Prevalence of Paradoxically Normal Serum Cholesterol in Morbidly Obese Women

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The paradox that cholesterol may be lower in extremely obese subjects versus those who are less overweight, although originally observed more than 40 years ago, has never been documented in a systematic fashion. We have therefore prospectively determined the body mass index (BMI) and serum cholesterol concentration in 3,312 women. The percentage of women with serum cholesterol in the normal range (<200 mg/dL) decreased with an increasing BMI, from 55% in women with a BMI less than 20 kg/m^2 to 28% in those with a BMI of 30 to 35 kg/m^2. Serum cholesterol greater than 300 mg/dL was found in only 2% of individuals with a BMI less than 20 kg/m^2 but in 6% of the group with a BMI between 30 and 35 kg/m^2. However, among morbidly obese women (BMI >40 kg/m^2, n = 46), 39% presented with serum cholesterol less than 200 mg/dL and only one woman had serum cholesterol more than 300 mg/dL. With the BMI, the fitted regression model shows an increase in cholesterol for low BMIs, while cholesterol appears to decrease with larger values for the BMI. The age-dependent increase in cholesterol is more evident in younger women versus older women, where it tends to disappear. It is concluded that among morbidly obese women (BMI >40 kg/m^2), there is a substantial subgroup with normal serum cholesterol.

THE ISSUE OF WHETHER serum cholesterol concentrations are related to body weight has been a matter of controversy for at least 40 years. Whereas the majority of investigators concluded that there is no such correlation[1] or that it is weak at best,[2,3] one early report suggested a considerable influence of body weight on cholesterol concentrations.[4] Without considering the possibility that there might be a subgroup of the morbidly obese characterized by normal or even low serum cholesterol, the latter study was subsequently criticized by others[3] since serum cholesterol in grossly obese subjects was found to be lower than in moderately obese persons.[4]

Normal serum concentrations of cholesterol in morbidly obese subjects are indeed a phenomenon encountered in the daily clinical routine. We were interested in documenting the distribution of serum cholesterol among subjects with different body mass index (BMI) levels in a systematic prospective fashion to determine whether normal lipid values are more prevalent among morbidly obese (BMI >40 mg/m^2) versus less obese persons. To this end, we have determined serum cholesterol concentrations in a large number of women, subsequently proven to be euthyroid, who were newly referred to our thyroid outpatient department.

SUBJECTS AND METHODS

Serum cholesterol concentrations were determined in each woman referred to our thyroid outpatient service after April 1, 1997. Patients with known malignant disease and women younger than 18 years were excluded, but no effort was made to exclude patients with any other disease(s) and/or medication. An assessment of thyroid function was made in each case by the determination of thyrotropin (TSH) supplemented by the determination of thyroxine, triiodothyronine, and TSH after stimulation by thyrotropin-releasing hormone when necessary. In patients with thyroid nodular disease, a determination of serum calcitonin, ultrasonography, and ^{131}Tc thyroid scanning were performed on a routine basis. Euthyroidism was thus documented in 3,313 women. This group included patients with diffuse and nodular thyroid disease, as well as women without any thyroid pathology. In patients with a BMI greater than 40 kg/m^2, blood samples were obtained for tests of liver function (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, and cholinesterase) and measurement of triglycerides, high-density lipoprotein (HDL) cholesterol, serum sex hormone–binding globulin (SHBG), leptin, insulin, and free serum cortisol.

The BMI was calculated as the body weight in kilograms divided by the square of the height in meters. Groups with a different BMI were defined according to the classification by Bray.[5] Serum concentrations of cholesterol, HDL cholesterol, and triglycerides and tests of liver function were determined in the routine biochemical laboratory. Insulin, SHBG, and free serum cortisol were determined by radioimmunoassay as described previously.[6-8] Serum concentrations of leptin were determined by a commercially available radioimmunoassay (Linco Research, St. Charles, MO). Intraassay and interassay coefficients of variation for this method were 4.1% and 5.5%, respectively.

Statistical Analysis

Results are reported as the mean ± SD. Two groups and more than 2 groups were compared by the Student *t* test and Duncan multiple-range test,[9] respectively. A linear regression model was fitted to the observed data with cholesterol as the independent variable and the age and BMI as covariates. The plot of studentized residuals versus both the age and BMI showed a systematic behavior, suggesting a quadratic effect. Thus, a quadratic term for both of the covariables was introduced in the final model. Parameters were estimated by least-squares, and *P* values refer to the *t* statistics to test if each parameter is significantly different from 0. Predicted values for cholesterol were computed. To show the shape of the relationship among cholesterol, age, and the BMI, a 3-dimensional plot was drawn based on interpolated predicted values for cholesterol.

RESULTS

Table 1 shows that serum cholesterol was higher in morbidly obese (BMI >40 kg/m^2) women (213 ± 37 mg/dL) than in the

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Table 1. Serum Concentrations of Total Cholesterol, HDL Cholesterol, LDL Cholesterol, and Triglycerides (mg/dL) in 3,312 Women Subdivided by BMI

BMI (kg/m²)	No. of Subjects	Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides
<20	380	198 ± 41†	64 ± 17†	114 ± 36†	89 ± 48†
20-25	1,339	219 ± 44	63 ± 17†	132 ± 38	105 ± 58†
25-30	975	227 ± 42†	58 ± 15†	142 ± 37	131 ± 67*
30-35	455	227 ± 44†	54 ± 14†	143 ± 39	147 ± 74
35-40	117	222 ± 42	52 ± 11*	142 ± 36	142 ± 61
>40	46	213 ± 37	48 ± 12	134 ± 33	150 ± 66

*Morbidly obese (BMI >40 kg/m²) *v* other groups, $P < .05$.
†Morbidly obese (BMI >40 kg/m²) *v* other groups, $P < .01$.

group with a BMI less than 20 kg/m² (198 ± 41 mg/dL) and was comparable to the value in the group with normal (BMI, 20 to 25 kg/m²) body weight (219 ± 44 mg/dL). However, their mean serum cholesterol was lower versus the groups with a more moderate degree of obesity (BMI, 25 to 35 kg/m²). The regression model shows a significant effect of both age and BMI on cholesterol (Table 2). Cholesterol increases with age. The age-dependent increase in cholesterol is more evident in younger women and tends to disappear in older women (Fig 1). With the BMI, the fitted regression model shows an increase in cholesterol for low BMI levels, while cholesterol appears to decrease with larger values for the BMI. The R^2 of the fitted model is .149, showing a limited percentage of explained variation.

HDL cholesterol was lower in the morbidly obese group than in the women with normal body weight or a more moderate degree of obesity. Except for women with a BMI less than 20 kg/m², low-density lipoprotein (LDL) cholesterol was comparable among all groups with a different body weight. Serum triglycerides tended to increase with the BMI, although mean triglyceride concentrations were similar in morbidly obese women compared with the groups with a BMI of 30 to 35 and 35 to 40 kg/m², respectively (Table 1).

The distribution (ie, the frequency and calculated raw percentage) of serum cholesterol concentrations among patients with various degrees of obesity are listed in Table 3. In patients with a normal BMI (20 to 25 kg/m²), the percentage of patients with normal (<200 mg/dL) and markedly elevated (>300 mg/dL) serum cholesterol was 34% and 4%, respectively. The percentage of individuals with markedly elevated serum cholesterol (>300 mg/dL) was comparable (5% to 6%) in groups with moderate obesity (BMI = 25 to 30 kg/m², 5%; BMI = 30 to 35 kg/m², 6%). However, among the 46 women with a BMI greater than 40 kg/m², 18 (39%) presented with normal serum cholesterol concentrations (<200 mg/dL) and only 1 had a serum cholesterol concentration more than 300 mg/dL.

Table 2. Multivariate Regression Model for Cholesterol

Variable	Parameter	Standard Error	T for H0: Parameter = 0	Prob >|T|
Intercept	64.077	14.137	4.532	.0001
BMI	5.045	1.020	4.945	.0001
Age	2.749	0.249	11.033	.0001
BMI²	−0.082	0.179	−4.592	.0001
Age²	−0.019	0.002	−7.792	.0001

Laboratory data for the 46 morbidly obese (BMI >40 kg/m²) individuals are shown in Table 4. None were on any medication known to interfere with lipid metabolism. The 2 groups of mordibly obese patients with normal (<200 mg/dL; mean, 180 ± 15 mg/dL) and elevated (>200 mg/dL; mean, 233 ± 28 mg/dL) serum cholesterol were comparable in age. The results of liver function tests were similar in both groups (data not shown), and there were no differences in the estimated concentration of free serum cortisol (5.7 ± 2.5 *v* 5.3 ± 1.9 ng/mL). Serum concentrations of SHBG were suppressed (<10 nmol/L) in most patients in either group. Serum insulin and leptin were also comparable, although a larger sample size would be needed to prove equivalence (Table 4).

DISCUSSION

Obesity is an extremely common, therapeutically frustrating, and hence expensive metabolic problem. It is associated with a risk of morbidity with regard to cardiovascular disease that is at least 3 times higher than in the general population.[10] In the United States, roughly 1 in every 3 adults are obese.[10] The ensuing costs are 1% to 5% of total health care costs.[11] We have studied the BMI and serum cholesterol in consecutive women referred to our thyroid outpatient service. In regard to the known effects of hyperthyroidism and hypothyroidism on both the BMI and serum cholesterol,[12] noneuthyroid individuals were excluded from further analysis. Although the evaluated outpatient population, by definition, does not represent a completely "normal" population chosen at random, we believe this bias is minor and are therefore confident that the obtained data are representative for Austrian women at the end of the millenium. Thus, about 48% of Austrian females between 18 and 80 years of age have a BMI greater than 25 kg/m².

Obesity is associated with hyperinsulinemia and an increased propensity for diabetes,[13,14] and has been identified as a correctable major determinant of atherogenic traits in the general population.[13] Serum cholesterol concentrations[15] and atherogenic lipoprotein subfractions[16] tend to increase with increasing body weight, but the correlation between the two variables is influenced by additional factors such as age, sex, and ethnic and socioeconomic background and hence has often been found to be weak.[2-4,17-18] One additional reason could be that serum cholesterol is lower in extremely obese subjects than

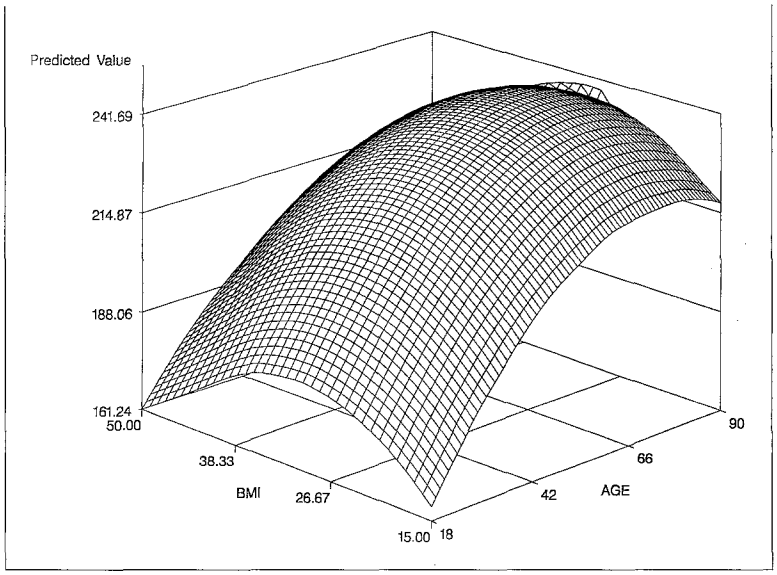

Fig 1. Predicted values for cholesterol according to the fitted regression model.

in patients with a less pronounced degree of overweight. This apparent paradox was first described, albeit indirectly, in 1958 by Miller et al,[4] but was subsequently never documented in a systematic fashion.

The serum cholesterol concentrations in our euthyroid patients emphasize that the relationship between serum cholesterol and body weight is not valid in patients with extreme degrees of obesity, ie, those with a BMI greater than 40 kg/m^2. These morbidly obese patients comprise a substantial subgroup with normal or even low serum cholesterol. Concentrations of LDL cholesterol were similar in all groups of women with a BMI greater than 25 kg/m^2, but HDL cholesterol decreased with increasing BMI, possibly due to a concomitant increase in triglycerides,[19] and this may help to explain the lower concentrations of total cholesterol in the morbidly obese group (BMI >40 kg/m^2). However, 18 of the 46 women in this latter group were characterized by serum concentrations of total cholesterol less than 200 mg/dL. In these individuals, the low total cholesterol concentrations were due to a concomitant reduction in the concentration of LDL cholesterol and not in HDL cholesterol. Indeed, these women presented a mean cholesterol to HDL cholesterol ratio of 3.9 (Table 4). A comparison of morbidly obese patients with elevated versus normal cholesterol fails to demonstrate differences in age, liver function tests, and/or other metabolic variables associated with obesity such as serum leptin, SHBG, and insulin. These additional variables were not determined in patients with normal body weight or less pronounced obesity. The importance of potential differences between these groups compared with massively obese patients therefore cannot be evaluated. In addition, although none of the massively obese patients were on any medication to control body weight and/or hyperlipidemia, we cannot exclude that the dietary habits may have differed in this group versus those with lesser degrees of obesity. Furthermore, the data obtained in this female population need to be confirmed in men. Finally, the analysis of our data confirms that age must be considered as an additional variable.

Among the extremely obese subgroup, serum insulin concentrations were similar in those with normal and elevated serum cholesterol, and there was no dependency between the concentration of insulin and the cholesterol to HDL cholesterol ratio. Likewise, serum concentrations of SHBG, free cortisol, and leptin, parameters either associated with or related to insulin resistance, were similar in both groups of the morbidly obese. In

Table 3. Frequency of Serum Cholesterol Concentrations in 3,312 Women in Different BMI Classes

BMI (kg/m^2)	Cholesterol (mg/dL)										No. of Subjects
	<200		200-225		225-250		250-300		>300		
	No.	%	No.	%	No.	%	No.	%	No.	%	
<20	208	55	96	25	41	11	28	7	7	2	380
20-25	460	34	325	24	259	19	246	18	49	4	1,339
25-30	264	27	225	23	211	22	228	23	47	5	975
30-35	129	28	94	21	108	24	97	21	27	6	455
35-40	35	30	26	22	31	26	21	18	4	3	117
>40	18	39	14	30	8	17	5	11	1	2	46
All	1,114	34	780	24	658	20	625	19	135	4	3,312

Table 4. HDL Cholesterol, LDL Cholesterol, Triglycerides, Cholesterol to HDL Cholesterol Ratio, Leptin, and Insulin in Morbidly Obese Women (BMI >40 kg/m²)

Parameter	Cholesterol >200 mg/dL	Cholesterol <200 mg/dL
No. of subjects	28	18
BMI (kg/m²)	42.6 ± 2.2	43.3 ± 2.9
Age (yr)	47 ± 12	45 ± 15
HDL cholesterol (mg/dL)	49.1 ± 10.7	49.2 ± 14.1
LDL cholesterol (mg/dL)	154.9 ± 27.8	101.8 ± 23.2*
Cholesterol/HDL cholesterol ratio	5.0 ± 1.2	3.9 ± 1.0*
Triglycerides (mg/dL)	165 ± 76	122 ± 43†
Leptin	44.7 ± 14.8	57.8 ± 32.9
IRI (μU/mL)	19.6 ± 8.7	20.8 ± 12.7

Abbreviation: IRI, immunoreactive insulin.
*$P < .01$.
†$P < .05$.

the absence of precise metabolic studies, this does not exclude differences in insulin sensitivity but argues against a major disparity in this respect. Alterations in the expression of a recently described receptor mediating the absorption of dietary cholesterol in the intestine,[20] an abnormal intestinal flora,[21] or a viral infection as described in animal models[22] might be considered as potential additional causes for the low serum cholesterol concentrations in morbidly obese patients.

Our data show that normal concentrations of total cholesterol are found in a substantial proportion of morbidly obese women and are more common than in females with less pronounced obesity. Whether putative differences in the underlying pathophysiologic mechanism(s) causing this type of obesity will result in a different morbidity with regard to the known sequelae of obesity remains to be investigated.

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