A DISSERTATION

ON

A CORRELATIVE STUDY OF METABOLIC SYNDROME AND CORONARY ARTERY DISEASE AMONG TYPE 2 DIABETICS AND NON-DIABETICS

Submitted to
THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY
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for the award of
M.D DEGREE IN GENERAL MEDICINE
BRANCH I

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CERTIFICATE

This is to certify that the Dissertation entitled **"A CORRELATIVE STUDY OF METABOLIC SYNDROME AND CORONARY ARTERY DISEASE AMONG TYPE$_2$ DIABETICS AND NON-DIABETICS"** is a record of bonafide research work done by **Dr.T.VADIVUKKARASI,** Post graduate in the Department of General Medicine Govt. Mohan Kumaramangalam Medical College, Salem, under my supervision and guidance and the conclusions are her own. This is being submitted in fulfillment of the rules and regulations for the degree of M.D (General Medicine) Examination in March 2007.

H.O.D **Unit Chief**

DEAN

DECLARATION

I solemnly declare that this dissertation **"A CORRELATIVE STUDY OF METABOLIC SYNDROME AND CORONARY ARTERY DISEASE AMONG TYPE$_2$ DIABETICS AND NON-DIABETICS"** was prepared by me at Government Mohan Kumaramangalam Medical College and Hospital, Salem under the guidance and supervision of **Prof. Dr. K. Sathyamoorthy M.D**, Professor of medicine, Govt. Mohan Kumaramangalam Medical College and Hospital Salem.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in fulfillment of the university regulations for the award of the degree of M.D. Branch 1 General Medicine.

Place: Salem

Date :

(Dr. T.VADIVUKKARASI)

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INDEX

INTRODUCTION

Over the decades, there has been a phenomenal rise in the incidence of CAD in India. The quantum rise in the prevalence of CAD in urban-India is very likely due to changes in lifestyle and food habits.

The twin epidemics of Diabetes mellitus and Heart disease are a major threat to the well being as well as the economic development of India. It is believed that a combination of factors, genetic and environmental including newer risk factors like the metabolic syndrome and hyper coagulability in addition to traditional risk factors like smoking, hypertension and hyper cholesterolemia is the culprit behind the explosive rise in the incidence of these diseases. [1]

WHO shows that India has 32 million diabetic subjects and this is projected to increase to 100 million by the year 2035.

It is obvious that we need to put in place preventive measures. But before instituiting preventive measures we must know who is at risk for these diseases. Here comes Metabolic syndrome, a deadly combination of Hypertension, Diabetes mellitus, Dyslipidemia and abdominal obesity.

The concept of the metabolic syndrome is perhaps the most significant development in the management of cardiovascular diseases in the last 10 years.

Avogaro and creapaldi first described the syndrome over 40 years ago. [2]

The importance of the concept for everyday clinical practice was only highlighted in 1988, however, when Gerald Reaven drew attention to a constellation of features associated with coronary heart disease. He suggested that Insulin resistance played a central etiologic role in providing a link between these components.[3]

In subsequent decades it has become evident that syndrome X is a cluster of risk factors for Diabetes and cardiovascular disease.

The prevalence of metabolic syndrome has varied markedly between different studies, most likely because of lack of accepted criteria.

In 1998 WHO proposed a unifying definition for the syndrome and chose to call it the “metabolic syndrome” rather than the Insulin resistance syndrome.

This name was chosen primarily because it was not considered established that Insulin resistance was the cause of all the components of the syndrome.

Present study was undertaken with the aim of studying the prevalence of metabolic syndrome among Type $_2$ Diabetics and Non-Diabetics and its influence upon the occurrence of Coronary Artery disease.

AIMS AND OBJECTIVES

1) To study the prevalence of metabolic syndrome among Type $_2$ Diabetics and Non-Diabetics.

2) To study the sex distribution and Age distribution in patients with metabolic syndrome among Type $_2$ Diabetics and Non-Diabetics.

3) To study the influence of metabolic syndrome on risk of CAD among Type $_2$ Diabetics and Non-Diabetics.

4) To study the risk of individual components of Metabolic syndrome on occurrence of CAD among Type $_2$ Diabetics and Non-Diabetics.

5) To study the influence of glycemic control in CAD among Type$_2$ Diabetics.

REVIEW OF LITERATURE

The prevalence of Coronary Artery disease is directly proportional to the prevalence of its risk factors. Risk factors for CAD can be divided into lipid factors and Non-lipid factors.

Non-lipid factors include

- Diabetes mellitus
- Hypertension
- Smoking
- Positive family history
- Gender, Body mass Index, Physical activity

Other emerging risk factors include,

- Thrombogenic factors
- Chlamydial infections
- Helicobacterial infections.

But in South Asians, the high incidence and the malignant course of CAD cannot be explained by these traditional risk factors. Here the metabolic syndrome dominates the scene. Many of the lipid

abnormalities present in this community can be attributed to this syndrome. [4]

HISTORICAL BACKGROUND OF METABOLIC SYNDROME

1923 - Kylin described the clustering of hypertension, hyperglycaemia, hyperuricaemia.

1936 - Himsworth noted that a large number of Diabetic patients were insulin resistant. Yalow and Berson devised the first radio immunoassay for insulin in 1959 and used it to show that Insulin resistance was accompanied by hyperinsulinaemia.

1988 - Reaven rejuvenated and immortalized their facts in his Banting memorial lecture-“The Role of Insulin Resistance in Human disease”.

1999 - WHO Definition was proposed

2001 - NCEP guidelines were proposed

The term metabolic syndrome has been used variously by disparate organizations to connote different entities.[5]

WHO have used this term to indicate a state of Insulin resistance with pervasive dysmetabolism.

WHO definition of this syndrome includes.

1) Impaired glucose regulation/Diabetes mellitus

2) Insulin resistance

3) Raised Arterial pressure >160/90

4) Raised plasma triglyceride >150 mg/dl and/or low HDL cholesterol <35 mg/dl in men or<39 mg/dl in women.

5) Central obesity [Males: waist to hip ratio >0.9 females: waist to hip ratio >0.85] and / or Body mass index >30 kg/m^2

6) Microalbuminuria

To satisfy the criterion of metabolic syndrome, a patient needed to have either criterion one or two positive along with atleast two of the four remaining criteria.[6]

Conceptualization of the metabolic syndrome as a unique, high risk Cardiovascular state, as defined by the National cholesterol Education program [NCEP], is gaining acceptance as the basis for diagnosing the metabolic syndrome [7].

The NCEP definition is based on clustering of multiple metabolic abnormalities associated with Insulin resistance but does not require a measure of Insulin sensitivity i.e., no requirement exists for an

experimental demonstration of Insulin resistance or a measurement of impaired insulin mediated glucose disposal.[5]

Definition of Metabolic syndrome – NCEP ATP III guidelines

Risk factor	**Defining level**
Abdominal obesity	
Men	> 40 inches
Women	> 35 inches
Triglycerides	≥ 150 mg/dl
HDL cholesterol	
Men	< 40 mg/dl
Women	< 50 mg/dl
Blood pressure	≥ 130/85 mm of Hg
Fasting glucose	≥ 110mg/dl

Any 3-5 symptoms is suggestive of metabolic syndrome.

The metabolic syndrome, as defined by the NCEP, is not to be confused with the Insulin resistance syndrome although such resistance is likely but not always in patients with metabolic syndrome. Based on the criteria of the NCEP, the diagnosis of metabolic syndrome is highly effective in predicting excess cardiovascular risk. Lakka et al in the

kuoppio study showed the impact of metabolic syndrome on cardiovascular mortality-which was three fold increase.[8]

It is important to emphasize, however, that although a common etiologic thread may account for the association between the components of the syndrome, large ethnic differences exist, both in the pattern of risk factors and in the manifestations of the syndrome. For example, based on the prevalence of obesity and hypertension, it was surprising that there were fewer cardiovascular deaths in North American Samoans, compared with Americans of European origin. Less risk of Cardiovascular death has been reported in Nauruans and pimas when compared with Caucasians, based on obesity and Type $_2$ Diabetes mellitus in these populations.[9]

In Diabetic African Americans, HDL was much higher and TGL was much lower when compared with Caucasians.

In south Indians where CAD is more prevalent, where the syndrome components are of a far more classical nature, same criteria cannot be used, because most of us would not meet the waist circumference defined in NCEP guidelines.

The international Diabetic federation has defined central obesity as waist circumference in males>90 cms in females > 80 cms

- TGL ≥ 150 mg%
- HDL – males ≤ 40 mg%

  Females ≤ 50 mg%
- Blood pressure ≥ 130/85 mm of Hg
- Fasting plasma glucose ≥ 100 mg% / known Diabetic

3 to 5 positive criteria is required for the diagnosis.

This criteria should be used as a model to diagnose metabolic syndrome which are suitable to our own people. [10]

ETIOLOGY

Both genetic and environmental factors contribute to the development of metabolic syndrome. Various hypothesis have been put forth.

1. Thrifty genotype hypothesis

Need [11] put forth this theory. He suggested how hyperinsulinemia provided a survival advantage in primitive humans in "feast and famine". The post prandial hyperinsulinemia, reduces glycosuria and promotes glucose storage and hence survive fast. Whereas the same in modern humans leads to Insulin resistance, β-cell failure and $Type_2$ Diabetes mellitus.

2. Reaven Cahill hypothesis [‘Not so’ thrifty genotype]

Reaven [12] based on cahill’s work has interpreted that muscle Insulin resistance supplied brain its substrate by

1) Increased serum glucose because of reduced muscle uptake.

2) Release of fatty acids by adipose tissue. But the same hypothesis lead to Insulin resistance, β-cell failure and $Type_2$ Diabetes mellitus in modern humans.

3. Thrifty phenotype hypothesis

This hypothesis suggests that metabolic syndrome is the result of the suboptimal environment during intra-uterine period and neonatal period.

Barker [13] studied data from Britain and showed that with increasing birth weight the death rate from heart disease fell and metabolic syndrome diagnosis progressively decreased.

4. Common soil hypothesis

Stern suggested that atherosclerosis and Diabetes share same genetic and environmental antecedents [14] stern was the one who categorised the metabolic syndrome components and that they would predict future arteriosclerosis.[15]

PATHOPHYSIOLOGY OF CAD IN RELATION TO COMPONENTS OF METABOLIC SYNDROME:-

1. HYPERGLYCAEMIA AND CAD

Increase in plasma glucose levels have long been recognised as a risk factor for CAD. Plasma glucose has been shown to have a continuous gradient relationship with CAD both in the diabetic range and in the non-diabetic range.[16]

DECODE study [17] proposed post-prandial hyperglycaemia to be associated with CAD occurrence than fasting hyperglycemia. Whereas, in the special analysis of the NHANES III database, there was a fivefold increase in the incidence of retinopathy in the fasting glucose interval of 110 to 119 mg/dl compared with the interval of 100 to 109 mg/dl.

Similarly the UKPDS used a fasting glucose level of 108 mg/dl to diagnose diabetes and encountered a 21% incidence of retinopathy in their newly diagnosed patients. [18] Thus much lower levels of fasting hyperglycemia may be associated with milder degrees of type $_2$ diabetes than the level currently used for the diagnosis of type $_2$ Diabetes mellitus [126 mg/dl]. The metabolic syndrome may overlap, to a variably greater extent, the diagnosis of type $_2$ diabetes and may ultimately be replaced by a more aggressive diagnosis of this disorder.

2. HYPERTENSION AND CAD

Studies have shown that an increase in BP by 5mm of Hg is associated with 34% increase in risk for CAD [19] and this applies to diabetics as well as Normoglycaemic individuals.

Whereas a reduction in BP by 5 mm of Hg can lead to significant reduction in cardiovascular mortality [20] uncomplicated hypertension without any risk factors should be controlled to less than 130/85 mm of Hg; complicated hypertension like Diabetes, CAD, chronic kidney disease, the target BP should be below 120/80 mm of Hg.[20]

Presence of left ventricular hypertrophy directly correlates with cardio vascular mortality and morbidity which can be regressed by Angiotensin converting enzyme inhibitors [esp. perindopril] and Indapamide. In hypertensives the entire cardiovascular mortality and morbidity rests on control of endothelial dysfunction which can be corrected with drugs like Angiotensin converting enzyme Inhibitors, Nebivolol, folic acid supplements, statins and calcium channel blockers.[21,22]

Tight glycaemic control in hypertensives prevent cardiovascular morbidity and mortality. The co-existence of hyperlipidemia and hypertension also play a role in the pathogenesis of CAD. If there are additional risk factors like Diabetes mellitus, chronic kidney disease,

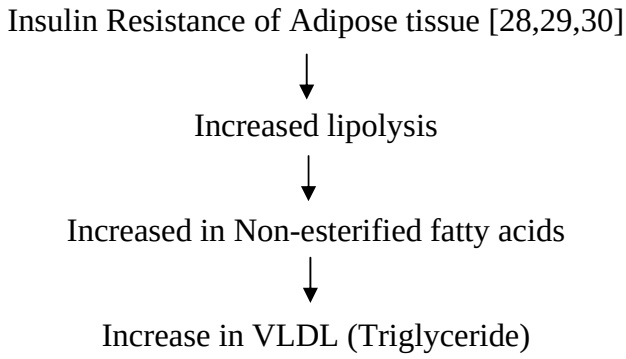
cerebro-vascular accident, irrespective of the lipid levels, statins have to be introduced to control the LDL levels to below 70 mg%. [23]

3. OBESITY AND CAD

Obesity was not a feature of the syndrome originally described by Reaven. It was Vague who first described in 1956 that Regional adiposity plays a greater role in the development of diabetes, Impaired glucose tolerance and atherosclerosis.[24] Larson et al demonstrated a significant association between waist-hip ratio and incidence of cardiovascular disease.[25]

Framingham study showed waist circumference was predictive of cardiovascular disease [26] waist circumference is measured at a point halfway between the lower costal margin and the superior iliacs. Despres and colleagues have shown that waist circumference alone provides a good measurement of visceral fat and that metabolic complications may first be observed with circumference of ≥100cm.[27]

This subcutaneous fat accounts for 80% of total adipose tissue, yet the intraperitoneal fat accounts for 6-20% of total adipose tissue volume. The latter is the most metabolically active and deleterious to health and is strongly associated with insulin resistance.



Lipoprotein lipase of Adipose tissue activity is depressed in Insulin resistance leading to reduced Triglyceride removal from VLDL resulting in hypertriglyceridemia. Also Insulin resistance leads to reduced apolipoprotein-B degradation resulting in formation of small, dense atherogenic LDL.

4. DYSLIPIDEMIA AND CAD

Individuals with Insulin resistance have a characteristic lipid disturbance:

Elevated VLDL Triglycerides, decreased plasma HDL. And plasma LDL levels are quantitatively within the same range as individuals with no insulin resistance, but qualitatively different in that the LDL particles are smaller and more dense.

Increase in Insulin resistance at the level of Adipose tissue

↓

↑in the release of Free fatty acids (FFA)

and ↓ in the uptake of FFA

↓

excessive flux of FFA s into the liver

↓

↑in VLDL secretion by the liver

and ↑ synthesis of apolipoprotein C-III synthesis which reduce degradation of VLDL

↓

VLDL exchange their triglycerides for cholesterol esters of HDL by the action of cholesterol ester transfer protein (CETP)

↓

Triglyceride rich HDL, acted upon by Hepatic lipase

↓

Apo A_1 is released and HDL size is reduced

↓

HDL is lost through the kidney. Thus HDL particle clearance is increased.

Several large prospective observational studies and intervention trials show a strong positive relationship between raised TGL and CAD- a dose response relationship. Hypertriglyceridemia is an independent

risk factor for CAD when it is associated with low HDL and / or raised LDL.[31]

There is an inverse relation between HDL and CAD. The Framingham heart study has established that individuals with HDL cholesterol <35 mg/dl have 8 times increase in CAD incidence than those with HDL >65 mg/dl.

The mechanism by which HDL confers decreased risk for CAD is poorly understood.

1. They indirectly initiate TGL catabolism and remnant removal.
2. They accept free cholesterol from cells and play a key role in cholesterol transport.

HDL_2 is large and more cholesterol rich than HDL_3 and hence is more anti-atherogenic.

Women have significantly high plasma levels of HDL_2 than men, giving the cardioprotection seen in premenopausal women.

As LDL is the major carrier of cholesterol, its levels are directly proportional to the risk of CAD. It is that LDL composition that influences CAD risk [32]. Based on electrophoretic pattern LDL has been divided into large or fluffy LDL (Pattern A) and small dense LDL (Pattern B). Pattern B is associated with a threefold increase in the risk

of MI. Pattern B individuals are more resistant to treatment than those with pattern A.

Lipoprotein (a) [LP(a)] is an independent risk factor for CAD [33]. The level of LP (a) is genetically determined, occurs as a complex between LDL and plasma apolipoprotein (a). It is ten times more atherogenic than LDL. Levels >30 mg/dl is associated with CAD risk. Screening for Lp (a) levels routinely is not recommended. Yet they should be measured in (1) patients with elevated LDL levels

(2) Premature CAD

(3) Family history of CAD

The only therapeutic option to lower Lp (a) is Niacin, alone or in combination with colestipol hydrochloride at 3-4 g/day.

Upon review of information on HDL and CAD, a causal relationship exists between them. For TGL the data are mixed.

The pattern of Dyslipidemia and CAD in Indians [4]

1. CAD is present with relatively lower levels of lipids and lipoproteins.

2. Raised TGL and low-HDL cholesterol occurs commonly.

3. Dysmetabolic syndrome X of Insulin resistance is more commonly associated with a high risk.

4. Lp (a) plays a very dominant role.

5. Elevated plasminogen Activator inhibitor-1

6. Atherogenic phenotype pattern B.

In south Asians, the high incidence of CAD that occurs prematurely and runs a malignant course cannot be explained by the traditional risk factors. Insulin resistance and the Dysmetabolic syndrome X dominate the scene. Many of the risk factors of CAD in their community can be attributed to this syndrome.

Clinical and therapeutic implications of Metabolic syndrome

The usefulness of this syndrome are:

1. Patients with any one of the components of the syndrome are at risk of having the other conditions, for which they should be screened.

2. Reduction in Cardiovascular risk in such a patient will require treatment of all risk factors, and it is important to recognize that treatment of one may sometimes lead to detrimental changes in another. For example, treating hypertension with thiazide

diuretics may lead to carbohydrate dysmetabolism and hyperlipidemia.

3. Obesity aggravates the syndrome and therefore adiposity, in particular visceral adiposity should be included in patient assessment.

Two important studies have shown direct correlation of these risk factors with the extent of underlying atherosclerotic lesions in young individuals. [34] Thus it has been argued that intervention should begin in childhood. The benefits of alteration in lifestyle, such as cessation of smoking, physical exercise and attention to weight, however are important interventions in both the young and adult population.

Weight loss is associated with marked improvement in metabolic and physiologic profiles. We have lifestyle modifications in the form of diet and exercise (5 or more sessions/week of approximately 3-5 miles/day consisting of a brisk walking pace of 3-4 miles/hour has good insulin sensitizing benefits) and pharmacological interventions that include, Orlistat and sibutramine for those failing life style modifications. [5]

Treatment of Dyslipidemia include [5]

1. Statins: Produce 30% to 40% reduction of LDL mass.

2. Fibric acid derivatives: for lowering TGL and raising HDL

3. Nicotinic acid: for raising HDL when TGL is not markedly elevated.

Treatment of hypertension [5]

Because endothelial dysfunction is an important part of metabolic syndrome ACE inhibitors and Aldosterone receptor antagonists are useful in improving hypertension and relieving endothelial dysfunction.

Treatment of impaired carbohydrate tolerance [5]

The impaired fasting glucose of metabolic syndrome may or may not be accompanied by Impaired glucose tolerance. Impaired glucose tolerance is associated with Insulin resistance, Impaired fasting glucose may or may not be associated with Insulin resistance-it is associated with declining B-cell function. Studies have demonstrated a clear benefit of metformin and Thiazolidinediones in the treatment of Impaired glucose tolerance. Here in patients with Impaired fasting glucose, who fail to adhere to lifestyle modifications, chemoprevention of Diabetes with metformin and Thiazolidinediones can be warranted.

MATERIALS AND METHODS

This study is an observational study conducted in a major public hospital from June 2004 to September 2006 and included total of 70 Diabetics and 50 Non-diabetics. The reference population is Tamil speaking population belonging to lower and low middle socio-economic status attending government hospitals. The experimental population were all >40yrs and taken from Diabetic outpatients department, general OPD and general wards.

Inclusion criteria

1. Males and females >40 yrs attending OPD for other illness [for Non-Diabetic population]

2. Known Diabetics on treatment/not on treatment; Newly detected Diabetics according to American Diabetes Association guidelines.

Exclusion criteria

1. Smokers, alcoholics

2. Age <40 yrs

3. $Type_1$ Diabetics

4. Diseases that affect lipid profile like hypothyroidsm, cushing's syndrome, chronic Renal failure, Nephrotic syndrome, and those with TGL levels >350 mg /dl

5. Family history of premature CAD [< 45 years in first degree male relatives and < 55 years in female relatives]

6. Patients with Valvular heart disease, primary cardiomyopathies.

7. Pregnant ladies and those who are on oral contraceptives.

8. Those who are on Drugs affecting lipid profile (Thiazides and Metformin and Tniazolidinediones β-blockers, statins, Nicotinic acid, fibric acid derivatives).

A standardised health questionnaire was used covering the subject's past medical history, including current and previous medications, information about other diseases-Hypertension, CAD, stroke, physical activity family history of Diabetes mellitus and CAD. Physical examination included-

1. Two Blood pressure recordings obtained from right arm of patients, in sitting position, after 30 min of rest and at 5 min interval and then mean value was calculated.

2. Waist circumference was measured with a soft tape on standing subjects, midway between the lowest rib and iliac crest.

Investigations

1. Fasting blood samples were drawn for measurement of blood glucose, Hb AIC, serum lipid profile

2. Routine 12 lead Electrocardiogram

3. 2-D echocardiogram

were performed in each and every patient.

The NCEP ATP III guidelines published in 2001 recommend that plasma levels of Triglyceride, HDL-C to be measured after a 12 hour overnight fast. [Harrison's principle of Internal Medicine 16th edition, Page. 2295].

In our lab, the total cholesterol and TGL were measured enzymatically and then the cholesterol in the supernatant was taken after precipitation of apo B-containing lipoproteins to determine HDL-C. LDL-C is estimated using the following equation:

$$\text{LDL-C= Total Cholesterol - } \left(\frac{Triglycerides}{5}\right) \text{ -HDL-C}$$

$$\text{VLDL-C=} \frac{Plasma\ TGL}{5}$$

This formula is reasonably accurate if test results are obtained on fasting plasma and if the TGL level < 350 mg/dl

Defining Criteria

Metabolic syndrome-NCEP, ATP III guidelines

Risk factor	Defining level
1. Abdominal obesity	
Men	waist circumference >40 inches
Women	waist circumference>35 inches
2. Triglycerides	≥150 mg/dl
3. HDL Cholesterol	
Men	<40 mg/dl
Women	< 50 mg/dl
4. Blood pressure	≥ 130/85 mm of Hg
5. Fasting glucose	≥ 110 mg/dl

Since the defining level for Abdominal obesity was very high for an average Indian, we considered the International Diabetic Federation, 2005, definition of obesity, for our experimental population which was ≥ 90 cm for men and ≥ 80 cm for women. IDF also includes "Diabetic" status in 5th component mentioned above. In our study, we also considered the 5th component as fasting glucose ≥ 110 mg/dl or Diabetic state together. Any 3-5 symptoms positivity was considered as metabolic syndrome.

Diabetes mellitus-ADA guidelines [Harrison's Principles of Internal medicine – 16th Edition]

Symptoms of Diabetes mellitus + Random blood sugar ≥ 200 mg/dl

(Or)

Fasting plama glucose ≥ 126 mg/dl

(or)

Post-prandial glucose ≥ 200 mg/dl after 2 hours of an oral glucose level of 75g.

CAD definition

- History of Nitroglycerine use
- Experiencing typical angina
- Previous Myocardial Infarction

Presence of any one of the three, was the minimum requirement. And this was Validated against

ECG changes

and

2D Echo

Presence of Q waves and ST-T changes in ECG were taken as positive for CAD. This was confirmed by Regional wall motion abnormalities in 2D Echo which was the gold standard finding for CAD in this study.

Glycaemic control

HbA_1, C < 7% is good

> 7% is poor

Data was collected, compiled and presented in tabular columns and graphic forms and analysed subsequently. Chi-square test was used as the statistical test for significance with ‘P’ value of <0.05 as significant.

OBSERVATIONS AND RESULTS

TABLE – 1

PREVALENCE OF METABOLIC SYNDROME IN TYPE$_2$ DIABETES – MELLITUS

METABOLIC SYNDROME	NO. OF CASES	PERCENTAGE
PRESENT	49	70%
ABSENT	21	30%
TOTAL	70	100%

Out of total 70 patients of Type$_2$ Diabetes mellitus, metabolic syndrome was seen in 49 (70%) patients. Thus the prevalence of Metabolic syndrome in type $_2$ Diabetes Mellitus is 70%.

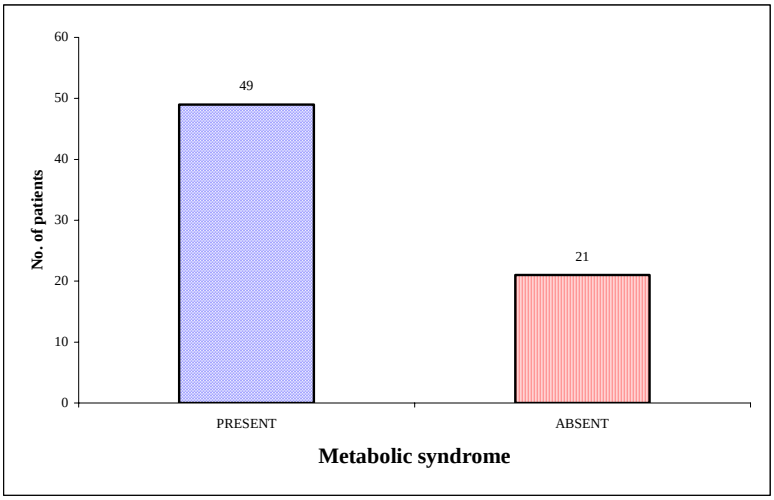


TABLE – 2

SEX DISTRIBUTION OF METABOLIC SYNDROME AMONG TYPE$_2$ DIABETICS

METABOLIC SYNDROME	MALE (n=45)	FEMALE (n=25)
PRESENT	32 (71.11%)	17 (68%)
ABSENT	13 (28.88%)	08 (32%)
TOTAL	45 (100%)	25 (100%)

Out of total 45 male patients of type$_2$ Diabetics, Metabolic syndrom was seen in 32 patients (71.11%) while almost similar prevalence (68%) was found in female patients of type$_2$ Diabetics.

Thus there was no significant difference found between prevalence of Metabolic syndrome in males and females with type$_2$ Diabetics.

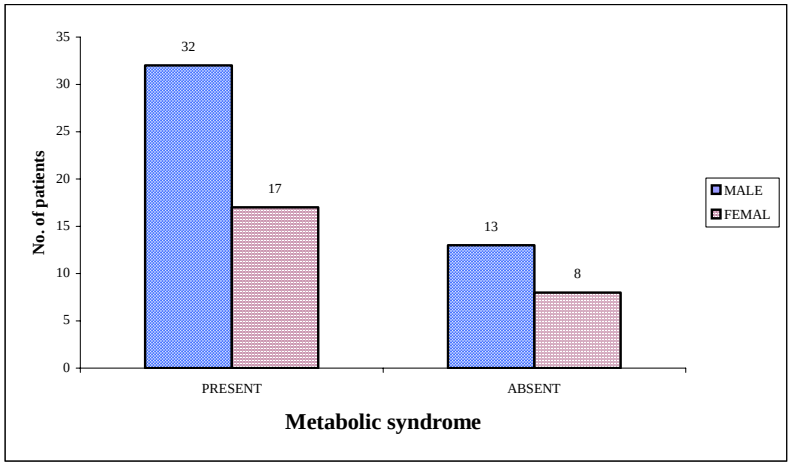


TABLE – 3

AGE DISTRIBUTION OF METABOLIC SYNDROME AMONG TYPE $_2$ DIABETICS

AGE-GROUP	METABOLIC SYNDROME		TOTAL
	PRESENT	ABSENT	
40-50	11 (61.11%)	07 (38.88%)	18
51-60	25 (71.42%)	10 (28.57%)	35
≥ 61	13 (76.47)	04 (23.52%)	17

In patients between the age group of 40 and 50 yrs Metabolic syndrome was present in 61.11% of patients.

In those between 51 and 60 yrs it was present in 71.42%.

In those ≥ 61 yrs it was present in 76.47%.

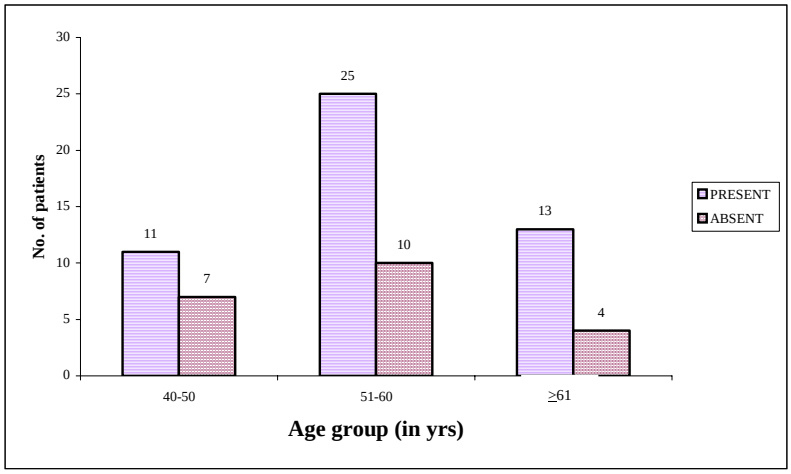


TABLE – 4

PREVALENCE OF CORONARY ARTERY DISEASE IN RELATION WITH GLYCAEMIC CONTROL IN TYPE $_2$ DIABETES MELLITUS

GLYCAEMIC CONTROL	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
GOOD (n=17)	03 (17.64%)	14 (82.35%)	17
POOR (n=53)	20 (37.73%)	33 (62.26%)	53
TOTAL	23	47	70

Coronary Artery disease was found in 37.73% patients of poor glycaemic control. Thus although there appears to be increase risk of CAD in patients with poor glycaemic control, by applying chi – square test, it was found that there was no statistically significant (P value > 0.05) association between risk of CAD and glycaemic control.

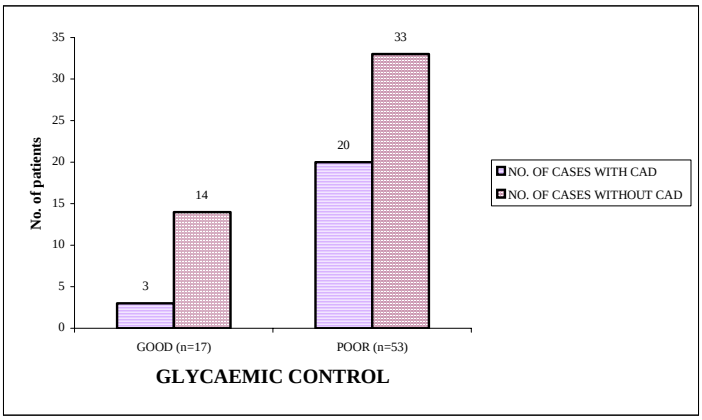


TABLE – 5

PREVALENCE OF CAD IN RELATION WITH METABOLIC SYNDROME AMONG TYPE$_2$ DIABETICS

METABOLIC SYNDROME	NO. OF CASES WITH CAD (n=23)	NO. OF CASES WITHOUT CAD (n=47)	TOTAL
PRESENT	20(86.95%)	29 (61.70%)	49
ABSENT	03 (13.04%)	18 (38.29%)	21
TOTAL	23	47	70

Out of 23 patients with evidence of CAD, 20 patients had metabolic syndrome (86.95%).

By applying chi-square test, there was a statistically significant association ($P<0.05$) between Metabolic syndrome and occurrence of CAD.

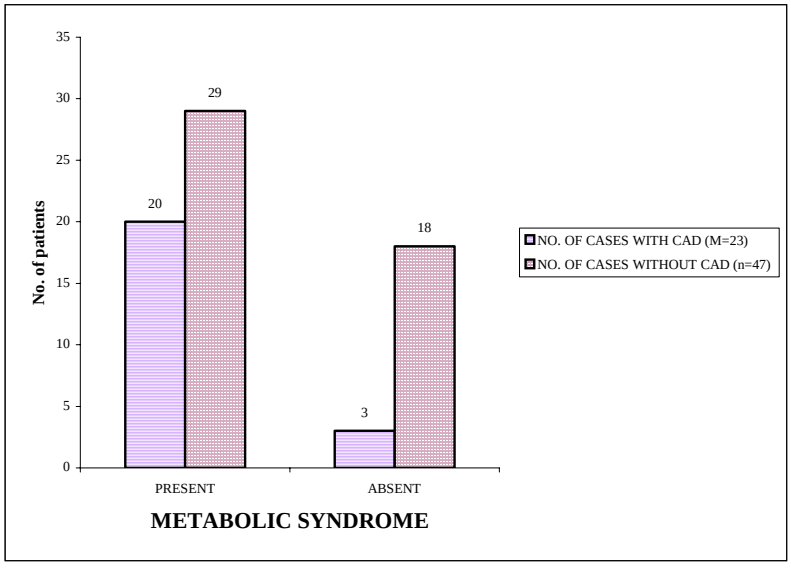


TABLE – 6

ASSOCIATION BETWEEN HYPERTENSION AND CAD IN TYPE$_2$ DIABETICS

HYPERTENSION	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	16 (44.44%)	20 (55.55%)	36
ABSENT	07 (20.58%)	27 (79.41%)	34
TOTAL	23	47	70

44.44% of Hypertension patients had CAD. By applying chi-square test (X^2=4.6 P<0.05) there was a statistically significant association between hypertension and occurrence of CAD

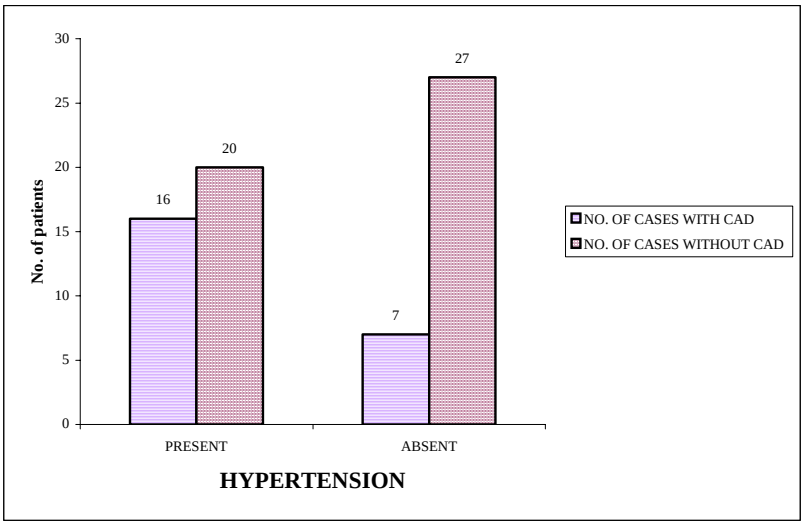


TABLE – 7

ASSOCIATION BETWEEN RAISED LDL AND CAD IN $TYPE_2$ DIABETES

LDL > 100 mg%	PATIENTS WITH CAD	PATIENTS WITHOUT CAD	TOTAL
PRESENT	16	20	36
ABSENT	07	27	34
TOTAL	23	47	70

By applying chi-square test, there was a statistically significant association (P value < 0.05 X^2 was 4.6) between LDL and occurrence of CAD.

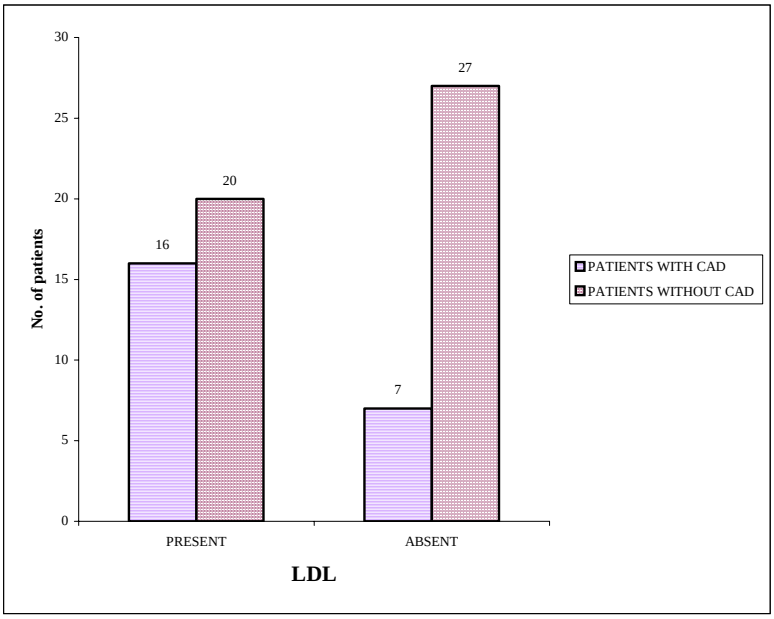


TABLE – 8

ASSOCIATION BETWEEN OBESITY AND CAD IN TYPE$_2$ DM

OBESITY	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	20 (86.95%)	29 (61.70%)	49
ABSENT	3 (13.04%)	18 (38.29%)	21
TOTAL	23	47	70

Out of 23 patients with CAD, 20 patients were obese (waist circumference >80cm in females, >90cm in males).

By applying chi-square test, there was a statistically significant association (X^2=4.77 P value < 0.05) between obesity and occurrence of CAD.

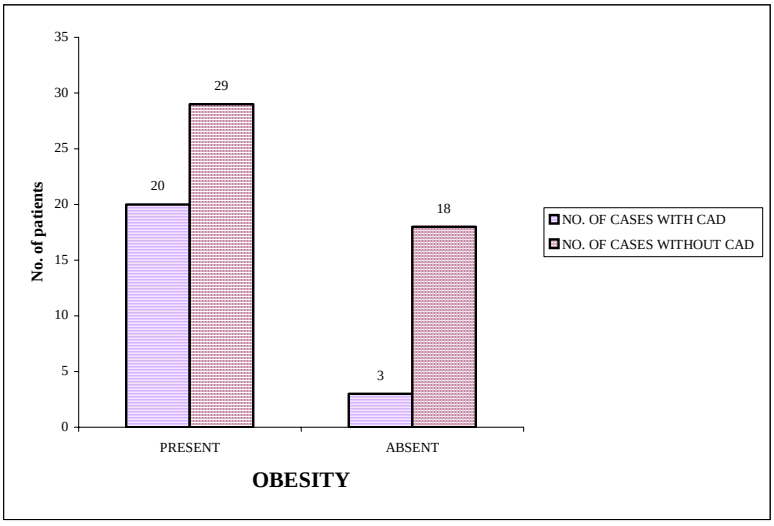


TABLE – 9

ASSOCIATION BETWEEN INCREASED TRIGLYCERIDES AND CAD AMONG TYPE$_2$ DIABETICS

TGL≥150mg%	PATIENTS WITH CAD	PATIENTS WITHOUT CAD	TOTAL
PRESENT	16	21	37
ABSENT	7	26	33
TOTAL	23	47	70

By applying chi-square test, there was a statistically significant association (X^2=3.91, P value <0.05) between TGL and occurrence of CAD.

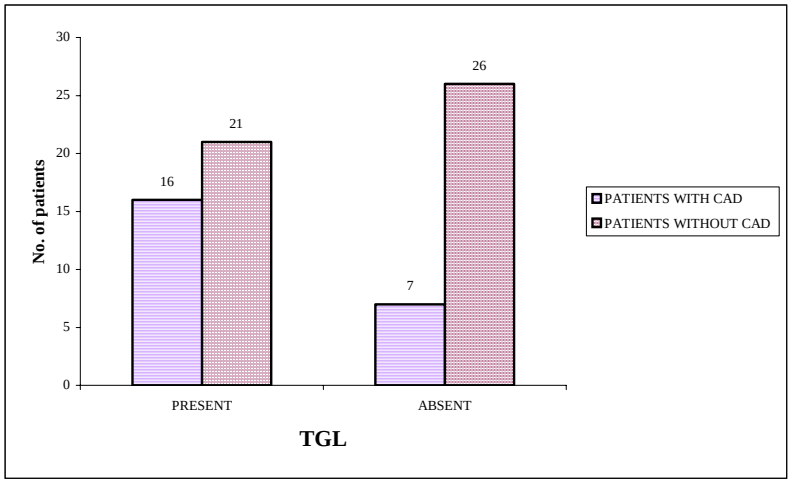


TABLE – 10

ASSOCIATION BETWEEN LOW HDL AND CAD AMONG TYPE$_2$ DIABETICS (IN MALES <40; IN FEMALES <50)

↓HDL	PATIENTS WITH CAD	PATIENTS WITHOUT CAD	TOTAL
PRESENT	13	9	22
ABSENT	10	38	48
TOTAL	23	47	70

By applying chi-square test, the x^2 was 10.2 and P value was thus <0.005 – A statistically significant association exists between low HDL and CAD.

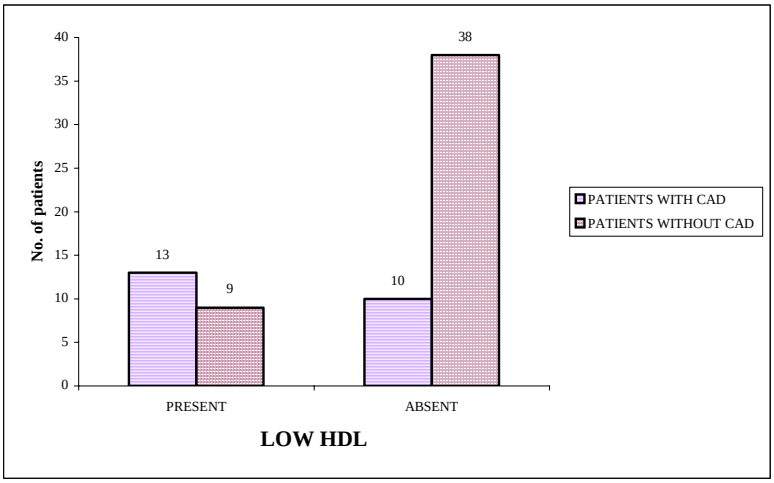


TABLE – 11

PREVALENCE OF METABOLIC SYNDROME AMONG NON-DIABETICS

METABOLIC SYNDROME	NO. OF CASES	PERCENTAGE
PRESENT	15	30%
ABSENT	35	70%
TOTAL	50	100%

Out of total 50 Non-Diabetic individuals, Metabolic syndrome was seen in 15 cases (30%) thus prevalence of Metabolic syndrome among Non-Diabetics was 30%.

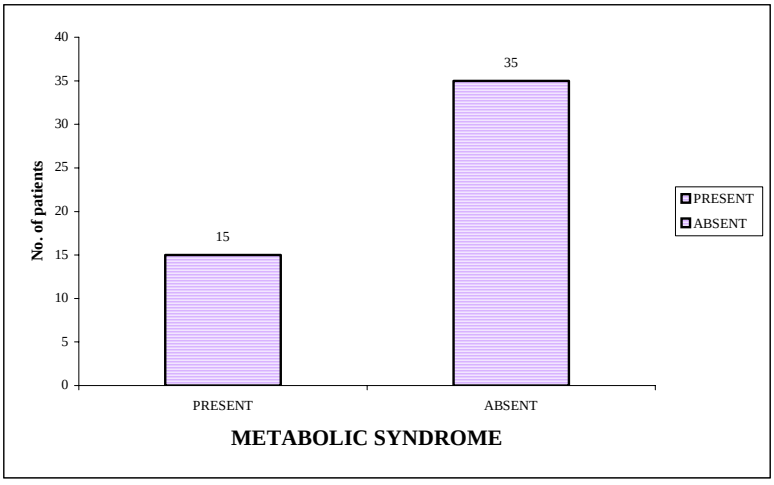


TABLE – 12

SEX DISTRIBUTION OF METABOLIC SYNDROME AMONG NON-DIABETICS

METABOLIC SYNDROME	MALE	FEMALE
PRESENT	8 (28.57%)	7 (31.81%)
ABSENT	20 (71.42%)	15 (68.18%)
TOTAL	28	22

Out of 28 male non-Diabetics, 8 persons had Metabolic syndrome (28.57%).

Out of 22 female non-Diabetics, 7 persons had metabolic syndrome (31.81%).

There is no much difference between the two groups.

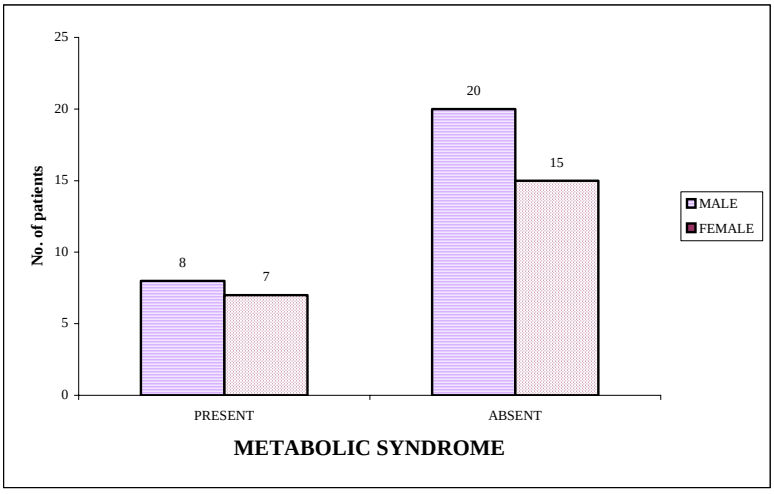


TABLE – 13

AGE DISTRIBUTION OF METABOLIC SYNDROME AMONG NON-DIABETICS

AGE-GROUP	METABOLIC SYNDROME		TOTAL
	PRESENT	ABSENT	
40-50	3 (13.04%)	20 (86.95%)	23
51-60	5 (33.33%)	10 (66.66%)	15
≥ 61	7 (58.33%)	5 (41.66%)	12

In individuals between 40 and 50 years metabolic syndrome is present in 13.04%

In individuals between 51 and 60 yrs, metabolic syndrome is present in 33.33%.

In individuals ≥ 61 yrs, it is present in 58.33%.

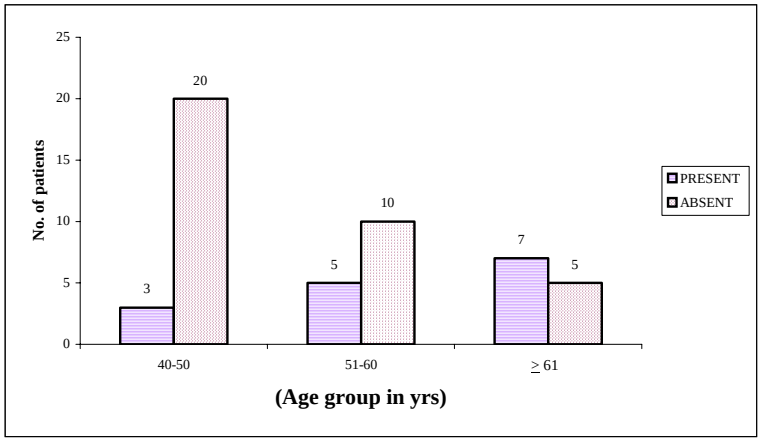


TABLE – 14

PREVALENCE OF CAD IN RELATION WITH METABOLIC SYNDROME AMONG NON-DIABETICS

METABOLIC SYNDROME	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	4	11	15
ABSENT	1	34	35
TOTAL	5	45	50

Out of 5 patients with evidence of CAD, 4 patients had metabolic syndrome.

By applying chi-square test, there was a statistically significant association (X^2=6.53, P value <0.02) between metabolic syndrome and occurrence of CAD.

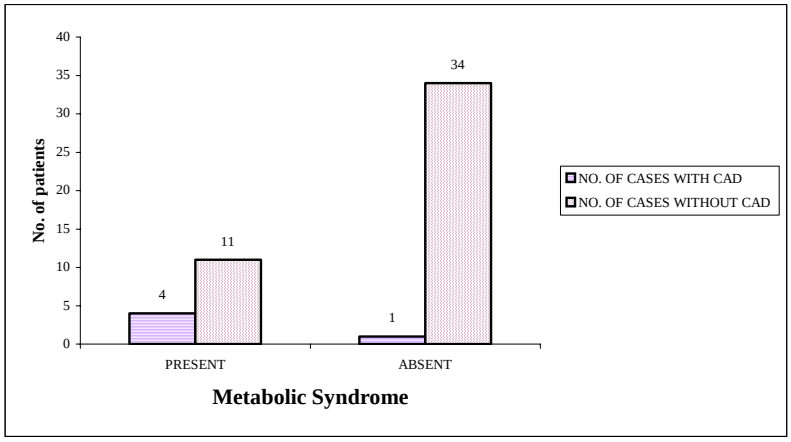


TABLE – 15

ASSOCIATION BETWEEN IMPAIRED FASTING GLUCOSE AND CAD AMONG NON-DIABETICS

IMPAIRED FASTING GLUCOSE	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	3	9	12
ABSENT	2	36	38
TOTAL	5	45	50

Out of 5 patients with CAD, 3 of them had Impaired fasting glucose.

By applying chi-square test, there was a statistically significant association between CAD occurrence and Impaired fasting glucose.

X^2=3.89, P value < 0.05

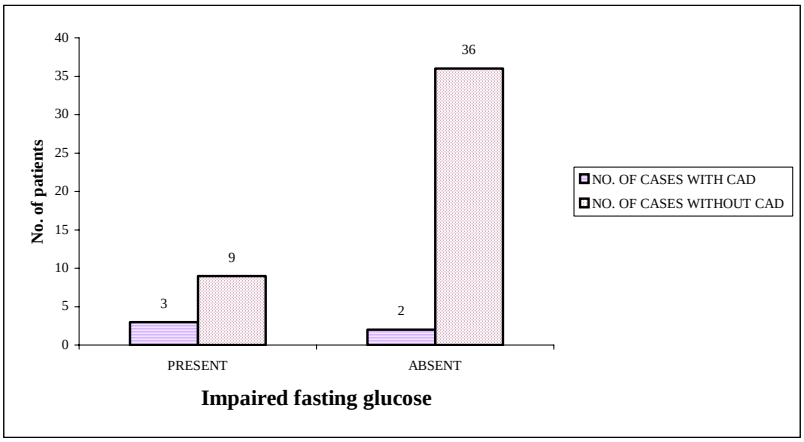


TABLE – 16

ASSOCIATION BETWEEN OBESITY AND CAD AMONG NON-DIABETICS

Here obesity is defined as waist circumference >90cm (in males) >80 cm (in females).

OBESITY	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	4	16	20
ABSENT	1	29	30
TOTAL	5	45	50

Among 5 patients with CAD, 4 of them were obese. By applying chi-square test, there was no statistically significant association between central obesity and CAD occurrence among Non-Diabetics

(x^2 was 3.69; P value between 0.1 and 0.05).

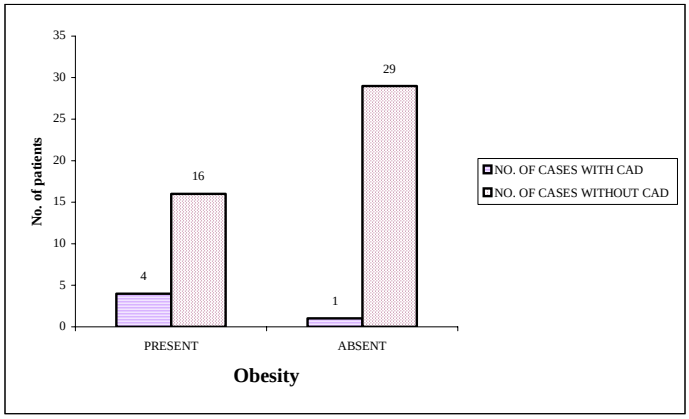


TABLE – 17

ASSOCIATION BETWEEN RAISED TRIGLYCERIDES AND CAD AMONG NON-DIABETICS

RAISED TRIGLYCERIDES	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	4	6	10
ABSENT	1	39	40
TOTAL	5	45	50

By applying chi-square test there was a statistically significant association between Raised triglycerides and CAD among Non-Diabetics.

(x^2=12.5; P value <0.001)

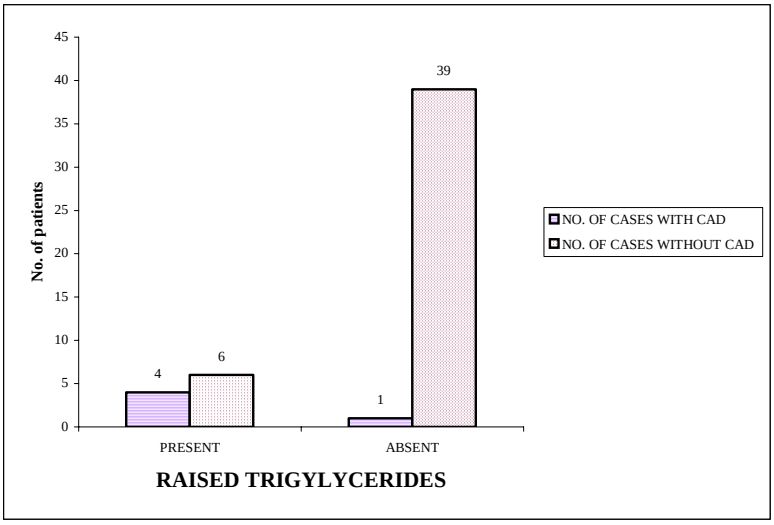


TABLE – 18

ASSOCIATION BETWEEN LOW HDL AND CAD OCCURENCE IN NON-DIABETICS

LOW HDL	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	3	-	3
ABSENT	2	45	47
TOTAL	5	45	50

By applying chi-square test, there was a statistically significant association between low HDL and occurrence of CAD among Non-Diabetics.

(x^2=28.72; P Value <0.001)

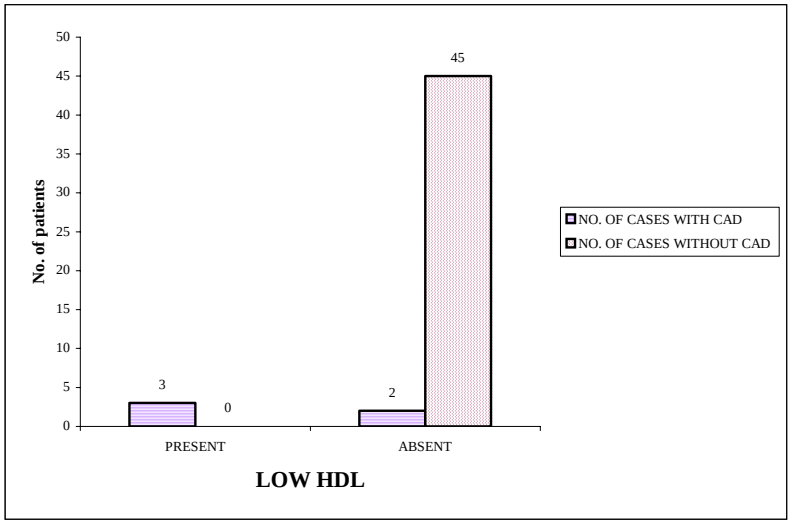


TABLE – 19

ASSOCIATION BETWEEN RAISED LDL AND CAD OCCURRENCE AMONG NON-DIABETICS

RAISED LDL	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	1	2	3
ABSENT	4	43	47
TOTAL	5	45	50

By applying chi-square test there was no statistically significant association between CAD occurrence and raised LDL among Non-Diabetics.

(x^2=1.92, P value between 0.5 and 0.1)

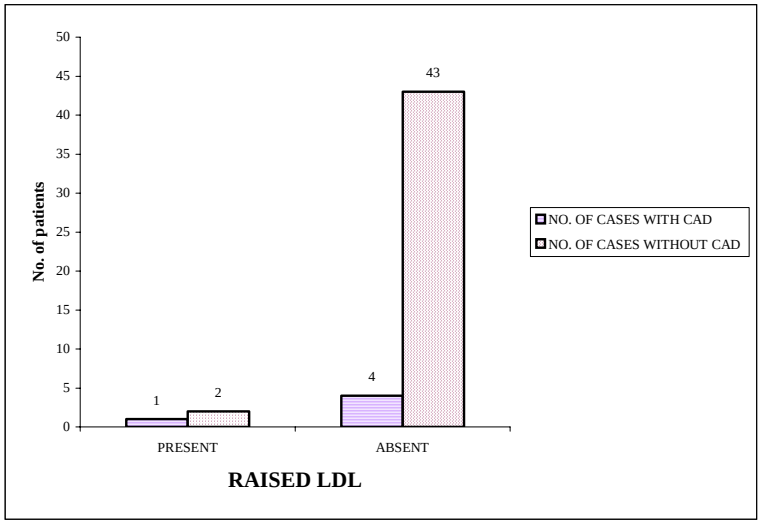


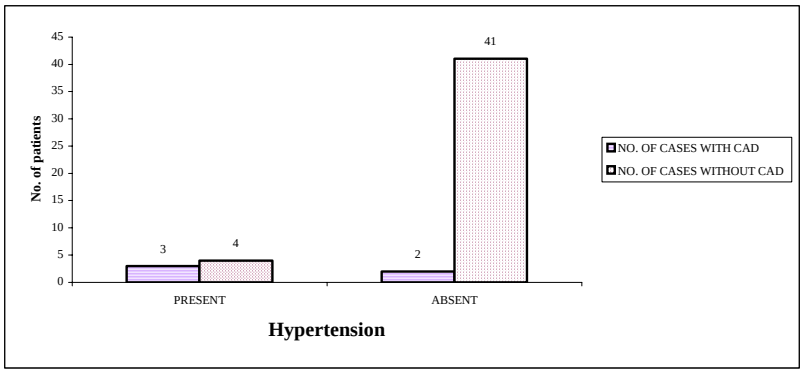
TABLE – 20

ASSOCIATION BETWEEN HYPERTENSION AND CAD AMONG NON-DIABETICS

HYPERTENSION	NO. OF CASES WITH CAD	NO. OF CASES WITHOUT CAD	TOTAL
PRESENT	3	4	7
ABSENT	2	41	43
TOTAL	5	45	50

Hypertension is defined as systolic BP≥140 and diastolic BP ≥90(JNC, VII Classification). Though systolic BP≥130 and Diastolic BP≥85 is considered a component of Metabolic syndrome, we considered only patients with BP≥ $\frac{140}{90}$ as hypertensives under this section.

Among 5 persons with CAD, 3 of them were hypertensives. By applying chi-square, test, there was a statistically significant association between CAD and Hypertension among Non-Diabetics. X^2=9.69; P Value <0.005



DISCUSSION

Out of 120 individuals who were taken up for final statistical analysis, the prevalence of metabolic syndrome among type $_2$ Diabetics was 70% and among Non-Diabetics was 30%.

A recent population based study by Isomaa and coworkers in finland [35] and Sweden concluded that metabolic syndrome was found in 80% of subjects with Type$_2$ Diabetics and 10-20% of Normal subjects. Another study by Groop L and Orho-Melander [36] which defined metabolic syndrome according to WHO criteria also had similar results. The prevalence has varied in other studies eg., Bruneck study [37] because of lack of accepted criteria for the definition of the syndrome.

Out of 45 male Diabetics the syndrome was present in 32 males-71.11%, in our study.

Out of 25 female diabetics the syndrome was present in 17 females-68%, in our study.

In the Italian longitudinal study on ageing [38] the prevalence of metabolic syndrome was 64.9% in Diabetic males and 87.1% in diabetic females.

In our study out of 28 male non-diabetics 8 persons had metabolic syndrome ie., 28.57%. out of 22 female non-diabetics, 7 persons had metabolic syndrome ie., 31.81%. This was 25.9% in non-diabetic men and 55.2% in Non-diabetic women in the Italian longitudinal study on Ageing. Thus the result of our study is consistent with the findings of other studies mentioned. When distributed in accordance with age, among diabetics in our study, metabolic syndrome was present in 61.11% of patients aged 40-50 years. 71.42% of patients aged 51-60 yrs; 76.47% of patients >61 yrs of age.

The same, among Non-diabetics was

13.04% in patients between 40-50 yrs.

33.33% in patients between 51-60 yrs

58.33% in patients ≥ 61 yrs

The increase in prevalence in metabolic syndrome was thus found with increasing age. This finding of our study was similar to the findings of Isomaa et al [35] and groop L and orho-melander [36]

Out of 53 patients with poor glycaemic control, CAD was found in 20 patients (37.73%). And out of 17 patients with good glycaemic control CAD was found in 3 patients (17.64%).

Although there appears to be increased risk of CAD in patients with poor glycaemic control, by applying chi-square test, it was found that there was no statistically significant association (P value >0.05) between risk of CAD and glycaemic control.

Thus in our study, it was found that chronic hyperglycaemia has little effect on macrovascular complications of Diabetes mellitus. This finding of our study is similar to that of UKPDS [18] which showed that improved glycaemic control did not conclusively reduce cardiovascular complications and mortality. This shows that along with hyperglycaemia, other factors like, Dyslipidemia, hypertension play a role in the occurrence of CAD.

In DCCT [39] the number of cardiovascular events did not differ between the standard and intensively treated groups. This may be because the duration of diabetes in the subjects included in this study was relatively short and the total number of events was very low.

In our study, among diabetics, out of 23 patients with evidence of CAD 20 patients (86.95%) had metabolic syndrome. By applying chi-square test, there was a statistically significant association (P<0.05) between metabolic syndrome and occurrence of CAD. Among non-Diabetics, out of 5 patients with evidence of CAD, 4 had metabolic syndrome, the P value was <0.02, statistically significant. This finding

of our study in similar with that of Isomaa et al [35] and Fagan TC et al [40].

Among Diabetics, there was a statistically significant association between hypertension and occurrence of CAD ($P<0.05$). And among non-diabetics also, the association between hypertension and CAD was statistically significant.

As far as obesity is concerned, there was a statistically significant association between obesity and CAD among diabetics and no such association in non-Diabetics.

This is because the association of obesity with cardiovascular disease is not direct: there is a strong etiologic association between obesity and other cardiovascular risk factors, especially for Diabetes; upto 75% of patients with type $_2$ Diabetes are reported to be obese. Therefore the association of obesity and CAD among diabetics would have been influenced by the underlying diabetic state itself.

Considering an association between increased TGL and CAD, it has a statistically significant association among both Diabetics and Non-Diabetics-especially in Non-diabetics the association is very strong (P Value <0.001) HDL has a strong correlation with CAD occurrence in both Diabetics (P value <0.005) and Non-diabetics (P Value <0.001).

Several large prospective observational studies showed that hypertriglyceridemia is an independent risk factor for CAD when it is associated with low HDL and /or raised LDL [31].

In prospective studies in which triglyceride has been considered jointly with HDL-C, LDL-C, total cholesterol and other known CAD risk factors, multivariate statistical analysis generally have not shown TGL to be an independent risk factor for CAD [41].

Because of a strong inverse correlation between TGL and HDL-C, relatively low precision of TGL measurements and considerably higher variability of TGL values compared with cholesterol values, and finally very high TGL levels such as those with lipoprotein phenotype I and V appear to have no increased risk of CAD, the role of TGL as a marker of CAD has been diminished.

This is what shown in our study where HDL is proved to be a better marker of CAD among both diabetics and non-diabetics.

In one study [42] high TGL was associated with higher social classes compared to lower social class-4. Whereas HDL levels showed no association with social class. This probably could explain why HDL levels show stronger correlation with CAD occurrence than TGL levels in our study which was done in lower social class mainly.

Among 19 prospective epidemiologic studies, 15 have shown a significant and strong inverse relationship between HDL-C and CAD, with a 2-3% decrease in CAD risk for each 1 mg/dl increase in HDL-C level, after adjustment to control for other risk factors.[4]

Association between IFG and CAD was tested in Non-diabetics and it showed a strong statistically significant association (P value <0.05). We never tested this component of metabolic syndrome among diabetics because almost 64 of 70 diabetics had fasting glucose >110 mg and Diabetes itself is CAD equivalent.

Testing IFG and CAD correlation shows that it is possible that much lower levels of fasting hyperglycemia may be associated with CAD and other microvascular complications than the level currently used for the diagnosis of Type $_2$ D.M. (126 mg/dl)

There was a statistically significant association between raised LDL and CAD among diabetics (P value <0.05) but among Non-diabetics the association failed (P value between 0.5 and 0.1) suggesting that LDL-C, as an independent risk factor of CAD, has failed… whereas as a component of Dyslipidemia (↑TGL, ↓ HDL and ↑ LDL) is a definite risk factor.

LIMITATIONS OF THE STUDY

1. Measurement of a single fasting Triglyceride may inadequately represent this lipid. Post-prandial TGL level is a better index of CAD risk than fasting value. [43]

2. Lp (a) levels were not measured which is 10 times more atherogenic than LDL. Levels >30 mg/dl are associated with a two fold greater risk for CAD and this is regardless of the absolute level of LDL.

SUMMARY AND CONCLUSIONS

1. (a) The prevalence of metabolic syndrome among Type $_2$ Diabetics in our study is 70%.

   (b) The prevalence of metabolic syndrome among non-Diabetics is 30%

2. There was no significant difference found in prevalence of metabolic syndrome in males and females among both Diabetics and non-Diabetics.

3. There was a clear increase in prevalence of metabolic syndrome found with increasing age in both the study population.

4. No statistically significant association between glycaemic control and CAD occurrence.

5. A Statistically significant association was found between MS and CAD among Diabetics and Non-Diabetics.

6. Among all the components of Metabolic syndrome low HDL was found to be the strong predictor of CAD in both the study population.

Thus it is concluded that:

1. Presence of metabolic syndrome influences risk of CAD among both Diabetics and Non-diabetics.

2. HDL can be used as a surrogate marker for CAD occurrence among diabetics and general population.

ABBREVIATIONS

1.	CAD	-	Coronary Artery Disease
2.	WHO	-	World health organisation
3.	NCEP	-	National cholesterol education programme
4.	ATP-III	-	Adult treatment panel
5.	HDL	-	High density lipoprotein
6.	LDL	-	Low density lipoprotein
7.	LP (a)	-	Lipoprotein (a)
8.	TGL	-	Triglycerides
9.	BP	-	Blood Pressure
10.	IFG	-	Impaired fasting glucose
11.	TGT	-	Impaired glucose tolerance
12.	ACE-I	-	Angiotensin converting enzyme-Inhibitor

13. ARB - Angiotensin Receptor Blocker

14. eg., - example

15. DM - Diabetes Mellitus

16. HB A_1C- Hemoglobin A_1 C

17. esp. - especially

18. MI - Myocardial Infarction

19. OPD - Out patient Department

20. ADA - American Diabetes Association

21. S.No - Serial Number

22. H/O - History of

23. M.S - Metabolic Syndrome

24. E/O - Evidence of

A CORRELATIVE STUDY OF METABOLIC SYNDROME AND CAD AMONG TYPE 2 DIABETICS AND NON DIABETICS – PROFORMA

Name .....

Age ..... Sex .....

Address .....

.....

Occupation .....

Roll Number .....

Family History of DM ..... Yes ☐ No ☐

Family history of CAD ..... Yes ☐ No ☐

Exclusion criteria history of smoking ..... Yes ☐ No ☐

Exclusion criteria history of Alcohol consumption. Yes ☐ No ☐

Does the patient have diabetes..... Yes ☐ No ☐

History of CAD..... Yes ☐ No ☐

History of hypertension ..... Yes ☐ No ☐

History of stroke..... Yes ☐ No ☐

Long term ongoing Treatment if any .....

Physical Examination

Ht..... Wt.....

Waist Measurement .....

BP .....

Investigations

Fasting Blood glucose .....

Serum Triglycerides .....

Serum HDL Cholesterol .....

Serum LDL Cholesterol .....

ECG .....

ECHO .....

.....

HbA_1 C .....

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