Original Papers

DISTRIBUTION OF CHOLESTEROL AMONG LIPOPROTEIN FRACTIONS IN DIABETES MELLITUS

Dr. Sidhartha Das

Summary

Since the advent of specific therapy there has been a steady rise in the incidence of atherosclerotic vascular disease (ASVD) amongst diabetics. In the West nearly 3/4th of diabetics die of ASVD. In India and other developing countries, where undernutrition is widely prevalent, the incidence of ASVD-CHD in particular/is relatively lower in diabetics. Further, recent knowledge about atherosclerosis has revealed that distribution of cholesterol between the lipoprotein fractions weigh to be the most important risk factor, more so at a premature age.

Keeping such diversities in view, 3 groups of NIDDM patients free of any infectious, vascular or metabolic complications grouped as : Well nourished diabetics (WND)-(A) 20 on sulphonylurea, (B) 22 on insulin : (X) 15 under nourished diabetics (UND) on insulin along with (Y) 17 cases of (PEM) and (C) 25 healthy standard weight controls were examined for detailed fractional lipoprotein cholesterol content besides total plasma cholesterol (TC).

Compared to (C) the VLDLc values were higher in both the types of (WND) whereas Tc was higher only in (A) On the otherhand neither HDLc nor LDLc showed any statistical difference between WND and controls. Between (A) and (B) the parameters were similar except VLDLc (A-B). All the fractional indices and Tc were lower in (PEM) compared to both (C) and (UND) despite similar nutritional status in (PEM) and (UND.) Between the insulin treated groups (B Vs X) the UND had lower LDLc. The ratios indicating relative distribution of cholesterol revealed similar HDLc/Tc and HDLc/LDLc values in (WND) compared to (C) whereas VLDLc/Tc was higher in the former. Both these ratios were higher but LDc/Tc lower in (PEM) then (C) The (UND) had significantly higher VLDLc/Tc than (PEM) even if other ratios were lower.

These results suggest that unlike in non-diabetics HDLc does not protect against the vulnerability to develop ASVD in patients of NIDDM. Type of therapy has little role to play in this respect. Undernutrition has a definite favourable distribution of cholesterol amongst lipoproteins so as to protect against ASVD. High VLDLc and VLDLc/Tc values in all diabetics point to a common denominator and demands further investigations.

Introduction

Diabetes mellitus a protein disease is known for its varieties of complications. Since the advent of specific therapy (insulin and oral hypoglycaemic drugs) there has been a great change in the pattern of morbidity and mortality amongst diabetics[1]. Today more than 3/4th of diabetics in the West die of atherosclerotic vascular disease (ASVD) amongst which coronary heart disease (CHD) tops the list[1]. Atherosclerosis is known to develop faster and more extensively in presence of diabetes. Lipid abnormalities have been

Research Associate, Dept. of Medicine SCB Medical College, Cuttuck.

recognised as the plausible mechanism promoting accelerated atherosclerosis[2]. Till late hyperlipidaemia was the only known positive risk factor in this context[3], but recently it has been shown that distribution of cholesterol in lipoprotein factions hold a much better correlation than total plasma cholesterol levels per se[4'5].

Further environmental factors play a great role in the expression of ASVD, CHD in particular, even amongst diabetics. The morbidity incidence in diabetics of Japan and developing countries like India from ASVD is much less as compared to U.S.A. and other developed countries of the West[6a]. Incidence of CHD is less in the undernourished diabetics (UND) than in their well nourished (UND) counterparts in the same population. Besides, prevalence of CHD per se is also much lower in populations of developing countries where undernutrition is widely prevalent[6b].

Levels of fractional lipoprotein cholesterol alters with the type and duration of therapy in diabetes mellitus. It is commonly observed that HDLc rises with institution of insulin[7,8], whereas in some studies HDLc has been found to be lower in diabetics on sulphonylurea therapy[9,10]. But the latter is not free of controversy since others have reported significant rise in HDLc levels following such treatment[11]. Thus the status of HDLc in diabetics on usual modes of treatment remains to be established.

In the forefront of all these discrepancies regarding the lipoprotein cholesterol status in diabetics, it was decided to estimate the fractional lipoprotein cholesterol content of plasma in cases of NIDDM both well and under nourished along with adult patients of PEM and health controls for proper analysis of data. The study was designed to be carried out under two schemes :

(I) Well nourished diabetics (WND) -
(A) NIDDM casea on sulphonylurea therapy
(B) NIDDM cases on insulin therapy

(II) Under nourished diabetics
(X) Undernourished NIDDM cases (UND)
(Y) Adult patients with protein energy malnutrition (PEM)

Materials and Methods

Patients of NIDDM reporting to the Endocrine section of S.C.B. Medical College Hospital were taken up for the study. Subjects selected were thoroughly screened to exclude the presence of metabolic, infectious, debilitating or vascular complications. Besides, care was taken to see that all cases included were on treatment with either insulin or sulphonylurea and euglycaemic for over 4 weeks. Patients with good nutritional history and within 5% of desirable weight were considered as well-nourished and those with history of prolonged nutritional deprivation, body mass index < 19, mid-triceps skin fold thickness < 7 mm were taken an undernourished diabetics.

Adult patients of PEM admitted to Medical wards were similarly selected after excluding the presence of any possible debilitating disease, giving long history of poor nutritional intake along with satisfactory anthropometric measurements and low serum protein (<5gm%).

Adequate number of well nourished healthy persons were included as controls (C). All patients and controls subjected to this study were below 50 years of age.

Overnight fasting venous blood samples were collected from each of the patients of NIDDM, PEM and control for the study of lipoprotein-cholesterol (LPc) status. Fractionation of the plasma samples was done by the 'Dual preciptation technique' of Wilson and Spiger[12]. The cholesterol content of each fraction and total plasma cholesterol was estimated by Zak's method[13].

Observations

The study consisted of 57 patients of NIDDM, 17 of PEM and 25 health controls. Amongst the NIDDM cases 42 were WND : 20 on sulphonylurea, 22 on insulin. The rest 15 were UND and on insulin.

The values of Tc and cholesterol content of HDL, LDL and VLDL i.e. HDLc, LDLc and VLDLc of each group of subjects are presented in Table-I. The Tc value was higher in the WND patients on sulphonylurea compared to controls where as there was no such difference between the insulin treated groups (B Vs X). The PEM cases had a remarkably lower Tc value than controls ($P<0.01$) Amidst the WND, there was no difference in the Tc levels (Table-I). Despite similar nutritional status the UND cases had much higher Tc levels ($F<0.01$) compared to that to PEM (X Vs Y).

Amnngst the fractional LPc Values, there was no statistical difference in the HDLc and LDLc levels between either groups of WND or when compared with controls (A Vs C, B Vs C) as shown in Table-l. The PEM group had a lower absolute value of HDLc/ ($P<0.05$) and LDLc ($P<0.01$) than the healthy controls (C Vs Y) and UND (X Vs Y). The VLDLc was however higher in both the WND subjects compared to controls (Table1). Between the undernourished groups VLDLc was significantly higher ($P<0.01$) in X as compared to Y. Comparing the two insulin treated NIDDM groups revealed no difference in any of these parameters except LDLc, which was substantially lower in the UND (mean-113.4±30.1mg%) than WND (136.2±45.5mg%).

Analysis of the relative distribution of cholesterol in different lipoprotein fractions as expressed in ratios (Table-2) revealed that only VLDLc/Tc was higher ($P<0.05$) in WND groups than in controls, and also higher in UND as compared to PEM ($P<0.05$) but no such difference was observed between PEM and controls (C Vs Y). Further, VLDLc/Tc did not differ statistically between the insulin treated groups (X Vs B). Interestingly there was no difference in HDLc/Tc, HDLc/LDLc or LDLc/Tc in between the WND, WND AND UND or control and WND. On the contrary both HDLc/Tc and HDLc/LDLc were much higher ($P<0.01$) and LDLc/Tc lower ($P<0.05$) in the patients of PEM compared to healthy controls (Table-2).

Discussion

This study was undertaken to assess the LPc status in NIDDM patients keeping in view the reported lower incidence of CHD among diabetics in India and several other developing countries. There are reasons to supose that this may be due to differences in

Table-1

Absolute mean valves of Tc and Fractional LPc in different groups (in mg%)

Type of cases		TC	HDLc	LDLc	VLDLc
(A)	(WND) NIDDM on Sulphonylurea	254.4	73.4	146.2	34.7
	S.D.	53.4	15.6	39.1	15.2
(B)	(WND) NIDDM on Insulin	230.3	67.3	136.2	26.7
	S.D.	50.5	21.7	45.5	9.1
(X)	(UND) NIDDM on Insulin	208.5	67.6	113.4	26.7
	S.D.	42.3	22.5	30.1	9.0
(Y)	P.E.M.	125.7	50.7	66.5	8.4
	S.D.	22.2	10.8	13.0	0.6
(C)	Healthy controls	216.4±31.5	68.7±15.0	131.0±29.1	16.6±9.0

Significance of differences

Groups compared			TC	HDLc	LDLc	VLDLc
C	Vs	A	*	NS	NS	**
C	Vs	B	NS	NS	NS	*
A	Vs	B	NS	NS	NS	*
B	Vs	X	NS	NS	NS	NS
X	Vs	Y	**	*	**	**
C	Vs	Y	**	*	**	*

* = P> 0.05, ** = P > 0 01, NS = Not Significant

Table-2

Ratios Between Fractional LPc and TC

Type of cases			ADLC/TC	HDLc/LDLc	LDLc/Tc	VLDLc/Tc
(A)	(WND) NIDDM on Sulphonylurea		0.30	0.54	0.57	0.13
		S.D.	0.07	0.21	0.07	0.04
(B)	(WND) NIDDM on Insulin		0.32	0.63	0.55	0.13
		S.D.	0.07	0.07	0.09	0.05
(X)	(UND) NIDDM on Insulin		0.32	0.63	0.55	0.13
		S.D.	0.08	0.22	0.07	0.05
(Y)	P.E.M.		0.40	0.77	0.53	0.07
		S.D.	0.05	0.12	0.13	0.03
(C)	Healthy Controls		0.32	0.55	0.60	0.08
		S.D.	0.06	0.22	0.08	0.04

Significance of differences

Groups compared			TC	HDLc	LDLc	VLDLc
C	Vs	A	NS	NS	NS	*
C	Vs	B	NS	NS	NS	*
A	Vs	B	NS	NS	NS	NS
B	Vs	X	NS	NS	NS	NS
X	Vs	Y	*	*	NS	*
C	Vs	Y	**	**	**	NS

* = P < 0.05, ** = P < 0 01, NS = Not Significant

diet and nutritional status rather than due to ethnic or genetic factors. Quite a significant proportion of NIDDM cases seen in our hospitals are not only no-obese but have such built as to be called lean or undernourished.

Incidence of macrovascular complications remain high inspite of anti-diabetic therapy[1], and till today there is no conclusive evidence to say that treatment of diabetes with insulin reduces the risk of ASVD. Treatment with sulphonylurea has also been blamed to be associated with higher incidence of CHD[14].

As alterations of plasma lipids have been incriminated as the major contributing factor towards the rising incidence of ASVD in diabetics[1], study of the LPc status in both well and under nourished cases of NIDDM might provide some clue to the mechanism by which under nutrition plays a protective role against the development of ASVD. Further, patients on both types of therapy were examined to find out whether any of the two had any beneficial effect on the lipid profile from a similar point of view.

Dyslipoproteinaemia is known to play its role as the most important risk factor before the sixth decade of life[2] hence patients aged below 50 years were only considered in this study. Diabetics with overt complications were excluded as the aim was to assess the potential vulnerability of the patients for developing ASVD. Cases of PEM were examined to asses the effect of prolonged nutritional deprivation on the LPc status and to establish if diabetes per se causes any significant change despite similar nutritional state in UND.

Analysis of results revealed similar distribution of cholesterol in the HDL fraction of all NIDDM cases irrespective of nutritional status or type of therapy instituted (Table 1 & 2). The LDLc was also not different in either groups of WND but the mean absolute value of UND was substantially lower than WND (B Vs X). As volumes of previous reports from both experimental work and population studies have put high predictive value on lower HDLc levels as positive risk factor for ASVD[15,16,17] our observations of normal levels in NIDDM cases raises valid doubts on HDLc as 'protective against ASVD' in diabetes mellitus. The lone support to this view comes from Finish workers[18]. Amazingly VLDLc and VLDLc/Tc both were higher in all groups of NIDDM patients thus indicating a common positive denominator.

Among the cases of PEM a remarkably high proportion of cholesterol was associated with HDL (40%), reciprocally the content of cholesterol was lower in LDL (Table-2). Unlike in diabetics this pattern is quite at par with the present day concept of a protective lipid profile and explains the possible rational to the lower incidence of CHD in the undernourished population of the Third World.

Adjudging from the update knowledge on the role of various fractions of plasma LPc on the incidence of CHD[19] it appears that UND possesses a lipid profile that is less vulnerable to these complications than their better nourished counterparts.

This study points to a conclusion that assessment of risk for developing ASVD in NIDDM can not be relied upon the LPc status, HDLc in particular, as accepted for nondiabetics. Further the type of therapy offers little difference if any as regards the LPc profile in an euglycaemic state.

Though VLDL has not been established as independent risk factor[19, 20] the role of high cholesterol content in VLDL has recently been the focus of attention[21]. Such a VLDL, termed, as Beta-VLDI, is found to be positively atherogenic in experimental models. Thus our observations of raised VLDLc in all the NIDDM groups may be important in this regard and deserves further exploration.

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