LEPTIN LEVELS IN NORMAL WEIGHT AND OBESE SAUDI ADULTS

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Objective: The purpose of the study was to measure serum leptin in normal weight and obese individuals, and assess its relation to anthropometric measures and metabolic indices.

Methods: The study was conducted at King Fahd Hospital of the University, Saudi Arabia, from January 2003 to June 2004. Subjects included in the study were all non-diabetic normotensive adults. Variables measured were body mass index (BMI), waist to hip ratio (WHR), blood pressure, serum leptin, insulin, glucose, and lipids.

Results: Included were 43 non-obese subjects (20 men and 23 women) with the mean age of 25.8 ± SD 5.3 years for men and 23.9 ± SD 1.9 years for women and their mean BMI was 23.1 ± 1.4 for men and 23.0 ± 1.8 for women. Serum leptin was significantly higher in women 8.8 ± SEM 2.10 ng/ml than men 2.2 ± SEM 0.26 ng/ml. Also included were 46 obese subjects (25 men and 21 women) with a mean age of 29.4 ± SD 7.6 years for men and 28.8 ± SD 6.2 years for women and a mean BMI of 35.5 ± 5.7 for men and 35.6 ± 4.4 for women. Serum leptin was significantly higher in women 23.0 ± SEM 3.98 ng/ml than men 12.5 ± SEM 2.24 ng/ml.

Conclusions: Serum leptin increased with obesity, and was higher in women than men, both lean and obese. Serum leptin correlated positively with BMI and hip circumference. Though, correlation between leptin and insulin resistance was found, they probably reflect two different metabolic compartments.

Key Words: Leptin, insulin, anthropometry, obesity, body fat distribution, body mass index.

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INTRODUCTION
Obesity is a major health problem in Saudi Arabia as it is in the developed world. Although the pathogenesis of obesity is not completely understood, excessive accumulation of fat is mostly due to interaction between genetic factors and environmental conditions. Since the discovery of leptin, its role in the pathophysiology of obesity has been intensively studied. Leptin broadened our understanding of the mechanisms underlying the neuroendocrine function, body weight and energy homeostasis. Leptin is a hormone secreted primarily from adipocytes, and acts centrally to decrease appetite and increase energy expenditure. Absence of leptin is associated with massive obesity in ob/ob mice and humans. Serum leptin concentrations are highly correlated with percentage body fat content. Most obese persons are insensitive to endogenous leptin production and have leptin resistance. Serum leptin is higher in women than men for any measure of obesity, and decreases with age. There is conflicting evidence regarding leptin production rates and ethnicity. This study was conducted to measure the level of serum leptin in a sample of our population with normal BMI and obesity and assess its relation to anthropometric measures, blood pressure, insulin and metabolic indices.

METHODS
Subjects
This cross-sectional correlational study, was conducted at King Fahd Hospital of the University in Alkhobar, Kingdom of Saudi Arabia, from January 2003 to June 2004. We recruited subjects with normal body mass index (BMI) between 20 - 25, and obese with BMI above 30. All had 75g oral glucose tolerance test. Out of 100 individuals recruited, 89 non-diabetic healthy Saudi adults, not taking any medication, were studied. They were mainly medical students, interns, residents, and hospital employees. Blood samples were obtained in the morning after an overnight fast. Serum specimens for hormonal assays were stored at – 70°C till analysis.

Anthropometric and blood pressure measurements
Height and weight were measured using Detecto scale to the nearest 0.5 cm and 0.1 kg. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the high point of the iliac crest and hip circumference at the maximum circumference of the buttocks, the waist to hip ratio was then calculated. Blood pressure (BP) was measured using a mercury sphygmomanometer, Baumanometer, W.A.Baum Co. Inc.,USA. BP measurement was carried out in the lying, sitting, and standing positions. The mean systolic and diastolic BP was calculated.

Biochemical and hormonal measurements
Serum leptin was measured by enzyme-linked immunosorbant assay (sandwich method), DRG Instruments Gmbh, Germany. The lowest limit of detection is 1 ng /ml. The coefficient of variation for intraassay is 3.3 – 5.4 % and for interassay 6.7 – 8.4%. Serum glucose, total cholesterol, triglycerides, and HDL-cholesterol were measured by Dimension RXL analyzer, Dade Behring. Serum insulin was measured by microenzyme immunoassay using IMX analyzer, Abbott diagnostics. The scores for Homeostasis model assessment of insulin resistance (HOMA IR) were calculated with the formula: fasting serum insulin (μU/ml) X fasting serum glucose (mmol/l) / 22.5 as described by Matthews and colleagues.

Statistical analysis
Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for windows, version 10.0.1, 1999. Student t-test, and Mann-Whitney test were carried out according to the results of Levene test of homogenety of variances as appropriate. Pearson correlation coefficients were measured.

RESULTS
The findings of the study are summarized in Tables 1 and 2. Table 1 reveals the following:

Subjects with normal BMI: There was no gender difference with regard to mean age or BMI. Women had significantly lower waist circumference and waist to hip ratio (WHR) than men. There was no difference in mean hip circumference. The mean systolic and diastolic BP were normal, but significantly higher in men.

Obese subjects: They were slightly older than the normal weight subjects. As in the normal group, there was no gender difference with regard to the mean age or BMI. Women had significantly lower waist circumference and WHR than men. There
### Table 1: Characteristics of the study subjects

| Variables          | Normal Weight | Obese | p-value | Normal Weight | Obese | p-value |
|--------------------|---------------|-------|---------|---------------|-------|---------|
| Number             | 20            | 23    | -       | 25            | 21    | -       |
| Age                | 25.8 ± 5.3    | 23.9 ± 1.9 | NS       | 29.4 ± 7.6    | 28.8 ± 6.2 | NS |
| Body mass index    | 23.1 ± 1.4    | 23.0 ± 1.8 | NS       | 35.5 ± 5.7    | 35.6 ± 4.4 | NS |
| Waist (cm)         | 81.2 ± 7.3    | 72.8 ± 8.9 | 0.002    | 109.8 ± 13.1  | 100.0 ± 13.4 | 0.016 |
| Hip (cm)           | 100.9 ± 15.6  | 95.9 ± 7.2 | NS       | 118.7 ± 13.1  | 119.6 ± 11.7 | NS |
| WHR                | 0.818 ± 0.116 | 0.758 ± 0.066 | 0.04    | 0.929 ± 0.063 | 0.836 ± 0.080 | 0.0001 |
| Mean systolic BP (mmHg) | 124.2 ± 12.1 | 103.5 ± 9.9 | 0.0001 | 125.6 ± 12.8 | 113.4 ± 14.4 | 0.004 |
| Mean diastolic BP (mmHg) | 76.1 ± 7.5   | 68.7 ± 7.8 | 0.003   | 78.9 ± 10.1  | 75.5 ± 9.0 | NS |

Mean ± SD, NS=Not significant

### Table 2: Hormonal and metabolic variables of study subjects

| Variables          | Normal Weight | Obese | p-value | Normal Weight | Obese | p-value |
|--------------------|---------------|-------|---------|---------------|-------|---------|
| Number             | 20            | 23    | -       | 25            | 21    | -       |
| Serum leptin (ng/ml) | 2.2 ± 0.3    | 8.8 ± 2.1 | 0.049    | 12.5 ± 2.2    | 23.0 ± 4.0 | 0.021 |
| Serum insulin (µU/ml) | 8.3 ± 0.7    | 8.8 ± 0.7 | NS       | 18.7 ± 1.7    | 13.6 ± 1.1 | 0.019 |
| HOMA IR            | 1.9 ± 0.2     | 2.0 ± 0.2 | NS       | 4.4 ± 0.5     | 3.1 ± 0.3 | 0.032 |
| Fasting glucose (mg/dl) | 91.6 ± 1.4   | 87.6 ± 1.3 | 0.047    | 93.7 ± 1.7    | 93.0 ± 2.3 | NS |
| 2h glucose post 75g OGTT | 92.4 ± 4.4   | 95.1 ± 4.1 | NS       | 99.7 ± 5.1    | 108.6 ± 3.8 | NS |
| Total cholesterol (mg/dl) | 173.8 ± 5.9  | 168.1 ± 5.7 | NS       | 180.6 ± 7.5   | 188.6 ± 6.0 | NS |
| Triglyceride (mg/dl) | 98.6 ± 9.6    | 57.1 ± 3.5 | 0.0001   | 120.7 ± 11.7  | 80.7 ± 8.3 | 0.020 |
| HDL-cholesterol (mg/dl) | 47.4 ± 2.0    | 65.6 ± 2.9 | 0.0001   | 42.4 ± 1.2    | 59.6 ± 2.6 | 0.0001 |
| TG/HDL-C ratio     | 2.2 ± 0.3     | 0.9 ± 0.1 | 0.0001   | 3.0 ± 0.3     | 1.5 ± 0.2 | 0.0001 |
| LDL-Cholesterol (mg/dl) | 106.7 ± 5.4  | 91.0 ± 4.2 | 0.024    | 114.1 ± 6.6   | 112.8 ± 6.0 | NS |

NS = Not significant

### Table 3: Correlation of serum leptin and HOMA IR with blood pressure anthropometric variables

| Variables          | Leptin | HOMA IR |
|--------------------|--------|---------|
| Age                | 0.061  | NS      |
| Body mass index    | 0.440  | 0.0001  |
| Waist              | 0.284  | 0.007   |
| Hip                | 0.425  | 0.0001  |
| WHR                | -0.042 | NS      |
| Mean systolic BP   | -0.100 | NS      |
| Mean diastolic BP  | -0.124 | 0.187   |

r = Pearson correlation coefficient, NS = Not significant

### Table 4: Correlation of serum leptin and HOMA IR with metabolic variables

| Variables          | Leptin | HOMA IR |
|--------------------|--------|---------|
| Leptin (ng/ml)     | -      | 0.344   |
| Insulin (µU/ml)    | 0.334  | 0.001   |
| HOMA IR            | 0.344  | 0.001   |
| Fasting glucose (mg/dl) | 0.208  | NS      |
| 75g OGTT 2h glucose (mg/dl) | 0.027  | NS      |
| Total cholesterol (mg/dl) | 0.002  | NS      |
| Triglyceride (mg/dl) | -0.006 | NS      |
| HDL-Cholesterol (mg/dl) | -0.032 | NS      |
| TG/HDL-C ratio     | 0.036  | NS      |
| LDL-Cholesterol (mg/dl) | 0.019  | NS      |

r = Pearson correlation coefficient, NS = Not significant
no difference in mean hip circumference. The mean systolic and diastolic BP were normal, but systolic BP was significantly higher in men.

Table 2 reveals the followings:

**Subjects with normal BMI:** Serum leptin was significantly higher in women than men. Women had significantly lower mean fasting glucose, triglyceride (TG), triglyceride to HDL-cholesterol ratio (TG to HDL-C ratio) and LDL-Cholesterol (LDL-C). Men had significantly lower HDL-Cholesterol (HDL-C). There was no gender difference with regard to mean fasting serum insulin, HOMA IR, 2h glucose post 75g OGTT or total cholesterol.

**Obese subjects:** Serum leptin was significantly higher in women than men. There was no gender difference in mean fasting glucose, 2h glucose post 75g OGTT, total cholesterol, and LDL-C. Women had significantly lower fasting insulin, HOMA IR, TG, and TG to HDL-C ratio but higher HDL-C.

Gender and obesity had an effect on serum leptin values. Overall serum leptin for women was 15.6 ± SEM 2.42 ng /ml higher than men 7.9 ± SEM 1.46 ng /ml, with p value 0.006. Serum leptin was significantly higher in the obese than normal weight women, with p value 0.002. Serum leptin was also significantly higher in obese than normal weight men, with p value 0.0001. There were variations in serum leptin within the same sex group with comparable BMI. Six men and 6 women with normal weight, and two obese men had serum leptin ≤ 1 ng /ml.

**Pearson correlation coefficients for serum leptin (Table 3)**

There was a significant positive correlation with BMI (r 0.440, p value 0.0001), hip circumference (r 0.425, p value 0.0001), and a weak positive correlation with waist (r 0.284, p value 0.007). There was no correlation with mean age, mean systolic BP, mean diastolic BP, or WHR. Significant positive correlations were present with fasting insulin (r 0.334, p value 0.001) and HOMA IR (r 0.344, p value 0.001), but not with the other metabolic variables.

**Pearson correlation coefficients for HOMA IR (Table 4)**

There were significant positive correlation with many measures of obesity including BMI (r 0.589, p value 0.0001), waist circumference (r 0.594, p value 0.0001), hip circumference (r 0.496, p value 0.0001), and WHR (r 0.367, p value 0.0001). There was a weak positive correlation with mean systolic BP (r 0.230, p value 0.030). There was no significant correlation with mean age or mean diastolic BP.

HOMA IR strongly and positively correlated with fasting insulin (r 0.982, p value 0.0001). There was significant positive correlation with fasting glucose (r 0.520, p value 0.0001), TG (r 0.555 p value 0.0001), and TG / HDL-C ratio (r 0.606, p value 0.0001). There was a significant negative correlation with HDL-C (r - 0.365 with p value 0.0001). These variables are indirect metabolic markers of insulin resistance. There was a weak positive correlation with LDL-C (r 0.217, p value 0.041). There was no significant correlation with 2h glucose post 75g OGTT or total cholesterol.

**DISCUSSION**

In this study, we report the serum leptin concentration in a sample of healthy Saudi adult subjects. The sample is not representative of the general population. Serum leptin is higher in women than men, both obese and lean. There is about 2-4-fold elevation in women as reported in other studies. The gender difference in leptin level was present though men had higher values of atherogenic variables, and obese men were even more insulin resistant than women. Serum leptin increased with obesity regardless of sex with a positive correlation between serum leptin and BMI as has been consistently found in previous studies. Variations of serum leptin in individuals of comparable BMI and of the same gender were noted. The variation in the leptin level and its correlation with BMI may be explained by the fact that BMI may be a poor surrogate for total fat mass and distribution. Accurate measurements of percentage body fat will therefore, yield a better correlation. The gender difference in leptin level was present though men had higher values of atherogenic variables, and obese men were even more insulin resistant than women. Serum leptin increased with obesity regardless of sex with a positive correlation between serum leptin and BMI as has been consistently found in previous studies. Variations of serum leptin in individuals of comparable BMI and of the same gender were noted. The variation in the leptin level and its correlation with BMI may be explained by the fact that BMI may be a poor surrogate for total fat mass and distribution. Accurate measurements of percentage body fat will therefore, yield a better correlation. The subjects of the study were young, so the effect of aging on leptin concentrations was not addressed.

Obese individuals are usually insulin resistant, hence the positive correlations between serum leptin, fasting serum insulin, and HOMA IR as shown in our study. HOMA IR correlates with all variables associated with insulin resistance. These include BMI, waist circumference, WHR, BP, serum TG, and TG to HDL-C ratio. Leptin correlates only with measures of obesity including BMI and hip circumference. Increased cardiovascular risk and hyperinsulinemia are
known to be associated with excess central visceral fat, which is clinically assessed by increased waist circumference and high WHR. Serum leptin correlates with hip circumference which reflects peripheral subcutaneous fat.20-22

The relationship between leptin and insulin resistance is not completely clear.23-26 It seems that both the extent of fat mass and its distribution are important determinants of leptin levels. Two metabolically distinct fat compartments might be a major explanation for the association between insulin, insulin resistance and leptin in lean and obese individuals. Central (visceral) fat is associated with hyperinsulinemia and insulin resistance, while peripheral (subcutaneous) fat is associated with hyperleptinemia.27,28 These observations and other potential genetic and ethnic factors contribute to the understanding of determinants of gender difference and variation of leptin levels.29,30

In conclusion, serum leptin concentrations increase with obesity, and are higher in women whether lean or obese. Serum leptin correlates positively with BMI and hip circumference. Though, correlations between leptin and insulin resistance are commonly reported, they probably reflect two different metabolic compartments. This may suggest that in a primary health care set-up, measurement of both serum leptin and serum insulin may differentiate between an atherogenic and somewhat less harmful obesity.

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