Serum Concentrations of Dehydroepiandrosterone Sulfate and Leptin in Obese Patients With Normal Serum Cholesterol

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Normal (< 200 mg/dL) serum concentrations of cholesterol and a favorable ratio of cholesterol/high-density lipoprotein (HDL)-cholesterol are frequently seen in morbidly obese (body mass index [BMI] > 35 kg/m^2) patients. Because it is unknown whether this subgroup is characterized by differences in other potential markers of cardiovascular disease, serum concentrations of dehydroepiandrosterone sulfate (DHEAS) and leptin were determined in 155 obese patients (BMI > 35 kg/m^2, aged 20 to50 years) with normal (n = 72) or with elevated (n = 83) total serum cholesterol. We found that seemingly negative marginal correlations between serum concentrations of DHEAS and cholesterol, as well as between DHEAS and the ratio cholesterol/HDL-cholesterol, were not any more apparent after correction for age, sex, and BMI. A negative correlation between serum leptin concentrations and the ratio cholesterol/HDL-cholesterol persisted after correction for age, sex, and BMI. In morbid obesity, there appears to be an association between serum concentrations of leptin and a more favorable lipid profile, whereas there is no direct interrelation between serum concentrations of cholesterol and DHEAS.

NORMAL CONCENTRATIONS of total cholesterol and a favorable ratio of cholesterol/high-density lipoprotein (HDL)-cholesterol are frequently seen in morbid obesity.[1,2] It is not known whether this subgroup of obese individuals is characterized by reduced obesity-dependent cardiovascular morbidity[3] or by differences in other metabolic variables linked to cardiovascular morbidity and mortality, such as dehydroepiandrosterone sulfate (DHEAS). DHEA and DHEAS are the most abundant circulating steroids in humans. Their concentrations are higher in women than in men[4] and decrease with age[5] and with body weight.[6] DHEAS has been linked to artherosclerosis[7] and coronary heart disease[8] and has been proposed as a discriminator of life expectancy.[9]

Concentrations of leptin, the neuroregulatory peptide produced by fat cells, are predominantly influenced by body weight.[10] They vary little with age[11] and whether an apparent gender difference in leptin concentrations is completely corrected by adjustment for obesity is, as yet, unclear.[11,12] In non-obese to moderately overweigth Asian Indians, leptin appears to be unrelated to serum cholesterol and to HDL-cholesterol concentrations.[13] Nevertheless, based on the recently reported leptin-enhanced intestinal cholesterol absorption in mice[14] and the possible direct link between leptin and the risk of thromboembolic complications in obese individuals,[15] it may be speculated that serum leptin concentrations in morbidly obese individuals with high serum cholesterol might differ from those with normal serum cholesterol concentrations.

SUBJECTS AND METHODS

Serum concentrations of DHEAS, leptin, total cholesterol, HDL-cholesterol, and the ratio, total cholesterol/HDL-cholesterol, were determined in 155 consecutive patients (134 women, and 21 men, aged 20 to 50 years) with a body mass index (BMI; calculated by body weight (in kilograms) divided by the square of body height (in meters) of $>$ 35 kg/m^2 who has been referred to our thyroid outpatient service. None of the patients was on a lipid-lowering medication. Euthyroidism (thyroid-stimulating hormone [TSH] $>$ 0.5 to $<$ 4.0 μU/mL) was documented in each case. This group comprised patients with diffuse and/or nodular goiter (n = 78; BMI: 39 $\pm$ 3 kg/m^2) as well as men and women without any thyroid pathology (n = 77; BMI: 40 $\pm$ 4 kg/m^2). Although the evaluated outpatient population does not, by definition, represent a completely 'normal' population chosen at random, we believe this bias to be minor, because the prevalence of sonographically documented goiter in the investigated age-group approaches 50%[16] and because we are not aware of any evidence suggesting that euthyroid goiter might be associated with changes in the metabolic variables investigated in this report.

Serum concentrations of cholesterol and HDL-cholesterol were determined in the routine biochemical laboratory. Serum concentrations of leptin were determined by radioimmunoassay as described previously.[2] Serum concentrations of DHEAS were determined by a commercially available radioimmunoassay (Orion Diagnostica, Espoo, Finland).

Statistical Analysis

Variables are presented as mean $\pm$ SD. Unpaired t tests and χ^2 tests were used for group comparisons of continuous and categorical data, respectively. To assess correlations of variables, Pearson's correlation coefficient was calculated marginally and adjusted (partialized) for age, sex, and BMI. P values $<$ .05 were considered statistically significant. The SAS System V8.1 (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

By definition, the age of the obese subjects ranged only from 20 to 50 years. Nevertheless, there was a correlation between the patients' age and their serum concentrations of DHEAS ($P < .001$) and cholesterol ($P < .005$). As shown in Table 1, mean BMI was comparable in patients with high- and in those with low-serum cholesterol, but the individuals with a serum cholesterol of $>$ 200 mg/dL were older (39 $\pm$ 8 years v 36 $\pm$ 8 years, $P < .01$). Concentrations of HDL-cholesterol were similar in both groups; consequently, the 2 groups differed in the calculated ratio of cholesterol/HDL-cholesterol ($P <$

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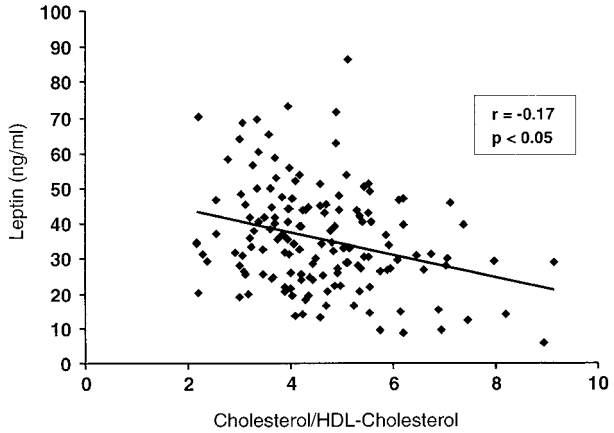

Fig 1. Relationship between serum concentrations of leptin (ng/mL) and the ratio cholesterol/HDL-cholesterol in 155 obese individuals (BMI > 35 kg/m^2) aged 20 to 50 years (corrected for age, sex, and BMI).

.0001). There were no differences in mean serum leptin concentrations. Serum concentrations of DHEAS were 2.2 ± 1.4 μg/dL in patients with low cholesterol and 1.7 ± 1.0 μg/dL in patients with high cholesterol ($P < .05$). Serum concentrations of DHEAS and cholesterol were negatively correlated ($r = -.21$, $P < .01$). There was also a negative (marginal) correlation between DHEAS and the cholesterol/HDL-cholesterol ratio ($r = -.133$, $P < .05$), although not with the concentrations of HDL-cholesterol per se ($r = -.08$, $P > .05$). However, when these correlations were adjusted (partialized) for age, sex, and BMI, they were no longer statistically significant.

Serum concentrations of leptin showed a positive (marginal) correlation with the serum concentrations of HDL-cholesterol ($r = .168$, $P < .05$) and negative (marginal) correlations with the serum concentrations of cholesterol ($r = -.173$, $P < .05$) and with the ratio cholesterol/HDL-cholesterol ($r = -.291$, $P < .0005$) (Fig 1). After adjustment for age, sex, and BMI, the negative correlation between leptin and cholesterol/HDL-cholesterol ratio remained statistically significant ($P < .05$). The adjusted (partialized) positive correlation between leptin and HDL-cholesterol was not statistically significant ($P < .08$).

DISCUSSION

Both obesity[10] and hypercholesterolemia[17] are known risk factors for cardiovascular disease. In addition, some,[9] albeit not all,[18] epidemiologic studies have demonstrated an inverse relationship between serum DHEAS concentrations and coronary artery disease. Some,[19,20] although not all,[21-23] previous investigations have reported decreased concentrations of DHEAS in obesity. This could either be due to an obesity-enhanced metabolic clearance rate of DHEA[24-26] and DHEAS[27,28] or, alternatively, to a decrease in total serum cholesterol induced by DHEA and/or DHEAS.[29,30]

Epidemiologic data have shown a relationship between DHEAS and serum concentrations, triglycerides, and HDL-cholesterol in men[31] and women.[32] However, the potential relationship between DHEAS and serum cholesterol in morbidly obese patients has not been studied in detail. We have previously demonstrated a positive relationship between body weight and serum cholesterol up to a BMI of 35 kg/m^2. Severe obesity (BMI > 35 kg/m^2) is, however, frequently associated with normal concentrations of cholesterol (< 200 mg/dL) and a favorable ratio of cholesterol/HDL-cholesterol.[2] The additional data obtained in the present, larger group of patients do not provide an explanation for this 'paradoxical' behavior of serum cholesterol in a substantial subgroup of obese individuals. Although some potential explanations have been suggested,[2] this question remains unsolved to date. It was the purpose of our study to investigate whether this subgroup of obese individuals might, in addition, be characterized by higher plasma concentrations of DHEAS. When analyzed by an uncomplicated statistical approach, the results of the present investigation seem to indicate that high total serum cholesterol concentrations (and high cholesterol/HDL-cholesterol ratios) in morbid obesity are associated with lower serum concentrations of DHEAS and vice versa, because there is a negative correlation between these variables. However, this correlation is not any more apparent after correction for age, sex, and BMI. Because serum cholesterol concentrations increase[2] and serum DHEAS concentrations decrease[5] with increasing age, it is obvious that the obtained results must be corrected for these two variables, even though only patients between 20 and 50 years had been included in the study. Indeed, after adjustment for age, sex, and BMI, the correlations between cholesterol, HDL cholesterol, and DHEAS were no longer seen as indicating that the two variables are not directly interdependent.

The adipogenic, neuroregulatory peptide, leptin, has recently been reported to enhance intestinal cholesterol absorption in normal and genetically obese mice.[14] Speculating that a similar mechanism might help to explain the dichotomous behavior in serum cholesterol concentrations in morbid obesity, we have tried to correlate serum concentrations of leptin and cholesterol in these individuals. However, in keeping with a previously reported trend,[2] the obtained (marginal) correlation between these 2 variables was negative. Therefore, the results do not support the contention of a leptin-enhanced intestinal cholesterol absoption in patients with high cholesterol. In addition,

Table 1. Serum Concentrations of Cholesterol, HDL-Cholesterol, the Ratio of Cholesterol/HDL-Cholesterol, LDL-Cholesterol, Triglycerides, Leptin, and DHEAS in Mordidly Obese Patients (BMI >35 kg/m^2)

	Cholesterol < 200 mg/dL	Cholesterol > 200 mg/dL	Prob > |T|
No.	72	83	
M/F	10/62	11/72	
Age (yr)	36 ± 8	39 ± 8	0.0074
BMI (kg/m^2)	39.9 ± 4.6	39.0 ± 3.4	0.1825
Chol (mg/dL)	169.8 ± 21.4	241.3 ± 30.1	< 0.0001
HDL-Chol (mg/dL)	45.4 ± 11.6	49.9 ± 13.1	0.0275
Ratio Chol/HDL-Chol	3.9 ± 1.1	5.1 ± 1.3	< 0.0001
LDL-Chol (mg/dL)	99.9 ± 22.3	155.9 ± 27.8	< 0.0001
TG (mg/dL)	128.2 ± 60.9	191.0 ± 116.6	< 0.0001
Leptin (ng/mL)	36.8 ± 15.2	34.3 ± 14.4	0.2983
DHEAS (μg/mL)	2.2 ± 1.4	1.7 ± 1.0	0.0171

Abbreviations: Chol, cholesterol; TG, triglycerides.

the association between leptin and a more favorable lipid profile (ie, higher HDL-cholesterol and a trend towards a lower cholesterol/HDL-cholesterol ratio) indicates that the possible direct link between leptin and the risk of thromboembolic complications in obese individuals[15] may, at least, not be compounded by an additional risk factor.

In summary, there is, in morbid obesity, an association between serum concentrations of leptin and a more favorable lipid profile. In morbidly obese individuals, serum concentrations of cholesterol tend to increase and serum concentrations of DHEAS tend to decrease with age. However, the two variables are not directly interrelated.

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