Differential Effects of Obesity With and Without Hyperinsulinemia on Plasma Lipoprotein(a) Concentrations in Men

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To determine the association of in vivo concentrations of insulin, obesity, and gender with lipoprotein(a) [Lp(a)] levels, we used a cross-sectional population-based survey of a multistage random sample of the Mexico City adult population. We studied 423 normoglycemic, normotensive subjects from an original sample of 825, comprised of 239 men and 189 women with a mean age of 38.6 years (range, 17 to 90). All subjects were divided into 8 groups according to body mass index, fasting insulin, and gender. Lp(a) concentrations (mg/dL) were similar in obese women with and without high insulin levels (19.9 *v* 18.6), but hyperinsulinemic obese men had significantly lower Lp(a) levels than normoinsulinemic obese men (7.9 *v* 29.4). In addition, the proportion of obese men with Lp(a) concentrations of ≥30 mg/dL was significantly higher in the normoinsulinemic than in the hyperinsulinemic (29.2% *v* 0.0%). The frequency distribution of Lp(a) levels was shifted to a lower range in hyperinsulinemic men compared with normoinsulinemic men. Our results show that in men, hyperinsulinemic obesity is associated with low Lp(a) levels, while obesity with normoinsulinemia is related to increased Lp(a) concentration. These observations were not found in women. These findings may explain the conflicting results reported by several studies.

SOME STUDIES HAVE found an association between obesity and coronary heart disease,[1] but the role of obesity in coronary heart disease morbidity and mortality has been widely debated. Univariate models have consistently shown that obesity contributes to cardiovascular disease.[1,2] In multivariate analyses, however, obesity often ceases to be an independent risk factor.[3] This has led to the proposal that obesity, by itself, is not a significant contributor to coronary heart disease, and that it becomes a problem only when it is associated with other risk factors. Hypertension, diabetes, dyslipidemia, hyperinsulinemia, and insulin resistance are commonly associated with obesity,[4-6] particularly when the excess body fat has a central distribution.[7,8]

The relationship of obesity, an insulin resistance condition, with lipoprotein(a) [Lp(a)] is controversial. Lp(a) is a complex formed by the assembly of low-density lipoprotein particles and a highly glycosylated protein called apolipoprotein(a) [apo(a)], which has a high degree of structural homology with plasminogen.[9,10] Plasma concentrations of Lp(a) vary widely among individuals and are highly heritable.[11] Most retrospective[12,13] and prospective studies[14-17] have found high Lp(a) levels associated with coronary heart disease. Consistent with its mainly genetically determined serum levels, Lp(a) appears to be largely unrelated to endocrine, metabolic, or anthropometric variables.[18] Some investigators have reported a significant inverse[19-22] or positive[23,24] association between Lp(a) levels and body mass index, while others have not.[25-27] Furthermore, weight reduction induced by diet and/or drugs has had variable effects. It has been reported that there was no change in the mean Lp(a) levels in obese patients with weight loss,[28] even in those patients with initial concentrations greater than 70 mg/dL.[29] In another study,[26] a reduction of Lp(a) was observed in obese patients after long-term diet resulting in a considerable weight loss. However, reduction of Lp(a) was seen only in patients with initial levels above 12 mg/dL.

Insulin resistance and hyperinsulinemia may play a role in the determination of cardiovascular disease.[30,31] In 2 studies of nondiabetic subjects, insulin concentrations were not related to Lp(a) concentrations.[18,27] Two recent papers[20,22] reported an inverse association between fasting insulin concentrations and Lp(a) levels in healthy men. Moreover, it has been shown that normoglycemic insulin-resistant subjects do not have elevated Lp(a) concentrations.[32]

No data are available on the association between in vivo concentrations of insulin and Lp(a) levels in obese individuals stratified by circulating insulin. To determine the association of in vivo concentrations of insulin, obesity, and gender with Lp(a) levels, we analyzed plasma Lp(a) levels in normoglycemic, normotensive obese subjects with normal fasting insulin, and the results were compared with those of obese healthy subjects with hyperinsulinemia in the fasting state.

MATERIALS AND METHODS

A cross-sectional survey was conducted between 1991 and 1992 to determine the prevalence of coronary risk factors in a random sample of the Mexico City population. A multistage random sample was obtained from the Mexico City metropolitan area, consisting of 825 individuals, including both working and nonworking residents. The study design, methodology, and other results have been reported previously.[33]

All participants had anthropometric measurements taken including weight, height, and waist and hip circumferences. Body mass index was calculated by dividing weight (in kilograms) by height (in meters) squared (kg/m^2). Venous blood samples were obtained for all participants in tubes containing EDTA (1 mg/mL) after a 12- to 14-hour overnight fast. Plasma glucose was determined by the glucose oxidase method (Boehringer Mannheim, Indianapolis, IN). Plasma concentrations of total cholesterol (TC) and triglycerides (TG) were determined

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by enzymatic methods (Boehringer Mannheim). High-density lipoprotein cholesterol (HDL-C) was measured after precipitating apolipoprotein B containing lipoproteins with the phosphotungstate method (Boehringer Mannheim).[34] Low-density lipoprotein cholesterol (LDL-C) concentrations were calculated by the Friedewald formula modified by De Long et al.[35] Intraassay variation coefficients were for TC, TG, and HDL-C, 1.1%, 0.62%, and 1.14%, respectively; and the interassay variation coefficients were 3.06%, 2.6%, and 3.9%, respectively. Our laboratory participates in the Lipid Standardization Program of the Center for Disease Control in Atlanta, GA. Fasting insulin was measured by a double antibody enzyme-linked immunosorbent assay (ELISA) method in a Boehringer Mannheim ES 33 automated spectrophotometer with intra- and interanalysis variation coefficients of 2.1% and 6.8%, respectively. Cross-reaction with proinsulin with this method was 40%. Lp(a) was measured with an ELISA method (Boehringer Mannheim) with intra- and interanalysis variation coefficients below 10%. In some subjects apo(a) isoform size was determined. The apo(a) isoforms were separated by a 5% acrilamide gel (C = 0.6%) in a MINI PROTEAN II (Bio Rad, Richmond, CA) chamber.[36] Western Blot transfer to 45-μm nitrocellulose paper was performed by Towbin's method.[37] The apo(a) isoforms were identified with a monoclonal anti-apo(a) antibody (Boehringer-Mannheim, M1A2 clone; IgG1) and a horseradish peroxidase labeled antimouse antibody (American Qualex GtxMsIgG H & L, San Clemente, CA) in a substrate of 3,3 diaminobenzidine and H_2O_2. A sensitivity of 50 ng was accomplished with this procedure. Blot analysis was performed in a Model GS-670 (Bio-Rad) densitometer.

For this study, we selected from the original sample of 825 all normoglycemic (fasting glucose <110 mg/dL), normotensive (diastolic pressure <90 mm Hg and systolic pressure <140 mm Hg) subjects, and we divided them in 2 groups: obese (body mass index ≥27) and nonobese (body mass index <27). Each 1 of these groups was further stratified according to their fasting insulin level: normoinsulinemic (NI), which included all those with an insulin level below the 75th percentile (<13 μU/mL) and hyperinsulinemic (HI), which included all those with insulin levels equal to or above the same percentile (≥13 μU/mL). Finally, the results of each variable stratified by obesity and hyperinsulinemia were analyzed for both sexes.

Results for continuous variables are presented as the mean ± standard deviation. Prevalence of risk factors are presented as percentages. Parametric and nonparametric analysis of variance (ANOVA) was used to examine the difference among intergroups for every variable by sex. Scheffé's test was performed to assess the significance of intergroup differences. χ^2 tests were used to assess the difference of the prevalence of risk factors among intergroups. Pearson's correlation coefficients and partial correlations adjusted for body mass index and age between Lp(a) levels and other variables were calculated. Insulin and Lp(a) concentrations were logarithmically transformed to improve the skewness and kurtosis of their distribution. Multiple stepwise linear regression analysis adjusted for age was used to investigate the independent association of common risk factors with Lp(a) levels. The model used Lp(a) as the dependent variable and LDL-C, HDL-C, TG, fasting insulin, fasting glucose, body mass index, systolic and diastolic blood pressure, and waist circumference as independent variables. Data analyses were performed with SPSS for Windows (SPSS Inc, Chicago, IL), version 8.0 statistical software.

RESULTS

We studied 423 normotensive, normoglycemic individuals, 239 men and 189 women, with a mean age of 38.6 years (range, 17 to 90). Figure 1 shows mean plasma Lp(a) concentrations after sequential stratification. Stratifying only by body mass index, mean Lp(a) values for obese subjects were similar to those of the nonobese (19.8 ± 27 *v* 16.6 ± 26, P = not significant [ns]). These 2 groups were then stratified by fasting insulin levels. Obese HI subjects had significantly lower Lp(a) values when compared with their NI counterparts (13.1 ± 19 *v* 24.2 ± 32, $P = .014$). Further stratification by sex showed that the difference between NI and HI obese subjects was only present in men. Obese NI males had the highest Lp(a) concentration (29.4 ± 36), which was more than 3-fold higher than that of obese HI men (7.9 ± 7, $P = .007$). Nonobese NI men did not have higher mean Lp(a) values than nonobese HI men (16.4 ± 24 *v* 10.7 ± 10, $P = .621$), but did have levels that were significantly ($P = .03$) lower than those observed in obese NI men. Similarly, the proportion of subjects with Lp(a) excess (Lp[a] ≥30 mg/dL) was significantly higher in obese NI men than in obese HI (29.27% *v* 0.0%, $P = .001$) (Table 1). In women, mean Lp(a) concentrations were not different when the 4 subgroups were compared (Fig 1). Because Lp(a) has a skewed distribution, a similar analysis was made using median values and Mann-Whitney *U* test; again, the results showed statistical differences between obese NI and obese HI subjects (12.0 *v* 6.45; $P = .038$), obese NI men, and obese HI males (12.9 *v* 6.0; $P = .0074$), and obese NI men and nonobese NI males (12.9 *v* 8.7; $P = .032$).

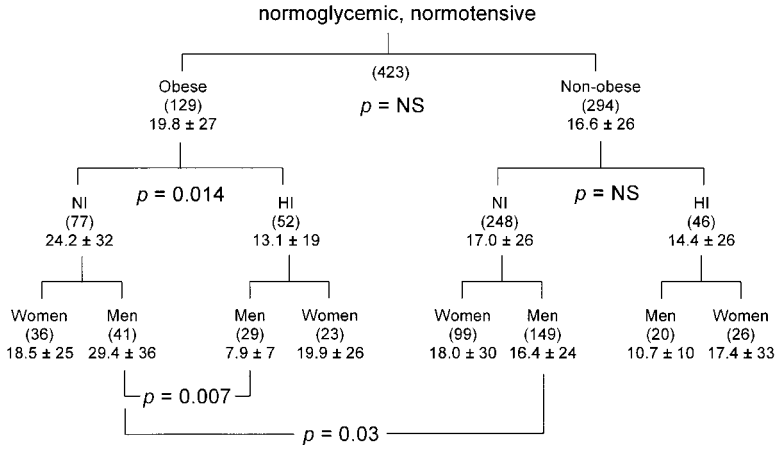

Fig 1. Mean plasma Lp(a) concentrations after sequential stratification by body mass index, insulin, and gender. Lp(a) values (mg/dL) represent mean ± SD; NI, normoinsulinemics; HI, hyperinsulinemics; *P* represents significance of Mann-Whitney's *U* between groups. In parenthesis, no. of subjects in each group.

Table 1. Mean Values for Anthropometric, Physiologic and Metabolic Variables by Body Mass Index and Fasting Insulin Levels in Men

	Nonobese (BMI < 27)			Obese (BMI ≥ 27)		
	Normoinsulinemic	Hyperinsulinemic	*P**	Normoinsulinemic	Hyperinsulinemic	*P**
No.	149	20		41	29	
Age (yr)†	38.1 ± 13‡	36.1 ± 14	.453	42.4 ± 10	41.1 ± 11	.716
Total cholesterol (mg/dL)	199.4 ± 42‡	200.8 ± 34	.999	219.3 ± 36	220.5 ± 29	.999
TG (mg/dL)	144.2 ± 82§	153.7 ± 87‡	.973	198.9 ± 91	226.6 ± 88	.609
LDL-C (mg/dL)	134.6 ± 36	135.6 ± 33	1.000	148.4 ± 32	148.0 ± 27	1.000
HDL-C (mg/dL)†	41.7 ± 11‡	40.6 ± 11	.855	39.0 ± 13	36.3 ± 6	.403
Fastin insulin (μU/mL)	6.5 ± 3	18.0 ± 6	<.001	7.7 ± 3	20.6 ± 8	<.001
Lp(a) (mg/dL)†	16.4 ± 24‡	10.7 ± 10	.621	29.4 ± 36	7.9 ± 7	.007
Systolic blood pressure (mm Hg)	116.3 ± 14	111.4 ± 14	.522	122.5 ± 13	121.3 ± 13	.989
Diastolic blood pressure (mm Hg)	73.6 ± 9	73.1 ± 7	.997	77.1 ± 9	78.6 ± 8	.926
Body mass index (kg/m^2)	23.9 ± 2‖	24.0 ± 2‖	.999	29.0 ± 2	30.4 ± 3	.044
Fasting glucose (mg/dL)	89.8 ± 8	92.2 ± 9	.628	92.1 ± 8	94.7 ± 7	.577
Waist circumference (cm)	85.9 ± 7‖	85.5 ± 8‖	.998	96.3 ± 7	102.8 ± 8	.005
LDL-C ≥ 160 (%)	22.2	30.0	.435	36.6	24.1	.273
HDL-C < 35 (%)	30.9	25.0	.592	41.5	51.7	.399
TG ≥ 200 (%)	20.1§	30.0	.313	43.9	58.6	.228
Lp(a) ≥ 30 (%)	14.8‡	10.0	.568	29.3	0.0	.001

NOTE. Normoinsulinemic (<13 μU/mL); hyperinsulinemic (≥13 μU/mL). Values express mean ± SD.

* *P* values were determined by parametric ANOVA and Scheffé's Post Hoc.

† Analyzed with Kruskal-Wallis ANOVA.

‡ $P < .05$ *v* corresponding obese group.

§ $P < .01$ *v* corresponding obese group.

‖ $P < .001$ *v* corresponding obese group.

Comparisons of anthropometric, physiologic, and metabolic variables by body mass index and fasting insulin for men are presented in Table 1. The only variable significantly different between NI and HI nonobese subjects was, as expected, fasting insulin. Among obese subjects, those with high insulin concentrations showed a significantly higher body mass index and waist circumference than NI subjects. Nonobese NI subjects had lower values of all the standard coronary risk factors when compared with obese NI individuals. Comparisons between nonobese and obese HI subjects showed lower values for TG in the nonobese.

Figure 2 shows a positively skewed distribution of Lp(a) levels in obese and nonobese subjects for men and women. Lp(a) distribution was shifted to lower levels in obese HI men than in NI obese men. The Mann-Whitney *U* test for equality of distributions by normal and high insulin levels was significantly different ($P = .007$). The highest value observed in the NI obese men was 132.9 mg/dL, whereas the highest value in

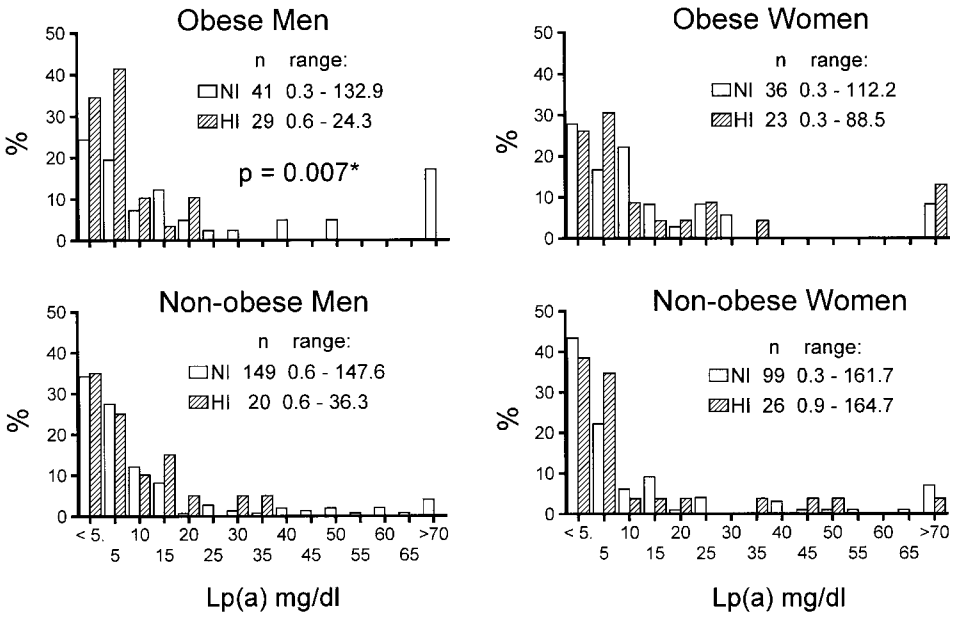

Fig 2. Lp(a) distribution by sex, body mass index, and fasting insulin. *Mann-Whitney *U*. HI, hyperinsulinemic; NI, normoinsulinemic.

the HI obese men was only 24.3 mg/dL. Because these differences in Lp(a) ranges were largely responsible for the significant effects observed, and considering that 90% of Lp(a) variation is genetic in nature, we decided to identify apo(a) isoforms' size to determine whether these 2 groups were or were not genetically similar. Apo(a) isoform measurement could be performed in 32 and 25 obese NI and HI men, respectively, whose plasma aliquots were available. There were no statistical differences in apo(a) size distribution ($P = .099$), indicating the absence of apo(a) genetic differences between NI and HI obese men. Pearson's correlation analyses of Lp(a) concentrations with age, blood pressure, LDL-C, HDL-C, TG, body mass index, waist circumference, fasting glucose, and insulin were performed in the 423 subjects studied. For men, Lp(a) was significantly correlated only with LDL-C ($r = .144$, $P = .026$) and fasting insulin ($r = -.150$, $P = .019$). For women, the correlation with insulin was of borderline significance ($r = -.14$, $P = .054$). Partial correlation coefficients adjusted for age and body mass index showed that Lp(a) remained significantly correlated with insulin ($r = -.160$, $P = .015$) in males, and the association became significant for women ($r = -.150$, $P = .039$).

Multiple regression analysis adjusted by age was next performed to examine the independence of associations between Lp(a) and other variables (Table 2). Independent variables were insulin, glucose, body mass index, waist circumference, blood pressure, lipids, and lipoproteins. In males, insulin was inversely and independently related to Lp(a) ($P = .003$), while LDL-C was directly and independently associated with Lp(a) levels ($P = .008$). In females, insulin levels were negatively and independently related to Lp(a) ($P = .011$). Lp(a) was not associated with any other of the independent variables entered into the model.

Multiple regression analysis was also used to evaluate the independence of the association between Lp(a) values and both insulin and body mass index as independent variables in each of the following groups: obese men, nonobese men, obese women, and nonobese women. Consistent with our findings in Fig 1, insulin was shown to have an independent inverse association with Lp(a) (β: $-.28$; $P = .01$) only in obese men. Body mass index did not show an independent association with Lp(a) in any of the 4 groups.

DISCUSSION

In this study, higher Lp(a) concentrations and a higher proportion of subjects with elevated Lp(a) levels ($\geq$30 mg/dL) were found in obese NI men compared with obese HI and with nonobese NI men (Table 1). The differences in Lp(a) between the 2 subgroups of obese men would seem to be associated with the different insulin levels, while the differences between nonobese and obese NI men might be due to the greater adiposity in the latter group. These significant differences found in men were not observed in obese women stratified by insulin levels.

Table 2. Multiple Stepwise Regression Analysis of Variables Associated With Lp(a)

	β	R^2 (%)*	P
Men			
Insulin†	−.1923	3.7	.003
LDL-C	.1714	0.7	.008
Women			
Insulin†	−.1889	3.6	.011

* The proportion explained by a given independent variable.
† Log-transformed.

In a study of a group of 54 healthy adult men by Duell et al,[20] fasting concentrations of insulin and Lp(a) were negatively and significantly correlated. The same study showed that in a stepwise regression model, the serum insulin level was the single best predictor of Lp(a) concentrations. These observations support the inverse association between insulin and Lp(a) found in our series of subjects by bivariate analyses and by using multiple regression analysis, where the negative relation of Lp(a) and insulin remained significant and independent in both men and women. Lind et al[21] also found that Lp(a) correlated in bivariate, but not in multivariate analysis with the insulin: glucose ratio. In other studies, however, fasting insulin and Lp(a) levels were not related.[18,26,27,38] More recently, a metabolic ward study performed in normoglycemic subjects showed that high nonoxidative glucose disposal is associated with increased Lp(a) concentrations and lower apo(a) molecular weight.[32] Insulin-resistant men tended to have lower Lp(a) levels than insulin-sensitive men. Because fasting insulin concentrations are proportional to the severity of insulin resistance,[39,40] our finding of higher Lp(a) levels in NI men compared with HI men are in agreement with the results reported by Haffner et al.[32] Furthermore, in support of our findings are the results of a recent study[41] showing that insulin decreased apo(a) synthesis by a direct effect on cynomolgus monkey hepatocytes. In addition, apo(a) mRNA concentrations were suppressed to a similar extent as the protein suggesting transcriptional regulation. This conclusion is supported by a preliminary report that apo(a) transcriptional activity was decreased by insulin.[42] These data may provide an explanation for the decreased plasma Lp(a) levels found in our obese HI males.

Reported data on the relationship between obesity and Lp(a) are not consistent. In univariate analysis, an inverse correlation between Lp(a) and body mass index has been observed by several investigators,[19-21] but in multivariate analysis, the significance of the association persisted only in 1 study[19] and only for the female sex. Several other studies[26,27,38,43] have found that body mass index and central body fat distribution, assessed by waist-to-hip ratio and waist circumference, are not related to Lp(a) levels. We also found no relationship between body mass index and waist circumference with Lp(a) concentrations. However, Lp(a) concentration and Lp(a) excess were significantly higher in obese NI men than in nonobese NI men. In these NI subjects of the male sex, a positive partial correlation coefficient, of borderline significance, controlled for insulin, was observed between Lp(a) and body mass index ($r = .14$, $P = .055$). These 2 observations suggest that obesity or some other unknown factor associated with obesity can indeed influence Lp(a) metabolism in men. In obese children, serum leptin concentrations are elevated[44] and a direct association between leptin and Lp(a) has been observed.[45] Interestingly, in this study the investigators found that Lp(a) and leptin levels were decreased after weight reduction. This association deserves further study.

As mentioned previously, women did not show the abnormalities in Lp(a) found in men. This suggests that factors other than insulin and obesity, probably sex hormones, may contribute to the alterations observed in men. Duell et al[20] found a complex interrelation between Lp(a), insulin, body mass index, and testosterone. Other investigators[46] did not find a significant correlation between Lp(a) and free testosterone, estradiol, and gonadotropins, but they did observe a positive and independent relationship between Lp(a) and dehydroepiandrosterone sulfate (DHEA-S). However, Haffner et al[47] found no association of Lp(a) with DHEA-S or with testosterone, estradiol, and sex hormone binding globulin (SHBG). Therefore, the influence of endogenous sexual hormones in Lp(a) metabolism, particularly in obese patients, remains to be determined.

Results of studies concerned with the effect of weight loss on Lp(a) levels have also been controversial. No changes in Lp(a) after weight loss were observed in early[48] and recent[29] reports. In other studies,[26,43,49,50] however, although Lp(a) levels were unrelated to body mass index and body fat distribution, significant reductions in Lp(a) concentrations were found in women,[50] in women, but not in men,[49] and in both men and women after weight loss.[26,43] Of note is that Lp(a) was lowered by weight reduction only in individuals with initial Lp(a) levels higher than 30 mg/dL[50] or 12 mg/dL.[26] In our study, NI and HI obese men had the highest and lowest Lp(a) concentrations, respectively. Weight reduction has been shown to reduce insulin levels[51] and insulin resistance.[52] Therefore, based on our results, obese NI subjects in whom we found the highest Lp(a) concentrations would be expected to reduce their Lp(a) levels, while obese HI subjects with the lowest Lp(a) would not change or even have some increase in their Lp(a) concentrations in response to weight reduction. This speculation needs to be explored in further studies assessing the response to weight lowering in obese patients classified by insulin levels.

One limitation of our study is that we could not assess the possible genetic differences among all the subgroups analyzed. However, we did find that apo(a) isoforms size phenotypes were similar for NI and HI obese men, indicating that Lp(a) differences between these 2 groups cannot be attributed to a different genetic background. A second limitation is that subgroup analysis has been considered of questionable value, and our sample size may be relatively insufficient to draw sound statistical conclusions. We realize that multistage stratification and a small sample size, by increasing the differences between subgroups, may be misleading. However, the sample size is only relatively small. It is important to note that the number of subjects in the normo- and hyperinsulinemic obese women is even smaller than that of men, and nonsignificant differences were found between the 2 subgroups of obese women. Therefore, stratification and small sample size is unlikely to be the reason for the differences found in men. Nonetheless, we feel that a hypothesis generated by a subgroup study, although useful, must be properly tested. For this reason, we are currently in the process of studying prospectively Lp(a) values in obese men with normal and high insulin levels. Also, we hope that our rather unexpected results motivate other research groups to conduct further studies on this subject.

In conclusion, this cross-sectional study shows that in obese normoglycemic, normotensive, NI men, but not in women, Lp(a) concentrations and Lp(a) excess are increased. Our results suggest that an interrelation of insulin, adiposity, and some unknown factors may possess a regulatory role on circulating Lp(a), but additional studies are needed to confirm this finding and uncover the underlying mechanisms.

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