Lipoprotein(a) Is an Independent Risk Factor for Peripheral Arterial Disease in Chinese Type 2 Diabetic Patients in Taiwan

CHIN-HSIAO TSENG, MD, PHD

OBJECTIVE — To examine the association between lipoprotein(a) [Lp(a)] and peripheral arterial disease (PAD) and determine the optimal cutoff in Chinese type 2 diabetic patients in Taiwan.

RESEARCH DESIGN AND METHODS — Serum Lp(a) was determined in 557 type 2 diabetic patients (243 men and 314 women) recruited consecutively from a diabetes clinic at the National Taiwan University Hospital. Ankle-brachial index (ABI) <0.9 was diagnosed as PAD ($n = 45$) and <0.8 as severe PAD ($n = 20$). Potential confounders included age, sex, BMI, waist-to-hip ratio (WHR), diabetes duration, insulin usage, smoking, hypertension, systolic and diastolic blood pressure, fasting plasma glucose (FPG), total cholesterol, triglycerides, and HDL and LDL cholesterol.

RESULTS — The distribution of Lp(a) was right skewed and no significant differences for sex, WHR, insulin usage, smoking, hypertension, and systolic and diastolic blood pressure were observed. In men, log[Lp(a)] was correlated positively with age, duration, and total and LDL cholesterol (borderline significant, $P < 0.1$) and negatively with BMI, triglycerides, and FPG ($P < 0.1$). In women, log[Lp(a)] was correlated positively with total and LDL cholesterol and negatively with triglycerides and BMI ($P < 0.1$). ABI was significantly correlated with log[Lp(a)], especially in men or in patients with PAD. The optimal cutoff determined by discriminant analysis was 13.3 mg/dl. Patients with Lp(a) above this value had a 2.7-fold higher risk of PAD after multivariate adjustment. Lp(a) also significantly increased from no PAD to mild and severe PAD (17.1 ± 14.4, 23.7 ± 20.3, and 36.9 ± 22.8 mg/dl, respectively, $P < 0.001$).

CONCLUSIONS — Lp(a) is an independent risk factor for PAD in type 2 diabetic patients in Taiwan. The optimal cutoff is 13.3 mg/dl.

Diabetes Care 27:517–521, 2004

Lipoprotein(a) [Lp(a)] is a heterogeneous macromolecule consisting of a glycoprotein apolipoprotein(a), which is disulfide-linked to apolipoprotein B-100 on an LDL core (1). Apolipoprotein(a) exhibits size polymorphism, which is closely linked to Lp(a) density and concentrations (2). The limited distribution of Lp(a) in a few animal species implies that it is not essential in lipoprotein metabolism (3). However, it is clinically important because its concentrations are primarily genetically determined, associated with atherosclerotic disease, and less affected by lifestyle or medication (4). Lp(a) concentrations are quite constant in an individual (2). Lipid-lowering statins appear ineffective, whereas niacin might have some effect on Lp(a) lowering (5). Lp(a) might be higher in type 2 diabetic patients, but glycemic control seems to have no effect on serum Lp(a) (6). With few exceptions (7,8), Lp(a) has been shown to be a risk factor for atherosclerotic disease, such as ischemic heart disease (9,10), myocardial infarction (11,12), stroke (13), and peripheral arterial disease (PAD) (14,15).

A community study in Taiwan examining the relationship between Lp(a) and socioeconomic and atherosclerotic risk factors demonstrated that Lp(a) was positively correlated with age and LDL and HDL cholesterol and negatively correlated with triglycerides, obesity, and insulin resistance (16). Socioeconomic status, smoking, alcohol consumption, systolic and diastolic blood pressure, and apolipoprotein A1 and B did not correlate with Lp(a) (16). Although this study demonstrated the association between Lp(a) and some of the atherosclerotic risk factors, whether Lp(a) is an independent risk factor for atherosclerotic disease in the Chinese population in Taiwan awaits further evaluation. Most studies evaluating Lp(a) and atherosclerotic disease focused on coronary artery disease, and only a few evaluated its association with PAD. Data in the Asian populations are especially rare, and nothing is known about Lp(a) and PAD in the Chinese population in Taiwan. It is not known whether the recommended cutoff of 30.0 mg/dl for Caucasians is appropriate for Chinese type 2 diabetic patients in Taiwan. Thus, the objectives of this study were to *1*) examine whether Lp(a) was an independent risk factor for PAD in Chinese type 2 diabetic

From the Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; the National Taiwan University College of Medicine, Taipei, Taiwan; and the Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Taipei, Taiwan.

Address correspondence and reprint requests to Chin-Hsiao Tseng, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, No. 7 Chung-Shan South Rd., Taipei, Taiwan. E-mail: ccktsh@ms6.hinet.net.

Received for publication 9 May 2003 and accepted in revised form 2 November 2003.

Abbreviations: ABI, ankle-brachial index; FPG, fasting plasma glucose; Lp(a), lipoprotein(a); PAD, peripheral artery disease; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

patients and 2) determine the optimal cutoff of Lp(a) for discriminating patients with and without PAD.

RESEARCH DESIGN AND METHODS

— A total of 557 type 2 diabetic patients (243 men and 314 women) were consecutively recruited from a diabetes clinic at the National Taiwan University Hospital in Taipei, Taiwan. The patients were treated with either oral antidiabetic drugs or insulin at recruitment. They did not show a history of diabetic ketoacidosis at the onset of diabetes or receive insulin treatment within 1 year of diagnosis. Patients with acute illness or taking niacin, estrogen replacements, or antibiotics were not included.

Diagnosis of PAD

Diagnosis of PAD was based on an ankle-brachial index (ABI) <0.9 on either leg as described in previous studies (17–19). In brief, Doppler ultrasound (Medacord PVL; MedaSonic, Mountain View, CA) was used to measure the systolic pressures on bilateral brachial, posterior tibial, and dorsal pedal arteries. The device calculated the right and left ABI automatically by dividing the higher pressure on the dorsal pedal or posterior tibial arteries on right and left sides, respectively, by the higher brachial pressure on either side. PAD was further categorized as a severe form (ABI <0.80 on either side of the extremities) or as a mild form (ABI <0.90 on either leg, but neither <0.80).

Risk factors

Risk factors included age, sex, BMI, waist-to-hip ratio (WHR), diabetes duration, hypertension, smoking, insulin usage, systolic blood pressure, diastolic blood pressure, fasting plasma glucose (FPG), serum total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Lp(a). While evaluating the association between Lp(a) and PAD, the other risk factors were treated as potential confounders. Blood pressure was measured on the right arm after a 20-min rest in a sitting position with a mercury sphygmomanometer by the auscultatory method. The first perception of successive sounds (Korotkoff phase I) was taken as systolic blood pressure, and the complete disappearance of sound (Korotkoff phase V) was taken as diastolic blood pressure. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (20) or if the patient was receiving antihypertensive therapy. Venous blood samples were collected in the morning after an overnight fast of >12 h. Serum samples were used to determine total cholesterol, triglycerides, and HDL and LDL cholesterol on an autoanalyzer (Hitachi 737) with reagents obtained from Boehringer Mannheim Diagnostics (Indianapolis, IN) (17,18). Serum Lp(a) was measured by turbidimetric immunoassay method [Biolatex Lp(a) assay; Biolatex, Logroño, Spain]. A 10-fold dilution was made before assay if the serum sample was turbid or if the triglyceride level was >400 mg/dl. FPG was determined by a glucose oxidase method (21). Measurements of anthropometric parameters are described elsewhere (22).

Statistical analyses

Because the distribution of Lp(a) was highly right skewed, the natural logarithm {log[Lp(a)]} was used for statistical tests when an assumption of normal distribution was required. The differences of log[Lp(a)] among different age-groups were compared by one-way ANOVA in separate sexes. Student's *t* test was used to test the differences of log[Lp(a)] between the diabetic men and women in each stratum of age and in all ages, between patients with and without hypertension, between insulin users and nonusers, and between smokers and nonsmokers. Pearson correlation coefficients were generated to evaluate the linear relationship between continuous covariates and log[Lp(a)] in separate sexes.

Log[Lp(a)] was used in discriminant analysis (Wilks' method) to determine the optimal cutoff of Lp(a). Patients were divided into different subgroups by using tertiles, quartiles, and quintiles of Lp(a), by using the cutoff of 30.0 mg/dl, and by the cutoff derived from the discriminant analysis. Prevalences of PAD in different subgroups of Lp(a) were analyzed by χ^2 test. Logistic regression was used to estimate the multivariate-adjusted odds ratios (ORs) and their 95% CIs for PAD among the different subgroups by using the lowest Lp(a) subgroups as reference groups. All potential confounders, including age, sex, BMI, WHR, diabetes duration, hypertension, smoking, insulin usage, systolic blood pressure, diastolic blood pressure, FPG, total cholesterol, triglycerides, and HDL and LDL cholesterol, were adjusted for in these models.

Table 1—*Baseline clinical characteristics of the subjects*

n	557
Age (years)	63.4 ± 10.4
Sex (% men)	43.6
BMI (kg/m^2)	24.7 ± 3.5
WHR	0.90 ± 0.08
Diabetes duration (years)	12.1 ± 7.9
Insulin user	20.1
Smoker	27.8
Hypertension	37.9
Systolic blood pressure (mmHg)	134.7 ± 17.5
Diastolic blood pressure (mmHg)	79.0 ± 9.7
FPG (mg/dl)	152.0 ± 51.3
Total cholesterol (mg/dl)	202.3 ± 38.8
Triglyceride (mg/dl)	174.1 ± 112.8
HDL cholesterol (mg/dl)	49.7 ± 33.9
LDL cholesterol (mg/dl)	112.6 ± 48.5
Lp(a) (mg/dl)	18.1 ± 15.5

Data are means ± SD or percent.

Lp(a) was also treated as a continuous variable while estimating the OR by logistic regression. Various model-based ORs were created, either before or after adjustment for confounders. Because age and sex are unmodifiable risk factors, respective models adjusted for age, sex, and both age and sex were first created to see the possible influence of these two factors on the estimated ORs. Further models were created by selecting, in addition to age and sex, *1*) a variable with $P < 0.1$ in any univariate analysis (i.e., age and sex plus one of the following variables at a time: BMI, diabetes duration, FPG, total cholesterol, triglycerides, or LDL cholesterol), *2*) all variables with $P < 0.1$ in any univariate analysis (i.e., age and sex plus all of the following variables: BMI, diabetes duration, FPG, total cholesterol, triglycerides, and LDL cholesterol), and *3*) all potential confounders (i.e., age, sex, BMI, WHR, diabetes duration, hypertension, smoking, insulin usage, systolic blood pressure, diastolic blood pressure, FPG, total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol). All continuous variables were not categorized while used for adjustment. One-way ANOVA was used to compare the differences of log[Lp(a)] among the three subgroups of patients in respect to PAD, i.e., patients without, with mild, and with severe PAD.

Whenever there was a significant *P* value of <0.05 in one-way ANOVA, multiple comparisons by least significant difference were further performed. Continuous variables were expressed as

means ± SD. $P < 0.05$ was considered statistically significant, and $0.05 < P < 0.1$ was considered borderline significant.

RESULTS — The baseline characteristics of the subjects are shown in Table 1. Log[Lp(a)] values were not significantly different among the different age-groups (<45, 45–54, 55–64, 65–74, and ≥75 years) in either sex and between sexes in each stratum of age. Lp(a) levels in the diabetic men and women were 18.2 ± 16.2 and 18.1 ± 15.0 mg/dl, respectively {Student's *t* test for log[Lp(a)], $P > 0.1$}. The differences of log[Lp(a)] were not statistically significant between patients with and without hypertension, smokers and nonsmokers, and insulin users and nonusers (data not shown). However, patients with PAD had a significantly higher level of Lp(a) than patients without PAD {29.5 ± 22.2 vs. 17.1 ± 14.4 mg/dl, Student's *t* test for log[Lp(a)], $P < 0.001$}.

Table 2 shows the Pearson correlation coefficients between log[Lp(a)] and continuous covariates in separate sexes and in total patients and between log[Lp(a)] and ABI in all patients, patients with PAD, and patients without PAD, respectively.

The cutoff of Lp(a) generated from the discriminant analysis was 13.3 mg/dl, which was approximately equal to the median value of 13.1 mg/dl. Sixty percent of the originally grouped cases with and without PAD would be correctly classified by this cutoff. Prevalences of and multivariate-adjusted OR for PAD in subgroups of tertiles, quartiles, quintiles, and cutoffs of 30.0 mg/dl and 13.3 mg/dl of Lp(a) are shown in Table 3. The OR for PAD after adjustment for all potential confounders when Lp(a) was treated as a continuous variable is also given in Table 3. While Lp(a) was treated as a continuous variable, the various model-based ORs for PAD were all highly significant ($P < 0.001$) with similar values either before or after various adjustments (data not shown). The percentile distributions of Lp(a) in patients without, with mild (n = 25), and with severe (n = 20) PAD are shown in Fig. 1. Mean values of Lp(a) in these subgroups of patients are shown in Fig. 2.

Table 3—*Prevalence and multivariate-adjusted ORs for PAD in different cutoffs of Lp(a)*

	Lp(a) (mg/dL)	PAD prevalence	Adjusted OR (95% CI)
Cutoff points (mg/dl)			
<30	11.68 ± 7.51	5.8	1.000
≥30	44.40 ± 11.50	17.3*	3.019 (1.433–6.360)*
<13.3	6.85 ± 3.43	4.9	1.000
≥13.3	29.96 ± 14.42	11.4*	2.685 (1.203–5.994)†
Tertiles			
I	4.84 ± 2.27	5.4	1.000
II	13.33 ± 3.18	5.4	1.111 (0.418–2.951)
III	36.22 ± 13.37	13.4*	2.460 (1.044–5.798)†
Quartiles			
I	3.89 ± 1.81	3.6	1.000
II	9.49 ± 1.74	6.5	1.558 (0.465–5.216)
III	18.29 ± 3.50	6.4	1.740 (0.519–5.832)
IV	40.88 ± 12.33	15.8*	4.666 (1.531–14.221)*
Quintiles			
I	3.28 ± 1.50	2.7	1.000
II	7.82 ± 1.19	7.1	1.967 (0.460–8.413)
III	13.09 ± 2.12	5.4	2.085 (0.461–9.423)
IV	22.29 ± 3.79	7.1	2.752 (0.642–11.797)
V	44.26 ± 11.53	18.0*	6.333 (1.629–24.612)*
Continuous			1.043 (1.021–1.066)*

Data are means ± SD or percent. *$P < 0.01$; †$P < 0.05$.

Table 2—*Pearson correlation coefficients between log[Lp(a)] and continuous covariates and ABI by sex*

Variables	Men	Women	Total
n	243	314	557
Age	0.150*	0.040	0.092*
BMI	−0.164*	−0.108†	−0.133‡
WHR	0.047	−0.059	−0.023
Diabetes duration	0.131*	0.012	0.065
Systolic blood pressure	0.011	−0.001	0.006
Diastolic blood pressure	−0.084	−0.019	−0.046
FPG	−0.121†	0.026	−0.041
Total cholesterol	0.156*	0.214‡	0.189‡
Triglyceride	−0.138*	−0.111*	−0.120‡
HDL cholesterol	0.077	0.023	0.034
LDL cholesterol	0.125†	0.199‡	0.169‡
ABI			
All patients	−0.261‡	−0.108†	−0.185‡
Patients with PAD	−0.108† (n = 16)	−0.176 (n = 29)	−0.340* (n = 45)
Patients without PAD	−0.101 (n = 227)	−0.019 (n = 285)	−0.073 (n = 512)

*$P < 0.05$; †$0.05 < P < 0.1$; ‡$P < 0.01$.

CONCLUSIONS — This study confirmed the association between Lp(a) and PAD, independent of potential confounders, in Chinese type 2 diabetic patients in Taiwan. The conventionally used cutoff of 30.0 mg/dl, which corresponded to approximately the 80th percentile of this sample, carried a three times higher risk of PAD (Table 3). However, the optimal cutoff in Chinese type 2 diabetic patients in Taiwan seemed to be at a lower level (13.3 mg/dl), which gave the greatest correct predictions (60%) for patients with and without PAD and significantly increased the risk of PAD by 2.7-fold (Table 3). About 40% of the originally grouped cases with and without PAD would not be correctly classified by this cutoff, suggesting that some other risk factors would also be important to the development of PAD in type 2 diabetic patients. Thus, one

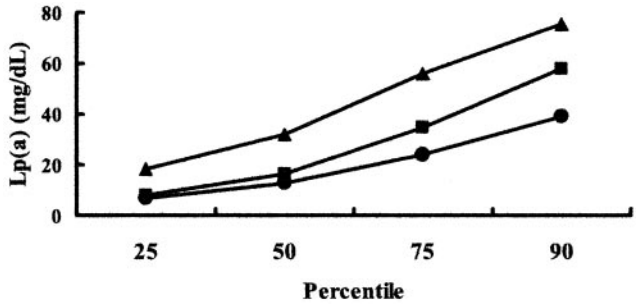

Figure 1—*The percentile distributions of Lp(a) in patients without* (n = *512,* ●)*, with mild* (n = *25,* ■) *and severe* (n = *20,* ▲) *PAD.*

should not neglect the possible existence of PAD in patients with a lower level of Lp(a).

In this study, Lp(a) was not only an independent risk factor for PAD, it was also correlated with ABI, especially when PAD was present (Table 2). Lp(a) also increased steadily from absence of PAD to mild and severe PAD (Fig. 2).

In the general population of Taiwan, age is a major determinant of Lp(a) in both sexes, and women tend to have slightly higher Lp(a) than their male counterparts (16). The proportion of people with Lp(a) ≥30.0 mg/dl is also higher in women in the general population (men versus women, 11.6 vs. 14.3%, $P < 0.05$) (16). However, these levels were not observed in the diabetic patients in this study. The correlation between Lp(a) and age was only observed in the diabetic men and not in the diabetic women (Table 2). The diabetic men and women have similar levels of Lp(a) (men versus women, 18.2 ± 16.2 vs. 18.1 ± 15.0 mg/dl, $P > 0.1$) and similar proportions of Lp(a) ≥30.0 mg/dl (men versus women, 19.8 vs. 19.7%, $P > 0.1$). These observations suggest that a higher proportion of diabetic patients would have Lp(a) ≥30.0 mg/dl than the general population, without much influence by age or sex.

Similar to the observation in the general population (16), log[Lp(a)] was negatively correlated with BMI and positively with total and LDL cholesterol and was not correlated with blood pressure (Table 2). In the diabetic patients, WHR and HDL cholesterol were not significantly correlated with log[Lp(a)], and FPG was only negatively correlated with log [Lp(a)], with borderline significance in men (Table 2). The significant correlation between log[Lp(a)] and triglycerides (negatively), as seen in the diabetic patients (Table 2), was also observed in the general population (16). Because Lp(a) is deemed a proatherogenic molecule, the negative association with BMI and triglycerides is puzzling and deserves further investigation. Similar to other studies (6), glycemic control seemed to have an insignificant effect on Lp(a) in type 2 diabetic patients in this study.

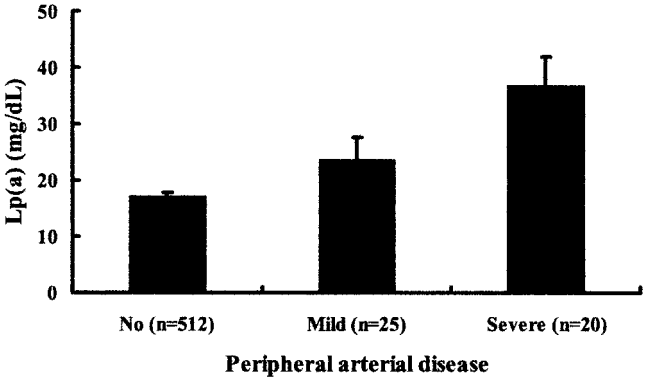

Figure 2—*The mean values of Lp(a) in patients without, with mild, and with severe PAD (error bars indicate SE). One-way ANOVA for log[Lp(a)] among the three groups:* $P < 0.001$*. Multiple comparison test by least significant difference: no PAD vs. mild PAD,* $P < 0.1$*; no PAD vs. severe PAD,* $P < 0.001$*; mild PAD vs. severe PAD,* $0.05 < P < 0.1$*.*

Elevated total cholesterol and triglycerides are not good markers for PAD in the Chinese population in Taiwan, in either the diabetic patients (23) or subjects living in a confined community (18). This could partly be ascribed to the fact that although Lp(a) is less influenced by lifestyle and medication, both total cholesterol and triglycerides tend to be modified significantly by diet, exercise, and drug treatment. This study demonstrated that Lp(a) could be a much better marker for atherosclerotic disease in the Chinese population in Taiwan.

Although Lp(a) concentrations are primarily affected by genetic factors, recent studies (1) have demonstrated that its atherothrombogenic effect may be modified by oxidative events and actions of lipolytic and proteolytic enzymes. This may partly explain the reported discrepancy in the association between Lp(a) and cardiovascular disease in different studies. More research is needed to explore the molecular and pathogenic mechanisms related to the atherogenic effect of Lp(a).

Limitations

This study was carried out in type 2 diabetic patients in a medical center in Taiwan. The possibility of referral bias cannot be ruled out. Furthermore, an association found in a cross-sectional study is not sufficient to conclude a causal relationship. It is also unknown whether Lp(a) is a risk factor for atherosclerotic diseases other than PAD. The usefulness of the optimal cutoff of Lp(a) found in this study also requires further investigation.

Summary

Lp(a) is a significant and independent risk factor for PAD in type 2 diabetic patients in Taiwan. It is also significantly predictive for the severity of PAD, especially in patients with existent PAD or an ABI <0.9. The optimal cutoff of Lp(a) for PAD in type 2 diabetic patients in Taiwan is 13.3 mg/dl, a level much lower than the commonly recommended 30.0 mg/dl in Caucasians.

Acknowledgments— This study was supported in part by grants from the Department of Health (DOH89-TD-1035) and the National Science Council (NSC-90-2320-B-002-197, NSC-92-2320-B-002-156), Executive Yuan, Republic of China.

References

1. Scanu AM: Lipoprotein(a) and the atherothrombotic process: mechanistic insights and clinical implications. *Curr Atheroscler Rep* 5:106–113, 2003
2. Rainwater DL, Kammerer CM: Lipoprotein Lp(a): effects of allelic variation at the LPA locus. *J Exp Zool* 282:54–61, 1998
3. Utermann G: The mysteries of lipoprotein(a). *Science* 246:904–910, 1989
4. Scanu AM, Lawn RM, Berg K: Lipoprotein(a) and atherosclerosis. *Ann Int Med* 115:209–218, 1991
5. Hunninghake DB, McGovern ME, Koren M, Brazg R, Murdock D, Weiss S, Pearson T: A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin. *Clin Cardiol* 26:112–118, 2003
6. Habib SS, Aslam M, Naveed AK, Sattar A: Lipoprotein(a) and glycemic control in Pakistani subjects with diabetes mellitus. *J Pak Med Assoc* 53:54–59, 2003
7. Ridker PM, Hennekens CH, Stampfer MJ: A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA* 270:2195–2199, 1993
8. Alfthan G, Pekkanen J, Jauhiainen M, Pitdaniemi J, Karvonen M, Tuomilehto J, Salonen JT, Ehnholm C: Relation of serum homocysteine and lipoprotein(a) concentrations to atherosclerotic disease in a prospective Finnish population based study. *Atherosclerosis* 106:9–19, 1994
9. Cantin B, Despres JP, Lamarche B, Moorjani S, Lupien PJ, Bogaty P, Bergeron J, Dagenais GR: Association of fibrinogen and lipoprotein(a) as a coronary heart disease risk factor in men (the Quebec Cardiovascular Study). *Am J Cardiol* 89:662–666, 2002
10. Schaefer EJ, Lamon-Fava S, Jenner JL, McNamara JR, Ordovas JM, Davis CE, Abolafia JM, Lippel K, Levy RI: Lipoprotein(a) levels and risk of coronary heart disease in men: the Lipid Research Clinics Coronary Primary Prevention Trial. *JAMA* 271: 999–1003, 1994
11. Kostner GM, Avogaro P, Cazzolato G, Marth E, Bitolo-Bon G, Qunici GB: Lipoprotein(a) and the risk for myocardial infarction. *Atherosclerosis* 38:563–568, 1981
12. Saku K, Zhang B, Liu R, Shirai K, Arakawa K: Associations among serum lipoprotein(a) levels, apolipoprotein(a) phenotypes, and myocardial infarction in patients with extremely low and high levels of serum lipoprotein(a). *Jpn Circ J* 63: 659–665, 1999
13. Zenker G, Koltringer P, Bone G, Niederkorn K, Pfeiffier K, Jurgens G: Lipoprotein(a) as a strong indicator for cerebrovascular disease. *Stroke* 17:942–945, 1986
14. Valentine RJ, Grayburn PA, Vega DL, Grundy SM: Lp(a) lipoprotein is an independent discriminating risk factor for premature peripheral atherosclerosis among white men. *Arch Intern Med* 154: 801–806, 1994
15. Wollesen F, Dahlen G, Berglund L, Berne C: Peripheral atherosclerosis and serum lipoprotein(a) in diabetes. *Diabetes Care* 22:93–98, 1999
16. Chien KL, Lee YT, Sung FC, Su TC, Hsu HC, Lin RS: Lipoprotein (a) level in the population in Taiwan: relationship to sociodemographic and atherosclerotic risk factors. *Atherosclerosis* 143:267–273, 1999
17. Tseng CH, Chong CK, Chen CJ, Tai TY: Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis* 120:125–133, 1996
18. Tseng CH, Chong CK, Chen CJ, Tai TY: Lipid profile and peripheral vascular disease in arseniasis-hyperendemic villages in Taiwan. *Angiology* 48:321–335, 1997
19. Tseng CH, Tseng CP: Lack of association between angiotensin-converting enzyme gene polymorphism and peripheral vascular disease in type 2 diabetic patients in Taiwan. *Circ J* 66:1014–1018, 2002
20. Guidelines Subcommittee: World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 17: 151–183, 1999
21. Tseng CH, Tai TY, Chong CK, Tseng CP, Lai MS, Lin BJ, Chiou HY, Hsueh YM, Hsu KH, Chen CJ: Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic villages in Taiwan. *Environ Health Perspect* 108:847–851, 2000
22. Tseng CH: Body composition as a risk factor for coronary artery disease in Chinese type 2 diabetic patients in Taiwan. *Circ J* 67:479–484, 2003
23. Tseng CH, Chong CK, Lin BJ, Chen CJ, Tai TY: Atherosclerotic risk factors for peripheral vascular disease in non-insulin-dependent diabetic patients. *J Formos Med Assoc* 93:663–667, 1994