

Plasma Lipids and Lipoprotein(a) Levels in the Chinese from China and Singapore

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Abstract

This study compared the influence of environmental factors on plasma lipid levels between the descendants of immigrant southern Han Chinese (Singapore Chinese, n = 275) and the native Chinese from southern China (n = 277). Their lipid profiles including lipoprotein (a) [Lp(a)] were measured and compared. The α level was set at 0.05 throughout the analysis. Body mass index (BMI), plasma total cholesterol (TC), low density lipoprotein cholesterol (LDLC), high density lipoprotein cholesterol (HDLC) and triglycerides (TG) levels were significantly elevated in the Singapore Chinese. Plasma Lp(a) however, was comparable in both groups for concentrations as well as frequency distributions. Since both groups were genetically identical, the similar Lp(a) level was in agreement with studies which reported that the apolipoprotein(a) [apo(a)] gene explained as much as 70% of the plasma Lp(a) variations in Chinese. No correlation of plasma Lp(a) level was observed with age and BMI while significant positive linear correlations were observed with TC and LDLC in the male subjects only. We concluded that environmental factors (possibly affluent lifestyle and westernised diet) have significantly influenced the lipid risk factor levels of the Singapore Chinese whereas Lp(a) levels, which are predominantly under genetic control, were not altered significantly.

Ann Acad Med Singapore 1997; 26:303-7

Key words: Apolipoprotein (a), High density lipoprotein cholesterol, Low density lipoprotein cholesterol, Total cholesterol, Triglyceride

Introduction

The incidence and mortality of coronary artery disease (CAD) is very low in the Chinese compared to that of the Caucasians. The male age-standardised CAD mortality rate (per 100 000 population) in China is 47.5 in urban areas and 22.8 in rural areas* compared to figures of above 400 for Caucasian countries like the United Kingdom, Finland and Australia.² The CAD mortality rate for the Singapore Chinese is 185, which is also among one of the lowest in the world³ although still more than three times higher than that of China. The relatively low levels of plasma atherogenic lipids in the Chinese is most probably one of the factors which contribute to their low CAD risk.⁴

The population in Singapore comprises 78% ethnic Chinese. The disease patterns and health needs of Singaporeans have altered dramatically over the last few decades as a result of rapid economic progress and socio-demographic changes. At present, Singaporeans have a high standard of living. This is reflected by the very low infant mortality rate and long life expectancy at birth. At the same time, chronic degenerative diseases such as

cancer and cardiovascular disease have replaced infectious diseases as the major causes of death, a trend observed similarly in industrialised countries throughout the world. The percentage of deaths due to CAD has risen from 2.95% thirty years ago to 20% in 1996.⁵ Among the three major ethnic groups in Singapore, the Chinese has the lowest mortality rate for cardiovascular diseases compared to the Malays and Indians.⁶

A high concentration of lipoprotein(a) [Lp(a)] in plasma is an independent risk factor for CAD.⁷⁻¹¹ Plasma Lp(a) level of above 30 mg/dl Lp(a) is the commonly accepted cut-off point for high Lp(a). Subjects with Lp(a) above 30 mg/dl have their risk of CAD increased by about 3-fold over those with low plasma Lp(a).¹¹⁻¹³ Unlike other lipids and lipoproteins, Lp(a) is the only major lipid risk factor whose concentration appears to be minimally influenced by metabolic, endocrine and anthropometric factors.¹⁴ It is independent of body mass index (BMI),¹⁵ age,^{15,16} diet,¹⁶ and oestrogen.¹⁷ A study of Hong Kong Chinese reported the lack of association between plasma Lp(a) concentration and known modifiable cardiovascular risk factors such as smoking, alcohol consump-

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tion, hypertension and obesity.¹⁸ However, some other studies reported alteration of **Lp(a)** levels by oestrogen and progesterone,¹⁹ androgenic steroids²⁰ and alcohol.^{21,22} Plasma **Lp(a)** level is controlled predominantly by genetics factors²³ and hence is a risk factor whose level cannot be easily modified. It has been shown that the apolipoprotein(a) [apo(a)] gene size polymorphism explained between 53% and 70% of the variation in **Lp(a)** levels of Singapore Chinese.^{24,25} This great extent of genetic influence is in sharp contrast to that of the Caucasians where alleles at the apo(a) locus determine only between 25% and 37% of their **Lp(a)** level variations.²⁴ Besides the control by apo(a) gene, **Lp(a)** level has also been shown to be affected by gene locus of the LDL receptor,²⁶ abetalipoproteinaemia²⁷ and most recently, by gene locus of the apoA-IV.²⁸

Results from comparative population studies of plasma **Lp(a)** levels showed that the Chinese from Singapore has the lowest serum **Lp(a)** concentration among 8 other populations consisting of Israelites, Welsh, Tyroleans, Sudanese, Indians, Malays, Hungarians and Icelandics.^{24,29} The majority of Singapore Chinese are third generation descendants of Southern Han Chinese immigrants who settled in Singapore in the early 19th century. In comparison to their counterparts in mainland China, they are more affluent and westernised in their lifestyle and dietary habits. The aim of this study was to investigate the influence of environmental and dietary factors on the level of plasma **Lp(a)** and lipids in the descendants of the immigrant Chinese in Singapore in relation to the mainland Chinese.

Subjects and Methods

Subjects

Two hundred and seventy-seven Han Chinese (217 males and 60 females) who were recruited as skilled factory workers formed the sample from China. Upon arrival in Singapore, they were enlisted into this study during their mandatory pre-employment medical examination at the Singapore Anti-Tuberculosis Association (SATA) Chest and Heart Clinic. Only those from the provinces of Fujian and Guangdong were selected in order to match the Chinese from Singapore, whose predecessors came predominantly from these two provinces in China. Two hundred and seventy-five Singapore Chinese skilled factory workers (208 males and 67 females) were also selected randomly from those who attended pre-employment medical examination at the same clinic. All subjects with a history of heart disease and diabetes were excluded from this study. Verbal informed consent was obtained from the subjects before phlebotomy.

Laboratory Procedures

The details of the methods were as published earlier.³⁰

Ten ml of venous blood was collected from each individual in EDTA tubes. Plasma was separated by centrifugation and aliquoted portions were stored at -20°C. Plasma total cholesterol (TC), high density lipoprotein cholesterol (HDL), and triglyceride (TG) levels were estimated by the enzymatic assay method while apoA-1 and apoB were estimated by a turbidometric assay on an autoanalyzer (Cobas Mira, Roche, Switzerland) using the manufacturer's reagent kits. Quality control was verified routinely with the reference laboratories (Wellcome Quality Assurance Programme, UK). Low density lipoprotein cholesterol (LDL) was calculated by the Friedewald formula.³¹ **Lp(a)** quantification was performed by a sandwiched enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Biopool, Umeå, Sweden). BMI was calculated using the formula: BMI = weight/height² (kg/m²).

Statistical Analysis

The distributions of all quantitative parameters were tested for normality and homogeneity of variance by the Lilliefors's test and Levene's test respectively. The null hypotheses of homogeneity and normality were accepted when $P > 0.05$. Distribution of TG and **Lp(a)** concentrations were positively skewed. Natural logarithmic (ln) transformation was used to normalise the distributions for parametric tests. In the case of **Lp(a)**, 1 mg/dL was added to all values before the logarithmic transformation since concentration of less than 1 resulted in negative logarithmic values and those with 0 mg/dL could not be logarithmically transformed. Values of TG and **Lp(a)** were presented as anti-ln and anti-ln minus 1 of the transformed values respectively. Differences for the means of anthropometric parameters, plasma lipids and **Lp(a)** levels between the two populations were estimated by the t-test. Spearman's rank-order correlation coefficients (r) were computed for **Lp(a)** with age, BMI and plasma lipids. All analyses for males and females were carried out separately with significance levels set at 0.05 in all cases. Statistical calculations were performed by Release 6.0 of the Statistical Package for Social Studies (SPSS) for Windows.

Results

Table I shows the mean anthropometric parameters, plasma lipids and **Lp(a)** levels in the Chinese from China and Singapore. Both groups were of comparable age. BMI was only significantly higher in Singapore males but not in females. Most of the plasma lipids studied, i.e. TC, TG, HDL, LDL and apoB were significantly higher in the Singapore population. However, there was no significant difference in plasma **Lp(a)** concentrations between subjects of the two countries for both genders. The frequency distributions of **Lp(a)** levels for the two Chinese populations were similar, with both

TABLE I: ANTHROPOMETRIC PARAMETERS, PLASMA LIPIDS AND Lp(a) LEVELS (mg/dl) IN THE CHINESE FROM CHINA AND SINGAPORE (MEAN $\pm$ SD)

	Males		Females	
	Singapore n = 208	China n = 217	Singapore n = 67	China n = 60
Age(y)	31.20 $\pm$ 9.31	32.43 $\pm$ 6.62	30.15 $\pm$ 9.79	28.33 $\pm$ 2.80
BMI (kgm-2)	22.38 $\pm$ 3.16*	21.00 $\pm$ 2.58	21.30 $\pm$ 4.16	20.24 $\pm$ 1.96
ln[Lp(a)+1]	2.039 $\pm$ 1.21	2.21 $\pm$ 1.21	2.26 $\pm$ 1.32	2.10 $\pm$ 1.06
Lp(a)	6.68	8.12	8.58	7.17
TC	209.15 $\pm$ 42.44**	161.56 $\pm$ 36.81	204.34 $\pm$ 38.55***	155.35 $\pm$ 26.72
LDLC	137.34 $\pm$ 37.97***	104.66 $\pm$ 56.71	124.04 $\pm$ 37.58***	87.17 $\pm$ 26.75
HDLC	44.79 $\pm$ 12.86***	36.20 $\pm$ 10.23	57.04 $\pm$ 16.14*	51.40 $\pm$ 14.79
lnTG	4.77 $\pm$ 0.52*	4.67 $\pm$ 0.45	4.62 $\pm$ 0.38	4.38 $\pm$ 0.33
TG	117.92	106.70	101.49***	79.84
ApoA-1	133.72 $\pm$ 21.42	129.88 $\pm$ 22.01	150.74 $\pm$ 25.30	148.58 $\pm$ 19.70
ApoB	96.36 $\pm$ 28.81**	75.11 $\pm$ 20.53	82.10 $\pm$ 24.78*	73.40 $\pm$ 15.71

Asterisks denote significant differences between the China and Singapore populations at $P < 0.05$ (*) and $P < 0.0005$ (**).

BMI: body-mass index; Lp(a): lipoprotein (a); ln: natural logarithm; TC: total cholesterol; LDLC: low-density lipoprotein cholesterol; HDLC: high-density lipoprotein cholesterol; TG: triglyceride; Apo: apolipoprotein

having highly skewed distribution towards low concentrations (Fig. 1). The mode plasma concentration for males and females in both groups was 0 mg/dl.

We found small but significant rank correlation of Lp(a) with LDLC ($P < 0.05$) for all the subgroups except for the females from China (Table II). There was no correlation of Lp(a) with age, BMI, TG, apoA-1 and apoB.

Discussion

This study is the first study conducted to compare Lp(a) levels of two ethnically identical populations with different mortality from CAD. As the Chinese from the two countries were residing in different geographical locations and leading dissimilar lifestyles, it was of interest to investigate whether plasma Lp(a) and lipids varied significantly under differing environmental conditions.

The recent influx of expatriate workers into Singapore from various countries has provided us with an invaluable opportunity to carry out this comparative study. Upon their arrival in Singapore, the blood samples of the mainland Chinese workers were collected during their pre-employment medical examination to ensure that the local environment and dietary factors had not caused any significant changes in their plasma lipid and lipoprotein concentrations. Quantifications of these biochemical risk factors from both countries were performed in the same laboratory, thus eliminating errors due to inter-laboratory variation. We had chosen the subjects from the two countries with similar nature of work (both groups were skilled factory workers). This was to eliminate any possible confounding effects that a sedentary or physically demanding job may have on the physical fitness of the workers, since there is known

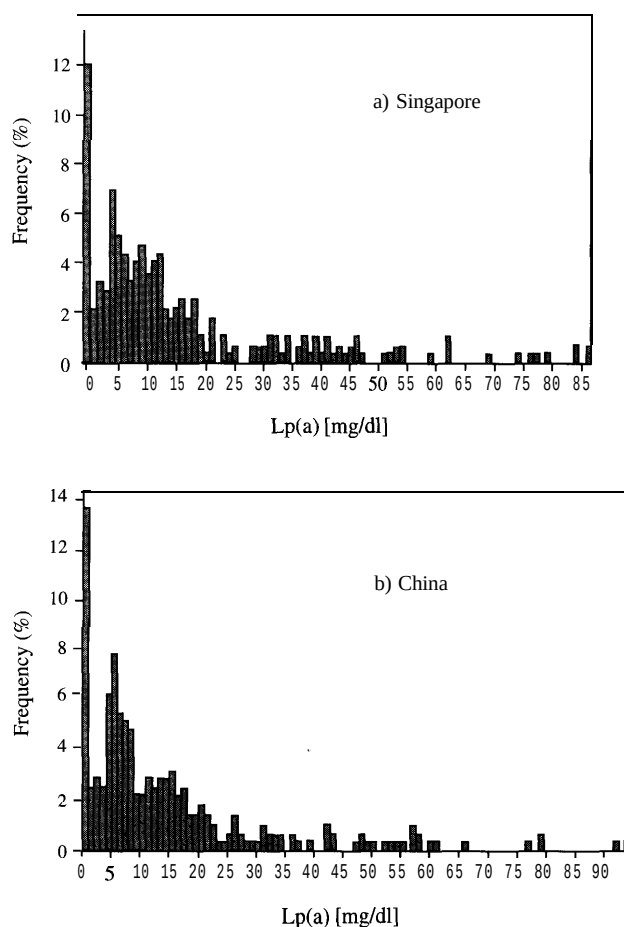


Fig. 1. Frequency distribution of lipoprotein(a) for Chinese from a) Singapore and b) China.

correlation between BMI and plasma lipid levels.

The effect of a generally more affluent lifestyle and westernised diet of the Singapore Chinese was clearly evident in the significantly elevated plasma TC, TG,

TABLE II: SPEARMAN'S RANK CORRELATION COEFFICIENT (r) FOR Lp(a) WITH AGE, BODY MASS INDEX AND PLASMA LIPIDS

	Males			
	Singapore		China	
	r	P	r	P
Age	0.043	ns	-0.009	ns
BMI	-0.094	ns	-0.069	ns
TC	0.065	ns	0.197	0.004
HDLC	-0.091	ns	0.001	ns
LDLC	0.140	0.006	0.256	<0.005
TG	-0.070	ns	-0.039	ns
ApoA-1	-0.056	ns	-0.028	ns
ApoB	0.105	ns	0.085	ns

	Females			
	Singapore		China	
	r	P	r	P
Age	-0.148	ns	0.199	ns
BMI	0.069	ns	-0.011	ns
TC	0.128	ns	0.170	ns
HDLC	-0.300	0.014	-0.001	ns
LDLC	0.303	0.013	0.167	ns
TG	-0.216	ns	0.009	ns
ApoA-1	-0.235	ns	-0.052	ns
ApoB	0.124	ns	0.156	ns

ns: not significant; BMI: body-mass index; Lp(a): lipoprotein (a); ln: natural logarithm; TC: total cholesterol; LDLC: low-density lipoprotein cholesterol; HDLC: high-density lipoprotein cholesterol; TG: triglyceride; Apo: apolipoprotein

LDLC and apoB of both genders. Such increase in lipid risk factors levels were commonly seen in other studies on migrant populations, e.g. Chinese in New York City³² and Mauritius.³³ In another migrant study of Japanese in Hawaii and California, a gradient exists in plasma TC and TG levels among men of Japanese ancestry, increasing from Japan to Hawaii to California.³⁴ Generally, Orientals who migrate to Western countries tend to become heavier, more obese, more sedentary, eat more saturated fat and cholesterol and consume less complex carbohydrate than their respective homeland counterparts.

Despite significant differences in their plasma lipid levels, the Lp(a) levels and frequency distribution of the 2 Chinese populations were not significantly different. This is consistent with the fact that in the Chinese, the apo(a) gene explains as much as 70% of the plasma Lp(a) variations. Therefore, both populations being genetically Han Chinese, external factors like environment and diet have not been able to alter Lp(a) concentrations significantly.

In this study, there was no significant correlation of Lp(a) with BMI. This was in agreement to the results of Corsetti et al,³⁵ who found no significant lowering in

plasma Lp(a) concentration of an obese population who underwent weight-reduction programme of diet, exercise and behaviour modification together with anorectic drug therapy. There was also no significant correlation of Lp(a) with age. Thus both BMI and age had no effect on plasma Lp(a) concentration.

The involvement of the LDL-receptor in Lp(a) catabolism is still a subject of controversy and was discussed in our earlier report.³⁰ The presence of a weak but significant correlation of Lp(a) with LDLC and TC in the male subjects of both countries was in agreement with our previous findings³⁰ as well as the results of de Knijff et al³⁶ for a Dutch population. This finding therefore suggests the possible involvement of the LDL-receptor in the breakdown of Lp(a). This trend was less obvious in female subjects owing to the small sample size although there was correlation with LDLC in local females.

The two Chinese populations residing in China and Singapore who were under the influence of different environmental and dietary factors, maintained similar levels of plasma Lp(a) although differing significantly in other plasma lipid risk factors. We conclude that the more affluent lifestyle and westernised diet of the Singapore Chinese had resulted in their elevated lipid risk factors whereas Lp(a) levels, which are predominantly under genetic control, were not altered significantly.

Acknowledgements

This study was supported by the National University of Singapore and the Singapore Anti-Tuberculosis Association (SATA). The technical assistance of Mrs Jumiah bte Basair and laboratory staff of SATA is gratefully acknowledged. The authors are grateful to the Medical Director of SATA for availing their facilities for this study.

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