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CERTIFICATE

I, Dr. K. RAGHU hereby declare that I have actually performed all the procedures listed / carried out the project under report.

Signature .....

Place :

Date : 21.11.90

Name in K. RAGHU capital letters

Forwarded. He has carried out the minimum requirement of procedures / etc.

Signature

Head of the department

LIST OF PROCEDURES DONE

PROJECT REPORT

TITLE OF THE PROJECT: Coronary heart disease in the young & old : A comparative study of risk factors & angiographic profiles.

NAME Dr. K. RAGHU

PROGRAMME : DM CARDIOLOGY

MONTH & YEAR OF SUBMISSION : NOVEMBER - 1990

Note:— (i) In the case compilation of procedures done, the contents and the subsequent pages should be made into different sections (a) Procedures done (b) Procedures assisted (c) Procedures participated (d) Procedures attended / participated etc. in Other Centres. Each section should be preceded by a leaf carrying the name of the section that is succeeding.

(ii) The Contents page will carry information as per model given under

PROCEDURES DONE

Closed Mitral valvotomy ..... 124 (say)

Patent ductus arteriosus-ligation 10

Atrial septal defects 20

PROCEDURES ASSISTED

Closed Mitral valvotomy ..... 100 (say)

(iii) In the subsequent pages details of each procedure done/assisted should be given in the format given below :—

Heading : Closed mitral valvotomy

Date	Name of the patient	Age	Sex	Patient No.

(iv) In the case of Project Report in the page immediately following the Certificate page the under-mentioned details should be given :—

(a) Title

(b) Duration

(c) Aim and scope

(d) 50 word summary of work done

CONTENTS

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INTRODUCTION

Atherosclerotic coronary artery disease is amongst the most serious health problems in industrialised nation. There is substantial and increasing evidence from basic and clinical research that atherosclerosis can be retarded, and that regression of atherosclerosis can be effected, with reduction in risk and by modification of enviromental and behavioural attributes that unfavourably influence the coronary risk status of populations It is thus advantageous to define the common risk factors that occur in individuals confirmed to have the disease and thereby apply it to screen the population for individuals who would be at a high risk in an attempt at modification of their risk factors. It is important that such modifications are targated to include relatively younger age groups as the beginings of atherosclerosis are in childhood and risk prone behaviours are acquired at a young age. Also, increasing age is an adverse prognostic sign for secondary prevention, given the less favourable outcome of established coronary disease with aging[1].

There have been few population studies analysing the prevalence rate for coronary artery disease in India. Sarvothaman et al[2] have reported rates of 66 per 1000 and Gupta et al[3] have shown that the rates are two and a half times lower in rural as compared to urban population. There is a general impression that coronary artery disease is being recognised at an early

age more frequently in recent years and there have been several reports addressing the problem of acute myocardial infarction in the young[4,5,6,7,8]. Coronary arteriographic studies in these patients have generally revealed significant atherosclerotic lesions though a small but substantial proportion of the cases have had normal coronaries. The latter in some studies have been shown to have fewer of the usual risk factor for atherosclerosis and the causes for myocardial infarction have been speculated upon. These include coronary artery spasm, coronary thrombosis with recanalisation, platelet aggregation and coronary embolism. There has been a striking male preponderance in many of these studies both from the western world and from India.

Comparison of risk factors between younger and older age groups have shown differences including a higher frequency of smoking, hypercholesterolemia, positive family history in the young while hypertension and diabetes mellitus were noted more frequently in the older age groups.

The aim of the study was to :

1. Define the common risk factors in patients confirmed to have myocardial ischemia, infarction or evidence of atherosclerotic coronary disease on a coronary arteriogram.
2. Study the lipid values in these patients and compare with healthy age and sex matched controls.

3. Compare the risk factors and arteriographic profiles between the younger and older age groups.

MATERIALS AND METHODS

The study group consisted of 242 patients with a documented MI or stable angina pectoris with a positive exercise ECG, who were reviewed in the outpatient department between January 1989 and May 1990. A majority of these patients (209) underwent coronary arteriographic study for standard indications. In the rest, coronary artery disease was presumed on the basis of a previous MI or the occurence of angina which was confirmed by a positive exercise ECG test. The diagnosis of previous MI was made on the basis of a history of prolonged chest pain and typical ECG changes of Q waves in the setting of transmural injury or primary ST-T wave changes consistent with subendocardialinjury. 68 of the 209 patients who were catheterised were 40 years or younger (range 18-40) while the rest were older than 40 (range 41-64). There were only 4 females.

RISK FACTORS: Information relating to age, duration of symptoms, functional class, location of MI and drug intake was tabulated. None of the patients included in the study were on lipid lowering drugs. No attempt was made to alter their drug intake prior to lipid analysis in view of their symptomatic status. Patients who had undergone recent revasularisation therapy (either PCA)

or CABG) were excluded as also patients with recent acute myocardial infarction, (within the previous 3 months), in view of known derangements in lipid levels during the acute phase. A questionaire was used to prospectively record the following risk factors.

SMOKING: Persons who had smoked on a regular basis including those who had stopped smoking for less than 2 years were classified as smokers. Persons who never smoked or smoked irregularly were classified as non smoker. Smokers were classified as light (less than 5 cigarattes/day) Moderate (Upto 15 cigarattes/day) and heavy (more than 15 cigarattes/day).

HYPERTENSION: Hypertension (Systolic ->150 mmHg, diastolic >90 mmHG) was considered to be present if documented by frequent recording or if the patients was on anti-hypertensive medication.

Diabetes Mellitus: Patients with clinically overt diabetes on treatment or with biochemical evidence of glucose intelerance. Positive family history of MI, or angina in parents and siblings before the age of 55 years.

Obesity: Obesity was defined as a relative body weight of ≥28 from Quetlett's formula'

$$\frac{\text{Weight in Kg.}}{\text{Height in M}^2}$$

CORONARY ARTERIOGRAM: Left heart catheterisation including LV angiography and coronary arteriography was performed. Arteriograms were exposed on 35mm film in multiple projections. A reduction of 50% or more in luminal diameter was considered evidence of significant coronary obstructive disease.

Lipid values were determined during admission for coronary arteriography. Blood sampling was done after an overnight fast of 12 hours. Serum total cholestorol and triglycerides (TG) were determined in duplicate by the enzymatic method using the kits from Bochinger Mannhoom, Germany. High density lipoprotein cholesterol (HDL-C) was isolated after precipitating low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein (VLDL) by PEG 6000, and the cholesterol content of HDL supernatant was quantiated using the same enzymatic method used for estimating cholesterol. HDL-C and fasting TG level were used to make an indirect estimate of LDL-C and VLDL-C using Friedwald's formula[11]. The method had been previously standardised and values of normal individuals in various age groups have been previously published[12]. Comparison of data from cases were made with the values age method controls reported earlier[12].

Statistics: Risk factors and coronary anatomy of younger patients with coronary artery disease were compared with patients who had normal coronaries in the same age group. A comparison between

younger and older patients was also made. Statisticalanalysis in the above comparisons was done by the use of Chi-square test. Comparison of lipid values between patients and controls was made by students unpaired 't' test.

RESULTS

Patients were classified into younger (age 40 and less) Group A and older (age more than 40 years) Group B. The former were divided into twogroups, I & II, based upon the presence or absence of significant atherosclerotic lesions on coronary arteriograms.

Table. I lists the clinical characteristics of the various patients.

Patients in Group B had longer duration of symptoms. However there was no significant difference in the functional class between the two age groups. The incidence of MI was much less in the older group.

Table. II compares the risk factor profile in the two groups of patients under 40 years. There were no differences in the frequency of any of the risk factors. Of the 51 smokers in group I, 36 patients were heavy smokers, 11 smoked moderately, while 4 were light smokers. In the other group (group II) 5 were heavy smokers while the other was a moderate smoker.

A comparison of the risk factor profile (Table III) of group A and Group B patients revealed that the incidence of smoking was significatly higher in group A while hypertension and diabetesmellitus were significantly more frequent in Group B. The frequency of other risk factors were not significantly different and the frequency of multiple risk factors (2 or more) was also similar.

Amongst the smokers in Group A, 72% were heavy smokers, 21% were moderate smokers and 7% were light smokers. In Group B, the percentages were 42.4%, 43.4% and 12.4% respectively. Angiographic differences between group A and B were those of single vessel disease being more common in the former and triple vessel disease in the latter. (Table IV).

Analysis of lipid values (Table V) revealed that in group A-I, total cholesterol, LDL C, ratio of TC/HDL and TGL were all significantly different from controls while in group A II HDL C, was low and the ratio of TC/HDL C higher. Though there was no statistical difference between group I and II, all the values were slightly higher in group I as compared, to group II. Lipid values of group B when compared to control were significantly different except for total cholesterol which though higher than contrpls did not attain statistical significance. Lipid values were more or less similar in both group A and B.

Table 1 Clinical Characteristics

	Group A		Group B
	Age 40years		Age 40years
	Group I CAD n=60	Group II Normal coronaries n=8	n=174
Mean age	36.87±4.29	32.75±4.83	50.67±6.15
Duration of symptoms	3y ± 4yrs	3M - 2yrs	3 moths- 10years
Functional class (NYHA)	2.13±0.7	2.0 ± 0.7	2.62 ± 1.12
Previous MI	49(81.6%)	7(87.5%)	75 (43%)
Use of Blocker	37(61.6%)	2(25%)	111(63.8%)

?

Table II Risk factor profile in group A

GROUP A

	GROUP I Coroonary atherosclerosis n=60	Group II Normal coronaries n=8	P
OKING	51 (85%)	6 (75%)	NS
PERTENSION	11 (18%)	0	
ABETES	9 (15%)	1 (12%)	NS
SITIVE FAMILY H/x	20 (33%)	2(25%)	NS
I ⩾28	1 (1.6%)	0	NS
PERCHOLESTEROMIA ⩾240 mg%	24 (47%)	2 (25%)	NS
W HDL-c ⩽35mg	50 (88%)	6 (75%)	NS

Table III Risk factor profile in Group A & B

	Group A 40yrs n=68	Group B 40yrs n=174	P
MEAN AGE	36.38±4.52	50.67 ± 6.15	
SMOKING	57 (84%)	113(65%)	0.001
HYPERTENSION	12 (18%)	57 (33%)	0.02
DIABETES	10 (15%)	47 (27%)	0.05
POSITIVE FAMILY HISTORY	22 (32%)	42 (24%)	NS
HYPERCHOLESTEROLE-MIA ⩾240mg%	26 (40%)	64 (37%)	NS
LOW HDL-c ⩽35mg%	56 (86%)	127(73%)	NS
Quetlett'e index ⩾28	1	6	NS
Mean No.of Risk Factors	2.50 ± 1.03	2.63 ± 1.14	

Table Iv angiographic profile in group A & B

	Group A n=68	Group B n=141	P
No lesion	8	4	<0.01
1 vessel	24	14	<0.001
2 vessel	14	35	NS
3 vessels	22	88	<0.001

ABLE V Table of Lipid values patients and controls

	T.CHOL	LDL-c	HDL-c	Tc/HDL-c	TGL
ROUP A- I n=60	237.35[2] ±71.46	169.13[4] ±67.62	30.93±[4] 7.10	7.92±2.51[4]	190.74±90.11[4]
oup A-II n=8	216.43[1]± 34.83	147.57±[1] 35.06	32.43±[4] 5.38	6.66±1.52[4]	156.86±30.87[1]
ONTROLS =24	198.74± 31.69	123.97± 32.24	50.02± 8.35	3.97±0.65	118.58±37.7
ROUP B =174	225.86±[1] 53.54.	158.51±[3] 50.56	32.02±[4] 7.42	7.38±[4] ±2.16	184.30 ±[2]
ONTROL =24	208.89 ±29.52	131.43± 29.36	48.62± 6.98	4.29±0.47	144.13±51.54

1= P NS 2.P <0.05 3 P<0.01 4 P<0.001

TABLE VI Lipid profile with & without B Blocker

	B Blocker + n=150	B Blocker - n=88	P
OTAL CHOLESTEROL	225.63±54.62	232.06±64.42	NS
DL-c	159.28±48.37	164.38±61.44	NS
DL-c	30.33±7.36	33.47±9.06	NS
.C/HDL-c	7.51±2.15	7.21±2.44	NS
RIGLYCERIDES	189.32±89.98	179.43±96.43	NS

TABLE VII Lipid profile in relation to extent of disease

	Normal	1 vessel	2 Vessel	3 Vessel
CHOLESTEROL	190.27 ±41.98	218.32 ±58.26	228.26± 48.33 ¶	39.25 ± 64.18 §
LDL-c	126±39.63	148.78 ± 50.45	157.56± 45.87 *	170.69 ± 60.16 *
HDL-c	31.55 ± 5.85	29.73± 2.26	32.15± 6.75	31.68 ± 7.4
Ratio Tc/ HDL-c	6.18 ± 1.57	7.43 ±2.26	7.43± 2.18	7.83 ± 2.39 #
TGL	175.09 ±112.16	193.68 ±75.28	230.50 ±95.22	207.32 ± 80.53

¶ P<0.05 Vs Normal

* P<0.05 Vs Normal

§ P<0.001 Vs Normal

\# P<0.02 Vs Normal

To ascertain whether the use of B blockers produced significant differences in lipid levels, the mean values in patients of both groups who were on the drug were compared with these not on B blocker. Since sub classification of patients according to the type of B blocker resulted in smaller numbers, the comparison was confined to the total group using B blocker. As shown in the table (Table VI) there was no statistical difference between the two groups.

A breakup of the lipid values in relation to extent of disease (Table VII) showed that patients with atherosclerotic coronary diseased had significantly higher cholesterol and LDL C level. As compared to patients with normal coronaries. However amongst the patients with one, two and three vessels disease, these were no statistically significant differences except for slightly higher values for TC and LDL C, and a higher TC/HDL C ratio in patients with triple vessel disease.

DISCUSSION

There is general agreement that ischemic heart disease is multifactional in etiology[13]. This study is in consonance with others in that multiplicity of risk factors was the rule in the majority with only a small fraction of the total 25/242 having one risk factor for coronary artery disease.

Cigarette smoking is firmly established as a leading risk factor for coronary artery disease (CAD). Previous studies both from the developed countries[4,5,6] and our country[9,14,15] have shown that smoking is the most common risk factor. This was borneout in the present study in which a history of smoking was present in 85% patients in group A and was significantly more common in the young than in the older patients. However even in the latter group smoking was twice as common as hypertension which was next in frequency. Another point of importance was the fact that even among smokers a greater percentage of the young smoked heavily as compared to the older patients.

The recent guidelines of the expert panel on National Cholesterol education programme[16] has stressed on the importance of raised cholesterol levels as a risk factor for CAD. While the prevalence of abnormal lipid values in the western world has been well documented in numerous epidemiological studies[17,18,19], there has been a paucity of reports on serum lipids from our country. The few that have been published have stressed mainly on cholesterol and triglycerides[7,9,14]. While the role of TC and LDL-C in the pathogenesis of CAD is compelling, the pathophysiologic connection between HDL and CAD is less secure [20,21]. Castelli etal[17] in the Framingham study reported that when HDL levels were less than 1.03mmol/L (40mg%) the incidence rates for

CAD was high regardless of total cholesterol. There have been other population studies however which have demonstrated low LDL-C in which the low HDL-C concentration seeminly do not convey increased risk for CAD[22,23]. Also, there are reports of populations with a high prevalence of CAD having relatively high HDL-C concentrations accompanying their higher LDL-C levels[24]. Till date there has been no trial in which the raising of HDL has been the sole or even the predominant mode of intervention[25]. Its importance in the transport of free cholesterol from blood to liver, role in preservation of endothelial cell function and release of endothelium derived relaxing factor have been cited. Recently HDL has been shown to promote release and stabilisation of PGI2. This action is surmised to retard atherogensis, prevent coronary vasospasm and inhibit platelet aggregability, (through PGI2)[26]. This study stresses on the importance of HDL-C and also the ratio of TC/HDL as risk factors for CAD. Low levels of HDL were present in 86% and 75% of Group A and B patients respectively. While the use of B blocker could result in a significant reduction in HDL levels, comparison of the mean values between the two groups belieed this a cause. Even adjusting for the use of nicotine did not change the result. Even in the group with normal coronary anatomy 7 of whom had prior MI, HDL was lower in 75%. This could be interprested to suggest that atleast in our population a low HDL may signify high risk. A certain amount of reasonable bias goes into the selection of

patients for coronary arteriography and information obtained may not reflect prevalence or pattern in community. However, the findings are sufficiently significant to warrant large scale epidemiological work up to throw more light on the matter. The ratio of TC/HDL of more than 5 was another important marker in these patients being present in 57 of the 68 Group A patients and 153 of the 174 group B patients. Thus in 91% of the patients, the ratio signified risk though in the majority of them serum cholesterol was in normal range. This if we were to estimate cholesterol and TGL only many with subtle yet significant lipid abnormalities would be overlooked.

The atherogenecity of plasma TGL has remained controversial. Infact, there is no consensus as to what constitutes hypertriglyceriodemia with at least one text book of cardiology stating that the values recommended by the Triglycerides C onsensus Conference of 250mg-500mg% (borderline elevation), above 500mg% (definitely abnormal) as being two high. The authors advocate values in the range of 200mg to 250mg as desirable. In this study 21/68 in group A and 62/174 in group B had values above 200mg%. Thus the low HDL in the majority cannot be explained by high TGL levels.

The frequency of other risk factors including raised cholesterol values are similar to the other studies. As anticipated hypertension and diabetes mellitus were more common in the older

age group. In the group with normal coronary anatomy, risk factors were more or less similar to the CAD group. These findings are similar to the report of Uhl etal[10] who had 9 cases of normal coronaries in their 165 cases of young MI, 8 of whom had more tnan one risk factors. Others[4,9], have reported differently with the number of risk factors being significantly lower in the group with normal coronaries.

That increasing age is by itself a risk factor for CAD is well known as also the fact that older patients have more number of arteries involved as compared to young[17]. This was confirmed in this study with single vessel disease being more common in the young and triple vessel in the older age group. However the younger group had a twofold greater incidence (84.5% vs. 43%) of myocardial infarction as compared to the older, with an MI being the presenting symptom in the majority.

CONCLUSIONS

1. Coronary artery disease is of multifactorial origin with the majority having more than 2 risk factors.
2. Smoking, low HDL below 35mg%, elevated ratio of TC/HDL-C of more than 5 are the most important risk factors. Except smoking, the other two were equally present in younger and older individuals.

3. Epidemiologic studies are needed to confirm the importance of low HDL-C levels in our population.

4. Lipoprotein abnormalities did not significantly predict the severity or extent of disease.

5. Older patients have more extensive disease than the young.

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