

Original Article

**Association of Serum Lipoprotein (a) with Hypertension
in Diabetic Patients**

Hamid Nasri

Hemodialysis Section, Department of Medicine, Hajar Medical Educational and Therapeutic Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

ABSTRACT. To evaluate the influence of serum Lp(a) concentration on hypertension in patients with diabetes mellitus (DM) and under treatment with oral hypoglycemic agents or insulin injections, we studied 122 patients, 82 females and 40 males with a mean age of 63 ± 10 years and duration of DM and HTN of 7.4 ± 5.8 and 3.2 ± 4.6 years, respectively. The mean systolic and diastolic blood pressure (BP) were 138 ± 23 mmHg and 83 ± 12 mmHg, respectively. In this cross-sectional study, we measured serum lipoprotein(a) (Lp(a), glycosilated hemoglobine (HbA1c) and other lipids while the patients were receiving either oral hypoglycemic agents or insulin. In addition, body mass index (BMI) and creatinine clearance (CrCL) were assessed. The mean serum Lp(a) was 22.2 ± 24.7 mg/dl (median: 18.3 mg/dl), and serum Lp(a) levels > 30 mg/dl was found in 29 (23.8%) patients. There were significant positive correlations of duration of DM and duration of hypertension, and serum Lp(a) levels with of systoli and diastolic levels of BP. However, a significant inverse correlation of serum Lp(a) with CrCL were observed. This study suggests that kidney function is an independent determinant of Lp(a) and HTN in diabetic patients. Furthermore, Lp(a) in diabetic patients may have important implications for the increased susceptibility to vascular disease in these patients.

Keywords: Hypertension, Lipoprotein(a), Diabetes mellitus, Creatinine clearance

Reprint request and correspondence

Hamid Nasri, M.D.
Internist, Nephrologist,
Associate Professor
Hemodialysis Section
Hajar Medical, Educational and
Therapeutic Center
Shahrekord University of Medical Sciences
P.O. Box:88155-468, Shahrekord, Iran
E-mail: hamidnasri@yahoo.com

Introduction

Hypertension (HTN) is an extremely common comorbid condition in diabetes, affecting 20%–60% of patients with diabetes, depending on obesity, ethnicity and age.¹

In type 2 diabetes, hypertension is often present as a component of the metabolic syndrome of insulin resistance, which includes central obesity and dyslipidemia, while in

type 1 diabetes, hypertension may reflect the onset of diabetic nephropathy.² Hypertension substantially increases the risk of both macrovascular and microvascular complications, including stroke, coronary artery disease, and peripheral vascular disease, retinopathy, nephropathy, and possibly neuropathy.^{2,3}

Lipoprotein(a) (Lp(a)) is a heterogeneous macromolecule that consists of a glycoprotein apolipoprotein(a), which is disulfide-linked to apolipoprotein B-100 on an LDL core.^{4,7} Apolipoprotein(a) exhibits size polymorphism, which is closely linked to Lp(a) density and concentrations.⁸ The limited distribution of Lp(a) in a few animal species implies that it is not essential in lipoprotein metabolism.⁹ However, it is clinically important because its concentrations are primarily genetically determined, associated with atherosclerotic disease, and less affected by lifestyle or medication.⁶⁻¹⁰ Lp(a) concentrations are quite constant in an individual.¹¹⁻¹⁴ Moreover, Lp(a) is an independent risk factor for cardiovascular disease.¹²⁻¹⁸

Several studies have reported high concentrations of Lp(a) in diabetic patients, which has led to speculation that Lp(a) may contribute to the greatly increased incidence of vascular disease associated with diabetes.¹⁹⁻²⁰ Considerable debate remains, however, regarding the precise cause of supranormal Lp(a) levels in diabetics.¹⁹⁻²¹

In nondiabetic patients, renal disease correlates with elevated levels of Lp(a) that are normalized by kidney transplantation.¹⁶ Recent studies have also demonstrated urinary excretion of Lp(a) degradation products,^{11,17,18} but evidence for active role of the kidney in Lp(a) catabolism is not established yet. Renal disease is a frequent complication of diabetes that has prompted speculation that kidney dysfunction is the principal cause of raised Lp(a) in type 1 and

type 2 diabetic patients.¹⁹⁻²³

Observational and clinical studies have demonstrated that elevated systolic blood pressure (SBP) confers significantly higher risk of all cause and coronary heart disease mortality than elevated diastolic blood pressure (DBP) or combined systolic/diastolic hypertension, especially in those with diabetes mellitus.^{24,25} More recent studies revealed an association between Lp(a) and hypertension. In vitro experiments have illustrated that oxidized Lp(a) is able to impair the arterial endothelium-dependent dilation, and suggested a possible role of Lp(a) in the genesis of essential hypertension.²⁶⁻³⁰

Hence, although dyslipidemia and hypertension occur together more often than can be explained by chance, few studies have carefully explored the nature of the relationship between plasma Lp(a) levels and hypertension in diabetic patients.

The aim of this study is to evaluate the influence of serum Lp(a) concentration on hypertension in diabetic patients with various kidney functions and not yet on dialysis.

Patients and methods

This cross-sectional study was conducted on diabetic mellitus patients who admitted in the hospital for controlling the diabetes with either oral hypoglycemic agents or insulin. We included in the study patients who developed hypertension and received antihypertensive therapy. Exclusion criteria included acute or chronic infections and use of lipid-lowering medications. The study was performed at Hajar Medical Educational and Therapeutic Center of Shahrekord University of Iran from July to August of 2005. All patients signed consent forms for participation in this study.

Table 1. Patients' data and laboratory tests of the 122 study patients

Parameters	Minimum	Maximum	Mean \pm SD	Median
Age (years)	25	84	63 \pm 11	64
Duration of DM (years)	0.1	25	7.4 \pm 6.8	6
Duration of HTN (years)	0.00	25	3.2 \pm 4.5	0.80
BMI(kg/m ²)	30	53	25.5 \pm 4.5	25.3
Systolic BP (mmHg)	100	180	138 \pm 23	140
Diastolic BP (mmHg)	50	130	83 \pm 12	80
Cretinine Clearance (ml/min)	10	110	64 \pm 24	64
Lp(a) (mg/dl)	0.10	134	22.2 \pm 24.8	18.3
Alb (g/dl)	2.5	7.5	4.9 \pm 1	4.9
Total protein (g/dl)	5	12.5	7.2 \pm 0.9	7
HgbA1C %	3.9	13.3	7.6 \pm 1.9	7.6
Chol (mg/dl)	90	388	198 \pm 52	192
Tg (mg/dl)	37	580	183 \pm 102	155
LDL (mg/dl)	44	210	112 \pm 37	112
HDL (mg/dl)	19	128	47 \pm 18	44

After admission to hospital, detailed medical history was obtained, and careful physical exam was performed. A trained physician measured all baseline BP using a random-zero manometer. Two BP and heart rate measurements were averaged to establish the baseline BP and heart rate variables. Follow-up BP included two measures on a single day after at least 30 minutes of rest. Hypertension was diagnosed according to WHO guidelines³¹ and the seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure.³²

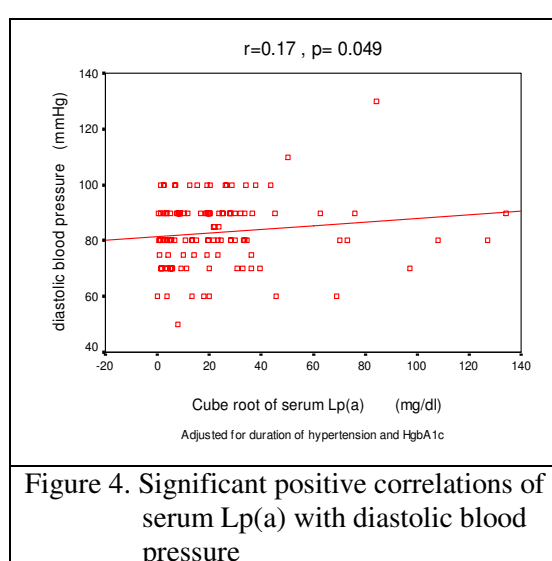
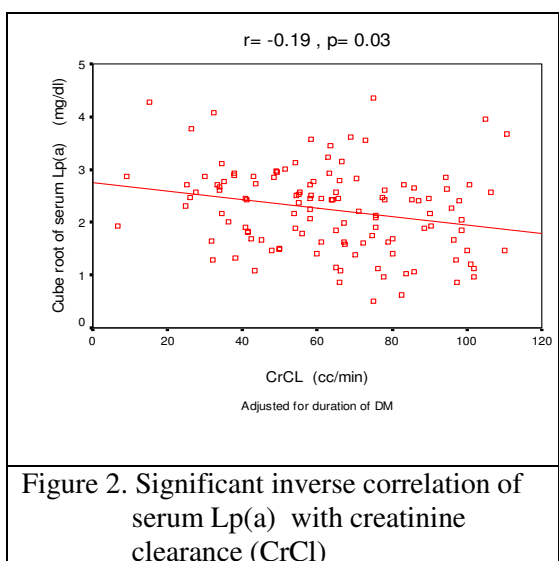
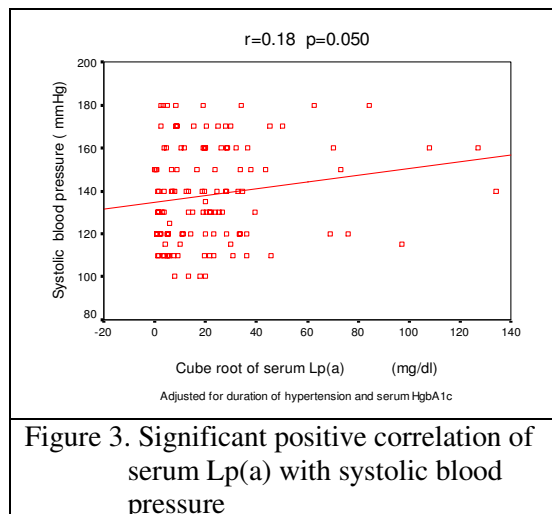
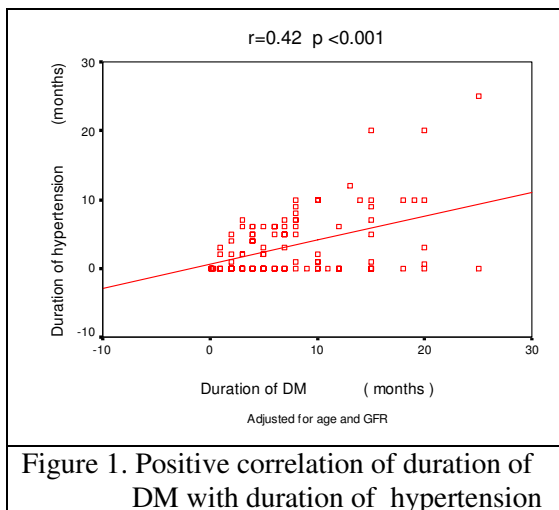
Blood samples were collected after 12 hour overnight fasting and centrifuged within 15 min of venopuncture. Serum Lp(a) were measured by enzyme-linked immunosorbent assay kit (Macra[®] Lp(a) manufactured by Strategic Diagnostics Inc. for Trinity Biotech USA, Jamestown, NY, USA). The test is a sandwich assay which utilizes both a monoclonal and polyclonal antibodies, which specifically bind to the apolipoprotein (a) moiety of Lp(a). All samples were run in duplicate and the results were

expressed in mg/dl; the intra- and inter-assay coefficients of variation for this method were < 5% and < 10%, respectively. Lp(a) levels of 30 mg/dl was considered as the threshold value of risk for its pathological effect.

Glycosilated hemoglobine (HbA1c) was measured by chromatography method using Hb-Gold of UK; normal level in our laboratory is \leq 6.1%. Levels of serum Albumin (Alb), serum creatinine (creat), blood urea nitrogen (BUN) total protein, triglycerids (Tg), cholestrol (Chol), and high density lipoprotein (HDL) were measured using standard methods. Body mass index (BMI) was calculated using the standard formula (weight in kilograms/height in square meters; kg/m²). Serum LDL-C was calculated by friedewald's formula.³³ Creatinine clearance(CrCL) was evaluated from serum creatinine, age and body weight.³⁴

Statistical analysis

Results are expressed as the mean \pm SD and median values. Statistical correlations



were assessed using a partial correlation test. Comparison between female and male genders data was assessed using students' t test. For normalization of the serum Lp(a) data, the cube root of Lp(a) was used. All analyses were performed with the SPSS statistical package (version 11.0 for Windows; SPSS, Chicago). Statistical significance was determined at value of $p < 0.05$.

Results

Table 1 shows the baseline characteristics of the study patients. The study included 122

patients (82 females, 40 males) with a mean age of 63 ± 10 years. The mean duration of diabetes and hypertension were 7.4 ± 5.8 years (median: 6 years) and 3.2 ± 4.6 years (median: 96 months), respectively. The mean systolic and diastolic BP were 138 ± 23 mmHg and 83 ± 12 mmHg, respectively. The mean serum Lp(a) was 22.2 ± 24.7 mg/dl (median: 18.3 mg/dl). Serum Lp(a) levels > 30 mg/dl was found in 29 patients (23.8%).

Figure 1 shows a significant positive correlation of duration of DM and HTN ($r=0.45$, $p < 0.0001$) including systolic ($r=$

0.32, $p < 0.001$) and diastolic BP ($r = 0.18$, $p = 0.04$). A significant positive correlation of duration of HTN with age of patients ($r = 0.32$, $p < 0.0001$) was also found. We found a significant inverse correlation of duration of DM with CrCL ($r = -0.51$, $p < 0.001$), and duration of HTN with CrCL ($r = -0.18$, $p = 0.041$).

Figure 2 shows a significant inverse correlation of serum Lp(a) with CrCL ($r = -0.19$, $p = 0.03$). We did not find a significant correlation of serum Lp(a) with age, duration of HTN or DM, BMI, serum Alb, total protein, lipids, and serum HgA1c.

Figure 3 shows a significant positive correlation of serum Lp(a) with systolic blood pressure ($r = 0.18$, $p = 0.05$).

Figure 4 shows a significant positive correlation of serum Lp(a) with diastolic HTN ($r = 0.17$, $p = 0.049$).

Discussion

Our results demonstrated significant positive correlations of duration of DM and HTN, and of serum Lp(a) concentration with systolic and diastolic blood pressure. In addition, we found a significant inverse correlation of duration of DM and serum Lp(a) with creatinine clearance.

Schaars et al, gathered data of 895 randomly selected diabetic patients from the electronic medical records of 95 general practitioners, showed that 652 patients (73%), were hypertensive in the last year.³⁵

Wildman et al, studied the relationship between baseline measures of serum lipoproteins and incident hypertension in older adults in 187 patients with systolic blood pressure (SBP) < 160 mmHg, diastolic blood pressure (DBP) < 90 mmHg) at baseline and followed them for 8 years, and measured total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein

cholesterol (HDL-C), HDL(2)-C, HDL(3)-C, triglycerides, and apolipoproteins 1, 2, and B. They demonstrated that older adults with abnormal serum lipoproteins were at increased risk of developing hypertension.²⁹

In 1992, Sesso et al, conducted a prospective study on 16,130 middle-aged and older female health professionals who had no history of high cholesterol level or hypertension. During 10.8 years of follow-up, incident hypertension developed in 4593 (28%) women. They illustrated with follow-up of lipid levels that atherogenic dyslipidemias were associated with the subsequent development of hypertension among healthy women.³⁶

Recent studies suggest that Lp(a) can act as a marker for determining vascular or tissue injury.^{6,30} In a study conducted by Bhavani et al, on a total of 37 essential hypertensive patients, it was observed that the hypertensive patients had higher plasma concentrations of Lp(a) (more than 30 mg/dl), total cholesterol (TC), low-Density lipoprotein-cholesterol, and triglycerides than controls. Lp(a) values correlated significantly with SBP and DBP.³⁰ In a similar study, Catalano et al, reported significantly elevated levels of plasma Lp(a) in 123 Caucasian essential arterial hypertensive patients.³⁷ Recent report from Fytilli et al, suggested that arterial hypertension is associated with elevated Lp(a) levels in patients of end-stage renal disease. In their study, it was observed that Lp(a) levels were significantly higher in the hypertensive patients, but that difference was not significant from the non-renal failure patients.³⁸

There are no adequate studies conducted on the influence of Lp(a) on HTN in diabetic patients, however, there is a strong epidemiological connection between hypertension in diabetes and adverse outcomes of diabetes. Recent studies demonstrated that

Lp(a) is an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria.^{39,40}

Macroalbuminuria was uniformly associated with significantly raised plasma concentrations of Lp(a) regardless of the marker used to identify kidney dysfunction. Moreover, altered kidney function, measured by creatinine clearance or creatinine levels, is a major determinant of raised Lp(a) levels in microalbuminuric and normoalbuminuric diabetics patients.^{12,16} Studies in nondiabetic patients have firmly established renal disease as a cause of increased plasma Lp(a) levels.¹⁶

Increased levels of Lp(a) are an independent risk factor for vascular disease in the general population^{9,10,13} and in diabetic patients.⁴¹⁻⁴⁶ In view of these considerations, defining the relationship between renal complications and Lp(a) in diabetic patients is important. Studies that have considered renal disease, usually expressed as albuminuria or the emerge of hypertension⁴⁷ and increased plasma levels of Lp(a) in patients with renal disease who have either type 2³²⁻³⁴ or type 1^{6,32,35-37} diabetes were reported.

In conclusion, our results suggest that serum Lp(a) concentration aggravate hypertension and identify kidney failure as a primary determinant of raised Lp(a) in diabetic patients. This has important implications for the increased susceptibility to vascular disease associated with Lp(a) in diabetic patients.

Acknowledgment

We would like to thank Dr. M. Khaksar M.D. for gathering the data, also thanking from laboratory technicians of our hospital for performing the laboratory tests.

References

1. Kannel WB. Elevated systolic blood pressure as a cardiovascular risk factor. *Am J Cardiol* 2000;85(2):251-5.
2. Cushman WC. The clinical significance of systolic hypertension. *Am J Hypertens* 1998;11(11.2):182S-5S.
3. Lackland DT, Egan BM. The dominant role of systolic hypertension as a vascular risk factor: Evidence from the southeastern United States. *Am J Med Sci* 1999;318(6):365-8.
4. Black HR. The paradigm has shifted, to systolic blood pressure. *Hypertension* 1999;34(3):386-7.
5. Antonicelli R, Testa R, Bonfigli AR, Sirrolla C, Marra M, Marcovina SM. Blood pressure levels in patients with essential hypertension. *Clin Exp Med* 2001;1(3):145-50.
6. Baradaran A, Nasri H, Ganji F. Association of serum lipoprotein(a) with intima-media thickness as a target-organ damage in essential hypertensive patients. *Iran Heart J* 2004;5:55-63.
7. Nasri H, Baradaran A. Relationship of early atherosclerotic vascular changes with serum Lipoprotein(a) in predialysis chronic renal failure and maintenance hemodialysis patients. *Turk J Endocrinol Metabol* 2003;7(4):169-74.
8. Armstrong VW, Cremer P, Eberle E, et al. The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis: Dependence on serum LDL levels. *Atherosclerosis* 1986;62(3):249-57.
9. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL. Lp(a) lipoprotein as a risk factor for myocardial infarction. *JAMA* 1986;256(18):2540-4.
10. Schaefer EJ, Lamon-Fava S, Jenner JL, et al. Lipoprotein(a) levels and risk of coronary heart disease in men: The Lipid Research Clinics Coronary Primary Prevention Trial. *JAMA* 1994;271(13):999-1003.
11. Baradaran A, Nasri H, Ganji F. Close relationship of serum lipoprotein(a) with ultrasonographically determined early atherosclerotic changes in the

- carotid and femoral artery in end-stage renal failure patients undergoing hemodialysis. *Timok Med J (Journal of Regional Section of Serbian Medical Association in Zajecar)* 2004;29(1):8-13.
12. Bolibar I, Thompson SG, von Eckardstein A, Sandkamp M, Assmann G. Dose-response relationship of serum lipid measurements with the extent of coronary stenosis: Strong, independent and comprehensive. *Arterioscler Thromb Vasc Biol* 1995;15(8):1035-42.
 13. Bostom AG, Gagnon DR, Cupples LA, et al. A prospective investigation of elevated lipoprotein(a) detected by electrophoresis and cardio-vascular disease in women: The Framingham Heart Study. *Circulation* 1994;90(4):1688-95.
 15. Jenkins AJ, Best JD. The role of lipoprotein(a) in the vascular complications of diabetes. *J Intern Med* 1995;237(4):359-65.
 16. Kronenberg F, Utermann G, Dieplinger H. Lipoprotein(a) in renal disease. *Am J Kidney Dis* 1996;27(1):1-25.
 17. Mooser V, Seabra MC, Abedin M, et al. Apolipoprotein(a) kringle 4-containing fragments in human urine: Relationship to plasma levels of lipoprotein(a). *J Clin Invest* 1996;97(3):858-64.
 18. Clodi M, Oberbauer R, Waldhausl W, Maurer G, Kostner GM, Kostner K. Urinary excretion of apo(a) fragments in NIDDM patients. *Diabetologia* 1997;40(12):1455-60.
 19. Jenkins AJ, Steele JS, Janus ED, Best JD. Increased plasma apolipoprotein(a) levels in IDDM patients with microalbuminuria. *Diabetes* 1991;40(6):787-90.
 20. Winocour PH, Bhatnagar D, Ishola M, Arrol S, Durrington PN. Lipoprotein(a) and microvascular disease in type 1 (insulin-dependent) diabetes. *Diabet Med* 1991;8(10):922-7.
 21. Cszasz A, Dieplinger H, Sandholzer C, et al. Plasma lipoprotein(a) concentration and phenotypes in diabetes mellitus. *Diabetologia* 1993;36(1):47-51.
 22. Haffner SM. Lipoprotein(a) and diabetes. *Diabetes Care* 1993;16(5):835-40.
 23. Mooser V, Seabra MC, Abedin M, Landschulz KT, Marcovina S, Hobbs HH. Apolipoprotein(a) kringle 4-containing fragments in human urine: Relationship to plasma levels of lipoprotein(a). *J Clin Invest* 1996;97(3):858-64.
 24. Arauz-Pacheco C, Parrott MA, Paskin P; American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care* 2003;26(Suppl 1):S80-2.
 25. Tomlinson JW, Owen KR, Close CF. Treating hypertension in diabetic nephropathy. *Diabetes Care* 2003;26(6):1802-5.
 26. Scanu AM. Lipoprotein(a) and the atherothrombotic process: Mechanistic insights and clinical implications. *Curr Atheroscler Rep* 2003;5(2):106-13.
 27. Rainwater DL, Kammerer CM. Lipoprotein Lp(a): Effects of allelic variation at the LPA locus. *J Exp Zool* 1998;282(1-2):54-61.
 28. Utermann G. The mysteries of lipoprotein(a). *Science* 1989;246(4932):904-10.
 29. Wildman RP, Sutton-Tyrell K, Newman AB, Bostom A, Brockwell S, Kuller LH. Lipoprotein levels are associated with incident hypertension in older adults. *J Am Geriatr Soc* 2004;52(6):916-21.
 30. Bhavani BA, Padma T, Sastry BK, Krishna Reddy N. Plasma Lipoprotein (a) levels in patients with untreated essential hypertension. *Indian J Hum Genet* 2003;9(2):65-8.
 31. WHO Technical report series on Hypertension, Geneva; 1996.
 32. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *JAMA* 2003;289(19):2560-72.
 33. Friedewald WT, Levy R, Fredrickson DS. Estimation of the concentration of Low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 1972;18(6):499-502.

34. Cockcroft DW, Gault MH. Prediction of creatinin clearance from serum creatinine. *Nephron* 1976;16(1):31-41.
35. Schaars CF, Denig P, Kasje WN, Stewart RE, Wolffebuttel BH, Haaijer-Ruskamp FM. Physician, organizational and patient factors associated with suboptimal blood pressure management in type 2 diabetic patients in primary care. *Diabetes Care* 2004;27(1):123-8.
36. Sesso HD, Buring JE, Chown MJ, Ridker PM, Gaziano JM. A prospective study of plasma lipid levels and hypertension in women. *Arch Intern Med* 2005;165(20):2420-7.
37. Catalano M, Perilli E, Carzaniga G, Colombo F, Carotla M, Andreoni S. Lp (a) hypertensive patients. *J Hum Hypertens* 1998;12(2):83-9.
38. Fytily CI, Passadakis PS, Progia EG, et al. Arterial hypertension is associated with serum lipoproteins (a) levels in end stage renal disease patients. *Hemodial Int* 2001;5:66-9.
39. Song KH, Ko SH, Kim HW, et al. Prospective study of lipoprotein(a) as a risk factor for deteriorating renal function in type 2 diabetic patients with overt proteinuria. *Diabetes Care* 2005;28(7):1718-23.
40. Boemi M, Sirolla C, Fumelli P, James RW. Renal disease as a determinant of increased lipoprotein concentrations in diabetic patients. *Diabetes Care* 1999;22(12):2033-6.
41. Heesen BJ, Wolfenbuttel BH, Leurs PB, et al. Lipoprotein(a) levels in relation to diabetic complications in patients with non-insulin dependent diabetes. *Eur J Clin Invest* 1993;23(9):580-4.
42. Ruiz J, Thillet J, Huby T, et al. Association of elevated lipoprotein(a) levels and coronary heart disease in NIDDM patients: Relationship with apolipoprotein(a) phenotypes. *Diabetologia* 1994;37(6):585-91.
43. James RW, Boemi M, Sirolla C, Amadio L, Fumelli P, Pometta D. Lipoprotein(a) and vascular disease in diabetic patients. *Diabetologia* 1995;38(6):711-4.
44. Hirata K, Saku K, Jimi S, Kikuchi S, Hamaguchi H, Arakawa K. Serum lipoprotein(a) concentrations and apolipoprotein(a) phenotypes in the families of NIDDM patients. *Diabetologia* 1995;38(12):1434-42.
45. Heller FR, Jamart J, Honore P, et al. Serum lipoprotein(a) in patients with diabetes mellitus. *Diabetes Care* 1993;16(5):819-23.
46. Durlach V, Gillery P, Bertin E, et al. Serum lipoprotein(a) concentrations in a population of 819 non-insulin-dependent diabetic patients. *Diabet Metab* 1996;22(5):319-23.
47. Appel GB, Blum CB, Chien S, Kunis CL, Appel AS. The hyperlipidemia of the nephrotic syndrome: Relation to plasma albumin concentration, oncotic pressure and viscosity. *N Engl J Med* 1985;312(24):1544-8.