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INCREASED LDL CHOLESTEROL IN NON-INSULIN-DEPENDENT DIABETICS WITH MACULOPATHY

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Disturbances in lipid metabolism have been implicated in the pathogenesis of diabetic retinopathy[3,8,9]. Recently a correlation between low density lipoprotein (LDL) cholesterol levels and retinopathy has been demonstrated in insulin-dependent diabetic subjects[4].

Diabetic maculopathy is a form of diabetic retinopathy in which visual loss occurs due to macular edema. It predominantly occurs in non-insulin-dependent diabetics. There is paucity of literature on the association of serum lipids with retinopathy, and particularly with diabetic maculopathy, in non-insulin-dependent diabetic subjects[6]. The present study deals with the various serum lipoprotein cholesterol fractions and triglyceride concentrations in matched groups of non-insulin-dependent diabetics with and without maculopathy.

PATIENTS AND METHODS

Fifty non-insulin-dependent diabetic patients were selected for the study, twenty-five with diabetic maculopathy (group B) and twenty-five with no evidence of diabetic retinopathy (group A). Both groups were matched for age, sex, body weight and duration of diabetes. The age at onset of diabetes was above 40 years in all patients. Twenty-five healthy, age and sex matched non-diabetic individuals formed the control group.

Ocular assessment - All diabetic subjects had detailed ocular assessment by an ophthalmologist. The visual acuity and ocular tension were recorded in all cases. The anterior and posterior segment examination was done to rule out any other causes of visual loss. A detailed fundus examination was done by both direct and indirect ophthalmoscopy after full mydriasis. Maculopathy was

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considered to be present when severe visual loss occurred due to macular edema in the presence of microaneurysms, hemorrhages and hard exudates[11].

Estimation of serum lipoprotein cholesterol fractions - Blood samples for the determination of lipids were collected after an overnight fast, between 07^{00} and 08^{00} to avoid the diurnal variation of plasma cholesterol in diabetic subjects[14]. Serum cholesterol was estimated by the method of ZAK et al.[17] and serum triglycerides by the method of VAN HANDEL and ZILVERSMIT[16].

High density lipoprotein (HDL) cholesterol in the serum was separated by complete and selective precipitation of LDL cholesterol and very low density lipoprotein cholesterol (VLDL) with sodium phosphotungstate and $MgCl_2$ as described by BURSTEIN et al.[2]. LDL cholesterol was measured after precipitation of VLDL cholesterol by 10% sodium dodecyl sulphate in 0.15 M NaCl[13]. Plasma glucose was estimated by the ortho toluidine method[7]. HbA_1 was determined by microcolumn chromatography (Biorad, U.S.A.).

Patients with nephropathy (24-h proteinuria exceeding 500 mg), familial hyperlipidemia, hypothyroidism and ischemic heart disease were excluded from the study. None of the subjects was on any lipid lowering agent.

Fasting and post-prandial plasma sugar, HbA_1 and all lipid parameters were estimated at the time of the patients' initial presentation at the Centre. The patients were placed on a diet consisting of 60% carbohydrate, 20% protein and 20% fat. No specific advice was given to take polyunsaturated fats. All patients were stabilized with diet and glibenclamide. Lipid parameters were again assessed after obtaining good metabolic control of diabetes.

Statistical analysis - Statistical comparisons of the different groups were done using the Student's *t*-test.

RESULTS

Clinical details of the diabetic subjects studied are shown in tab. 1. There were no significant differences in mean age, body mass index, and duration of diabetes between group A (no retinopathy) and group B (with maculopathy).

	non-diabetic subjects	diabetic subjects	
		group A (no retinopathy)	group B (with maculopathy)
total number	25	25	25
male/female	15/10	15/10	15/10
age (years)	45 ± 11	52 ± 9	56 ± 6
duration of diabetes (years)	-	14 ± 4	15 ± 7
body mass index*	22.3 ± 2.1	23.5 ± 4.6	23.8 ± 3.0
diastolic blood pressure (mmHg)	85 ± 3	85 ± 5	87 ± 8

Results are expressed as mean ± SD; * B.M.I. = weight in kg/height in meters^2

Tab. 1 - Clinical characteristics of the subjects studied.

lipid parameters	diabetic subjects		
	group A (no retinopathy) (n = 25)		group B (with maculopathy) (n = 25)
total cholesterol	5.1 ± 0.9	$p<0.001$*	6.2 ± 1.4
HDL cholesterol	1.2 ± 0.2	n.s.	1.2 ± 0.2
LDL cholesterol	3.0 ± 0.6	$p<0.001$*	3.9 ± 1.0
VLDL cholesterol	0.8 ± 0.5	n.s.	0.8 ± 0.5
triglycerides	1.7 ± 0.7	n.s.	2.1 ± 0.9
total/HDL cholesterol	4.1 ± 0.7	$p<0.01$*	4.9 ± 1.2
LDL cholesterol/HDL cholesterol	2.4 ± 0.7	$p<0.01$*	3.3 ± 1.3
fasting plasma sugar (mmol/l)	10.8 ± 3.8		10.3 ± 4.7
post-prandial plasma sugar (mmol/l)	17.3 ± 4.5		14.5 ± 5.1
HbA_1 (%)	11.7 ± 1.6		11.1 ± 2.0

Values are expressed as mean ± SD; * p values obtained for group A *vs* group B; n.s. not significant

Tab. 2 - Mean serum lipid concentrations (mmol/l) in diabetics before control of diabetes.

Mean serum lipid concentrations of the diabetics at the time of presentation are shown in tab. 2 and those obtained after control of diabetes are shown in tab. 3. Mean serum total cholesterol and mean LDL cholesterol levels were significantly raised in group B as compared to group A ($p<0.001$) before control of diabetes as well as after good control of diabetes was achieved.

Mean total cholesterol/HDL cholesterol and LDL/HDL cholesterol ratios were also significantly increased in group B ($p<0.01$) as compared to group A before and after control of diabetes (tabs 2 and 3, respectively).

There were no statistically significant differences in the HDL and VLDL cholesterol and triglyceride concentrations between group A and B except the fact that a slight decrease in serum triglycerides was observed in both groups after control of diabetes.

DISCUSSION

Studies on the role of lipids in diabetic retinopathy have led to conflicting results[1,10,12]. DORNAN et al.[4] have shown a good correlation between LDL cholesterol level and severity of diabetic retinopathy in insulin-dependent diabetes mellitus (IDDM). In this study it has been shown that LDL cholesterol levels were significantly increased in non-insulin dependent diabetic patients with maculopathy both in the uncontrolled state, as well as after good metabolic control of diabetes had been achieved. Since patients with primary lipid disorders have been excluded from this study, this observation indicates that

lipid parameters	non-diabetics (n = 25)	diabetic subjects	
		group A (no retinopathy) (n = 25)	group B (with maculopathy) (n = 25)
total cholesterol	5.0 ± 0.7	5.0 ± 1.0	6.0 ± 0.9
		p<0.001*	
HDL cholesterol	1.3 ± 0.2	1.25 ± 0.23	1.3 ± 0.14
		n.s.	
LDL cholesterol	2.9 ± 0.6	2.9 ± 0.5	4.0 ± 1.22
		p<0.001*	
VLDL cholesterol	0.8 ± 0.4	0.7 ± 0.5	0.72 ± 0.5
		n.s.	
triglycerides	1.3 ± 0.1	1.4 ± 0.7	1.8 ± 0.9
		n.s.	
total/HDL cholesterol	4.0 ± 0.6	4.0 ± 0.3	4.68 ± 0.94
		p<0.001*	
LDL cholesterol/HDL cholesterol	2.3 ± 0.5	2.3 ± 0.6	3.16 ± 0.8
		p<0.001*	
fasting plasma sugar (mmol/l)	6.3 ± 1.2	7.2 ± 1.2	6.4 ± 2.1
post-prandial plasma sugar (mmol/l)	8.2 ± 1.6	9.1 ± 3.0	9.9 ± 1.7
HbA_1 (%)	6.9 ± 0.6	8.1 ± 0.4	8.0 ± 0.6

Values are expressed as mean ± SD; * p values obtained for group A *vs* group B; n.s. not significant

Tab. 3 · Mean serum lipid concentrations (mmol/l) after control of diabetes as compared with non-diabetic subjects.

probably LDL cholesterol may have a positive correlation with diabetic maculopathy in patients with non-insulin-dependent diabetes mellitus (NIDDM).

However, definitive evidence for a pathogenetic role for LDL cholesterol in diabetic maculopathy can only come from a long-term prospective study of serum lipids at various stages of the natural history of diabetic retinopathy.

The findings in the present study, though preliminary, assume importance in view of the earlier observations of VAN ECK[15] that a treatment apt to lower plasma lipid levels reduced the size of perimacular hard exudates. Diets enriched in polyunsaturated fats have also been associated with shrinkage of exudates[10]. Treatment with a lipid lowering agent such as clofibrate has also been shown to have a similar effect though in none of these subjects has the visual acuity been shown to have improved[5]. In view of these findings the role of LDL cholesterol in the pathogenesis of diabetic maculopathy deserves further evaluation.

SUMMARY

Serum cholesterol and its various lipoprotein fractions and triglycerides were measured in 50 non-insulin-dependent diabetic patients, 25 without retinopathy (group A) and 25 with diabetic maculopathy (group B) initially before control of diabetes, and again, after achieving good metabolic control. The lipid parameters were also estimated in 25 healthy non-diabetic subjects. The groups were well matched for sex, age, duration of diabetes and body weight. Mean serum total cholesterol and LDL cholesterol levels were significantly higher in group B when compared

to group A, before and after achieving good metabolic control of diabetes ($p < 0.001$). Mean total/HDL cholesterol and mean LDL/HDL cholesterol ratios were also significantly increased in group B as compared to group A ($p < 0.01$) both before and after good diabetic control in these patients. Mean serum HDL and VLDL cholesterol and triglyceride concentrations were similar in groups A and B. The mean serum lipid concentrations in the diabetic patients without retinopathy (group A) were comparable to those of non-diabetic subjects.

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