Faculty of medicin

Asymptomatic Ischemic Heart Disease in Diabetic Patients in Benghazi

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A dissertation submitted to Faculty of Medicine university of Benghazi for partial fulfillment of the requirements for the Master degree in Internal Medicine.

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Faculty of medicine

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الإهداء.....

إلى من جـ رع الكأس فاراً لسقني قطرة حب ,,,,إلى من كلّت أم ليقدم لنا لحظة سعادة

إلى من حصد الأشواك عن دربي يمهد لي طريق العلم ,,,, إلى القلب اكير (واي العزز).

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إلى شاطئي عندما أضيع، ومبع الحنان عندما تقسـ و الأم، والقلب اكير عندما أفقد كل القلوب... الروح لجسدي، والماء لصحرائي... زوجتى الغالية (جيهان)

إلى أخوتى ورفقاء دربي وهذه الحياة بدوكم لاشيء معك أون أ وبدونك أون مل أي شيء .. .. إلى أ صحاب القلوب الطيبة والنوا الصادقة.....(أخوتى)

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إيهم جميعاً أهدي هذا البحث المتواضع .....

B y : Hatem A. A. Fageh

MBChB

A dissertation submitted to Faculty of Medicine university of Benghazi for partial fulfillment of the requirements for the Master degree in Internal Medicine.

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supervised by

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Declaration

This is to declare that I have not submitted this research work to any other university for purpose of obtaining any postgraduate degree in medicine

Candidate: Hatem A. A. Fageh

2014-2015

Certification

This thesis entitled

(Asymptomatic Ischemic Heart Disease in 140 diabetic patients) prepared by Hatem A. A. Fageh *has been approved for submission to*

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Chapter 1

Abstract

Abstract:

Introduction: Type 2 diabetes mellitus (DM) has got a distinct association with coronary artery disease (CAD); and diabetic patients have 2-4 fold higher risk of developing CAD than people without DM [1]. However,
progressive coronary artery disease remains asymptomatic in many cases of type 2 diabetes and this makes diagnosis difficult at proper time. **Objective:** To determine the risk factors for asymptomatic IHD in diabetic patients who underwent tread mail test. **Patients and method:** Cross-sectional study, a structured pre-tested questionnaire was developed to seek information on demographics of patient, duration of DM, presence of arterial hypertension, F/H IHD. The questionnaire also used to record observations on various investigational parameters for each patient (HbA1C, lipid profile,urine for micoalbuminuria, resting ECG, Echocardiography and . **Results:** The present study included 140 diabetic patients from Diabetic Clinic and Al Hawari general hospital (44.3% males and 55.7%) females . Exercise ECG Treadmill test ,(TMT) was positive in 16.4% of the patients , 22.2% was equivocal and 61.4% was negative .Exercise ECG was positive in 22.6% of males and 11.5% of females, but this difference was not statistically significant (P = 0.136). Duration of diabetes was 6 years or more in73.6% of patients, with mean duration(10.1± 7.5) .Family history of IHD was detected in 19.3%. Hypertension was recorded in 44.3% of the patients. Un-controlled hypertension was found in 59.3%. Dyslipidemia was recorded in 18.6% of the patients, exercise ECG results were positive in 19.2% of patients who had dyslipidemia , while positive in 15.8% of patients without dyslipidemia .However this difference was not statistically significant (P = 0.144). Level of HbA1c <7 constitute to 20 % , while ≥7 constitute to 80% . Exercise ECG results were positive in 10.7% of patients with level of HbA1c <7 compared to 17.9% in patients with HbA1c ≥7, but this difference not statistically significant P = (0.257). Microalbuminuria was positive in 29.3% of the patients .Exercise ECG results were positive in (29.3%) of patients with microalbuminurea, compared to 11.1% in patients who were negative for microalbuminurea, this difference was statistically significant (P = 0.0383).**Conclusion:** 1) From this study we found that the most important risk factor for asymptomatic IHD in type 2 NIDDM patients were microalbuminuria

2) Proportion of silent ischemia in type 2 DM patients was 16.4% in this study, which was within the limit recorded internationally (10 – 20%).

Recommendation: we recommend screening for IHD with TMT in patients with DM for early diagnosis and early treatment to get better prognosis for the diabetic patients.

Chapter 2

Introduction

i. Atherosclerotic burden associated with diabetes:

Diabetes mellitus is estimated to affect more than 150 million people worldwide, with an expected doubling number in the next 25 years, reaching 5.4% of the total adult population [2]

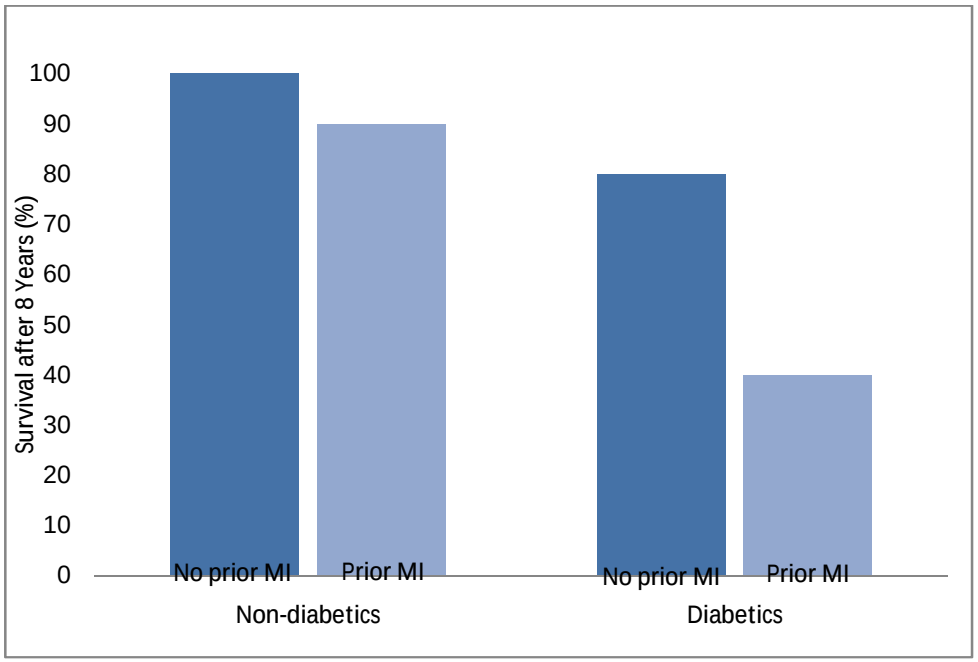
In the United States 17 million people are diabetics, a 95% of whom have type 2 diabetes. Among these 5-6 million are unaware of their condition and do not receive treatment [3,4]

An additional 35 million 20% of all people in the middle- adult life and 35% of the entire older population- have some degree of abnormal glucose tolerance and show signs of insulin resistance, this higher-risk group will account for a significant proportion of CVD and premature mortality. [5]

The incidence of and mortality from all forms of CVD are two to eight fold higher in persons with diabetes than in those without diabetes[6,7].

Coronary artery disease (CAD) account for 75% of all deaths in individuals with diabetes [8,9] and as many as 30% of patients presenting with acute coronary syndromes have the disease [4]

Both in hospital and long-term mortality rates after an acute myocardial infarction (MI) are twice as high for patients with diabetes as for those without diabetes (Fig 1) .



In one population-based study[7] ,the 7 year incidence of first myocardial infarction or death for patients with diabetes was 20 % but was only 3.5 % for non-diabetic patients.

A history of myocardial infarction increased the rate of recurrent M.I or cardiovascular death events for both groups(18.8% in non-diabetic persons and 45% in those with D.M).

Thus patients with diabetes but without previous M.I carry the same level of risk for subsequent acute coronary events as non-diabetic patients with previous M.I.

Such results led the adult treatment panel III of the national cholesterol education programme to establish diabetes as a CAD risk equivalent mandating aggressive anti-atherosclerotic treatment [8].

The increased in the incidence of diabetes, its association with CAD, and the accompanying high morbidity and mortality make diabetes a serious public-health issue.

ii. Definition and classification:

Diabetes Mellitus is metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or a combination of both.

Type 1 diabetes is due to a lack of endogenous pancreatic insulin production while the increased blood glucose in type 2 diabetes results from more complex processes.

Traditionally diabetes was diagnosed based on symptoms due to hyperglycemia, but during the last decades emphasis has been placed on the need to identify diabetes and other forms of glucose abnormalities in asymptomatic subjects.

Diabetes mellitus is associated with development of long term organ damage including retinopathy ,nephropathy, neuropathy and autonomic dysfunction.

Patients with diabetes are at a particularly high risk for cardiovascular, cerebrovascular and peripheral artery disease.

Four main etiologic categories of diabetes have been identified in diabetes. Type 1, Type 2, other specific types such as Maturity-onset Diabetes in Young (MODY) or secondary to other conditions or diseases e g. surgery and gestational diabetes.

The current classification criteria (table 1) have been issued by World Health Organization (WHO) and American Diabetes Association (ADA) [9]

The WHO recommendations for glucometabolic classification are based on measuring both fasting and two hours post-load glucose concentrations and recommend that 75 g oral glucose tolerance (OGTT) should be performed in the absence of overt hyperglycemia.

Table 1 criteria used for glucometabolic classification from WHO (1999 and 2006) and ADA (1997 and 2003)

Glucometabolic	**Source**	**Classification criteria mmol/L(mg/dl)**
Normal glucose regulation (NGR)	WHO ADA(1997) ADA(2003)	FPG<6.1(110) +2h PG<7.8(140) FPG<6.1(110) FPG<5.6(100)
Impaired Fasting glucose (IFG)	WHO ADA(1997) ADA(2003)	FPG~6.1(110) and<7(126) +2hPG<7.8(140) FPG~6.1(110) and <7(126) FPG~5.6(100) and<7(126)
Impaired glucose tolerance (IGT)	WHO	FPG<7(126)+2hPG~7.8 And<11.1(200)
Impaired glucose (IGH)	WHO	IFG or IGT
Diabetes mellitus (DM)	WHO ADA(1997)	FPG~7(126) or2h PG~11.1(200) FPG~7(126)

Venous plasma glucose

(mmol/L)(mg/dl)

	ADA(2003)	FPG>7(126)

Glycated haemoglobin (HbA1,c) is useful for measuring metabolic control and the efficacy of glucose lowering treatment in people with diabetes.

It represents a mean value of blood glucose during the preceding six to eight weeks (life span of erythrocytes).

Importantly, new to the diagnostic criteria in 2010, glycosylated haemoglobin (A1c) level ≥6.5% has been added.

Diabetes is among the most common chronic disease in the world, affecting an estimated 180 million people in 2008. [10]

Confounding this high global burden is the increasing incidence and prevalence of type 2 diabetes.

Driven by increasing population age, obesity and physical inactivity as well as by the increase longevity of patient with diabetes; estimated project that more than 360 million persons will be affected by diabetes by 2030.

Where as much attention historically has focused on the prevention and treatment of microvascular disease complications of diabetes (i.e. retinopathy, nephropathy and neuropathy), cardiovascular disease (CVD) remains the principle cause of morbidity and driver of mortality in the setting of diabetes-most commonly in the form of coronary heart disease (CHD), but also in the

incremental risk associated with diabetes for cerebrovascular disease, peripheral vascular disease and heart failure.

iii. Coronary heart disease in patients with diabetes:

Traditional CHD risk factors such as hypertension, dyslipidemia and adiposity cluster in patients with impaired glucose tolerance or diabetes and each condition directly influence atherosclerosis disease risk.

However, this clustering doesn't completely account for increased risk observed among patients with diabetes with numerous other implicated mechanisms (Table.2) [11].

Table .2(Examples of mechanisms implicated in diabetic vascular diseases):

I. Endothelium:
a. Increased 'NF-kB activation.
b. Decrease Nitric Oxide production.
c. Decrease Prostacyclin bioavailability.
d. Increase 'Endothelium activity.
e. Increase 'Angiotensin II acivity.
f-Increased 'Cyclo-oxygenase 2 activity.
g. Increase thromboxane A2 activiy.
h. Increase reactive oxygen species.

i. Decrease RAGE expression.
2.Inflammation:
a. Increase IL A 1B,IL6,CD 36, MCP-1
b. Increase ICAMs, VCMs and selectins
c. Increase activity of protein kinase C
d. Increase AGEs and AGE/RAGE interactions
3.Vascular smooth muscle cells and vascular matrix:
a. Increased proliferation and migration into intima
b. Increased matrix degradation altered matrix components

CHD in the patients with DM (Mechanism consideration linking DM and atherosclerosis):

The pathobiologic attribution of hyperglycemia to CVD risk per se remains poorly understood; but given the clear association between severity of, hyperglycaemia and CVD risk in both type 1 and type 2 diabetes ,hyperglycaemia is linking to directly influence atherosclerosis development ,progression and instability [11].

The principle vascular perturbation linked to hyperglycemia include endothelial dysfunction, vascular effects of advanced glycation end products ,adverse effects of circulating free fatty acids ,and increased systemic inflammation.

Endothelial dysfunction, a hall mark of diabetic vascular disease is associated with increased hypertension and adverse CVD outcomes [12] .

The Myriad mechanisms contributing to endothelial dysfunction include:

Abnormal nitric oxide biology, increased endothelin and angiotensin II and reduced prostacyclin activity, all of which contribute to abnormal control of blood flow.

In the setting of ACS events, no reflow after percutaneous intervention reflecting acute endothelial dysfunction occur more commonly in the presence of diabetes or hyperglycemia and may contribute to increased

myocardial injury, resulting in large infarctions, increased arrhythmia and worse systolic function.

Abnormalities in lipid metabolism also contribute to the increased atherosclerotic risk associated with DM [13].

Diabetic dyslipidemia is characterized by high TG level, low HDL concentration and increased LDL particles.

Perturbations in the proteo-fibrinolytic system and platelets biology further compound the direct vascular effects of diabetes, yielding a constitutive prothrombotic milieu. [14]

These abnormalities include increased circulating tissue factors, factor VII, Von willebrand factor and plasminogen activator inhibitor 1, with decreased levels of Antithrombin III and Protein C. In addition, disturbances of platelets activation, aggregation, morphology and life span further contribute to increased thrombotic potential, as well as to the acceleration of atherosclerosis.

Table 3

Perturbations of platelets structure and function associated with diabetes:
l.Reduced membrane fluidity.
2.Altered Ca+2 and Mg+2 haemostasis .
3.Increased arachidonic acid metabolism.
4.Increased thromoxane A2 synthesis.
5-Decreased nitric oxide and prostacyclin production.
6. Decreased antioxidant levels.
7.Increased expression of activation dependent adhesion molecule e.g., glycoprotein IIb/IIIa, P.selectin.
8.Increased platelets microparticles formation.
9.Increased platelets turnover.

Increased systemic inflammation portends an increased risk for diabetes and diabetic atherosclerotic disease and diabetes is associated with increased oxidative stress and the accumulation of advanced glycation end products. [15]

For examples, diabetes is associated with lipid rich atherosclerotic plaque and increased inflammatory cell infiltration, increased expression of the receptor for advanced glycation end products, yielding plaques with characteristics of higher risk in both coronary and carotid arteries [11,16].

iv, Silent myocardial ischemia

The prognostic importanance and mechanisms of silent ischemia have been the subject of considerable interest for almost 30 years.

Patients with silent ischemia have been stratified into three categories by Cohn and associates.

This first and least common form, **type 1** silent ischemia, occurs in totally asymptomatic patients with obstructive CAD, which may be sever.

These patients do not experience angina at any time; some type 1 patients do not even experience pain in the course of MI.

Epidemiologic studies of sudden death, as well as clinical and postmortem studies of patients with silent MI and studies of patients with chronic angina pectoris, have suggested that many patients with extensive coronary artery obstruction never experience angina pectoris in any of its recognized form (stable , unstable or variant).

These patients with type 1 silent ischemia may be considered to have a defective angina warning system.

Type II silent ischemia is the form that occurs in patients with documented previous MI.

The third and much more frequent forms, designated **type III** silent ischemia, occurs in patients with the usual forms of chronic stable angina, unstable angina, and Prinzmetal angina. When monitored, patients with this form of silent ischemia exhibit some episodes of ischemia associated with chest discomfort and other episodes that are not- that is ,episodes of silent (asymptomatic) ischemia. The total ischemic burden in these patients refers to the total period of ischemic, both symptomatic and asymptomatic.

v. Mechanism Of Silent Ischemia:

It is not clear why some patients with unequivocal evidence of ischemia do not experience chest pain, whereas other are symptomatic.

Difference in peripheral and central neural processing of pain have been proposed as important factors underlying silent ischemia.

PET imaging of cerebral blood flow during painful versus silent ischemia has pointed toward difference in handling of different signals by the central nervous system.

Specifically, overactive gating of different signals in the thalamus may reduce the cortical activation necessary for perception of pain from the heart.

Autonomic neuropathy has also been implicated as a reason for reduced sensation of pain during ischemia. Although increased release of endorphins may play a role in some patients with silent ischemia, some researchers have

suggested that anti inflammatory cytokines are at play in reducing inflammatory processing that may participates in the genesis of chest pain .

Cardiac autonomic neuropathy and silent

myocardial ischaemia ;

Autonomic neuropathy is a serious and common complication of diabetes. It has been estimated that about 20% of asymptomatic diabetic patients have abnormal cardiovascular autonomic function [17,18]. The risk for cardiovascular autonomic neuropathy depends on the duration of diabetes and the degree of glycaemic control. It is caused by injury to the autonomic nerve fibers that innervate the heart and blood vessels. The hypotheses concerning its etiology include metabolic insult to nerve fibers, neurovascular insufficiency, neurohormonal growth factor deficiency and autoimmune damage [19]. The main consequences are dysfunctional heart rate control, abnormal vascular dynamics and cardiac denervation, which become clinically overt as exercise intolerance [20], orthostatic hypotension [21], intraoperative cardiovascular liability [22] and silent myocardial ischemia.

The earliest sign is often a vagal deficiency leaving sympathetic innervations unopposed. A manifestation of this is that diabetic patients tend to have higher resting heart rate and less heart rate variability during the day than their non-diabetic counterparts. A clinical setting where this may be particularly unfavorable is at the onset of a myocardial infarction causing unnecessary myocardial oxygen consumption in a situation with decreased nutritional blood supply.

The autonomic nervous system influences coronary blood flow regulation independently of endothelial cell function. Diabetic patients with sympathetic nervous system dysfunction have impaired dilatation of coronary resistance vessels in response to cold pressure testing when compared with diabetics without defects in cardiac adrenergic nerve density. Global myocardial blood flow and coronary flow reserve, studied by positron emission tomography in response to adenosine provocation, were subnormal in diabetics with cardiovascular autonomic neuropathy. It is obvious that cardiovascular autonomic neuropathy may provoke ischemic episodes by upsetting the balance between myocardial supply and demand.

As a result of autzonomic neuropathy, silent myocardial ischemia is prevalent in diabetic patients but is often symptomatically apparent only in advanced

stages of disease. Instead of typical angina, patients often complain of shortness of breath, diaphoresis, or profound fatigue.

Knowledge on the actual prevalence of cardiovascular autonomic neuropathy and its related mortality rates is conflicting. However, different studies and meta analyses reveal that mortality rates among diabetic subjects with cardiovascular autonomic neuropathy are many times higher than among those without. Subject with diabetes and low levels of autonomic function parameters (baroreflex sensitivity, heart rate variability and classical Ewing tests) had an approximately double risk of mortality); in the HOORN Study [23]. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD study) cardiac autonomic dysfunction, assessed by the Valsalva maneuver, was a strong predictor of ischemia, whereas traditional and emerging risk factors were not. Impaired angina perception largely accounts for such an increased mortality. Indeed, silent myocardial ischaemia delays treatment of acute coronary events and makes it more difficult to monitor anti-ischemic treatment or determine whether restenosis has occurred after a coronary intervention. Although silent myocardial ischemia has a reported prevalence of **10-20%** in diabetic populations compared with only **1-4%** in non-diabetic populations, routine screening for silent myocardial ischaemia in diabetics remains debatable. In the DIAD study [24],22% of 522 type 2 diabetic patients randomized to adenosine stress testing with myocardial perfusion imaging by means of single photon emission computerized tomography

(SPECT) and silent ischemia .This would indicate that that asymptomatic diabetic patients have at least an intermediate probability of CAD , prevalence that may justify routine screening for CAD by non invasive testing .In a series of 203 diabetic patients [25] , the prevalence of functional silent myocardial ischemia , assessed by stress ECG and thallium myocardial scintigraphy , was 15.7% . In this study, the positive predictive value of exercise was 90% , compared with 63% of thallium myocardial scintigraphy . Thus, available evidence highlights the need for non invasive screening by means of stress testing in diabetic subjects, especially considering the high sensitivity, feasibility and low costs of exercise ECG.

Based on cardiovascular autonomic neuropathy associated coronary blood flow impairment, misdiagnosed CAD, and the consequently higher risk of mortality, it is presently recommended that a baseline determination of cardiovascular autonomic function is performed upon diagnosis in type 2 diabetic and within 5 years of diagnosis for type 1 diabetes, followed by yearly repeated tests. [26]

vi. ECG Signs in Diabetic Patients

Fibrotic changes, especially in the basal area of the left ventricle, have frequently been observed in diabetic patients, even when cardiac involvement is clinically not yet evident. An example of the ECG tracing in a diabetic patient with no apparent heart disease is given in Figure2.

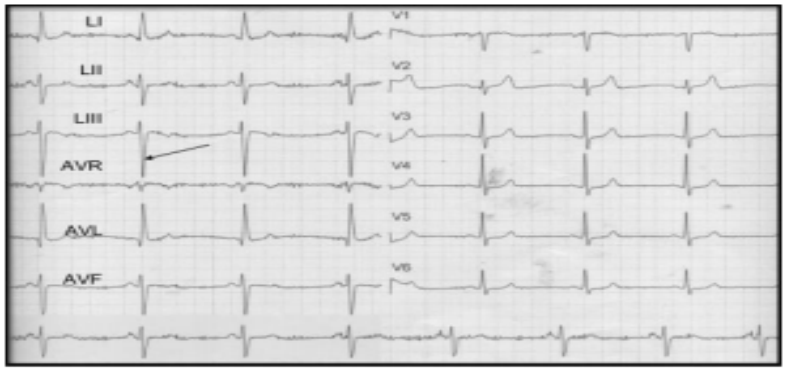


Figure 2. ECG of a 64-year-old woman with type 2 diabetes mellitus without other risk factors. Note the deep S-wave (arrow) in LIII (19 mm) and the high R-wave in aVL (15 mm); ECG indicates basal left ventricular hypertrophy.

Even in healthy individuals, hyperinsulinemia-induced hypoglycemia can prolong the QTc interval and decrease T-wave area and amplitude. [27] In the Europe and Diabetes (EURODIAB) study [28], on diabetic individuals with a normal QTc at baseline, female sex and higher values of hemoglobin A1C and systolic blood pressure were associated with increased risk of prolonged QTc, whereas physical activity and normal body mass index were protective factors. Correlation was found between the QT duration and the amount of coronary calcium; this association was driven by the QRS and not by JT interval duration. [29] Okin et al [30] also found that both QTc prolongation and ST depression predicted all-cause mortality in patients with type 2 diabetes mellitus. Genetic variants in previously identified candidate genes may be associated with QT interval duration in individuals with diabetes mellitus. [31], Sawicki et al [32] found QT, dispersion to be the

most important independent predictor of total mortality and also an independent predictor of cardiac and cerebrovascular mortality; these observations were not confirmed in a later study.[33]

The EURODIAB Insulin-Dependent Diabetes Mellitus Complications Study (EURODIAB IDDM) [34] investigated 3250 type 1 diabetes patients with an average diabetes duration of >30 years; the prevalence of left ventricular hypertrophy was found to be 3 times greater than that reported in the general population of similar age. Okin et al [35] followed up nearly 9000 non diabetic hypertensive patients. During follow-up, regression or persistent absence of left ventricular hypertrophy on the ECG during antihypertensive treatment was associated with a lower rate of new-onset diabetes mellitus.

vii .Ambulatory Electrocardiography:

The use of ambulatory electrocardiographic monitoring has led to greater appreciation of the high frequency of type III silent ischemia, occurring in up to one third of patients with stable angina treated with appropriate therapy.

It has become apparent that anginal pain underestimates the frequency of significant cardiac ischemia. [36].

The role of myocardial O2 demand in the genesis of myocardial ischemia has been evaluated by measuring the heart rate and blood pressure changes preceding silent ischemic events during ambulatory studies.

In one series, 92% of all episodes were silent, and 60% to 70% were preceded by significant increase in heart rate or blood pressure.

This and other studies have suggested that increase in myocardial O2 demand have a significant role in the genesis of silent ischemia.

The mechanisms underlying the development of ischemia as detected by ambulatory electrocardiographic and exercise testing, may be different and, in patients in the ACIP study, concordance between the ambulatory ECG and SPECT was only 50%.

For identification of silent ischemia, the two techniques probably complement each other.

Transient ST-segment depression of 0.1 MV or more that lasts longer than 30 second is rare finding in normal subjects.

Patients with known CAD show a strong correlation between such transient ST-segment depression and independent measurements of impaired regional myocardial perfusion and ischemia, determined by rubidium-82 uptake as measured by PET.

In patients with type III silent ischemia, perfusion defects occurs in the same myocardial regions during symptomatic and asymptomatic episodes of ST-segment depression.

Analysis of ambulatory electrocardiographic recording of patients with CAD who had symptomatic and silent myocardial ischemia has shown that 85% of ambulant ischemic episodes occur without chest pain and 66% of angina reports are unaccompanied by ST-segment depression.

In patients with stable CAD enrolled 1 to 6 months after hospitalization for an acute ischemic event, only 15% had angina with exercise, but 28% had ST-segment depression and 41% had reversible myocardial perfusion on thallium scinitigraphy.

Episodes of silent ischemia have been estimated to be present in approximately one third of all treated patients with angina, although, a higher prevalence has been reported in diabetic. [37].

Episodes of ST-segment depression, symptomatic and a symptomatic exhibit a circadian rhythm and are more common in the morning.

A symptomatic nocturnal ST-segment changes are almost invariably an indicator of double - or triple vessel CAD or left main coronary artery stenosis.

viii. Exercise stress test

Exercise stress testing is a non-invasive, safe and affordable screening test for coronary artery disease (CAD), provided that there is careful patient selection for better predictive value.

Patients at moderate risk for CAD are best served with this kind of screening, with the exception of females during their reproductive period, when a high incidence of false positive results has been reported. Patients with a high pretest probability for CAD should undergo stress testing combined with cardiac imaging or cardiac catheterization directly. Data from the test, other than ECG changes, should be taken into consideration when interpreting the exercise stress test since it has a strong prognostic value, i.e. workload, heart rate rise and recovery and blood pressure changes. The ECG interpretation with myocardial perfusion imaging follows the same criteria, but the sensitivity is much lower and the specificity is high enough to overrule the imaging part.

Exercise stress testing has been used for decades as a noninvasive test to diagnose and risk stratify coronary artery disease (CAD).

However, it lacks adequate sensitivity, which nevertheless depends on the pretest probability of CAD in the population tested. The overall sensitivity has ranged from 60% to 70% with a specificity of 85% [38,39,40]

Indications and safety of exercise testing

Although exercise testing is generally a safe procedure, both myocardial infarction and death have been reported and can be expected to occur at a rate of up to 1 per 2500 tests. Good clinical judgment should therefore be used in deciding which patients should undergo exercise testing.

Common indications and contraindications are listed in Table 4 The prognosis of the individual tested is not only linked to the result of the test whether it is positive or negative, but also depends on the exercise capacity, heart rate rise, heart rate recovery and blood pressure rise and recovery.

Exercise capacity is based on metabolic equivalents (MET) achieved, (one MET is defined as 3.5 mL O2 uptake/kg per min, which is the resting oxygen uptake in a sitting position). Less than 5 METS is poor, 5-8 METS is fair, 9-11 METS is good, and 12 METS or more is excellent. An inability to exercise >6 minutes on the Bruce protocol, or an inability to increase heart rate (HR) to >85% of maximum predicted heart rate (MPHR) are significant indicators of increased risk of coronary events with a 5-year survival ranging from 50% to 72%.

However, patients who attain >10 METS enjoy an excellent prognosis regardless of the test result even in the presence of known CAD, with a 5-year survival of 95%.The heart rate should reach or exceed 85% of MPHR calculated according to the formula, MPHR=220−age. The HR rises

proportionately with the intensity of the workload. An excessive rise in rate results primarily from a reduced stroke volume, which in turn is often caused by physical deconditioning, cardiac disease or arrhythmias like atrial fibrillation or supraventricular tachycardia and other noncardiac abnormalities like anemia and hypovolemia. In these situations the HR reaches its peak early, which limits maximum exercise capacity. An impaired chronotropic response to exercise as defined by failure to achieve 85% of MPHR and/or a low chronotropic index (<0.8 of heart rate reserve at peak exercise) caused by sinus node dysfunction, medications like β−blockers, or ischemia, are occasionally associated with increased mortality and cardiac events even after adjusting for left ventricular function and the severity of exercise-induced myocardial ischemia[31]The HR should decrease by at least 12 beats in the first minute of recovery, which is mediated through vagal reactivation. Otherwise, recovery is considered abnormal, which has a bad prognosis, with a 6-year mortality 2-3 times greater than those with normal recovery.[41,42]

Blood pressure should increase by at least 10 mm Hg during exercise except in patients on antihypertensive treatment where a blunted response is observed. Diastolic blood pressure (DBP) exhibits little or no change (<10 mm Hg) during exercise because of peripheral vasodilatation.

A sustained drop of SBP>10 mm Hg, confirmed within 15 seconds, often indicates severe left ventricular dysfunction and severe CAD and is an indication to stop the test immediately and refer for further evaluation and treatment .

Failure to increase systolic blood pressure by 10 to 30 mm Hg during exercise testing is an independent predictor of adverse outcome in patients after myocardial infarction [43]. However, it is crucial to exclude other causes that could cause a drop in SBP with exercise without the presence of severe CAD or left ventricular dysfunction, i.e. vasovagal syncope, cardiac arrhythmias, left ventricular outflow obstruction or hypovolemia. In addition, an abnormal BP recovery, defined by the SBP at 3 minutes of recovery over an SBP at 1 minute of recovery >1, is associated with a greater likelihood of severe angiographic CAD. [44]

An abnormal rise of SBP to a level > 214 mm Hg in patients with a normal resting BP predicts an increased risk for future sustained hypertension, estimated at approximately 10% to 26% over the next 5 to 10 years [45].

However, in adults evaluated for CAD, exercise hypertension is associated with a lower likelihood of angiographically severe disease and a lower adjusted mortality rate on follow up.[46]

Table 4. Common indications and contraindications for exercise stress testing.

Indications

• Evaluating the patient with chest pain or dyspnea with other findings suggestive, but not diagnostic of coronary artery disease (CAD)
• Risk stratification post-myocardial infarction
• Determining prognosis and severity of coronary artery disease
• Evaluating the effects of medical and surgical therapy
• Screening for latent coronary disease
• Evaluation of congestive heart failure
• Evaluation of arrhythmias
• Evaluation of congenital heart disease

Table 5. **Contraindications (absolute)**

• Very recent MI, < 3-4 days
• Unstable angina, not previously stabilized by medical therapy
• Severe symptomatic left ventricular dysfunction
• Life threatening dysrhythmias
• Severe aortic stenosis
• Acute pericarditis, myocarditis or endocarditis
• Acute aortic dissection

Contraindications (relative)

• Left main coronary stenosis
• Moderate stenotic valvular heart disease
• Electrolyte abnormalities
• Severe arterial hypertension (SBP>200 mmHg or DBP>110 mmHg)
• Tachyarrhythmias or bradyarrhythmias
• Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
• Mental or physical impairment leading to inability to exercise adequately
• High-degree atrioventricular block

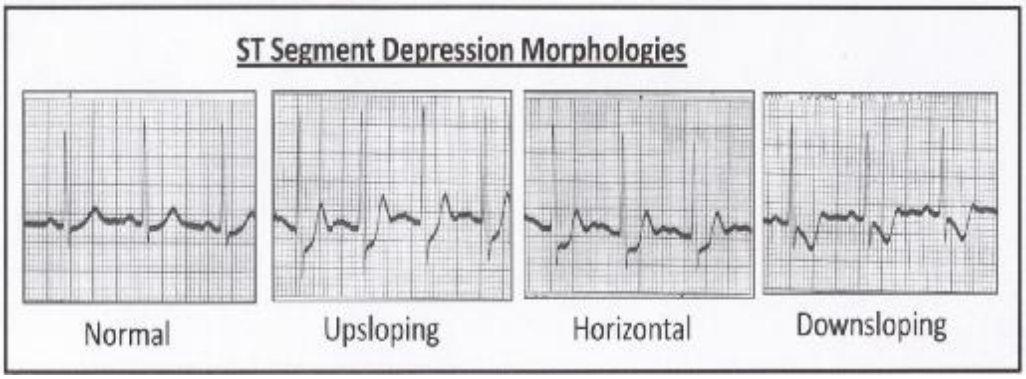
Interpretation of the electrocardiogram

ST segment changes should be read at 60 to 80 ms from the J point,[47] and the test should be considered positive for ischemia if there is a 2 mm or more rapidly up sloping ST depression (when the slope is more than 1 mV/s) ,[48,49] . A 1.5 mm or more slowly up-sloping ST depression (when the slope is less than 1 mV/s), or a 1 mm or more horizontal or down sloping ST depression (Figure 2).Ischemic ST-segment changes developing during recovery from treadmill exercise in apparently healthy individuals has adverse prognostic significance similar to those appearing during exercise. Resting ST-segment depression has been identified as a marker for adverse cardiac events in patients with and without known CAD [50,51,52,53] Diagnostic end points of 2 mm of additional exercise-induced ST-segment depression or down sloping depression of 1 mm or more in recovery were

particularly useful markers in these patients for diagnosis of any coronary disease (likelihood ratio 3.4, sensitivity 67 percent, specificity 80 percent) [53-55] .

In a recently published study, after 23 years of follow up, patients with frequent ventricular ectopic (a run of 2 or more consecutive premature ventricular contractions (PVC) making up more than 10% of all PVCs on any 30 seconds ECG) had an increased risk of death from cardiovascular causes by a factor of 2.5 times, similar to that observed in patients who had a positive ischemic response to exercise.

Fig2,3,4,5



Frequent PVCs at rest or during recovery were not associated with an increase in cardiovascular mortality in this study, but in another study a

stronger association between ventricular ectopic during recovery and increased 5-year mortality was noted. [56]

Table 6

Exercise-induced right bundle branch block

(RBBB) or left bundle branch block (LBBB) is usually considered non specific unless it is associated with evidence of ischemia, i.e. angina, and then it is strongly suggestive of ischemia.

- Causes for a false positive test include left ventricular hypertrophy

(LVH), which is associated with decreased exercise testing specificity, but sensitivity is un affected.[57]

Digitalis causes exercise-induced ST depression in 25% to 40% of normal subjects.[58,59,60].Other diseases that might cause a false positive test include mitral or aortic valve dysfunction or mitral valve prolapsed, pulmonary hypertension, pericardial constriction, hypokalemia, glucose ingestion prior to the test and in females during reproductive years.

- Causes of false negative test include use of β-blockers, which may reduce the diagnostic or prognostic value of exercise testing because of inadequate heart rate response, but the decision to remove a patient from β-blocker therapy for exercise testing should be made on an individual basis and should be done carefully to avoid a potential hemodynamic “rebound” effect, which

can lead to accelerated angina or hypertension[59,61] Acute administration of nitrates can attenuate the angina and ST depression associated with myocardial ischemia.

Atrial repolarization waves are opposite in direction to P waves and may extend into the ST segment and T wave. Exaggerated atrial repolarization waves during exercise can cause down sloping ST depression in the absence of ischemia.[62,63]

The final Interpretation of the ECG is positive if the ST criteria are met at any heart rate, and there are no factors to preclude appropriate interpretation of the test.

The interpretation is negative if no significant ST changes are noticed.

The test is non diagnostic if the patient fails to achieve 85% of the MPHR and the test was negative.

The results are indeterminate if the patient has baseline LBBB, a paced rhythm, LVH with repolarization changes and/or is on digoxin therapy.

Patients with an abnormal exercise ECG, but a normal perfusion scan have a low risk for future cardiac events (<1%).[40]

The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines [43] for exercise testing recommend this test as a first-line test for those with a normal resting 12-lead ECG and for those capable of performing maximal stress.

Although maximal stress may be defined by achieving 85% of predicted maximal heart rate, care should be taken when interpreting a woman's heart rate response. For deconditioned patients, a hyper exaggerated response to physical work may result in marked increases in heart rate. Thus, the test should be continued until maximal symptom-limited exercise capacity. Women incapable of performing a minimum of 5 METS of exercise should be considered candidates for myocardial perfusion imaging with pharmacologic stress.

Women with diabetes are a special population worthy of mention. They are at an increased risk for premature atherosclerosis and at significant risk for myocardial infarction and cardiac death. The unique pathophysiology of diabetes mellitus makes traditional symptoms less reliable and diagnosis of CAD more challenging. The ECG is often a less reliable indicator of significant CAD in the diabetic patient.

Myocardial perfusion imaging has been shown to be accurate in the risk assessment and prediction of future cardiac events in the diabetic woman.

ix .Prognosis:

Although some controversy remains sample evidence has supported the view that episodes of myocardial ischemia, regardless of whether they are symptomatic or asymptomatic, are of prognostic importance for patients with CAD.[64]

In asymptomatic patients (type I), the presence of exercise -induced ST-segment depression has been shown to predict a fourfold to fivefold increase in cardiac mortality in comparison with patients without this finding.

Similarly, in patients with stable angina or prior MI, the presence of inducible ischemia evident by ST--segment depression or perfusion abnormalities during exercise testing is associated with unfavorable outcomes, regardless of whether symptom save present.

The strength of this association is greatest when the ischemia is found to occur at low workload, several studies evaluating the prognostic implication of silent ischemia on ambulatory monitoring in patients with stable angina (type III) have demonstrated that the presence of myocardial ischemia on the ambulatory ECG, whether silent or symptomatic, is also associated with an adverse cardiac outcome.

In the ACIP study, in patients treated medically myocardial ischemia detected by the ambulatory ECG and by abnormal exercise treadmill test were each independently associated with adverse cardiac outcomes.

Never the less, when a sub group of patients with ischemia on stress testing is considered, silent ischemia on holter monitoring is also a significant predictor of subsequent death or MI.

In addition, patients with ischemia on the ambulatory ECG are more likely to have multi vessel CAD, substantial improvements in technology have made long term ambulatory monitoring for ischemia more convenient and reliable with respect to data quality. [65] .

The exercised ECG can identify most patients likely to have significant ischemia during their daily activity and remains the most important screening test for significant CAD.

i. Management

Drugs that are effective for preventing episodes of symptomatic ischemia (e.g., nitrates, calcium channel blockers, beta blockers) are also effective for reducing or eliminating episodes of silent ischemia. A number of studies have shown that beta blockers reduce the frequency, duration, and severity of silent ischemia in a dose dependent fashion. For example, in the Atenolol Silent Ischemia Study Trial (ASIST) , 4 weeks of atenolol

therapy decreased the number of ischemic episodes detected on ambulatory ECG (from 3.6 to 1.7; $P < 0.001$) and also the average duration (from 30 to 16.4 minutes/48 hours; $P < 0.001$). Coronary revascularization is also effective in reducing the rate of angina and ambulatory ischemia. In the ACIP pilot study, 57% of patients treated with revascularization were free of ischemia at 1 year, compared with 31% and 36% in the ischemia- and angina-guided strategies, respectively ($P < 0.0001$). In the Swiss Interventional Study on Silent Ischemia Type II (SWISSI-II) trial in 201 patients with silent myocardial ischemia who were recovering from acute MI (>2 months), PCI was associated with a significant reduction in late (up to 10 years) mortality as compared with medical therapy,[66] but the medical therapy as used in this study was not as intensive as in the COURAGE and BARI 2D trials, thus making the results of this fairly small study somewhat difficult to interpret. In addition, aggressive secondary prevention with lipid-lowering therapy has also been shown to reduce ischemia on ambulatory monitoring. Although suppression of ischemia in patients with asymptomatic ischemia appears to be a worthwhile objective, whether treatment should be guided by symptoms or by ischemia as reflected by the arnbulatory ECG has not been established. In a study of bisoprolol, nifedipine, and a combination of the two, patients achieving complete eradication of

ischemia, symptomatic and asymptomatic, were less likely to suffer death, MI, or angina requiring revascularization.

Similarly, amelioration of all symptomatic and asymptomatic ischernia in the ASIST trial conferred an advantage with respect to the primary endpoint of death, resuscitated ventricular tachycardia or ventricular fibrillation, MI, unstable angina, revascularization, or worsening angina. However, in the ACIP trial, no differences in outcome were detected between the groups allocated to ischemia- versus angina-guided therapy In contrast, the early benefits of revascularization on ischemia were associated with improved clinical outcome. Specifically, the rate of death or MI was 12.1 % in the angina-guided strategy, 8.8% in the ischemia-guided strategy, and 4.7% in the revascularization strategy and a strong reduction was also seen in re hospitalizations and the revascularization strategies. Patients who continue to suffer silent ischemia after revascularization may have increased risk for recurrent cardiac events compared with those who are free of any ischemia.

Chapter 3

Aim

Objective:

To determine the risk factors for asymptomatic IHD in diabetic patients who underwent TMT.

Chapter 4

Methods & Subjects

Patients and method:

Study population

This study included one hundred and forty adults with type 2 DM patients without symptoms of coronary artery disease of any age and of both sex attending the out patients Diabetic clinic and Al Haware hospital in Benghazi during four months from (September 2010 to December 2010) targeted for the study.

Study design

cross-sectional study, a structured pre-tested questionnaire was developed to seek information on demographics of patient, duration of DM , history of DM, clinical examination etc. The questionnaire paper also included columns to record observations on various investigational parameters for each patient (data collection sheet).Exclusion criteria were a history of myocardial infarction, heart failure, arrhythmia and smoking.

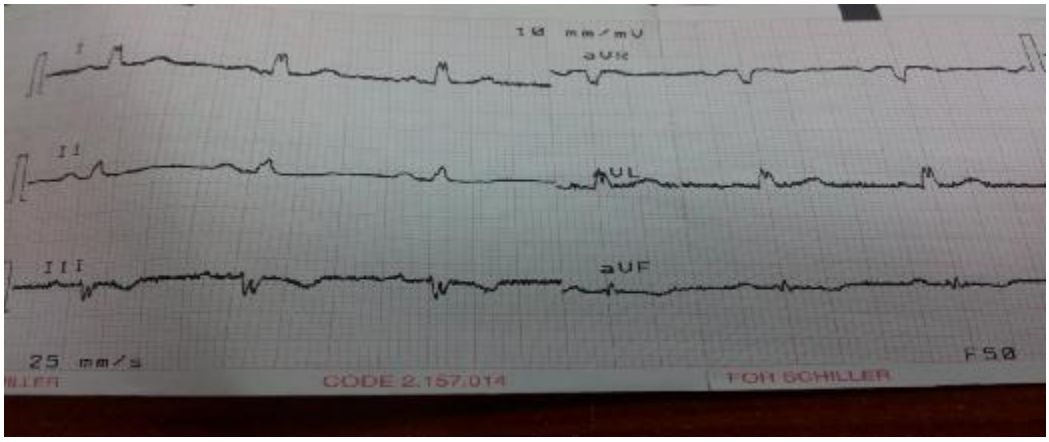
Biochemical tests

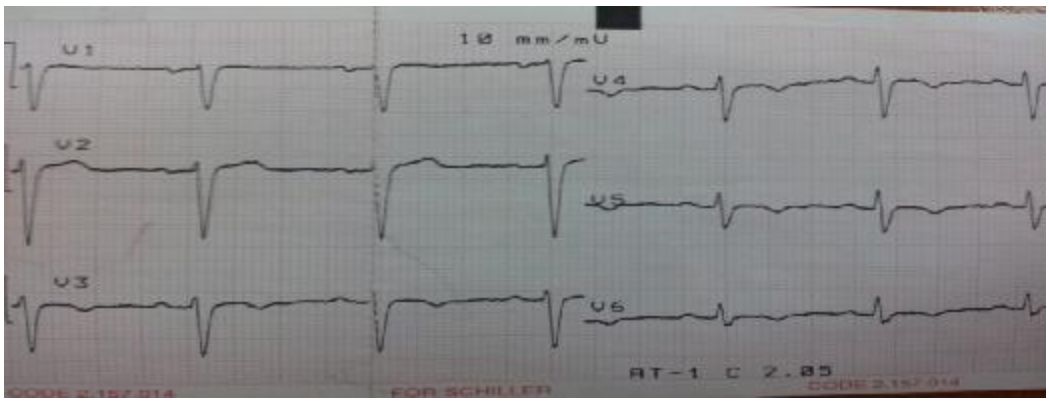
HbA1C and fasting lipid profile was done. Lipid parameters were assessed, dyslipidemia was defined as TC $\geq$ 240 mg/dl, TG $\geq$ 150 mg/dl, LDL $\geq$ 100 mg/dl and high density lipoprotein (HDL)<40 mg/dl in men and<50 mg/dl in women.

Urine for micralbuminuria was also done.

ECG

Resting 12 leads ECG performed to all patients





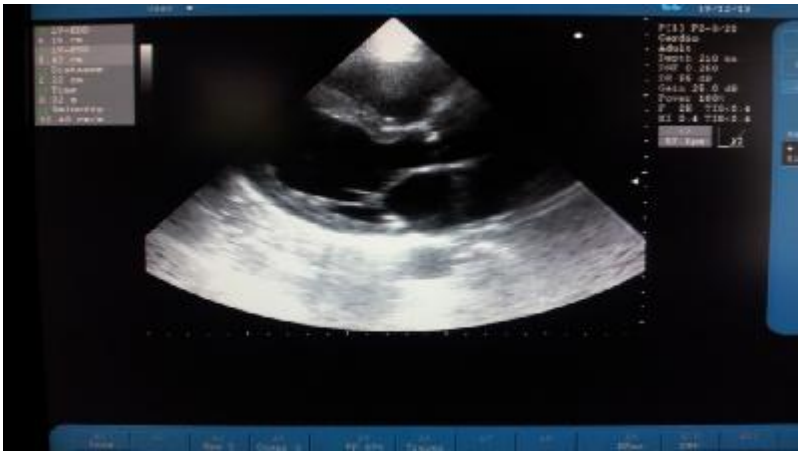
2D Echo

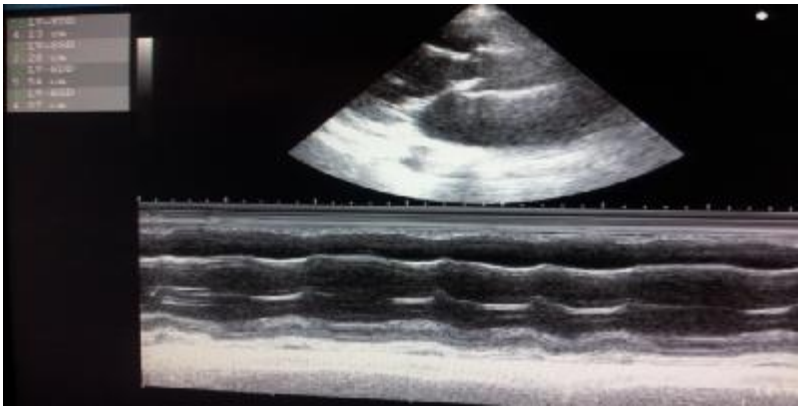
All patients included in the study was done on Phillips and GE machines with a 3 MHZ cardiac probe.

Patients were screened in supine, left lateral position, Para sternal short axis, parasternal long axis, apical four chamber, apical two chamber and along with M-mode Echo and Doppler pulse wave Echo wave was used to assess regional wall motion abnormality (RWMA),and left ventricular systolic and diastolic function.

Presence or absence of RWMA was determined.

Resting 2D Echo was done considering that ischemic changes can be picked up on 2D Echo even before the presence of patient's symptoms of IHD.

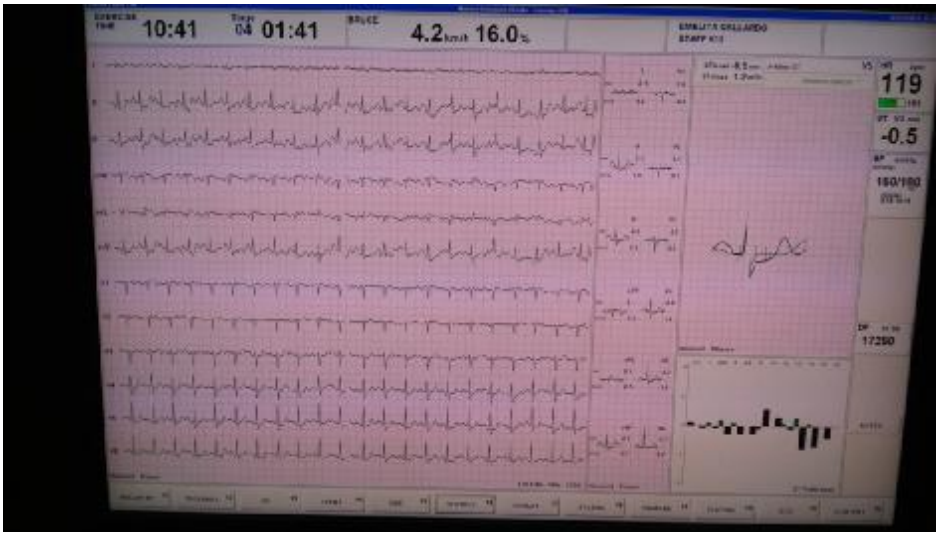




Treadmill test

TMT was performed using the Bruce protocol which is multi stage maximal treadmill protocol, has 3 minutes period to allow achievement of steady state before work load is increased .

A positive response, i.e. ischemic heart disease, was defined as ST segment depression > 1 mm horizontal or down sloping, (THR = 220- age in years).



Statistical methods

Data was fed into a Microsoft Excel table which was used to construct tables and figures. The Statistical Package for Social Sciences (SPSS), version 18.0 program was used to form the statistical analysis. Descriptive statistics on demographic characteristics of patients were

obtained The statistics included mean and standard deviation for continuous variables and frequencies (percentage) for categorical variables. Student's t-test for independent samples was used to determine statistical significance of difference in the mean values of continuous variable between TMT positive and negative groups. Chi-square test was used to determine if the frequency distribution across the levels of categorical variables has any statistical association with TMT findings . The differences were considered to be statistically significant when the P-value obtained was less than 0.05.

Chapter 5

Results

Results:

Table 7: Distribution of the sample according to sex.

Sex	No.	%
Male	62	44.3
Female	78	55.7
Total	140	100

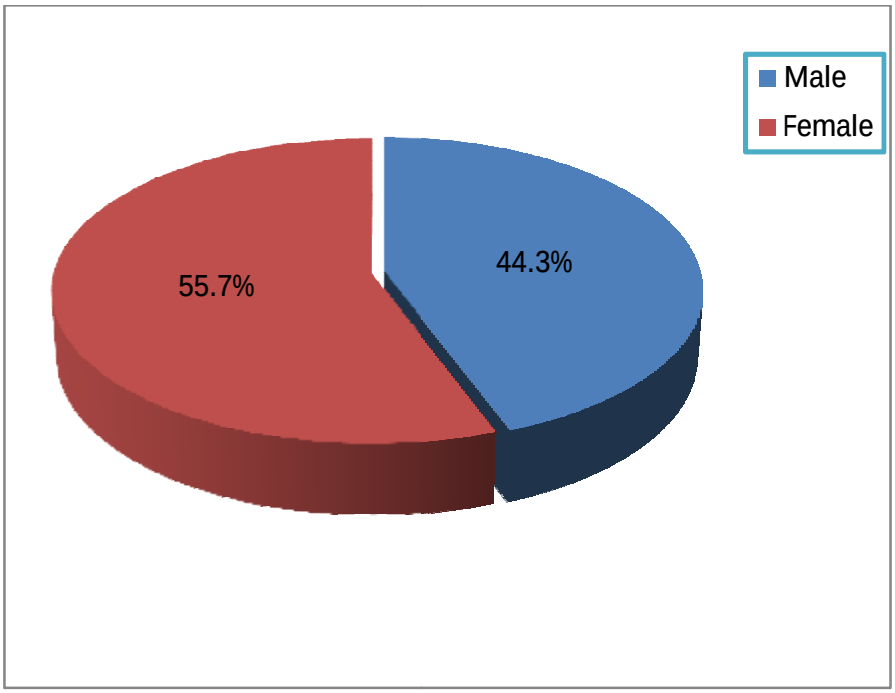


Fig. 6:Distribution of the sample according to sex.

Table 8:Distribution of the patients according to age.

Age / years	No.	%
40 – 49	33	23.5
50 – 59	46	32.9
60 – 69	47	33.6
70 - 79	14	10
Total	140	100

Mean= 57. 5 years. Std. Deviation= 9.9years. Median =

58years.Mode=50years. Minimum age=40years . Maximum = 79years.

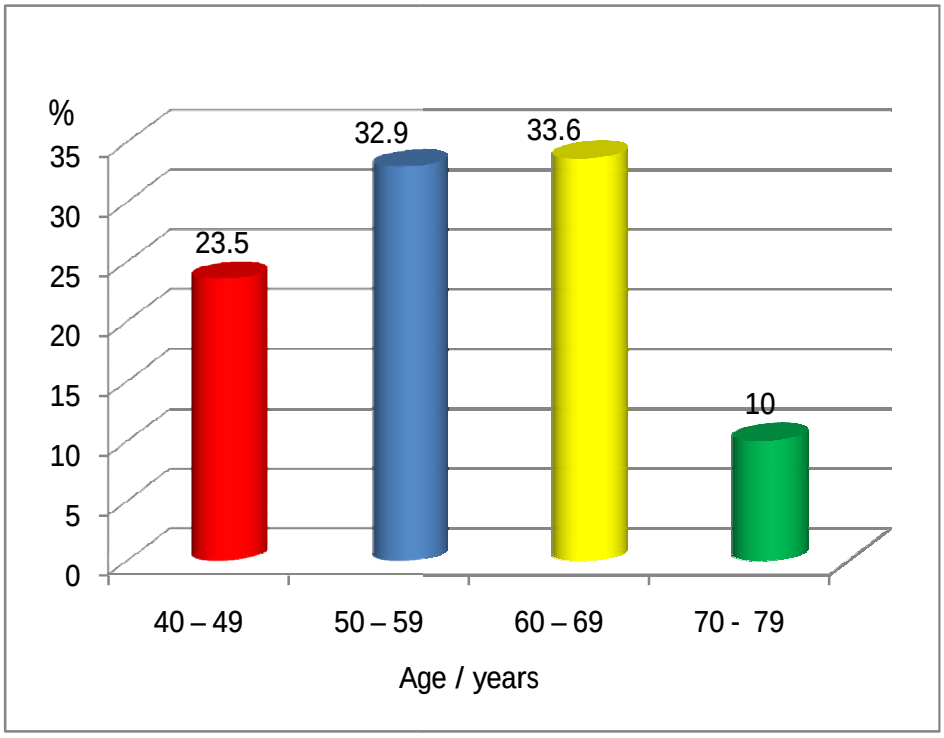


Fig. 7:Distribution of the sample according to age.

Table 9:Distribution of the patients according to duration of diabetes.

Duration of diabetes/ years	No.	%
<1	8	5.7
1 -5	29	20.7
6 – 10	45	32.1
>10	58	41.5
Total	140	100

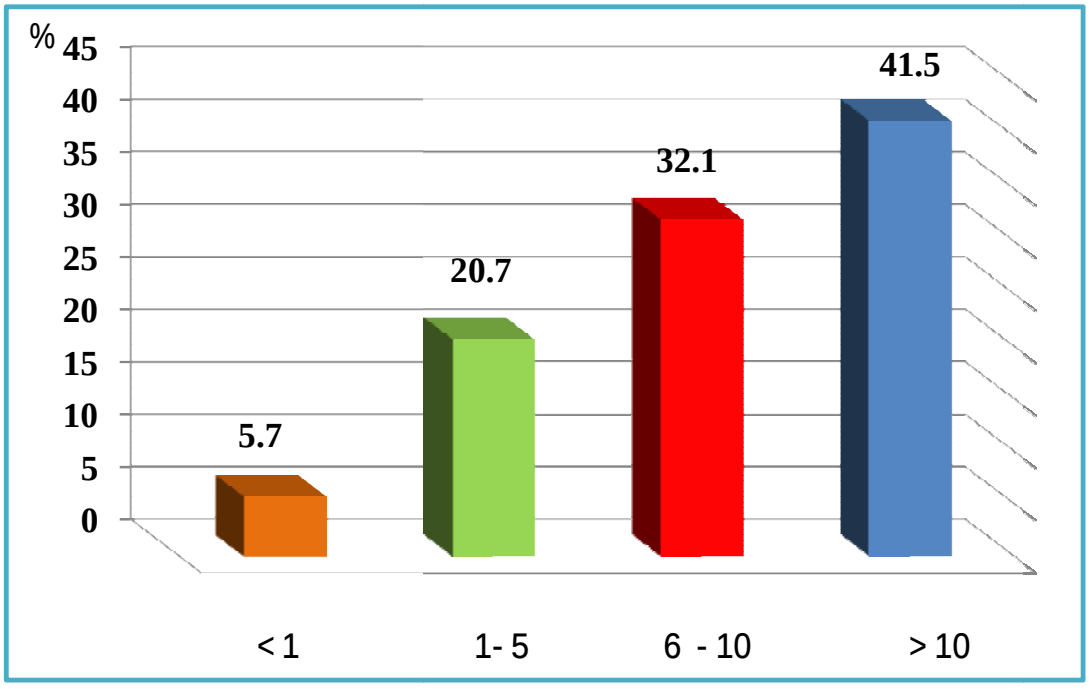


Fig. 8:Distribution of the patients according to duration of diabetes.

Table 10:Distribution of the patients according to family history of IHD.

Family history of IHD	No.	%
Yes	27	19.3
No	113	80.7
Total	140	100

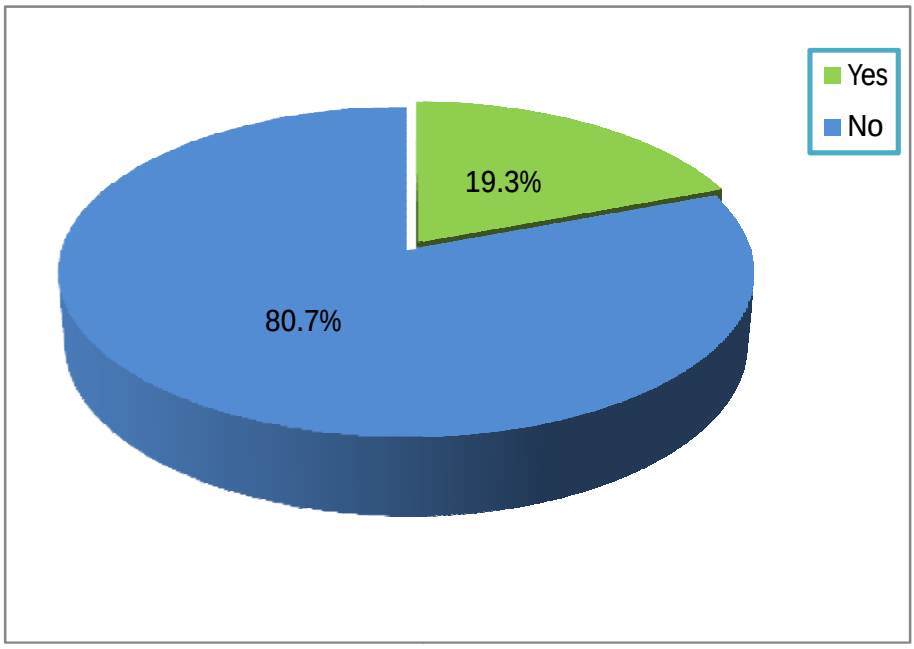


Fig. 9:Distribution of the patients according to family history of IHD.

Table 11: Distribution of the patients according to history of hypertension.

Hypertension	No.	%
Yes	62	44.3
No	78	55.7
Total	140	100

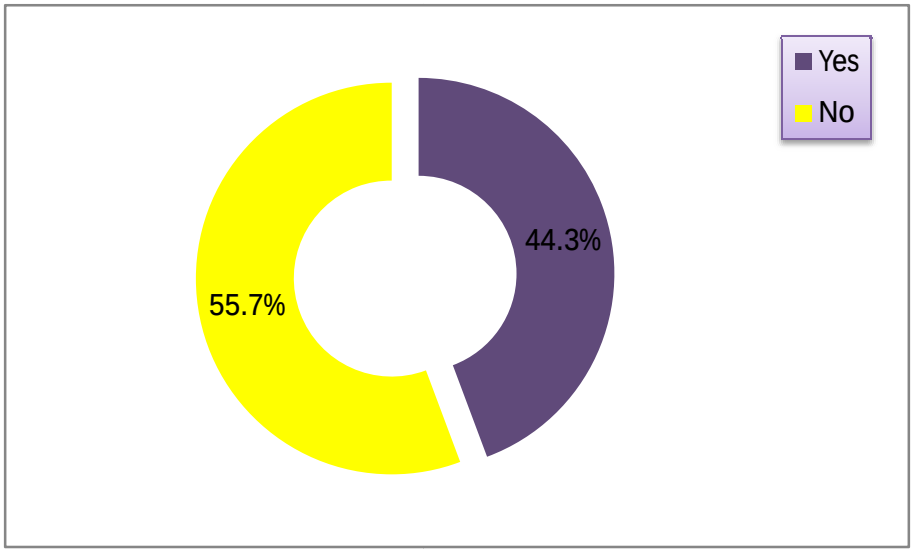


Fig. 10:Distribution of the patients according to history of hypertension.

Table 12:Distribution of the patients according to presence of of dyslipidemia

History of dyslipidemia	No.	%
Yes	26	18.6
No	114	81.4
Total	140	100

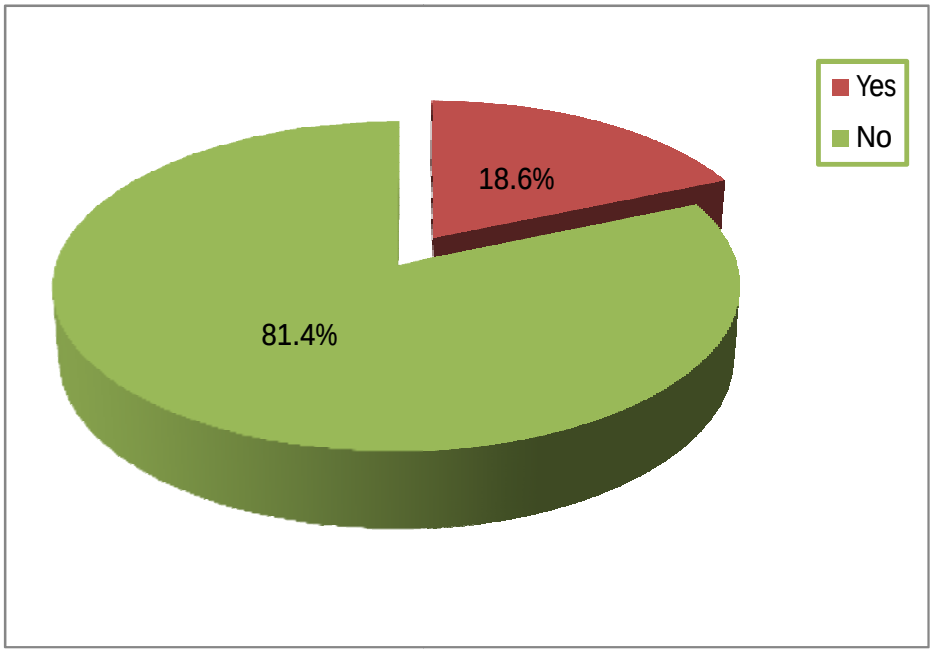


Fig. 11:Distribution of the patients according to presence of dyslipidemia

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Table 13:Distribution of the patients according to body mass index.

Body mass index	No.	%
Normal	19	13.6
Over weight	34	24.3
Obese	87	62.1
Total	140	100

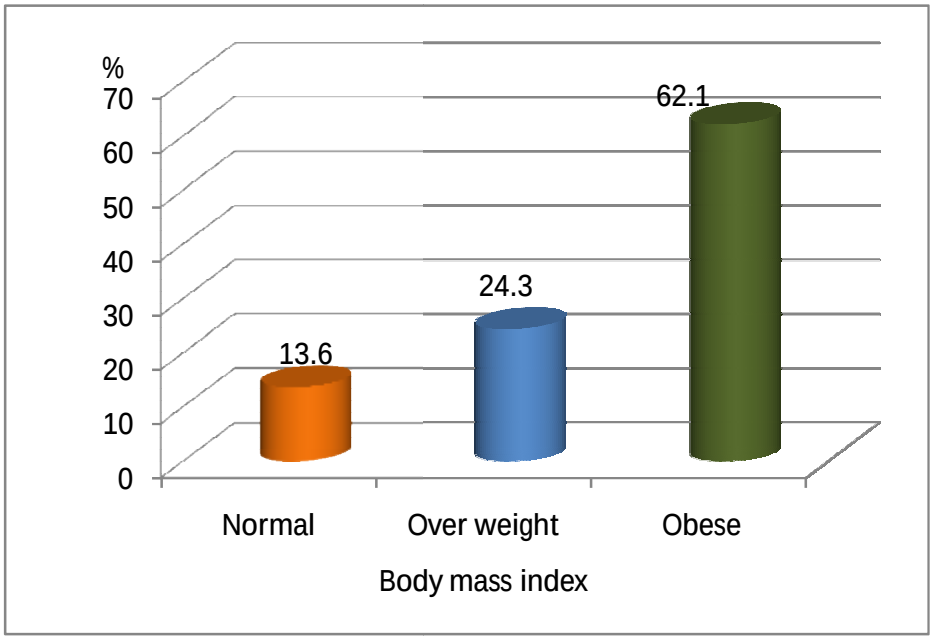

Fig. 12:Distribution of the patients according to body mass index.

Table 14:Distribution of the patients according to level of HbA1c.

Level of HbA1c	No.	%
<7	28	20
≥7	112	80
Total	140	100

Mean = 8.05 . Std.Deviation =1.55. Minimum=2.3. Maximum =13.

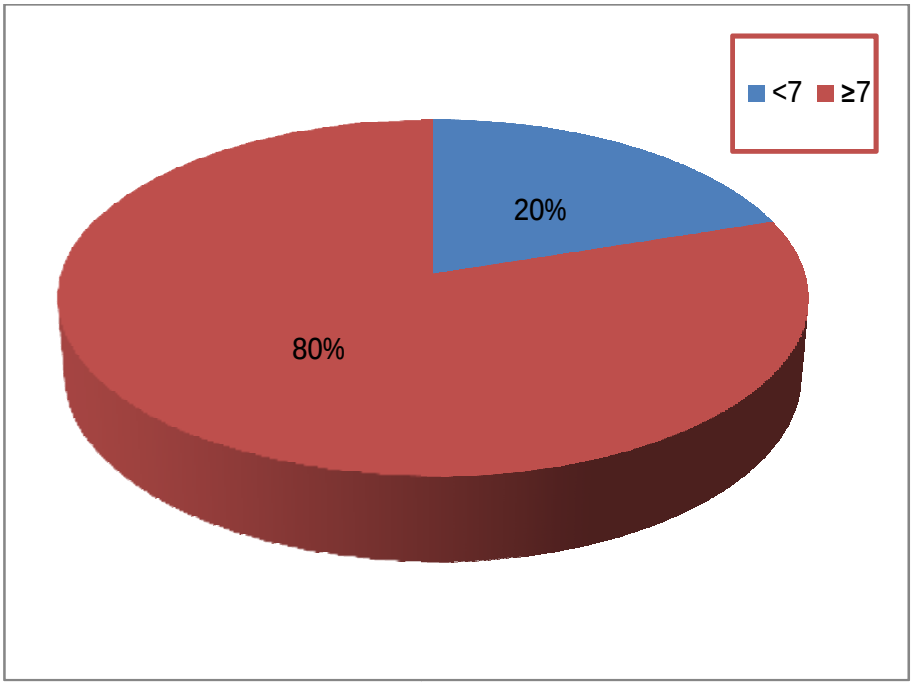

Fig. 13:Distribution of the patients according to level of HbA1c.

Table15:Distribution of the patients according to presence of microalbuminuria.

Presence of microalbuminuria	No.	%
Positive	41	29.3
Negative	99	70.7
Total	140	100

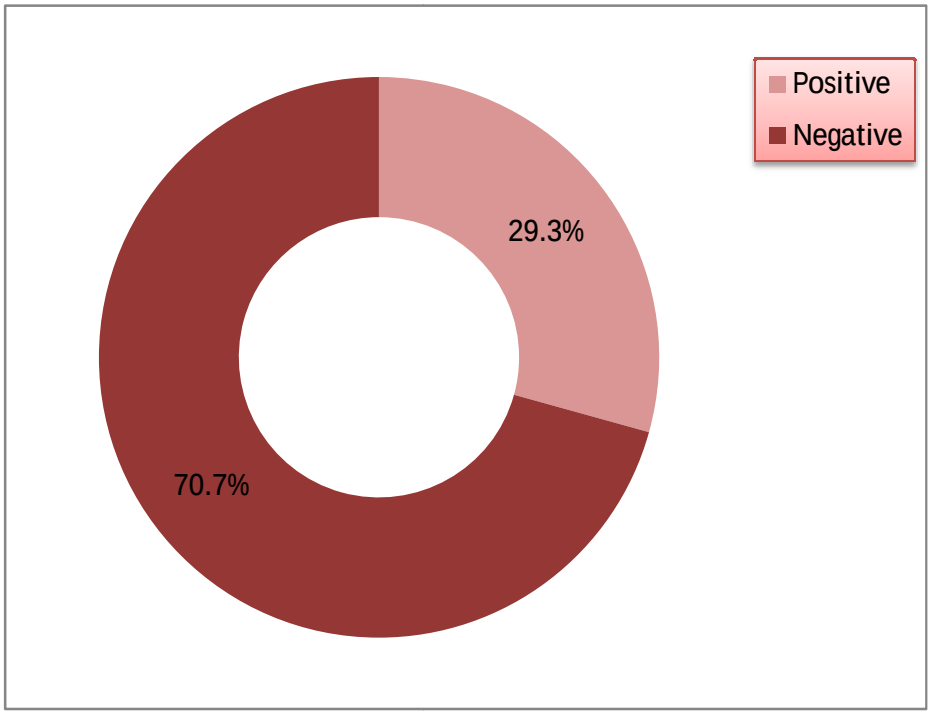

Fig. 14:Distribution of the patients according to presence of microalbuminurea.

Table16: Distribution of the patients according blood pressure control.

Blood pressure situation	No.	%
Controlled	83	59.3
Uncontrolled	57	40.7
Total	140	100

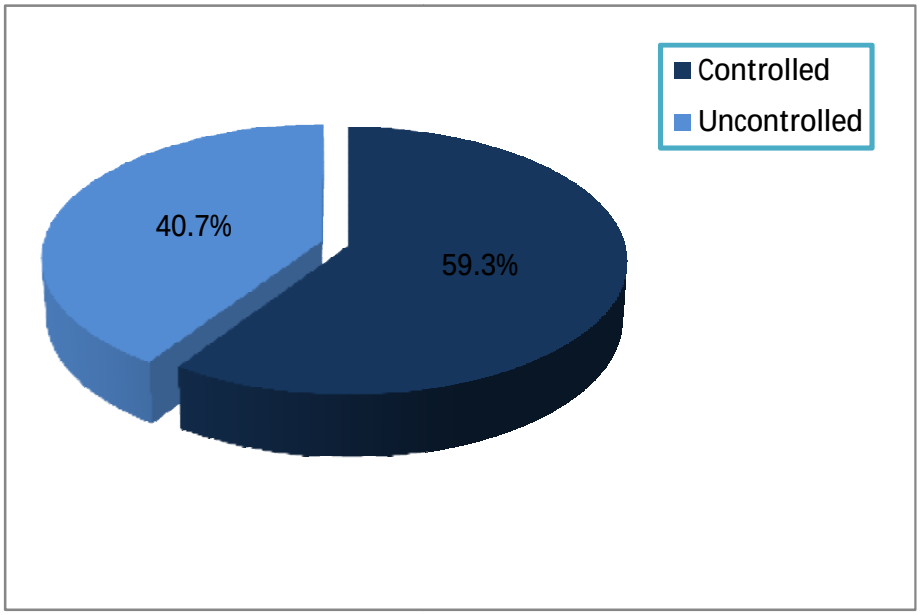

Fig.15:Distribution of the patients according blood pressure situation.

Table17:Distribution of the patients according results of resting ECG.

ECG	No.	%
Normal	122	87.1
Abnormal	18	12.9
Total	140	100

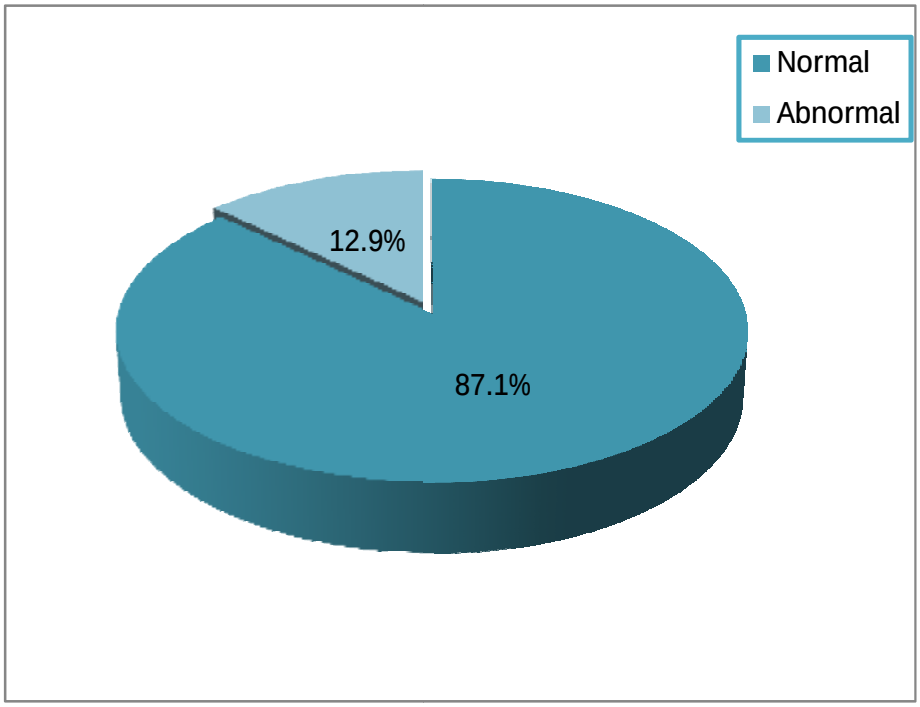

Fig. 16:Distribution of the patients according results of ECG.

Table18:Distribution of the patients according result of Echo.

Results of Echo	No.	%
Normal	136	97.1
Abnormal	4	2.9
Total	140	100

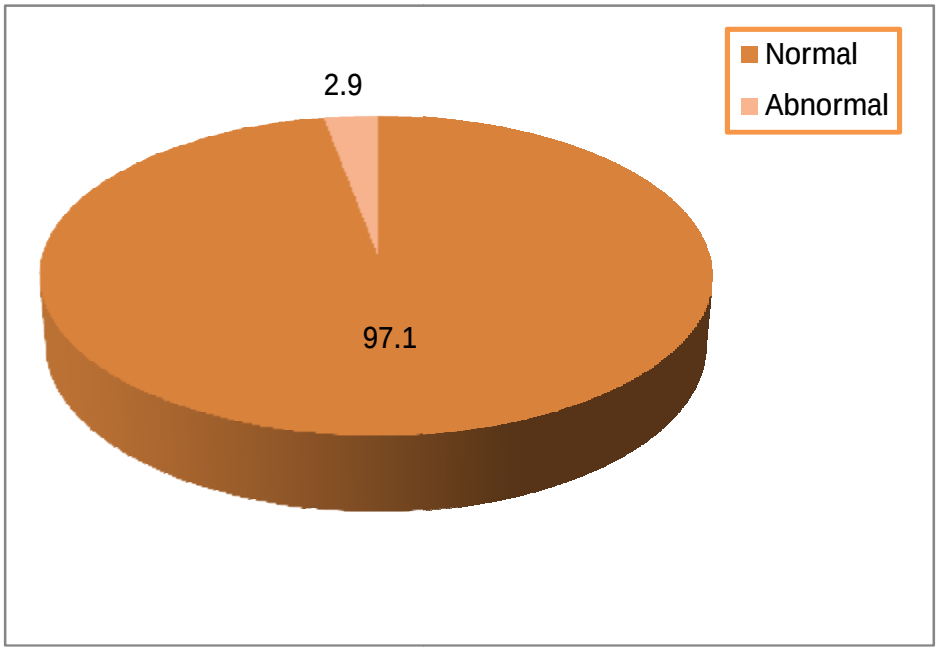

Fig. 17:Distribution of the patients according result of Echo.

Table19:Distribution of the patients according to results of exercise ECG.

Exercise ECG	No.	%
Negative	86	61.4
Positive	23	16.4
Equivocal	31	22.2
Total	140	100

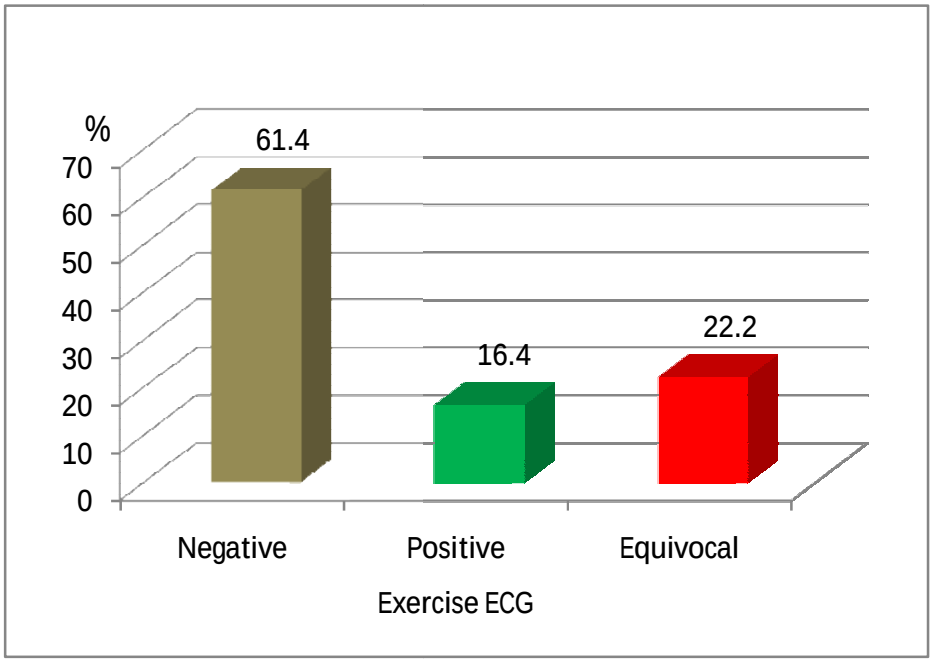

Fig. 18:Distribution of the patients according to results of exercise ECG.

Table20:Distribution of the patients according to results of Coronary angiography.

Coronary angiography	No.	%
Negative	5	45.5
Positive	6	54.5
Total	11	100

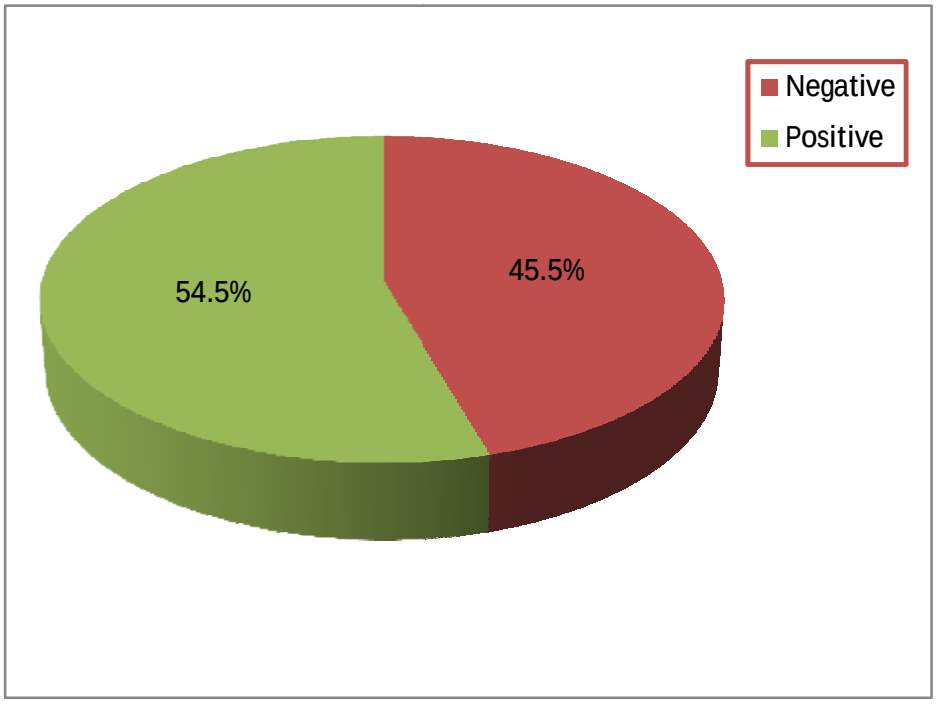

Fig. 19:Distribution of the patients according to results of Coronary angiography.

Table 21:Distribution of the patients according to results of Angio. finding.

Angio. finding	No.	%
SVD	1	16.7
TVD	4	66.6
MVD	1	16.7
Total	6	100

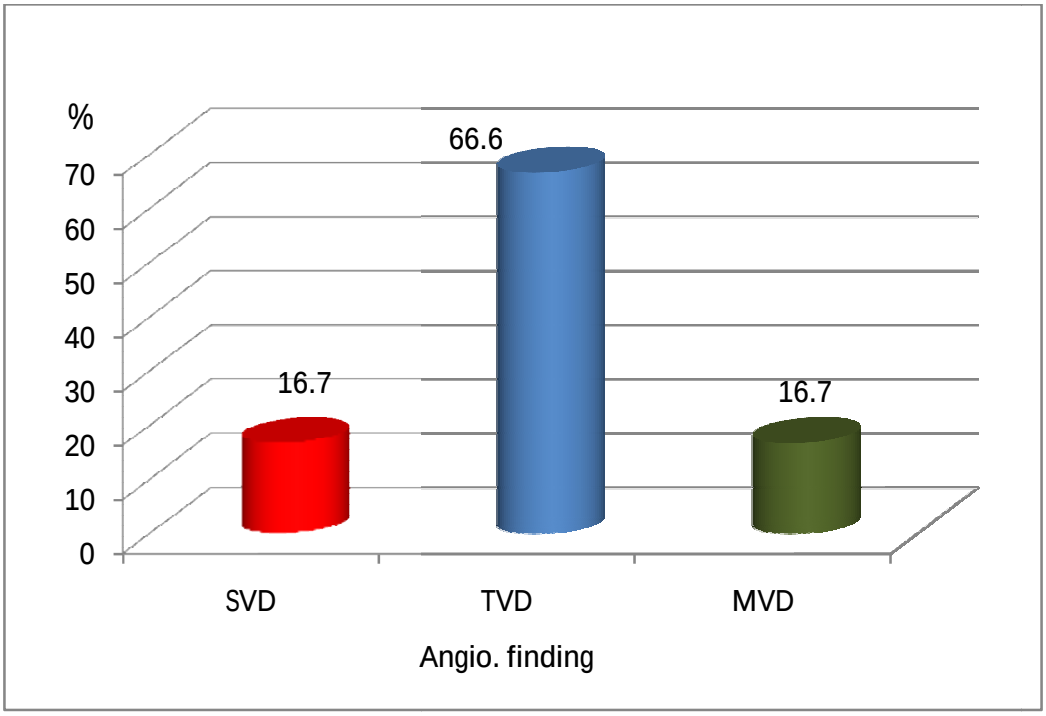

Fig. 20 :Distribution of the patients according to results of Angio. finding.

Table 22:Distribution of the patients with positive coronary angio according to recommendation.

Recommendation	No.	%
Medical treatment	4	66.6
PCI	1	16.7
CABG	1	16.7
Total	6	100

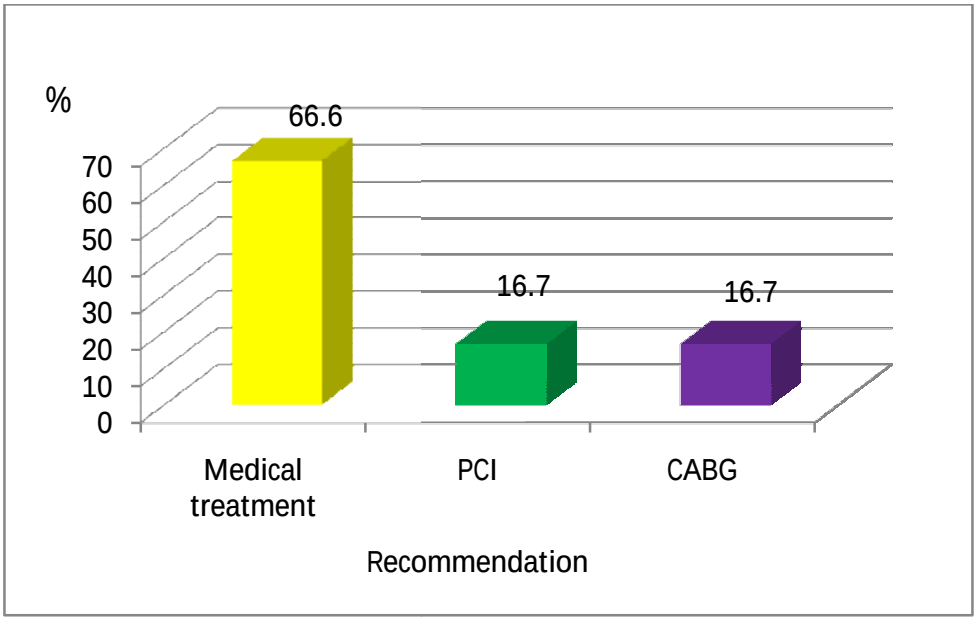

Fig. 21:Distribution of the patients according to recommendation.

Table 23: Distribution of patients according to exercise ECG results and age.

Age/years	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
40 – 49	22	66.7	7	21.2	4	21.1	33	100
50 – 59	35	76.1	6	13	5	10.9	46	100
≥60	29	47.5	10	16.4	22	36.1	61	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2=13.929 df=4 p= 0.008(Highly significant).

For Positive: Mean = 57.4 years. +/- 8.1 years.

For negative: Mean age = 54.8 years. +/-8.9 years.

t-test=0.655 df= 107 p=0.514 . (Not significant).

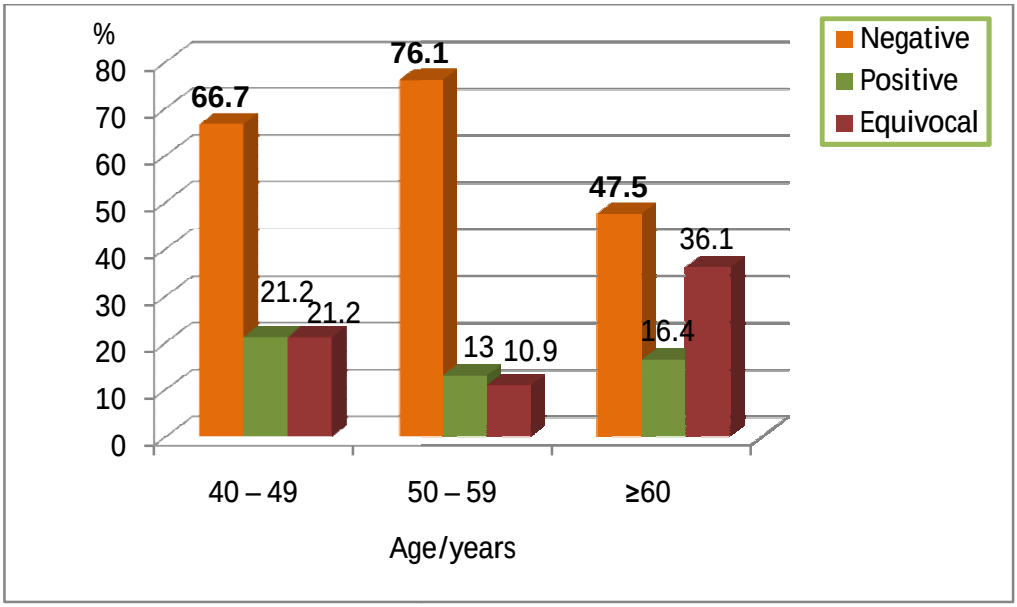

Fig. 22: Distribution of patients according to exercise ECG results and age.

Table 24: Distribution of pts. according to exercise ECG results and sex.

Sex	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
Male	33	53.2	14	22.6	15	24.2	62	100
Female	53	68	9	11.5	16	20.5	78	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2= 3.994 .df= 2 p= 0.136(Not significant).

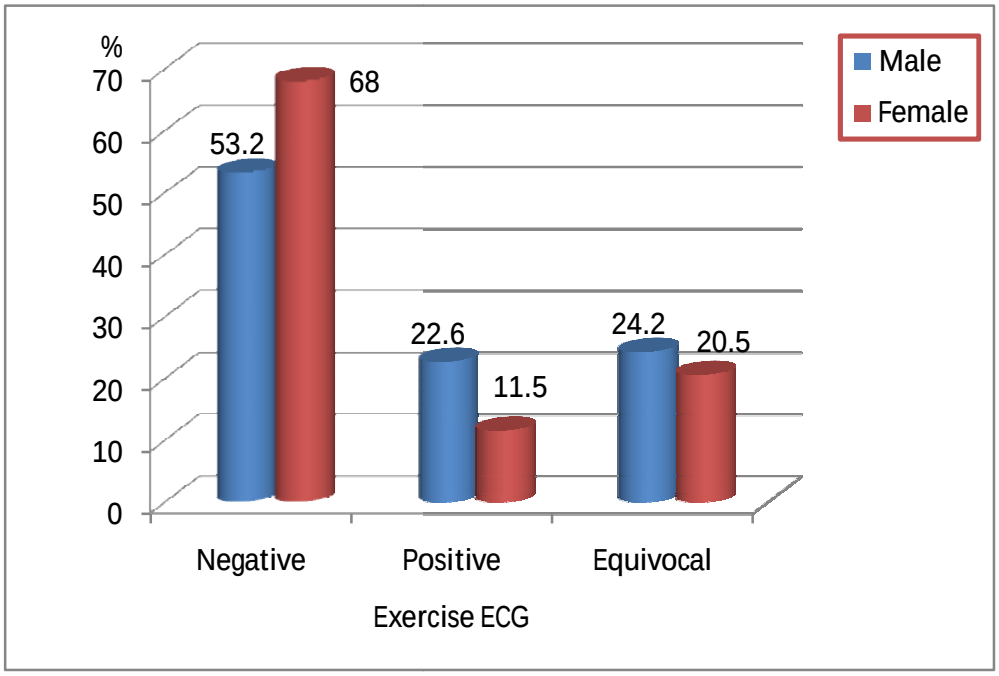

Fig 23: Distribution of patients according Exercise ECG results and sex.

Table 25: Distribution of patients according Exercise ECG results and duration of diabetes.

Duration of diabetes	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
<1*	7	87.5	1	12.5	0	0	8	100
1 -5*	22	75.9	1	3.4	6	20.7	29	100
6 – 10	29	64.4	10	22.2	6	13.3	45	100
>10	28	48.3	11	19	19	32.8	58	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2= 29.608 .df= 6 p= 0.000(Highly significant).

*Combined to calculate x2

For Positive: Mean= 12.7years. +/_= 7.9 years.

For negative: Mean=8.9 years. +/_=7.3 years.

t-test= 1.127 df= 107 p=0.262 . (Not significant).

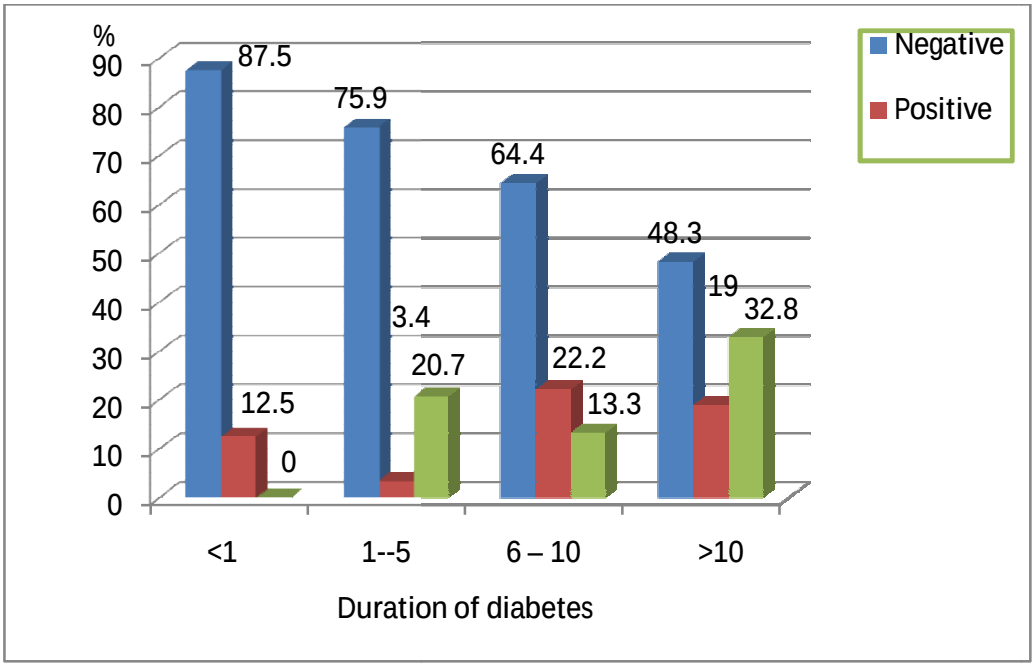

Fig. 24: Distribution of patients according exercise ECG results and duration of diabetes.

Table 26: Distribution of patients according exercise ECG results and Family history of IHD.

Family history of IHD	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
Yes	16	59.3	5	18.5	6	22.2	27	100
No	70	61.9	18	15.9	25	22.2	113	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2= 0.115 . df= 2. P= 0.944. (Non - significant).

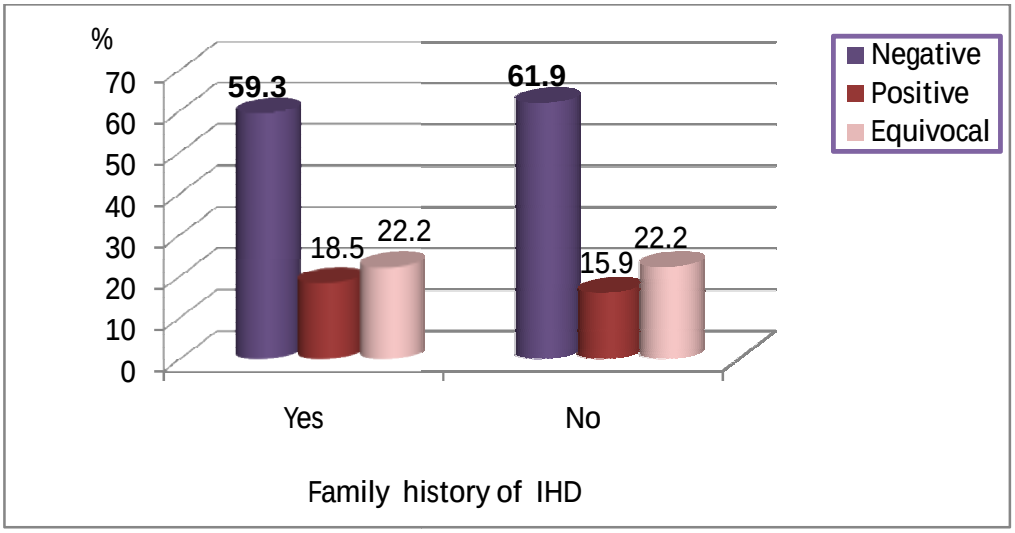

Fig. 25: Distribution of patients according exercise ECG results and Family history of IHD.

Table 27 : Distribution of patients according to Exercise ECG results and history of Hypertension.

Hypertension	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
Yes	59	64.1	14	15.2	19	20.7	92	100
No	27	56.2	9	18.8	12	25	48	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2=0.828. df= 2 p= 0.661 (Not significant).

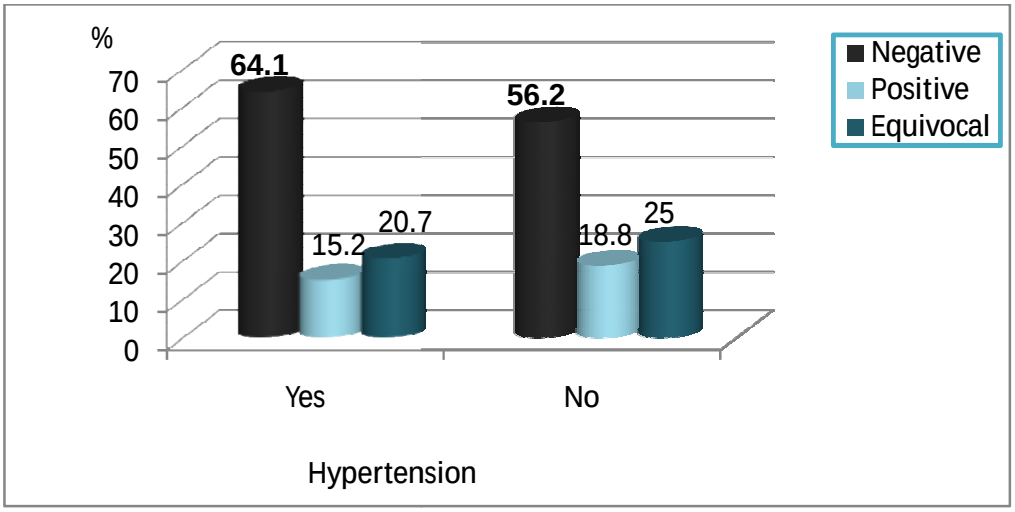

Fig. 26 : Distribution of patients according to Exercise ECG results and history of Hypertension.

Table 28: Distribution of patients according to Exercise ECG results and history of dyslipidemia.

History of dyslipidemia	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
Yes	19	73.1	5	19.2	2	7.7	26	100
No	67	58.8	18	15.8	29	25.4	114	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2= 3.869. df=2 p= 0.144 (Not significant).

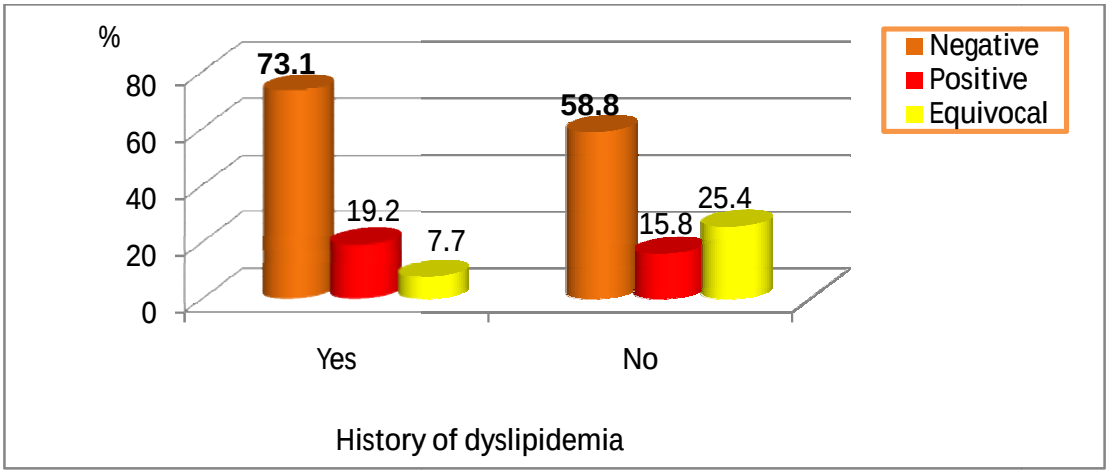

Fig. 27: Distribution of patients according to exercise ECG results and presence of dyslipidemia

Table 29: Distribution of patients according to Exercise ECG results and body mass index.

Body mass index	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
Normal	7	36.8	5	26.3	7	36.8	19	100
Over weight	23	67.6	7	20.6	4	11.8	34	100
Obese	56	64.4	11	12.6	20	23	87	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2= 7.989. df= 4 p= 0.092 (Not significant).

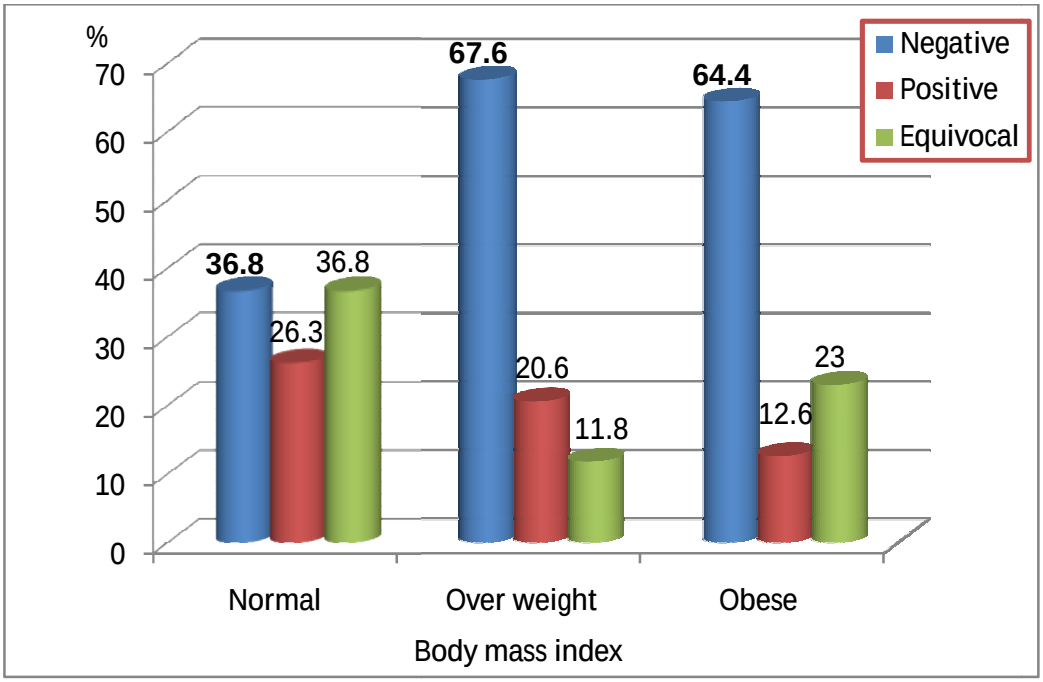

Fig 28: Distribution of patients according to Exercise ECG results and body mass index.

Table 30: Distribution of patients according to Exercise ECG results and level of HbA1c.

Level of HbA1c	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
<7	21	75	3	10.7	4	14.3	28	100
≥7	65	58	20	17.9	27	24.1	112	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2= 2.721. df= 2. p= 0.257 (Not significant).

For Positive: Mean HbA1c= 8.2. Std. +/_ 2.1.

For negative: Mean=7.9. Std. Deviation=1.4.

t-test= 0.421 df= 107 p=0.675 . (Not significant).

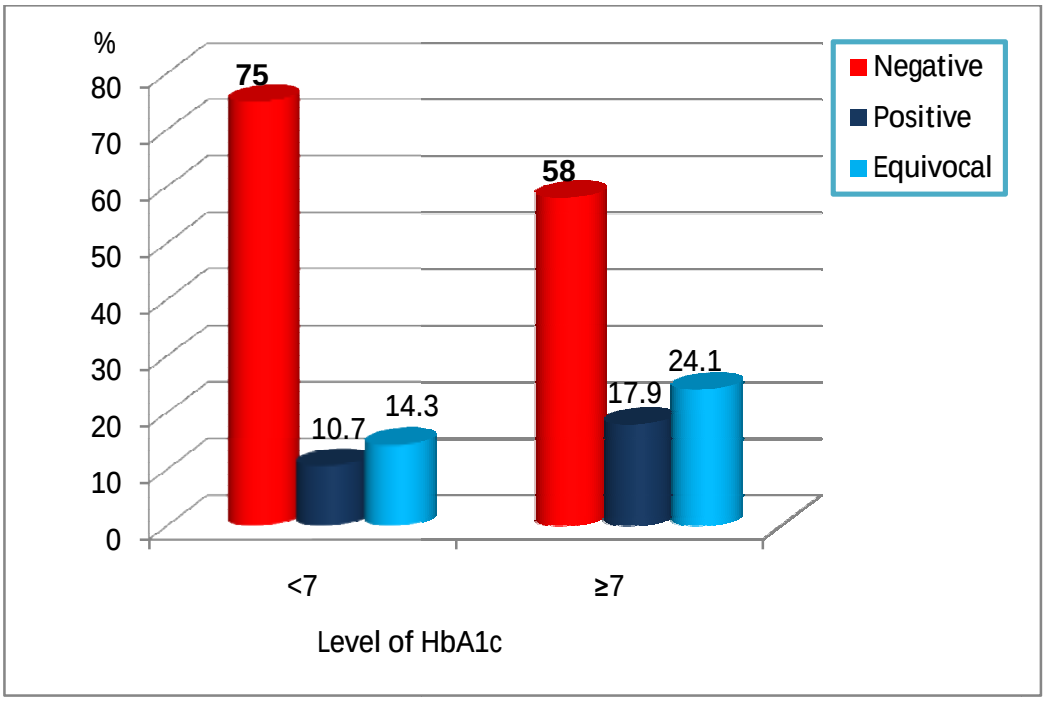

Fig. 29: Distribution of patients according to exercise ECG results and level of HbA1c.

Table 31: Distribution of patients according to exercise ECG results and presence of microalbuminurea.

Presence of microalbuminurea	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
Positive	21	51.2	12	29.3	8	19.5	41	100
Negative	65	66.6	11	11.1	23	23.2	99	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2= 6.983. df= 2 p= 0.030(significant).

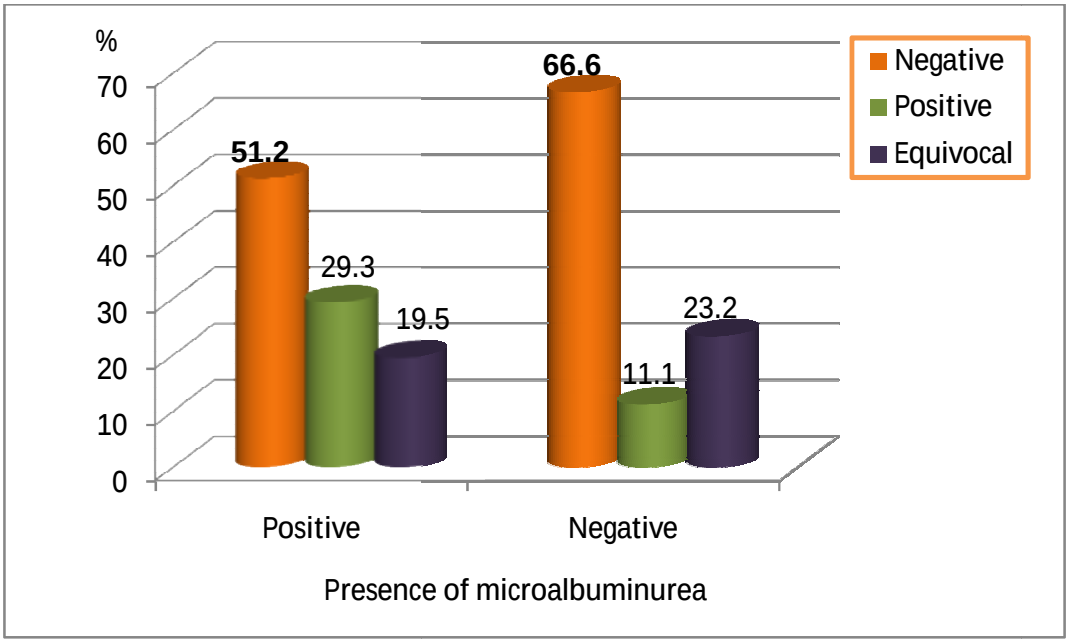

Fig. 30: Distribution of patients according to exercise ECG results and presence of microalbuminurea.

Table 32: Distribution of patients according to exercise ECG results and resting ECG results.

ECG results	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
Normal	79	64.8	16	13.1	27	22.1	122	100
Abnormal	7	38.9	7	38.9	4	22.2	18	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2=8.051. df= 2. p= 0.018 (significant).

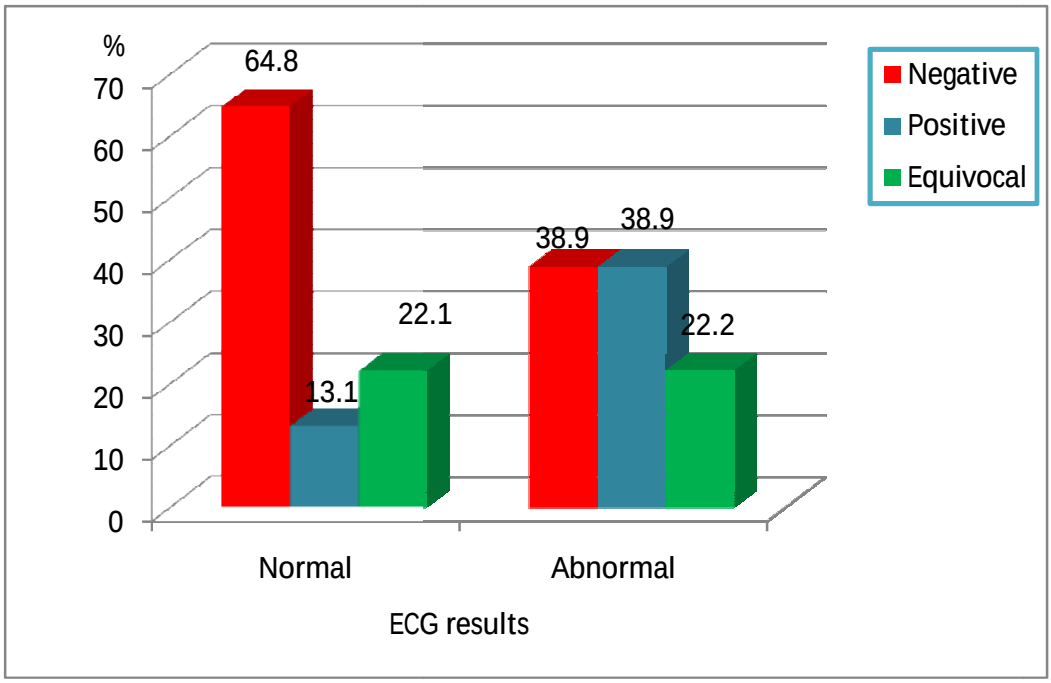

Fig .31: Distribution of patients according to exercise ECG results and resting ECG results.

Table 33: Distribution of patients according to exercise ECG results and Echo result.

Results of Echo	Exercise ECG							
	Negative		Positive		Equivocal		Total	
	No.	%	No.	%	No.	%	No.	%
Normal	86	63.2	21	15.4	29	21.4	136	100
Abnormal	0	0	2	50	2	50	4	100
Total	86	61.4	23	16.4	31	22.2	140	100

X2= 6.797. df=2 p= 0.033 (significant).

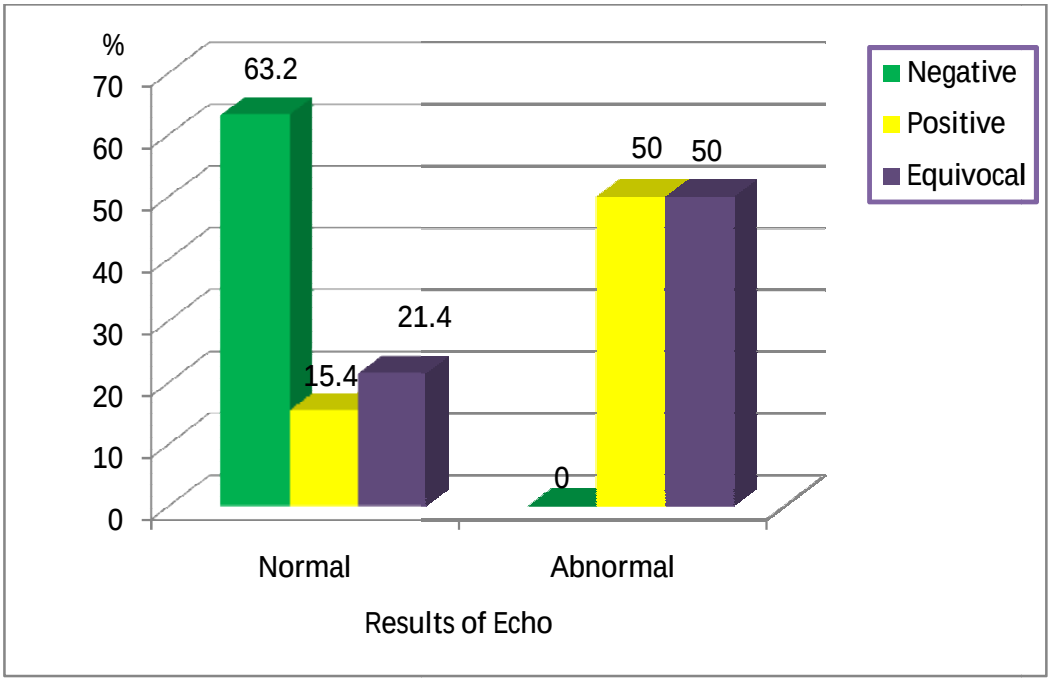

Fig. 32: Distribution of patients according to exercise ECG results and Echo result.

Chapter 6

Discussion:

The present study included 140 diabetic patients ,44.3% males and 55.7% females, ,66.5% their age ranged between 50 to 69 years, with mean age 57.5±9.9 years. Minimum age was 40years and maximum age was 79 years, in a similar study mean age was 59.6years.[66]

Exercise ECG (Treadmill test,TMT)was positive in 16.4% of the patients , 22.2% was equivocal and 61.4% was negative. In other study they found that out of 161 patients, 34 (21.1%) patients were (TMT) positive, while 90 patients were negative (55.9%) and 37 (22.9%) were inconclusive for IHD based on TMT test.[67]

Diabetes Mellitus appears to confer a dramatic increase in the risk of silent ischemia with most studies suggesting a prevalence of 10 – 20%.[68]

In this study exercise ECG were positive in 21.2% in age group 40-49years,13% in age group 50-59years, 21.3% in age group 60- 69years and this difference between the age group was statistically significant ($p < 0.05$). The risk of coronary heart disease increases with age in persons with or without diabetes, but diabetes appears to accelerate the process.[69]

The mean age of Exercise ECG positive patients was 57.4±8.1years and in negative patients the mean age was 54.8 ± 8.9years and this difference was not statistically significant, while in other study the mean age of subjects in TMT positive group 53.56± 7.41 years)was significantly higher than that of TMT negative group (48.71 ± 8.72years),with a P value of 0.0023, [68] our result it was not significant difference could be due to small sample size.Exercise ECG was positive in 22.6% of males and 11.5% of females , but this difference was not statistically different(p= 0.136). Diabetes is the only condition that causes women to have heart disease rates similar to those of men. The reason for this effect is uncertain. It is unlikely that it reflects differential loss of men with coronary heart disease through excess mortality. In the Rancho Bernardo Study, diabetic women had ischemic heart disease mortality rates similar to both non-diabetic and

diabetic men, while non-diabetic women had a clear longevity advantage.[70]

Duration of diabetes was 6 years or more in73.6% of patients, with mean duration(10.1± 7.5) , minimum duration was one month and maximum duration was 31 years, compared with other study the mean duration of diabetes was(12.4± 6.1years) .[66]

Exercise ECG results were positive in duration of diabetes in< 1, 12.5%, 3.4% in 1-5years, 22.2% in 6-10 years and 19% in >10 years and this difference was statically significant .Mean duration for positive patients was (12.7years ±7.9 years) and for the negative patients was (8.9 ± 7.3 years), and there was no statistical difference between the two means were the p value was equal to 0.262.This results was different from other study were they found the mean duration of diabetes in TMT positive group (74.79 ±48.2 months) was significantly higher than that of TMT negative group (47.41 ±31.66 months) with a P value of 0.0007. [67] Other study found the onset of NIDDM is less obvious than IDDM, and it has been difficult to distinguish between an effect of age and an effect of duration of diabetes on heart disease risk.[71] However, in the Nurses' Health Study, a longer duration of clinically recognized maturity onset diabetes in women was found to be associated with an increased risk of coronary heart disease, even after age adjustment.[72]

Duration of diabetes is not a proven risk factor for silent ischemia according to American Diabetic Association guide lines. However, there are several studies reporting positive correlation between the two. [73-75]

Family history of IHD was recorded in 19.3%.Exercise ECG results was positive in 18.5% of patients with family history of IHD, while positive in 15.9% in patients with negative family history of IHD, this difference

was not statistically significant (p=0.944). In similar study they reported that the family history of IHD showed significant association with TMT results with a P value of 0.0136 (P<0.05). [67] IHD has long been observed to aggregate in families [76]. A study by Roncaglioni et al. showed that in first- degree MI patients of either sex with a positive family history of MI (first degree relative affected, the adjusted estimate of the RR of MI is 2.0 (95% CI, 1.6-2.5) when compared to cases with a negative family history .[77] Their data also showed that in both sexes, the risk of MI increases according to the number of relatives affected; RR of 3.0 in cases with two or more relatives affected. Many studies support the hypothesis that a positive family history of IHD is an independent risk factor. In a 10-year follow-up study of more than 5500 healthy men, multivariate logistic regression analysis identified that family history of MI followed LDL cholesterol as the strongest predictor of MI, at a significance level of P < 0.01 . [78]. In a study by Jousilahti et al., a parental history of premature IHD conferred an adjusted RR for AMI of 1.71 in men and 2.87 in women (AMI < 55 years of age) .[79].Hypertension was recorded in 44.3% of all patients. Un-controlled hypertension was present in 59.3%. Exercise ECG results were positive in 15.2% of patient who suffer from hypertension, while positive in 18.8% of patient free from hypertension and this difference was not statistically significant (p=0.661). Dyslipidemia was recorded in 18.6% of the

patients, exercise ECG results was positive in 19.2% in patients who had dyslipidemia, while positive in 15.8% of patients without dyslipidemia and this difference was not statistically significant (p=0.144). Dyslipidemia in T2D worsens cardiovascular risk due to the peculiar atherogenic profile composed by increased very low-density lipoprotein (VLDL) cholesterol, triglycerides and small dense LDL cholesterol levels and decreased high-density lipoprotein (HDL) cholesterol levels. With such lipoproteins modified by oxidation and glycosylation there is a reduction on vascular compliance predisposing to early and aggressive atherosclerosis . [80 .]This was evidenced in an experimental study which concluded that either diabetic hyperlipidemia or hyperglycemia accelerates distinct phases of atherogenesis in diabetes.[81]

Dyslipidaemia is a significant predictor of CVD events and mortality in diabetes patients. [82] However, some contrasting results were obtained from the DIAD study and several others showing that there is hardly any correlation of dyslipidemia with silent ischemia .[83,84] .Over weight was found in 24.3% and obesity in 62.1% of all patients. Exercise ECG results was positive in(26.3%) patients with normal BMI, 20.6% in over weight and 12.6% in obese patients, this difference not statistically significant (p=0.092). This result was similar to result of other study

were the mean BMI was statistically insignificant between the two groups with P=0.1364.[67]

Level of HbA1c <7 constitute to 20 %, while ≥7 constitute to 80%, exercise ECG results was positive in 10.7% of patients with level of HbA1c <7 and 17.9% in patients with HbA1c ≥7, this difference not statistically significant p=(0.257). In other study, Glycemic control (HbA1C) showed increased risk of inducible ischemia with adjusted odds ratio of 1.341 (95% CI: 1.055-1.734), which was statistically significant with P value 0.019.[67].

While some studies have found a significant association between glucose levels and the prevalence or incidence, ,[85] of heart disease, others have not.[86] A Finnish study examined the association of glycosylated hemoglobin and heart disease in individuals with NIDDM.[85] After adjustment for duration of diabetes, glycemic control was significantly associated with 3.5-year coronary heart disease mortality but not with incidence. It is very difficult to separate the effect of glycemic control from age and duration of diabetes. [85]

Micralbuminuria was positive in 29.3% of the patients ,exercise ECG results was positive in(29.3%) of patients with microalbuminurea , while 11.1% in patients who was negative to microalbuminurea, this difference was statistically significant (p= 0.0383). In an other study

microalbuminuria was significantly associated with prevalent coronary heart disease based on history or electrocardiogram, microalbuminuria is proven risk factors for CAD in type 2 DM patients. [87,88] ECG was abnormal in 12.9 % of the patients, exercise ECG result in 13.1% of patients with normal ECG and 38.9% in patients with abnormal ECG, this difference was statistically significant (p=0.018) .

Exercise ECG results were positive in 15.4% in patients with normal Echo, compared to 50% of patients with abnormal Echo, this difference was statistically significant (p= 0.033).

Chapter 7

Conclusion

Conclusion :

1) In this study we found that the most important risk factor for asymptomatic IHD in type 2 NIDDM patients were microalbuminuria

2) Proportion of silent ischemia in type 2 DM patients was 16.4% in this study, which was within the limit recorded internationally (10 – 20%).

3) Most of known risk factors were not statistically significant as(age , duration of the disease) with the IHD, this result could be explained by the small sample size .

Chapter 8

Recommendations

Recommendation:

1) We recommended screening for IHD with TMT in patients who are suffering from DM for early diagnosis and early treatment to improve the prognosis for type 2 diabetic patients.

2) TMT should be done in asymptomatic type 2 NIDDM with microalbuminuria.

3) Our study may need to be followed by a future study, involving a large number of diabetic patients with different design as cohort - follow up study.

Chapter 9

References

DATA COLLECTION SHEET

ASYMPTOMIC IHD IN DM

S.N	AGE	DURATION OF DM	HTN	Dyslipid.	FIH IHD	D/H	CONTROLED BP

MALB	BMI	HbA1C	RESTING ECG	Echo	STRESS ECG	COROARY ANGIOGRAPHY

Reference

Reference

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Chapter 10

Appendix

Abbreviations

ACS = Acute coronary syndrome

ACC =American college of cardiology

ADA =American diabetic association

AGES = advanced glycation end products

AHA = American heart association

CAD= Coronary artery disease

CHD = Coronary heart disease

CVD = Cardiovascular disease

DBP= diastolic blood pressure

DM= diabetes mellitus

ECG= electrocardiography

FPG = fasting plasma glucose

HbA1c = glycated hemoglobin A1c

HDL = high density lipoprotein

HR = heart rate

IHD = ischemic heart disease

IGF = impaired fasting glucose

IGT = impaired glucose tolerance

ICAMS = intracellular adhesion molecules

LDL = low density lipoprotein

LBBB = left bundle branch block

LVH = left ventricular hypertrophy

METS = metabolic equivalents

MI = myocardial infarction

MODY= maturity -onset diabetes in young

MCP-1 =monocyte chemoattractant protein

MPHR = maximum predicted heart rate

NGR = normal glucose regulation

NF-KB =nuclear factor

OGTT = oral glucose tolerance test

PET = positron emission tomography

PG = plasma glucose

PVC = premature ventricular contraction

PCI = percutaneous coronary intervention

RAGE = receptor for advanced glycation end products

RBBB= right bundle branch block

RWMA = regional wall motion abnormality

SBP = systolic blood pressure

TC= total cholesterol

THR = target heart rate

TMT = treadmill test

VLDL = very low density lipoprotein

WHO = world health organization

VCAMS = vascular cell adhesion molecules

التشخيص المبكر لمرض الشرايين التاجيه في مرضى السكري

ورقة جمع البيانات

تحكم بضغط الدم	الأدوية	التاريخ المرضى العائلى	أرتفاع الدهون	ضغط الدم	فترة السكرى	العمر	الرقم التسلسلى

القسطرة القلبية	تخطيط القلب بالأجهاد	صدى القلب	تخطيط القلب	السكر التراكمى	مؤشر كتلة الجسم	الزلال الضعيف

التشخيص المبكر لمرض الشرايين التاجيه في مرضى السكري

الملخص :

مقدمة: نوع 2 داء السكري (DM) وقد حصلت علاقة متميزة يعانون مع مرض الشريان التاجي؛ ومرضى السكري لديهم خطر أعلى 2-4 أضعاف تطوير من الناس دون السكرى`.[1] ذلك ،لا يزال التدريجي مرض الشريان التاجي بدون أعراض في العديد من مرض السكري من النوع 2 الحالات وهذا ما يجعل التشخيص صعبا في الوقت المناسب.
الهدف: لتحديد عوامل الخطر لاعرضي في مرضى السكري الذين خضعوا لاختبار تخطيط القلب بالأجهاد. **المرضى والأسلوب:** دراسة مقطعية، تم وضع استبيان قبل اختبارها للحصول على معلومات حول التركيبة السكانية للمريض، ومدة السكري ، وجود ارتفاع ضغط الدم الشرياني، التاريخ المرضى العائلى. الاستبيان تستخدم أيضا لتسجيل الملاحظات على مختلف المعلمات الفحص لكل مريض (نسبة السكر التراكمى، لمة الدهون والزلال الضعيف البول,والمستريح تخطيط القلب ، و صدى القلب.

النتائج: شملت الدراسة 140 مرضى السكري من مستشفى عيادة السكري و آل الهواري العام (44.3٪ من بين الذكور و 55.7٪) من الإناث. كان ممارسة تخطيط القلب بالأجهاد ، واختبار الأجهاد إيجابي في 16.4٪ من المرضى، وكانت 22.2٪ ملتبسة، وكان 61.4٪ كان. الأجهاد سلبية ,إيجابيا في 22.6٪ من الذكور و 11.5٪ من الإناث، ولكن هذا الفرق لا يعتد به إحصائيا .(P = 0.136) وكانت مدة مرض السكري 6 سنوات أو أكثرin73.6 ٪ من المرضى، مع متوسط مدة (10.1 ± 7.5) تم الكشف عن التاريخ. العائلى في 19.3٪. تم تسجيل ارتفاع ضغط الدم في 44.3٪ من المرضى. تم العثور على ارتفاع ضغط الدم تسيطر عليها في 59.3٪. وسجلت أرتفاع الدهون في 18.6٪ من المرضى، وكانت النتائج ممارسة الأجهاد إيجابية في 19.2٪ من المرضى الذين لديهم أرتفاع الدهون ، في حين إيجابية في 15.8٪ من المرضى دون أرتفاع الدهون ومع ذلك كان هذا الفرق لا يعتد به إحصائيا .(P = 0.144) مستوى نسبة نسبة السكر التراكمى 7> تشكل إلى 20٪، في حين تشكل ≤7 إلى 80٪. وكانت النتائج إيجابية في ممارسةتخطيط الأجهاد10.7 ٪ من المرضى الذين يعانون من

مستوى نسبة HbA1c <7 مقارنة ب 17.9٪ في المرضى الذين يعانون من نسبة السكر التراكمى7≥ ، ولكن هذا الاختلاف لا يعتد بها إحصائيا .(0.257) = P كان الزلالي إيجابيا في 29.3٪ من المرضى وكانت النتائج. ممارسة تخطيط القلب بالأجهاد إيجابية في (29.3٪) من المرضى الذين يعانون من الزلال الضعيف، مقارنة مع 11.1٪ في المرضى الذين كانت سلبية لل الزلال الضعيف ، وكان هذا فروق ذات دلالة إحصائية(P = 0.0383)

الاستنتاج: 1) من هذه الدراسة وجدنا أن عامل الخطر الأكثر أهمية مرض الشريان التاجي بدون أعراض في نوع 2 المرضى السكرى 2 كانت الزلالي وكانت **2)** نسبة نقص تروية صامت في نوع 2 المرضى16.4 DM ٪ في هذه الدراسة، والتي كانت في حدود المسجلة دوليا (10-20٪). **التوصية:** نوصي الكشف مع تخطيط القلب بالأجهاد في المرضى الذين يعانون من داء السكرى للتشخيص المبكر والعلاج المبكر للحصول على أفضل تنبأ تشخيص لمرضى السكري.