Changes in Plasma Triglyceride Levels Shift Lipoprotein(a) Density in Parallel With That of LDL Independently of Apolipoprotein(a) Size
Kei Nakajima, Janet Hinman, Ditta Pfaffinger, Celina Edelstein, Angelo M. Scanu

Abstract—Lipoprotein(a) [Lp(a)] represents a class of low density lipoprotein (LDL) particles that have as a protein moiety apolipoprotein B-100–linked covalently to a single molecule of apolipoprotein(a) [apo(a)], a specific multikringle protein of the plasminogen family. Lp(a) is polymorphic in density because of either the density heterogeneity of constitutive LDL, apo(a) size, or both. Authentic LDL also represents a set of heterogeneous particles whose density is affected by metabolic events. Whether in vivo these events may also affect Lp(a) density is not clearly established. To this effect, we studied 75 subjects with plasma Lp(a) protein levels between 7 and 50 mg/dL and containing a single apo(a) size isoform. We used density gradient ultracentrifugation to simultaneously monitor the changes in the peak density of LDL and Lp(a) at entry and during the course of treatments directed at reducing plasma triglyceride levels. In each case, we found that at entry, Lp(a) peak density was correlated with LDL peak density ($r=0.71, P<0.0001$) and that during treatment, changes in plasma triglycerides were associated with shifts of Lp(a) peak density that paralleled those of LDL peak density. A high correlation ($r=0.94, P<0.0001$) was particularly evident in subjects with initial plasma triglycerides in the 300-mg/dL range. In vitro assembly studies showed that an apo(a) isoform containing 14 kringle IV type 2 repeats, exhibited, on incubation with LDL, a comparable degree of incorporation into LDL species varying in density between 1.035 and 1.057 g/mL Taken together, our results indicate that metabolically dependent changes in the peak density of Lp(a) can occur independently of apo(a) size. These changes may have to be taken into account in assessing the cardiovascular pathogenicity of this lipoprotein particle in hypertriglyceridemic subjects. (Arterioscler Thromb Vasc Biol. 2001;21:1238-1243.)

Key Words: hypertriglyceridemia | lipoprotein(a) density | LDL density | apolipoprotein(a) size polymorphism | lipoprotein(a) cardiovascular pathogenicity

Lipoprotein(a) [Lp(a)] constitutes a class of lipoprotein particles that is more commonly represented by LDL having as a protein moiety 1 molecule of apoB-100 linked covalently to 1 molecule of apo(a).1,2 Apo(a) varies in size between 300 and 800 kDa, depending on the number of kringle IV (KIV) type 2 repeats. This size polymorphism is an important determinant in the density heterogeneity of Lp(a).3,4 Another important contributing factor to the density of Lp(a) is the density of its constitutive LDL, which is the resultant of the surface concentration of phospholipids, unesterified cholesterol, core cholesteryl esters, and triglycerides and the content of apoB-100.5-7 Several density-dependent species of LDL may be present in the plasma as a function of genetic effects and metabolically related events. An example is provided by the shift in density between small dense and larger buoyant LDLs occurring as a function of the plasma levels of triglyceride-rich particles.8 As an LDL variant, Lp(a) would be expected to undergo metabolically dependent density remodeling. However, the information on this subject is limited. Thus, in the present study, we used temporally spaced density gradient ultracentrifugal analyses to determine the peak densities of LDL and Lp(a) in each of our study subjects who expressed in their plasma a single apo(a) size isoform at entry and while undergoing treatment for their dyslipidemia. In the present study, we show that at entry, the peak density of Lp(a) was highly correlated with that of LDL peak density and that modifications of the plasma triglyceride levels were attended by parallel shifts of the 2 peak densities independently of apo(a) size.

Methods

Materials
Materials were purchased from the following sources: 4-amidinophenylmethanesulfonyl fluoride, tris+trehalose EDTA, di-thioerythritol, 2-mercaptoethanol, and butylated hydroxytoluene from Sigma Chemical Co; molecular weight standards for native gradient gels from Pharmacia-LKB; DNA size standards and polyacrylamide from Bio-Rad; Immobilon-P membranes from Millipore; and an enhanced chemiluminescent kit (ECL Western Blot...
Human Subjects

The 75 subjects were chosen from the patient population of ~300 patients followed in the Lipid Clinic of the University of Chicago because of a personal and/or family history of a plasma lipoprotein abnormality and atherosclerotic cardiovascular disease. The latter was assessed by the occurrence of ≥1 cardiovascular events, positive coronary angiographic analyses, or a thallium stress test. The characteristics of the population studied are summarized in Table 1. All of these subjects were diagnosed as having a mixed hyperlipidemia for which they were undergoing or about to undergo treatment based on changes in lifestyle and the use of hypolipidemic agents, either a statin, a fibrate, or both. The subjects under study had plasma levels of Lp(a) protein ≥7.0 mg/dL, a single apo(a) size isoform, and a single peak of LDL and Lp(a) in the density gradient ultracentrifugal profile (see below).

Blood Collection

All subjects gave informed consent according to a protocol approved by the Institutional Review Advisory Board. Blood samplings were carried out at least 8 weeks after an acute cardiovascular event. The subjects were fasted overnight, and the blood was obtained from the antecubital vein. For plasma analyses, the blood was collected into EDTA-containing tubes (purple top), which were spun within 30 minutes from collection. The plasma after the addition of an antiproteolytic cocktail9 containing tubes (purple top), which were spun within 30 minutes from collection. The plasma was stored at 4°C in airtight containers until use.

Plasma Analyses

Total plasma cholesterol, triglycerides, and HDL cholesterol were determined in a Vitros DT60 II System (Ortho Clinical Diagnostics) according to the instructions of the manufacturer and with the use of calibrators verified by the College of American Pathologists. The LDL cholesterol was calculated according to the Friedewald formula16 and thus included Lp(a) cholesterol.11 The Lp(a) concentration in terms of protein was determined by ELISA with the method of Fless et al.12

Antisera

Antisera to purified preparations of apo(a), Lp(a), and LDL were raised in the rabbit, and affinity-purified antibodies to apo(a), Lp(a), and LDL (anti-apoB) were prepared as previously described.12 Both anti-apo(a) and anti-Lp(a) were devoid of immunoreactivity to LDL and plasminogen; anti-apoB was unreactive to apo(a).

Phenotyping and Genotyping of Apo(a)

Apo(a) phenotyping was performed on either reduced plasma, isolated apo(a), or Lp(a) samples by 4% SDS-PAGE, followed by immunoblotting with the use of anti-Lp(a). In the plasma, we found only a major phenotype identified in the major Lp(a) peak in the ultracentrifugal density gradient profile (see below). The mobility of the individual apo(a) bands was compared with isolated apo(a) isoforms of known molecular weights. Some of the standards consisting of number-based recombinant apo(a) KIVs were a gift from Dr Angles-Cano (INSERM U143, Paris, France). Among the individuals studied, the apo(a) phenotype in that peak contained from 9 to 27 KIV type 2 repeats. For apo(a) genotyping, DNA plugs were prepared from blood mononuclear cells and subsequently fractionated by pulsed-field electrophoresis, and the blots were probed with an apo(a) specific probe essentially as described earlier.13 All subjects had 2 alleles that ranged between 148 and 52 kb.

Isolation of Apo(a) From Lp(a)

Apo(a) was isolated from Lp(a) essentially as described previously with some modifications. Briefly, 1 mg/mL protein was incubated with dithioerythritol at a final concentration of 1.25 mmol/L, ε-Amino-n-caproic acid (EACA) at a final concentration of 100 mmol/L was then added, and the mixture was incubated at room temperature for 1 hour under argon. After dialysis against 10 mmol/L phosphate buffer, pH 7.5, containing 1 mmol/L EDTA, 0.02% NaN3, and 100 mmol/L EACA, the sample was diluted with D2O (3:1 [vol/vol]) containing 100 mmol/L EACA, and the resulting mixture was placed into a Ti80 rotor and ultracentrifuged at 15°C and 80 000 rpm for 20 hours. After centrifugation, the top fraction contained LDL free of apo(a) and untreated Lp(a). The bottom 2-mL fraction contained free apo(a) in pure form.

Isopycnic Density Gradient Ultracentrifugation

Isopycnic density gradient ultracentrifugation was carried out according to an updated version of a previously described technique.15 In brief, a nonlinear salt gradient was constructed to maximize the separation of LDL, Lp(a), and HDL classes. VLDL remained at the top of the tube. The gradient consisted of 1 mL of a 1.21 g/mL solution made of NaCl and NaBr, 4 mL of 4 mol/L NaCl, and 0.2 mL plasma, and the rest of the tube was filled to a total of 13.2 mL with 0.67 mol/L NaCl. This discontinuous gradient was centrifuged in a swinging bucket rotor (SW40, Beckman) at 39 000 rpm for 50 hours.

TABLE 1. Characteristics of Subjects

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, N</td>
<td>75</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.8±14.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4±5.7</td>
</tr>
<tr>
<td>Sex (male/female), n</td>
<td>44/31</td>
</tr>
<tr>
<td>Race (white/African American), n</td>
<td>64/11</td>
</tr>
<tr>
<td>Smoking (yes/ex/no), n</td>
<td>7/10/58</td>
</tr>
<tr>
<td>Diabetes (yes/no), n</td>
<td>11/64</td>
</tr>
<tr>
<td>Medication, n</td>
<td></td>
</tr>
<tr>
<td>Monotherapy (statin)</td>
<td>41</td>
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<tr>
<td>Combined therapy (statin/fibrate/niacin)</td>
<td>17</td>
</tr>
<tr>
<td>Fibrate alone</td>
<td>9</td>
</tr>
<tr>
<td>Diet alone</td>
<td>8</td>
</tr>
<tr>
<td>CVD (yes/no), n</td>
<td>24/51</td>
</tr>
<tr>
<td>Family history of CVD,* n</td>
<td>51/20</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>222±56</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>190±120</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>44±17</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>139±44</td>
</tr>
<tr>
<td>Lp(a) protein, mg/dL</td>
<td>12.7 (7.0–50.3)</td>
</tr>
<tr>
<td>LDL density (median), g/mL</td>
<td>1.045 (1.035–1.057)</td>
</tr>
<tr>
<td>Lp(a) density (median), g/mL</td>
<td>1.069 (1.048–1.086)</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease. Values are mean±SD, number of subjects, or median (with range in parentheses). *Four patients could not be clearly determined.

Apolipoprotein(a) Phenotyping and Genotyping

Apo(a) phenotyping was performed on either reduced plasma, isolated apo(a), or Lp(a) samples by 4% SDS-PAGE, followed by immunoblotting. Apo(a) phenotyping results showed that the majority of apo(a) bands ranged from 9 to 27 KIV type 2 repeats. The apo(a) phenotype was determined by comparing the mobility of the individual apo(a) bands with isolated apo(a) isoforms of known molecular weights. Some of the standards consisting of number-based recombinant apo(a) KIVs were a gift from Dr Angles-Cano (INSERM U143, Paris, France). Among the individuals studied, the apo(a) phenotype in that peak contained from 9 to 27 KIV type 2 repeats. For apo(a) genotyping, DNA plugs were prepared from blood mononuclear cells and subsequently fractionated by pulsed-field electrophoresis, and the blots were probed with an apo(a) specific probe essentially as described earlier. All subjects had 2 alleles that ranged between 148 and 52 kb.

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At the end of the run, each tube was pierced at the bottom, and a dense solution (Fluorinert, ISCO) was pumped in at a flow rate of 1 mL/min. The effluent emerging from the top of the tube was monitored at 280 nm in a UA-5 ISCO absorbance monitor and recorded on a chart with a chart speed of 60 cm/h and a flow of 1 mL/cm. Density calibration was carried out by measuring the densities of each collected gradient fraction (0.9 mL) with use of a Mettler/Paar Precision Density Meter (model DMA 02C), as we reported previously. The distribution of Lp(a), in terms of protein, was determined throughout the profile by ELISA on fractions collected in a fraction collector. Figure 1 shows the density curve superimposed on the lipoprotein absorbance profile of the plasma of a subject with a plasma Lp(a) protein level of 5.0 mg/dL. The distribution of apo(a) by 4% SDS-PAGE, followed by immunoblotting. The apo(a) isoform ranging between 14 and 20 KIV type 2 repeats as
assessed by reduced 4% SDS-PAGE carried out on the gradient fractions. In the longitudinal studies, the correlation between migration and peak density in each ultracentrifugal profile was defined by the following equation: $y = 1.0339 - 0.0005979x + 0.00091978x^2$, where $y$ is the density, and $x$ is the distance in centimeters on the chart from the origin of the gradient (top of tube) to the lipoprotein peak. The validity of this equation was determined by ELISA as described by Fless et al. 12 The apoB-100:apo(a) covalent complex was collected, and the concentration of collected individual fractions was determined by open circles.

**In Vitro Assembly Studies**

In vitro assembly studies were carried out according to the method previously described by Edelstein et al. 14 In brief, apo(a), 1 μg of a defined phenotype obtained from Lp(a) by the procedure outlined above, was incubated separately with 6 single species of LDL varying in density between 1.035 and 1.057 g/mL isolated by density gradient ultracentrifugation from selected subjects with levels of Lp(a) protein <1 mg/dL. The incubations were carried out at an apoB-100:apo(a) molar ratio of 25:1 for 6 hours at 37°C in the presence of 50 μL butylatedhydroxytoluene, aprotinin (10 000 kallikrein inhibitory units/mL), and 1 mmol/L phenylmethylsulfonyl fluoride, under nitrogen. At the end of the incubation period, aliquots of the incubation mixture were analyzed on Western blots of SDS-PAGE under nonreducing and reducing conditions. To quantify the amount of Lp(a) assembled, an aliquot (125 μL) of the reaction mixture was diluted with an equal volume of 60% sucrose in 10 mmol/L phosphate buffer containing 200 mmol/L EACA to prevent noncovalent association between apo(a) and apoB-100 and spun in a Beckman TLA 100 rotor (tube capacity 250 μL) at 412 160g at 15°C for 18 hours. The top fraction containing the apoB-100:apo(a) covalent complex was collected, and the concentration was determined by ELISA as described by Fless et al. 15 The bottom 100 μL containing free apo(a) was also quantified by a sandwich ELISA specific for apo(a) with the use of anti-Lp(a) for coating and alkaline phosphatase–conjugated anti-apo(a) for detection.

**Results**

**Baseline Studies**

The general characteristics of the 75 subjects at the initiation of the study is shown in Table 1. They had relatively high plasma total cholesterol, LDL cholesterol, and triglyceride levels. The Lp(a) protein was also elevated (upper limit of normal 7.0 mg/dL, or 10th percentile). The distribution of LDL and Lp(a) peak density and that of LDL was assessed by the nonparametric Spearman rank test. The change in LDL cholesterol and Lp(a) protein between the initiation of the studies and during the treatment period was evaluated by the Mann-Whitney rank sum test. We considered values of $P<0.05$ to be significant.
Of note, the 2 peak densities showed no correlation with either plasma baseline LDL cholesterol or Lp(a) protein concentrations.

Longitudinal Studies

Longitudinal studies were conducted to determine whether changes in plasma triglycerides levels in any given individual who expressed in their plasma a single major apo(a) isoform could result in changes in the concentration and density of LDL and Lp(a). In terms of concentration, the LDL cholesterol values dropped by 22% (P<0.05), from a mean of 139±44 to 108±36 mg/dL. This drop was recorded after 1 year, when normalization of the plasma triglyceride levels was also attained. On the other hand, during the same period of observation, the Lp(a) protein level remained essentially unchanged (17.4 to 19.4 mg/dL, P>0.5). In terms of density, during the total period of observation that varied from 1 to 15 years, important changes were observed, as shown in the 3 representative profiles in Figure 5 obtained in the same subject at 1 and 2 years from baseline after the initiation of a statin therapy. The lowering of the plasma cholesterol and triglycerides was associated with a parallel shift of both LDL and Lp(a) peaks to a higher density (Figure 5, middle panel). We observed a reverse shift of the density of both lipoproteins when, because of lack of compliance, a rise in the fasting plasma triglycerides occurred (bottom panel). These shifts were measured in centimeters on the chart output, indicating the migration of the lipoprotein from the top of the gradient to the isopycnic position. The density was calculated according to the formula given in Methods. The parallel shifts of the LDL and Lp(a) peak densities as a function of changes in plasma triglyceride levels were observed in all subjects (r=0.82, P<0.0001). However, the correlation was particularly striking (r=0.94, P<0.0001) in 23 subjects. Some of them were studied when their plasma triglyceride levels decreased from the 300-mg/dL range to normal, and some were studied when the values increased from normal to high because of a lack of therapeutic compliance (Figure 6). In this figure, positive density shifts correspond to changes of triglycerides from high to normal levels, and negative density shifts correspond to changes from normal to high levels. In data not included in Figure 6, we also found that within the 23 subjects, the density shifts from high to low and from low to high were observed.

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**Figure 3.** Relationship between total plasma triglyceride levels and the peak densities of LDL (top) and Lp(a) (bottom) of each subject. Open circles are data points of the densities of individual plasma LDL and Lp(a) peaks resolved by density gradient ultracentrifugation.

**Figure 4.** Relationship between plasma LDL and Lp(a) peak densities in the plasma. Open circles are data points of the densities of individual plasma LDL and Lp(a) peaks resolved by density gradient ultracentrifugation.

**Figure 5.** Shifts in the LDL and Lp(a) peak densities in a representative subject before and during treatment: top, before treatment; middle, 1 year after treatment, when a significant lowering of the plasma triglycerides was achieved; and bottom, 2 years after treatment, when the plasma triglyceride levels were again elevated.
high occurred more than once as a function of variations of the plasma triglyceride levels.

In Vitro Assembly Studies

As detailed in Methods, a constant amount of apo(a) of a defined size was incubated separately with each of the 6 LDL fractions, varying in density between 1.035 and 1.057 g/mL. At the end of this incubation period, each mixture was subjected to immunoblot analyses, with the use of anti-apo(a) and anti–apoB-100 antibodies, to determine on a qualitative basis whether a covalent linkage between apo(a) and the apoB-100 of each of the donor LDLs had occurred. Immunoblots of nondenaturing gels showed that most of the apo(a) had migrated with apoB-100 in the position of a standard Lp(a). Subsequent immunoblots of denaturing SDS gels showed that the band corresponding to the apo(a):apoB-100 complex in the nonreduced gel was no longer present in the reduced gel. To quantify the reassembly process, each incubation mixture was spun in a Beckman TLA 100 rotor in the presence of 200 mmol/L EACA at 1.127 g/mL, the floating fraction was collected, and the amount of apoB-100:apo(a) complex was quantified by ELISA. The percentage of apo(a) incorporated into Lp(a) was calculated relative to the total mass of apo(a) added before incubation. Data are the mean of 5 experiments.

Discussion

Our present study has shown that when apo(a) size polymorphism is factored out, the density of an Lp(a) particle parallels that of authentic LDL. We derived this conclusion by using density gradient ultracentrifugation to determine the peak density of these 2 lipoproteins in the plasma of hypertriglycerideremic subjects exhibiting a single apo(a) isoform. By statistical analyses, after correction for the effects of apo(a) size, the residual density of Lp(a) attributed to metabolic factors was found to be correlated with that of LDL. Of additional interest in the present study, although perhaps not unexpected,1 was the observation that despite the marked drop in plasma triglyceride and LDL cholesterol, the attending change in Lp(a) density had no significant effect on the plasma concentration of Lp(a) protein. Our results also suggest that the components of constitutive LDL in Lp(a) are readily exchanged with the authentic LDL species in the plasma and that apo(a) may not hinder these lipid exchange processes.

Among our subjects, apo(a) varied widely in size (from 9 to 27 KIV type 2 repeats). In each case, a shift in the peak density of Lp(a) occurred as a function of the change in plasma triglyceride levels, indicating that apo(a) size was not a factor in this shift and thus pointing to its dependence on the LDL density. This conclusion received support from the in vitro data showing that the same apo(a) can be incorporated into a comparable degree into LDL species of a different density. These observations may be taken to indicate that in vivo, apo(a), in terms of covalent association, does not discriminate among LDL species. However, a definitive conclusion on this specificity of association would require metabolic studies within subjects during normotriglyceridemia and hypertriglyceridemia, taking into account both apo(a) size polymorphism and LDL density heterogeneity. These studies were outside the immediate scope of the present study. However, it is apparent that in the same individual, an apo(a) of a given size can affiliate with either a small, intermediate, or a large buoyant LDL, depending on the availability of these particles in the plasma. Up to 34 apo(a) size isoforms have been reported.17 Given the fact that there is 1 molecule of apo(a) per Lp(a) particle,18 one would predict, on genetic considerations only, an equivalent number of Lp(a) particles in the plasma. However, on the basis of our present results, this theoretical number is likely to be an

![Graph](https://example.com/graph.png)

**Figure 6.** Relationship between plasma LDL and Lp(a) peak density shifts. The data were obtained from 23 subjects with entering plasma triglyceride levels in the 300-mg/dL range. Each data point represents the difference in the density of the LDL and Lp(a) peaks during changes in plasma triglycerides. Positive density shifts correspond to changes of triglycerides from high to normal levels. Negative density shifts correspond to changes of triglycerides from normal to high levels.

<table>
<thead>
<tr>
<th>LDL Density, g/mL</th>
<th>Reconstituted Lp(a), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.035</td>
<td>67.8±5.4</td>
</tr>
<tr>
<td>1.037</td>
<td>73.5±6.3</td>
</tr>
<tr>
<td>1.040</td>
<td>66.7±10.3</td>
</tr>
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<td>1.043</td>
<td>66.5±2.0</td>
</tr>
<tr>
<td>1.050</td>
<td>71.2±5.3</td>
</tr>
<tr>
<td>1.057</td>
<td>73.3±7.1</td>
</tr>
</tbody>
</table>

Reconstituted Lp(a) values are mean±SD. The LDL of the specified density was isolated from individual subjects by ultracentrifugation. Reassembly of apo(a), containing 14 KIV type 2 repeats, with each LDL species was conducted at 37°C for 6 h at an apoB-100:apo(a) molar ratio of 25:1. After centrifugation overnight in sucrose containing 200 mmol/L EACA at 1.127 g/mL, the floating fraction was collected, and the amount of apoB-100:apo(a) complex was quantified by ELISA. The percentage of apo(a) incorporated into Lp(a) was calculated relative to the total mass of apo(a) added before incubation. Data are the mean of 5 experiments.
underestimate, because any given apo(a) size isoform can potentially bind to different individual LDL density species.

The above observations raise the question of whether the density of the LDL constituent of Lp(a) might have an influence on the cardiovascular pathogenicity of this lipoprotein independently or in addition to that of apo(a). For instance, we may ask whether the affiliation with a given apo(a) phenotype may increase the recognized risk for coronary heart disease of small dense LDL particles. In other words, it would be important to consider that pathogenicity may relate to Lp(a) density, which is the resultant of the density of the constitutive LDL and apo(a) size. Because of the relatively low number and diversity of subjects, our results provide no answer to this question but should invite large-scale studies in which measurements of plasma Lp(a) levels and apo(a) size isoforms are conducted in parallel with those of Lp(a) and LDL density. In this regard, normotriglyceridemic subjects may represent another useful model. In preliminary studies on 6 subjects with heterozygous familial hypercholesterolemia, we have observed that the Lp(a) density is a function of apo(a) size and is not significantly affected when the plasma levels of LDL but not its density are modified by the action of statin-based therapies (A.M. Scanu, unpublished data, 2001). In the case of familial hypercholesterolemia, high plasma levels of Lp(a) have been reported to underestimate, because any given apo(a) size isoform can potentially bind to different individual LDL density species.

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Acknowledgments

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References

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