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Chapter 8

HDL, apo B/apo A1 ratio, Diabetes Mellitus and Cardiovascular Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/56476

1. Introduction

In India, diabetes is not an epidemic anymore but has turned into a pandemic. According to the International Journal of Diabetes in developing Countries India is labelled as the diabetic capital of the world. The International Diabetes Federation estimates that the number of diabetic patients in India more than doubled from 19 million in 1995 to 40.9 million in 2007. It is projected to increase to 69.9 million by 2025.Type II diabetes and its complications constitute a major worldwide public health problem. Patients with type II diabetes have 2 - 4 times higher risk of experiencing cardiovascular disease(CVD) than adults without diabetes (Fox et al. 2004; Laakso,2001) and their relative risk for CVD is about twice as high(Liu et al. 2005), much of which may be preventable with appropriate treatment of dyslipidemia.

The elevated CVD risk affecting patients with Type II diabetes may be attributed to a combined dyslipidemia characterized by elevated triglycerides, elevated triglyceride rich remnant lipoproteins(TGRLP), elevated apolipoprotein (apo) B and low levels of HDL cholesterol, with a predominance of small, dense low density lipoprotein(LDL) particles amid relatively normal LDL Cholesterol levels (Chih-yuan wang et al. 2004).

The association of low plasma levels of high-density lipoprotein (HDL) with states of impaired glucose metabolism and type 2 diabetes mellitus is well established, but the mechanistic links remain to be fully elucidated. Recent data suggests that HDL directly influences glucose metabolism through multiple mechanisms. (Drew et al., 2012).

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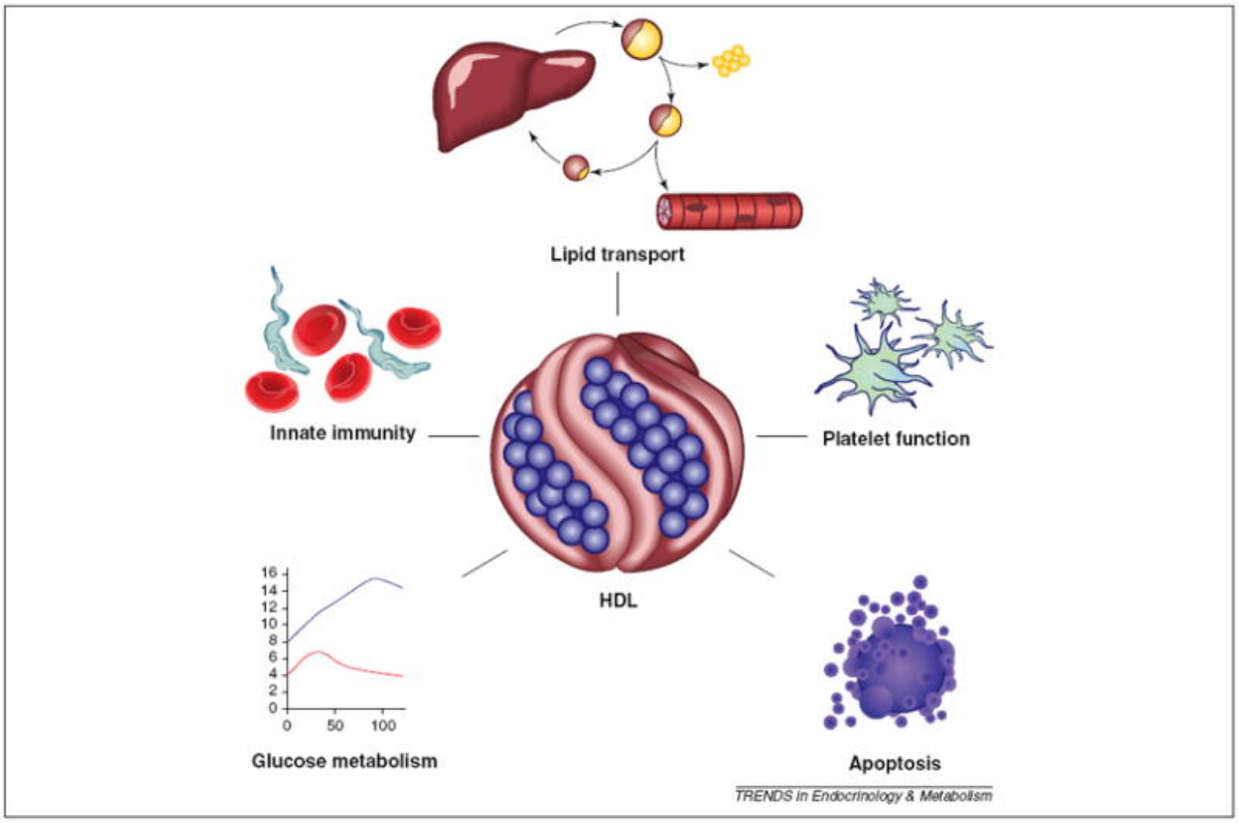


Figure 1. High density Lipoprotein- Main Functions

2. Materials and methods

Study was done on 109 subjects aged 40-75 years from HIGH-Tech Hospital, Cardiology Unit, Vinayaka Missions, Salem, India. Subjects were selected by simple random technique from the group of patients who were referred to the department of cardiology for coronary angiography and who met the inclusion criteria set out above. From all patients a written informed consent was obtained All data collected during a regular visit to the hospital included, anthropometric parameters including weight, height and waist circumference were measured using standard protocols Also a completed questionnaire regarding their medical history, coronary artery disease(CAD) and its complications, hypertension, age of onset of diabetes mellitus, chronic diseases other than CAD and diabetes mellitus, medications, socio-economic factors, dietary habits as well as the family medical history.

3. Grouping of patients

The patients were sub divided into two groups

1. Group I comprised of 52 coronary artery disease patients without type 2 diabetes(T2D) mellitus.(CAD WDM)

http://dx.doi.org/10.5772/56476

2. Group II comprised 57 coronary artery disease patients with type 2 diabetes mellitus(T2D).(CAD WNDM).
3. Control Subjects comprised of 71 age-matched healthy subjects.

PARAMETERS	CONTROL (N=71)	CAD WNDM(N=52)	CAD WDM (N=57)
Age(Years)	52.42 ±6.7	55.4 ± 5.657	52 ±9.5
BMI (kg/m2)	20.05±0.95	27.82 ± 3.359[a]	32.05 ± 0.33[a,b]
SBP (mmHg)	116.14±10.25	140.9 ± 16.97[a]	147.5 ± 28.28[a,b]
DBP (mmHg)	77.14±7.8	88.92± 14.14[a]	95.78 ± 21.21[a,b]

BMI: Body mass index,, SBP: Systolic blood pressure, DBP: diastolic blood pressure. Data are expressed as (mean ± S.D).All comparisons by t- test. Statistical analysis was done by Anova (post hoc test : Bonferroni.[a]: Statistically significant from control group at $p<0.05$; [b]:Statistically significant from CAD patients without type 2 DM at $p<0.05$..

Table 1. Demographic details of study subjects.

4. Coronary angiography and grading of CAD patients

The coronary angiogram was assessed by two cardiologists who were unaware of the current study. Selective coronary angiography was performed with Judkins technique in all patients. The severity of coronary atherosclerosis was estimated by calculating the coronary atherosclerotic score (CAS). Jenkins et al.,1978., based on the number of stenotic coronary artery segments, the degree of their lumen stenosis. The extend and severity of the CAD was assessed by assigning points to each lesion as follows: less than 50% stenosis of the luminal diameter 1;50-74% stenosis,2;75-100%, 3.The point for each lesion in coronary arteries including proximal,medial and distal segments were summed and a cumulative CAS obtained. The severity of CAD was further classified as one, two, three vessel disease according to the number of stenotic coronary artery in the three major vessels.Significant CAD was defined as more than 50% stenosis in at least one coronary artery segment.(Fievet. et al.,1991).(Table.2-given below)

GRADE I	<50% stenosis with single vessel disease .(mild)
GRADE II	50-74% stenosis with double vessel disease.(moderate)
GRADE III	75-100% stenosis with triple vessel disease.(severe).

Table 2. Add caption

Anthropometric measurements like Body Mass Index (BMI), Waist Circumference (WC) and Blood Pressure(BP) were done by standard procedures.

5. Measurement of Mean Arterial Pressure (MAP)

MAP = [(2 x diastolic) +systolic] / 3 Diastole counts twice as much as systole because 2/3 of the cardiac cycle is spent in diastole (Zheng et al 2008)

5.1. Biochemical estimations

Routine biochemical investigations were done using serum and plasma. Serum was used for the determination of insulin and blood glucose on the same day of sample collection. Remaining serum and plasma were stored at -20^{0}C for analyzing other parameters.

5.2. Determination of Homeostasis Model Assessment (HOMA) — IR

The Homeostasis Model Assessment (HOMA) estimates steady state beta cell function (%B) and insulin sensitivity (%S), as percentages of a normal reference population. (HOMA-IR) is used in clinical diabetes research to measure insulin sensitivity. The calculation helps correct for the effects of fasting hyperglycemia (high blood sugar). (Levy JC *et al.,*1998.)

HOMA IR = (FBS mmol/L)X(Fasting Insulin μU/ml.)/22.5

5.3. Biochemical studies

Serum samples taken were subjected to estimations of glucose, Glycated hemoglobin, insulin, lipid profile including apo A 1 and apo B. by standard automated methods

5.4. Result

Study was done on 109 subjects who were selected by simple random technique from the group of patients referred to the department of cardiology for coronary angiography and who met the inclusion criteria. Study subjects were 39% control subjects(n=71), 29% coronary artery disease patients without type 2 DM (CAD WNDM, n=52) and 32 % were coronary artery disease patients with type 2 DM (CAD WDM, n=57). Among the control subjects 65% were males and 35% were female. Among the CAD WNDM patients 88% were males and 12% were female and in CAD WDM 82% were male and 18% were female.The base line characteristics of study subjects are shown in Table 1. Age of the study subjects were from 40 to 75 years. The mean age of onset of CAD in the group with type 2 DM was 52 ± 4.5 when compared to 59± 6.4 in CAD WNDM. 79% of CAD WDM subjects and 48% of CAD WNDM subjects were of the age group 51-60 years. The mean duration of diabetes in CAD WDM was 6.2±2.5. Statistically no significant difference in SBP and DBP was observed in CAD WDM when compared to CAD WNDM. Significant difference in BMI was observed in the CAD WDM subjects when compared to CAD WNDM and control (with $p<0.001$).The mean BMI level was 32.05 ± 0.33 in CAD WDM, 27.82 ± 3.359 in CAD WNDM and 20.05±0.95 in the control group respectively.

The occurrence of CAD was computed in relation to age, BMI, and hypertension. (Table. 3.below)

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Variables		CAD WNDM N(%)	CAD WDM N(%)	P value
Age (years)	40-50	15 (29 %)	1 (2%)	0.0001
	51-60	25 (48 %)	45(79%)	
	61-70	12 (23%)	11(19 %)	
BMI (kg/m^2)	18.5-24.9	1(2 %)	6(11 %)	0.0004
	25. - 30	28(54 %)	12(21 %)	
	>30	23(44 %)	39(68%)	
Smoking	Yes	13(25%)	9(16 %)	0.6807
	No	39(75 %)	48(84 %)	
Alcoholism	Yes	5(10 %)	11(19 %)	0.2445
	No	47(90 %)	46(81 %)	
SBP	<140mmofHg	2(4 %)	4 (7 %)	0.6807
	>140m of Hg	50(96 %)	53 (93 %)	

BMI: Body mass index, SBP: Systolic blood pressure Statistical analysis was done by Chi square test. Statistically significant from CAD patients without type 2 DM at p<0.001.

Table 3. Relation of Coronary Artery Disease (CAD) to different variables.

Among the study subjects 2% of CAD WNDM had BMI in the range of 18.5-24.9 kg/m^2 compared to 11% in CAD WDM. 54% of CAD WNDM had BMI in the range of 25-30 kg/m^2,when compared to 21% in CAD WDM. Also 44% of CAD WNDM had BMI value >30 kg/m^{2}when compared to 68% in CAD WDM.

CADsubjects	Severity of CAD		
	Grade I	Grade II	Grade III
CAD WNDM	24(46%)	15(29%)	13(25%)
CAD WDM	9(16%)	12(21%)	36(63%)

CAD WDM: coronary artery disease with diabetes. CAD WNDM coronary artery disease without diabetes.. Statistical analysis was done by Chi square test.

Table 4. Severity of CAD among the study subjects.

According to the percentage of stenosis and involvement of coronary vessels, severity of CAD was assessed and classified as Grade I(mild), Grade II(Moderate) and Grade III(Severe). Analysis on frequency of distribution has revealed that severity was significantly high in CAD WDM. (Table : 4) The percentage of patients with severe coronary artery disease-Grade III was 63% in CAD WDM Vs 25 % in CAD WN DM(p<0.001). 21% of CAD WDM patients had Grade

II (moderate) compared to 29% in CAD WNDM.16% of CAD WDM had Grade I (mild) disease compared to 46% in CAD WNDM. A significantly high percentage of multivessel atherosclerosis was observed in CAD WDM when compared to CAD WNDM.

PARAMETERS	CONTROL(N=71)	CAD WNDM (N=52)	CAD WDM (N=57)
FBS (mg/dL)	85.04±6.20	85.65 ± 5.66	147.05 ± 30.40[a,b]
PPBS (mg/dL)	101.81±5.10	109.4± 7.07	403.00 ± 53.70[a,b]
Insulin (μIU/ml)	8.41±0.33	8.76 ± 5.37	22.93 ± 3.25[a,b]
HOMA - IR	1.77±0.33	1.80± 0.45	9.70 ± 1.10 [a,b]

Table 5. Serum Fasting Blood glucose, Insulin and HOMA-IR of study subjects

Data are expressed as (mean ± S.D). Statistical analysis was done by Anova (post hoc test : Bonferroni) [a]: Statistically significant from control group at $p<0.05$; [b]:Statistically significant from CAD patients without type 2 DM ($p<0.05$.).

The mean fasting blood glucose of the normal controls, CAD WNDM and CAD WDM subjects were 85.04±6.2, 85.65 ± 5.657 and 147.05 ± 30.4 respectively. There was significant ($p <0.05$) increase in mean Fasting blood glucose in CAD WDM when compared to CAD WNDM and control. The mean Post prandial blood glucose of the normal controls, CAD WNDM and CAD WDM were 101.81±5.1, 109.4± 7.071and 403 ± 53.7 respectively. The mean Post Prandial blood glucose in CAD WDM was significantly high ($p<0.05$) when compared to CAD WNDM and control. The mean insulin level among the three groups were 8.41±0.334, 8.76 ± 5.37 and 22.93 ± 3.25 respectively. The CAD WDM patients had significantly high insulin level ($p<0.05$) when compared to CAD WNDM and control. The mean HOMA IR of controls, CAD WNDM and CAD WDM were 1.77±0.33, 1.8± 0.445 and 9.7 ± 1.1 respectively. The CAD WDM patients had significantly high IR level ($p<0.05$) when compared to CAD WNDM and control.(Table.5.)

One of the basic factor which was found to be significantly elevated in CAD WDM group when compared to other two groups was Insulin resistance – which is the underlying defect in >90% of patients with type 2 diabetes mellitus.

IR	SEVERITY OF CAD		
Grade I	Grade II	Grade III	
<1.6	30(58%)	18(35%)	4(8%)
>1.6	9(16%)	12(21%)	36(69%)

Table 6. IR and Severity of CAD among the CAD subjects

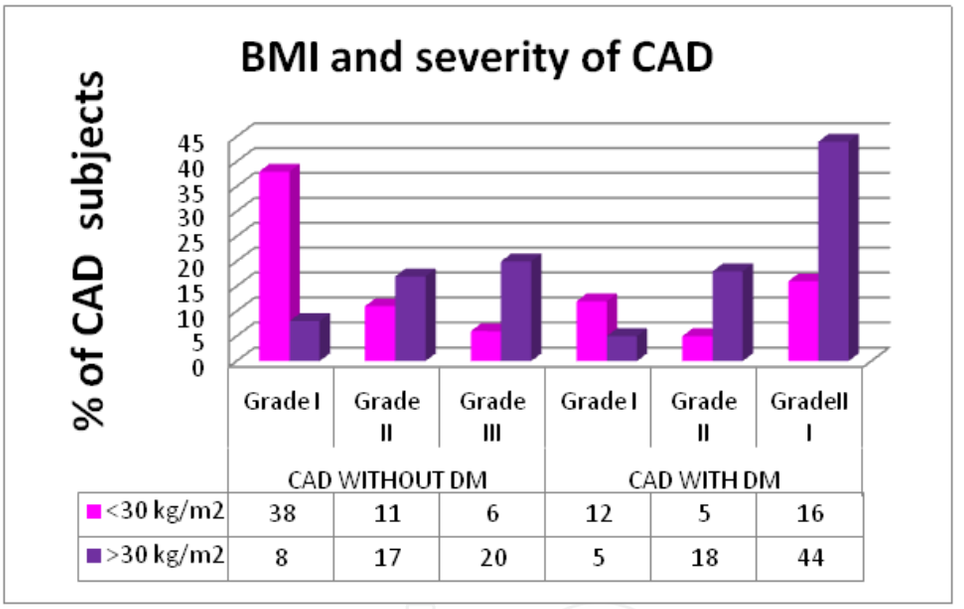
The median value 1.6 was considered as Cut off values in our study.IR: Insulin resistance. Statistical analysis was done by Analysis was done by Chi square test. (Gary *et al.*, 1997)

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Analysis on frequency of distribution has revealed that severity was significantly high in CAD subjects with IR >1.6. (Table 6) The percentage of patients with IR >1.6 and Grade III-coronary artery disease - was 69%, Grade II coronary artery disease - was 21% and Grade I -coronary artery disease- was 16% respectively. The percentage of subjects with IR <1.6 and Grade III -severity- was 8%, Grade II coronary artery disease - was 35% and Grade I -coronary artery disease- was 30% respectively.

6. Body Mass Index (BMI)

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. The WHO defines a BMI greater than or equal to 25 is overweight and a BMI greater than or equal to 30 is obesity(World Health Organization,2007).



BMI: Body mass index. The subjects were graded into I,II,III based on severity Statistical analysis was done by Chi square test.

Table 7. BMI and severity of CAD among CAD subjects.

Analysis on frequency of distribution has revealed that severity was significantly high in CAD subjects with BMI >30kg/m^2.The percentage of CAD WDM patients with BMI>30 kg/m^2 and Grade III-coronary artery disease - was 44%, Grade II coronary artery disease - was 18% and Grade I -coronary artery disease- was 5% respectively. The percentage of CAD WDM subjects with BMI<30 kg/m^2 and Grade III -severity- was 16%, Grade II coronary artery disease - was 5% and Grade I -coronary artery disease- was 12% respectively.(Table.7.)

The percentage of CAD WNDM patients with BMI>30 kg/m^2 and Grade III-coronary artery disease - was 20%, Grade II coronary artery disease - was 17% and Grade I -coronary artery

disease- was 8% respectively. The percentage of CAD WDM subjects with BMI<30 kg/m^2 and Grade III -severity- was 6%, Grade II coronary artery disease - was 11% and Grade I -coronary artery disease- was 38% respectively.

7. Lipid parameters

7.1. Total cholesterol, triglycerides, HDL-C, LDL-C and VLDL

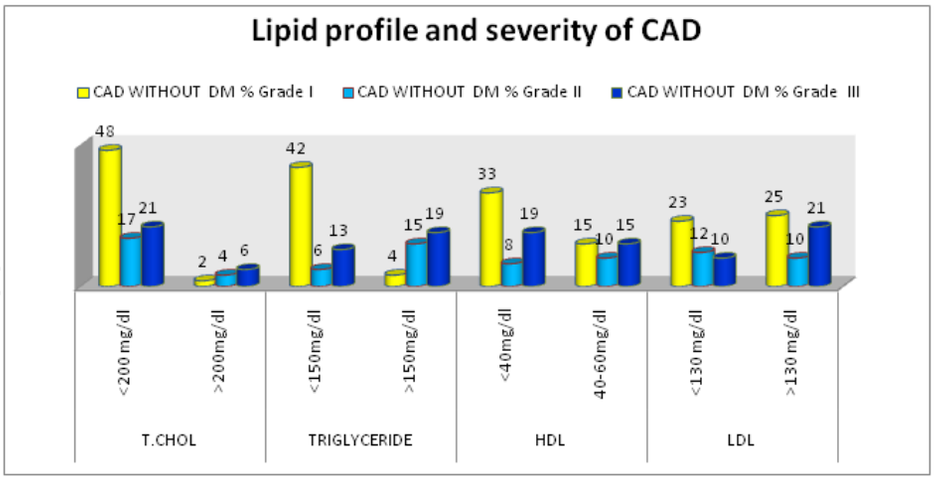
CAD WDM subjects were 169±3.0, 182.2 ± 8.485 and 197.49 ± 7.77 respectively. The level of total cholesterol was significantly high in CAD WDM and CAD WNDM) when compared to control. But no difference was observed between the CAD WDM and CAD WNDM. The triglyceride level was I21.35±11.28, 131.6 ± 6.4 and 157.5 ± 8.5 in normal controls, CAD WNDM and CAD WDM subjects respectively.The triglyceride level in CAD WDM was significantly high ($p<0.05$) when compared to CAD WNDM. The mean HDL cholesterol level of the normal controls, CAD WNDM and CAD WDM subjects were 41.48±5.59, 38.4 ± 2.07 and 35.05 ±1.44 respectively.Also the HDL level in CAD WDM was found to be low when compared to normal controls but was not significant in CAD WDM Vs CAD WNDM. The LDL-cholesterol level was 104.48±33.5, 129.50 ± 8.8 and 144.25 ± 8.2 respectively in normal controls, CAD WNDM and CAD WDM subjects. LDL level was significantly($p<0.05$) high in CAD WDM when compared to CAD WNDM and control subjects. The mean VLDL level of the normal controls, CAD WNDM and CAD WDM subjects were 24.27±2.26, 26.3±13.01 and 31.5 ± 9.617 respectively.(Table.8.)

PARAMETERS	CONTROL(N=71)	CAD WDM(N= 52)	CAD WNDM(N=57)
Total cholesterol (mg/dL)	169.00±8.00	182.20 ± 8.49[a]	197.49 ± 7.77[a,]
Serum Triglycerides (mg/dL)	I21.35±11.28	131.60 ± 6.40	157.50 ± 8.50[a,b]
HDL cholesterol (mg/dL)	41.48±5.59	38.40 ± 2.07[a]	35.05 ± 1.44[a,b]
LDL cholesterol (mg/dL)	104.48±33.50	129.50 ± 8.80 [a]	144.25 ± 8.20[a,b]
VLDL (mg/dL)	24.27±2.26	26.3± 13.01	31.5 ± 9.62[a]
ApoA1(g/L)	1.39±0.31	1.187 ± 0.21	0.873 ± 0.07[a,b]
ApoB (g/L)	0.79±0.12	1.64±0.62[a]	1.66±1.10[a,b]
ApoB/A1 ratio	0.59±0.17	2.04±0.84	2.069±1.23[a]

Table 8. Lipid profile and Apolipoproteins of study subjects.

Data are expressed as (mean ± S.D). Statistical analysis was done by Anova analysis (post hoc test : Bonferroni).a: Statistically significant from Control group at $p<0.05$; b: Statistically significant from CAD WNDM at $p<0.05$. HDL-high density lipoprotein; LDL-low density lipoprotein; VLDL-very low density lipoprotein

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Statistical Analysis was done by Chi Square Test

Figure 2. Lipid profile and severity of CAD in non diabetic subjects.

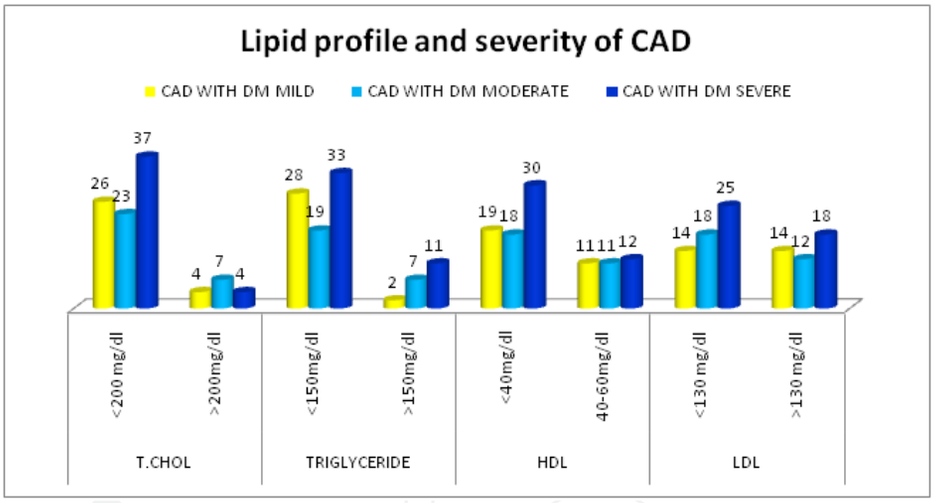


Figure 3. Lipid profile and severity of CAD in Diabetic subjects.

The CAD patients without diabetes and with total cholesterol level <200 mg/dl were 21% with grade III stenosis, 18% with grade II and 48% with grade I stenosis. The CAD subjects without diabetes and Total cholesterol level >200 mg/dl had 6% with grade III stenosis, 4% with grade II and 2% with grade I stenosis. Among the CAD without diabetes subjects with total triglyceride level <150 mg/dl 13% subjects had grade III stenosis, 6% had grade II and 42% had grade I stenosis. Compared to 19% subjects with grade III stenosis, 15% with grade II and 4% with grade I stenosis and triglyceride level >150 mg/dl. The CAD subjects without diabetes and HDL level <40 mg/dl had 19% with grade III stenosis, 8% with grade II and 33% with grade I stenosis. The CAD subjects without diabetes and HDL >40 mg/dl had 15% with grade III stenosis, 10% with grade II and 15% with grade I stenosis. Among the CAD without diabetes

subjects with LDL level <130 mg/dl 10% subjects had grade III stenosis, 12% had grade II and 23% had grade I stenosis,compared to 21% subjects with grade III stenosis, 10% with grade II and 23% with grade I stenosis with LDL level >130 mg/dl.

Among the CAD with diabetes subjects with total cholesterol level <200 mg/dl 37% subjects had grade III stenosis, 7% had grade II and 4% had grade I stenosis. Among the CAD subjects with >200 mg/dl cholesterol level,4% of subjects had Grade III,7% had grade II and 4% had grade I stenosis.Among CAD with diabetes and triglyceride level <150 mg/dl 33% had grade III stenosis, 19% had grade II and 28% had grade I stenosis. Among CAD subjects with triglyceride level >150 mg/dl were found to have 11% of subjects with grade III,7% with grade II and 2% with grade I stenosis. Among the CAD with diabetes subjects with total HDL level <40 mg/dl 30% subjects had grade III stenosis, 18% had grade II and 19% had grade I stenosis. Among the CAD subjects with 40-60 mg/dl HDL level 12% of subjects had Grade III,11% had grade II and 11% had grade I stenosis.

The CAD subjects with diabetes and LDL level <130 mg/dl had 25% with grade III stenosis, 18% with grade II and 14% with grade I stenosis. The CAD subjects with diabetes and LDL level >130 mg/dl had 18% with grade III stenosis, 12% with grade II and 14% with grade I stenosis.

Lipid parameters	**IR IN CAD WITH DM**	
r value	**p value**	
T.Cholesterol (mg/dl)	-0.211	0.115
Triglyceride (mg/dl)	0.343	0.009**
HDL-C (mg/dl)	0.026	0.847
LDL-C (mg/dl)	-0.109	0.12
VLDL (mg/dl)	-0.357	0.006**

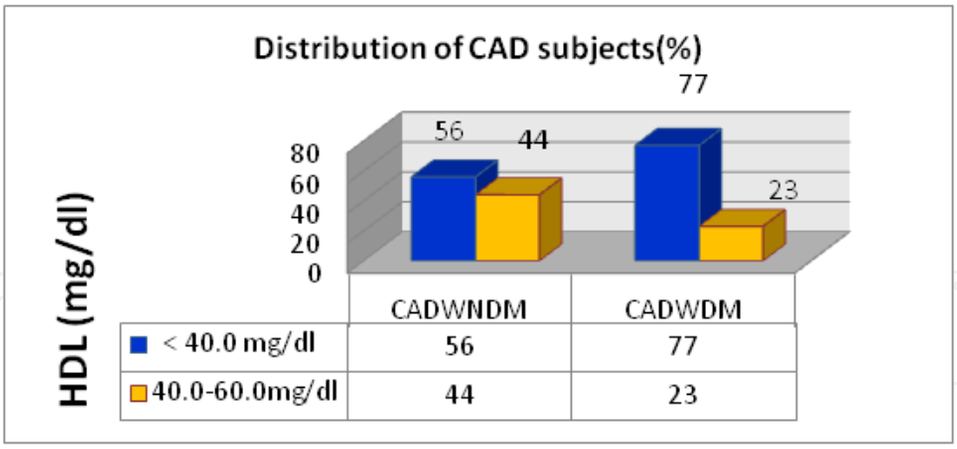
** significant at p<0.01 and * denoted significant at p<0.001. statistical analysis was done by Pearson correlation.

Table 9. Correlation analysis of Lipid profile with Insulin Resistance

Table.9.depicts the results of the Pearson correlation analysis between different variables in CAD patients. In CAD with type 2 diabetes population triglyceride showed significant association with IR (r=..343, p<0.01) and VLDL showed significant correlation with IR.(r=. 357,p<0.01).

In CAD WDM subjects 77% had HDL-C level less than 40 mg/dl when compared to 56% in CAD WNDM. In CAD WDM 23% had HDL-C level >40mg/dl when compared to 44% in CAD WNDM.The HDL-C level was found to be not significant between the CAD WDM and CAD WNDM.

http://dx.doi.org/10.5772/56476



CADWDN: Coronary artery disease patients with DM and CAD WNDM : Coronary artery disease patients without type 2 diabetes.. Statistical analysis was done by Anova(post hoc test : Bonferroni).

Table 10. HDL C level in CAD subjects

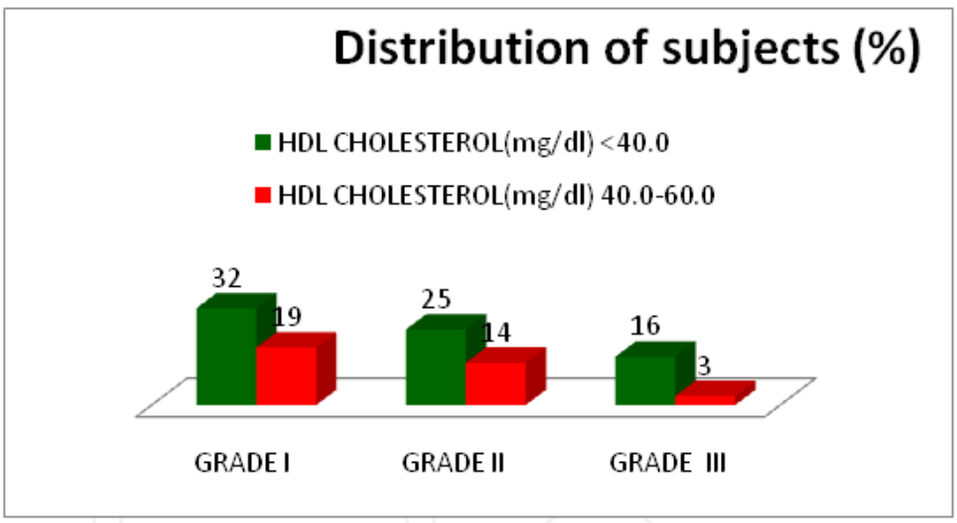
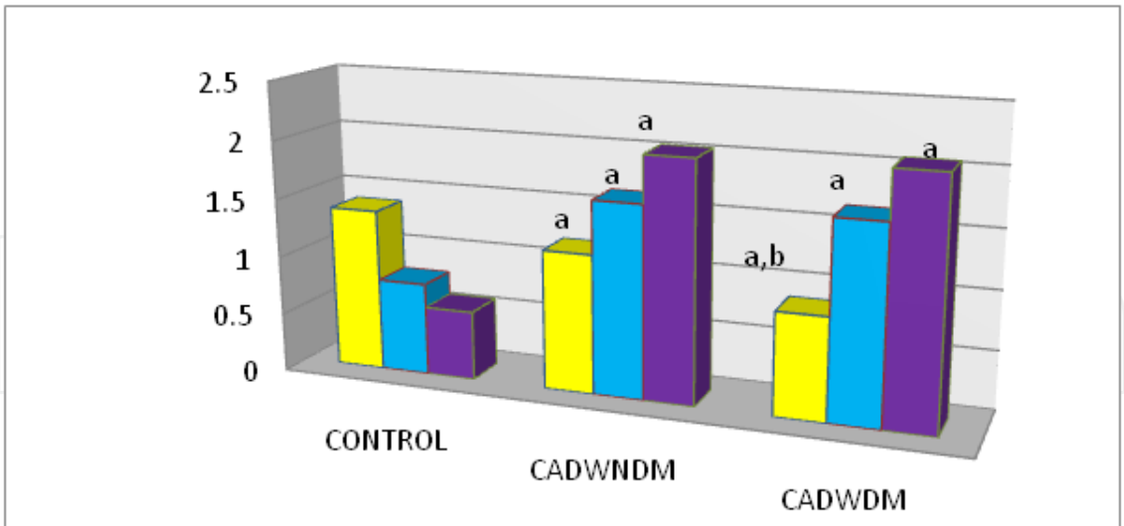


Figure 4. HDL –C among the CAD subjects based on severity of CAD.

The CAD subjects were graded into I,II,III based on severity. Statistical analysis was done by Chi square test.

The distribution of subjects based on HDL cholesterol level <40 mg/dl had shown that 32% had Grade I stenosis,25% had Grade II stenosis and 16% had Grade III stenosis.. Among the CAD subjects with HDL level 40-60 mg/dl 19% had grade I stenosis,14% had Grade II stenosis and 3% had Grade III stenosis.(Fig.4)

The mean ApoA1 level was 1.39±0.31, 1.187 ± 0.205 and 0.873 ± 0.007 in normal controls, CAD WNDM and CAD WDM subjects.ApoA1was found to be significant with $p<0.05$ in CAD WDM



	CONTROL	CADWNDM	CADWDM
ApoA1(g/L)	1.39	1.187	0.873
ApoB (g/L)	0.79	1.64	1.66

Figure 5. ApoA1,ApoB,and ApoB/A ratio in study subjects

compared to normal control. ApoB level was 0.79±0.12, 1.64± 0.621and for 1.66 ± 1.10 respectively in normal controls,

CAD WNDM and CAD WDM subjects. ApoB/A1 ratio in normal subjects in CAD WNDM and in CAD WDM was 0.59±0.173, 2.04 ± 0.84712 and 2.06 ± 0.84712 respectively. ApoB/A ratio was found to be significant at $p<0.05$ in CAD with diabetic subjects when compared to CAD with no diabetes and normal controls. (Fig.5)

Data are expressed as (mean ± S.D). a: significantly different from control group at $p<0.05$; b: significantly different from CAD patients without DM at $p<0.05$.. Statistical analysis was done by Anova analysis (post hoc test : Bonferroni)

Cut off values: ApoB/A1 ratio above 1.0 was considered to be at risk. (Benton *et al.,* 2005). Statistical analysis was done by chi square test.

In CAD WNDM 8% had grade I CAD and ApoB/A ratio less than 1.0 g/L when compared to 4% with grade I CAD in CAD WDM,4% of CAD WNDM had grade II CAD and ApoB/A ratio less than 1.0 g/L when compared to an equal 4% in CAD WDM. 4%of subjects had CAD WNDM and grade III when compared to5% in CAD WDM and grade III severity with an ApoB/A1 ratio < 1.0. In CAD WNDM 48%had ApoB/A ratio >1.0 and grade I CAD when compared to 14%in CAD WDM.15% of CAD WNDM had ApoB/A ratio >1.0and grade II CAD when compared to 28% in CAD WDM.21% of CAD WNDM subjects had ApoB/A ratio >1.0 and grade III CAD when compared to 49%in CAD WDM. (Fig.6)

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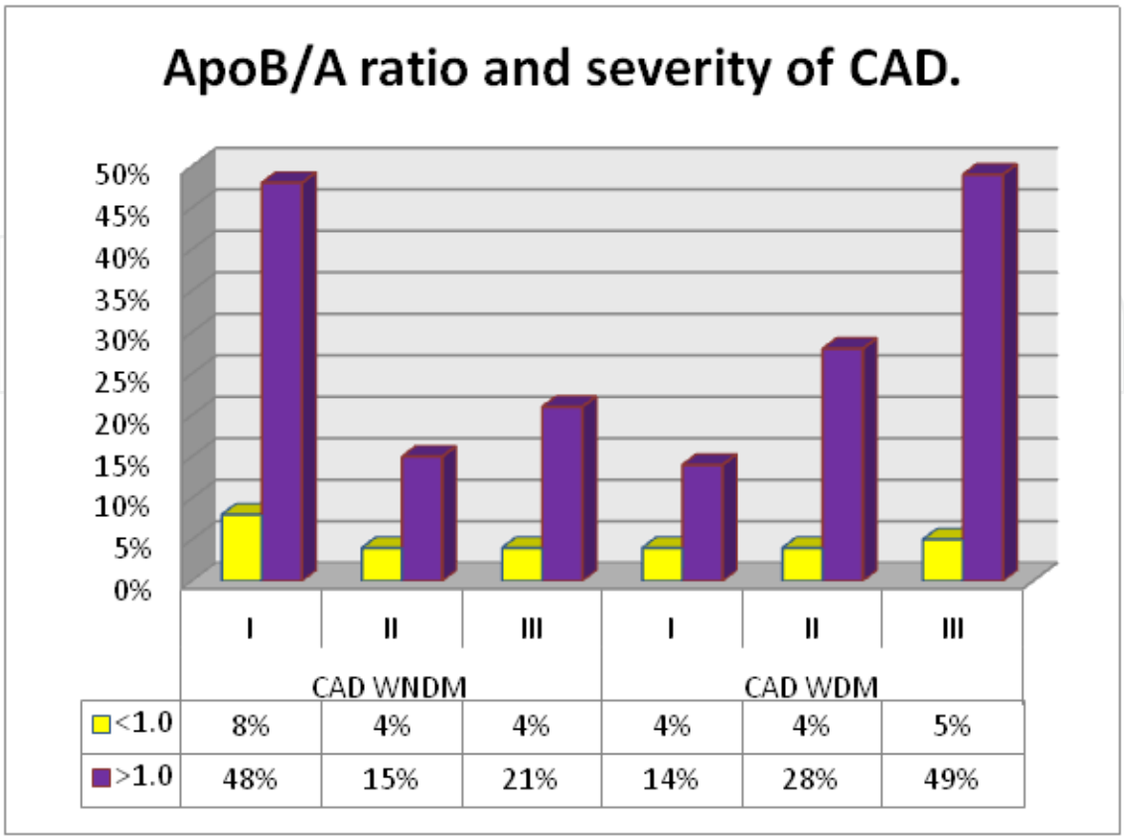


Figure 6. ApoB/Apo A1 ratio and Severity of CAD.

Apolipoproteins	IR IN CAD WDM	
	r value	p value
ApoA1**(g/L)**	.098	-.073
ApoB **(g/L)**	.467	.591
ApoB/A1 ratio	**-.413**	**.001****
Statistical Analysis was done by Pearson correlation		

Table 11. Correlation studies of Apoproteins with Insulin resistance in CAD subjects

Table 11 depicts the results of the Pearson correlation analysis between different variables in CAD patients.. In CAD with type 2 diabetes population,ApoB/A1 ratio showed negative correlation with IR (r,-..413, p,0.001).

Statistical analysis was done by Anova analysis (post hoc test : Bonferroni)

The level of Apo A1 was found to be significantly low (p <0.001) in CAD WDM compared to CAD WNDM.18% of CAD WDM patients had ApoA1 level >1g/L compared to 38% in CAD

CAD subjects	Apo A1(g/L)	
	<1.0	>1.0
CAD WN DM	**32(62%)**	**20(38%)**
CAD W DM	**47(82%)**	**10(18%)**

ApoA1 level of 1.0 g/L. was considered as cut off value

Table 12. Level of ApoA1 in CAD patients

WNDM. 82%of CAD WDM subjects had ApoA1 level <1g/L compared to 62 % in CAD WNDM. (Table.11)

Correlation analysis between ApoA1 and lipid profile in CAD WDM had shown a significant positive association with HDL-C (r,.755, p=.000).ApoA1 also showed significant positive association with HDL-C (r,.415, p=.002) in CAD WNDM.(Table.12)

7.2. Discussion

Age has not been considered to be a modifiable risk factor but, it out-ranks all other factors like lipids, blood pressure, and smoking—as a predictor of clinical events(Lloyd-Jones *et al.*, 2004). Conventional analyses do not distinguish between the biological changes of ageing within arteries—the non-modifiable effects of disintegration of tissues over time—and those produced by exposure over time to risk factors such as atherogenic dyslipoproteinaemia. (Lloyd-Jones *et al.*, 2004). The incidence of CAD was high among the patients of the age group 51-60 (77%) in CAD with type 2 DM patients when compared to CAD without DM (46%).

Smoking has been considered as a predictor of the transition from normoglycaemia to impaired fasting glucose and was found to increase the risk of type 2 diabetes, independent from possible confounders. Smoking and diabetes are two important hazards to the health of many individuals and contribute substantially to the global burden of disease in various ways. Smoking can not only aggravate the diabetes complications such as macro- or microvascular disease, but has also been shown to deteriorate glucose metabolism in normal subjects and thereby may provoke the onset of type 2 diabetes (Robert, Fagard, Nilsson, 2009)

Pathophysiological mechanisms by which smoking causes glucose intolerance and worsens clinical outcomes in established diabetes include greater insulin resistance, impaired beta-cell function and insulin secretion, chronic low grade inflammation, endothelial dysfunction, as well as interacting indirectly with other factors known to aggravate diabetes and lifestyle factors. (Robert *et al.*, 2009) Table 1. had shown that there was no significant difference between two groups with respect to smoking, alcoholism and SBP.

According to the percentage of stenosis and involvement of coronary vessels, severity of CAD was assessed and classified as Grade I(mild), Grade II(Moderate) and Grade III(Severe). Analysis on frequency of distribution has revealed that severity was significantly high in CAD WDM. (Table : 4) The percentage of patients with severe coronary artery disease-Grade III was

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63% in CAD WDM Vs 25 % in CAD WN DM($p<0.001$). 21% of CAD WDM patients had Grade II (moderate) compared to 29% in CAD WNDM.16% of CAD WDM had Grade I (mild) disease compared to 46% in CAD WNDM. A significantly high percentage of multivessel atherosclerosis was observed in CAD WDM when compared to CAD WNDM. These findings showed a delayed recognition of CAD in type 2 DM. The typical symptoms of cardiac ischemia are often masked in diabetic patients. Hence the pathological events are not identified at the preliminary stages (Hanif *et al.,* 2009). This might be the reason for the observed high frequency of grade III severity in CAD WDM and high percentage of CAD related mortality in diabetic patients as observed in various epidemiological studies. (Goraya *et al.,* 2002)

8. Insulin resistance

Insulin resistance has been defined as a condition of low insulin sensitivity, in which the ability of insulin to lower circulating glucose levels is impaired (DeFronzo 2009). The gold standard for assessing insulin resistance and insulin sensitivity is the hyperinsulinemic euglycemic clamp technique; however, this test was found to be too labor intensive, time consuming, and costly for routine clinical practice. The Homeostasis Model Assessment (HOMA) may be used alternatively as it is minimally invasive, easy to apply in a standard office setting and provide reasonable indices of insulin action in pre diabetes and diseases of recent onset(Matthews *et al.,* 1985; Katz A *et al.,* 2000). The biochemical defects that provoke insulin resistance involve impaired insulin signaling as well as reductions in glucose transport within insulin-sensitive tissues. (Lewis *et al.,* 2002).So subjects with insulin resistance require more insulin to promote glucose uptake by peripheral tissues, and genetically predisposed individuals may lack the necessary beta-cell secretory capacity. Insulin resistance mainly influence the metabolism related to Liver, Muscle and fat cells. Thus resulting relative insulin insufficiency disrupts the regulation of glucose production in the liver, glucose uptake in muscle, and the release of fatty acid from adipose tissue, the outcome being postprandial, and later fasting hyperglycemia. (Hajer GR *et al.,* 2007)

Analysis on frequency of distribution has revealed that severity was significantly high in CAD subjects with IR >1.6. (Table 6)The percentage of patients with IR >1.6 and Grade III-coronary artery disease - was 69%, Grade II coronary artery disease - was 21% and Grade I -coronary artery disease- was 16% respectively. The percentage of subjects with IR <1.6 and Grade III - severity- was 8%, Grade II coronary artery disease - was 35% and Grade I -coronary artery disease- was 30% respectively. Our results have shown that severity was significantly high in patients with an elevated IR level.($p<0.0001$) and coincide with the findings of Bodlaj. (Bodlaj et al. 2006).

Insulin resistance not only contributes to the pathogenesis of type 2 diabetes but also linked to cardiovascular risk factors and premature cardiovascular disease. It has been reported that insulin resistance predisposes individuals to the development of obesity and dyslipidemia which are considered as the traditional risk factors.

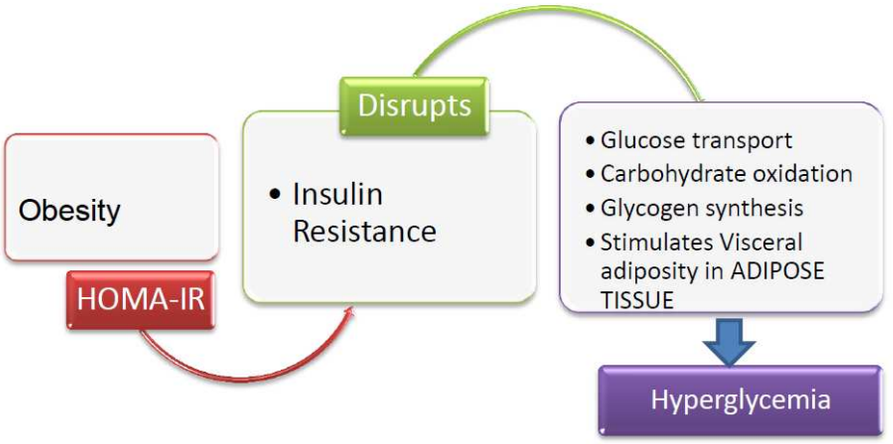


Figure 7. Obesity and IR related to hyperglycemia

As insulin stimulates the production of NO which has both antiatherogenic and anti inflammatory effects, IR is considered as an endothelial dysfunction risk equivalent (Zeng G *et al.*, 2000;. Kuboki K *et al.*, 2000) IR results in the down regulation of the antiatherogenic phosphatidylinositol-3-kinase–mediated insulin receptor signaling pathway, and maintained activity of the proatherogenic mitogenic activated protein kinase pathway(Bansilal S *et al.*, 2007). It also results in a state of low-grade, chronic, systemic inflammation, which in turn links the metabolic and the vascular pathologies (Romano *et al.*, 2003; Hsueh and Law,2003; Haffner SM.,2003) All these might have lead to accelerated atherosclerosis and increased severity of CAD in patients with type 2 DM.

9. Body Mass Index (BMI)

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. The WHO defines a BMI greater than or equal to 25 is overweight and a BMI greater than or equal to 30 is obesity(World Health Organization, 2007).BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. Raised BMI is a major risk factor for non-communicable diseases such as CAD (Niraj et al.2007) In our study significantly high level of BMI was observed in the CAD WDM subjects when compared to CAD WNDM and control (with $p<0.001$).The mean BMI level was 32.05 ± 0.33 in CAD WDM, 27.82 ± 3.359 in CAD WNDM and 20.05±0.95 in the control group respectively (Table.7.). Abbasi *et al* had shown similar results in their studies. (Abbasi *et al.*, 2002).

This increase in BMI might be due to the Insulin resistance, the major causative factor for type 2 DM. (Goossens, 2008) IR greatly reduces the sensitivity of cell walls to insulin. So the vital

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process whereby glucose passes through the cell wall via insulin to be converted into energy gets greatly impaired.

As a result, excess glucose remains in the blood stream, causing elevated levels of blood sugar, which are sent to the liver. (Niraj et al/ 2007) Once it reaches there, the sugar gets converted into fat and carried via the blood stream throughout the body. This process can lead to weight gain and obesity.

Evidences have revealed that normal function of Adipose issue is disturbed during obesity and adipose tissue dysfunction plays a prominent role in the development and/or progression of insulin resistance (Goossens.,2008). Boden and Chen et al had identified that Insulin-resistant fat cells of obesity can confer insulin resistance to muscle through the excessive release of free fatty acids into the general circulation and/or through the accumulation of intra myocellular triglyceride (Boden, 1997 and Chen *et al.,* 1988). Since obesity has been recognized as a significant contributor to hypertension, dyslipidemia and Insulin resistance, it has been recognized as a major modifiable risk factor for cardiovascular disease (Sharma,2003). This might be the reason for the observed significantly high percentage of incidence of CAD and severity in CAD patients with BMI >30 kg/m^2.

The athero-thrombotic process that underlies CVD implies a central role for cholesterol metabolism. The average concentration of blood cholesterol within a population has been found to be an important determinant of the risk of CHD in the population (Corti Salive *et al.,* 1997). Girard, had found that high cholesterol levels augments the risk of several diseases, most notably cardiovascular diseases(Girard-Mauduit,2010). In the present study cholesterol level was found to be significantly high in CAD patients when compared to control subjects. As its concentration increases, Cholesterol-rich apoproteins B containing lipoproteins may infiltrate the subendothelial space and initiate an inflammatory process that leads to atherosclerotic lesions. This progresses to fibrous plaques, with necrotic scores. (Paik.and Blair.,1995). Abnormal concentration of cholesterol also increase platelet aggregation, which exacerbates the severity of athero-thrombotic process. Hence cholesterol metabolism occupies a central role in the pathophysiology of CVD and found to be high in CAD patients (Enas,yousuf, Mehta, 1992).

In the present study total cholesterol level in CAD patients does not show any significant change with severity of CAD which underlines the fact that blood cholesterol alone may be a relatively poor predictor for CHD. (Table 9) This might be due to the fact that the other major risk factors might have exerted a component of their adverse effects via their effects on the above mentioned aspects of cholesterol metabolism. (David.,2001)

In the study, plasma triglyceride and VLDL were found to be significantly high in CAD WDM when compared to control and CAD WNDM.(Table 9) Hypertriglyceridemia has been found to be one of the most consistent finding in type 2 diabetes patients (Saxena et al., 2005).

Evidence from both animal and human studies implied that insulin resistance which causes increased synthesis and/or decreased clearance of VLDL – has been an important underlying cause of hypertriglyceridemia in subjects with type 2DM (Hopkinns et al.2009).

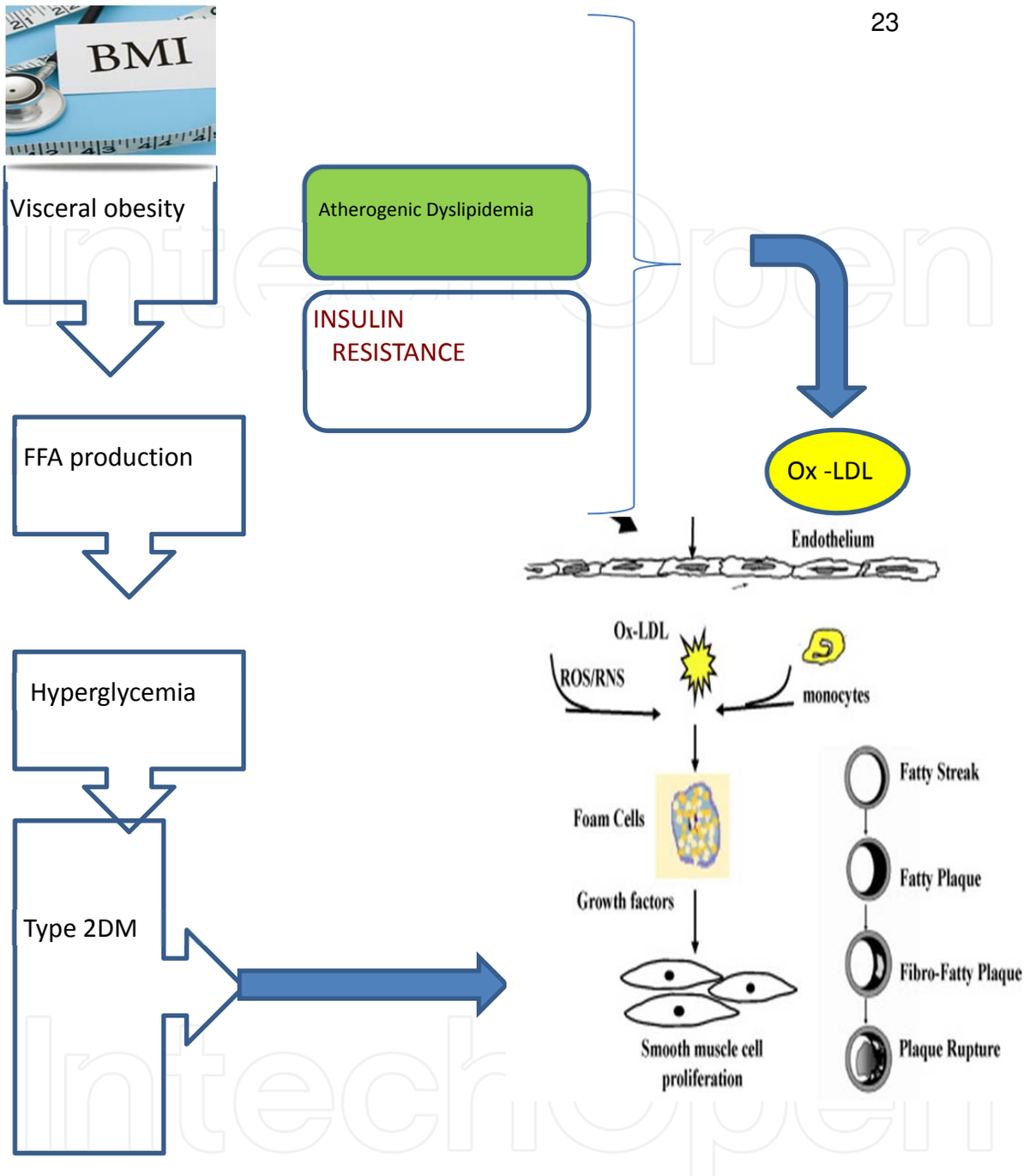


Figure 8. Possible Link Between Body Mass Index (BMI),Type 2 Diabetes Mellitus T2DM) And Coronary Artery Disease(CAD).FFA-Free fatty acid

Insulin an anabolic hormone was found to play a central role in the lipid synthesis and inhibition of lipolysis. Insulin inhibit VLDL production from the liver indirectly by decreasing FFA flux from adipose tissue to the liver and directly by its inhibitory effect on the rate of ApoB 100 synthesis and degradation in hepatocytes It has also been identified that Insulin can inhibit the assembly and secretion of VLDL by increasing posttranslational degradation of ApoB and

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reducing the expression of MTP (microsomal triglyceride transfer protein) in the liver(Meshkani and Adeli 2009).

One of the major abnormalities in insulin resistance was found to be hepatic overproduction of VLDL(Meyer *et al.,* 1996). It influences hepatic VLDL production by increasing the free fatty acid flux to liver and by affecting the rate of ApoB synthesis. It also reduces VLDL and intermediate density lipoprotein(IDL) catabolism by reducing the activity of lipoprotein lipase and decrease the hepatic uptake of VLDL and IDL. (Miller M;1999) These could have been the reason behind the significantly high level of TG and VLDL in CAD with diabetes subjects. (Figure 2 and 3)

Triglyceride was widely accepted as a CAD risk factor synergistic with other lipid risk factors. Helsinki Heart Study and 6-year follow-up of the observational Prospective Cardiovascular Muenster (PROCAM) study, revealed the importance of triglyceride as major risk factor. (Antonio Jr, 1998) Gianturco *et al.,* had shown that macrophages may take up triglyceride-rich lipoproteins by a mechanism that was independent of the ApoB/E receptor, there by facilitating the formation of atherogenic foam cells. (Gianturco *et al.,* 1994) Hypertriglyceridemia was found to have some adverse effect on endothelial dysfunction and activation on coagulation.These involvement of hyper triglyceridemia in atherogenesis at various level could have resulted in positive correlation of TG level with severity of CAD. (Table 9).

10. Low density lipoprotein — C

The concentration of serum LDL was found to be directly related to the development of atherosclerosis. One current theory which relates the role of LDL in the institution of atherosclerosis propose that oxidized LDL plays a major role in the development of foam cell-laden fatty streaks in the arterial wall. Elevated low-density lipoprotein cholesterol (LDL-C) has been a well-established independent risk factor for coronary artery disease (CAD). A number of primary and secondary trials have demonstrated that lowering of LDL-C decreases the incidence of CAD.

The present study has shown that LDL level was significantly elevated in CAD with diabetes subjects when compared to the CAD without diabetic group and normal controls. Reports have revealed that T2D patients show decreased hepatic uptake of VLDL, IDL and LDL that lead to increased plasma levels of these lipoproteins particularly in the postprandial state. This condition is observed particularly when there is marked insulin deficiency or poor glycemic control in type T2D (Lewis *et al.,* 2002). It has also been reported that clearance of LDL was limited due to the decreased availability of LDL receptors. So the high insulin resistance reported in CAD WDM might be the etiology behind the observed high level of LDL.

Patients with type 2 diabetes frequently have normal or only slightly elevated LDL-cholesterol concentrations but increased numbers of atherogenic LDL particles owing to the predominance of small, dense LDL particles. The basis for formation of sdLDL in insulin resistant states relates to the action of two proteins; cholesteryl ester transfer protein (CETP) and hepatic

lipase. CETP mediates the exchange of VLDL triglyceride for LDL cholesteryl ester, creating a triglyceride-enriched, cholesterol depleted LDL particle. This LDL particle is a substrate for hepatic lipase leading to hydrolysis of triglyceride and formation of the sdLDL (Olofsson *et al.,* 2005) Increased CETP and hepatic lipase activity, observed in insulin resistant and type 2diabetes subjects, favor the formation of sdLDL (Bagdade *et al.,* 1993 and Riemens *et al.,* 1998)A predominance of small, dense LDL particles is associated with increased risk of CHD (Austin *et al.,* 1988, Gardner *et al.,* 1996).These particles are more powerful than larger LDL particles to penetrate the vessel intimal wall and are more exposed to oxidation; oxidized LDL are then taken up by macrophages as part of atherosclerotic plaque formation. Small, dense LDL is also associated with early vascular dysfunction in the form of impaired endothelial response in patients with diabetes independent of other risk factor variables, including lipid levels, body mass index (BMI), blood pressure and severity. (Tan *et al.,* 1999).

Hence the absolute LDL-cholesterol concentration could be misleading, since it does not directly reflect the increased number of atherogenic particles. This might have led to the lack of positive correlation between LDL cholesterol with Insulin resistance and severity of CAD. (Tan *et al.,* 1999).

The CAD patients without diabetes and with total cholesterol level <200 mg/dl were 21% with grade III stenosis, 18% with grade II and 48% with grade I stenosis. The CAD subjects without diabetes and Total cholesterol level >200 mg/dl had 6% with grade III stenosis, 4% with grade II and 2% with grade I stenosis. Among the CAD without diabetes subjects with total triglyceride level <150 mg/dl 13% subjects had grade III stenosis, 6% had grade II and 42% had grade I stenosis. Compared to 19% subjects with grade III stenosis, 15% with grade II and 4% with grade I stenosis and triglyceride level >150 mg/dl. The CAD subjects without diabetes and HDL level <40 mg/dl had 19% with grade III stenosis, 8% with grade II and 33% with grade I stenosis.

The CAD subjects without diabetes and HDL >40 mg/dl had 15% with grade III stenosis, 10% with grade II and 15% with grade I stenosis. Among the CAD without diabetes subjects with LDL level <130 mg/dl 10% subjects had grade III stenosis, 12% had grade II and 23% had grade I stenosis,compared to 21% subjects with grade III stenosis, 10% with grade II and 23% with grade I stenosis with LDL level >130 mg/dl.

Among the CAD with diabetes subjects with total cholesterol level <200 mg/dl 37% subjects had grade III stenosis, 7% had grade II and 4% had grade I stenosis. Among the CAD subjects with >200 mg/dl cholesterol level,4% of subjects had Grade III,7% had grade II and 4% had grade I stenosis.Among CAD with diabetes and triglyceride level <150 mg/dl 33% had grade III stenosis, 19% had grade II and 28% had grade I stenosis. Among CAD subjects with triglyceride level >150 mg/dl were found to have 11% of subjects with grade III,7% with grade II and 2% with grade I stenosis. Among the CAD with diabetes subjects with total HDL level <40 mg/dl 30% subjects had grade III stenosis, 18% had grade II and 19% had grade I stenosis. Among the CAD subjects with 40-60 mg/dl HDL level 12% of subjects had Grade III,11% had grade II and 11% had grade I stenosis.

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The CAD subjects with diabetes and LDL level <130 mg/dl had 25% with grade III stenosis, 18% with grade II and 14% with grade I stenosis. The CAD subjects with diabetes and LDL level >130 mg/dl had 18% with grade III stenosis, 12% with grade II and 14% with grade I stenosis.

The distribution of subjects based on HDL cholesterol level <40 mg/dl had shown that 32% had Grade I stenosis,25% had Grade II stenosis and 16% had Grade III stenosis.. Among the CAD subjects with HDL level 40-60 mg/dl 19% had grade I stenosis,14% had Grade II stenosis and 3% had Grade III stenosis.

HDL-C has been considered as an antiatherogenic lipid factor as it helps in reverse cholesterol transport (Hersberger et.al.,2005). Furthermore HDL particles have been shown to have cardioprotective nature due to its - antioxidant properties, protective effect on endothelial cells, inhibitory effect on endothelial adhesion and activation of leukocytes, inhibitory action on platelet activation (Nofer *et al.,* 2002). In our study, HDL-C level has been found to be significantly lowered in CAD patients when compared to normal. These results draw a parallel with the existing reports (Grundy,et.al., 2004). Reduced HDL levels have been commonly observed in metabolic syndrome and type 2 diabetes subjects. The reduced HDL cholesterol levels found in CAD WDM may be due to the high Apo E-containing triglyceride-rich lipoproteins found in these patients. Apo E is involved in HDL catabolism and can transfer from triglyceride-rich lipoproteins to HDL. Furthermore, when present on HDL particles, apo E is predominantly associated with LpAI/AII (Lipoprotein lipase AI/AII) particles. Therefore, the elevation of circulating apo E-containing triglyceride- rich lipoproteins could lead to increased transfer of apo E to LpAI/AII (Lipoprotein AI/AII) and enhanced catabolism of this fraction. (Juying Ji *et al.*, 2006)

Functions and properties of HDL particle vary according to its particle size and apoproteins content. It exists as particles of different sizes, with HDL- 2 being the largest and containing the most lipid in its core. HDL-3 particles are smaller and pre-b-HDL is the smallest, and these may be the most active particles in taking up peripheral cholesterol (Benton *et al.,* 2005). Apolipoprotein composition can be used to separate HDL into subpopulations: HDL containing apo A-I and apo A-II (HDL A-I : A-II), and HDL containing apo A-I but not apo A-II (HDL A-I)(Kuller *et al.,* 2002). HDL A-I is more effective than HDL A-I : A-II in promoting cholesterol efflux (Kuller *et al.,* 2002), which is consistent with the atheroprotective effect of apo A-I on LCAT (Walldius *et al.,* 2001 and Sharet *et al.,* 1994). The Prospective Epidemiological Study of Myocardial Infarction (PRIME) study examined the association between the incidence of CHD and several HDL related parameters, including HDL-C itself, apo A-I, HDL A-I, and HDL A-I : A-II (Ensign *et al.,* 2006). All four parameters were related to CHD risk, however, HDL apo A-I, and apo A-I were the strongest predictor. This might be the reason why HDL had no positive correlation with severity of CAD in the present study.

10.1. Apolipoprotein A1

An inverse relationship between the concentration of high-density lipoprotein (HDL) cholesterol and the risk of developing cardiovascular is well established. There are several documented functions of HDLs that may contribute to a protective role of the lipopro-

teins. These include the ability of HDLs to promote the efflux of cholesterol from macrophages and foam cells in the artery wall and to anti inflammatory/antioxidant properties of these lipoproteins. (Gotto AM J *et al.,* 1983) The fact that the main apolipoprotein of HDLs, ApoA-I, plays a prominent role in each of these functions adds support to the view that ApoA-I should be measured as a component of the assessment of cardiovascular risk in humans (Robinson D *et al.,* 1987). Moreover there is mounting evidence that HDL subpopulations vary in terms of their ability to protect against CHD. Case-control studies have suggested that the inverse relationship between HDL cholesterol concentration and CHD is a function of the concentration of the HDL subfractions (Miller *et al.,* 1987). In another study relating HDL subpopulations to CHD, it was found that both the severity and the rate of progression of coronary lesions correlate significantly and inversely with the concentration of types of HDL(Stamper *et al.,* 1991).

Level of Apolipoproteins overwhelms the lipids because ApoA1are under more genetic control than lipid components and hence depicts the number of lipoprotein particles more accurately (Walldius G and I Jungner I, 2006) The present study has shown that the level of Apo A1 was significantly low in CAD with diabetic subjects when compared to CAD without diabetes. This might be due to the presence of high level of Apo E which cause the catabolism of Apo A1 and HDL.

APO-A1 is the major structural protein of HDL(70%)and it has major role is centripetal movement of cholesterol from peripheral tissues including the arterial wall to the liver for eventual elimination of through the biliary system in to the gut.(Sniderman A D *et al.,* 2003)The transport of cholesterol and formation of HDL are the basic roles of APO-A1.,low levels of this proteins have been identified as the risk factor in the development and progression of coronary damage. (Sniderman A D e*t al.,* 1997). Apo A1 not only initiates the reverse cholesterol transport by activating the LCAT but also manifests antioxidant and antiinflammatory effects (Walldius G and Jungner I.,2004) It also removes oxidative seeding molecules from endothelium, Scavenges toxic products from arterial wall, 'Reduces smooth muscle cell, apoptosis/ necrosis', Reduces plaque lipid content, Reduces plaque macrophage content and Improves endothelial dysfunction. Furthermore, apo A-I is the ligand for the ATP-binding cassette (ABC) protein, ABCA1,and hence is involved in the docking procedure by which excess cholesterol in peripheral cells is externalized to HDL (Oram et al., 2000 and Wang N et al., 2001) for further reverse cholesterol transport either directly or indirectly via LDL back to the liver Hence it can be considered as a better marker than HDL-C (Oram et al., 2000).

10.2. Apolipoprotein B(apoB)

For over three decades it has been recognized that a high level of total blood cholesterol, particularly in the form of LDL cholesterol (LDL-C), is a major risk factor for developing coronary heart disease (CHD) (Walldius G and Jungner I.,2001)However, recent research has shown that LDL-C is not the only lipoprotein species involved in atherogenesis. Elevated levels of intermediate- density lipoprotein (IDL) and very low density lipoprotein (VLDL) are also associated with increased cardiovascular risk. All these potentially atherogenic lipoprotein

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contain one Apo B molecule.and therefore the total apo B value indicates the total number of potentially atherogenic lipoproteins (Scharnagl H et al., 2001 and Nissen et al. 2003)

In our study Apo B was found to be significantly high in CAD with type 2 DM when compared to CAD without DM and control subjects. This observation coincide with the findings several studies related to coronary heart disease

Apo B is essential for the binding of LDL particles to the LDL receptor, allowing cells to internalize LDL and thus absorb cholesterol (Alfonso Troisia,, Alberto D'Argeniob,2006). The concentration of plasma apo B particles is highly correlated with the level of non-HDL cholesterol (non-HDL-C), defined as TC minus HDL-C (Chapman and Caslek, 2004) As HDL is known to be protective against cardiovascular risk, non-HDL-C reflects the fraction of blood cholesterol that is not contained in atheroprotective lipoproteins. Thus apo B has been found to be a better predictor of risk than LDL-c, VLDL and chylomicrons. In most conditions, more than 90% of all ApoB in blood is found in LDL. In some cases where LDL C is in the normal/low range, high ApoB levels were observed which indicate an increased number of sd-LDL particles, - most atherogenic particles as they are easily oxidized and promote an inflammatory response and the growth of plaques. Furthermore Apo B has been found to be an independent predictor of endothelial vasodilatory function, increased carotid IMT and arterial stiffness. These properties and the observation from the present study that Apo B is positively correlated to the severity of the CAD underline the simple fact that an excess of apo B- particles always denote proatherogenic condition.

10.3. ApoB/A ratio

An early detection of the people at high risk for CAD can reverse or reduce the worsening of condition by modification of lifestyle of patient, an establishment of robust and precise risk indicator for lipid imbalance and atherogenesis will be of great practical advantage for patients and physicians. (Nam BH, 2006).

LDL-C had been considered as the major atherogenic lipoprotein particles for many years and the prime predictor for CAD (Vogel RA, 1998).Now it has been identified that Apolipoprotein B represent total atherogenic particles and is better predictor than other lipoproteins. (Walldius G, Jungner I.,2004). ApoA-I the major apolipoprotein in HDL particles has a central role in the 'reverse cholesterol transport'and manifests anti-inflammatory and antioxidant effects. It has been identified that Apo A1 can be risk factor than HDL cholesterol and can be considered as for antiatherogenic marker. (Walldius G and Jungner I. 2004).

So to get a precise picture of both atherogenic and antiatherogenic lipid related risk, ratio of ApoB/ApoA1 was considered. The ratio between the concentrations of ApoB and ApoAI (henceforth ApoB/A) reflect the balance between the opposing processes of arterial internalization of cholesterol and the reverse transport of cholesterol back to the liver (Walldius G and Jungner I.,2005). The reason for improved predictive effect of ApoB/A ratio might be due to the fact that the ratio reflects and integrates the " cholesterol balance " between potentially atherogenic lipoprotein particles (ApoB) in relation to all antiatherogenic particles.(ApoA1). It has been found to be better than one single lipid fraction or the LDL-C/HDL-C ratio. Another

contributing explanation is that the methodological errors of the apolipoprteins are smaller than those for lipids. (Walldius G and Jungner I, 2005).

In the present study the ApoB/A ratio was found to be markedly elevated (p≤ 0.001)in CAD patients irrespective of their Diabetes status. The ApoB/A ratio and severity of CAD was not found to be significant in CAD WNDM (r=1.000,p =.809) whereas the ratio and severity was significant(p<.05) in CAD WDM with(r=.547 p =.034.The risk relationship between ApoB and ApoA1 was expressed as Odds ratio. The Odds ratio for CAD WNDM was 0.48 while Odds ratio for CAD WDM was found to be 4.5 (95% CI: 1.122 - 18.31).(Table.8-10)

The ratio reflects the balance of cholesterol transport and can be expressed as one number which integrates the risk associated with an imbalance between atherogenic and antiatherogenic lipoproteins. The strongest single variable in AMORIS, related to increased risk of fatal MI, was the ApoB/ApoA-I ratio. AMORIS study showed that the ratio of ApoB /A1 can indicate the risk of MI irrespective of lipid phenotype and even if lipid levels are normal/low.(van Lennep *et al.,* 2008) This ratio had a stronger relationship with CV risk than any other lipid ratio such as total cholesterol (TC)/HDL-C, LDL-C/HDL-C, or non-HDL-C/HDL-C. Talmud et al have confirmed the results from the AMORIS study and found that the ratio was a better predictor of cardiac risk than LDL-C, and that both apo B with TG and found to have the strongest associations with CHD. (Talmud PJ *et al.,* 2002)

Epidemiologic studies indicated that the ratio of ApoB to ApoA-I was the strongest predictor of CAD (Barter etal.,2006). Similarly, van Lennep et al. (van Lennep *et al.,* 2000) reported in patients with CAD on statin therapy that only ApoB and the ApoB/ApoA-I ratio predicted myocardial infarction and all-cause mortality, whereas LDL-C and TG did not. In both men and women from the AMORIS (Apolipoprotein-Related Mortality Risk) study, the superiority of the ratio of ApoB to ApoA-I, compared with the TC/HDL-C ratio, became more obvious as risk of CAD increased.

Our study had shown that instead of still remaining with the old paradigm:'LDL cholesterol-the lower the better, a new paradigm ApoB/A1 ratio indicating the cholesterol balance –the lower the better 'might be more appropriate.

11. Conclusion

Type 2 diabetes mellitus is associated with a three to fourfold increase in risk for coronary artery disease (CHD). (Diabetes mellitus is associated with sharp increased risk of CVD and mortality). People with type 2 DM develop CVD at a younger age, have a high rate of multivessel disease. The typical symptoms of cardiac ischemia are often masked in diabetic patients Hence the pathological events are not identified at the preliminary stages. Despite advances in our knowledge, the established risk factors could not fully explain its occurrence: and cannot be explained by conventional risk factors which lead to delayed recognition of CAD in type 2 DM. Mechanism underlying the accelerated atherosclerosis in DM patients are not fully understood. Insulin resistance which is the major etiological factor of T2DM influence (affect)

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HDL,LDL and TG level- which can increase the risk of CAD. ApoB/ApoA1 ratio which reflects both atherogenic and antiatherogenic lipid related risk, can be used as a better predictor than traditional lipid markers like LDL and HDL to analyze the atherogenicity.

12. Future implications

It is now reported that HDL can influence glucose metabolism directly and possibly improve insulin resistance by altering plasma membrane composition through enhanced cholesterol efflux. Balancing cholesterol efflux and influx HDL can promote insulin sensitivity enhancing or activating insulin receptor function, its tyrosine kinase activity and downstream regulation of cellular function. It is reported that glycation of certain residues of apo A1 could inhibit its anti-oxidant activity converting HDL into a dysfunctional molecule which may affect its protective properties including its newly emerging role in insulin action and glucose metabolism.

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