±1.1 18.5-24.5	Obese 32.5±1.12-25-40
Fertile Serum leptin (ng/ml)	r=0.707 p<0.01 n=16	r=0.55 p<0.05 n=15	r=0.86 p<0.01 n=15	r=0.65 p<0.01 n=15
Infertile Serum leptin (ng/ml)	r=0.51 p<0.02 n=15	0.28 p<0.05 n=15	0.54 p<0.05 n=15	0.56 p<0.01 n=15
Female Fertile serum leptin (ng/ml)	r=0.48 p<0.02 n=15	r=0.17 p<0.05 n=15	r=0.67 p<0.01 n=15	r=0.51 p<0.023 n=15
Infertile serum leptin (ng/ml)	r=0.83 p<0.02 n=15	r=0.26 p>0.05 n=15	r=0.66 p<0.02 n=15	r=0.49 p<0.02 n=15

P<0.05 are considered as statistical Significant by two tail test.

Table 2 represents the correlation of serum leptin value with different groups of age and BMI in fertile and infertile male and female. Serum leptin in fertile and infertile male is positively correlated with age group of 25-35years. This correlation is statistically significant ($r=0.7$ $p< 0.0$) in fertile and infertile male ($p<0.02$ and $p< 0.01$). In old fertile and infertile male, value of correlation coefficient is $r=0.86$ and 0.54 which are significant at the level of $p<0.02$ and $p<0.01$. In infertile women, age group of 36-45years this correlation is also statistically significant.

Serum leptin level is directly associated with BMI in fertile and infertile male and female. This relation of BMI with leptin levels is statistically significant in both fertile($r=0.86$ $p<0.01$) and infertile ($r=0.54$ $p<0.01$) male, and fertile($r=0.51$, $p<0.023$) and infertile ($r=0.49$, $p<0.02$) female.

DISCUSSION

In present study BMI was found to be higher in infertile male and female as compared to control fertile subjects. Our results are similar to several studies that correlate the BMI with infertility of male and female (Crowley, 2008; Speroff, 1999; Frisch, 1980; Sallmén *et al.*, 2006; Mehmood and Sadia, 2001; Ruby *et al.*, 2007). High value of BMI may disrupt the reproductive system, and stops ovulation in starving women and testosterone levels decrease in men (Nguyen *et al.*, 2007; Fejes *et al.*, 2006). Excess weight has been related directly or indirectly to biological changes that could reduce male fertility (Speroff, 1999; Frisch, 1980; Sallmén *et al.*, 2006; Mehmood and Sadia, 2001; Ghafoor *et al.*, 2010; Sudha *et al.,* 2009; Nguyen *et al.*, 2007). Sudha and Co-workers (2009) reported that if body BMI is too high or too low, it can have a great effect on fertility; a higher BMI in women can cause insulin to increase. This can cause testosterone not to be converted in to estrogen and ovaries will not release eggs without sufficient estrogen production. A man's sperm count can possibly be impacted by higher BMI as well. Approximately half of all women with polycystic ovary syndrome (PCOS) are overweight or obese. There is increasing evidence that intra-abdominal or visceral fat is either causative or a very early effect of polycystic ovary syndrome (Lord and Wilkin, 2002). Obese men produced substantially less sperms than average men. Men with higher BMI have also exhibited altered quantity and quality of sperm (Jensen *et al.*, 2004; Magnusdottir *et al.*, 2005; Kort *et al.*, 2006; Vogel, 1996).

This work has previously been reported in population studies and are probably due to gender differences in body fat distribution. Subcutaneous lipid produces more leptin than visceral (Almaskari *et al.*, 2006). Women, carry most of their higher body fat content subcutaneously, where as men carry most of their lower body fat content viscerally (Ostlund *et al.*, 1997; Minocci *et al.*, 2000). This content in women would, therefore, explain their elevated serum leptin concentrations. It however, has also been suggested that the gender differences in serum leptin may be related to the differences in sex hormones (Minocci *et al.*, 2000; Ostlund *et al.*, 1997; Considine *et al*., 1996); Lonnqvist *et al.*, 1997; Campostano *et al.*, 1998; Reseland *et al.,* 2001).

The present study shows that serum leptin concentration is significantly raised in infertile male and female subjects as compared to the fertile control. It assesses the rate of fertility of obese in the Pakistani male and female population. These results are consistent with the result of various workers (Hanafy *et al.*, 2007; Zorn *et al*, 2007) who worked serum leptin in men and found the relation of leptin levels with fertility and obesity. Leptin levels were directly associated with BMI infertility in both male and female. The male study of Hanafy and worker (2007) reported that the fertile oligozoospermic group showed elevated mean serum leptin levels compared with the fertile normozoospermic group and also non-significant correlation with sperm concentration. Shafi and Afzal (2008) also reported increase values of serum leptin level in infertile obese woman as compared with control groups. They explained that hyperleptinemia is generally associated with infertility in female. Increased leptin level as a result of overweight may deregulate as hypothalamic-pituitary gonadal system, leading to reproductive dysfunctions, including infertility (Lakho *et al.*, 2001; Luukkaa *et al.*, 1998; Berra *et al.*, 2006; Wabitsch *et al.*, 1997; De Luca *et al.*, 2005; Ostlund, *et al.*, 1996; Ishikawa *et al.*, 2007; Tena-Sempere and Barreiro, 2002; Giagulli *et al.*, 1994; Lima *et al.*, 2000; Soyupek *et al.,* 2005; Ishikawa *et al*., 2007).

Conflicting reports were administered on whether circulating leptin levels changes with age. Our study showed that it had a significant positive correlation with the patient's age and BMI in male, explained by the increase in body fat mass and decrease serum total testosterone with the increasing age.

Hanafy and Coworkers (2007) reported that adult human body weight show gradual decline of serum leptin level during aging higher in women than in men, while Koistinen and associates (1998) described that fasting serum leptin levels were similar to different age groups in male. As major changes in body composition and gonadal function occur during human adolescence, they had assessed serum leptin concentration through childhood. They found that influence of BMI on leptin is a significant factor throughout the prepubertal and pubertal years of both sexes. The additional negative effect of testicular volume in the boys contributes to the sexual dichotomy in leptin concentration at the completion of puberty. The similar rise in leptin over the prepubertal

years into early puberty in both sexes, related not only to BMI but also independently to age, would suggest that leptin may have a facilitator role in human pubertal development.

It is concluded that obesity is associated with infertility in men and women. Sex hormonal imbalance may also be associated BMI and serum leptin in infertility.

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