The objective of this work was to evaluate the relationship between sex steroid hormones, sex hormone-binding-globulin, leptin, insulin and insulin resistance in obese men. Anthropometrical indexes, total testosterone (Tt), free testosterone (fT), estradiol (E), sex hormone-binding-globulin (SHBG), glucemia, insulin and leptin were measured in 77 men, with ages between 20 and 60 years. According to their body mass index (BMI), subjects were grouped into three categories: normal body weight (<24.9 kg/m²), overweight (25–29.9 kg/m²) and obese group (>30 kg/m²). Insulin resistance index was obtained by the homeostasis assessment model for insulin resistance (HOMA-IR). Total testosterone and SHBG concentrations were lower in the obese group compared with normal and overweight subjects (p < 0.05). The mean insulin concentration was significantly higher in the obese group compared with the other groups (p < 0.05). T was negatively correlated with the BMI (r = −0.447; p < .01), WC (r = −0.464); p < .01, leptin (r = −0.382; p < .01), insulin (r = −0.391; p < 0.01) and also with the HOMA-IR (r = −0.416; p < 0.01). The SHBG negatively and significantly correlated with BMI (r = −0.334; p < 0.01) and WC index (r = −0.322; p < 0.01), as well with insulin levels (r = −0.313; p < 0.01) and insulin resistance (r = −0.266; p < 0.05). Our results shows that in a sample of men, Tt and SHBG concentrations proportionally diminished with both the increase of BMI and insulin resistance index.

Keywords BMI, insulin, leptin, SHBG, testosterone
Insulin resistance is one of the metabolic problems most investigated in the last two decades because of its relation with the increased risk of cardiovascular disease [9, 10, 27]. Obesity may result in hyperinsulinism and insulin resistance, with a close relationship between the increased accumulation of visceral fat and the degree of insulin resistance as well as hyperinsulinism [4, 6, 36].

Obesity has been associated with various endocrine abnormalities, both in men and women. It is well known that plasma testosterone levels in the obese decline with increasing body weight, particularly in men with central obesity [2, 7, 31, 37]. Testosterone levels are lower in obese men because of the decreased levels of sex-hormone binding globulin (SHBG); these hormone changes get worse in massively obese men, creating a relative hypogonadal state, which seems to be closely related to insulin resistance [2, 7, 31, 37]. Moreover, in both sexes, a positive association between SHBG and various insulin sensitivity markers has been demonstrated. In obese men, hyperinsulinism is associated with lower SHBG concentrations, suggesting that the decrease of SHBG may be one of the components of the metabolic syndrome [8, 13]. Laaksonen et al. [19] have postulated that low testosterone and SHBG levels predict the development of the metabolic syndrome and diabetes in middle-aged men, independently of other factors related to insulin resistance. Nevertheless, the interrelation between androgens, adipose tissue and insulin sensitivity has not been clearly elucidated. It has been postulated that androgens regulate adipose tissue and insulin sensitivity, whereas adipocytes and insulin regulate testosterone levels. It is possible that both mechanisms operate, depending among other factors, like testosterone concentrations [2, 22].

Leptin is another important factor in the physiopathology of obesity [5, 21]. This is a protein with 167 amino acid content, predominantly produced by the adipocytes. Leptin level increases exponentially with the adipose tissue mass. There is a close relationship between leptin secretion and insulin concentration; high insulin levels in the postprandial phase stimulate leptin secretion, in this way regulating the food intake [18].

It has been demonstrated the existence of a sexual dimorphism in the leptin adult plasma concentration. It is possible that a greater central adiposity in women would be related with higher leptin concentration than that observed in males [28]. Experimental studies give support to the idea that androgens exert a negative influence on leptin synthesis [20]. Moreover, in hypogonadal men, usually obese, leptin levels are increased [14, 29, 31].

Body circumference indexes, like waist-to-hip circumference ratio (WHR) have been used to estimate the risk probabilities for developing health problems related to obesity, particularly cardiovascular disease [12]. Different studies have demonstrated that low plasma testosterone
levels had a predictive value for increasing central adiposity [16, 34]. To some authors, the obesity degree is the most important risk factor, independent of the body fat distribution, since there is an inverse relationship between the obesity degree and the testosterone and SHBG levels; hence, with the development of metabolic abnormalities [24].

Whether the endocrine changes are secondary to obesity, or the opposite, that some endocrine changes may occur before obesity is established is still a controversial matter. The endocrine and metabolic changes that may occur in subjects with increased body weight has stimulated us to study a group of men in order to evaluate the relationship between androgens, adipose tissue and insulin sensitivity.

**RESEARCH DESIGN AND METHODS**

Seventy men, aged between 20 and 62 years, were studied. Voluntary consent was obtained verbally and in a written form. Each individual was interviewed and clinically evaluated in the Endocrinology Unit at the University Hospital of Los Andes, Mérida, Venezuela. Inclusion criteria: they should be in good health, without signs or symptoms of endocrine disorders or other pathologies.

**Protocol**

Anthropometrics values were registered in a special form: weight and height, waist (WC) and hip circumferences (HC) were measured to calculate the waist-to-hip ratio (WHR). The BMI was calculated by the formula weight (kg)/height^2 (m^2). According to the BMI, the subjects were grouped in three categories: group (A), 21 subjects with BMI < 24.9 kg/m^2, mean age 35.30 ± 2.4 years; group (B), 31 subjects with BMI between 25.0 and 29.9 kg/m^2, mean age 38.9 ± 2.0 years; and group (C), 25 subjects with BMI > 30.0 kg/m^2, mean age 38.0 ± 1.2 years. We considered central obesity when the WHR was greater than 0.9 m and the WC greater than 102 cm. Peripheral blood sample (10 mL) was obtained in fasting condition. Glucemia was measured by enzymatic spectrophotometry (Biosystem Laboratories). The insulin, leptin (L), total testosterone (T), free testosterone (fT), estradiol (E), the luteinizing (LH) and follicle stimulating hormone (FSH) were measured by radioimmunoanalysis (RIA), with reactives from Diagnostic Products Corporation (USA). The sex hormone-binding globulin (SHBG) was measured by double antibody immunoradiometric assay (IRMA). The glucose and insulin levels were used to calculate the homeostasis model assessment for insulin resistance (HOMA-IR). The intraassay and interassay variation coefficients for hormonal values were between 2 to 5% and 3 to 8%, respectively.
Statistical Analysis

Results are presented as the mean ± SE; the Student-t test was used to get the differences between the groups; and the Pearson correlation coefficient was used to determine the inter-variable associations.

RESULTS

The anthropometrics measures, and the endocrine and metabolic basal values from the three groups of subjects of this study presented differences that are discussed below. The mean age of the three groups were similar. WC index was significantly greater in groups B and C; meanwhile, the WHR was greater only in group C ($p < 0.05$). Leptin concentration increased progressively from 3.6 ng/mL in the normal weight subjects, up to 6.4 ng/mL in the overweight group and up to 14.4 ng/mL in the obese group.

**FIGURE 1** Correlation between Tt, BMI, WC, insulin and HOMA-IR in obese men.
In obese men, T concentration was significantly lower than in others groups; however, the LH, FSH, Ft and E were not different between them. T showed a positive correlation with the SHBG ($r = 0.446; p < 0.01$) and a negative correlation with the BMI, WC, leptin and insulin levels, as well as HOMA-IR values (Figure 1). The SHBG concentration was significantly lower in the obese group ($p < 0.05$) and showed a negative correlation with the BMI, WC, leptin, insulin levels and the HOMA-IR. Fasting plasma insulin concentration was greater in the obese group ($p < 0.05$) compared with the normal and overweight subjects. The insulin resistance in the obese group showed a mean value of $5.95 \pm 0.73$, significantly greater ($p < 0.05$) than the value obtained in groups A and B.

**DISCUSSION**

There are interactions between low SHBG and insulin concentrations, and a relationship between low total and free testosterone concentrations with increased insulin resistance in obese men [1, 7, 8, 11, 13, 19, 37]. We found that T and SHBG serum concentrations decreased as the BMI increased. Similar results have been reported by others [1, 24, 37]. There is a possible role of sexual steroid hormones and SHBG in metabolic disturbances associated with obesity. Obesity is associated with a decrease in T, fT, SHBG levels [37]. There is also an inverse correlation between the fT levels and central obesity [11]. In our results, the fT levels were not changed in the three groups. This discrepancy may occur because the methodological limitation to measure bioavailable testosterone.

In normogonadal non-diabetic men, the variability of the bioavailable testosterone (free testosterone) is predictive of the variability in the adipose tissue distribution, both central and peripheral, but it did not have a predictive value for insulin resistance for the β cell disfunction [1]. Nevertheless, the possible role of testosterone in the insulin resistance pathogenesis due to its effect on the fat distribution and on the body composition.

In obese men, hyperinsulinism degree is related with the adipose tissue distribution. In individuals with central fat distribution, with both high WC and WHR values, they have a greater risk of presenting insulin resistance and other metabolic syndrome manifestations [4, 23, 24, 26].

The decrease on SHBG and testosterone serum levels may play an important role in the development of insulin resistance. Insulin is an important factor in the regulation of SHBG synthesis at the liver [25, 33]. There is an inverse association between the bioavailable testosterone levels and insulin resistance markers [35].

In middle-age men, hypoandrogenism is an early marker of glucose metabolism and insulin alterations, which may progress toward a metabolic syndrome, or to an overt diabetes [19]. Thus, the pathogenesis of both
conditions may be related to the decrease in testosterone and SHBG levels. In our study there was an inverse and significative correlation between insulin, T and SHBG.

In obese subjects, high estradiol levels may be a product of peripheral androgen aromatization. Estrogen excess is one of the factors involved in the decrease of LH levels in massive obesity [17]. In this study, there was no relation between estradiol levels and BMI, as others have reported [15].

In conclusion, we found an inverse correlation between levels of testosterone and leptin, as well with insulin resistance in obese men. The leptin concentration increases exponentially with the increase in body adipose tissue. Moreover, both humans and rodents show a sexual dimorphism related to the leptin levels. Leptin levels are lower in men than in women, independently of the obesity degree [21, 28, 30]. Testosterone may have a negative effect on the leptin concentration [3, 14]. The relation between T and leptin affects the differences observed in the leptin values [32]. In our study, there was a negative correlation between leptin and total testosterone, suggesting that high leptin levels could be involved in the reduction of total testosterone serum levels.

REFERENCES