

Serum leptin, estradiol and testosterone concentrations in normal healthy fertile women with different weights

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Abstract

Background: Leptin, the product of the ob gene, is a hormone secreted by adipocytes. Animals with mutations in the ob gene are obese, leptin affects not only nutritional homeostasis but also reproductive events. A prospective study was done to investigate serum leptin, estradiol and testosterone levels in 100 fertile healthy women with regular cycle aged (18-45) years with different weights and to see the influence of obesity on these parameters, the correlation of leptin with body mass index, waist/hip ratio, estradiol and testosterone level was determined. **Methods** fasting blood samples were obtained for the measurement of all studied parameters. serum concentrations of leptin was measured using (ELISA), estradiol and testosterone concentrations measured by (ELFA) technique (enzyme linked fluorescent assay) by microtiter, the body-mass index was defined as the weight in kilo-grams divided by the square of the height in meters. **Results:** according to the body mass index (BMI), the women were divided into 3 groups: Group (1) normal weight (30 women) with $BMI \leq 24.9 \text{ kg/m}^2$, group (2) Overweight (30 women) with $BMI = 25-29.9 \text{ kg/m}^2$, group (3) obese (40 women) with $BMI \geq 30 \text{ kg/m}^2$. The mean value \pm SD of the weight in normal weight group was $(53 \pm 5) \text{ kg}$, of overweight group was (65.8 ± 4.7) and of obese group was (91.6 ± 16) so there was a highly significant difference between the 3 groups ($p\text{-value} = 0.000$), the Mean \pm SD of waist/hip ratio in normal, overweight and obese groups were $(0.79 \pm 0.06, 0.81 \pm 0.03 \text{ and } 0.84 \pm 0.05)$ respectively and there was significant difference between the 3 groups ($p\text{-value} = 0.04$), the leptin mean \pm SD of normal, overweight and obese groups were $(12.4 \pm 6.7, 18.2 \pm 5.8 \text{ and } 24.4 \pm 16.4)$ respectively, and $p\text{-value} = 0.000$. Estradiol mean \pm SD of normal, overweight and obese groups were $(46.2 \pm 30.2, 54.6 \pm 25 \text{ and } 79.9 \pm 52.7)$ respectively, $p\text{-value} = 0.03$, Testosterone mean \pm SD of normal, overweight and obese groups were $(0.14 \pm 0.06, 0.16 \pm 0.07 \text{ and } 0.2 \pm 0.09)$ respectively, $p\text{-value} = 0.00$. **Conclusions.** Leptin correlate significantly with BMI, W/H ratio and estradiol level, the women with higher BMI (obese) has higher level of leptin, estradiol and testosterone so the leptin clearly appears to be linked to the reproductive system.

Key Words: Leptin, Estradiol, Body mass index, fertile women.

الملخص

هرمون اللبتين هو ناتج أل(وب) جين، يفرز من الخلايا الدهنية. لوحظ ان الحيوانات التي لديها تغير في هذا الجين تعاني من السمنة، هرمون اللبتين لا يؤثر على التوازن الغذائي فقط بل على الأحداث التكاثرية. في دراسة احتمالية تم فحص هرمون اللبتين والاستراديول والتستستيرون في مئة امرأة في سن الإخصاب أعمارهن 18-45 سنة ولديهن دورة شهرية منتظمة وبأوزان مختلفة وذلك لمعرفة تأثير السمنة على هذه المعلمات، تم تحديد العلاقة بين هرمون اللبتين مع مؤشر كتلة الجسم، نسبة الخصر على الورك، استراديول والتستستيرون.

طريقة العمل

تم سحب عينات الدم من النساء قبل تناول الفطور وذلك من أجل قياس الهرمونات المذكورة سابقاً، نسبة اللبتين تم قياسها بجهاز إلاليزا، هرمون الاستراديول والتستستيرون تم قياسهما بواسطة جهاز المنيفايذ وتم حساب مؤشر كتلة الجسم بتقسيم الوزن بالكيلو غرام على مربع الطول بالمتر.

نتائج البحث

تم تقسيم النساء حسب مؤشر كتلة الجسم إلى 3 مجاميع

1. ذوات الوزن الطبيعي (30) امرأة مؤشر كتلة الجسم ≥ 24.9 كغم²

2. النساء اللواتي لديهن وزن زائد (30) امرأة مؤشر كتلة الجسم $25-29.9$ كغم²

3. النساء اللواتي يعانين من السمنة (40) امرأة مؤشر كتلة الجسم ≤ 30 كغم²

كان متوسط \pm الانحراف المعياري للوزن في مجموعه الوزن الطبيعي (53 ± 5)، ولذوات الوزن الزائد (65.8 ± 4.7) وللواتي يعانين من السمنة (91.6 ± 16) كان هناك فرق إحصائي واضح بين المجاميع الثلاثة في الوزن ($0.000 \geq$ ب)، كان متوسط \pm الانحراف المعياري لنسبة الخصر على الورك لكل من مجموعة الوزن الطبيعي، الوزن الزائد واللواتي يعانين من السمنة (0.06 ± 0.79)، 0.81 ± 0.03 و 0.84 ± 0.05 على التوالي وكان هناك فرق إحصائي واضح بين المجاميع الثلاثة ($0.04 \geq$ ب) ومتوسط \pm الانحراف المعياري للبتين في مجموعه الوزن الطبيعي وذوي الوزن الزائد والمصابين بالسمنة (12.4 ± 6.7 ، 18.2 ± 5.8 ، 24.4 ± 16.4) على التوالي و $0.000 =$ ب. ومتوسط \pm الانحراف المعياري للاستراديول في المجاميع أعلاه كان (46.2 ± 30.2 ، 54.6 ± 25 و 79.9 ± 52.7) على التوالي و $0.03 =$ ب ومتوسط \pm الانحراف المعياري للتستستيرون في المجاميع (0.14 ± 0.06 و 0.16 ± 0.07 و 0.2 ± 0.09) على التوالي و $0.00 =$ ب.

استنتاجات البحث

هرمون اللبتين له علاقة ذات مغزى إحصائي مع مؤشر كتلة الجسم، نسبة الخصر على الورك ومستوى الاستراديول والنساء ذوات مؤشر كتلة الجسم الأعلى (اللواتي يعانين من السمنة) لديهن نسبة أعلى من اللبتين والاستراديول والتستستيرون وهذا يدل على إن هناك ارتباط بين اللبتين والجهاز التناسلي.

Introduction

Leptin is a 16 KD a protein produced in adipose tissue and secreted into the peripheral blood in pulsatile fashion.^[1,2,3] The effects of leptin were observed by studying mutant obese mice that arose at random within a mouse colony at Jackson Laboratory in 1950.^[4]

These mice were massively obese and excessively voracious, Ultimately, several strains of laboratory mice have been found to be homozygous for single-gene mutations that cause them to become grossly obese, and they fall into two classes: "ob\ob", those having mutations in the gene for the protein hormone leptin, and "db\ob", those having mutations in the gene that encodes the receptor for leptin, when ob\ob mice are treated with injections of leptin, they lose their excess fat and return to normal body weight. Leptin itself was discovered in 1994 by Jeffrey M.Friedman and colleagues at the Rockefeller University through the study of such mice.^[5]

It is apparent paradox that leptin which was named after the Greek word which was termed ob protein or leptin (from the Greek leptos, meaning thin)is encoded by the obesity gene (ob).This unfortunate misnaming occurred because is leptin deficiency that was discovered first in obese mice .^[6]

Human leptin is a protein of 167 amino acids . Transcription of the leptin gene in mice yields

a mRNA of that is expressed primarily in adipose tissues, but recent studies have confirmed that some other tissues also express leptin, including placenta, ovaries, skeletal muscle and stomach ,but It is manufactured primarily in the adipocytes of white adipose tissue, and the level of circulating leptin is directly proportional to the total amount of fat in the body.^[7]

Leptin acts on receptors in the hypothalamus of the brain,^[8] where it inhibits appetite by the effects of neuropeptide Y (a potent feeding stimulant secreted by cell in the gut and in the hypothalamus). In humans, there is also evidence that leptin is involved in reproduction function, including puberty, and with the maintenance of normal menstrual cycles.^[9] A number of studies have proposed that if leptin is the signal that there are adequate fat stores

to start and maintain ovulation and menstruation, it may account for these changes through its effects on the ovary^{[10],[11],[12]} or on the brain.^[13] Another study suggested that, at the level of the central nervous system, leptin may stimulate gonadotropin- releasing hormone (GnRH) release from the hypothalamus, and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release from the pituitary, probably by acting on its

own receptor and promoting nitric oxide release.^[14]

The known function of leptin is regulating energy homeostasis by influencing feeding behavior and energy expenditure, so that low fat stores and hypoleptinemia stimulate appetite and reduce thermogenesis while excessive accumulation of body fat is prevented through hyperleptinemia inducing the opposite effect.^[6]

Serum leptin concentrations are correlated with the percentage of body fat, suggesting that most obese persons are insensitive to endogenous leptin production.^[15]

Body weight is regulated by complex mechanisms involving numerous afferent metabolic and hormonal signals informing the brain about the body's energy status. Insulin, cholecystokinin, and cortisol are just a few examples of these signals.

Abnormal production or action of any of the afferent messengers may lead to weight gain. A subsequent increase in leptin production may reflect the body's attempt to counterbalance the increase in body fat stores. Weight gain evokes an increase in the basal metabolic rate, which is significantly related to fat mass (as is the serum leptin concentration).^[16]

Studies have found that a relationship between estrogen and leptin has been described during the follicular phase of both spontaneous cycles and cycles stimulated with exogenous FSH.^[17]

Aim of the Study is to

1. Measure leptin, estradiol and testosterone level in fertile women aged (18-45) years old with different body weight.
2. See the difference in leptin, estradiol and testosterone level in normal weight, overweight and obese fertile women.
3. Assess any correlation between body mass index, waist/hip ratio, estradiol and testosterone with leptin level.

Subjects Materials and methods

The study was conducted at the women health center of al-kansa hospital.

In a prospective study a one hundred healthy women in reproductive age (18-45) years old were included in this study their Mean±SD of age was 31±7.9 years old, has regular menstrual cycle (28-30) days, multiparous Mean±SD of number of children was 3±2.

They had not used any hormonal medication for at least 2 months before the study. None of them had a history of coronary heart disease, diabetes mellitus, Hypertension, not pregnant and not lactating.

They were divided in to 3 groups according to the body-mass index (BMI), which defined as the weight in kilograms divided by the square of the height in meters :

1. thirty women normal weight $BMI \leq 24.9$ kg/m².

2. thirty women Over weight $BMI = 25-29.9$ kg/m².

3. forty women obese $BMI \geq 30$ kg/m²

All subjects enrolled in the study were interviewed and the general information was taken to fill the questionnaire .

A verbal informed consents were taken from all participants.

For every women in all groups:

1. height was measured to the nearest millimeter using a standard stadiometer, with the participant bare foot and wearing light weight clothing,

2. weight was measured to the nearest (0.1)kg using a standard digital scale

3. BMI (kg/m²) was computed by dividing the weight in kilogram (kg) over the height in square meters (m²).

4. waist measurement in centimetres was performed by locating the point halfway between the crest of the hip (iliac crest) and the lowest rib at the side, passing the tape measure around the waist parallel to the floor, whilst the person is in expiration (breathing out) with a relaxed abdomen .

5. the hip circumference measurement in centimetres should be taken by tape measure around the widest portion of the buttocks.

6. WHR waist\hip ratio was calculated by dividing waist circumference in centimetres over the hip .

Specimens:

The subjects were instructed to have an overnight fasting in 2nd day of menstrual cycle, through antecubital venepuncture fasting blood samples were obtained from all subjects included in the study. 1 milliliter (ml) of venous blood had been collected in plain tube then incubated for 37°C for 15 minutes in water bath, centrifugation for 10 minutes at 3000 rotation per minute (rpm), aspiration of supernatant serum divided into three plain tube , then freezed at -20°C till time of assay. Each of which was used for the following measurement:

1. serum leptin level.
2. serum estradiol level.
3. serum testosterone level.

Materials

1. Minividas, 99739 IVD 1203553 (Biomerieux, Italy).
2. Bio-Tek, ELX 800 (Instru. Inc., USA).
3. water bath, standard digital scale, tape measure

4. Centrifuge 3E-I (Sigma, Germany).

Methods

Leptin measurement: Leptin was measured by (ELISA) using ELISA kit provided by DRG company, (Germany) Based on a solid phase ELISA of a sandwich type(EIA-2395). The inter- and intra – assay coefficient of variation which ranged between (8.66-11.55%) and (5.95-6.9%), respectively. The analytical sensitivity of zero standard was equal to (1.0ng/mL) and the assay dynamic range was(1-100ng/mL).

Estradiol and testosterone hormones level measurement: Both hormones measured by ELFA technique (enzyme linked fluorescent assay)by midividus(Biomereux, Italy) using kit provided by biomereux SA.

Statistical Analysis

SPSS version 11.5 was used for the statistical analysis.

1. Descriptive results were represented as mean \pm standard deviation (SD).
2. The comparisons between groups and within each group were done by ANOVA one – way analysis of variance followed by Duncan's multiple range tests (DMRT).
3. Linear regression analysis [Pearson correlation coefficient (r)] was preformed to identify the relationship between different biochemical parameters.

Results

1.The anthropometric parameters of 100 women as shown in table no.1 , divided in to 3 groups according to the body mass index(BMI),

Group 1. with BMI \leq 24.9 kg/m² are normal weight (30 women) ,

Group 2. With BMI 25-29.9 kg/m² are overweight (30 women) .

Group 3. with BMI \geq 30 kg/m²are obese (40 women) .

There was no significant deference in age, height and no. of children the p-values were (0.07,0.14,0.51)respectively, while the mean value \pm SD of the weight in normal weight group was (53 \pm 5)kg ,mean value \pm SD of overweight was(65.8 \pm 4.7) and mean value \pm SD of obese was(91.6 \pm 16) so there was significant difference between the 3 groups (p-value=0.000) ,the Mean \pm SD of waist\hip ratio in normal, over weight and obese groups were (0.79 \pm 0.06, 0.81 \pm 0.03 and 0.84 \pm 0.05) respectively.

2.The hormonal assay of the 3 groups in table no.2 shown significant difference between the 3 groups ,the leptin mean \pm SD of normal ,overweight and obese groups were(12.4 \pm 6.7, 18.2 \pm 5.8 and24.4 \pm 16.4)respectively, and p-value =0.000.

Estradiol mean \pm SD of normal ,overweight and obese groups were (46.2 \pm 30.2 ,54.6 \pm 25 and79.9 \pm 52.7)respectively ,p-value =0.03.

Testosterone mean \pm SD of normal ,overweight and obese groups were (0.14 \pm 0.06, 0.16 \pm 0.77 and 0.2 \pm 0.09)respectively, p-value =0.00 .

3. There was positive and significant correlation between leptin level and BMI, waist\hip ratio and estradiol ($r=0.652$ and p -value $=0.000$, $r=0.587$ and $p=0.02$ and $r=0.577$ and 0.03) respectively, but no correlation between leptin and testosterone level as shown in table no.(3).

Discussion

Leptin, an ob gene product, is produced by the human fat body stores and appears to be involved in the regulation of reproductive axis in healthy fertile women (18-45) years old with different body weights, there was no significant difference in age or height this will make the weight and BMI are the main difference between the 3 groups, so we divide the women according to the BMI to 3 groups: (1). with $BMI \leq 24.9$ kg/m^2 are normal weight (30 women) (2). with $BMI 25-29.9$ kg/m^2 are overweight (30 women) and (3). with $BMI \geq 30$ kg/m^2 are obese (40 women).

In the present study we measure leptin level our result confirm a strong and highly significant association between serum leptin level and BMI as the weight increase (BMI increase) the leptin level increase significantly, and positive significant correlation between leptin and BMI has been reported ($r=0.652$, $p=0.000$) as in numerous scientific studies [18,19,20,21]. who found a strong and highly significant positive association between plasma leptin concentrations and BMI.

An interesting result in this study is that women with $BMI \geq 30$ kg/m^2 have almost 2 times the circulating level of leptin compared

with those with $BMI < 25$ kg/m^2 . this may indicate that at certain BMI level, serum leptin tend to increase rapidly; this may explain the complication related to obesity, apart from the function of leptin in the central nervous system on the regulation of food intake and body energy balance, it may be one of the hormonal factors that signal the body's readiness for reproduction. [22]

The waist \hip ratio was significantly different between the normal, over weight and obese groups (p -value $=0.04$) and there was apposite significant correlation between leptin and waist\hip ratio ($r=0.578$, $p=0.02$) this agreed with Brzechffa p. et al.(1996), who found a positive correlation between leptin level and waist hip ratio ($r=0.431$; $p<0.001$) in normal healthy fertile women (control of his study). [23]

so in this study we found significantly higher leptin levels when BMI and waist \hip ratio in accordance with previous studies. [24,25]

All blood samples were taken in the 2nd day of menstrual cycle but there was significant difference in estradiol level between the normal weight group and the obese group the main value were (46.2 ± 30.2 , 70.9 ± 52) respectively p -value $=0.03$, this result can be explained that the obesity particularly central obesity is associated with supranormal estrogen production, due to increased activity of aromatase system, several authors have reported that central obesity may have higher estrone concentrations compared with normal weight women this agreed with (pasquali et al.,1994;morales et al.,1996) [26,27], in addition, reduced sex hormone binding

globulin(SHBG) values ,which usually accompany obesity ,may favour greater amount of free estradiol to be delivered to target tissue ,obese women are also characterized by reduced formation of inactivated estrogen metabolites (i.e.estradiol metabolites hydroxylated in the C2 position and oxidized at 17 position)and greater availability of estrone sulphate in the target tissue .[28] All these conditions concur in favouring a hyper estrogenic state in obese women.

In the present study there was significant difference in testosterone level between obese group and overweight (p-value=0.00)and between obese group and normal weight group(p-value=0.00)this result is agreed with the result Korhonen J.et al.(2003). [29]

This can be explained that in premenopausal women, approximately 50% of plasma

testosterone is derived in equal proportions from ovarian and adrenal secretion. The remaining 50% derives from conversion of androstenedione in peripheral tissues, including

adipose tissue,[30] In obese individuals with insulin resistance, the associated hyperinsulinemia acts as a co-gonadotropin with LH to increase androgen production by ovarian theca cells, as the ovary remains sensitive to the actions of insulin.[31]

Successful weight loss programs lead to reduced plasma testosterone, increased SHBG, an consequently reduced circulating free testosterone.[32]

There was no any correlation between testosterone level and leptin level in all

healthy fertile women in the present study, this agree with Spitzer P. in 2001.[33]

Recommendations

- 1.to measure leptin level before and after dieting program for 8week to see the changes in leptin level by decreasing weight.
2. measure leptin in follicular phase and luteal phase of menstrual cycle.

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Table (1) anthropometric measures of the 3 groups. *Using ANOVA and Duncan test**mean with different letters a,b,c...differ significantly.

Parameters	Normal weight No.(30) Mean±SD	Over weight No.(30) Mean±SD	Obese No.(40) Mean±SD	P –value
Age	29.1±8.4	31.6±8.7	33.4±6.3	NS
No. of children	2.8±1.3 (a)	3.3±1.8 (a)	2.9±1.9 (a)	NS
Weight(kg)	53±5 (a)	65.8±4.7 (b)	91.9±16 (c)	0.0000***
Height(cm)	158±6.2 (a)	157±3.9 (a)	155.9±4.7 (a)	NS
Waist\hip ratio	0.79±0.06 (a)	0.81±0.03 (b)	0.84±0.05 (c)	0.04**

* p -value ≤0.05 is significant , ** p-value = 0.01 is highly significant.

Parameters	Normal weight No.(30) Mean±SD	Over weight No.(30) Mean±SD	Obese No.(40) Mean±SD	P –value
Leptin ng\ml	12.4±6.7 (a)	18.2±5.8 (b)	24.4±16.4 (c)	0.000***
Estradiol pg\ml	46.2±30.2 (a)	54.6±25 (ab)	70.9±52.7 (b)	0.03*
Testosterone ng\ml	0.14±0.06 (a)	0.16±0.77 (a)	0.2±0.09 (b)	0.00**

Table (2) hormonal assay in the 3 groups. *Using ANOVA and Duncan test**mean with different letters a,b,c...differ significantly.

* p -value ≤ 0.05 is significant , ** p-value = 0.01 is highly significant.

Parameters	Correlation with leptin	
	r	p
BMI	0.652	0.000***
Waist\hip ratio	0.587	0.02*
Estradiol pg\ml	0.577	0.03*
Testosterone ng\ml	0.05	NS

Table no.(3) correlations between BMI, waist\hip ratio and estradiol and testosterone hormones with leptin in healthy fertile women(18-45)years old.

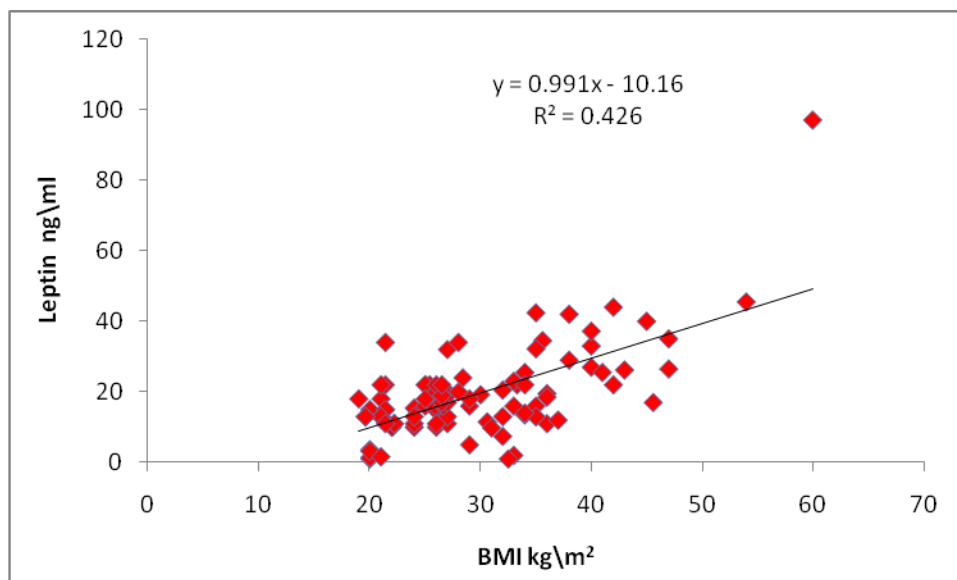


Fig (1) Positive correlation between leptin and BMI in healthy fertile women (18-45)years old .

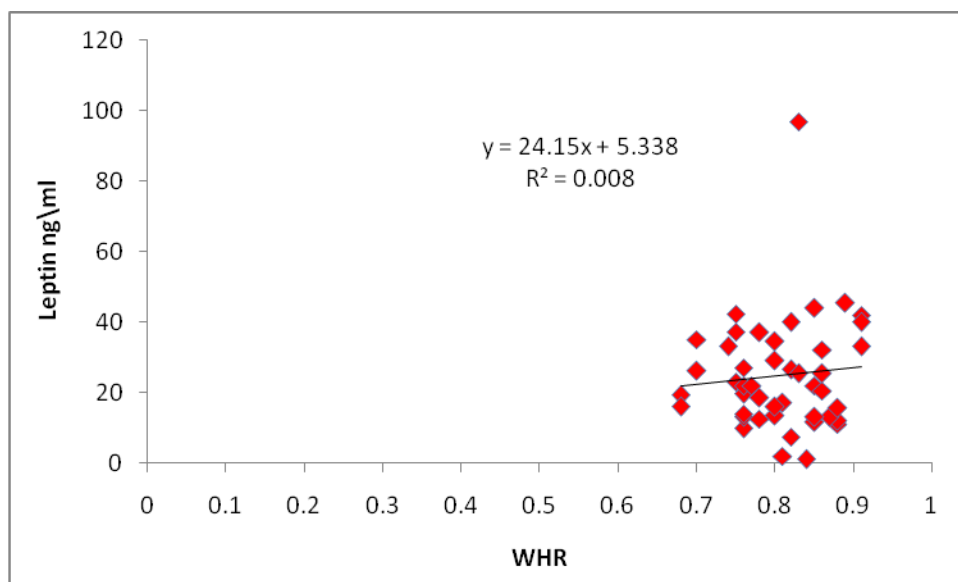


Fig (2) Positive correlation between leptin and WHR in healthy fertile women (18- 45)years old .

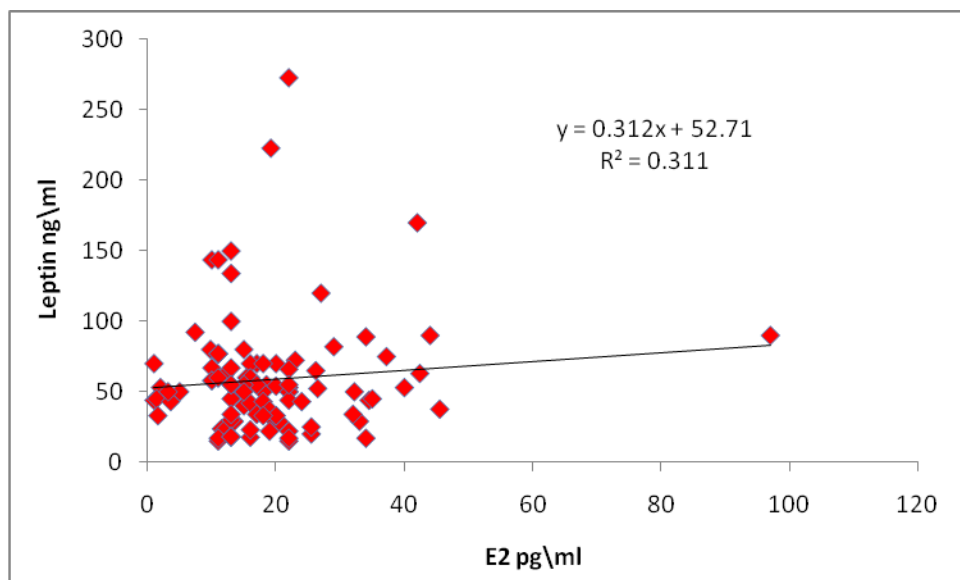


Fig (3) Positive correlation between leptin and Estradiol level in healthy fertile women (18-45) years old .