CORONARY HEART DISEASE, DIABETES AND CIRCULATING LIPOPROTEIN CHOLESTEROL

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Introduction

Coronary heart disease (CHD) and stroke have been recognised to be responsible for more than 50 percent of deaths in the developed countries of the West[1]. The former ranks first as the major killer and is the protean clinical outcome of autherosclerotic occlusive vascular disease (ASVD)[1,2]. Atherosclerosis develops both faster and more extensively in diabetics than in general population[3]. ASVD, CHD in particular, is not only the commonest complication of diabetes mellitus but also accounts for nearly 3/4th of the mortality amongst diabetics[3]. Lipid abnormalities have been widely acknowledged as the prime mechanism promoting accelerated atherosclerosis, more so at a premature age [2,4,5].

Till late hypercholesterolaemia was the only recognised risk factor in this regard. But recent knowledge, has revealed that distribution of cholesterol among lipoprotein fractions (LP) i.e High. density lipoprotein (HDL), Low density lipoprotein (LDL) and Very low density lipoprotein (VLDL) correlate better than levels of total plasma cholesterol (Tc) perse [4,7,8]. Various population studies have shown that an independent and inverse correlation exists between cholesterol content of HDL (HDLc) and prevalence of CHD [7,9,10]. However, hypertriglyceridaemia and raised VLDL have been shown to be the most important lipid disorder in diabetics [10,11,12,13]. Role of these abnormalities as independent risk factors for ASVD, CHD in particular, is not yet established[5,13,14]. The high prevalence of CHD in diabetics could be medicated through alterations in the levels of HDLc, but data available so far do not contribute to the elucidation of such a mechanism[15,16]

Thus it was decided to examine in detail LP cholesterol status in cases of premature CHD of both diabetic (NIDDM) and non-diabetics along with uncomplicated patients of NIDDM, with a view to findout the common lipid key factor either responsible for or predisposing to premature CHD.

Materials and Methods

Forty six male patients of CHD below 50 years of age, diagnosed from clinical presentation, electrocardiography and serum enzyme studies (SGOT & SGPT) reporting to the Department of Medicine and Cardiology were included in this study. Eight of them were cases of NIDDM and on sulphonylurea therapy for over 5 years. Accordingly 20 male patients of NIDDM matched for age and free of any infection, vascular or metabolic complications and on sulphonylurea therapy for more than 5 years were selected from amongst those attending the Endocrine section alongwith 25 healthy controls matched for age and sex.

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The patients and controls selected were such that they were comparable from the point of views of nutritional status, (2200 to 2300 Kc/day & BM1 - 21 to 24), alcohol, intake, smoking and physical activity etc. inorder to avoid interference of other known parameters on the LPc profile. The subjects of study were grouped as :

(A) Healthy controls, (B) Non-diabetics with CHD,

(C) Diabetics with CHD & (D) Diabetics without CHD.

Blood samples were collected from each of the patients and controls after an over-night fast. In case of the CHD patients the samples were collected not later than 24 hours following diagnosis in hospital. Fractionation of the major lipoproteins in plasma was done by the dual precipitation technique of Wilson and Spiger (1973)[17]. Estimation of cholesterol content of each fraction i.e. HDLc, LDLc & VLDLc and total plasma cholesterol (Tc) was done by Zak's method (1957).is Plasma triglycerides (Tg) was estimated by the method of Van Handel and Zilversmit (1957).[19]

Observations.

A total of 28 diabetics (NIDDM) on sulphonylurea therapy were studied out of which 8 had CHD. From amongst the 63 non-diabetics, 38 were cases of CHD and rest healthy controls. All subjects studied were between 35 to 50 years of age.

As shown in Table-I, the plasma Tc values were similar in both groups of CHD patients, but was higher (P< 0.5) in the diabetics without CHD when compared with healthy controls (A Vs D). The Tg level was much higher. (P< 0.01) in the non-diabetics with CHD than healthy controls (A Vs B), so also in the patients of Group D than in Group A (PL 0.05). But no such difference could be observed between the two groups of CHD cases (B Vs C), while these values were far higher than in controls (Table-I). Further, both Tc and Tg levels were similar in the 2 groups of diabetics (C Vs D).

Mean HDLc was lower (P< 0.01) and LDLc higher (P< 0.05) in the non-diabetic CHD cases than in controls (A Vs B). There was no significant di(l'erence in these two parameters either between Groups A & D or Groups C & D. On the contrary HDLc value was significantly higher (P< 0.01) in the diabetics with CHD as compared to non-diabetics with CHD (B Vs C), but LDLc did not reveal any statistical difference.

VLDLc was the only fractional cholesterol value found to be signifcantly higher (P< 0.01) in both groups of CHD cases (B-30.4 ± 10.9 & C-30.6 ± I5.1 mg/dl) and diabetics without CHD (D-34.7 ± 15.2 mg/dl) than in healthy controls (16.60 - 9~0 mg/dl).

The ratios between the fractional lipoprotein cholesterol and Tc, depicting the relative distribution of cholesterol amongst LP, are presented in Table-II. Amongst the ratios HDLc/Tc and HDLc/LDLc (which are known to be inversely related to the risk of developing (CHD) were much lower (PL 0.01) in the non-diabetics with CHD as compared to

TABLE-I
Mean Total and Fractional Lipoprotein Chotesterol aed Trtglyceride Levels in Controls and Patients
(in mg/dl)

Group of subjects	HDLc	LDLc	VLDL	Tc	Tg
(A) Healthy controls	68.7	131.0	16.6	216.4	92.3
	S.D. (±) 15.0	29.0	9.0	31.5	30.9
(B) Non-diabetics	44.8	166.0	30.4	240.1	127.5
with CHD	S.D. (±) 10.9	45.6	10.9	52.8	46.0
(C) Diabetics with	68.9	136.6	30.6	236.6	157.5
CHD	S.D. (±) 16.4	33.6	15.1	64 5	45.5
(D) Diabetics	73.4	146.2	34.7	254.4	143.6
without CHD	S.D. (±) 15.6	39.1	15.2	53.4	53.4

Significance of differences

Groups compared	HDLc	LDLc	VLDLc	Tc	Tg
A Vs B	P< 0.01	P< 0.05	P< 0.01	NS	P< 0.01
A Vs D	NS	NS	P< 0.01	P< 0.05	P< 0.05
B Vs C	P< 0.01	NS	NS	NS	NS
C Vs D	NS	NS	NS	NS	NS

NS=not significant

TABLE-II
Ratios between Fractional I.ipoprntein Cholesterol and Total Cholesterol in Patient and Controls

Group of subject	HDLc/Tc	HDLc/LDLc	LDLc/Tc	VLDLc/Tc
(A) Healthy controls	0 32	0.55	0.60	0.08
S.D. (+_)	0.06	0.22	0.08	0.04
(B) Non-diabetics with	0.19	0.29	0.68	0.13
CHD S.D. (±)	0.04	0.09	0.08	0.06
(C) Diabetics with	0.30	0.52	0.58	0.12
CHD S.D. (±)	0.06	0.15	0.06	0.04
(D) Diabetics without	0.30	0.54	0.57	0.13
CHD S. D. (+)	0.07	0.21	0.07	0.04

Significance of differences

Groups compared	HDLc/Tc	HDLc/LDLc	LDLc/Tc	VLDLc/Tc
A Vs B	P< 0.01	P< 0.01	P< 0.01	P< 0.05
A Vs D	NS	NS	NS	P< 0.05
B Vs C	P< 0.01	P< 0.01	P< 0.05	NS
C Vs D	NS	NS	NS	NS

NS : Not significant.

both healthy controls (A Vs B) and diabetics with CHD (B Vs C). Not only the diabetics with CHD had higher HDLc/Tc and HDLc/LDLc but also the diabetics without CHD had similar higher ratios and there was no difference in between them (C Vs D). LDLc/Tc was higher in Group-B than Group A ($P < 0.01$) and Group C ($P < 0.05$). Interestingly VLDLc/Tc was the only common parameter raised in both groups of diabetics and nondiabetics with CHD when compared with controls (Table-II) indicating higher cholesterol content in the VLDL fraction than normal in all these three groups of patients.

Discussion

Lipid abnormalities have been shown to be the most important single risk factor in the development of ASVD, before the sixth decade of life[l,2,4]. Thus this study was conducted on subjects below 50 years of age. Reports from the West on lipoprotein cholesterol have established that alterations in HDLc and LDLc pesse can predispose to accelerated ASVD and premature CHD in the general population[7,8,9]. However, studies on the LPc status in premature CHD cases are sparse in Indian literature. Moreover, reports on the LPc profile in patients of NIDDM with CHD are equally scanty[20] even if it is widely accepted that CHD is more common amongst diabetics than in general population.

Our observations of a raised Tg level in the patients of CHD whether diabetic or not along with those of Group-D is quite in agreement with most recent reports from both within and abroad[2l,22].

The significantly lower values of HDLc, HDLc/Tc and HDLc/LDLc and higher LDLc in the non-diabetic CHD patients is in keeping with most studies since the leading work of Miller and Miller (1975) supports the view that HDLc has an inverse relation with the occurance of CHD[6,23]. Over and above the absolute values of HDLc, its relative proportion to Tc and LDLc have been identified to be independently predictive of CHD[8]. Analysis of the ratios obtained from this study (Table-II) revealed striking differences between the two groups of CHD patients.

The mean HDLc levels were not found to be different in either group of diabetics when compared with controls and parodoxically diabetics with CHD had significantly higher ($P< 0.01$) HDLc than their non-diabetic counterparts (B Vs C).

Rise in HDLc in diabetics consequent to insulin therapy is well documented [l2,l5] The interesting finding here is that a11 these diabetics were on sulphonylurea therapy for periods over 5 years. Therefore, the present consensus that HDLc levels may not be lower in NIDDM cases whether on insulin or sulphonylurea[24,25] with or without CHD[20] is borne out of this study.

In view of the above it is difficult to attribute a protective role entirely to HDLc or an atherogenic role to LDLc in the pathogenesis of CHD at a premature age. However, the observations of a significantly higher VLDLc and VLDLc/Tc in both groups of CHD patients and diabetics(with and without CHD)may point to a common denominator although levels of Tg and VLDL have not been generally accepted as independent risk factors, the update report on the atherogenic potency of a cholesterol rich VLDL (Beta-VLDL) by Mahley[26] in experimental models calls

attention to the involvernent of VLDL in this process. Partially metabolised VLDL, still rich in cholesterol (Remnant Particles) have also been found to be highly atherogenic[4,6]. Thus the high cholesterol content of VLDL as revealed in the present study demands further exploration and may provide a clue to a common lipid key factor, responsible for premature ASVD in general.

Summary

Of 46 male patients below 50 years of age, with established CHD, eight were diabetics. Plasma lipids viz, triglycerides, total cholesterol as well as cholesterol content of major lipoprotein fraction, i.e. HDLe, LDLc and VLDLc were estimated in the above along with 25 age matched controls and 20 diabetics without CHD. Both groups of diabetics were on sulphonylurea therapy for over 5 years.

Compared to controls non-diabetics with CHD had significantly lower levels of HDLc, and higher levels of LDLc, VLDLc and Tg where as there was no difference in HDLc and LDLc levels and diabetics with or without CHD, HDLc, HDLc/Tc and HDLc/ LDLc were significantly higher ($P < 0.01$) in diabetics with CHD than in non-diabetics with CHD. Although VLDLc and VLDLc/Tc were significantly higher in diabetics, compared to controls the values were similar in patients of CHD whether diabetic or non-diabetic.

These results suggest that higher incidence of premature CHD amongst diabetics is unrelated to alternations in levels of HDLc or LDLc, while VLDL with high cholesteral content (Beta-VLDL) can not be ruled out as an important risk factor for both diabetics and non-diabetics.

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