Elevated Serum Lipoprotein(a) Levels in Young Women With Endometriosis

David Crook, Rosemary Howell, Mandeep Sidhu, D. Keith Edmonds, and John C. Stevenson

Elevated serum lipoprotein(a) [Lp(a)] levels increase the risk of cardiovascular disease if levels of low-density lipoproteins (LDLs) are also high. The biological function of Lp(a) is unknown, but plasma levels may be elevated in inflammatory disease. Endometriosis is a common gynecologic disorder in which endometrial tissue is found outside of the lining of the uterine cavity. There is an immune component to this condition whereby the number of peritoneal macrophages is increased and the level of prostanoids and cytokines in peritoneal fluid is elevated. In the present study, we measured serum lipid, lipoprotein, and apolipoprotein levels in 29 women with endometriosis and in 29 matched healthy controls. Fasting serum triglyceride and apolipoprotein (apo) AI levels were higher in women with endometriosis (+28.1%, $P < .001$, and +12.3%, $P < .01$, respectively), but there were no significant differences in LDL or high-density lipoprotein (HDL) cholesterol levels. Serum Lp(a) levels were fivefold higher ($P < .01$) in the patients (median, 15.0 mg/dL; range, 0.05 to 60.0) than in controls (median, 3.1 mg/dL; range, 0.05 to 57.2). The distribution of apo(a) isoforms was similar in the two groups, but in women with endometriosis the individual apo(a) isoforms tended to be associated with higher serum Lp(a) levels. Endometriosis may represent a relatively common condition in which to investigate the role of Lp(a) in human metabolism.

LIPOPROTEIN(a) [Lp(a)] is a cholesterol-rich lipoprotein of unknown function that differs from low-density lipoprotein (LDL) by virtue of a covalently bound glycosylated protein, apolipoprotein(a) [apo(a)]. The amino acid sequence of apo(a) resembles that of plasminogen,[1] enabling Lp(a) to bind fibrin, to compete with plasminogen for receptor binding sites, and to exhibit other antifibrinolytic actions consistent with an atherogenic role.[2] Elevated serum Lp(a) levels are associated with an increased risk of cardiovascular disease, but only if LDL levels are also high.[2]

Endometriosis is a common gynecologic condition of unknown etiology in which functional endometrial tissue is implanted in sites other than the uterine cavity, notably within the pelvis.[3,4] The most widely supported theory invokes retrograde menstruation,[5] whereby endometrial tissue is transported to ectopic sites after being refluxed down the Fallopian tubes during menstruation. Endometriosis may occur where there is a disturbance of the peritoneal macrophage dispersal system that controls the prevention of ectopic endometrial tissue.[6] Consistent with this theory, peritoneal fluid levels of macrophages and their products are elevated in women with endometriosis.[7]

In a clinical trial of danazol,[8] we noted that women with endometriosis often had elevated serum Lp(a) levels, although this was not statistically significant ($P = .06$). Since the investigation of conditions wherein serum Lp(a) levels are abnormal may provide clues to the true function of this potentially important lipoprotein, we studied a new series of patients to investigate a possible link between Lp(a) levels and inflammatory disease. Serum Lp(a) levels in white populations are to a large extent determined according to a complex system of alleles,[9] so we also sought to exclude the possibility that any elevation in Lp(a) levels was due to an abnormal distribution of apo(a) isoforms in women with endometriosis.

SUBJECTS AND METHODS

Participants

We studied 29 premenopausal white women aged 21 to 41 years in whom endometriosis had been confirmed by laparoscopy (revised American Fertility Society[10] [rAFS] median score, 8; range, 4 to 119). The median interval between laparoscopy and metabolic evaluation was 13 days (range, 3 to 85). Seven women had taken analgesics during this time, but none had taken any drugs known to affect lipid metabolism during the previous 6 weeks. None were obese (defined as >120% of ideal body weight, Metropolitan Life Tables 1959), all were otherwise healthy, experienced regular menstrual cycles, and had plasma follicle-stimulating hormone levels within the premenopausal range, and none had been pregnant within the previous 6 months.

For each case, we selected a healthy, premenopausal white woman matched for age and adiposity. These controls had been recruited as part of a concurrent study of the metabolic effects of oral contraceptives.[11] None had taken any drugs known to affect lipid metabolism (including oral contraceptives) for at least 6 weeks before the metabolic evaluation. Full written informed consent was obtained, and the study was approved by the Ethics Committees of Queen Charlotte's and Chelsea Hospital and the Wynn Division of Metabolic Research.

Procedures

Women attended the day ward at 9:00 AM following an overnight (>12-hour) fast. Height and weight were recorded, and a standard questionnaire was used to assess alcohol intake, cigarette smoking, and other factors. Alcohol intake was estimated as units per week; 1 U (nominally 10 g ethanol) was a glass of wine, a small glass of beer, or a small glass of spirits. Cigarette smoking was graded according to the number smoked each day (zero, <five, five to 14, 15 to 26, or >26).

After subjects rested in a semirecumbent position for 10 minutes, 20 mL blood was drawn into plain plastic tubes for preparation of serum. Serum levels of total cholesterol and triglycerides were measured by enzymatic procedures. High-density lipoprotein (HDL), HDL_2, and HDL_3 levels were measured following sequential precipitation with heparin and manganese ions[12] and dextran sulfate,[13] respectively. LDL cholesterol levels were calculated.[14] Serum levels of apolipoprotein (apo) AI, AII, and B were measured by immunoturbidimetry[15]; Lp(a) levels were measured by enzyme-linked immunosorbent assay (Bio-

From the Wynn Division of Metabolic Medicine, Imperial College School of Medicine at the National Heart and Lung Institute, London; and the Department of Obstetrics and Gynaecology, Queen Charlotte's and Chelsea Hospital, London, England.

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Address reprint requests to David Crook, PhD, Wynn Division of Metabolic Medicine, 21 Wellington Rd, St John's Wood, London NW8 9SQ, England.

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pool, Umea, Sweden). This assay measures the total mass of the Lp(a) particle; plasminogen does not interfere with this assay at levels less than 1 mg/mL in the undiluted sample. Serum Lp(a) values less than the lower limit of sensitivity of the assay (.05 mg/dL) were scored as that value. Apo(a) phenotyping was performed with immunoblotting proteins separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis.[16] Apo(a) bands were identified using standards from Immuno (Vienna, Austria) containing bands corresponding to F, S1, S2, and S3 phenotypes. Bands migrating more slowly than S3 were classified as S4.

Apolipoprotein and Lp(a) assays were performed on samples stored at −20°C, whereas fresh samples (stored at 4°C) were used for lipid and lipoprotein assays. Typical within- and between-batch coefficients of variation were 1% to 2% (total cholesterol and triglycerides), 2% to 3% (HDL cholesterol), 5% to 7% (HDL_3 cholesterol), 6% to 8% (HDL_2 cholesterol), 2% to 4% (apos AI, AII, and B), and 10% to 12% [Lp(a)].

Statistical Analyses

Student's *t* test (unpaired, two-tailed) was used to compare age, height, body weight, and adiposity between the two groups. Due to the skewed distribution, differences in alcohol intake and cigarette smoking were assessed using the Mann-Whitney *U* test. Serum lipid, lipoprotein, and apolipoprotein levels in cases and controls were compared using Student's *t* test (unpaired, two-tailed). Due to the skewed distribution, triglyceride and Lp(a) values were logarithmically transformed before statistical analysis; for purposes of clarity, these values are presented as the median and range. These analyses were repeated using analysis of covariance (ANCOVA). Student's *t* test (unpaired, two-tailed) was used to examine between-group differences in Lp(a) levels associated with individual apo(a) genotypes. The chi-square test was used to compare distribution of the various apo(a) genotypes between groups.

Relationships between serum lipids and lipoproteins and continuous variables such as disease severity and the interval between laparoscopy and blood sampling were investigated by plotting these relationships and then deriving Spearman correlation coefficients from untransformed data. All statistical procedures were performed using SYSTAT software (Evanston, IL).

RESULTS

The two groups were well matched, although women with endometriosis tended to be shorter in stature (Table 1). There were no differences in cigarette smoking or exercise habits, but alcohol intake was lower in women with endometriosis (median, 2 U/wk; range, 0 to 21) than in controls (median, 7 U/wk; range, 0 to 28; $P < .01$).

Women with endometriosis had higher levels of triglycerides (+28.1%, $P < .001$) and of the HDL protein apo AI (+12.3%, $P < .01$) (Table 2). There were no differences in HDL or LDL cholesterol levels. Serum Lp(a) levels were fivefold higher in women with endometriosis (median, 15.0 mg/dL; range, 0.05 to 60.0) than in controls (median, 3.1 mg/dL; range, 0.05 to 57.2; $P < .01$) (Fig 1). This difference was maintained when the data were reanalyzed using ANCOVA with height and alcohol intake as covariates. Furthermore, neither height nor alcohol intake correlated with Lp(a) levels ($r = -.187$ and $-.163$, respectively, both $P > .05$). These elevated Lp(a) levels in women with endometriosis were not related to the interval between laparoscopy and blood sampling ($r = -.213$, $P > .05$) or to the severity of the disease as assessed by the rAFS score ($r = .098$, $P > .05$).

The distribution of apo(a) genotypes in these women resembled that reported in other populations[9]: the majority had a single band corresponding to S1, S2, S3, or S4. There were no significant differences in the distribution of apo(a) genotypes between women with endometriosis and controls ($\chi^2 = 11.7$, $P = .232$), but for a given apo(a) genotype, median serum Lp(a) levels tended to be higher in women with endometriosis (Table 3).

Table 1. Age, Weight, Height, and Adiposity in Endometriosis Cases and Healthy Controls

Characteristic	Endometriosis Cases (n = 29)	Healthy Controls (n = 29)
Age (yr)	29.9 ± 5.0	31.3 ± 5.4
Weight (kg)	59.3 ± 7.2	61.4 ± 7.5
Height (cm)	162.8 ± 4.7	166.0 ± 6.0*
Ideal body weight (%)	99.2 ± 9.7	99.1 ± 9.5

NOTE. Values are the mean ± SD.
*$P < .05$ by Student's *t* test (unpaired).

Table 2. Fasting Serum Lipid, Lipoprotein, and Apolipoprotein Concentrations in Endometriosis Cases and Healthy Controls

Parameter	Endometriosis Cases	Healthy Controls
Total cholesterol (mmol/L)	4.22 ± 0.61	3.94 ± 0.72
Triglycerides (mmol/L)	0.76 (0.38-1.29)	0.59 (0.37-0.95)*
LDL cholesterol (mmol/L)	2.45 ± 0.55	2.27 ± 0.58
HDL cholesterol (mmol/L)	1.41 ± 0.29	1.39 ± 0.36
HDL_2 cholesterol (mmol/L)	0.55 ± 0.19	0.55 ± 0.25
HDL_3 cholesterol (mmol/L)	0.86 ± 0.14	0.84 ± 0.14
Apo AI (mg/dL)	130.6 ± 20.1	116.4 ± 19.7*
Apo AII (mg/dL)	34.0 ± 4.8	35.6 ± 6.0
Apo B (mg/dL)	49.3 ± 10.2	52.8 ± 10.7
Lp(a) (mg/dL)	15.0 (0.05-60.0)	3.1 (0.05-57.2)*

NOTE. Values are the mean ± SD, except for triglycerides and Lp(a) (median and range).
*$P < .01$ by Student's *t* test (unpaired).

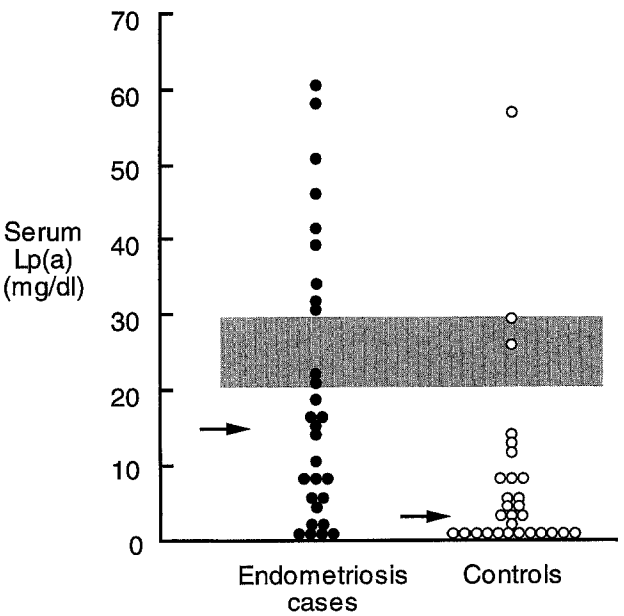

Fig 1. Serum Lp(a) levels in women with endometriosis and in controls. Horizontal arrows represent median values in each group. (▨) Area between 2 candidate upper limits of normality.[17,50]

Table 3. Percentage of Different Apo(a) Phenotypes in Endometriosis Cases and Healthy Controls

	Endometriosis Cases		Healthy Controls	
Genotype	Genotype Frequency (%)	Serum Lp(a) (mg/dL)	Genotype Frequency (%)	Serum Lp(a) (mg/dL)
F	3.4	21.0	—	—
S1	10.3	22.0 (18.6-32.1)	3.4	29.0
S2	27.6	41.9 (0.05-60.0)	20.7	3.4 (0.05-26.0)
S3	10.3	14.2 (10.4-16.5)	20.7	0.08 (0.05-8.1)*
S4	31.0	5.6 (0.05-15.0)	34.5	2.05 (0.05-12.7)
Null	6.9	0.05	3.4	0.05
S1S2	—	—	3.4	2.4
S1S3	10.3	34.4 (30.0-41.2)	—	—
S1S4	—	—	—	—
S2S3	—	—	—	—
S2S4	—	—	10.3	7.2 (0.05-57.2)
S3S4	—	—	3.4	7.3

NOTE. Lp(a) values are the median and range, where applicable.
*$P < .05$, between-group comparison of Lp(a) levels within individual genotypes (Student's t test).

DISCUSSION

This demonstration of a fivefold elevation in median serum Lp(a) levels in women with endometriosis involves one of the largest differentials so far reported for this lipoprotein. Apo(a) exhibits extensive size polymorphism, and an understanding of this heterogeneity is critical to the interpretation of differences in serum Lp(a) levels. Over 90% of the variability in serum Lp(a) levels within populations is genetically determined,[19] mainly due to differences in the number (between 12 and 51) of copies of a domain homologous to plasminogen kringle 4. The precise number of kringles determines the size of apo(a), which in turn is inversely associated with Lp(a) serum concentrations due to variability in apo(a) production rate.[20]

We have attempted to exclude the possibility that the elevated Lp(a) levels in women with endometriosis were due to an inherited overrepresentation of small apo(a) isoforms. The relatively simple phenotyping system used in our study lacks the sophistication of a combination of pulsed-field gel electrophoresis and genomic blot analysis,[21] but would be sufficient to detect the major shift in apo(a) isoform size needed to explain a fivefold increase in serum Lp(a) concentrations. Additional factors in the apo(a) gene or in the promotor region may also be involved. A genetic basis for this abnormality could be ruled out by studying first-degree relatives unaffected by the disease.

Following the discovery of Lp(a) by Berg[22] over 30 years ago, numerous cross-sectional and case-control studies have shown an association between elevated serum levels of this lipoprotein and the presence or severity of cardiovascular disease.[23] Extensive laboratory evidence has further implicated Lp(a) in atherogenesis, both as a component of atherosclerotic lesions and as a promoter of thrombosis.[24] Despite this, there exist various conflicts within the published literature that challenge the simple concept of Lp(a) as an atherogenic particle. For example, the extent of diet-induced arterial disease in transgenic mice expressing the gene for human apo(a) is strikingly increased in one strain,[25] but not in another.[26] Decreasing Lp(a) levels in patients at high risk for cardiovascular disease by LDL apheresis was of little benefit in angiographically defined disease,[27] and two large prospective studies of serum Lp(a) as a predictor of cardiovascular disease failed to demonstrate any association.[28,29]

This latter discrepancy may have been resolved by Maher and Brown,[2] who propose that cardiovascular risk is elevated in subjects with high Lp(a) levels only if LDL levels are concomitantly high. This may reflect an aggregation of Lp(a) and LDL particles when both are present in excess. Such aggregates may be pathogenic when trapped within the intima. This unifying hypothesis may help explain why several African populations have very high Lp(a) levels compared with whites[30] but have little evidence of cardiovascular disease.

These findings raise a major question over the physiologic role of Lp(a). One intriguing possibility is that Lp(a) binds to fibrin in clots at the site of vessel-wall damage and thus provides rapid delivery of cholesterol for membrane repair and wound healing.[1] The possibility that Lp(a) is an acute-phase reactant was first raised by Maeda et al,[31] who found that serum Lp(a) levels peaked 10 days after acute myocardial infarction or unspecified "surgery," normalizing by 30 days. This link with myocardial infarction was found to be weak in a subsequent study,[32] but elevated serum Lp(a) levels have now been reported in leukemia,[33] rheumatoid arthritis,[34] and renal disease.[35,36] The relationship between serum Lp(a) and acute-phase reactants has been confirmed in a series of 570 patients with rheumatic disease.[37] A possible mechanism behind these increases in Lp(a) levels is suggested by the demonstration of multiple functional interleukin-6 (IL-6)–responsive elements in the apo(a) gene promoter,[38] although recent studies using YAC transgenic mice fail to support an active role for these elements.[39]

Endometriosis involves cell-mediated immunity,[7] although the clinical significance of this is controversial.[4] Women with endometriosis have a high volume of peritoneal fluid that contains elevated levels of macrophages and activated macrophage products such as prostanoids, tumor necrosis factor, and interleukins.[40-42] Increased levels of T and B lymphocytes have been described in their peripheral circulation.[43] There is evidence for an involvement of IL-6 in endometriosis. Peritoneal fluid IL-6 levels are normal in women with endometriosis, but stimulated macrophages isolated from the peritoneal fluid released more IL-6 than macrophages isolated from controls.[44,45] Serum IL-6 levels are elevated in rats given endometrial implants,[46] and these levels decrease following surgery for endometriosis.[47] The possibility that IL-6 causes elevated serum levels of Lp(a) in women with endometriosis should be explored. Treatment of endometriosis with gonadotropin-releasing hormone agonists such as goserilin does not affect Lp(a) levels (Crook D, Howells R, unpublished data, April 1994), but these levels decrease 79% when women are treated with danazol.[8] This is intriguing because only the latter has immunosuppressive properties.[48]

The elevated triglycerides in women with endometriosis may be due to the ability of cytokines to affect hepatic synthesis of lipids and inhibit lipoprotein lipase, a key enzyme in triglyceride metabolism.[49] The increased apo AI levels seen in these women conflict with the lack of a difference in HDL cholesterol content. It is conceivable that HDL composition may be altered in this condition.

Although there are no prospective data on the relationship

between serum Lp(a) and coronary heart disease in women, case-control studies in men suggest upper limits of normal of 30 or 20 mg/dL.[17,18] Using these cut-off points, 28% to 38% of women with endometriosis would be considered at risk (Fig 1), compared with 3% to 7% of controls. We are not aware of any increased incidence of cardiovascular disease in these women, perhaps because their LDL levels tend to be low, thus reducing the atherogenic impact of Lp(a).

The prevalence of symptomatic endometriosis, often presenting as cyclic pelvic pain and dyspareunia, has been estimated[50] at 1%, whereas 21% of women under investigation for infertility have the disease.[51] In the absence of a reliable noninvasive diagnostic test, the true incidence of this disease is unknown, but endometrial deposits are evident in perhaps 6% of all women undergoing procedures such as laparoscopic sterilization.[51] Thus, endometriosis represents a relatively common condition in which to study the regulation of Lp(a) levels by the immune system, as well as the influence of elevated Lp(a) levels on other systems. The recent identification of transforming growth factor-β (TGF-β) as a key inhibitor of atherogenesis has led to the development of a model of this disease[52] in which both Lp(a) and plasminogen activator inhibitor-1 act as independent inhibitors of tissue plasminogen activator, preventing activation of TGF-β. These hypotheses could be tested in women with endometriosis, whose elevated serum Lp(a) levels would be predicted to profoundly influence both fibrinolysis and TGF-β activation.

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