Dose-Dependent Inverse Relationship Between Alcohol Consumption and Serum Lp(a) Levels in Black African Males

Pierre Fontana, Vincent Mooser, Pascal Bovet, Conrad Shamlaye, Bernard Burnand, Vincent Lenain, Santica M. Marcovina, Walter Riesen, Roger Darioli

Abstract—Serum or plasma levels of Lp(a) vary widely between individuals and are higher in Africans and their descendants compared with white persons. In whites, high serum levels of Lp(a) are associated with the premature development of atherosclerosis. In both ethnic groups, serum Lp(a) levels are highly genetically determined and only a few environmental or physiological factors, like testosterone or estrogen, have been shown to lower serum Lp(a) levels. In whites, alcohol consumption is associated with lower serum Lp(a) levels. However, the mechanism underlying this association and whether it holds true for blacks is not known. To address these questions, we analyzed serum Lp(a) levels in 333 middle-aged males of African descent from the Seychelles Islands (Indian Ocean). In addition, we analyzed the size of the apo(a) isoforms and the serum levels of albumin and sex hormones in a subset of 279 subjects. Serum Lp(a) levels were similar in teetotalers (median, 32.5 mg/dL; n=42) and occasional drinkers (median, 34.1 mg/dL; n=96) had a 9% and 32% lower median Lp(a) level than teetotalers, respectively (P=0.01). The size distribution of the apo(a) isoforms and the mean serum levels of albumin, estradiol, and luteinizing hormone were similar in teetotalers and occasional drinkers compared with moderate and heavy drinkers. These latter 2 groups had lower serum levels of testosterone and sex hormone–binding globulin. These data indicate that alcohol intake is associated in a dose-dependent manner with lower serum Lp(a) levels in males of African descent and that this association is not related to the size of the apo(a) isoforms, to the synthetic function of the liver, or to sex hormone biochemical status. (Arterioscler Thromb Vasc Biol. 1999;19:1075-1082.)

Key Words: lipoprotein(a) • alcohol • black African • population study • atherosclerosis

Lp(a) is an enigmatic particle of unknown function that circulates in serum of a restricted number of species including the hedgehog, great apes, and humans.1 In humans, serum or plasma Lp(a) levels [referred to below as “Lp(a) levels”] vary between individuals from <0.1 to >100 mg/dL.2 In white persons, Lp(a) levels of >20 to 30 mg/dL are associated with the premature development of atherosclerosis,3 which has prompted studies to identify factors that contribute to Lp(a) levels. Lp(a) levels are largely genetically determined by sequences linked to the locus encoding apo(a), the glycoprotein that is attached to apolipoprotein B-100 (apoB) of LDL in the Lp(a) particle.4 The apo(a) gene is highly polymorphic in size and sequence because of a variable number of tandemly repeated copies of a motif called kringle 4 (K4).5 The number of K4 repeats ranges from 12 to 51 and determines the size of the apo(a) isoforms in serum.6 In general, smaller apo(a) isoforms are associated with higher Lp(a) levels whereas isoforms containing >30 K4 repeats are usually associated with Lp(a) levels of <5 mg/dL.7 Individuals of African descent have a 2- to 3-fold higher median Lp(a) level compared with whites.8–10 The determinants of Lp(a) levels and the architecture of the apo(a) gene in African Americans have been recently investigated.11,12 As is the case in whites, sequences at the apo(a) locus are the major determinant of Lp(a) levels in this ethnic group. Lp(a) levels tend to be higher in African Americans over the entire size range of the apo(a) gene; this may relate to the presence of a common ancient Lp(a)-elevating apo(a) allele in this ethnic group or, more probably, to the presence of 1 or more African-specific yet-to-be identified factor(s) acting in trans that would enhance the synthesis or retard the clearance of Lp(a).11 Accordingly, it is conceivable that individuals of
African descent have higher Lp(a) levels because of resistance to an environmental or physiological factor(s) that lowers Lp(a) levels in other ethnic groups. Alternatively, higher Lp(a) levels in Africans may be due to an increased susceptibility to Lp(a)-elevating factors.

Only a few physiological or environmental factors have been identified that impact on Lp(a) levels. Estrogen and testosterone lower Lp(a) levels, whereas growth hormone has the opposite effect. Among environmental factors, cholesteryl-lowering drugs like statins or bile acid sequestrants have no significant effect on Lp(a) levels, whereas fish diet has recently been shown to lower Lp(a) levels in Tanzanians. In whites, a great deal of evidence suggests that alcohol intake is associated with lower Lp(a) levels. In studies involving heavy drinkers, alcohol withdrawal was associated with a rapid increase in Lp(a) levels in both men and women. In addition, administration of alcohol at a dose of 60 g/d to healthy volunteers led to a significant decrease in Lp(a) levels. The mechanism by which alcohol withdrawal is associated with an increase in Lp(a) levels is poorly understood and may implicate changes in insulin-like growth factor–binding protein-1. However, whether the inverse association between alcohol intake and serum Lp(a) levels holds true for the entire size spectrum of apo(a) isoforms and whether it is because of altered synthetic function of the liver or changes in sex hormone status has not been investigated. Finally, the association between alcohol intake and Lp(a) levels in individuals of African descent has only been documented incompletely.

In this study, we specifically examined the association between alcohol consumption and serum Lp(a) levels in a sample of middle-aged individuals of African descent. Our study was restricted to men, as hormonal status affects Lp(a) levels. The following values were used for volume per unit of alcohol beverage and alcohol content: beer (0.3 L/bottle; 5.45 vol%), spirits (0.05 L/measure; 43 vol%), wine (0.2 L/glass; 12 vol%), kalou (0.75 L/bottle; 8 vol%), baka and lapire (0.75 L/bottle; 9 vol%). Subjects were interviewed and asked a series of predetermined questions and a limited physical examination was performed. The questionnaire on alcohol consumption was designed to quantify individual alcohol intake in the context of Seychelles where alcoholic beverages are available in limited types and measures. All participants were initially asked how frequently, on average, they drank alcoholic beverages, irrespective of type and amount. The following 4 answers were possible: (1) never, (2) only on some occasions but less than once a week on average, (3) once or twice a week on average, and (4) almost every day or every day. Subjects who declared to never drink were categorized as teetotalers, whereas those who reported drinking any alcoholic beverage less often than once a week on average were classified as occasional drinkers. Individuals who declared drinking any alcoholic beverage at least once a week on average were considered regular drinkers and were further systematically questioned about their weekly consumption of each of the alcoholic beverages available in Seychelles. The average daily intake of ethanol in regular drinkers was calculated from the reported number of units of alcoholic beverages and the content of alcohol of each type of imported or locally produced beverage. Of the home brews, “kalou” or palm toddy is made of fermented palm sap, “baka” of fermented sugar-cane juice, and “lapire” of fermented juice of various vegetables (eg, potatoes and lentils) or fruits (baka and lapire are generally supplemented with substantial amounts of sugar before fermentation). The alcohol content of home brews was determined from 8 samples of each of the 3 local brews, which were collected in 1996 at several semicommercial plants throughout the country. Their alcohol content was analyzed at the Laboratory of Analytic Toxicology, Institute of Legal Medicine, University of Lausanne, Switzerland, <2 weeks after they were purchased. Analysis was performed by using gas chromatography with flame ionization detection, introduction by head-space and direct injection, and separation on either Carbowax 20 (partition chromatography) or Chromosorb 102 (adsorption chromatography). This analysis did not reveal any significant amount of formaldehyde, which indicated that no lactic acidosis had occurred in the samples. No significant amount of methanol was detected. Previous analyses conducted in 1989 in a UK laboratory on fewer samples showed similar alcohol contents.

In the absence of standardization of the Lp(a) measurement, this study was restricted to the 333 male individuals of African descent. Participants were interviewed and asked a series of predetermined questions and a limited physical examination was performed. The questionnaire on alcohol consumption was designed to quantify individual alcohol intake in the context of Seychelles where alcoholic beverages are available in limited types and measures. All participants were initially asked how frequently, on average, they drank alcoholic beverages, irrespective of type and amount. The following 4 answers were possible: (1) never, (2) only on some occasions but less than once a week on average, (3) once or twice a week on average, and (4) almost every day or every day. Subjects who declared to never drink were categorized as teetotalers, whereas those who reported drinking any alcoholic beverage less often than once a week on average were classified as occasional drinkers. Individuals who declared drinking any alcoholic beverage at least once a week on average were considered regular drinkers and were further systematically questioned about their weekly consumption of each of the alcoholic beverages available in Seychelles. The average daily intake of ethanol in regular drinkers was calculated from the reported number of units of alcoholic beverages and the content of alcohol of each type of imported or locally produced beverage. Of the home brews, “kalou” or palm toddy is made of fermented palm sap, “baka” of fermented sugar-cane juice, and “lapire” of fermented juice of various vegetables (eg, potatoes and lentils) or fruits (baka and lapire are generally supplemented with substantial amounts of sugar before fermentation). The alcohol content of home brews was determined from 8 samples of each of the 3 local brews, which were collected in 1996 at several semicommercial plants throughout the country. Their alcohol content was analyzed at the Laboratory of Analytic Toxicology, Institute of Legal Medicine, University of Lausanne, Switzerland, <2 weeks after they were purchased. Analysis was performed by using gas chromatography with flame ionization detection, introduction by head-space and direct injection, and separation on either Carbowax 20 (partition chromatography) or Chromosorb 102 (adsorption chromatography). This analysis did not reveal any significant amount of formaldehyde, which indicated that no lactic acidosis had occurred in the samples. No significant amount of methanol was detected. Previous analyses conducted in 1989 in a UK laboratory on fewer samples showed similar alcohol contents. The following values were used for volume per unit of alcohol beverage and alcohol content: beer (0.3 L/bottle; 5.45 vol%), spirits (0.05 L/measure; 43 vol%), wine (0.2 L/glass; 12 vol%), kalou (0.75 L/bottle; 8 vol%), baka and lapire (0.75 L/bottle; 9 vol%). Subjects consuming 10 to 80 g of ethanol/d were considered as moderate drinkers, whereas those consuming >80 g of ethanol/d were considered heavy drinkers. Regular drinkers were administered the 4-question CAGE questionnaire, which is an easy-to-use and validated tool in screening for alcohol dependence. Serum carbohydrate-deficient transferrin (CDT) levels, which have a sensitivity and a specificity equal to or better than γ-glutamyl transpeptidase levels in the evaluation of alcoholism, were also measured. Smoking was defined as currently smoking at least 1 cigarette a day. People who reported to walk ≥30 minutes/d, to have a job requesting strong physical activity, or to engage in leisure physical activity more than once a week were considered as having regular physical activity. Blood pressure, body weight, and height were measured according to the WHO MONICA study protocol. High blood pressure was defined as systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg.

Blood samples were obtained from subjects between 8 AM and 2 PM. Samples were centrifuged within 1 hour and sera were collected and frozen immediately. Frozen samples were shipped on dry ice to Switzerland where they were stored at −20°C. All assays were performed within 3 months of collection, except for the measurement of sex hormones and albumin levels and the determination of the size of the apo(a) isoforms, which were done after 3 years. Serum Lp(a) levels were measured by using a commercial solid-phase 2-site immunoradiometric assay (Apolipoprotein(a)RIA-100, Pharmacia). In the absence of standardization of the Lp(a) measurement, this method was compared with a ELISA, which used 2 monoclonal antibodies of well-defined specificity. A close correlation (r = 0.96) was observed between values obtained with these 2 methods,

Methods

Subjects included in the present study were identified between July and December 1994 during a cross-sectional survey designed to determine the prevalence of cardiovascular risk factors among the adult population of Mahé, the largest island of the Republic of Seychelles (Indian Ocean).

A detailed description of the demographic, educational, and socioeconomic characteristics of the study participants has been reported previously (with full text on http://www.seychelles.net/smdj/orig2.htm#Heart Study II). Geographically, Seychelles belongs to Africa. Although most of the population is of East African descent, many cultural traits were inherited from France by way of Mauritius and to a lesser extent from East Africa, East Asia, and Britain. The Seychellois people have developed their own distinctive Creole culture that clearly differs from societies of neighboring continental East African countries. The very rapid socioeconomic development of Seychelles (an increase in gross national product per inhabitant from $600 US to $6000 US over the last 20 years), which results in accelerated westernization, qualifies Seychelles more as a “small island tropical state” than to continental Africa. Mahé’s population is predominantly of African descent (65%) whereas the remaining 35% are of white, Indian, Chinese, or mixed descent. During this survey, a random age- and sex-stratified sample was drawn out of the entire population aged 25 to 64 years. From the 1247 eligible subjects, 1067 participated in the survey (87% participation rate). Informed consent was obtained from all subjects and the study protocol was approved by the Ministry of Health of Seychelles. The present analysis was restricted to the 333 male individuals of African descent.

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Detection was performed by using the horseradish peroxidase–15 V and transferred onto nitrocellulose for 6 hours at 50 V. minigel (Danaphor). Proteins were size-fractionated for 14 hours at the skewed distribution. Trends across ordered categories of alcohol for Lp(a) levels, which are expressed as median values because of well-characterized standards.

The size of the apo(a) isoforms was determined as using the DPC and the Axsym assays (Abbott), respectively. All testosterone and luteinizing hormone serum levels were quantified by Immulite chemiluminescent enzyme immunoassay (DPC). Free testosterone levels were measured by using the DPC. CDT levels were assayed using the STATA 4.0 package (Stata Corp).

Although values obtained when using RIA were 1.4-fold higher than those observed by ELISA. Serum cholesterol and triglyceride levels were determined enzymatically using an automated analyzer (Cobas Mira, Roche). HDL cholesterol levels were quantified after precipitation of apoB-containing lipoproteins by using phosphotungstic acid–saturated magnesium, as recommended by the manufacturer (Boehringer-Mannheim). LDL cholesterol levels were calculated by using the Friedewald formula. In 10 subjects, triglyceride levels exceeded 4.5 mmol/L, so that LDL cholesterol levels were not calculated.

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**Results**

A total of 333 apparently healthy male individuals of African descent were included in this study. Based on their reported alcohol consumption, participants in this study were considered teetotalers (n = 42, 13%), occasional drinkers (defined as consuming <1 alcoholic beverage per week, n = 112, 34%), moderate drinkers (10 to 80 g of ethanol/d, n = 83, 25%), or heavy drinkers (>80 g of ethanol/d, n = 96, 29%). The clinical characteristics of each group are summarized in Table 1. Reported mean ± SEM alcohol consumption averaged 33 ± 2 g/d in moderate drinkers and 257 ± 17 g/d in heavy drinkers. Reported daily alcohol intake correlated with the CAGE score and higher alcohol intake was associated with higher CDT levels (from 20.6 ± 3.3 U/L in teetotals to 38.2 ± 2.7 U/L in heavy drinkers; P = 0.01). Moderate and heavy drinkers tended to smoke more than teetotals and occasional drinkers.

**TABLE 1. Clinical Characteristics of 333 Male Individuals of African Descent According to Alcohol Intake**

<table>
<thead>
<tr>
<th></th>
<th>Teetotals (n = 42)</th>
<th>Occasional Drinkers (n = 112)</th>
<th>Moderate Drinkers (n = 83)</th>
<th>Heavy Drinkers (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>46.7 ± 1.9</td>
<td>43.0 ± 1.2</td>
<td>44.4 ± 1.2</td>
<td>46.1 ± 1.1</td>
</tr>
<tr>
<td>Alcohol intake (g/d)</td>
<td>0</td>
<td>&lt;10</td>
<td>33.2 ± 2.0</td>
<td>257.3 ± 17.3†</td>
</tr>
<tr>
<td>CAGE score‡</td>
<td>NA</td>
<td>NA</td>
<td>1.9 ± 0.1</td>
<td>2.7 ± 0.1†</td>
</tr>
<tr>
<td>CDT (U/L)§</td>
<td>20.6 ± 3.3</td>
<td>23.1 ± 1.7</td>
<td>29.6 ± 2.6</td>
<td>38.2 ± 2.7†</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>44.8 ± 4.4</td>
<td>NA</td>
<td>NA</td>
<td>45.9 ± 4.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3 ± 0.7</td>
<td>24.2 ± 0.4</td>
<td>24.2 ± 0.4</td>
<td>23.7 ± 0.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>132 ± 3</td>
<td>134 ± 2</td>
<td>138 ± 2</td>
<td>145 ± 2†</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>85 ± 2</td>
<td>90 ± 1</td>
<td>90 ± 1</td>
<td>95 ± 1†</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>10 (24)</td>
<td>28 (25)</td>
<td>33 (40)</td>
<td>65 (68)‡</td>
</tr>
<tr>
<td>Physical activity¶, n (%)</td>
<td>27 (64)</td>
<td>71 (63)</td>
<td>61 (73)</td>
<td>66 (69)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM values. NA indicates not available.

*Occasional drinkers, <1 drink per week; moderate drinkers, average daily alcohol intake, 10–80 g/d, heavy drinkers, >80 g/d.

†P<0.01, by trend test.

‡Four-item questionnaire used to evaluate alcohol dependence, as described in Methods.

§Carbohydrate-deficient transferrin.

¶Number of individuals having a regular physical activity as defined in Methods.
HDL cholesterol ratio [from 4.01±0.19 in teetotals to 3.16±0.16 in heavy drinkers (P=0.01)]. The trends in HDL and LDL cholesterol levels across alcohol intake groups were paralleled by corresponding trends in levels of apoA1 and apoB.

Median Lp(a) levels were inversely and dose-dependently associated with alcohol intake. Teetotals and occasional drinkers had similar median Lp(a) levels (32.5 versus 34.1 mg/dL) and 32% (22.1 mg/dL) in moderate and heavy drinkers, respectively (P=0.01). This dose-dependent inverse relation between Lp(a) levels and alcohol intake was characterized by a progressively more pronounced skewness in the distribution of Lp(a) levels from low to high alcohol intake categories (Figure 1). In teetotals and occasional drinkers, the distribution of Lp(a) levels was similar to that previously reported in other groups of African descent.4,9 with 59% (CI, 44% to 75%) and 54% (CI, 45% to 64%) of the subjects having Lp(a) levels of >30 mg/dL, respectively. In contrast, 49% (38% to 60%) of moderate drinkers and 39% (30% to 49%) of heavy drinkers had Lp(a) levels of >30 mg/dL. The inverse relation between alcohol intake and levels of LDL and Lp(a) tended to be even more pronounced in the subgroup of individuals aged ≥45 years, with these proportions being 37% (CI, 18% to 56%), 34% (CI, 21% to 47%), 24% (CI, 10% to 37%), and 12% (CI, 3% to 22%), respectively.

Multivariate linear regression analysis indicated that the magnitude of the regression coefficient of alcohol intake on ln-Lp(a) levels did not change substantially after adjustment for age, body mass index, blood pressure, physical activity, and smoking habits (Table 3). The regression coefficient came substantially closer to the null value and the relation was no longer significant when adjusted for LDL cholesterol levels, in addition to the above-mentioned covariates. However, the relation between alcohol intake and ln-Lp(a) levels adjusted for LDL cholesterol levels remained significant when the levels of LDL cholesterol considered in the analysis did not include the cholesterol amount contained in Lp(a) particles.

To determine whether the inverse relation between alcohol intake and Lp(a) levels was observed over the entire size spectrum of apo(a) isoforms or was restricted to a limited range of alcohol-sensitive apo(a) isoforms, apo(a) isoforms were analyzed by immunoblotting and their size was determined according to their migration relative to well-characterized standards. An example of such an analysis is illustrated in Figure 2A. In this particular blot, 6 individuals had 2 apo(a) isoforms of different sizes (lanes 1, 2, 3, 5, 6, and 7). In 2 samples, only 1 band was visualized (lanes 4 and 8), which is caused by either a nonexpressing (or null) apo(a) allele of unknown size or the superposition of 2 apo(a) isoforms of similar sizes. This type of analysis was performed for a subset of 32 teetotals, 92 occasional drinkers, 65 moderate drinkers, and 85 heavy drinkers, because of a shortage of serum for the remaining participants. The proportion of subjects with 0, 1, or 2 apo(a) isoforms detected on immunoblot was similar for each alcohol intake category and averaged 2%, 50%, and 48%, respectively. The distribution of apo(a) isoforms is depicted in Figure 2B. In this analysis, teetotals and occasional drinkers were pooled as nondrinkers whereas moderate and heavy drinkers were grouped as drinkers. The size distribution of all apo(a) isoforms detected by immunoblot is shown in this figure. This distribution was
similar between drinkers and nondrinkers ($P = NS$) and was similar to distributions previously reported for African Americans.\(^9\)–\(^{12}\) This type of analysis may lead to a slight underestimation of the prevalence of the most frequent apo(a) isoforms, as 2 apo(a) isoforms of similar size can possibly be counted only once. To circumvent this problem, we performed a subanalysis restricted to individuals with 2 bands detected on immunoblot (data not shown). In this analysis, we calculated the average size of the 2 apo(a) isoforms detected on immunoblot for each individual, which was similar in drinkers and nondrinkers (25.7 ± 3.4 versus 25.3 ± 3.0 K4 repeat, respectively, NS). Taken together, these data indicated that the inverse relation between alcohol intake and Lp(a) levels occurred over the entire size spectrum of apo(a) isoforms.

To determine whether the inverse relation between alcohol intake and Lp(a) levels was mediated by changes in sex hormone status, we next measured the serum levels of estradiol, testosterone, SHBG, and luteinizing hormone in 279 individuals. Alcohol intake was inversely associated with testosterone levels, as free testosterone levels averaged 22.6 ± 1.4 pmol/L in teetotalers and 17.4 ± 0.6 pmol/L in heavy drinkers ($P = 0.01$) (Table 4). A similar inverse relation was found between alcohol intake and SHBG levels [55.4 ± 4.1 nmol/L in teetotalers versus 40.7 ± 1.7 nmol/L in heavy drinkers ($P = 0.01$)]. In contrast, no significant relation was observed between alcohol consumption and estradiol and luteinizing hormone levels. As testosterone and estradiol are known to lower Lp(a) levels, these findings indicate that the lower Lp(a) levels in heavy drinkers were not explained by changes in serum levels of these sex hormones.

**Discussion**

The present study was designed to investigate the relation between alcohol intake and serum Lp(a) levels in a large sample of a general population of middle-aged males of African descent with a wide range in alcohol intake. We found that individuals who consumed moderate or large daily amounts of alcohol had a 9% and 32% lower median Lp(a) level, compared with teetotalers or occasional drinkers, respectively. This inverse dose-dependent relation between alcohol intake and Lp(a) levels was independent of the size of the apo(a) isoforms and did not seem to be mediated by changes in sex hormone status or by a deterioration in the synthetic capacity of the liver. Finally, changes in Lp(a) levels across categories of alcohol intake were paralleled by changes in LDL cholesterol levels and were mirrored by HDL cholesterol levels.

The determinants of Lp(a) levels in subjects of African descent and the mechanisms by which they have higher Lp(a) levels than whites are only incompletely understood. The apo(a) gene is the major determinant of Lp(a) levels in both ethnic groups.\(^4\)\(^,\)\(^11\)\(^,\)\(^12\) Consistent with this finding is the present observation that alcohol intake, although significantly associated with lower Lp(a) levels, only comprised 1% to 4% of the total variability in Lp(a) levels. The inverse association between alcohol consumption and Lp(a) levels both in whites and in individuals of African descent challenges a reduced sensitivity to environmental Lp(a)-lowering factors as being responsible for the higher Lp(a) levels in individuals of African descent. The recent observation that fish oil reduces Lp(a) levels in Tanzanians\(^16\) is consistent with this view. These data, however, do not rule out the possibility that Africans and their descendants are less responsive to other yet-to-be identified Lp(a)-lowering factors. The mediators of the effect of alcohol on Lp(a) levels remain obscure. In our study, the proportion of subjects who consumed 1 type of alcohol beverage exclusively was too small to determine whether 1 particular beverage was associated with specific changes in serum Lp(a) levels. That alcohol intake is associated with lower Lp(a) levels both in whites and in Africans, despite these 2 groups consuming different types of alcohol

![Figure 1. Frequency distribution of serum Lp(a) levels in males of African descent according to alcohol intake. A total of 333 subjects were classified, according to their reported daily alcohol intake, as teetotalers, occasional drinkers (<1 alcoholic beverage per week), moderate drinkers (10 to 80 g of ethanol/d), or heavy drinkers (>80 g of ethanol/d) as described in Methods. Lp(a) levels were measured by radioimmunometric assay as described in Methods.](image-url)
banners, strongly suggests that these mechanisms implicate primarily ethanol rather than other substances like flavonoids.

Changes in sex hormones levels did not seem to mediate the inverse relation between Lp(a) levels and alcohol intake. In addition, our study does not provide support for the hypothesis that the lower Lp(a) levels in heavy drinkers are caused by chronic liver damage induced by alcohol. In our study, the synthetic capacity of the liver appeared to be maintained in heavy drinkers, as assessed by similar serum albumin levels in heavy drinkers and teetotalers. In addition, HDL cholesterol levels were significantly higher in heavy drinkers compared with other groups, whereas testosterone and SHBG levels were slightly lower and estradiol levels were similar across alcohol-intake categories. In contrast, it has been well documented that severe liver damage is accompanied by a profound decrease in HDL cholesterol and testosterone levels, with a corresponding increase in estradiol and SHBG levels. That alcohol withdrawal in heavy drinkers leads to a rapid increase in Lp(a) levels supports that the Lp(a)-lowering effect of alcohol intake is caused by metabolic and/or hormonal disturbances associated with alcohol rather than by permanent liver damage.

Alcohol intake may be associated with lower Lp(a) levels due to decreased levels of growth hormone (GH), a hormone that is known to increase Lp(a) levels in GH-deficient children and adults. Alcohol intake dramatically blunts the GH surges that occur at night and this effect has been documented in healthy volunteers and in rodents. Serum GH levels were also measured in the present study and these levels were similar in teetotals and heavy drinkers. (1.53±0.50 versus 1.76±3.37 pmol/L, NS). These present data, however, do not rule out a role for GH or insulin-like growth factor–binding protein-1 in mediating the inverse relation between alcohol intake and Lp(a) levels, as, in our study, blood was drawn during daytime and insulin-like growth factor–binding protein-1 was not measured.

The molecular mechanism by which alcohol or its mediators are associated with lower Lp(a) levels in serum remains speculative. The liver is the major (and possibly exclusive) site of synthesis of apo(a). One cannot rule out the possibility that alcohol interferes with the transcription of the apo(a) gene, although the elements that regulate the transcription of the apo(a) gene have not been fully identified yet. A large proportion of newly synthesized apo(a) undergoes endoplasmic reticulum–associated degradation, and the rate of endoplasmic reticulum degradation increases in proportion to the size of the apo(a) glycoprotein. It is conceivably that alcohol per se or other associated metabolic or redox disturbances promote a misfolding of the very large and cysteine-rich apo(a) glycoprotein, contributing to a higher proportion of apo(a) being degraded in the endoplasmic reticulum. This hypothesis, however, is unlikely, as this would lead to a smaller proportion of large apo(a) isoforms in serum of heavy

**Figure 2.** A, Immunoblot analysis of apo(a) isoforms in 8 unrelated individuals. A total of 0.5 μL of plasma was subjected to immunoblot analysis and apo(a) was detected by using IgG-a5, an anti-apo(a) monoclonal antibody, as described in Methods. The number of K4 repeats was determined based on the migration of apo(a) isoforms relative to well-characterized standards. B, Distribution of the size of the detected apo(a) isoforms in drinkers and nondrinkers. The size of the apo(a) isoforms was determined as described above. Teetotals and occasional drinkers were pooled as nondrinkers, whereas moderate and heavy drinkers were grouped as drinkers. All apo(a) isoforms detected on immunoblots were included in this analysis.
apo(a) undergoes a proteolytic cleavage that generates fragments that are cleared by the liver via the LDL receptor. This pathway has been identified as the main clearance mechanism for Lp(a) and is thought to be impaired by alcohol or that alcohol potentiates the catabolic pathway responsible for the clearance of Lp(a). The mechanism by which alcohol affects Lp(a) levels is not fully understood, but it is known that alcohol intake is associated with lower Lp(a) levels, even in moderate drinkers. Which of these favorable metabolic changes, if any, explain the beneficial effect of moderate alcohol consumption on cardiovascular diseases? Our data do not permit to draw conclusions on this issue. Furthermore, the public health relevance of the relation between alcohol intake and Lp(a) levels in subjects of African descent will depend on whether Lp(a) promotes the development of atherosclerosis in this ethnic group, which remains an unresolved issue.

In our study, high alcohol intake was associated not only with lower Lp(a) levels, but also with higher HDL cholesterol levels and lower LDL cholesterol levels, even in moderate drinkers. Which of these favorable metabolic changes, if any, explain the beneficial effect of moderate alcohol consumption on cardiovascular diseases? Our data do not permit to draw conclusions on this issue. Furthermore, the public health relevance of the relation between alcohol intake and Lp(a) levels in subjects of African descent will depend on whether Lp(a) promotes the development of atherosclerosis in this ethnic group, which remains an unresolved issue.

In our study, levels of apo(a) fragments were not measured, as it is not known whether long-term storage of frozen samples alters serum levels of apo(a) fragments. As studies on the metabolism of Lp(a) are difficult to perform in humans, examination of rabbits or mice expressing the human apo(a) transgene under control of its own promoter may help clarify this issue.

TABLE 4. Sex Hormone and GH Status in 279 Individuals of African Descent According to Alcohol Intake*

<table>
<thead>
<tr>
<th></th>
<th>Teetotals (n=32)</th>
<th>Occasional Drinkers (n=93)</th>
<th>Moderate Drinkers (n=70)</th>
<th>Heavy Drinkers (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free testosterone (nmol/L)</td>
<td>22.6±1.4</td>
<td>19.2±0.7</td>
<td>16.1±0.6</td>
<td>17.4±0.6†</td>
</tr>
<tr>
<td>Estradiol (nmol/L)</td>
<td>0.16±0.02</td>
<td>0.15±0.01</td>
<td>0.12±0.01</td>
<td>0.15±0.02</td>
</tr>
<tr>
<td>Estradiol/free testosterone (%)</td>
<td>0.84±0.15</td>
<td>0.87±0.08</td>
<td>0.88±0.08</td>
<td>0.87±0.08</td>
</tr>
<tr>
<td>SHBG (mmol/L)</td>
<td>55.4±4.1</td>
<td>44.4±1.6</td>
<td>36.8±1.3</td>
<td>40.7±1.7†</td>
</tr>
<tr>
<td>LH (mU/L)</td>
<td>6.8±0.5</td>
<td>5.8±0.3</td>
<td>6.4±0.5</td>
<td>7.5±0.6</td>
</tr>
</tbody>
</table>

Data are mean±SEM values. LH indicates luteinizing hormone; NA, not available.

*As defined in Table 1.
†P<0.01, by P for trend test.

References
1082 Alcohol and Lp(a) in Black Males


