Antibodies to Lysophosphatidylcholine Are Decreased in Borderline Hypertension

Ruihua Wu, Carola Lemne, Ulf de Faire, Johan Frostegård

Abstract—Atherosclerosis is characterized by infiltration in the lesions of cytokine-producing T cells and macrophages, where oxidized LDL may play an important role. However, little is known about the role of the immune system in the development of hypertension. Lysophosphatidylcholine (LPC) is formed by phospholipase A₂–induced hydrolysis and/or by oxidation of LDL and other phospholipid-containing membranes. The objective of the present study was to investigate the role of antibodies to LPC in borderline hypertension (BHT). Seventy-five men with BHT were compared with 75 age-matched normotensive (NT) men (diastolic blood pressure 85 to 94 and <80 mm Hg, respectively). Antibody levels to LPC of IgM and IgG isotypes and IgG subclasses were determined with ELISAs. BHT men had significantly lower anti-LPC antibody levels of both IgG class ($P=0.0002$) and IgM class ($P=0.0003$) than did NT controls. Subclass analysis indicated that IgG₁ ($P=0.0005$), but not IgG₂, was decreased. Anti-LPC antibodies or immunoglobulin subclasses thereof were negatively associated with atherosclerosis on the basis of intima-media thickness ($P=0.02$), metabolic factors ($P=0.02$), smoking ($P=0.02$), and endothelin ($P=0.03$). LPC has proinflammatory properties and is toxic at higher concentrations and thus may play a role in atherogenesis. Furthermore, LPC functions as a vasoconstrictor in experimental systems by inhibiting NO-mediated vasorelaxation. An intriguing possibility is that anti-LPC antibodies counteract these effects. Taken together, our data indicate that anti-LPC antibodies may constitute a novel factor in the development of hypertension and atherosclerosis. (Hypertension. 2001;37:154-159.)

Key Words: antibodies ■ lysophosphatidylcholine ■ hypertension, borderline ■ atherosclerosis

Hypertension is an important risk factor for atherosclerosis, although the mechanisms by which hypertension is related to atherosclerosis are not yet known. Recent data indicate that atherosclerosis is an inflammatory disease and that proinflammatory cytokines are produced at significant levels in the lesions, which are characterized by an infiltration of monocytes/macrophages and T cells. Knowledge regarding the precise role of the immune system in hypertension is scarce, but alterations in immunological factors such as decreased T-cell responses and abnormalities in complement function, as well as enhanced immunoglobulin levels, have been reported in hypertension.

Oxidized (ox)LDL is one factor that is implicated in atherogenesis. We and others have reported that oxLDL has proinflammatory and immunostimulatory properties and thus may contribute to the inflammation in the artery wall. At higher concentrations than those that induce immunostimulation, oxLDL is also inhibitory and even toxic, a property that may also contribute to endothelial damage and atherogenesis. Potentially atherogenic proinflammatory properties of oxLDL are mediated by platelet-activating factor–like lipids formed in oxLDL. Antibodies to oxLDL (aoxLDL) are present in normal healthy individuals and have been demonstrated to be associated with the degree of established atherosclerosis. On the other hand, immunization with oxLDL decreased the development of early atherosclerosis in experimental animals, and we recently showed that aoxLDL are decreased in early cardiovascular disease, as in borderline hypertension (BHT).

Lysophosphatidylcholine (LPC) is formed by phospholipase A₂–induced hydrolysis or by oxidation of PC in phospholipid-containing structures as LDL and cell membranes. LPC has the capacity to mimic proinflammatory properties of oxLDL, such as induction of proinflammatory cytokines, and may also function as a platelet-activating factor–like lipid in an experimental model, possibly after further enzymatic modification. Furthermore, LPC is an antigenic epitope in oxLDL, a finding that does not exclude that other antigens are also important in oxLDL.

Recently, borderline hypertension (BHT) was also demonstrated to be a risk factor for atherosclerosis. BHT is a condition that represents early cardiovascular disease and...
therefore interesting in determination of the role of immune reactions and inflammatory factors in early stages of disease development. We therefore studied the antibody levels to LPC in a group of 75 middle-aged men with BHT, compared with age-matched normotensive (NT) controls. The levels of antibodies to LPC (aLPC) were decreased in patients with BHT, and aLPC or subclasses thereof were also negatively associated with intima-media thickness, smoking, and metabolic factors. We discuss the possible implications of these observations.

Methods

Study Group

Patients were recruited from a population screening program as previously described. BHT was defined as diastolic blood pressure (DBP) of 85 to 94 mm Hg, and the screening identified 81 men who remained within the range for BHT during repeated measurements during a 3-year period. From the same population, 80 age-matched controls were recruited whose BP was measured on 2 occasions a few weeks apart and was <80 mm Hg on both occasions.

The study was approved by the local ethics committee of Karolinska Hospital and conducted in accordance with the Helsinki Declaration. All subjects gave informed consent before entering the study. Of the 81 men with BHT and the 80 NT controls who agreed to participate, 75 in the BHT and 75 in the NT group completed all procedures of the present study. None of the subjects had any other illnesses or were regularly using any drugs known to influence BP or metabolic or inflammatory variables.

Study Protocol

All subjects were investigated according to the same schedule. Both BHT and NT controls were investigated simultaneously when possible and no more than 4 weeks apart. Blood samples for analyses were taken after the subjects had rested for 5 minutes in the supine position. Systolic BP (SBP) and DBP were defined according to Korotkoff phases I and V, respectively, and the same specially trained nurse took all measurements.

Blood Pressure Measurements

All BP measurements were performed with a mercury sphygmomanometer according to an identical procedure throughout the study. The cuff was placed at heart level, and the BP was recorded as the phase V of Korotkoff sounds (Korotkoff phase V). Systolic BP according to an identical procedure throughout the study. The cuff was placed at heart level, and the BP was recorded as the phase V of Korotkoff sounds (Korotkoff phase V). Systolic BP (SBP) and DBP were defined according to Korotkoff phases I and V, respectively, and the same specially trained nurse took all measurements.

Total Serum Immunoglobulin Levels

Serum immunoglobulin IgG, IgM, and IgA levels were determined with immunoturbidimetry. Specific anti-IgG, anti-IgM, and anti-IgA reagents and calibrators were obtained from DAKO. The turbidimetric reaction was quantified in an Hitachi 911 analyzer by measuring light transmission at a 340-nm wavelength.

Lipoproteins, Endothelin, and Metabolic Factors

Lipid and lipoprotein levels were determined with a combination of preparative ultracentrifugation followed by lipid analyses in the lipoprotein fractions as previously described.

The insulin resistance was calculated (cIR) with the formula

\[
\text{IR} = \frac{\text{fasting insulin}}{22.5 + \text{fasting glucose}}. \]

Endothelin-1 in plasma was analyzed with a competitive immunoassay as described in detail previously.

The metabolic syndrome is based on the presence of ≥2 of the following 3 conditions: body mass index >27 kg/m², insulin levels above the 90th percentile of the normal population, and dyslipoproteinemia.

Lipids and Reagents

1-a-Lysophosphatidylcholine (LPC; from egg yolk type 1, produced with phospholipase A₁ treatment) was obtained from Sigma Chemical Co.

LDL was isolated as described from the plasma of healthy donors through sequential preparative ultracentrifugation in a 50.3-T Beckman fixed-angle rotor (Beckman LS-80 ultracentrifuge) for 48 hours at 4°C and collected in the density interval of 1.025 to 1.050 kg/L. The LDL was oxidatively modified as previously described.

Determination of Antibody Levels

IgG and IgM antibodies against LPC were analyzed essentially as described previously. Briefly, Titertek 96-well polystyrene microplates (Flow Laboratories) were coated with 50 μL/well of 50 μg/mL LPC dissolved in ethanol and allowed to dry overnight at 4°C. Blocking was accomplished with 20% adult bovine serum (ABS)-PBS for 2 hours. Fifty microliters of serum samples, diluted 1:30 in 20% ABS-PBS, was added to each well.

After 3 washings with PBS, the plates coated with LPC were incubated with 50 μL/well of alkaline phosphatase–conjugated IgG (Sigma A-3150) diluted 1:9000 or IgM (Sigma A-3275) diluted 1:7000 with PBS at 37°C for 2 hours. After 3 washings, 100 μL substrate (phosphatase substrate tablets; Sigma 104; 5 mg in 5 mL diethanolamine buffer) was added. The plates were incubated in room temperature for 30 minutes and read in an ELISA Multiskan Plus spectrophotometer at 405 nm. Each determination was made in triplicate. The coefficient of variation between triplicate tests was <5%.

The aoxLDL were determined as described in detail previously. For aLPC subclass determination, Titertek 96-well polystyrene microplates (Flow Laboratories) were coated with 50 μL/well of 50 μg/mL LPC dissolved in ethanol and allowed to dry overnight at 4°C. Blocking was accomplished with 20% ABS-PBS for 2 hours. Fifty microliters of serum samples, diluted 1:30 in 20% ABS-PBS, was added to each well. The plates were washed with PBS buffer containing 0.05% micro-zwitterionic detergent. Blocking was accomplished with 20% ABS for 1 hour at room temperature. After washing, serum specimens of 50 μL diluted 1:50 in 20% ABS-PBS were added to each well. The plates were covered with plate sealers and incubated for 1 hour at room temperature on a horizontal orbital microplate shaker set at 550±50 rpm. After washing, the antibodies used were mouse anti-human IgG1, IgG2, IgG3, and IgG4, (Sigma Chemical Co; I-2513, I-5635, I-7260, and I-7385; the dilutions of each reagent were 1:1000 diluted alkaline phosphatase–conjugated goat anti-mouse IgG (Sigma A-5153). After washing, 50 μL/well of phosphatase substrate (p-nitrophenyl phosphate; Sigma N-2640) was added.
Table 1. Basic Characteristics of the Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT Group (n=73)</th>
<th>BHT Group (n=73)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.0±6</td>
<td>50.0±6</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>125/75±11/4</td>
<td>141/89±10/2</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.6±2.9</td>
<td>25.9±2.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.90±0.05</td>
<td>0.92±0.05</td>
<td>0.022</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>37±5</td>
<td>32±5</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>5.5±1.0</td>
<td>5.5±0.9</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>1.27±0.27</td>
<td>1.16±0.28</td>
<td>0.016</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>0.34±0.80</td>
<td>1.57±0.77</td>
<td>0.015</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.85±0.69</td>
<td>1.0±0.68</td>
<td>0.029</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>14.2±4.5</td>
<td>17.4±5.7</td>
<td>0.0004</td>
</tr>
<tr>
<td>Endothelin, pmol/L</td>
<td>1.5±0.7</td>
<td>2.0±0.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are given as mean±SD.

added. The plates were incubated at room temperature for 30 minutes and then read in an ELISA reader at 405 nm.

Statistical Methods

For skewed variables, nonparametric tests were used for comparisons between the groups (Mann-Whitney U test), whereas Student’s t test was used for normally distributed variables. Spearman rank correlation coefficients were calculated to estimate interrelations among antibody levels, metabolic variables, and BP levels. The significance level was put at P<0.05.

Results

Characteristics of Cases and Controls

Basic characteristics of the 2 study groups are presented in Table 1. The mean BP level in the NT group was 125/75±11/5 mm Hg compared with 141/89±10/2 mm Hg in the BHT group.

The BHT men had a significantly altered metabolic profile with fasting hyperinsulinemia and dyslipoproteinemia (Table 1). In the BHT group, 26% of the subjects had detectable carotid plaques on 1 or both sides, whereas the corresponding figure for the NT group was 16% (19 versus 10 subjects, NS). The BHT group also had a significantly higher body mass index and waist-to-hip ratio.

Associations With Blood Pressure Risk Factors and Atherosclerosis

aLPC of IgG and IgM were significantly lower in the BHT group compared with the NT group (Table 2). To further elucidate the finding that aLPC were decreased in BHT, IgG subclass analysis was performed. As indicated in Table 2, aLPC of IgG1 subclass were significantly decreased in BHT compared with NT individuals.

DBP was negatively associated with aLPC levels of IgG class (R=0.33, P=0.0001) and IgM class (R=0.31, P=0.0002). Twenty-four-hour DBP tended to be negatively associated with aLPC of IgG1 subclass (P=0.08) and IgM isotype (P=0.058) but not with other antibodies tested (data not shown). SBP tended to be negatively associated with aLPC of IgG1 subclass (P=0.08) and IgM isotype (P=0.07) but not with other antibodies tested (data not shown). Twenty-four-hour SBP was negatively associated with aLPC levels of IgG1 (R=0.233, P=0.005) and IgG2 (R=0.162, P=0.05) class.

Associations With Risk Factors and Atherosclerosis

IMT was negatively associated with aLPC of IgG1 (R=0.191; P=0.02) and IgG2 (R=0.195, P=0.02) subclasses. There was no association between antibodies of IgM class and IMT. However, there was a trend to a positive association between IMT and aLPC of IgM class in the BHT group (data not shown).

There was a negative association between smoking and metabolic syndrome and aLPC antibodies (Table 2). There was a weak negative association between VLDL and aLPC of IgG class (R=0.161, P=0.049).

An interesting finding was a negative association between endothelin, the most potent vasoconstrictor described, and aLPC of IgM isotype (R=0.181, P=0.03).

Table 2. Antibody Levels to LPC in BHT and NT Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>aLPC IgM</th>
<th>aLPC IgG</th>
<th>aLPC IgG1</th>
<th>aLPC IgG2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT (n=75)</td>
<td>0.212±0.016</td>
<td>0.393±0.016</td>
<td>0.207±0.007</td>
<td>0.243±0.006</td>
</tr>
<tr>
<td>BHT (n=75)</td>
<td>0.156±0.007</td>
<td>0.317±0.015</td>
<td>0.175±0.006</td>
<td>0.245±0.007</td>
</tr>
<tr>
<td>P</td>
<td>0.0003</td>
<td>0.0006</td>
<td>0.0005</td>
<td>NS</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=104)</td>
<td>0.184±0.011</td>
<td>0.359±0.014</td>
<td>0.193±0.006</td>
<td>0.251±0.006</td>
</tr>
<tr>
<td>Yes (n=46)</td>
<td>0.183±0.018</td>
<td>0.346±0.02</td>
<td>0.185±0.008</td>
<td>0.228±0.007</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.028</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=98)</td>
<td>0.189±0.010</td>
<td>0.366±0.006</td>
<td>0.190±0.006</td>
<td>0.252±0.006</td>
</tr>
<tr>
<td>Yes (n=52)</td>
<td>0.173±0.018</td>
<td>0.335±0.008</td>
<td>0.192±0.008</td>
<td>0.229±0.007</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM.
To exclude the possibility that differences in antibody levels simply reflect differences in total antibody levels, IgG and IgM levels were determined. There was no difference between the BHT group and controls (IgG $9.71 \pm 1.9$ versus $9.76 \pm 2.3$ mg/mL, IgM $2.25 \pm 0.8$ versus $2.1 \pm 0.9$ mg/mL, respectively).

There was a significant correlation between antibody titers against oxLDL and LPC of both IgG ($R=0.57$, $P<0.0001$) and IgM ($R=0.56$, $P<0.0001$) isotypes.

Age was not associated with aLPC levels (data not shown). aLPC of IgG3 and IgG3 subclasses were low (data not shown).

### Discussion

The main finding in the present report was that aLPC levels are decreased in BHT and negatively associated with both SBP and DBP. aLPC were significantly associated with aoxLDL, a finding in line with our recent observation that LPC is a major compound in oxLDL. Whether LPC (and other phospholipids) is an antigen in itself or, more likely, in the form of a complex formed with protein cofactors remains to be elucidated.

Antibody titers to relevant antigens were not generally decreased in BHT. Instead, antibodies to both heat shock proteins and endothelial cells and antigens related to endothelial cells and recognized by antibodies to endothelial cells, $\beta_2$-glycoprotein-I, and platelet-activating factor (data not shown) were raised. These antibodies were significantly associated with both BP and atherosclerosis.

In addition, total antibody concentrations showed no difference between controls and BHT patients, indicating that the results do not simply reflect changes in total immunoglobulin levels. Decreased aLPC titers are thus not likely to be only an artifact.

In principle, decreased antibody levels may reflect an increased consumption of aLPC in BHT, a decreased production, or both. Immune complexes against apoB-containing particles in sera were not higher in BHT individuals than in controls, indicating that aLPC levels are not decreased because of increased binding to LPC in oxLDL with subsequent immune complex formation and enhanced removal. However, the possibility that aLPC may also bind other LPC-containing compounds or be trapped in early atherosclerotic lesions cannot be excluded. aLPC were not decreased in individuals with established carotid plaques compared with those without, arguing against this latter possibility.

The decreased immunoreactivity to LPC in BHT individuals may also be due to a decreased production, either because of a lower exposure to the antigen, leading to a low immune response, or because this immune response is downregulated due to some other as yet unidentified mechanism. In general, immunological tolerance may be induced by an oral intake of an antigen, as exemplified by collagen II in rheumatoid arthritis rat models. Whether oral tolerance may also be present as a specific response against certain lipid-containing and even oxidized compounds in the food is not known. To clarify this issue, further research both in animal models and in humans is warranted.

Although oxLDL and LPC are implicated in atherogenesis, it is not well known whether oxLDL and LPC play any role in hypertension. Available experimental evidence suggests that oxLDL may increase vascular tonus by inhibiting nitric oxide release. LPC, as a major factor in oxLDL, is responsible for these properties of oxLDL. Furthermore, HDL could inhibit oxLDL- and LPC-induced hypertension by removing LPC from oxLDL. In principle, alPC could thus protect against hypertension by blocking and/or removing LPC from the vascular system and therefore represent a novel mechanism by which BP is modulated, with possible therapeutic implications.

In the present study, aLPC levels were negatively associated with endothelin, a potent vasoconstrictor; this finding may constitute yet another, nonmutually exclusive possibility as to how aLPC may modulate BP.

The role of aLPC in developing atherosclerosis, as determined here by IMT, seems to be more complex. Little is known about aLPC in animal models, but immunization with oxLDL leading to an enhanced immune response to oxLDL was shown to decrease atherosclerosis in both mice and rabbit models. Our finding that aLPC of IgG class, but not aoxLDL, were negatively associated with IMT is therefore compatible with a protective function of an immune reaction to LPC that may be more efficient than aoxLDL.

aLPC of IgM class, on the other hand, were not associated with IMT and were even positively associated with IMT in the BHT group. Furthermore, a negative association between IMT and aLPC of IgG isotype was not detected in the BHT group, only in the NT group and in the whole study group. In a study focused only on late-stage disease development, the interpretation may thus well have been that aLPC were indeed positively associated with atherosclerosis.

Previous studies have demonstrated a positive association between the degree of established atherosclerosis and antibody levels to oxLDL, and it is possible that at a later stage of disease development, enhanced antibody levels may simply reflect the chronic inflammation in the artery wall. Likewise, in established hypertension, our data indicate that aLPC and aoxLDL were not decreased and for some antibodies increased (unpublished observation), a finding in line with published data on aoxLDL and established hypertension. aLPC and aoxLDL may therefore play different roles in atherogenesis depending on disease stage.

aLPC levels of IgG3 subclass were decreased in both smoking and the metabolic syndrome. The cause of this intriguing finding remains to be elucidated but may in principle predispose to the development of atherosclerosis. Potential mechanisms include both a specific downregulation due to tolerance development and an enhanced consumption of antibodies.

The role of immune reactions in atherosclerosis is unclear in general, because cell-mediated immune reactions have been reported to be related to both an increase and a decrease in the development of disease. These apparently conflicting data may be related to the different animal models used, but it is also possible that the role of the cell-mediated immune system in atherogenesis may depend on the disease stage and on the presence of other risk factors.
Even less is known about the role of the immune system in the development of hypertension. In established hypertension, alterations of immune reactions such as decreased T-cell responses and abnormalities in complement function, and also hypergammaglobulinemia, have been reported, although the significance of these findings is not clear. In animal models we have investigated the role of humoral immune reactions in a series of studies in BHT to clarify the role of immune reactions, especially humoral, in the early stages of hypertension (and of atherosclerosis). We demonstrated that antibodies to endothelial cells were positively associated with BHT and early atherosclerosis. Aβ₂-glycoprotein-I was an important antigen on the endothelial cells, and antibodies to Aβ₂-glycoprotein-I were significantly associated with BHT. A recent interesting study indicates that immunization with this compound aggravated atherosclerosis in a mouse model. Likewise, antibodies to HSP65 were raised in BHT, and immunization with HSP65 enhanced atherosclerosis in rabbits. On the other hand, immunization with oxLDL, generating enhanced aoxLDL levels, decreases atherosclerosis in both rabbit and mouse models, which is in line with our recent observation that aoxLDL were decreased in early cardiovascular disease. Evidence from immunization experiments with animal models are thus in line with our findings in humans.

The nature of the antigen thus may have fundamental effects on the outcome of immune reactions in atherosclerosis and early cardiovascular disease, as in BHT. The finding that aLPC were low only for IgG1 subclass in BHT may indicate the significance of these findings is not clear. We have investigated the role of humoral immune reactions in a series of studies in BHT to clarify the role of immune reactions, especially humoral, in the early stages of hypertension (and of atherosclerosis). We demonstrated that antibodies to endothelial cells were positively associated with BHT and early atherosclerosis. Aβ₂-glycoprotein-I was an important antigen on the endothelial cells, and antibodies to Aβ₂-glycoprotein-I were significantly associated with BHT. A recent interesting study indicates that immunization with this compound aggravated atherosclerosis in a mouse model. Likewise, antibodies to HSP65 were raised in BHT, and immunization with HSP65 enhanced atherosclerosis in rabbits. On the other hand, immunization with oxLDL, generating enhanced aoxLDL levels, decreases atherosclerosis in both rabbit and mouse models, which is in line with our recent observation that aoxLDL were decreased in early cardiovascular disease. Evidence from immunization experiments with animal models are thus in line with our findings in humans.

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References


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