Magnitude of Lipoprotein (a) in Diabetes Mellitus

Pages with reference to book, From 11 To 13

Mudassir Ahmad Khan (Department of Biochemistry and Clinical Chemistry, Khyber Medical College, Peshawar.)
Abdul Baseer (Department of Biochemistry, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi.)

Abstract

One hundred and three patients, 76 with diabetes mellitus alone (48- Non-Insulin dependent diabetes and 28 Insulin dependent diabetes) and 27 diabetics having coronary heart disease (CHD) and 27 normal control subjects were included in this study. All the 27 diabetics with CHD were Non-Insulin dependent. The patients and the controls were investigated for serum Lp (a), triglycerides, cholesterol, VLDL-C, LDL-C, HDL-C, apo Al and apo B. The objective was to assess and compare the level of lipoproteins, especially the lipoprotein (a), in diabetic and non-diabetic subjects and to compare the level of the aforementioned parameters in diabetics with and without CHD. The Lp (a) and other lipid parameters were significantly raised (P

Introduction

Diabetes mellitus is a well established risk factor for atherosclerosis, coronaiy heart disease (CHD), stroke and peripheral arterial disease[1-4]. Accelemted atherogenesis in diabetic patients may be due to increased frequency of dyslipidemia, hyperglycemia. obesity, hypertension and associated nephropathy[4]. Lipid disorders are very common in both IDDM and NIDDM persons and are related to the degree of glycernic control[5]. The most common type of lipid abnormalities encountered in a subject with diabetes mellitus are elevated plasma levels of triglycerides, very low density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C) and lipoprotein (a) p (a)] and decreased high density lipoprotein cholesterol (HDL-C)[1,6,7]. The American Diabetes Association (ADA) and the National Cholesterol Education Programme (NCEP) recommends glycemic control as the first step towards controlling diabetic dyslipidemia. There is no doubt that glycernic control improves lipid profile but still a significant number of diabetic subjects require direct lipid management[7]. The stabilization of lipid and lipoprotein levels, decrease the incidence of atherosclerotic CHD[8].

one or more apoproteins are present in each lipoprotein[9]. Apoprotein Al (apo AD is a major protein component of high density lipoprotein (HDL) whereas apoprotein B (apo B) is the major constituent of low density lipoprotein (LDL), vely low density lipoprotein (VLDL) and chylomicrons[10]. Lp (a) is a variant of LDL and is similar to LDL in lipid composition[11]. It consists of one or two molecules of apoprotein (a) [apo (a)} linked to apoprotein B-100 by a disulfide bridge[12,13].

Apo (a) is a distinctive glycoprotein of Lp (a) and is structurally homologous to plasminogen[12,14,15] a key protein of the fibrinolytic system. Lp (a) does not have fibrinolytic activity and it competes with plasminogen for the binding site on surface of the endothelial cells. Thus it prevents the activation of plasminogen by the tissue plasminogen activator[16] and may, therefore promote a procoagulant state. Epidemiologic and prospective studies have revealed elevated levels of Lp (a) in persons with CHD[6,17,18] suggesting the importance of Lp (a) in the underlying mechanisms for the development of atherosclerosis in diabetics. But its mie has not been evaluated so far in these subjects. The present study was undertaken to determine and compare the levels of Lp (a) and lipid profile in people with diabetes mellitus alone and diabetics having CHD.

Material and Methods

A total of 103 patients (25 - 75 years) and 27 nonnal control subjects ofsimilarage and socio-economic group were included in the study. The patients were known diabetics. They were divided into two groups. Those who had diabetes mellitus alone (n=76) and those who had CHD alongwith diabetes mellitus (n=27). The patients with diabetes mellitus only were of both NIDDM (n=48)and IDDM (n=28) type. The group comprising of diabetic patients with CHD were all of non-insulin dependent diabetes mellitus (NIDDM) type. The classification of diabetes, as recommended by World Health Organization (WHO) was adopted'9 and all the patients had a duration of atleast one year. Diabetic patients who had a first attack of myocardial infarction in the last seven days were included in the second group. Patients on thrombolytic therapy, lipid lowering drugs or contraceptive drugs were excluded.

Venous blood samples were withdrawn after an overnight fast of 12-14 hours and sera were separated and stored at -70°C till analysis. Lp (a) levels were measured using enzyme linked immunosorbent assay (Immuno-Diagnostics, USA). Plasma cholesterol, triglycerides, and HDL-C were measured by enzymatic method using the kits supplied by Bio Systems, Spain. Serum apo A-i and apo-B were determined by immuno-tuibidimetric method, using the kits obtained from Boehringer Mannheim GmbH, Germany and Spinreact, S.A. Spain respectively. LDL-C was calculated by a modification[20] of the Friedwald formula[21]: LDL cholesterol= Total Cholesterol - (Triglycerides/5)- HDL Cholesterol - 0.3 Lp (a) and VLDL-C by the formula of Wilson[22]. The results were expressed as mean±SEM and all statistical calculations were made by applying Student's t-test and $P<0.005$ was regarded as a significant value between the two groups.

Results

The lipid profile and Lp (a) levels in the fasting blood of control subjects, diabetic patients and diabetics having CHD are shownin Table I.

Table I. Lipid profile of control subjects and diabetics with and without CHD.

	Control (n=27)	Diabetics (n=76)	Diabetics with coronary heart disease (n=27)
Gender (Male/ Female)	13/14	22/54	21/6
Age (years)	49.50±2.23	50.60±1.68#	53.04±1.22#b
Cholesterol (mg/dl)	183.14±4.94	232.80±3.37*	333.26±8.21*a
Triglycerides (mg/dl)	131.00±2.68	184.89±3.84*	192.70±6.95*b
HDL-C (mg/dl)	51.88±1.51	34.24±0.54*	29.88±0.58*a
LDL-C (mg/dl)	98.24±5.32	154.57±3.01*	251.20±8.10*a
VLDL-C (mg/dl)	26.18±0.55	37.00±0.77*	38.63±1.39*b
Apo A-1 (mg/dl)	101.59±2.03	90.85±1.02*	77.11±0.89*a
Apo B (mg/dl)	79.77±3.17	99.96±1.41*	193.55±5.84 *a
Lp (a) (mg/dl)	22.75±0.81	27.71±0.92*	45.42±1.73 *a

* P<0.001 as compared to control subjects.
a P<0.001 as compared to patients having diabetes mellitus alone.
b P value non - significant as compared to patients having diabetes mellitus alone.
P value non - significant as compared to control subjects.

A highly significant increase (P<0.OOl) was seen in the magnitude of serum total cholesterol, triglyceride, LDL-C, VLDL-C, apo-B and Lp (a), whereas the levels of HDL-C and apo A-i showed a significant decrease (P<0.00l) in both diabetics with and without CHD, as compared to control subjects. Significantly higher (P<0.001) levels of serum cholesterol, LDL- C, apo-B, and Lp (a), while significantly low (P<0.OOl) HDL-C and apo A-i values were observed in diabetics having CHD as compared to patients with diabetes mellitus alone. However, no significant change was observed in any

of the above parameters in NTDDM patients when compared with insulin dependent diabetes mellitus (IDDM) patients (Table II).

Table II. Lipid profile of patients with NIDDM and those with IDDM.

	NIDDM (n=48)	IDDM (n=28)
Gender (Male/Female)	11/37	11/17
Age (Years)	59.56±1.21	35.25±1.76 #
Total cholesterol (mg/dl)	237.44±3.36*	228.43±6.02 *b
Triglycerides (mg/dl)	190.20±5.03*	175.86±5.48 *b
HDL-C (mg/dl)	33.81±0.68*	34.96±0.88 *b
LDL-C (mg/dl)	157.06±3.54*	150.29±5.48 *b
VLDL-C (mg/dl)	38.04±1.00*	35.21±1.11 *b
Apo A1 (mg/dl)	90.05±1.20*	91.50±1.85 *b
Apo B (mg/dl)	98.80±1.89*	102.00±1.98 *b
Lp (a) (mg/dl)	28.30±1.08*	26.70±1.65*a

* P <0.001 as compared to control subjects (Table 1).
a P<0.05 as compared to control subjects (Table 1).
b P value non significant compared to NIDDM patients.
# P<0.001 as compared to NIDDM patients.

Discussion

The finding of the present study revealed an elevated level of Lp (a) in patients with diabetes mellitus alone as well as in diabetics with CHD. Ramirez and Co-workers[6] reported that poorly controlled diabetes mellitus is associated with a high Lp (a) level and also suggested that this metabolic abnormality contributes to the elevated coronary risk in diabetic persons. However, the mechanism

ofincreasedLp(a) levels in poorly controlled diabetics is not clear. According to a hypothesis there exists a defect in the clearance of the apoprotein B-l00 in diabetic persons. On the other hand, a decrease in LDL in cellular metabolism in diabetes mellitus is proposed to be due to glycation of the LDL particle and the LDL receptor. Taupin et al[23] found no difference in Lp (a) concentrations between diabetics and non-diabetic subjects. Haffner et al[24] reported slightly lower Lp(a) concentrations in diabetic patients than in non-diabetic subjects, but there was no statistical significance whereas Morishita et al[25] showed significantly elevated levels of Lp (a) in patients with NIDDM. Our results also show significantly increased concentrations of Lp (a) in diabetic patients. Alaupovic and colleagues[26] reported significantly high concentrations of triglycerides but normal levels of total cholesterol in diabetic patients in companson with nonnal control subjects. In diabetic patients the concentration of VLDL-C was significantly higher and the concentration of HDL-C was showing a significant decrease than in control subjects, however, slight but not significant increase was seen in LDL-C in diabetic patients. They also stated significantly reduced levels of apo Al and increased concentrations of apo B in diabetics as compared to the control subjects. As far as triglycerides, VLDL-C, HDL-C, apo Al and apo- B are concerned our results are in agreement with Alaupovic and colleagues[26]. Onthe otherhandthe significantincrease intotal cholesterolandLDL-C indiabeticpatients, showninourstudy is in accordance with the observations of Ramirez and his group[6]. A group of research workeis[27] observed highly significant difference for total cholesterol, triglycerides, HDL-C, LDL-C and VLDL-C while Lp (a) concentrations were shown to be similar in NIDDM and IDDM. However, no association of raised Lp (a) could be observed in diabetics having CHD. Our results also reveal no significant difference in level of above mentioned parameters inNIDDM and IDDM patients, whereas, increased levels of Lp (a) were exhibited in diabetics with CHD. It was concluded from the results of the study that the elevation of serum Lp (a) can prove as a useful tool in the prediction of onset of atherosclerotic CHD in diabetic patients.

References

1. Schwartz C.J Pathogenesis of the atherosclerotic lesion. Implications for diabetes mellitus. Diabetes Care, 1992; 15:1156-67.
2. Celentano, A. Early abnormalities ofcardiac function in non- insulin-dependent diabetes mellitus and impaired glucose tolerance. Am. J. Cardiol., 1995;76: 1173-6.
3. Bohannon, N.J.V. Lipid metabolism in type II diabetes. Postgrad. Med., I 992;92: 105-13.
4. Garg, A. Lipid lowering therapy and macrovascular disease in diabetes mellitus. Diabetes, 1992;41 (suppl 2):l 11-115 (Abstract)
5. Taskinen, MR. Quantitative and qualitative lipoprotein abnormalities in diabetes mellitus. Diabetes, l992;41 (suppl 2):12-17.
6. Ramirez, L.C., Pacheco, C.A., Lackner, C. et al. Lipoprotein (a) levels in diabetes mellisus: Relationship to metabolic control. Ann. Intem. Med., 1992;1 1742-7.
7. Stem, MR Does glycaemic control of type 2 diabetes suffice to control diabetic dyslipidaemia?. Diabetes Care, 1992;15:638-44.
8. Besseridge, D.J. Diabetes, lipoprotein metabolism and atherosclerosis. Br. Med. Bull., 1989;45:285-311.
9. Mayes, PA. Lipid transport and storage. In: Harper's Biochemistry. 24th ed., Connecticut, Stamford, USA, Appleton and Lange, 1996, pp. 254-70.
10. Donma, M.M. and Donma, 0. Apolipoproteins: Biochemistry, methods and clinical significance. Biochem. Educ., 1989; 17:63-8.
11. Davies, OH., Rayman, 0. and Day, J. Increased incidence of coronary heart disease in people with

impaired glucose tolerance: Link with increased lipoprotein(a)concentrations? Br. Med. J., 1992;304:1610-1611.
12. Scanu, A.M. Lipoprotein (a) a genetic factor for premature coronary heart disease. J.A.M.A., 1992:267:3326-9.
13. Scott, J. Lipoprotein (a): thrombotic and atherogenic. Br. Med. 3., 1991 ;303:663-4.
14. Jurgens, 0., Mcinitzcr, A. and Petek, W. Lipoprotein (a): its atherogenicity, structure and quantification. Lab. Medica. Int., 1994;1 :7-9.
15. Ridker, P.M., Stampfer, M.J. and Hennekena, C.H. Plasma concentration of lipoprotein (a) and the risk of future stroke. J.A.M.A., I 995;273 :1269-73.
16. Miles, L.A. A potential basis for the thrombotic risks associated with lipoprotern (a). Nature, 1989;339:301 -3.
17. Martinez-Triguero, ML. Lipoprotein (a) and other risk factors in patients with non-inaulin-dependent diabetes mellitus. Coron. Artery Dis., 1994;5:755-60. Abstract.
18. Bostom, AG. Elevated plasma lipoprotein (a) and coronary heart disease in men aged 55 years and younger. A prospective study. J.A.M.A., 1996;276:544-8.
19. Zilva, JR Carbohydrate metabolism and its inteuelationshipa. In: Clinical chemistry indiagnosia and treatment. 5th ed.,Singapore, PG Publishing Pte Ltd., 1988, pp. 200-30.
20. Sandkamp, M. Lipoprotein (a) is an independent risk factor for myocardial infarction at a young age. Clin. Chem., 1990;36(1):20- 23.
21. Friedewald, W.T.,Levy, RI. and Fredrickson, D.S. Estimation oftheconcentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem.. 1972; 18:499-502.
22. Delong, D.M. A comparison, of method for the estimation of plasma low and very low density lipoprotein cholesterol. J.A.M.A., 1 986;256:2372-77.
23. Taupin, 3M. ipoprotein (a) and diabetes: Relationship based on 224 cases] Diabetes Metab., 1993;1 9:250-6. Abstract.
24. Haffner, SM. Lp (a) concentrations in NIDDM. Diabetes, I 992;4 1:1267-72.
25. Morishita, E. Hypercoagulability and high lipoprotein (a) levels in patients wtth type 11 diabetes mellitus. Atherosclerosis. 1 996;1 20(1 -2):7- 14 Abstract.
26. Alaupovic, P. Identification of apo B-containing lipoprotein families in NIDDM Diabetes, 1992;41(suppl. 2):I8-25.
27. Ritter, MM. Lipoprotein (a) in diabetes mellitus. Clin. Chem. Acts, I 993;2 14:45-54.