SERUM Lp(a) LEVELS IN PATIENTS OF DIABETES MELLITUS

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ABSTRACT

The relationship between serum levels of lipoprotein (a) [Lp(a)] was studied in 50 patients of diabetes mellitus, aged 18-60 years, M:F 24:26, with duration of diabetes varying from six months to 25 years. They were taking various treatments (diet with oral hypoglycemic agents (OHA) and/or insulin). Metabolic status, prevalence of diabetes and various diabetic complications were assessed by detailed history, physical examination, laboratory and ECG analysis. Mean serum Lp(a) levels in diabetes mellitus patients were 44.2±35.8 mg/dl, which was significantly higher when compared to control cases (mean 21.1±11.2 mg/dl, $p < 0.05$). Significantly higher Lp(a) values were also observed in diabetic patients who had complications i.e. retinopathy (mean 52±41.8 mg/dl), neuropathy (mean 57.4±42.5 mg/dl) or nephropathy (mean 69.7±47.5 mg/dl). Serum Lp(a) was also higher in type 2 patients with coronary artery disease (CAD) (mean 65.5±46.8 mg/dl). Subjects with insulin requiring, type 2 diabetes (n=21) had significantly higher Lp(a) values (mean 82.9±42.7 mg/dl) when compared with type 2 patients who were on OHA (mean 31.7±27.0 mg/dl).

KEY WORDS: Lipoprotein(a): Diabetes mellitus, type 1 and type 2; Coronary artery disease; Oral hypoglycemic agents.

INTRODUCTION

The risk of cardiovascular disease is increased in both type 2 [1-3] and type 1 [4-5] diabetes mellitus, when compared with the non-diabetic subjects. Furthermore, the risk is only partially explained in the patients who had increased levels of standard risk factors. Chronic complications were also common in patients with type 2 diabetes mellitus [6]. The role of diabetes as an independent risk factor for cardiovascular disease is well established [7-8]. Recently, therefore, much interest has been focussed on Lp(a), which is a complex lipoprotein consisting of lipids, carbohydrates and two large apoproteins, (b) and (a). The composition of Lp(a) is comparable with that of LDL cholesterol, but the most important difference is the presence of a specific apoprotein (a). Lp(a) was first demonstrated in human serum by Berg [9]. The serum level of Lp(a) is an independent indicator of risk development of vascular disease [10-12]. A clear correlation was found between the serum level of Lp(a) and its accumulation in the vessel wall [13,14]. The level of Lp(a) is genetically determined,, and when elevated, cannot be lowered by alterations in food intake or by most of the cholesterol lowering agents [15]. Diabetic patients are reported to have higher Lp(a) values than non-diabetic persons [16-18]. The data on relationship between Lp(a) and diabetes is scarce and the data on Lp(a) in Asian Indian diabetics is still meager. Therefore the present study has been undertaken to assess the serum concentration of Lp(a) in patients with diabetes mellitus and to analyze the results according to the type of diabetes mellitus, its relation with the mode of treatment, the presence or absence of complications and to compare them with the control cases.

METHODS AND MATERIALS

50 diabetic patients (20 type 1 and 30 type 2), who were admitted in the wards of medicine, M.Y. Hospital, Indore, were examined. They were divided into type-1 diabetes and type-2 diabetes according to WHO criteria. They were further subdivided on the basis of presence or absence of CAD and other complications like retinopathy, neuropathy and nephropathy. Treatment regime was further used to differentiate them into subgroups. The patients selected were those who had a BMI < 25 kg/m^2, body weight < 90 kg, waist hip ratio < 0.95, who were nonalcoholic, non-smokers and had no history of intake of hypolipidemic drugs, beta blockers or hormonal preparations, in the past. Age varied between 18-60 years, and the duration of diabetes ranged from six months to 25 years, in both the groups. There were 24 male patients and 26 female patients in the study

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group. CAD was evaluated in all patients on the basis of clinical data and ECG abnormalities, but none of the patients were subjected to coronary angiography. A subset of 14 patients, in whom at least two successive BP measurements were available, and/or who were treated with anti-hypertensive drugs, were considered as hypertensive [BP > 140/90 according to WHO]. Microalbuminuria / overt proteinuria was determined by laboratory evaluation. Retinopathy was diagnosed by fundus examination. Patients with peripheral neuropathy were scored by Boulton criteria [1-7]. 12 patients of type 2 diabetes were on insulin treatment and 18 patients were on oral hypoglycemic agents (sulphonylurea + metformin). A control population of 30 non-diabetic subjects, age and sex matched, non-hypertensives, nonsmokers, non alcoholics, with no family history of the diabetes and no history of any hormone intake in the past, were selected for the study from medical and paramedical staff of the hospital.

After an overriight fast, blood samples were collected for the measurement of Lp(a). The serum Lp(a) concentration was measured by ELISA (INNOTEST Lp(a) kit, Belgium). Fasting blood sugar, urea and creatinine were also simultaneously measured.

Statistics : All data is expressed as mean ± SD. The statistical analysis was done using Student's 't' test and 'Z' test (for correction of multiple comparison and for analysis of variance when the data was insufficient). P values of < 0.05 were considered statistically significant.

RESULTS

In the control population mean Lp(a) was 21.1±11.2 mg/dl. 16.6% had Lp(a) values >30 mg/ dl. The mean in diabetics was 44.2 ± 35.8 mg/dl ($p < 0.05$). Type-1 patients had higher Lp(a) (mean 29.8 ± 20.2 mg/dl) ($p>0.05$) while type 2 patients had significantly, still higher Lp(a) values ($p<0.05$, mean 53:8 ± 43.8 mg/dl), when compared with the controls and when compared with the type 1 group [Table 1]. Frequency distribution of Lp(a) values in patients with diabetes and type 2 diabetes is shown in Figure 1 and 2 respectively.

Table 1 : Showing Mean Lp(A) values in mgldl in Control Subjects and Diabetes Patients and various Subgroups of Diabetes Patients under Study.

	Control	Diabetics	Type 1	Type 2	Type 2 with CAD	Type 2 without CAD	Type 2 with HTN	Type 2 without HTN	Type 2 on insulin treatment	Type 2 on OHA treatment	Retinopathy	Neuropathy	Nephropathy
n	30	50	20	30	10	20	14	16	12	18	24	10	8
x	21.1	44.2	29.8	53.8	65.5	48.0	65.3	43.8	82.9	31.7	52	57.4	69.8
SD	11.2	35.8	20.2	41.3	46.8	38.1	49.4	30.9	42.7	27.0	41.8	42.5	47.5
p		<0.05	>0.05	<0.05	<0.05	<0.05	>0.05	<0.05	<0.05	<0.05	<0.05		

Fig 1 : Frequency Distribution of patients of Diabetes with different LP (a) values

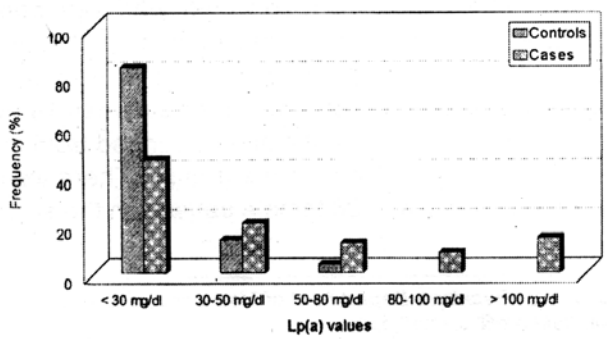
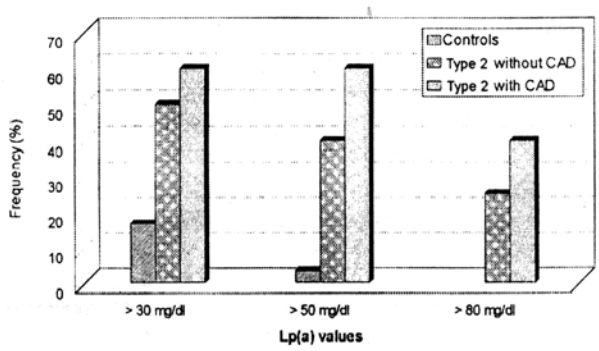


Fig 2 : Frequency Distribution of patients of Type 2 Diabetes with different LP (a) values

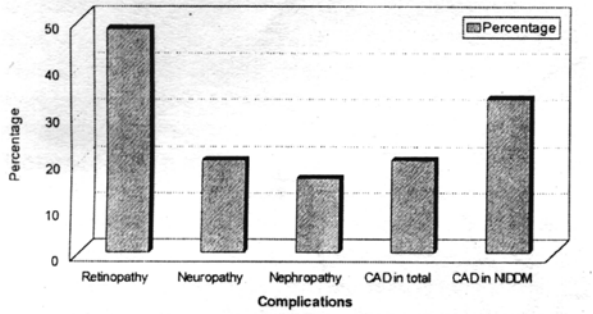


The overall prevalence of vascular complications in diabetic subjects was high and considerably higher than that usually found in non-diabetic subjects. Prevalence rates for CAD was 20%, nephropathy - 16%, retinopathy - 48% and neuropathy - 20% [Table 2 and Figure 3].

Table 2: Percentage of Patients Showing Various Complications of Diabetes

	Percentage
Retinopathy	48
Neuropathy	20
Nephropathy	16
CAD	
- Total	20
- Type 2 diabetes	33

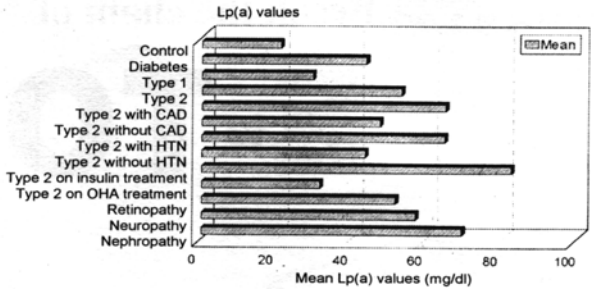
Fig 3 : Patients showing various Complications of Diabetes



The mean Lp(a) in various groups of complications was retinopathy (52±41.7 mg/dl), neuropathy (57.4±42.5 mg/dl) and nephropathy (69.7±47.5 mg/dl), and these were significantly higher than controls [Table 1]. None of the type 1 patients had CAD. Among the type 2 population, ten patients had CAD, and the mean in this group of population was 65.5±46.8 mg/dl, which was significantly higher when compared with the control population ($p < 0.05$) (mean 21.1±11.2 mg/dl). Group of type 2 patients without CAD (n=20), had mean Lp(a) values 48.0±38.1 mg/dl which was also significantly higher ($p < 0.05$) when compared with the control group. Although the mean Lp(a) in patients with CAD (65.5 ± 46.8 mg/dl) was higher than in type 2 patients without CAD (48.0 ± 38.1 mg/dl), this was not statistically significant ($p > 0.05$). Mean values of Lp(a) in different subgroups show in figure 4.

The type 2 patients requiring insulin treatment (n=12), had significantly higher Lp(a) values ($p < 0.05$), mean 82.9 ± 42.7 mg/dl, as compared to type 2 patients on oral hypoglycemic agents (n=18, mean 31.7 ± 27.0 mg/dl).

Fig 4 : Mean LP (a) (mg/dl) in Control Subjects and Diabetes Patients and various Subgroups of Diabetes Patients under study



Diabetics with hypertension (n=14) had higher Lp(a) values (mean 65.28 ± 49.4 mg/dl), than diabetics without hypertension (mean 43.8 ± 30.9 mg/dl), but this was statistically insignificant ($p > 0.05$).

DISCUSSION

In the present study we found that Lp(a) levels were elevated in diabetes, especially type 2, when compared with the non-diabetic subjects or type 1. Lp(a) levels were significantly [Lp(a) value > 30 mg/dl] elevated in diabetic patients with retinopathy, neuropathy or nephropathy, as compared to controls or as compared to those without complications. Type 2 with CAD did not have significantly higher Lp(a) values when compared with type 2 without CAD, although both the groups of type 2 (i.e. with CAD and without CAD) had higher Lp(a) values when compared with the controls.

When percentage distribution of patients of type 2 was compared using different cut off values of Lp(a) (Fig. 2), it was found that using 30 mg/dl as cut off value, 16.6% controls, 50% of type 2 without CAD and 60% of type 2 with CAD had higher Lp(a). When 50 mg/dl was taken as the cut off value, 3.3% controls, 40% type 2 without CAD and 60% type 2 with CAD had higher Lp(a) values and when 80 mg/dl was taken as the cut off value, none of the control subjects, 25% of type 2 without CAD and 40% type 2 with CAD had higher Lp(a) values. This shows that percentage Lp(a) values are higher in each of these groups in type 2 patients with CAD, than type 2 without CAD or controls [Table 3]. This suggests that elevated Lp(a) levels were consistently more in Diseased cases, at all the cut off values. This conveys an impression that these patients are more prone for atherogenesis than the control cases.

Table 3 : Comparison of Percentage Distribution of Patients of Type 2 Diabetes using different Cut off values of Lp(a)

Cut-off Lp(a)	Controls	Type 2 without CAD	Type 2 with CAD
> 30 mg/dl	16.6%	50%	60%
> 50 mg/dl	3.3%	40%	60%
> 80 mg/dl	Nil	25%	40%

Mean Lp(a) was also significantly higher in type 2 patients requiring insulin than in type 2 patients requiring OHA for treatment. The reason why Lp(a) levels were found higher in this group of type 2 population remains unclear [18]. There are conflicting data concerning Lp(a) levels in diabetic patients. Raised serum Lp(a) levels have been reported in type 2 patients in comparison with non-diabetic subjets [16,17] but not in all studies [19] Guillauseau et al [22], Nagashima et al [23] and Guerci B et al [24] have reported higher Lp(a) in type 1 while Austen et al [25], Gall et al [26] and Calamazra P et al [27], found no significant increase in Lp (a) in type 1 patients as compared to controls. Cooper et al [28] also found increase in Lp (a) in type 1 diabetic patients, but recently Haffner et al[29] did not find an increase in Lp(a) values in type 1 patients. Relatively few studies have been performed on relation of Lp(a) to CAD in diabetes [30, 31]. Velho et al [30] and Mohan V et al [32] found raised Lp(a) levels in diabetes with CAD as compared to diabetics without CAD, while Maser et al [33] found no significant correlation between the same Our study correlates with Maser et al.

Increased advanced glycation end product formation may account for the increased risk of diabetic complications in patients with higher Lp(a) values [24]. Regarding relation of hypertension with increased Lp(a) values, more studies on a larger scale are required.

Type 2 patients have higher serum Lp(a) values, than non-diabetic subjects of similar age Whether diabetes per se, causes this increased Lp(a) values is not known [35]. Complicated diabetes (retinopathy, neuropathy, nephropathy) have higher Lp(a) values have an independent role in causing these complications, requires further studies. Type 2 patients on insulin have higher Lp(a) values. Probably; patients with increased Lp(a) (especially type 2 patients with complications such as retinopathy. neuropathy and nephropathy have already been exposed to accelerated atherogenesis, which is further supported by rise in level of Lp(a). Further studies are required on Asian Indian subjects to confirm these findings.

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