LIPID ABNORMALITIES IN DIABETES MELLITUS

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ABSTRACT

To determine the lipid abnormalities in Type2 diabetes mellitus, a study was conducted in two parts. Part I included assessment of serum cholesterol and triglycerides in 100 non diabetic control subjects and 81 newly diagnosed diabetes. 55 patients of the latter group were followed up for one year, with quarterly lipid determination. Part II of the study included 168 diabetics who were already on therapy for a duration exceeding six months. In all subjects, a mean value of lipids was determined from two samples taken a fortnight apart. Serum cholesterol and triglyceride values were compared between controls, newly diagnosed diabetics at the time of enlistment and during their follow up. The lipid values were also linked to glycemic control, body weight, type of therapy and duration of therapy. In Part II of the study, similar comparison of the lipid values was made with caloric intake, body weight, glycemic control, body weight, type of therapy and duration of therapy. We found significantly raised triglyceride and cholesterol levels in diabetics as compared to controls. Patients already on therapy for diabetes (Group II) had significantly higher plasma triglyceride levels as compared to newly diagnosed diabetics (Group 1). Poor metabolic control and diet more than 2000 kilocalories was linked to significantly higher cholesterol levels. The mode of therapy (diet, chlorpropamide, or insulin) was not linked to either raised triglycerides or cholesterol. However, abnormal lipid patterns tended to normalise with therapy of diabetes.

KEY WORDS - Diabetes Mellitus, Lipid Abnormalities.

INTRODUCTION

Atherosclerosis is the major cause of premature death in the diabetic patients, whether it be Type 1 or Type 2 diabetes (1-4). The metabolic syndrome, proposed by Reaven[5], includes a clustering of risk factors including hyperinsulinemia, hypertension, obesity, hypertriglyceridemia and impaired glucose tolerance and is a strong predictor of coronary artery disease (CAD). In non diabetic subjects hypercholesteremia has a direct linkage with CAD, but the link with hypertriglyceridemia is controversial [6-10]. Results of Paris prospective study follow up in 1992[11-12] showed that predictors of CAD are different in diabetes and stressed the importance of body fat distribution as a indicator. It has been shown that many of the predictors of CAD also predispose to development of Type 2 diabetes [3].

One of the major enigmas in diabetes mellitus which remains, is the exact mechanism leading to atherosclerosis[14]. It is clear that abnormalities of lipid and lipoprotein metabolism contribute[15], but abnormalities of coagulation, hyperinsulinism and glycation also pay a part. UGDP study[16] has linked increased cardiovascular mortality of Type 2 diabetes and this in part could be due to sue of oral hypoglucemic agents.

PATIENTS AND METHODS

In Part I of this study we report on the blood lipid levels of 100 non diabetics and 81 newly diagnosed diabetes (hereon referred to as Group 1). Of the newly detected diabetics, 55 were followed up at quarterly intervals for one year on different modes of treatment for their diabetes. In Part II of the study we report on the blood lipid levels of 168 diabetics already receiving different forms of treatment for over six months duration (hereon referred to as Group II).

Part I

100 non-diabetic, healthy individuals, ages 25-60 years, were studies. Diabetes was excluded on the basis of a normal fasting and 2 hour post-glucose blood glucose. This formed the control group. Eightyone recently diagnosed, untreated Type 2 diabetic patients, age group 25-60 years, were studies. 55 patients out of this group (Group 1) were followed at quarterly intervals for one year. At baseline, lipid studies and vascular evaluation (E.C.G., fundus examination, B.P.readings, urine for proteinuria) was done. At quarterly visits, lipid studies were repeated. At the end of one year, vascular evaluation was repeated. Two lipid studies were done at a two week interval in all patients and controls. The values reported are a mean of these two values.

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After baseline studies, patients were initiated on appropriate treatment for their diabetes. The mode of therapy was selected by the usual clinical criteria and not randomised. For example, patients were normal weight, mildly elevated or normal fasting blood glucose and mildly elevated post-glucose blood glucose were put on diet alone; patients having normal body weight, or mild obesity, moderate elevation of fasting and post-glucose blood glucose were put on chlorpropamide; patients having obesity and mild elevation of fasting and post-glucose blood glucose were put on phenformin and patients having undernutrition, weight loss and marked elevation of blood glucose were put on insulin. The dosage of drugs was altered as per need to regulate fasting and post-prandial blood glucose. In all groups, 1200-2000 calories diabetic diet was prescribed depending upon the body weight and physical activity of the patients. In all, 13 patients were put on diet alone, 16 on chlorpropamide, 14 on phenformin and 12 on insulin. Most of them completed four quarters of follow-up, except the patients in the insulin group.

Part II

168 diabetics attending the diabetic clinic were studied (group 2). The duration of diabetes varied between 6 months to 20 years. They were in the age group of 20 to 65 years Their more of treatment and remained unchanged for six months prior to the study. Lipid studies was done twice, at two week intervals.

Methods

Blood glucose was estimated by Somogyi-Nelson method, plasma cholesterol was estimated by Bloor and Pelkan's method, Plasma triglycerides was estimated by Van Handel and Zilversmidt's method. Lipid studies were done after 12-14 hours fast. A pooled plasma sample having a predetermined cholesterol value was included in every run. Its cholesterol value did not vary more than 5 mg in any run. A tripalmitin standard was also included in every run and its value did not vary more than 5 mg. Glycemic control was graded into good, fair and poor as follows:

	Fasting blood glucose (mg/dl)	*Post prandial blood glucose (mg/dl)*
Good	80-120	80-160
Fair	121-140	161-180
Poor	> 140	> 180

Hypercholesteremia was defined as serum cholesterol more than 200 mg/dl hypertriglyceridemia as serum trigflycerides more than 150 mg/dl. Underweight and overweight was diagnosed if patients body weight was 10 per cent lower/higher by the height-weight charts of Life Insurance Corporation of India.

RESULTS

Part I

Plasma lipids of diabetics is compared to non-diabetics (controls in Table 1. Cholesterol and triglycerides were significantly elevated in untreated diabetics as compared to non-diabetics.

Table 1: Plasma lipids in non-diabetics (controls subjects and newly diagnosed diabetics (Group 1)

	Cholesterol (mg/dl) mean ± S.D.	t test	Triglycerides (mg/dl) mean ± S.D.	t test
Non-diabetics n = 100	181.6 ± 36	79.6 ± 22		
		p<0.001		p<0.001
Untreated diabetics n = 81	210.8 ± 45		128.7 ± 18	

The trend of plasma cholesterol and triglycerides during quarterly follow-up is presented in Table 2 and 3 respectively. The mean plasma cholesterol did

Table 2 : Plasma Cholesterol (mg/dl), mean±S.D.) (Group 1)

Time (months)	0	3	6	9	12	P value
Diet n =	219.3 ± 38.2 (13)	192.1 ± 31.9 (13)	208.4 ± 34.1 (13)	201.9 ± 20.6 (13)	201 ± 10.1 (12)	N.S.
Chlorpropamide n =	220.8 ± 34.6 (16)	196.5 ± 28.4 (16)	207.8 ± 21.6 (15)	198.9 ± 20.6 (13)	200.7 ± 10.1 (12)	N.S.
Phenformin n =	243.4 ± 50.3 (14)	227.7 ± 52.2 (14)	228.6 ± 40.4 (13)	233.4 ± 28.5 (10)	227.3 ± 35.9 (9)	N.S
Insulin n =	241.2 ± 39.2 (12)	238.0 ± 39.5 (12)	239.5 ± 46.6 (10)	228.5 ± 35.5 (5)	—	N.S.

Figures in paranthensis represent the number of patients.

Table 3:Plasma Triglycerides (mean, mg/dl±S.D.) (Group 1)

Time (months)	0	3	6	9	12	P value
Diet n =	114.6 ± 20.3 (13)	88.2 ± 23.4 (13)	87.7 ± 24.5 (13)	90.7 ± 31.1 (13)	82.7 ± 28.2 (12)	< 0.025*
Chlorpropamide n =	124.1 ± 37.5 (16)	115.3 ± 33.4 (16)	109.6 ± 56.1 (15)	85.9 ± 25.8 (13)	91 ± 35.2 (12)	< 0.05*
Phenformin n =	129.0 ± 43.3 (14)	122.7 ± 53.3 (14)	117.3 ± 47.9 (13)	114.4 ± 29.4 (10)	122.2 ± 34.5 (9)	N.S.**
Insulin n =	115.7 ± 14.5 (12)	122.9 ± 34.5 (12)	108.2 ± 18.0 (10)	108.6 ± 25.7 (5)	—	N.S.***

* significance at 3,6,9, and 12 months compared to basal.
** Not significant at all times except at 9 months, compared to basal
*** Not significant at all times compared to basal
Figures in paranthesis indicate number of patients

not alter significantly with any form of therapy. Mean plasma triglycerides were reduced significantly in patients on diet therapy alone or on chlorpropamide. The fasting blood glucose was lowered significantly in all groups (Table 4) except the phenformin group. In this group, inspite of 100 mg of phenformin administered to most patients, fasting blood glucose could not be lowered as effectively as in other groups. The fasting blood glucose also stayed relatively high in the insulin group as compared to the diet and chlorpropamide group. We found a significant correlation of fasting blood glucose with plasma triglycerides ($r = 0.4250$, $p < 0.05$). Therefore, the significant lowering of triglycerides in diet and chlorpropamide group was due to better control of diabetes in these groups.

Table 4: Fasting blood glucose (mean, mg/dl±S.D.)(Group 1)

Time (months)	0	3	6	9	12	P value
Diet n =	140 ± 25.2 (13)	111.4 ± 19.0 (13)	105.6 ± 20.0 (13)	102.6 ± 12.6 (13)	99.3 ± 12.6 (12)	< 0.01*
Chlorpropamide n =	191.5 ± 25.3 (16)	133.6 ± 30.2 (16)	129.0 ± 30.0 (15)	105 ± 25.1 (13)	103 ± 12.1 (12)	< 0.001*
Phenformin n =	177.4 ± 28.2 (14)	164.9 ± 60.2 (14)	143.8 ± 50.2 (13)	147.1 ± 40.9 (10)	140.2 ± 28.7 (9)	N.S.*
Insulin n =	245.3 ± 15.8 (12)	138.6 ± 31.8 (12)	133.9 ± 24.1 (10)	154.0 ± 41.0 (5)	—	<0.001*

NS — not significant
* significance at 3,6,9 and 12 months as compared to basal value at 0 months
Figures in paranthesis indicate number of patients

There was no significant change in weight in any of groups (Table 5). Although w desired to induce weight loss in the phenformin group, we failed to do so even by discussing the diet with the patients at each visit.

Table 5 : Weight (kg. mean ± S.D.) (Group 1)

Time (months)	0	3	6	9	12	P value
Diet n =	66.8 ± 13.2 (13)	64.3 ± 12.3 (13)	62.8 ± 10.5 (13)	62.6 ± 10.5 (13)	62.3 ± 10.6 (12)	N.S.*
Chlorpropamide n =	72.2 ± 9.7 (16)	71 ± 12.2 (16)	72.2 ± 10.6 (15)	70.6 ± 11.7 (13)	70.6 ± 10.6 (12)	N.S.*
Phenformin n =	85.6 ± 18.7 (14)	82.8 ± 12.7 (14)	82.8 ± 18.1 (13)	86.1 ± 16.9 (10)	84.4 ± 17.2 (9)	N.S.*
Insulin n =	67.6 ± 13.1 (12)	68.8 ± 12.7 (12)	68.9 ± 15.0 (10)	68.9 ± 16.6 (5)	—	N.S.*

* No significant changes observed when values at 0 month (basal) were compared with those at 3,6,9 and 12 months respectively.
Figures in paranthesis indicate number of patients

The trend of individual lipid abnormalities is presented in Table 6. The lipid abnormalities were distributed fairly evenly in all the treatment groups and tended to revert to normal in all the groups with treatment, and hence, they have been presented collectively. At baseline, abnormalities of triglycerides were more frequent than abnormalities of cholesterol. However, 60% of the abnormalities of triglycerides and cholesterol cleared with treatment. Although the mean cholesterol was not lowered significantly (Table 2), individual diabetics with elevated cholesterol appeared to have a good prospect of normalising plasma cholesterol with treatment of diabetes.

Table 6 : Incidence of hyperlipidemia at 0, 3, 6, and 9 months (Group 1)

S. No.		Total No. studied	Number with hyperlipidemia			
			0 months	3 months	6 months	9 months
1.	Triglycerides	55	25	19	12	10
2.	Cholesterol	55	15	6	7	6
3.	Triglycerides & Cholesterol	55	6	2	4	3

The date on the vascular status of the 55 patients at baseline and at one year do not justify any conclusions because of the small number of patients and a brief duration of follow-up. However, at the outset, of the 81 diabetics studies, 30 patients had vascular complications (hypertension, coronary disease, retinopathy and nephropathy). Their triglycerides were significantly elevated as compared to the 51 patients without complications ($p<0.05$).

Part II

The frequency of lipid abnormalities in 168 diabetics (Group 2) are presented in Table 7. The plasma lipid were analysed to bring out their relationship with caloric intake (Table 8), body weight, mode of treatment of diabetes and degree of control of diabetes.

The caloric intake did not influence the lipids, except that a caloric intake of greater than 2000 kcal/day elevated the plasma cholesterol significantly. The body weight and mode of treatment of diabetes also did not influence the plasma lipids. However, poor control of diabetes elevated the plasma cholesterol significantly.

The mean lipids, cholesterol and triglycerides were higher in this group of 168 diabetics (Group 2) as compared to 55 diabetics on long-term follow-up (Group 1). This difference was significant ($p<0.001$) in case of triglycerides. Majority of patients (144 out of 168) in this part of the study, had fair[71] or poor[73] control of diabetes. This group of patients represents a cross-section of the clinic population which is not being monitored closely or are not strictly compliant regarding their diet. The individual lipid abnormalities were also frequent in this group.

Table 7 shows classification of patients with lipid abnormality based on absolute level of serum cholesterol and triglycerides in Group 2 patients. 46% had elevated cholesterol, 33% elevated triglycerides and 18% had both

Table 7 Lipid abnormalities in 168 diabetics (Group 2)

	Number	Percent of patients
No abnormalities	36	21.4
Elevated cholesterol	77	45.8
Elevated triglycerides	55	32.7
Elevated cholesterol & triglycerides*	30	17.8

* these patients are also included in 2 and 3 above.

Table 8 : Cholesterol & triglycerides (mean, mg/dl ± S.D.) and caloric intake (Group 2)

Calories	n	Cholesterol (mg/dl)	r (calories & cholesterol)	Triglyceride (mg/dl)	r (calories & Triglyceride)
1000	34	239 ± 46	N.S.	130 ± 43	N.S.
1000-5000	95	244 ± 53	N.S.	120 ± 35	N.S.
1500-2000	32	222 ± 61	N.S.	115 ± 27	N.S.
> 2000	7	262 ± 53	r = 0.0935	135 ± 47	N.S.
			p < 0.001		

DISCUSSION

A large number of lipid abnormalities have been associated with diabetes mellitus. The type of lipoprotein abnormality in diabetes mellitus. The type of lipoprotein abnormality in diabetes depends upon many factors such as type of diabetes, endogenous insulin reserve, degree and distribution of obesity, degree of glycemic control, type of therapy and the presence or absence of nephropathy[17]. The most frequent serum lipid abnormality in Type2 diabetes is an elevation of serum triglycerides to 1.5 - 3.0 times as compared to sex, age, and body weight matched non-diabetic controls. Reduction of HDL cholesterol (by 10-20%), primarily due to a fall of HDL cholesterol is also seen[18]. There is reduced concentration of ApoA-1 and cholesterol to ApoA-1 ratio is low. Apo B levels may be increased. Though LDL maybe in the normal range, abnormal LDL (oxidised LDL) is observed in Type 2 diabetes. Hypercholesteremia and raised LDL cholesterol levels may also be observed in Type 2 diabetes. This has been linked to increased rates of synthesis of LDL cholesterol [19,20]. As observed in Part I of our study, elevation of triglycerides was more frequent in newly detected diabetics. This I corroborated by a study of 507 Type 2 diabetes patients from Delhi, wherein 50% of subjects had hypertriglyceridemia[21]. In another study from Jammu[22], 50 obese Type 2 diabetics were studied. Both cholesterol and triglycerides were significantly elevated a long with a significant rise of LDL cholesterol. There was no significant change in the HDL cholesterol levels. In part II of the study, hypercholesteremia was also seen frequently, because this group included a large number of uncontrolled diabetics.

Control of glycemic status had a salutory effect on blood lipids especially triglycerides. In group I patients, triglycerides were lowered significantly in the diet and chlorpropamide group. The fasting blood glucose also came within the normal range. Additionally, triglycerides showed a significant correlation with fasting blood glucose. The individual cholesterol abnormalities were also normalised in over half of the abnormal patients on follow-up. the body weight and mode of treatment bore no relationship to the lipids, as seen in Group 2 patients. Thus the best mode of therapy for hyperlipidemia in diabetes seems to be adequate glycemic control; the type of therapy being inconsequential.

Rosenstock et at[23] and Hellman et al[24] have demonstrated that intensive treatment for diabetes markedly lowers the cardiovascular mortality due to diabetes. The Oslo diet and exercise study[25] also linked exercise with lowering of serum triglyceride levels.

The mode of therapy bears no direct relationship with serum lipids. Though the biguanides have been credited with a lowering property[26], we were

unable to demonstrate this effect. The results of UGDP study[16] also did not demonstrate any significant effect of any particular mode of treatment on serum cholesterol.

Glycemic control seems to be of paramount importance, rather than the mode of therapy in the management of diabetes-induced lipoprotein abnormalities. Newer modes of therapy, specificially aimed at normalising the lipid abnormalities in diabetes include dietary modifications (caloric control, supplementation with monounsaturated fats), and the use of pharmacological agents for lowering triglycerides and cholesterol, when they are not controlled by intensive therapy of diabetes alone[27]. All efforts to ensure good glycemic control should be made prior to initiation of drug therapy for hyperlipemia. This date indicates that the currently employed modes of therapy for diabetes mellitus have no deleterious effects on blood lipids. In fact the blood lipids are lowered or normalised when good control of diabetes is achieved with these agents.

CONCLUSIONS

1. Plasma cholesterol and triglycerides are significantly elevated in diabetics compared to non-diabetics.

2. Abnormal lipid patterns tend to normalize with therapy of diabetes. The mode of therapy is inconsequential and non of the modes of therapy studied here produced elevation of plasma lipids.

3. Control of diabetes is the most important factor that tends to normalise the lipids in diabetes. It corrected 60% of the individual lipid abnormalities in our follow-up study. The mean plasma triglycerides were significantly lowered with control of diabetes and correlated closely with fasting blood glucose.

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