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Impact of Kisspeptin on Prematur Puberty in Obese Girls

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Abstract: *Kisspeptin is a peptide hormone that appears to play a major role in the regulation of GnRH secretion,the researchaims to study the relationship between obesity and premature puberty touched by influence of kisspeptin concentration.*
The study was included 150girls and women divided into three groups. first group include fifty girls before menses with age range (9 -12years), twenty five girls were normal weight, the rest were obese girls .Second group with the same division system but these fifty women have normal menstrual cycle with age range (25 -45 years).Third group with age range (50 -60 years) after menopause age also divided into normal weight women and obese women. Hormones investigations included serum kisspeptin,leptin and IGF-1 were determined by ELISA.BMI was determined by anthrometeric mesurments.
The mean (± SD) value of serum kisspeptin level of obese girls was highly significantly increased (16·83 ± 12·4 pmol/l ,p=0.001) in comparison to that of normal weight girls with same age range (8·99 ± 4·10 pmol/l) ,same highly significant findings was found with serum leptin and IGF-1 of obese girls (25.7 ± 3.8 ng/ml ,10.22± 2.50 pg/ml, 170 ±9.95 ng ml consequently) but serum Estadiol shows no significant difference between these two groups. Serum kisspeptin in obese girls before menses show positive significant correlation with serum leptin, Estradiol and IGF-1(r=0.45, p= o.o1), (0.40, P=0.01), (r= 0.39, p= 0.01) consequently. Despite that the mean of serum leptin of obese female with regular menses (28.7± 3.54 ng/ml) was significantly higher than that of normal weight female with regular menses (19.5± 3.4 ng/ml),their serum kisspeptin ,estradiol and IGF-1 didn't differ significantly.
Serum kisspeptin level of obese women after menopause was highly significantly increased (44.39± 4.3 pmol/l, p=0.001) in comparison to that of normal weight women (30.76 ±3.80 pmol/l), same significant findings was found with serum leptin and Estradiol of obese women (28.9 ± 5.44 ng/ml, 20.33 ± 4.22 pg/ml; consequently)
In conclusion, the activity of serum kisspeptin (by other means the activity of kiss-1 neurons) increase with obesity, consequently the reproductive hormone kisspeptin tiger the premature puberty in obese girls in response to the effect of leptin.

Keywords: *early puberty, kisspeptin, growth hormone, obesity, leptin*

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I. Introduction

Diet and lifestyle are the main causes of obesity changes (1).It is well known that obesity is associated with various complications, such as diabetes, cardiovascular problems, several cancer types, osteoarthritis, metabolic disorders, and reproductive problems and function including puberty (2, 3, and 4), and age of maturity in females (2). Puberty is a crucial transitional period when reproductive capacity is acquired and somatic development completed (5). Genetic basis and neuroendocrine mechanisms for the control of puberty are attracting growing interest due, in part, to the worrying trend of altered (mostly, earlier) puberty reported in girls and boys (6). puberty onset is frequently coupled to decreased physical activity and behavioral changes, including unhealthy nutritional habits, which predispose to or worsen the development of obesity. These associations warrant a better understanding of the basis of puberty and its deviations.

Leptin is produced in adipose tissue, circulates in proportion to energy stores, it plays role in control feeding and the action of spending funds by its effect on hypothalamus (7).Many studies reported that Congenital leptin deficiency and loss-of-function mutations of leptin receptor (LepR) in patients and rodents result in a failure of pubertal maturation and infertility (7-8).Some researchers suggest that good nutritional status (such as insulin and IGF-1) have a role in releasing GnRH but what signals tell these nerve cells to release GnRH in this manner has not been determined (9). The onset of puberty is triggered by pulsatile release of the hormone GnRH from nerve cells in a region of the brain known as the hypothalamus. Exactly what signals tell these nerve cells to release GnRH in this manner has not been determined, although it has been suggested that hormones associated with good nutritional status (such as insulin and IGF-1) have a role(10).

II. Material And Methods

The study was carried out at the College of Medicine, University of Baghdad and Teaching Medicine City during the period from January 2017 to march 2017. It included 150girls and women divided into three groups. first group include fifty girls before menses with age range (9 -12years), twenty five girls were normal weight, the rest were obese girls .Second group with the same division system but these fifty women have normal menstrual cycle with age range (25 -45 years).Third group with age range (50 -60 years) after menopause age also divided into normal weight women and obese women. Hormones investigations included serum kisspeptin,leptin and IGF-1 were determined by ELISA.BMI was determined by anthrometeric mesurments.

III. Results

Table1: Mean (±SD) levels of hormones (kisspeptin, leptin, IGF-1and Estradiol) in obese and normal weight girls before puberty changes

Hormones	Obese girls before menses with age range (9-12) years, No=50. Mean ± SD	Normal weight girls before menses With age range(9-12)years, No.=50 Mean ± SD	P-value
S. kisspeptinPmol/L	16.83 ± 12.40	8.99 ± 4.10	<0.01
S. leptin ng/ml	25.7 ± 3.8	17.0 ± 9.95	<0.01
S.IGF-1 ng/ml	252.50 ± 15.78	200.4 ± 10.12	<0.01
S. Estradiol Pmol/L	90.45 ± 15.67	75.76 ± 14.78	N.S.

Obese girls have significant higher level of s. kisspeptin, s. leptin and s.IGF-1 (16.83 ± 12.40 Pmol/L, 25.7 ± 3.8 ng/ml, 252.50 ± 15.78 ng/ml) in comparison with normal weigh girls (8.99 ± 4.10 Pmol/L, 17.0 ± 9.95 ng/ml, 200.4 ± 10.12 ng/ml).While Estradiol level show no significant difference between the two groups. Significant positive correlation between serum kisspeptin and each of the following hormones serum leptin(r=0.45, p= o.o1), serum Estradiol (0.40, P=0.01) and serum IGF-1(r= 0.39, p= 0.01).

Table2: Mean (± SD) levels of hormones (kisspeptin, leptin, IGF-1and Estradiol) in obese and normal weight women with regular menstrual cycle

Hormones	Obese women had regular menstrual cycle with age range (25-45)years, No.=50 Mean ± SD	Normal weight women had regular menstrual cycle with age range(25-45) years, No.=50 Mean ± SD	P-value
S. kisspeptinPmol/L	33.89 ± 4.9	30.3 ± 3.9	N.S.
S. leptin ng/ml	28.7 ± 3.54	19.5 ± 3.4	<0.01
S.IGF-1 ng/ml	168.67 ± 18.88	166.89 ± 17.98	N.S.
S. Estradiol Pmol/L	150.98 ± 12.8	165.43 ± 19.99	N.S.

All hormones show no significance difference (p> 0.5) between obese women and their control, except leptin who shows significant higher level than their control

Table3: Mean (± SD) levels of hormones (kisspeptin, leptin, IGF-1and Estradiol) in obese and normal weight women after menopause

Hormones	Obese women after menopause with age range (50- 60) years, No.=50 Mean ± SD	Normal weight women after menopause age range (50-60)years, No.=50 Mean ± SD	P-value
S. kisspeptinPmol/L	44.39 ± 4.3	36.76 ± 3.8	< 0.01
S. leptin ng/ml	28.9 ± 5.44	22.3 ± 2.12	<0.01
S.IGF-1 ng/ml	115.43 ± 12.4	110.3 ± 13.32	N.S.
S. Estradiol Pmol/L	88.78 ± 15.50	75.86 ± 10.98	<0.01

Obese women after menopausal age have higher with significant level (p<0.01) of kisspeptin, leptin and Estradiol in comparison with their control, while serum IGF-1 level show no significant difference. Serum kisspeptin level of obese women after menopause have deepened correlation (r= -0.39, p =0.01) with serum Estadiol The only significant negative correlation which was found between serum kisspeptin and estradiol with r= -0.39, p=0.01

IV. Discussion

It's well known that the maturation age is affected by both genetic factors and by environmental factors such as nutritional state and social circumstances (11).table 1 showed that obesity may have effect on early maturation this is clear to the eye through the estradiol level even the differences between the two studied groups is no reached the significant level, but the higher level of estradiol is a good pointer for early maturation,

in one hand leptin might be the cause of the GnRH rise. Leptin has receptors in the hypothalamus which synthesizes GnRH (12) .Factors that may signal nutritional status to the hypothalamus include the growth factors insulin and IGF-1. It is unclear which hypothalamic neuronal subpopulation these factors affect to regulate GnRH neuron function in puberty and reproduction (12),on the other, leptin is known to mediate the formation of estrogens from circulating androgen precursors and to affect thermoregulation (13,14). These opinions were supported by study which found that individuals who are deficient in leptin fail to initiate puberty.

Researchers hypothesized that the levels of leptin increase with the beginning of maturity, and then decline to adult levels when puberty is completed (15), these results supports the results which was found in the current study (table 1& table2) but there is a possibility the rise in GnRH might also be caused by genetics. A study (16) discovered that a mutation in genes encoding both Neurokinin B as well as the Neurokinin B receptor can changing the age of maturation. Neurokinin B, a ten-peptide chain found in humans, expressed along with the peptides kisspeptin and dynorphin A in the neuronal cells of the arcuate nucleus , might play a role in regulating the secretion of Kisspeptin, responsible for triggering direct release of GnRH consequently release of LH and FSH.

Three main hormones are produced by adipose tissue; leptin, adiponectin, and resistin(17) ,Leptin have valuable association with body mass(15).Increase the probability of height increase in obese girls as table1 shows represented by significant increase in IGF-I may be back to believe that adiponectin, similar to GHRH, induces GH secretion (17).Add to that there is a suggestion that leptin was shown to directly stimulate GH secretion (15,16,17)and increase the level of IGF-1 receptor.

Findings of many studies suggest there is a frank link between leptin and linear growth that leptin administration to the leptin-deficient *ob*/*ob* mice corrected their metabolic abnormalities and also led a significant increase in femoral length (17, 18). But Wang (19) showed that children with a congenital mutation in the leptin receptor had normal linear growth. The possible cause related to the fact that the effect of leptin may differ between rodents and humans.

Numerous studies have recently documented the importance of kisspeptin, the endogenous ligand of the G protein-coupled receptor 54 (GPR54), in the regulation of reproduction and the initiation of puberty (20, 21). These studies found that number of neurons expressing KiSS-1 mRNA increased in the infundibular nucleus of postmenopausal women, their data give strong probability that the increased gene expression of KISS-1 neurons in postmenopausal women are secondary to the loss of ovarian estrogen.

It's well documented that the growth hormone have the highest level during the age of maturation and then decline with age (22). Consequently to the decline in the secretion of growth hormone (GH), the plasma insulin-like growth factor I (IGF-I) concentration declines (22), this opinion in agreement with findings of the table3 of the study.

As ovaries age and release fewer hormones, FSH and LH can no longer perform their usual functions to regulate estrogen, progesterone and testosterone. Natural decline of estrogen levels during menopause can significantly affect many system of the body, the inhibition in GH secretion may be related to estrogen effect which play a role in the regulating the GH secretion and depends on the administering pathways of estrogens that probably affect the secretion of hepatic IGF-1.As well as, the direct effect of estradiol on adipose tissue that estradiol increase leptin messenger expression and leptin secretion (23,24),all these findings telescope and give documentation to fact that obesity in pre maturation age may accelerate puberty as findings of table1 .

V. Conclusion

Obese girls mature faster than others and the main culprit may be back to kisspeptin which stimulated by existence of leptin

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