Original Article

Plasma lipoprotein (a) concentrations and apolipoprotein (a) phenotypes in an Aboriginal population from Western Australia

Zuowei Xiong[1] MD, PhD, Mark L Wahlqvist[2] MD, FRACP, Beryl Biegler[3†] FAIMLS, Nicholas DH Balazs[4] BSc FAACB, Paul Van Buynder[5] MB, BS, DipRACOG, MPH, FAFPHM and Naiyana Wattanapenpaiboon[6] MSc(Pharm), PhD

[1]*National Heart Centre, Singapore*
[2]*International Health and Development Unit, Faculty of Medicine, Monash University, Melbourne, Victoria, Australia*
[3]*Monash University Department of Medicine, Monash Medical Centre, Melbourne, Victoria, Australia*
[4]*Department of Clinical Biochemistry, Monash Medical Centre, Southern Healthcare Network, Melbourne, Victoria, Australia*
[5]*South-eastern Public Health Unit, Goulburn, New South Wales, Australia*
[6]*Asia Pacific Health and Nutrition Centre, Monash Asia Institute, Monash University, Melbourne, Victoria, Australia*

Factors contributing to the variation in plasma lipoprotein (a) (Lp(a)) concentration were surveyed in an Aboriginal population (175 men and 219 women), aged 24–86 years, from Western Australia. The plasma Lp(a) levels were highly skewed towards low levels in this population, with a median of 84 mg/L and a mean of 166 mg/L. Approximately 20% had plasma Lp(a) above the threshold value of 300 mg/L, while 52% had Lp(a) levels below 100 mg/L. The most commonly occurring phenotype was apolipoprotien(a) S4. In this phenotype, Lp(a) concentrations ranged from not detectable to 468 mg/L. There was a positive relationship between cigarette smoking and plasma Lp(a) concentration in men. Apolipoprotein A1 and bilirubin were positively associated with Lp(a) in the 40–60 age group and a positive relationship between weight and Lp(a) concentrations was observed in those aged 60 years or over. Thus, although Lp(a) is mainly genetically determined, there are clearly other factors which contribute to variations in Lp(a) concentrations.

Key words: Aboriginal Australians, apolipoprotein (a), independent variables, lipoprotein (a), phenotypes, risk threshold.

Introduction

Aborigines had been living in Australia for perhaps 50 000 years before the incursion of the British settlers. In earlier times, because their traditional hunter–gatherer lifestyle provided them with an adequately nutritious diet and frequent exercise, they appeared to be in good health and free from diseases such as hypertension, diabetes mellitus and coronary heart disease (CHD).[1] However, since the impact of European colonization in the late 1700s, the Aboriginal traditional culture has been virtually destroyed and the indigenous people have undergone a rapid acculturation to a Westernized lifestyle and diet, leading to high prevalences of obesity, diabetes mellitus and CHD along with factors predisposing to CHD such as abnormal lipid profiles and hypertension, consistent with the 'Syndrome X' described by Reaven.[2]

Lipoprotein (a) (Lp(a)) status, a predictor of CHD, has not previously been reported in Aboriginal Australians. This study was carried out on an Aboriginal population from Western Australia and has provided an opportunity to review the contribution of cultural influences on Lp(a) concentration, as well as an evaluation of how it contributes to the health status of these Aboriginal people and, in turn, to the prevention of emergent macrovascular disease.

A plasma Lp(a) level of 300 mg/L is the generally accepted threshold for increased risk of atherosclerosis, despite the lack of internationally accepted standards or reference methods. A previous comparison of various analytical procedures showed very clearly that the risk threshold for CHD is highly method dependent. In this study, a low cost immunoturbidimetric assay (ITA) with a risk threshold value of 190 mg/L was selected to measure concentrations.

Methods

Subjects

The investigation of Lp(a) was undertaken as one component of a broad-scale intervention program into lifestyle diseases

Correspondence address: Professor M L Wahlqvist, International Health and Development Unit, PO Box 11A, Monash University, Melbourne, Victoria 3800, Australia.
Tel.: 61 39905 8145; Fax: 61 39905 8146
Email: mark.wahlqvist@med.monash.edu.au
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[†]Deceased

in Western Australian Aborigines. This project included identification of risk factors, lifestyle, education and specialist therapeutics follow up. Participants were recruited from a mixture of Aboriginal communities in Western Australia, ranging from smaller outstations to major rural towns. Of the participants, 175 men and 219 women were assessed for plasma Lp(a) concentration and apolipoprotien(a) (Apo(a)) phenotypes.

Ethic approval was obtained from the Northern Region Ethnics Committee working to National Health and Medical Research Council guidelines; this committee had Aboriginal representation. Informed consent was obtained by trained Aboriginal support staff.

Laboratory methods

Plasma Lp(a) concentration

Lp(a) concentrations were measured by an in-house ITA using a COBAS 'FARA' II centrifugal analyser (Roche, Basle, Switzerland), polyclonal antihuman Lp(a) antisera and reaction buffer were obtained from Incstar (Stillwater, MN, USA). The reaction buffer contained 2.25% polyethylene glycol in phosphate-buffered saline, a surfactant and 0.2% gelatin. Three microlitres of sample and 180 µL of reaction buffer were incubated at 30°C for 5 min, 12 µL of Lp(a) antibody were added to each cuvette and incubated for a further 10 min. Results were recorded in mg/L after the 10 min reaction time. For statistical purposes, Lp(a) levels which were below the limit of sensitivity of the assay used were recorded as zero.

Apolipoprotein (a) phenotyping

Apolipoprotein (a) phenotypes were assessed by sodium docyl sulphate–polyacrylamide gel electrophoresis (SDS–PAGE), using a modification of the method of Huang *et al.*[3] based on the original procedure of Utermann *et al.*[4] Sodium docyl sulfate is an anionic detergent which dissociates proteins into their polypeptide subunits and imparts a negative charge to these subunits. Protein denaturation is aided by heating the samples under investigation in buffer containing excess SDS and mercaptoethanol. Under these conditions proteins migrate in polyacrylamide gel according to their molecular size. A discontinuous gel, consisting of a running gel and a stacking gel was used. The stacking gel concentrates large sample volumes, resulting in improved resolution of protein bands. Samples with known phenotypes were run concurrently to help phenotype determination. When no visible banding pattern was seen on PAGE, the putative homozygous null phenotype was recorded as 'NULL'.

Apo(a) phenotypes S3, S4, S3S4 and NULL were categorized as large molecular weight (MW), and all other phenotypes as small MW. Similarly, Apo(a) phenotypes F, B, S1, S2, S3, S4 and NULL were classified as homozygous, while the combination of these phenotypes, such as S1S2, S1S3, were heterozygous.

Statistical analyses

All statistical analyses were performed using a Statistical Analysis System (SAS Institute; NC, USA) software package. The Lp(a) frequency distribution in the population studied was skewed to low levels which, for statistical purposes, is an abnormal distribution, therefore a non-parametric evaluation of the Lp(a) data was obligatory. The significance level was set at 5%.

Results

Distribution of plasma Lp(a) concentration

Descriptive statistics for plasma Lp(a) concentrations are presented in Table 1 and Fig. 1. The frequency distribution for plasma Lp(a) concentrations in Aboriginals was highly skewed toward low levels, with a median of 84 mg/L and a mean of 166 mg/L. About 53% of the population (25% men, 28% women) had Lp(a) concentrations below 100 mg/L, while 31% (13% men, 18% women) had values in excess of 190 mg/L, which is the risk threshold for the method used in this study; and 20.3% (8.6% men, 11.7% women) had Lp(a) values above the generally accepted risk threshold of 300 mg/L. Median and mean Lp(a) concentrations were higher in women than in men in this population.

Factors associated with plasma Lp(a) concentration

It was observed that, in men only, Lp(a) concentration was negatively correlated with mid-arm, and mid-thigh circumferences, as well as systolic blood pressure (BP), plasma triglycerides and insulin concentrations, but was positively correlated with cigarette smoking and low-density lipoprotein (LDL) cholesterol, with and without adjustment for age and alcohol consumption (Table 2). A positive relationship was observed between Lp(a) levels and LDL cholesterol, after adjusting for age and alcohol intake, in women. Multiple regression analyses showed that 15% of the variance of Lp(a) concentrations was explained by high-density lipoprotein (HDL) and LDL cholesterol, serum and red blood cell (RBC) folate, aspartate transaminase (AST) and diastolic BP.

Table 3 shows that Lp(a) was negatively related to blood pressure (both diastolic and systolic), triglycerides, AST and insulin, but positively related to LDL in the young age group (< 40 years). In the 40–60 age group, Lp(a) concentration was increased with increasing age and ApoA1. However, Lp(a) was inversely associated with ApoA1 and hemoglobin in those aged 60 and over. After adjustment for age and alcohol consumption, these relationships persisted, except for AST in the < 40 age group and ApoA1 in the 40–60 age

Table 1. Percentile distribution of plasma lipoprotein (a) (Lp(a)) concentrations

	n	Mean	SD	Mean
Total	394	166	189	84
Men	175	153	174	78
Women	219	177	201	102
Age < 40 years				
Men	78	57	50	41
Women	83	62	55	48
Age 40–60 years				
Men	37	66	51	46
Women	41	57	59	24
Age ≥ 60 years				
Men	9	35	34	18
Women	24	74	53	70

group. In addition, it was found that, among those aged ≥ 60 years, about 11 and 12%, respectively, of variance of Lp(a) were accounted for by hemoglobin and ApoA1. Interestingly, subjects with a high concentration of serum folate tended to have a low Lp(a) concentration; presumably, the much smaller magnitude of a positive relationship with RBC folate reflects some residual effect after accounting for colinearity with plasma folate.

Table 2. Spearman partial correlation coefficients (r_s) of lipoprotein (a) (Lp(a)) concentration and selected parameters, after adjustment for age and alcohol consumption

Parameters	Men (n = 175)	Women (n = 219)	Total (n = 394)
Cigarette smoking	0.17*	0.03	0.09
Diastolic blood pressure (mmHg)	–0.14	–0.13	–0.13†
Systolic blood pressure (mmHg)	–0.20†	–0.07	–0.12*
Subscapular skinfold thickness (mm)	–0.13	–0.11	–0.10*
Mid-arm circumference (cm)	–0.15*	–0.00	–0.06
Mid-thigh circumference (cm)	–0.18*	–0.04	–0.10
Hip circumference (cm)	–0.15*	–0.004	–0.06
Total cholesterol (mmol/L)	–0.01	0.07	0.03
Triglycerides (mmol/L)	–0.16*	–0.12	–0.14†
HDL cholesterol (mmol/L)	0.03	0.06	0.04
LDL cholesterol (mmol/L)	0.16*	0.14*	0.14†
Cholesterol/LDL cholesterol ratio	–0.04	–0.02	–0.12*
Apo-A1 (g/L)	0.08	0.04	0.05
Apo-B (g/L)	–0.01	0.01	–0.002
Aspartate transaminase (U/L)	–0.03	–0.12	–0.11*
Glucose (mmol/L)	–0.15	–0.07	–0.10*
Insulin (IU/L)	–0.16*	–0.12	–0.14†

Significantly different from zero: *, $P < 0.05$; †, $P < 0.01$.
Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Apo(a) phenotype and its relationships with plasma Lp(a) concentration

The distribution of Apo(a) phenotypes is shown in Fig. 2. It was observed that large MW and homozygous Apo(a) phenotypes were the most frequently occurring in both men and women (Table 4). Subjects with either heterozygous or small MW Apo(a) phenotypes tended to have a high plasma Lp(a) concentration ($P < 0.0001$).

Table 3. Spearman partial correlation coefficients (r_s) of lipoprotein (a) (Lp(a)) concentration and selected parameters, after adjustment for age and alcohol consumption, in three age groups

Parameters	Age group < 40 years (n = 161)	40–60 years (n = 78)	≥ 60 years (n = 31)
Diastolic blood pressure (mmHg)	–0.14*	–0.05	–0.27
Systolic blood pressure (mmHg)	–0.17†	0.03	–0.11
Total cholesterol (mmol/L)	0.04	0.05	–0.05
Triglycerides (mmol/L)	–0.13*	–0.17	–0.02
HDL cholesterol (mmol/L)	0.06	0.05	–0.22
LDL cholesterol (mmol/L)	0.16*	0.15	–0.07
ApoA1 (g/L)	0.07	0.14	–0.36*
ApoB (g/L)	0.01	–0.02	0.03
Aspartate transaminase (U/L)	–0.11	–0.16	0.07
Haemoglobin (g/L)	–0.05	0.05	–0.39*
Insulin (IU/mL)	–0.14*	–0.11	–0.09

Significantly different from zero:*, $P < 0.05$; †, $P < 0.01$.
Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

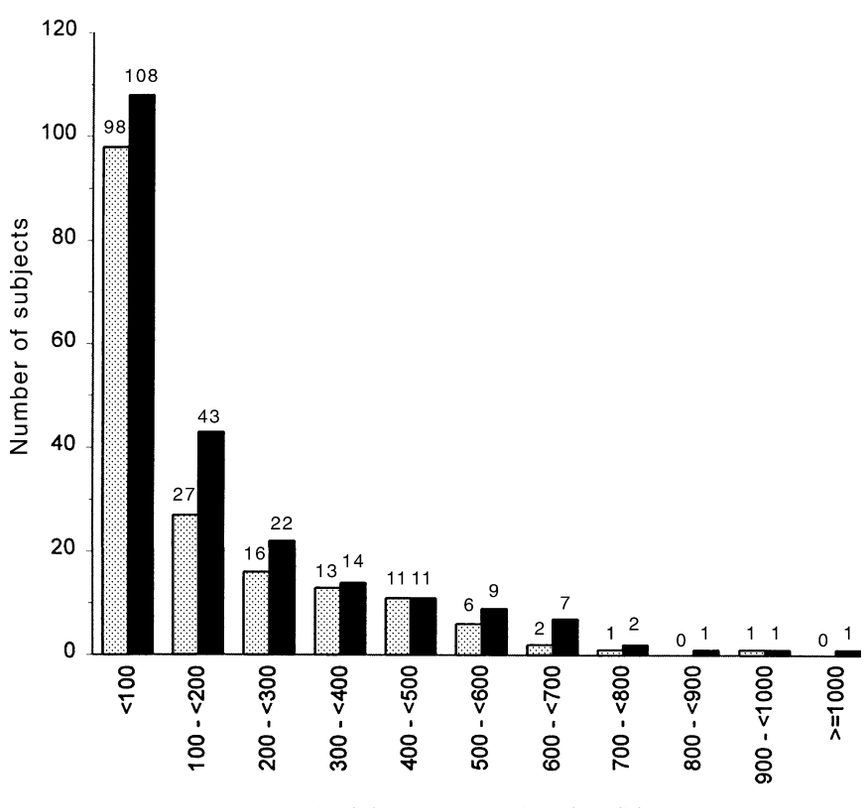

Figure 1. Distribution of plasma lipoprotein (a) (Lp(a)) concentrations (▨), men; (■), women.

Discussion

It was hypothesized that the Lp(a) distribution of the Aboriginal Australians would be similar to that of ethnic African populations, where a bell-shaped or normal distribution exists.[5] However, it was demonstrated in the present study that the distribution of plasma Lp(a) in this Aboriginal population was highly skewed towards lower concentrations. This is similar to our other studies on Lp(a) in Chinese, Anglo-Celtic and, to a lesser degree, Indian Australians.[6]

As ITA was used for Lp(a) measurements, the risk threshold was adjusted for this specific method to 190 mg/L. About one-third of the subjects had Lp(a) levels equal to or greater than this threshold value, while only one-fifth had Lp(a) in excess of the 300 mg/L, once again indicating the necessity to derive threshold values for each method utilized.

Factors affecting plasma Lp(a) concentration

Sex and age

As there was no gender difference in the proportion of subjects who had Lp(a) concentrations above the two risk thresholds (> 190 mg/L and > 300 mg/L), it was suggested that men and women had a similar Lp(a) related risk of CHD in this population. Results from the stepwise mulitiple regression analysis show that Lp(a) rises with advancing age only in the middle age group. This suggests that age with its associated elevation in Lp(a), may be a risk factor for CHD.

Cigarette smoking and alcohol consumption

Mood-altering substances, high current smoking and alcohol abuse have been a matter of concern and a major problem in many Aboriginal communities. The Aborigines' hunter–gatherer lifestyle made available smoking materials from natural flora and provided indigenous tobaccos for chewing and pipe smoking. Nicotine in tobacco increases the heart rate and blood pressure in the short term and carbon monoxide partially replaces blood oxygen. Smoking may also influence Lp(a) levels.[7–9] It was observed in the present study that, in men only, Lp(a) concentration was higher in smokers than in the non-smoker (175 vs. 124 mg/L). This suggests that tobacco, modulated by gender, influences plasma Lp(a) concentrations.

Alcohol consumption among Aboriginal Australians is generally higher than that of non-Aboriginals, in terms of numbers of alcohol consumers and average quantities consumed.[10] It was also reported in Western Australia in a 1983 survey that alcohol abuse contributed to the high death rate of Aboriginals.[10] However, the effect of alcohol on plasma Lp(a) concentration was not demonstratable in the present

Table 4. Lipoprotein (a) (Lp(a)) concentrations in relation to the zygosity and molecular weight of apolipoprotein (a) (Apo(a)) phenotypes

		Lp(a) concentration (mg/L)		
Apo(a) phenotypes	*n*	%	Mean	SD
Zygosity*				
Men (*n* = 175)				
Homozygous	121	69.1	109	129
Heterozygous	54	30.9	252	215
Women (*n* = 219)				
Homozygous	149	68.0	128	171
Heterozygous	70	32.0	281	220
Molecular weight†				
Men (*n* = 175)				
Large MW	135	77.1	96	125
Small MW	40	22.9	346	176
Women (*n* = 219)				
Large MW	170	77.6	114	144
Small MW	49	22.4	396	215

*Zygosity: homozygous include phenotypes F, B, S1, S2, S3, S4 and 'null', and heterozygous include the combination of these phenotypes, such as S1S2, S1S3.
†Molecular weight: large MW includes phenotypes S3, S4, S3 S4 and 'null', and all other phenotypes are small MW.

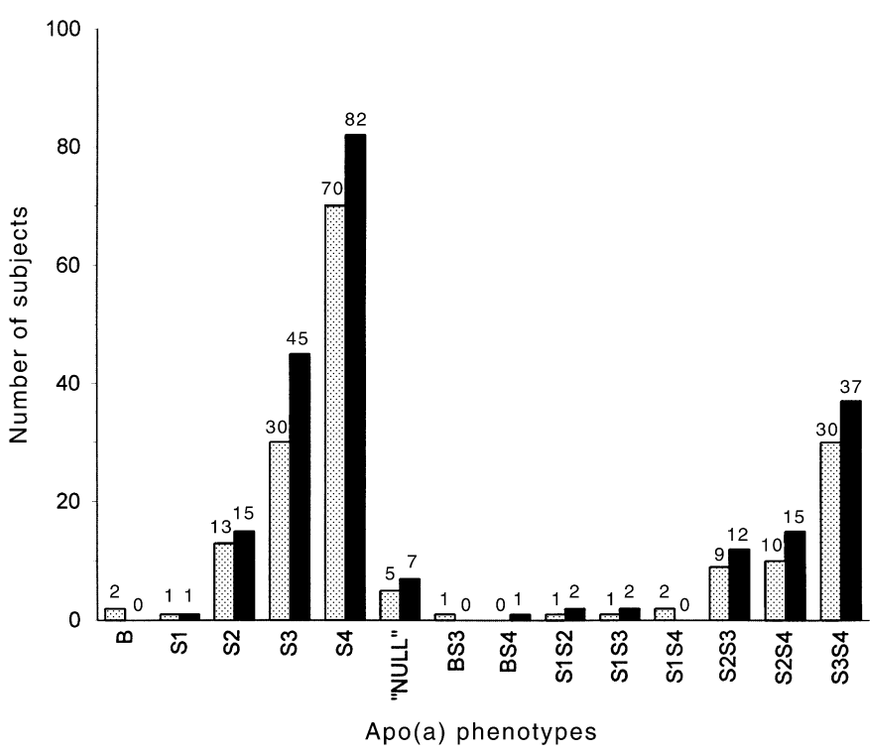

Figure 2. Distribution of apolipoprotein (a) (Apo(a)) phenotypes (▨), men; (■), women.

study. In addition, no significant difference in Lp(a) was observed between alcohol drinkers and teetotallers. A possible reason for this could be that subjects indulging in alcohol abuse did not survive.

Blood pressure

Hypertension has been found to be two- to threefold higher in peri-urban Aborigines than in non-Aboriginal Australians,[10,11] but not in Aboriginals adhering to a traditional lifestyle. Heinrich *et al.* demonstrated a significant independent positive relationship between systolic BP and Lp(a) levels in a healthy population,[7] while Slunga *et al.* also found a significant positive relationship between Lp(a) and systolic BP in hypertensive patients for the Northern Sweden WHO Monitoring of trends and determinants in cardiovascular diseases (MONICA) Study.[12] In contrast, the present study demonstrated that Aboriginal people with reduced levels of both diastolic BP and systolic BP had higher Lp(a) concentrations. This result might reflect a normotensive blood pressure range among the study group, or indicate that Lp(a) concentrations are negatively associated with blood pressure in normotensive people.

Steinmetz *et al.* reported no association between Lp(a) and diastolic BP.[13] However, it was observed in the present study that, among subjects aged < 40 years, Lp(a) was inversely related to both diastolic BP and systolic BP. The younger age of the subjects in their study (age range 19–53, mean 26 years), may account for the disparities in the results.

Body fatness

Obesity has been strongly associated with diabetes mellitus type II in many Aboriginal adults, particularly in women.[14] In the present study, we failed to demonstrate a relationship between Lp(a) concentration and body mass index, which is used as a marker of total body fat status. In contrast to our hypothesis, Lp(a) concentrations were higher in the underweight group body mass index (BMI) < 20) than in acceptable weight (BMI 20.0–24.9) and overweight groups (BMI ≥ 25) in the Aboriginal men and women, possibly due to chronic energy deficiency (CED). It was also found that when Lp(a) levels were in excess of 300 mg/L, the concentrations in women were higher than those of men in the underweight, acceptable weight and overweight groups, respectively. Perhaps factors associated with CED and protein undernutrition may contribute to higher Lp(a), for example, infection, where Lp(a) may behave as an acute-phase reactant and may play an important role in recovery from tissue damage. Furthermore, it was found in the present study that, among those aged ≥ 60 years, weight was positively related to Lp(a), possibly suggesting that a beneficial effect of Lp(a) in relation to increased body lean mass.

Blood lipids

The most frequent lipid abnormality in Aboriginal populations is hypertriglyceridemia.[15] Although it has been suggested that Lp(a) may be secreted in large triglyceride-rich particles,[16] the present study shows a negative correlation between Lp(a) and triglycerides. This discrepant result indicates that understanding of the control of Lp(a) metabolism is far from complete. The fact that Lp(a) and LDL have a common synthetic pathway is likely to be an explanation for the positive association of Lp(a) and LDL cholesterol (Tables 2 and 3).

Insulin

As many Aborigines have accepted a Westernized lifestyle and diet, obesity and diabetes have become prevalent in this population.[10,17] Diabetes mellitus is the most common endocrine disorder with hyperglycemia, due to deficiency or diminished effectiveness of insulin. A major finding of this population-based study was that reduced insulin was significantly associated with increased Lp(a) concentrations, especially in men. This may suggest an association of elevated Lp(a) with the development of diabetes, although Aboriginal subjects with diabetes mellitus were not included in the present study. However, Lp(a) may have a protective role in early diabetes mellitus type II with hyperinsulinemia.

Folate

The finding that serum or RBC folate was associated with Lp(a) was not clearly understood. Folic acid is essential for red cell DNA synthesis, and glycosylated hemoglobin (GHb) is derived from hemoglobin A, which is an oxygen-carrying pigment in red cells. The GHb was significantly related to Lp(a) concentrations in patients with insulin dependent diabetes mellitus in the studies of Ramirez *et al.*[18] From these observations, it could be suggested that DNA and hemoglobin A are related in some way to Lp(a).

Relationship between Apo(a) phenotype and Lp(a) concentration

Comparison of Lp(a) concentrations in different Apo(a) phenotypes reveals that there is an inverse association between the plasma Lp(a) concentration and the apparent molecular mass of the different Apo(a) phenotypes.[19,20] However, subjects with the same Apo(a) phenotype may also have different plasma Lp(a) concentration.[21–23] The present study demonstrated that in this Aboriginal population the concentration of Lp(a) was threefold higher in the small MW group than in the large MW, and was twofold higher in heterozygotes than in homozygotes (Table 4). These results are consistent with the findings in other studies. The smaller MW phenotypes, namely F, B, S1 and S2, are associated with higher Lp(a), and occur more frequently among patients with coronary artery disease. However, the large MW phenotypes, S3 and S4, together with the operational 'null' allele, are associated with lower or non-detectable Lp(a).[24,25]

Conclusion

The present study has revealed a distribution of Lp(a) concentration which is highly skewed toward low levels in the Aboriginal Australians surveyed. The findings have confirmed an inverse correlation between plasma Lp(a) concentration and Apo(a) size or molecular mass. We have also showed that although, it is believed, Lp(a) is mainly genetically determined, there are other factors which contribute to variations in Lp(a) concentrations.

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