Diabetes, Lipids and Coronary Artery Disease in Indians

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ABSTRACT

Diabetes mellitus (DM) is a protean metabolic disorder that adversely affects the vascular channels of the body leading to occlusive vascular events like coronary artery disease (CAD) and peripheral vascular disease (PVD). Besides the diabetic state, higher levels of triglycerides, lower HDL cholesterol and more of glycated Apo B100 contributes to the excess of atherogenesis in these subjects. In Indian subjects with DM the lipid profile and pattern is greatly influenced by the ethnic origin, food habit, nutritional status and lifestyle influences. There has been a quantum increase in the incidence of CAD amongst urbanites while the picture in rural India has changed very little, suggesting the major impact of lifestyle modifications on lipid profiles and the deleterious effect of the latter in causing accelerated and more extensive CAD as evident angiographically. These alterations in lipid profiles precede the events much in advance and also prevalent in the adolescent siblings of patients with CAD. In our social setup, it is the nurture which has been the main determining factor than the nature per se. Conventional dyslipidemias of hypercholesterolaemia with high LDLc may not be the commonly found abnormalities in our subjects and due attention should be given to Type IV and Type IIb hyperlipidemias as cause of excessive CAD in our population groups besides tight glycemic control to avert increased glycation of functional proteins and apoproteins. Raised triglyceride levels can be used as surrogate lipid markers for CAD in the susceptible population and families.

INTRODUCTION

Insulin is an anabolic hormone having widespread influence on various processes which are growth-enhancing and beneficial to the organism. Insulin exerts profound influence on the expression and activity of genes regulating various key enzymes involved in lipid metabolism as well as synthesis and expression of apolipoproteins both in the liver and peripheral tissues (adipocytes, skeletal muscle, endothelial cell, fibrocyte etc). In the peripheral bed at the endothelial tissue interphase, it primes the lipolytic enzymes (lipoprotein lipase (LPL)) and enhances the clearance of very low density lipoprotein (VLDL) and chylomicrons. These triglyceride (Tg)-rich lipoproteins breakdown to liberate free fatty acids (FFA) and glycerol. While FFA is used as the main source of energy in the post-absorptive state, glycerol recycles back to the liver. In the process of hydrolysis of fat, mono and diglycerides are also liberated at these sites.[1]

Levels, composition, size and metabolism of plasma lipoproteins in subjects with diabetes mellitus (DM) are influenced by factors such as:

1. Type of diabetes mellitus
2. Habitus i.e. lean, standard weight and obese
3. Nutritional status: undernourished or well-nourished
4. Insulin sensitive or resistant stage

Table 1 : Types of Lipid Abnormalities In DM

Type 1 DM :	
Usual level of glycemia (Euglycemia)	: Similar to non-diabetics
Poor glycemic control	: ↑Tg level and ↑LDLc oxidation
Diabetic nephropathy	: ↑LDLc and Lp(a), ↓HDLc
Type 2 DM :	
Usual levels of glycemia (Euglycemic)	: ↑Tg, ↓HDLc, prevalence of small dense LDL, ↑LDL susceptibility to oxidation
Poor glycemic control	: Worsening of hypertriglyceridemia
Diabetic nephropathy	: ↑Tg, ↑Lp(a) , ↓HDL

5. Glycaemic status and type of treatment
6. FFA influx to the liver vis-a-vis insulin level in portohepatic bed
7. Presence of complications like nephropathy

Broadly the lipid abnormalities (dyslipidaemia) seen in Type 1 and Type 2 diabetes are presented in Table 1. Hypertriglyceridaemia is the common dyslipidemia seen in uncontrolled diabetic state, insulin resistant stage and presence of nephropathy in Type 2 diabetics.[2] Fig. 1 and Table 2 depict the influence of nutritional

Table 2: Lipid profile in Controls, Untreated and Treated Undernourished (UND) and Well-nourished (WND) Type 2 diabetics (mg%).

Sub	Tg	Tc	HDLc	LDLc	VLDLc
Untr. UND	157.1	283.4	63.6	158.8	64
Trt.UND	107.8	199	70.4	104.6	24
Cont.	95.3	216.4	68.7	131.2	16.5
Untr.WND	168.4	300.2	52.8	182.2	65.2
Trt.WND	123.2	230.2	67.3	136.2	26.7

Das, Tripathy, Samal & Panda, Diabetes Care, 1984

Table 3: Lipids and Lipoprotein Cholesterol Normograms in Indians (mg%)

Zone	Triglycerides	Total Cholesterol	HDLc	LDLc
East	115	185	42	115
South (a)	155	180	38	107
(b)	119	172	40	108
West	107	188	38	129
North	132	150	43	101

Based on population studies as reported from different parts of India
Sidhartha Das & V.Mohan, Chapter on Lipids, API Text Book of Medicine, 7th Edn.,2003

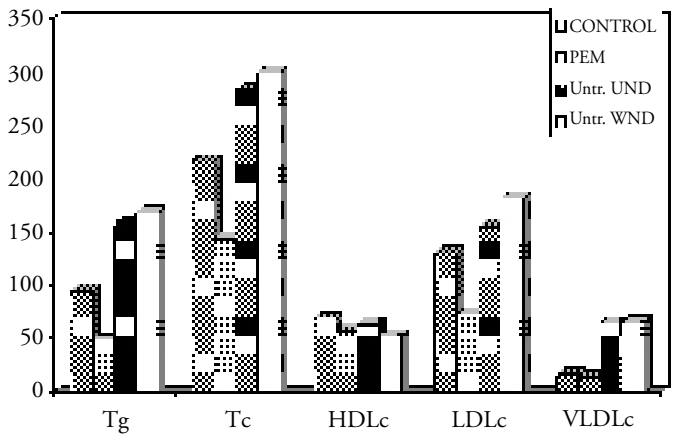

Fig. 1: Lipid Profile in Controls, Adult-PEM, Untreated - Undernourished (UND)& Well nourished (WND) Type 2 Diabetics.(mg%)
Das, Tripathy, Samal & Panda, Diabetes Care. 1984

status and glycaemic control in patients with Type 2 diabetes. Again, in Indian diabetics hypertriglyceridemia with increased VLDL is more common dyslipidaemia than low high density lipoprotein (HDL) cholesterol levels.[3] This is very likely due to overproduction of VLDL by the liver.

VLDL Tg is endogenous in origin and thus the dyslipidemia is Type IV hyperlipoproteinemia. The hypertriglyceridemia is consequent to both over-production by liver and poor clearance of VLDL in the peripheral tissues due to inappropriate action of LPL. The suppressed activity of LPL is because of the insulin resistant or insensitive state in metabolically uncontrolled diabetics. With adequate glycemic control and maintenance of euglycemia it reverts to near normal levels. Therefore, presence

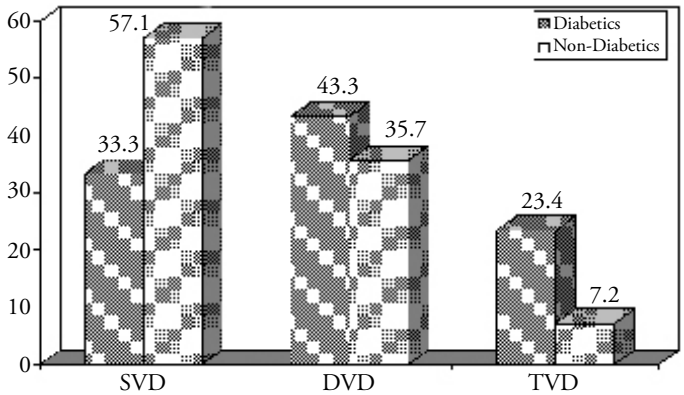

Fig. 2: Mean Cholesterol levels in different Socio-Economic Groups, Cuttack (mg%)
Das S, Recent Advances in Nutriology Vol.2 '90

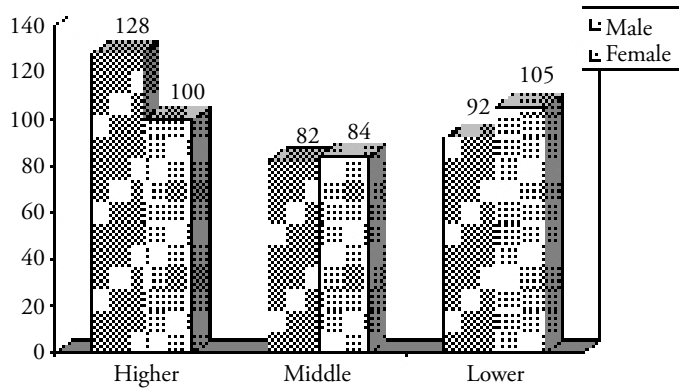

Fig. 3: Mean Triglyceride levels in different Socio-Economic Groups, Cuttack (mg%).
Das S, Recent Advances in Nutriology Vol.2 '90

of hypertriglyceridemia is a good indicator of the state of poor metabolic control in patients with DM. Alterations in cholesterol levels are not uniform in patients with DM. In the diabetics in the West as well as affluent populations of our country, a rise in cholesterol levels along with Tg is seen, so the type of hyperlipoproteinemia is Type IIb.[4] However diet, nutritional status and anthropometry play a vital role and the picture is different in most of our diabetics.[5] Even in an uncontrolled state, only about one-fourth of diabetics revealed hypercholesterolemia.[2]

LIPID PROFILE IN INDIAN POPULATION

Interpretation of dyslipidaemia in diabetics has to be done keeping in view the lipid normogram of the inherent population. The National Lipid Normogram is presented in Table 3.[1]

Population-based studies on lipid profiles, done at our center are depicted in Figures 2 and 3.[3] The Tg levels revealed U-shaped distribution in upper, middle and lower socio-economic groups (SE Groups) respectively. While higher Tg levels in the upper SE group is very likely to be due to higher fat intake compounded with slower VLDL clearance, relatively higher levels in the lower SE group is mostly due to very high carbohydrate diet. Interestingly, analysis of lipid profile done in persons living in a geographical area of 10 kilometers radius but belonging to different ethnic groups as well as having different lifestyle and food habits revealed significant differences in the lipid profiles, as shown in Table 4.[6] The fishermen (Naulia) had the most ideal

Table 4: Lipid profile in Tribals, Fishermen and Urban elite population in mg/dl.

Sub	HDLc	LDLc	VLDLc	Tc	Tg
Urban	41.8	114.8	28.8	185.4	144.4
Fishermen	43.5	71.4	24.8	139.8	124.2
Tribals	33.6	70.9	28.9	133.5	144.9

Mondal, Das, Mohanty et al, Jr. Nutr. Med. 1994.

lipid profile to be followed by tribals where the cholesterol profile was ideal but Tg levels were similar to urban elite population. The fishermen were physically most active, consumed on an average 500 gms of fish per day while the tribals were nutritionally deprived with poor protein intake. Both these communities were on high carbohydrate diets while the urbanites had more refined carbohydrate food, richer in both fat and proteins. This further confirms that high carbohydrate diet had a great influence in modulating Tg levels vis-a-vis physical activity in our populations. The National Lipid Normogram again reflects the influence of inherent dietary peculiarities on the lipid profile of people from east, west, north and south zones of India.[1]

LIPID LEVELS AND THEIR INTERPRETATIONS IN DIFFERENT TYPES OF DM :

Type-1 DM

This is a typical situation where insulin production is minimal to nil and therefore its concentration is low both in the porto-hepatic circulation and peripheral blood. The lipoprotein composition is accordingly affected with low high density lipoprotein-cholesterol (HDLc), poor esterification of cholesterol, more of Tg with less VLDL clearance. This is more so in inadequately treated patients with poor glycemic control. The activity of enzymes like lecithin cholesterol acyl transferase (L-CAT) and lipases are suppressed due to low circulating insulin levels. This adversely affects HDL metabolism. Besides, higher concentration of free cholesterol in low density lipoprotein (LDL) and intermediate density lipoprotein (IDL) makes them more atherogenic. However, institution of insulin treatment and maintenance of euglycemia rapidly reverses lipid metabolism to normal.

Type-2 DM

In patients with Type-2 DM there is global dysfunction of lipoprotein metabolism. The degree of dyslipidemia is more widespread (Table 1). There is am increase in small dense LDL (LDL3) which is highly atherogenic. In patients with poor glycemic control, levels of Tg-rich lipoproteins are higher. This rise is not only due to overproduction of VLDL but also poor peripheral clearance consequent to lesser expression of ApoB100 receptors on endothelial cell surface. In uncontrolled patients with Type-2 DM the recycling of receptors is also slow. Glycated ApoB100 has longer interaction with its receptors and so prolongs the half-life of both LDL and VLDL molecules. The HDL levels may not be low in these type of diabetic subjects, more so with fair glycemic control. Unlike Type-1 DM, patients with Type-2 DM have good insulin reserve and so much higher porto-hepatic insulin concentration which keeps the HDL cycle and hepatic

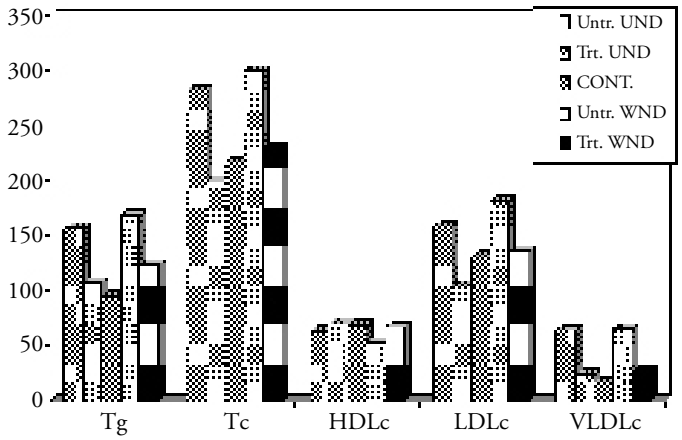

Fig. 4: Lipid Profile in Controls, Untreated and Treated Undernourished (UND)& Well nourished (WND) Type 2 Diabetics. (mg%) Das, Tripathy, Samal & Panda, Diabetes Care. 1984

enzyme system at an optimum. Patients with poor peripheral insulin levels may therefore have near normal HDLc levels while values of VLDLc, LDLc, IDLc and Tg may be higher. Such discordance is peculiar to Type 2 DM. Type IV, Type IIb and Type III dyslipoproteinemias commonly met with in Type 2 DM often reverses with diet and hypoglycemic drug therapy (Fig. 4).[4,7]

Low body weight Type 2 DM (Lean Type-2 DM) :[2,3,8]

The diabetic state differentiates lean Type-2 DM from PEM in many respects including lipid profile. Cholesterol content in LDL and VLDL are higher as is Tg content, although the absolute values of these lipid levels are much lower than in well nourished diabetics (WND). Levels of mean HDLc are visibly higher in lean Type-2 DM irrespective of glycemic status. The Tg levels in Indian subjects with DM are higher both in lean Type-2 DM as well as in WND when compared with data from the west. This profile is likely to be the true reflection of the influence of nutritional status lipid profile in developing societies rather than a consequence of any specific biological alterations.

Studies done by Seshiah et al from Chennai had also revealed similar alterations in the lipid profile in obese, non-obese and lean diabetics in their population.[9] While in the WND there was a positive correlation suggesting slower removal of Tg in the obese, there was no correlation in the lean Type-2 DM. Studies on lean Type-2 DM have shown that pre-existing dyslipidemia found in an uncontrolled state improves with establishment of glycemic control. Hypercholesterolemia is very unusual in such lean patients with DM.

It is a well established fact that hypertriglyceridaemia and Tg content of muscle bears a negative relationship to whole body insulin sensitivity. The patients with Type-2 DM invariably have serious breakdown in lipid dynamics often reflected as elevated levels of FFA and Tg together with excessive deposition of fat in various tissues including muscle bed. The high FFA levels adversely affects insulin-mediated glucose disposal in peripheral blood. Such FFA arises from hydrolysis of Tg. In peripheral circulation. Therefore Tg is considered to be a surrogate marker for fatty acids in general. Levels of long chain fatty acids and their derivatives increase in states of insulin resistance (obesity, IGT,

Table 5: Prevalence of CAD in Urban and Rural India

Author	Year	Place	CAD(%±SD)
URBAN POPULATION			
Mathur KS	1960	Agra	1.05 ± 0.3
Padmavathi	1962	Delhi	1.04 ± 0.3
Sarvotham SG	1968	Chandigarh	6.60 ± 0.6
Gupta SP	1975	Rohtak	3.63 ± 0.5
Chaddha SL	1990	Delhi	9.67 ± 0.3
Shety KS	1994	New Delhi	10.9
Gupta R	1995	Jaipur	7.59 ± 0.6
Singh RB	1995	Morababad	8.55 ± 2.3
Begom TR	1995	Trivandrum	12.65 ± 1.5
Ramchandran	2001	Chennai 3.9	
Mohan V	2001	Chennai	11
Gupta R	2002	Jaipur	7.30
RURAL POPULATION			
Dewan BD	1974	Haryana	2.06 ± 0.4
Jajoo UN	1988	Vidarbha	1.69 ± 0.3
Kutty VR	1993	Kerala	7.43 ± 0.8
Wander GS	1994	Punjab	3.09 ± 0.5
Gupta R	1994	Rajasthan	3.53 ± 0.3
Singh RB	1995	U.P	3.09 ± 1.4

Gupta OP, Phatak S. Int. J. Diab. Dev. Count., 2003

Type-2 DM) which involves in disrupting the insulin signaling cascade and interferes with movement of glucose transporter–4 (GLUT-4) from an intracellular compartment to muscle cell surface.[10]

CORONARY ARTERY DISEASE (CAD)

Over the decades, there has ben a phenomenal rise in the incidence of CAD in India. The prevalence of CAD in urban and rural population of India as observed by various investigators since 1960 are presented in Table 5.[11] The diagnosis of CAD was done in these studies on clinical basis with the help of ECG. In the urban population there has been a steady increase in the prevalence of CAD from 1.05% to 7.3% on an average while it was as high as 11% in New Delhi and 12.6% in Trivandrum respectively, suggesting an epidemic-like situation in these places. However the change in profile of CAD in rural areas has not been that significant (Table 5).The quantum rise in the prevalence of CAD in urban-India is very likely due to changes in lifestyle, neo-affluence and changes in food habits. Besides stress and strain of urban life, the changes in the content of food viz. high lipid, salt with less of fibre and green vegetable intake could be one of the major determinants. The biochemical marker is the ensuing dyslipidemia in them.[6]

Study on mortality profile in patients with CAD from different Asian countries had revealed that the prevalence was highest

Table 6: CAD mortality in Asian countries (/100,000 population)

Country	1992
China	
Urban (M, F)	90,61
Rural (M, F)	45,31
Hong Kong (M, F)	55,33
India (Bombay)	158
Indonesia	60
Malaysia(West)	60
Philippines	32
Singapore (M, F)	154, 84
Taiwan (M, F)	35
Thailand	56

Chandalia HB, Lipid India,1996.

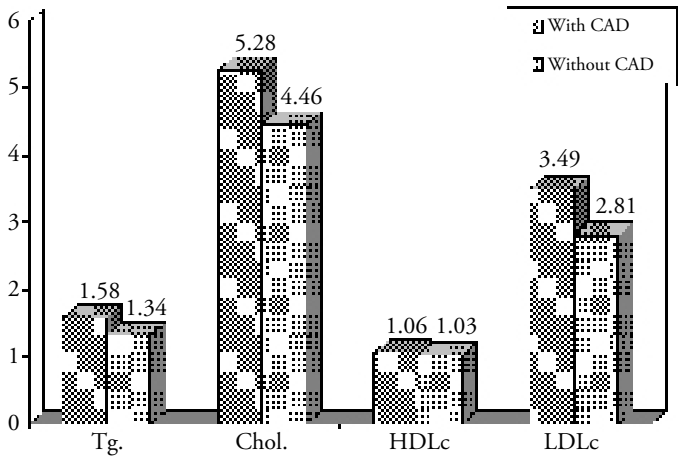

Fig. 5: Lipid Profile In Subjects With And Without Cad, Chennai "CUPS No.5" (mMol/L)
Mohan, Shanthi Rani & Premalatha, Jr. Amer. Coll.Card.,2001

amongst Indians as compared to people of Chinese origin, Indonesians and Malaysians (Table 6).[12] Premier study done by us had shown HDLc was lower and LDLc higher in non-diabetics with CAD while such dyslipidaemia was not obvious in diabetics with CAD.[13] As reported by us, more than decades ago, Tg levels were much higher in diabetics with CAD. Recent studies from Chennai "CUPS NO.5" revealed no difference in HDL values amongst subjects with or without CAD (Fig. 5).[14] Hospital-based studies from Patna also did not reveal any statistical difference in mean lipid levels in patients with CAD and controls (Fig. 6).[15] The conventional dyslipidemia of low HDL and high LDL is probably not the significant cause behind higher prevalence of CAD in Indians.

Further data from studies using coronary angiography as a tool to diagnose CAD done at different centres revealed that higher

Table 7 : Lipid and Lipoprotein levels in angiographically proved CAD and controls, Delhi and Vellore

Sub	Tc		LDLc		HDLc		LDL/HDLc		VLDLc		Tg	
	Del.	Vell.	Del.	Vell.	Del.	Vell.	Del.	Vell.	Del.	Vell.	Del.	Vell.
Patients	211	206.72	117	124.14	43.5	36.43	2.6	X	49.7	X	155	193.3
Controls	186	180.47	88	107.5	42.1	37.98	2.2	X	56.1	X	167	155.19

Del.-Delhi, Chopra, Lipid India,'99; Vell.-Vellore, Krishnaswami S, Lipid India,'96

Table 8: Prevalence of CAD amongst Diabetics, In India

Author	Year	Place	Prevalence of CAD (%)	
ICMR*	1984-87	Multicentric	8.1%	Males
			4.7%	Female
Ramchandram A	1998	Chennai	14.2% (3.9+10.3%)	
Mohan V	2001	Chennai	21.4%	
PODIS**	2001	Multicentric	4.5%	
Gupta PB	2001	Surat	19%	
Gupta S	2001	Nagpur	33.5%	Males
			21.5%	Females
Phatak SR	2002	Ahmedabad	20.2%	Males
			26.1%	Females

** ICMR – Indian Council of Medical Research ** PODIS – Prevalence of Diabetes in India Study*

triglycerides with marginally raised LDLc where associated dyslipidemia in patients from South India, whereas increase in total cholesterol and LDLc was common in those from North India (Table 7).[16,17] This again reflects the influence of dietary habits on lipid parameters as there is visible difference in dietary practices in these populations.

CAD amongst patients with DM

Now focusing on prevalence of CAD amongst diabetics in India, starting with the data of the multicentric study conducted by ICMR (1984-87) to recent publication from Ahmedabad, there has been substantial rise in the prevalence of CAD from 5.8% to 20-30% amongst diabetics over the period of time (Table 8).[11] This is an alarming situation and needs introspection with reference to the quantum increase in prevalence as well as risk factors.

Studies done by us in patients with established acute myocardial infarction (AMI) with or without diabetes and publication from Bangalore on diabetics with CAD showed serum Tg levels to be higher in the diabetic group whereas other lipid fractions were nearly similar and not significantly elevated as would have been expected Table 9.[18,19] The diabetic state per se is the major determinant for developing CAD amongst diabetics and thus the American Heart Association has correctly conferred that DM is coronary equivalent and should be treated as aggressively as non-diabetics with atherogenic dyslipidemias.

Furthermore, studies done on siblings of patients with CAD showed existing dyslipidemia in the siblings as compared to healthy controls (Fig. 7).[20] From the latter study it was observed that risk factors for CAD were more frequently met in the siblings of patients with CAD from a very early age. Both in age groups of 0-19 and 20-59 years the levels of serum Tg, LDL cholesterol and VLDL cholesterol were higher as compared to young controls of the corresponding age group. The study pointed to the fact that even at the age of 19 years a person from the family of CAD should be screened for lipid profile and primary prevention instituted at this stage.

Such dyslipidaemia casts its shadow much before the event manifests and so can be used as a marker for both detection and prevention of CAD in vulnerable population.

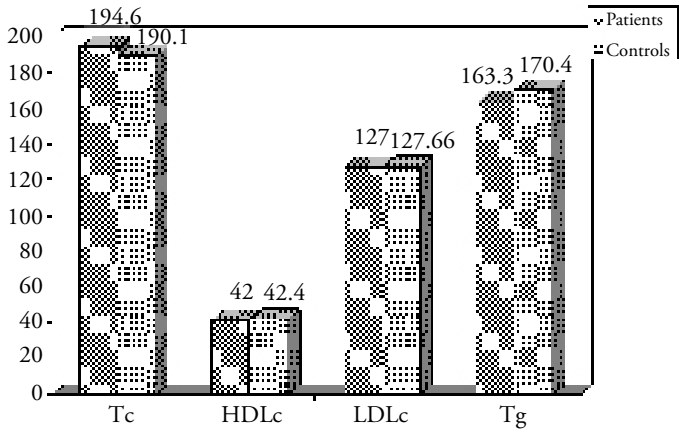

Fig. 6: Mean Lipid levels in patients with CAD and controls, Patna in mg/dl
Thakur, Vijay Achari, Lipid India,'98

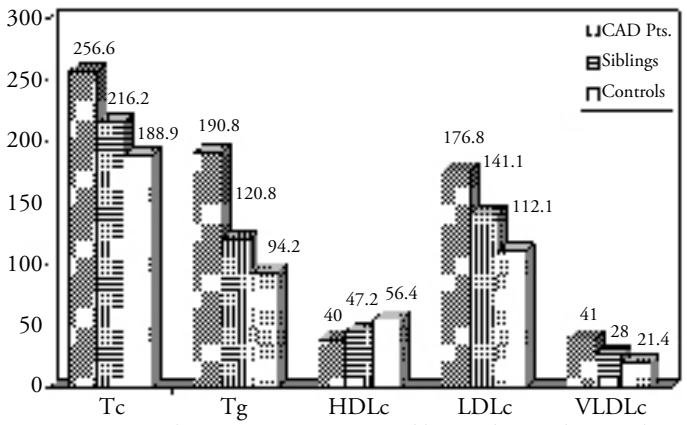

Fig. 7: Mean Lipid Pattern in CAD Patients, Siblings and Controls, Cuttack (mg%)
Dalai R.K. & Das S, Lipid India '98

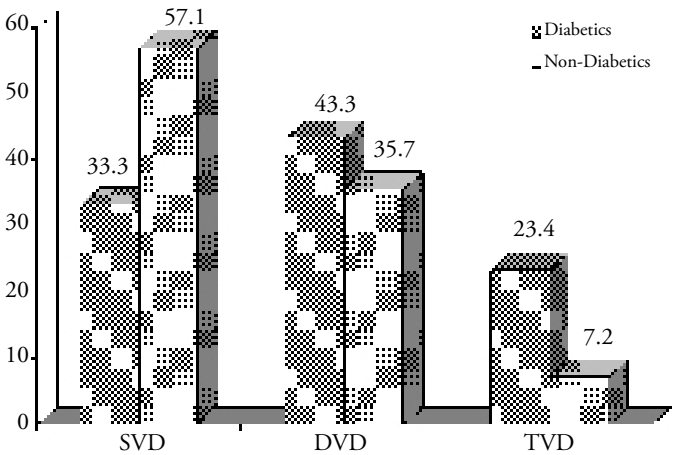

Fig. 8: Quantum of Coronary Vessel involvement by Angiography, Cuttack (in percent)
Patnaik U.K., Compl. in Diab. Indian Scenario, 2000 (Ed. Das S)

Coronary angiography is one of the most reliable procedures adopted to diagnose CAD. Angiographic data on Indian patients with suspected CAD had revealed that triple vessel disease (TVD) was much higher in diabetics as compared to non-diabetics, to be followed by double vessel disease (DVD) while single vessel disease (SVD) was more common in non-diabetics (Fig. 8).[21]

Table 9 : Lipid profile in patients with CAD –Diabetics and Non-Diabetics, Cuttack and Banglore (mg%)

Sub	Tc		HDLc		LDLc		VLDLc		Tg	
	Ctc.	Bang.	Ctc.	Bang.	Ctc.	Bang.	Ctc.	Bang	Ctc.	Bang.
CAD -Diabetics	192.2	194.1	39.2	40.2	118.3	105.9	34.7	48.4	150.6	209.4
CAD-Non-diabetics	197.1	200.4	41.5	44.9	116.2	128	39.3	27.5	120.3	137.6

Ctc.-Cuttack : Das S. and Panda R. , Jr. Diab. Asso.India, 1998

Bang.-Bangalore : Pitchumani, Dharmalingam, Deva & Prasanna Kumar, Lipid India,'98.

Table 10 : Coronary Angiographic Profile in Diabetics and Non Diabetics (n=147 in each group) in %.

Sub	Left main	SVD	DVD	TVD
Diabetics	6.1	11.6	42.9	39.4
Non-Diabetics	1.3	33.4	34.6	30.7

Mishra, Routray, Das, Behera, Satpathy & Pattnaik, Cuttack, 2003

This is corroborative of Western observations that diabetics have more extensive involvement of coronary artery (CA) as compared to non-diabetics.[22] To further elucidate the extensiveness of atherosclerotic involvement of coronary arteries, in diabetics and non-diabetics, in the same cohort and to analyze the existing dyslipidaemia in such patients, a prospective study was undertaken at our centre. The coronary angiogram was analysed as per the criteria laid down by American Heart Association with regards to segments (fifteen in toto) and severity of occlusion (Grade 0-4). The gross angiographic profile is given in Table-10 where it is obvious that occlusion of left main coronary artery DVD and TVD were more in diabetics whereas SVD was higher in non-diabetics respectively. The extensiveness of involvement and degree of occlusion was categorized as per Ledru et al as described below.[23]

Coronary score: No. of coronary arteries exhibiting stenosis > 75%.

Extent score: No. of segments exhibiting lesions ≥ Grade - 1 (adjusted to 15 coronary segments)

Severity score: Average grade of stenosed coronary segments

Atherosclerotic score: Calculated as average severity of all analyzable segments.

The degree of atherosclerosis of coronary arteries and corresponding mean lipid levels are presented in Table-11. The diabetics had statistically significant higher values for all the above four scores suggesting both extensive and higher grade of occlusive CAD. The associated dyslipidemia was lower HDL cholesterol with higher levels of serum triglycerides.

The crux of the issue is now well known that majority of diabetics have dyslipidemias. Central characteristics of such dyslipidemias are increase in triglyceride levels, more of triglyceride-rich VLDL and lower HDL levels in those with overt CAD. LDL cholesterol levels may not be raised as compared to non-diabetics but could have more of small dense LDL with glycated ApoB100 which is highly atherogenic. This lipid triad confers a risk for cardiovascular disease that equals or exceeds the risk conferred by LDLc levels of 150-220mg/dl. Therefore diabetic dyslipidaemia even without established CAD should be treated as aggressively as non-diabetics with CAD. Hypertriglyceridaemia and lower

Table 11 : Degree of Atherosclerotic Involvement of CA and Corresponding Lipid levels (Mean and S.D.)

		Diabetics	Non-diabetics	P value
Coronary score	:	0.91 (0.63)	0.43 (0.39)	<0.001
Extent score	:	4.91 (3.1)	2.3 (1.81)	<0.001
Severity score	:	1.85 (0.41)	1.2 (0.32)	<0.001
Atherosclerotic score	:	0.52 (0.31)	0.21 (0.26)	<0.001
Lipid values (mMol/L)				
Total cholesterol	:	4.81 (0.31)	4.70 (0.29)	N.S.
HDL cholesterol	:	0.84 (0.13)	1.12 (0.15)	<0.001
LDL cholesterol	:	3.29 (0.19)	3.23 (0.22)	N.S.
Triglycerides	:	2.98 (0.07)	2.41 (0.06)	<0.001

Mishra, Routray, Das, Behera, Satpathy & Patnaik , Cuttack, 2003

HDLc levels may preceed development of overt Type2 DM/ insulin resistant state and so can be used as markers.

Diabetes mellitus, Type 2 in particular, is a progressive macrovascular disease with universally established excessive predilection for coronary arteries irrespective of race, ethnicity, gender or geography. Salient biochemical markers for this vasculopathy are chronic hyperglycaemia and non-HDL dyslipidemia.

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