A Dissertation on

CARDIAC DYSAUTONOMIA IN TYPE-2 DIABETES MELLITUS

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERISTY

CHENNAI

In partial fulfillment of the regulations

For the Award of the Degree of

M.D. (GENERAL MEDICINE)
BRANCH -1

KILPAUK MEDICAL COLLEGE
CHENNAI

MARCH – 2007

CERTIFICATE

This is to certify that this dissertation on **"CARDIAC DYSAUTONOMIA IN TYPE-2 DIABETES MELLITUS"** is a work done by **Dr. M. TARAKESHWARI**, under my guidance during the period February 2004 to March 2007. This has been submitted in partial fulfillment of the award of M.D. Degree in Internal Medicine by The Tamilnadu Dr. M.G.R. Medical University, Chennai.

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ACKNOWLEDGEMENT

I wish to express my sincere thanks to our Dean, **Prof. Dr. THIAGAVALLI KIRUBAKARAN, M.D.**, Kilpauk Medical College and Hospital, Chennai and **Prof. Dr. D.S. SOMASEKAR, M.D.,** Superintendent, Govt. Royapettah Hospital, for granting me permission to utilize the facilities of the hospital for the study.

I express my heartfelt gratitude to **Prof. Dr. S.R. SAKUNTHALA, M.D.**, Head of the Department of Internal Medicine for her esteemed guidance and valuable suggestions. It is my privileged duty to thank my teacher guide and Unit Chief **Prof. Dr. N. RAGHU, M.D.,** under whom I have had the great honour of learning as a post graduate student.

I express my sincere and heartfelt thanks to (Retd.) **Prof. Dr. U.S. ANANDAKUMAR, M.D.,** for his timely suggestions and valuable guidance.

I am greatly indebted to my Unit Assistant Professors, **Dr. M. SARAVANABHAVA, M.D., Dr. SULAIMAN, M.D., Dr. K.E. GOVINDARAJULU, M.D.,** and **Dr. K. KRISHNAKUMAR, M.D.,** who have put in countless hours in guiding me in many aspects during the conduct of this study.

I also express my sincere thanks to the ECG Technician, Statistician and the Staff for their efforts and suggestions that helped to complete this study.

I am thankful to my family, friends and colleagues for their valuable suggestions and sincere support during the conduct of this study.

I am thankful to all the patients without whom this study would not have been completed.

CONTENTS

Introduction

INTRODUCTION

The term diabetes mellitus describes several diseases of abnormal carbohydrate metabolism that are characterized by hyperglycemia. It is associated with a relative or a absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin.

The American Diabetes Association recommends the fasting plasma glucose because it is easier, faster and less expensive to perform. With the FPG test, a fasting glucose level between 100 and 126 mg/dl signals pre-diabetes. A person with a fasting blood glucose level of 126 mg/dl or higher has diabetes. One can also use oral glucose tolerance test (OGTT) to diagnose diabetes, but OGTT is cumbersome and hence is not preferred at most centers. It is performed by measuring a blood glucose level in the fasting state and again two hours after taking 75g of glucose or any glucose rich beverage. If the two hour blood glucose value is at 200 mg/dl or higher, the person tested has diabetes.

The estimated prevalence of diabetes worldwide is about 3,822,720 for the year 2003. This amounts to 5% of the world population. The South East Asian Region accounts for 705,292 cases. The estimated population affected in India is 6,03,677. With such high prevalence it is essential to institute measures to prevent diabetes hence the ADA has introduced the term prediabetes for IFG and IGT to create awareness.

The diabetes control and complications trial showed that intensive control of the blood sugar over a 7 year study interval reduced the progression of diabetic retinopathy, nephropathy and neuropathy[1].

The relationship between control and complications in type 2 diabetes was evaluated in the united kingdom prospective diabetes study[2]. The study concluded that for every 1% decrease in glycosylated hemoglobin A_{1c} there was a 35% reduction in the risk of microvascular complications. Diabetes complicates almost every organ and is the fourth major cause of mortality and morbidity world wide.

With the agreeable exception of pain, the autonomic manifestations of diabetes are responsible for the most troublesome and disabling feature of diabetic neuropathy and results in a significant proportion of the mortality and morbidity associated with the disease. A broad constellation of symptoms occur that affect cardiovascular, urogenital, gastro intestinal, pupillomotor, regulatory and sudomotor functions. The impairment is usually gradual and progressive, although severe autonomic dysfunction occurs shortly after the diagnosis of type 2 diabetes in rare cases[3]. The availability of sensitive, specific and reproducible non invasive tests of autonomic function has enhanced our understanding of the prevalence, pathophysiology and clinical manifestations of this disorder[4]. Estimates of the prevalence of diabetic autonomic neuropathy are dependent on the criteria used for diagnosis and the specific population under study.

The cardiovascular autonomic neuropathy has diverse manifestations. An increased resting heart rate is observed frequently in diabetic patients; most likely this is due to the vagal cardiac neuropathy that results in unopposed cardiac sympathetic nerve activity.

The tachycardia may be followed by a decrease in heart rate and ultimately a fixed heart rate due to the progressive dysfunction of the cardiac sympathetic nervous system[5].

Orthostatic hypotension, the most incapacitating manifestation of autonomic failure, is a common feature of diabetic cardiovascular autonomic neuropathy. This is a consequence of efferent sympathetic vasomotor denervation than causes reduced vasoconstriction of the splanchic and other peripheral vascular beds. Diminished cardiac acceleration and cardiac output, particularly in association with exercise, also may play a role in the presentation of this disorder.

Several authors have drawn attention to the association between increased mortality and cardiovascular autonomic dysfunction in patients with diabetes. Estimates of the mortality associated with cardiovascular autonomic neuropathy range from 27% to 56% over a period of 5-10 years after its onset. There is also an increased frequency of sudden death in patients with cardiac autonomic neuropathy.

Proposed mechanisms by which the autonomic nervous system may result in sudden death or influence the outcome of patients with diabetes who have cardiovascular disease include absent or altered perception of

myocardial ischemia and infarction, deficient hemodynamic response to cardiovascular stresses such as surgery, infection and anesthesia; increased predisposition to cardiac arrhythmias due to QT interval dispersion; and alterations in sympathetic – parasympathetic cardiac innervation balance [6,7].

It is in this background that we endeavour to analyse the prevalence of cardiac autonomic neuropathy in type 2 diabetic patients using clinical methods and cardiovascular autonomic function tests. This study also aims to find the electrocardiographic changes associated with diabetes mellitus.

Aim of the Study

AIM OF THE STUDY

1. To study the prevalence of cardiac dysautonomia in type 2 diabetic patients by clinical and electrocardiographic methods.
2. To study the prevalence of various ECG abnormalities in type 2 diabetic patients as compared to controls.
3. To study the correlation between symptoms and signs of cardiac dysautonomia in type 2 diabetic patients.

Review of Literature

REVIEW OF LITERATURE

Diabetes mellitus comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

The worldwide prevalence of DM has risen dramatically over the past 2 decades. Likewise, prevalence rate of impaired fasting glucose are also increasing. Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence type 2 DM is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels.

WHO FACT SHEET

Prevalence of Diabetes World Wide

Region	Prevalence (Year 2000)	Projected estimate (Year 2030)
World	171,000,000	366,000,000
South East Asia	49,903,000	119,541,000
India	31,705,000	79,441,000

In 2000, the prevalence of DM was estimated to be 0.19% in people <20 years old and 8.6% in people >20 years old. In individuals >65 years of

age the prevalence of DM was 20%. The prevalence is similar in men and women throughout most age groups but is slightly greater in men after 60 years of age.

There is considerable geographic variation in the incidence of both type 1 and type 2 DM. The prevalence of type 2 DM and its harbinger, IGT is highest in certain Pacific Islands, intermediate in countries such as India and the United States and relatively low in Russia and China. This variability is likely due to genetic, behavioural and environmental factors.

The results of prevalence studies of DM in India were systematically reviewed with emphasis on those utilizing the standard WHO criteria for diabetes diagnosis. The prevalence of diabetes in adults was found to be 2.4% in rural and 4.0 – 11.6% in urban dwellers [8].

High frequencies of impaired glucose tolerance, shown by these studies, ranging from 3.6 – 9.1%, indicate the potential for further rise in prevalence of diabetes mellitus in the coming decades[8].

Recently the WHO in consultation with an expert committee of the American Diabetes Association has approved a new diagnostic criteria for DM.

Diagnostic criteria

Category	FPG	PPG
Normal	<100mg/dl (5.6 mmol/L)	<140mg/dl (<7.8 mmol/L)
IFG	100 – 125 mg /dl (5.6 – 6.9 mmol/L)	-
IGT	-	140 – 199 mg/dl (7.8 – 11.0 mmol/L)
Diabtes	≥ 126 mg /dl (≥ 7.0 mmol/L)	≥ 200 mg /dl (≥11.1 mmol/L)
Fasting: No caloric intake for atleast 8 hours.		

When the diagnosis of diabetes is made it is confirmed by a repeat testing done on a different day.

DIABETES AND THE HEART

Diabetes is a major risk factor for cardiovascular mortality. It affects the heart in these ways.

- Coronary artery disease
- Small vessel disease
- Diabetic cardiomyopathy
- Heart failure
- Cardiac autonomic neuropathy

Coronary Artery Disease

Coronary artery disease is about twice as frequent in diabetic men and four times as frequent in diabetic women after menopause compared to the respective non diabetics. In fact one third of all deaths occurring in diabetics after 40 years of age have been attributed to coronary artery disease. CAD in diabetes is characterized by greater prevalence of triple vessel disease. Clinically CAD in diabetic subjects is associated with prematurity and asymptomatic heart disease. An abnormal resting ECG has been documented in about 40% of normotensive, ambulant diabetic subjects. On exercising, the prevalence of ECG abnormalities among diabetic subjects is twice compared to non - diabetics. Silent myocardial infarction is an entitity with a greater prevalence in diabetic subjects.

Small Vessel Disease

In addition to the classical atherosclerosis affecting the large extramural vessels, occlusive disease process affecting the smaller vessels is the hallmark of diabetic heart disease. Pathological changes are seen in the endothelium, elastic and intima in the small arteries. The resultant ischemia produces widespread fibrosis in the ventricular interstitium with impaired left ventricular function. Syncope, conduction disturbances, arrhythmias and even sudden death may be produced by small vessel disease of sinoatrial node or atrioventricular node.

Diabetic Cardiomyopathy

This refers to the derangement in the myocardium in the absence of extramural coronary atherosclerosis. Increased accumulation of connective tissue in the myocardium surrounding the smaller intramural vessels has been histologically documented. The localized saccular aneurysms of arterioles may involve any layer of ventricular myocardium. Morphological analysis of the diabetic myocardium reveals accumulation of glycoprotein material with a less compliant ventricular wall. Non invasive and invasive techniques have enabled the identification as well as quantification of the degree of ventricular impairment. ST and T wave changes in ECG are very early changes in diabetic cardiomyopathy. The thickness of the ventricular septum has been correlated with the insulin concentration. The systolic time interval is a very sensitive index of left ventricular dysfunction. The ratio of pre-ejection period: left ventricular ejection time is increased in diabetic subjects and is

attributed to asynchronous and incoordinate myocardial contraction, and has been found to correlate with the ambient blood glucose levels. The delay in mitral valve opening relative to minimum cavity dimensions accounts for the prolonged relaxation of the diabetic myocardium.

Heart Failure

There is a high frequency of diastolic dysfunction accompanied by an increased mortality risk for patients with diabetes. The poor prognosis for these patients has been explained by an underlying diabetic cardiomyopathy exacerbated by hypertension and ischemic heart disease. Epidemiological data shows that heart failure is two times as common in diabetic men and five times as common in diabetic women as in age – matched non diabetic subjects .Evidence from large clinical trials has shown that remodeling can be attenuated, ventricular function improved and mortality and morbidity reduced by drugs that interfere with the enhancement of the neurohormonal systems.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system innervates the entire neuraxis and permeates all organ systems. It regulates blood pressure, heart rate, sleep and bladder and bowel function. It operates in the background, so that its full importance becomes recognized only when its function is compromised, resulting in dysautonomia.

The preganglionic neurons of the parasympathetic nervous system leave the central nervous system in the third, seventh, ninth and tenth cranial nerves as well as the second, third and fourth sacral nerves, while the preganglionic neurons of the sympathetic nervous system exit the spinal cord between the first thoracic and second lumbar segments. The post ganglionic neurons located in ganglia outside the CNS gives rise to post ganglionic autonomic nerves that innervate organs and tissues throughout the body.

Functional consequences of normal ANS Activation

Parameters	Sympathetic	Parasympathetic
Heart rate	Increased	Decreased
Blood pressure	Increased	Mildly decreased
Bladder	Increased sphincter tone	Voiding
Bowel motility	Decreased motility	Increased
Lung	Bronchodilation	Bronchoconstriction
Sweat glands	Sweating	_
Pupils	Dilation	Constriction
Adrenal Glands	Catecholamine release	_
Sexual function	Ejaculation, orgasm	Erection
Lacrimal Glands	_	Tearing
Parotid Glands	_	Salivation

Responses to sympathetic and parasympathetic stimulation are frequently antagonistic, reflecting highly coordinated interactions within the CNS; the resultant changes in parasympathetic and sympathetic activity provide more precise control of autonomic responses than could be achieved by the modulation of a single system.

Diabetic Autonomic Neuropathy

DAN, a subtype of the peripheral polyneuropathies that accompany diabetes, can involve the entire autonomic nervous system. DAN is a serious and common complication of diabetes. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple systems and impairment, the significance of DAN has not been fully appreciated.

DAN has been called a silent killer, because so few patients realize that they suffer from it and yet its effects can be so lethal.

DAN may be either clinically evident or subclinical. It is manifested by dysfunction of one or more organ systems (cardiovascular, gastrointestinal, genitourinary, sudomotor, ocular)[9].

Sub clinical autonomic dysfunction can occur within a year of diagnosis in type 2 diabetics and within 2 years in type 1 diabetics[10,11,12].

Based even on asymptomatic subjects with abnormality only in autonomic function tests, the overall mortality rate may be as high as 25% to 40% over 10 years[13].

SYMPTOMS AND SIGNS OF DAN

Cardiovascular System [14]

- Postural hypotension
- Painless myocardial infarction
- Resting tachycardia
- Loss of heart rate variation

Gastro Intestinal System

- Impaired esophageal motility
- Gastroparesis
- Diarrhea
- Colonic atony
- Enlarged gall bladder

Urogenital System

- Bladder dysfunction
- Impotence
- Retrograde ejaculation
- Loss of testicular sensation

Respiratory System

- Respiratory arrest

Pupillary Abnormalities

- Reduced resting diameter
- Delayed or absent response to light
- Diminished hippus

Vasomotor System

- Loss of skin vasomotor responses
- Peripheral vascular changes
- Osteopathy (Charcot's arthropathy)
- Dependent edema

Sudomotor Features

- Diabetic anhydrosis
- Gustatory sweating

Hypoglycemia Unawareness

- Decreased catecholamine release with loss of warning symptoms of hypoglycemia
- Decreased pancreatic glucagons and pancreatic polypeptide release.

DIFFERENTIAL DIAGNOSIS OF CAN

Clinical features	Differential Diagnosis
Tachycardia Exercise intolerance	• Idiopathic Orthostatic Hypotension • Multiple system atrophy with parkinsonism • Hyperadrenergic hypotension
Cardiac denervation Painless myocardial infarction	• Shy Drager Syndrome • Panhypopituitarism • Pheochromocytoma
Orthostatic hypotension	• Hypovolemia • Congestive Heart Disease • Carcinoid syndrome

ETIOPATHOGENESIS

The precise pathogenesis of diabetic neuropathy is still not fully understood however clinical observation and studies using animal models of experimental diabetes suggest that hyperglycemia and other metabolic derangement might directly induce damages to neurons and nerve parenchyma[15].

In parallel reduced neurovascular blood flow might also cause ischemic neuronal damages[15].

Multiple abnormalities in diabetic states, including the activation of protein Kinase C, enhanced oxidative stress, formation of advanced

glycosylation end products in neuronal tissues and altered expression of neurotrophic factors such as nerve growth factor and IGF -1 have all been reported to be important determinants for the pathogenesis of diabetic neuropathy [16,17].

Vascular etiology in diabetic neuropathy is supported by multiple abnormalities in the microvasculature, including the deposition of AGE in the perineuronal vascular wall, basement membrane thickening, endothelial cell swelling and loss of pericytes, reduced endothelial nitric oxide activity and capillary occlusion[16] and degeneration of blood vessels supplying neuronal tissues[18]. All the changes eventually contribute to hyperglycemia induced decrease in neurovascular blood flow and the subsequent hypoxia – ischemic damage[19].

Gene transfer of VEGF in experimental diabetic animal models has been reported to restore blood flow in neuronal tissues and rectify the conductivity of the nerves that were impaired in diabetic states[18,20].

Vascular (Ischemic – hypoxic) Theory[20]

According to this theory, endoneural ischemia develops because of increased endoneural vascular resistance to hyperglycemic blood. Various metabolic factors, including formation of AGE products also have been implicated. The end results are capillary damage, inhibition of axonal transport, decreased sodium / potassium ATPase activity, and finally axonal degeneration.

Metabolic Theory

This theory proposes that hyperglycemia causes increased levels of intracellular glucose in nerve, leading to saturation of the normal glycolytic pathway. Extra glucose is shunted through polyol pathway and converted to sorbitol and fructose by the enzymes, aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose lead to decreased nerve myoinositol, decreased membrane sodium/ potassium ATPase activity, impaired axonal transport and structural breakdown of nerves, causing abnormal action potential propagation.

Altered Neurotrophic Support Theory

Nerve growth factor is the best studied of the neurotrophic factors. This protein promotes survival of sympathetic and small fibre neural crest derived elements in the PNS. Antioxidants have been used to enhance the effects of NGF.

Laminin Theory

Laminin is a large heteromeric glucoprotein composed of a large α and two smaller β chains, β1 and β2. In altered neurons, laminin promotes neurite extension. Lack of normal expression of the laminin β2 gene may contribute to the pathogenesis of diabetes neuropathy.

Autoimmune Theory

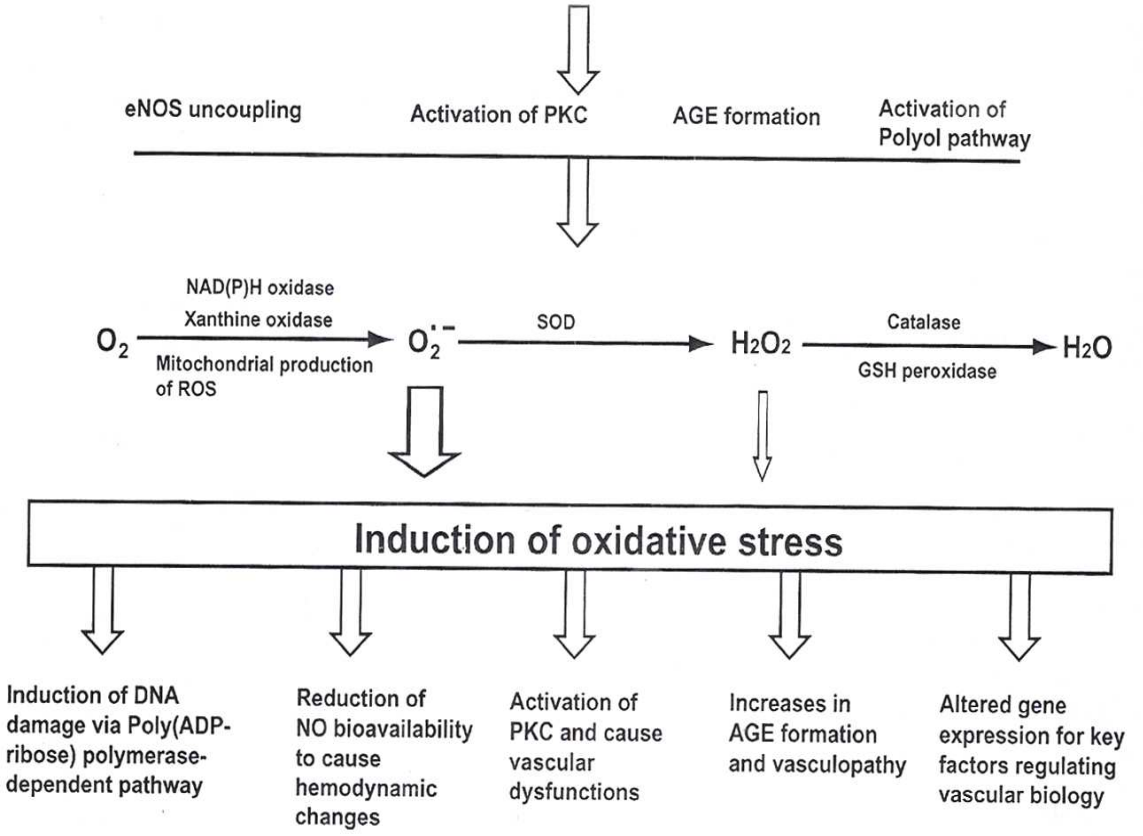
This favours autoimmune damage to endothelial capillary cells. Antibodies to endothelial cells decreases microvascular supply to neurons.

Inflammatory Theory

Diabetic patients have increased plasma level of inflammatory markers such as C reactive protein, IL-6, and TNF - α that are associated with endothelial dysfunction[21].

OXIDATIVE STRESS

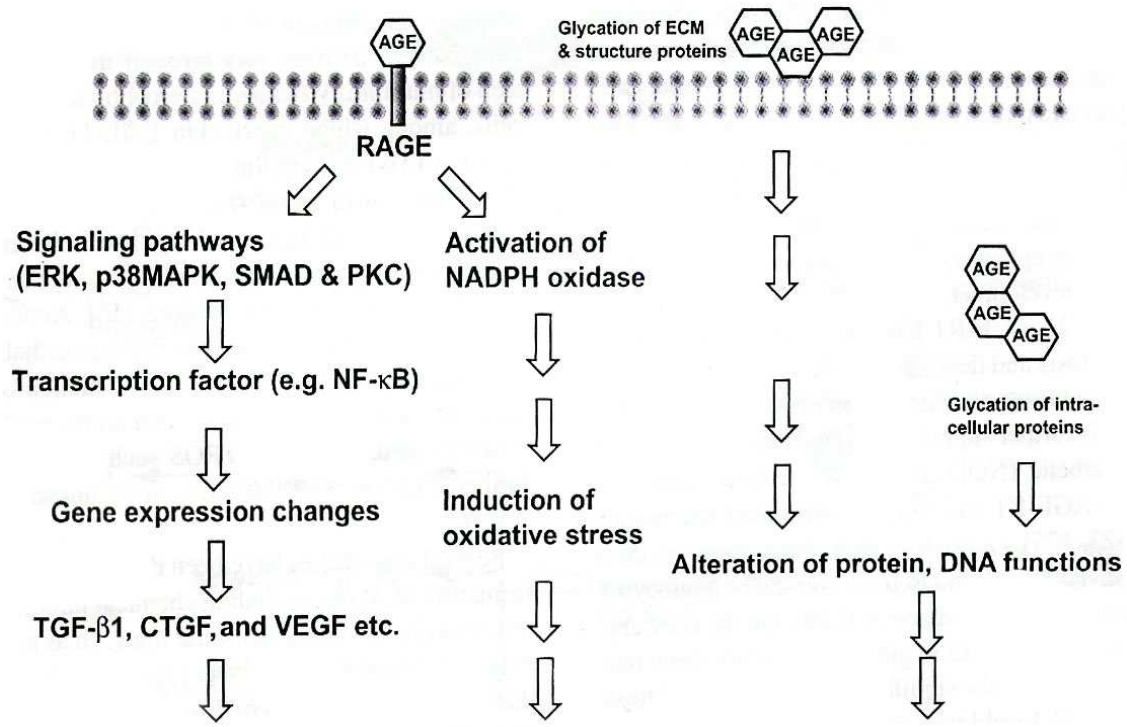
Hyperglycemia



The roles of hyperglycemia – induced accumulation of ROS and oxidative stress in diabetic vascular complications. In diabetic states, hyperglycemia regulates the multiple steps of the production and clearance of ROS and is in favour of ROS accumulation. Such events include the production of superoxide from endothelial nitric oxide synthase (eNOS) uncoupling, activation of PKC, AGE formation, and increased flux through polyol pathway. In addition to the increased activity of NAD(P) H oxidase, mitochondrial production of ROS is also increased and results in the overproduction of superoxide O_2, which is the major from of ROS that causes vascular oxidative stress. This is turn, contributes to diabetic vascular complications as illustrated.

VASCULAR PATHOLOGY

Hyperglycemia

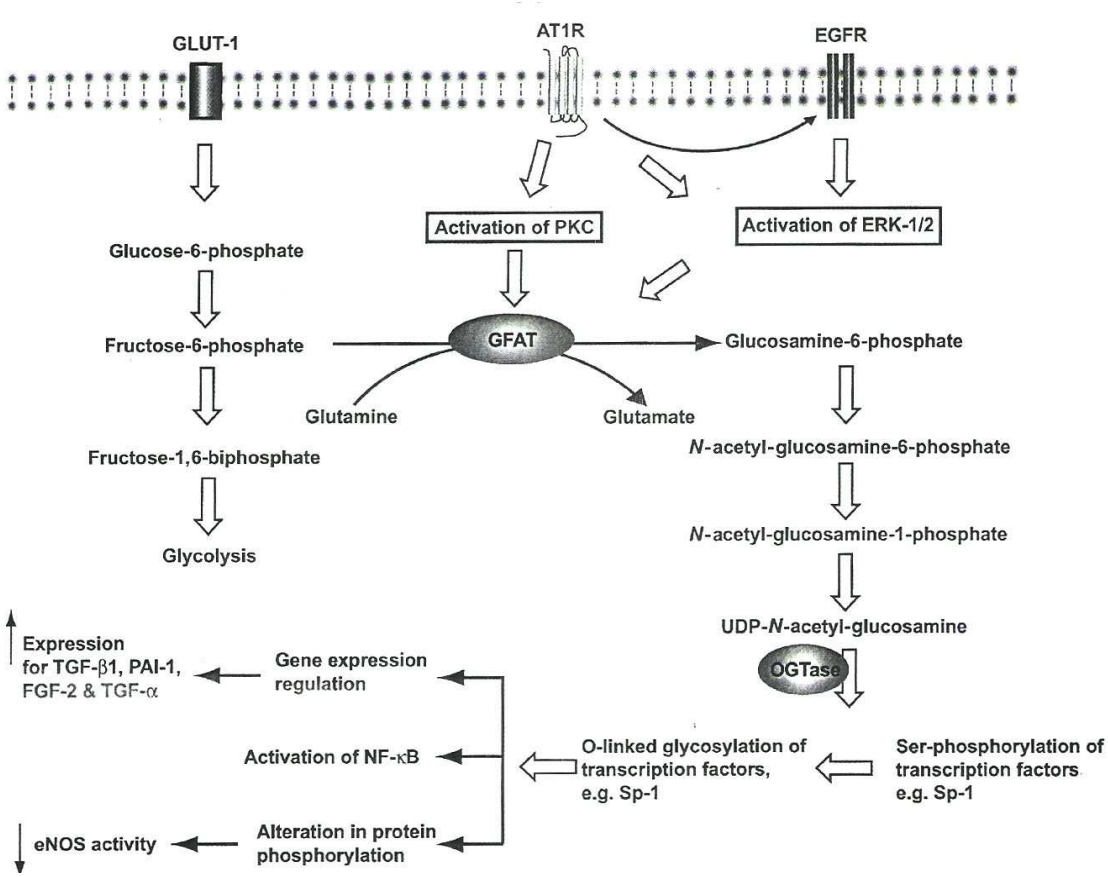


Vascular pathological changes

Role of AGE accumulation in diabetic vascular complications. Hyperglycemia induces the glycation of multiple extracellular and intracellular proteins known collectively as AGE. The glycation modification of proteins not only alter the function of strcture proteins, but also activate intracellular signaling pathways through receptor for AGE (RAGE) that contributes to the development of diabetic vascular complications.

INTRA CELLULAR PATHWAYS

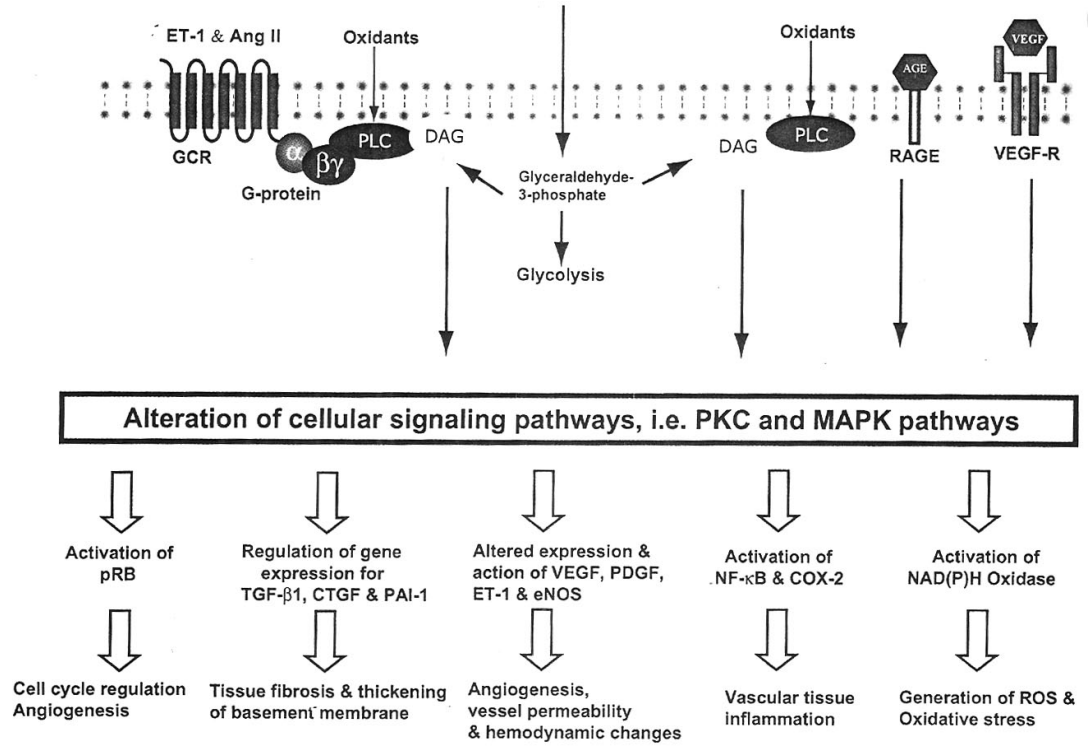
Hyperglycemia



Activation of the hexosamine pathway in response to hyperglycemia and its role in diabetic vascular complications. Increased action of the key enzymes in the hexosamine pathway including glutamine: fructose – 6 – phosphate aminotrasferease GFAT and O- GlcNAC transferase OGTase induces the flux through the hexosamine pathway that can result in the O-linked glycosylation of may proteins. Increased glycolysis induces the induction of flux through the hexosamine pathway. There is also cell culture study suggested the increased transcription of GFAT in response to AT- IR activation that requires that transactivation of epidermal growth factor receptor (EGFR). The increased hexosamine pathway activity is modification can prevent hte serine phsophorylation of multiple key enzymes and transcriptional factors that alter vascular hemodynamic and gene expression. These changes have been suggested to play a role in and transcriptional factors that alter vascular hemodynamic and gene expression. These changes have been suggested to play a role in the develoopment of diabetic vascular complications.

TRANSCRIPTION DEFECTS

Hyperglycemia



Activation of intracellular signaling cascades by hyperglycemia lead to multiple vascular pathological changes in diabetes. Hyperglycemia could activate intracellular signaling pathways via several mechanisms independently, including actions of cell surface receptors, formation of AGE, oxidative stress, and intermediates of the glycolysis pathways. The activation of these intracellular signaling molecules, especially the PKC-β and -δ isoforms, have been shown to regulate vascular cell growth and apoptosis, gene expression, vascular permeability, hemodynamic changes, oxidative stress, and inflammation. Clinical trials are ongoing evaluating selective inhibition of PKC-β in the treatment of diabetic retinopathy and neuropathy.

CARDIOVASCULAR AUTONOMIC NEUROPATHY

This occurs in about 17% of patients with type 1 DM and 22% of those with type 2 DM. An additional 9% of type 1 patients and 12% of type 2 patients have borderline dysfunction[22].

Using cardiovascular reflex tests, the prevalence is reported to be 17% to 40% [23-27]. Of teenagers with type 1 DM 31% have abnormal results[23].

The prevalence is associated with both duration of diabetes[28]and with age and is equal to or higher in type 2 than in type 1 DM[29].

When symptoms of autonomic neuropathy are present, the anticipated mortality rate is 15% - 40% with in five years [30,31,32].

A metaanalysis of eleven studies concluded that five year mortality was 5% among patients with normal heart rate variability compared to 27% among those with abnormal HRV[33]. A recent prospective study has shown the prevalence of DAN in the EURODIAB IDDM complication study to be 36%[34].

There has been a considerable variation in prevalence as is evident in these studies. The reported prevalence of DAN varies with community based studies finding lower rates than clinic and hospital based studies in which the prevalence may be as high as 100%[35.]

Pathology

In an autopsy study of patients with symptoms of autonomic neuropathy, Duchen and colleagues found infiltration of lymphocytes, macrophages and plasma cells in and around autonomic nerve bundles and ganglia[36].

Further studies in diabetic rodents and human sympathetic ganglia at autopsy have demonstrated axonal and dendritic pathology in sympathetic ganglia in the absence of significant neuron loss as the neuropatholgoical hallmark of DAN[37].

A recurring theme in sympathetic ganglia as well as in the post ganglionic autonomic innervations of various end organs, is the involvement of distal portions of axons and nerve terminals by degenerative or dystrophic changes. There is a marked enlargement of distal preterminal axons and synapses, and this is the most notable alteration in sympathetic ganglia in diabetic patients[38].

MANIFESTATIONS OF CAN

Resting Tachycardia and Diminished HRV

Resting tachycardia is an early sign of autonomic neuropathy. Tachycardia increases the risk of atherosclerosis[39,40] and distensibility of the vascular wall is reduced by tachycardia[41]. It is important to realize that clinical implication of HRV analysis has been clear recognized in only 2 clinical conditions[42].

a. as a predictor of risk of arrhythmogenic events or SCD after acute myocardial ischemia.
b. As a clinical marker of evolving diabetic neuropathy.

Left Ventricular Dysfunction

There is evidence of left ventricular dysfunction in particular diastolic dysfunction in patients with DAN[43]. Parasympathetic impairment and nocturnal elevations in blood pressure could be the link between autonomic neuropathy and diastolic ventricular dysfunction[44]. Diastolic function is usually impaired first followed by systolic dysfunction[45].

Decreased Myocardial Reserve

DAN patients have a decreased myocardial perfusion reserve capacity when challenged with a vasodilator. The underlying mechanism may be defective myocardial sympathetic vasodilatation, a lack of ability to maintain blood pressure during vasodilatation or both[46]. The heart rate, blood pressure and cardiac output responses to exercise are significantly impaired in diabetic neuropathic patients[47].

Silent Myocardial Ischemia

During a 4.5 year followup of diabetic patients with autonomic neuropathy accompanied by silent myocardial ischemia, a serious cardiovascular event was recorded in 50%[48].

Increased Risk Of Coronary Artery Disease

Recent studies have shown an association between autonomic neuropathy and increased coronary heart disease risk[49].

Autoimmune neuropathy 5 years after diagnosis of type 2 diabetes is associated with an unfavourable metabolic risk profile, and parasympathetic neuropathy in type 2 diabetes patients is associated with features of the insulin resistance syndrome[50]. The high platelet activation may reflect an increased pro-thrombotic state in diabetic cardiovascular autonomic dysfunction[51].

Further more, cardiovascular autonomic neuropathy is related to increased plasminogen activator inhibitor[52]. Increased arterial stiffness may be of importance in the increased susceptibility to cardiovascular complications in diabetic women[53]. Sympathetic denervation of arteries leads to medial smooth muscle degeneration and calcification[54].

Loss Of Circadian Rhythm Of Blood Pressure

Nocturnal blood pressure in patients with diabetic autonomic neuropathy is higher than that in non diabetic subjects. Monitoring blood pressure over 24 hours confirms this flattening in nocturnal blood pressure reduction at night and shows increased blood pressure values[55]. This may cause cardiac hypertrophy and is postulated as one possible cause of increased mortality[56].

Postural Hypotension

Maintenance of blood pressure on standing depends on afferent impulses from baroreceptors and efferent sympathetic impulses to the heart and blood vessels. Postural hypotension; that is a fall in systolic pressure of more than 30 mm Hg, on standing, occurs in diabetic subjects with advanced neuropathy, although symptoms are infrequent.

Blood flow studies show that the reduction in foot blood flow on standing observed in normal subjects is diminished in diabetic patients with postural hypotension, although significant vasoconstriction still occurs[57].

Another important mechanism is the failure of the splanchnic bed to vasoconstrict on standing. Failure of cardiac acceleration and reduced cardiac output both contribute to the problems. Nor adrenaline levels are generally reduced in diabetic patients with postural hypotension.

Insulin is known to have cardiovascular effects[58]. It causes a reduction in plasma volume, an increase of peripheral blood flow from vasodilatation and an increase in heart rate. In patients with autonomic neuropathy, insulin may cause an exacerbate postural hypotension to the point of fainting, whether it is given intravenously or subcutaneously and occasionally a blackout may occur from hypotension.

Both hypotension and its symptoms fluctuate spontaneously to a remarkable degree and may persist for many years without necessarily deteriorating[59].

Postprandial Hypotension

In diabetic patients with autonomic neuropathy observations established that while food causes a large increase in mesentric blood flow, the latter does not coincide with an exacerbation of their hypotension[60].

CARDIOVASCULAR AUTONOMIC FUNCTION TESTS

Tests for Parasympathetic Function

- Heart rate response to deep breathing

- Heart rate response to standing
- Heart rate response to valsalva manuover.

Tests for Sympathetic Function

- Blood pressure response to standing
- Blood pressure response to sustained hand grip

Sl.No	Cardiac autonomic function tests	Normal	Abnormal
1	Heart rate variation during deep breathing (E:I ratio)	>1.1	≤1.1
2	Heart rate increase on standing 30: 15 ratio	>1.04	<1.00
3	Valsalva ratio	>1.2	<1.2
4	Blood pressure response on standing (Systolic pressure fall at 2 min [mm Hg])	<10	>30
5	Blood pressure to sustained hand grip (rise in diastolic blood pressure [mmHg])	>16	<10

NONINVASIVE CARDIOVASCULAR REFLEX TESTS

Heart Rate Response to Deep Breathing

The normal acceleration and deceleration of heart rate during respiration (sinus arrhythmia) is decreased early in course due to cardiovagal involvement. This phenomenon provides the basis for the simplest and most sensitive test for the presence of cardiac dysautonomia. The patient takes breath deeply and evenly at a rate of 6 breaths per minutes (i.e.,) 5 seconds for inspiration and 5 seconds for expiration. The maximum and minimum heart rate during this breathing cycle is calculated from the ECG recording. The difference between 3 successive breathing cycles gives max – min heart rate variation as E: I ratio.

Heart Rate Response To Standing

When the patient is made to stand from a lying posture there is a characteristic rapid increase in heart rate. This is maximum at 15^{th} heart beat after standing followed by a relative overshoot bradycardia which is maximum at 30^{th} beat. This is represented as a ratio (30^{th} Beat) R-R : (15^{th} Beat) R-R minute ratio in the ECG recording.

Heart Rate Response To Valsalva Manoeuvre

Blood pressure falls and heart rate increases during strain phase of valsalva manoeuvre and after release the blood pressure rises with the slowing of heart rate. In patients with cardiac dysautonomia there is a fall is blood pressure during the strain phase and after release, slowly the blood pressure returns to normal with no variation in heart rate. This test can be performed

using an aneroid manometer. The valsalva ratio is the ratio of longest R-R / shortest R-R intervals; the normal value being more than 1.1.

Blood Pressure Response to Standing

Blood pressure recording is done when the subject is lying down and again two minutes after standing up. The difference in systolic blood pressure from lying to standing posture is taken as a measure of postural hypotension. The response is abnormal if the blood pressure decreases by more than 30 mmHg within two minutes of standing.

Blood pressure response to Sustained Exercise

A hand grip dynamometer is squeezed to 30% of maximum (predetermined in the subject) for 5 minutes. The normal response is an increase of diastolic blood pressure of approximately 16 mm Hg. A rise of less than 10mmHg is considered abnormal.

These tests form the core of diagnosis of cardiac autonomic neuropathy. They are validated, reliable and reproducible. They correlate with each other and with tests of peripheral somatic nerve functions.

A recent study has provided age specific and sex specific reference values for a wide range of different autonomic function measures in elderly population[61].

Spectral Analysis of Heart Rate Variability

The development of power spectrum analysis has facilitated the diagnosis of autonomic neuropathy. HRV can be assessed in the time domain (by statistical analysis of RR intervals) and in the frequency domain (by spectral analysis of a series of successive RR intervals). Electrocardiogram recording is made for at least five minutes to allow spectral analysis to be carried out.

In the time domain, the simplest parameter is the standard deviation of RR intervals. Three frequency domains are usually measured.

- A high frequency (HF) component that is a reflection of respiratory sinus arrhythmia and is an index of vagal activity;
- A low frequency (LF) component reflecting vasomotor activity and is dependent on both sympathetic and vagal tone;
- Among low frequency (VLF) band representing the influence of the peripheral vasomotor and renin – angiotensin system[62].

DAN is associated with a reduction of HRV. Both the LF and HF components diminish before onset of clinical neuropathy. This suggests similar damage to both sympathetic and parasympathetic pathways of the heart.

Measurement of baroreflex sensitivity

The arterial baroreflex maintains the stability of blood pressure. Changes in BP lead to stimulation of the baroreceptors, which activates cardiac vagal fibers and sympathetic outflow to the heart and the peripheral blood vessels. Vagal tone is maintained by reflex mechanisms that activate the baroreceptors. Thus baroreflex sensitivity can be measured from the reflex heart rate response to changes in BP.A change in BP can be induced pharmacologically, or the spontaneous fluctuations of BP in steady state conditions may be used.

Thus short noninvasive recording of the BP and RR interval signals are taken in the supine position. The baroreflex sensitivity is determined by the regression analysis of changes induced in the length of RR interval by spontaneous fluctuations in BP. Baroreflex sensitivity is impaired in diabetics and is helpful in the early detection of cardiac autonomic neuropathy.

MANAGEMENT

MANAGEMENT OF PATHOGENETIC MECHANISMS

Strict glycemic control

When we detect DAN the first and foremost important focus of treatment is blood sugar control. Until recently, researchers were unaware as to whether high blood sugar levels were actually responsible for the complications of diabetes. In 1993, the results of DCCT largely put those doubts to rest. The most important thing that we can do for patients with diabetes are to make them aware of autonomic neuropathy, to let them know whether they have it and keep blood sugar levels within acceptable range.

Aldose reductase inhibitors

- Alrestatin
- Sorbinil
- Tolrestat
- Zenerestat

Aldose reductase inhibitors reduce the flux of glucose through the polyol pathway,inhibiting tissue accumulation of sorbitol and fructose and preventing reduction of redox potentials.

Myo -inositol

There are several studies suggesting that myo-inositol supplements of the normal diet improves neuropathy, but the treatment may have to be prolonged for atleast six months for significant results to be achieved.

Trends for the future

Alpha Lipoic acid

This is a derivative of octanoic acid and is present in food and is also synthesized in liver. It has been shown to be effective in ameliorating both somatic and autonomic neuropathy in diabetes.

Gamma Linolenic acid

Linoleic acid, an essential fatty acid is metabolized to gamma linolenic acid, which serves as an important constituent of neuronal membrane phospholipids, and also serves as a substrate for prostaglandin E formation which is vital for preserving nerve blood flow.

Aminoguanidine

It is an inhibitor of AGE and inspite of its serious toxic profile, successive generations of aminoguanidine are under trial and holds promise for the future.

Neurotrophic Therapy

Nerve growth factor binds to high and low affinity nerve growth factor receptors present on small, unmyelinated fibers of the sensory neurons of the peripheral nervous system, on sympathetic neurons in the autonomic nervous system, and in regions of the central nervous system. This therapy is under trial and is directed towards regeneration of damaged nerves.

MANAGEMENT AIMED AT SYMPTOMS

Postural hypotension in the patient with DAN can present difficult management problem. Elevating the blood pressure in the standing position must be balanced against preventing hypertension in the supine position

Supportive garment

Attempts should be made to increase venous return from the periphery using total body stockings. The patient should be instructed to put them on in the lying down position and not to remove them until returning to the supine position. In severe cases an air force anti-gravity suit may be needed.

Drug therapy

Some patients may benefit from treatment with 9-fludrocortisone 0.5 mg daily and supplementary salt 2 to 6 g daily. Metoclopramide 10 mg three times daily may be helpful in patients with dopamine excess or increased sensitivity to dopaminergic stimulation. Patients with alpha 2 adrenergic receptor excess may respond to yohimbine, 10 mg three times a day. Other drugs that are helpful include clonidine, midodrine, dihydroergotamine, caffeine and octreotide.

Nutritional Supplements

Antioxidants

Antioxidants play a pivotal role in preventing progression of diabetic neuropathy.Their role in autonomic neuropathy is validated through many trials., eg. Ziegler et al proved the efficacy of anti oxidant in CAN. The following agents are recommended.

- Vitamin A
- Vitamin C
- Vitamin E
- Selenium
- N Acetyl Cysteine
- Gingko Biloba Extract

Others

Chromium, Biotin, Niacin, Inositol, Taurine, Magnesium have also been tried and is recommended for prevention of DAN.

ECG CHANGES IN DIABETES

The length of the QT interval is influenced by autonomic nervous tone. A long QT interval may reflect an imbalance between right and left heart sympathetic nerve activity.

Autonomic instability reflected by abnormally long QT intervals increases the risk of severe abnormal rhythms and sudden death. In the EURO Diabetes IDDM complications study, 16% had prolonged corrected QT interval. Studies have shown that QTc prolongation is associated with major degrees of autonomic neuropathy[63].

A meta analysis concluded that QTc prolongation is a specific indication of autonomic failure[64].

Increase of QT dispersion is a major determinant of risk of mortality in type 2 diabetes. QT dispersion is the difference between longest and shortest QT intervals recorded by 12 lead ECG.

Increasing QT dispersion reflects electrical instability of left ventricular musculature[65].

Diabetics have prolonged PR interval and more leftward frontal QRS axis than their non diabetic counterparts[66].

There is an increased incidence of intraventricular conduction blocks in diabetic patients that that of the normal[67].

Materials & Methods

MATERIALS AND METHODS

MATERIALS

1. Study Population

Fifty diabetic patients attending Diabetology Outpatient Department, Govt. Royapettah Hospital, Chennai. These subjects were selected after scrutinizing them for exclusion criteria.

2. Control Populations

Fifty patients attending General Medical Outpatient Department at Govt. Royapettah Hospital. These subjects were age and sex matched controls.

3. Place of Study

Out patient department

Diabetology department

Govt. Royapettah Hospital

Kilpauk Medical College.

Chennai.

4. Period of Study

February 2005 – July 2005.

METHODS

All study group patients and controls were subjected for thorough physical examination. Blood samples were drawn and subjected to estimation of plasma glucose and renal function tests.

Exclusion Criteria

- Age >65 years
- Documented coronary artery disease
- Documented valvular or congenital heart disease
- Hypertension
- Chronic obstructive pulmonary disease
- History of drug intake – Beta Blocker, digoxin, calcium channel blockers.
- Hypothyroidism
- Chronic kidney disease and uremia
- Treatment for parkinsonism

Autonomic dysfunction was assessed using following parameters

Parasympathetic functions

- Tachycardia in resting ECG
- Heart rate response to deep breathing

Sympathetic Functions

- Blood pressure response to standing
- QTc prolongation

Electrocardiogram

Resting ECG taken in both study group and control group using a three leaded Schillar Cardiovit AT machine. ECG during deep breathing was recorded only in study group (Diabetics) using single leaded BPL ECG machine.

The patients were made to lie down quietly. Then they were asked to take deep breath in and out at a rate of 6 breaths / minute. (5 seconds for inspiration and 5 seconds for expiration) which produces a maximum heart rate variation. A continuous ECG was recorded for minute.

E: I ratio was measured and the mean of the longest of the R-R interval during expiration to the mean of shortest R-R interval during inspiration was calculated. The E:I ratio was ≤1.10 in diabetic autonomic dysfunction.

QTc interval

R-R and QT intervals were measured in the resting ECG tracing. The lead considered here is V_2 chest lead.

The QT interval was measured from the beginning of QRS complex to the end of downslope of the T wave (crossing the iso-electric line). When a U wave was present, the QT interval was measured to the nadir of T and U wave. The corrected QT interval for the given cardiac cycle length (QTc) was calculated using BAZETT 's formula.

$$QTc = \frac{QT}{\sqrt{\text{R-R interval (sec)}}}$$

A QTc interval of more than 460 msec is considered abnormally prolonged.

STATISTICAL ANALYSIS

Statistical significance of the data obtained in the study were done using Students T test. In places where the data did not follow Normal distribution, Mann Whitney test was employed. For the other datas unpaired t test was used to arrive at probability values and to test Null hypothesis.

Observations & Results

OBSERVATIONS AND RESULTS

TABLE - 1

AGE DISTRIBUTION

Age (Years)	Study Group		Control Group	
	No.	%	No.	%
20 – 30	1	2	2	4
31 – 40	9	18	2	4
41 – 50	19	38	21	42
51- 60	21	42	25	50

Inference

Most of patients in the study population belong to the age group of 40 to 60 years.

TABLE - 2

AGE

Group	Age	
	Range (Years)	Mean (Years)±SD
Study	36 – 58	48.52 ± 6.9377
Control	29 – 61	49.94 ± 7.5279

P = 0.3292

Inference

There is no statistically significant difference in the mean age of both study and control population proving that there is no age bias.

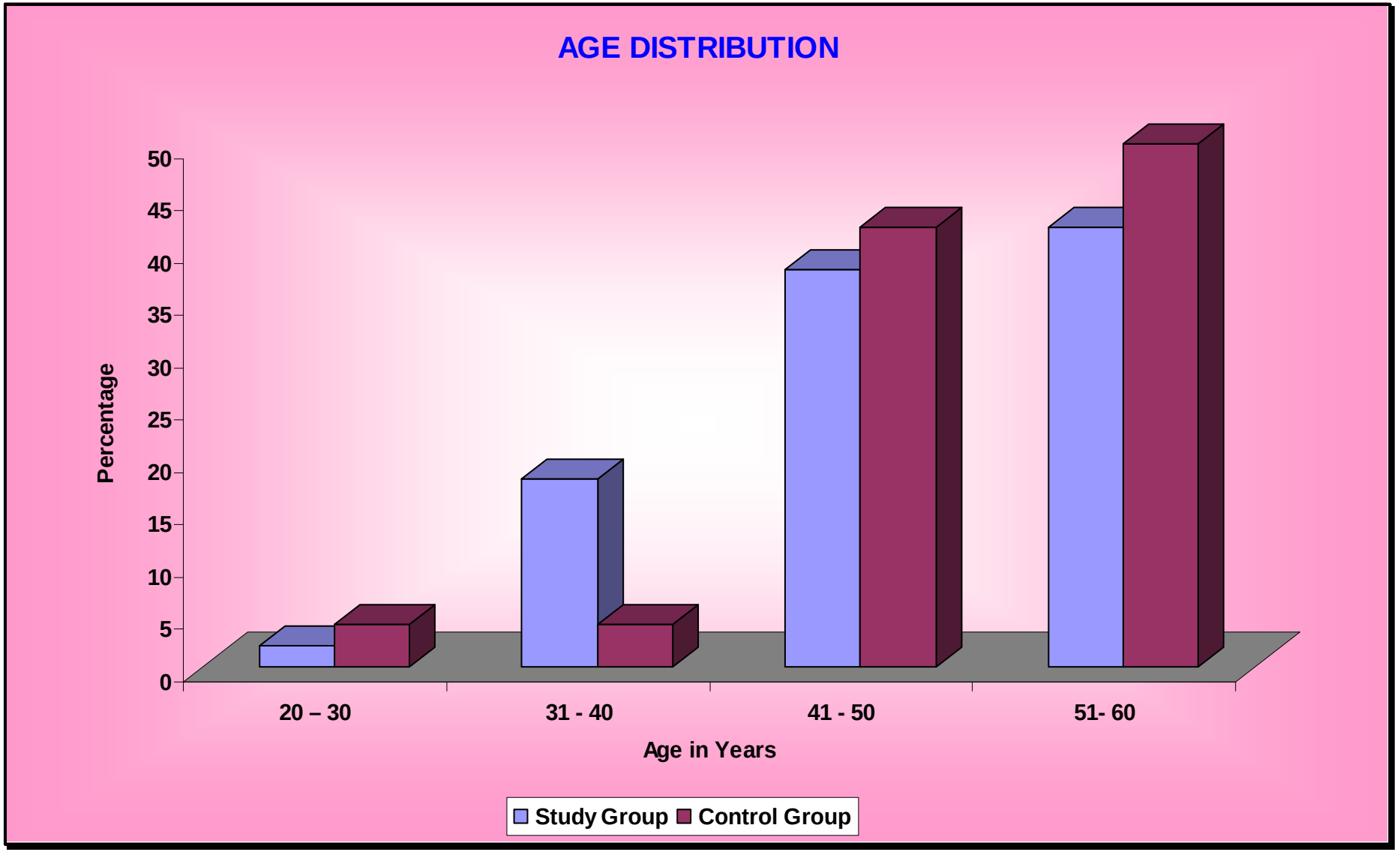

AGE DISTRIBUTION
Percentage
50
45
40
35
30
25
20
15
10
5
0
20 – 30
31 - 40
41 - 50
51- 60
Age in Years
Study Group
Control Group

TABLE – 3

AGE AT DIAGNOSIS

STUDY GROUP

Years	Number	Percentage (%)
21- 30	4	8
31 – 40	16	32
41 – 50	23	46
51 – 60	7	14

Inference

46% of the study group had their diabetes diagnosed at age between 41 and 50 years.

TABLE - 4

GENDER DISTRIBUTION

Group	Male		Female	
	No.	%	No.	%
Study	19	38	31	62
Control	31	62	19	38

Inference

62% of the study population were females suggesting the higher prevalence of diabetes in them.

TALBE - 5

PERCENTAGE OF SMOKERS

Group	Smokers		Non Smokers	
	No.	%	No.	%
Study	15	30	35	70
Control	16	32	34	68

Inference

Among the study population 30% were smokers. There is no significant difference in risk factor of smoking between study and control group.

TABLE - 6

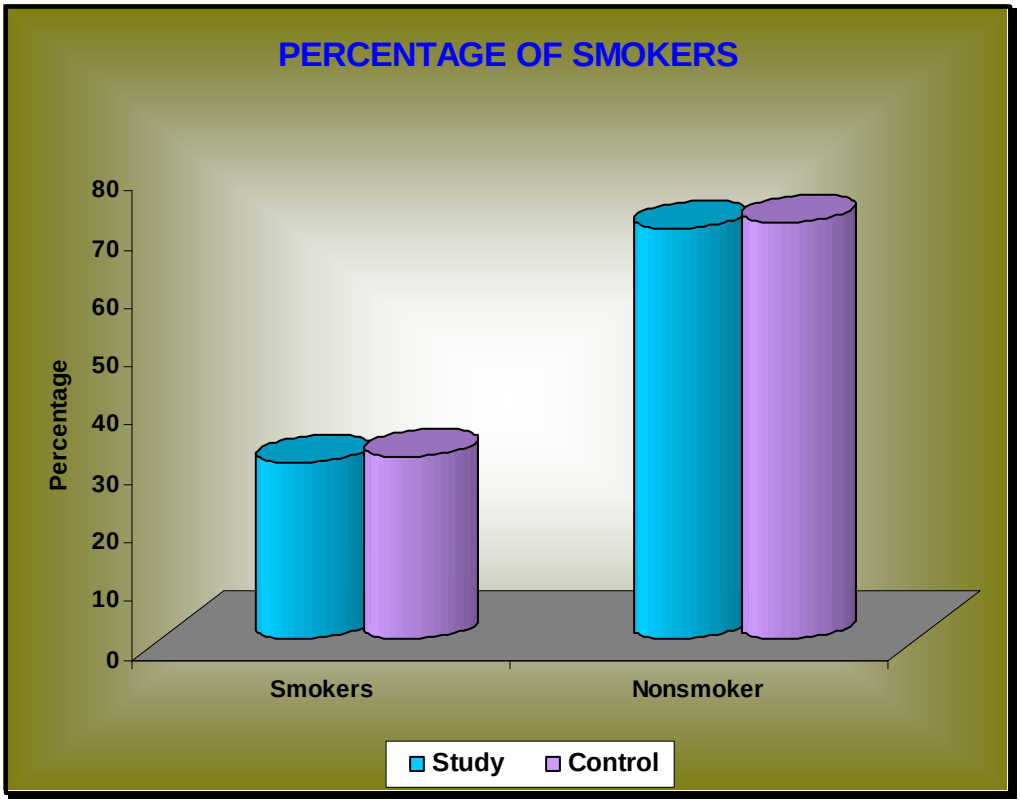
PERCENTAGE OF ALCOHOLICS

Group	Consumes Alcohol		No Consumption	
	No.	%	No.	%
Study	12	24	38	76
Control	9	18	41	82

Inference

24% of the study population consumed alcohol.

16% of the study population were both smokers and alcoholics.


PERCENTAGE OF SMOKERS
Percentage
80
70
60
50
40
30
20
10
0
Smokers
Nonsmoker
Study
Control

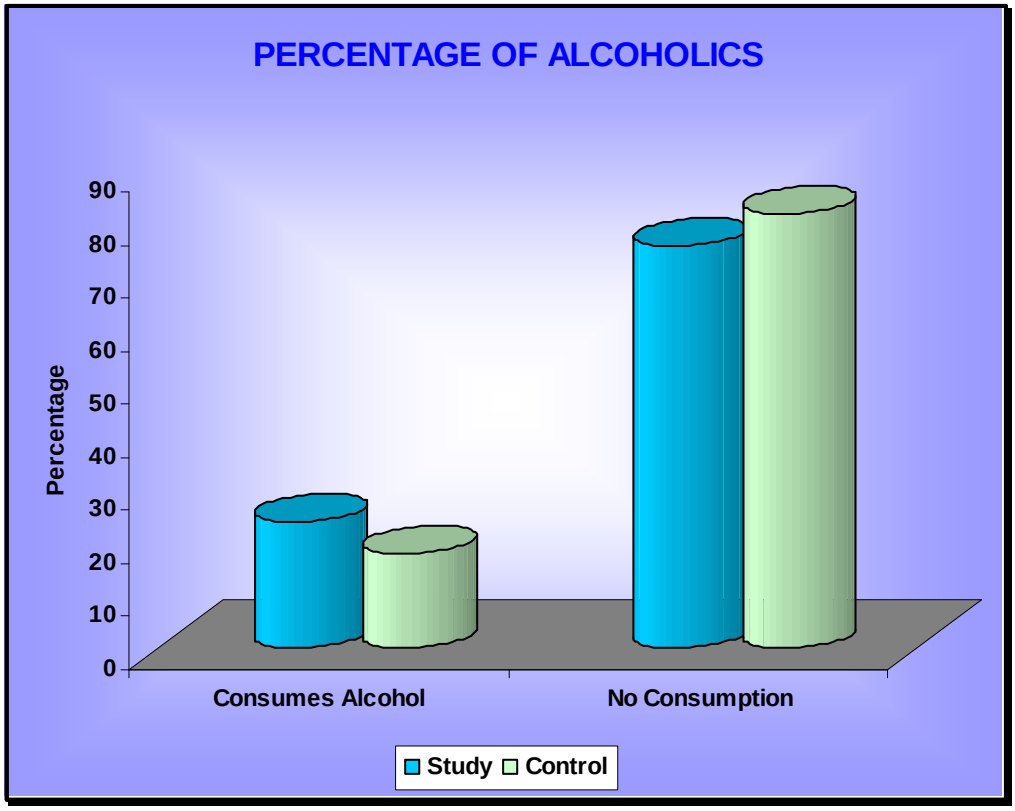

PERCENTAGE OF ALCOHOLICS
Percentage
90
80
70
60
50
40
30
20
10
0
Consumes Alcohol
No Consumption
Study
Control

TABLE - 7

DURATION OF DIABETES MELLITUS

Duration (years)	Study Group	
	No.	%
0 – 5	27	54
6-10	17	34
11 – 15	3	6
16 – 20	3	6

Mean ± SD (years): 6.228 ± 4. 815112

Inference

Nearly 54% of the patients in the study group have had diabetes for less than 5 years.

TABLE – 8

SIGNIFICANT POSTURAL DROP OF SYSTOLIC BLOOD PRESSURE

Postural fall of SBP (>30mm Hg)	Number	Percentage (%)
Study	5	10%
Control	-	-

Inference

10% of the diabetic study group had significant postural drop of systolic blood pressure on standing suggesting sympathetic nervous system dysfunction.

DURATION OF DIABETES MELLITUS

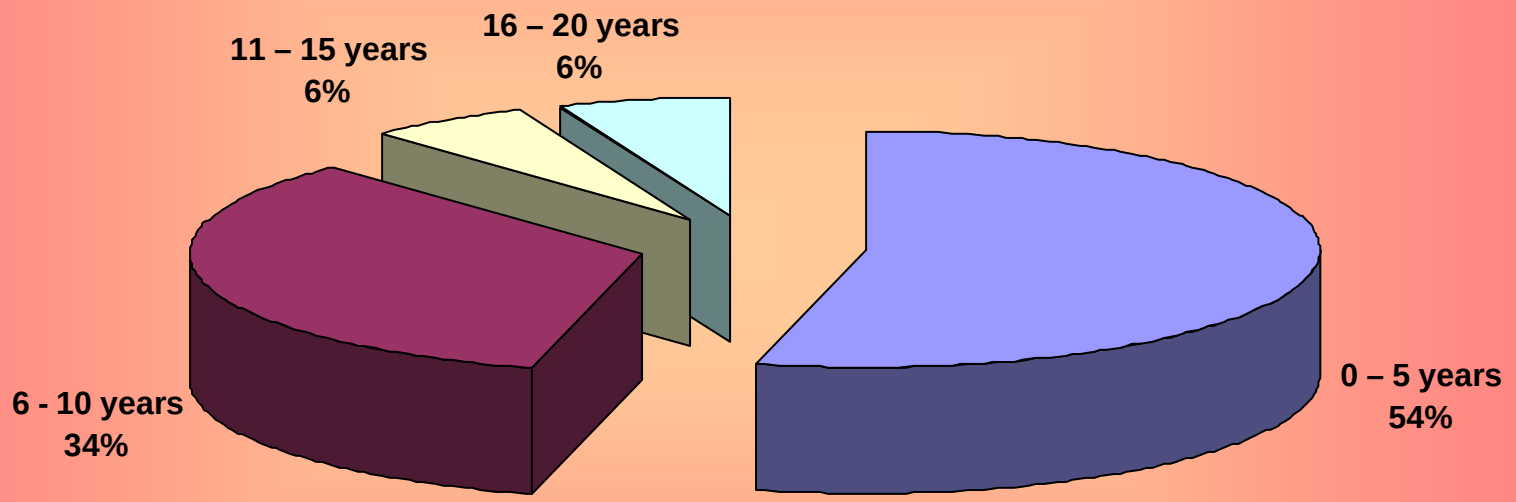


TABLE - 9

RESTING HEART RATE

Group	Range (bpm)	Mean (bpm)±SD
Study	56-100	86.16±7.6
Control	60-100	76.64±9.18

P = 0.0000

Inference

The resting heart rate of study population (86.16±7.6) is significantly higher than that of the control population (76.64±9.18).

TABLE – 10

R–R INTERVAL

Group	Range (m sec)	Mean (m sec)±SD
Study	600 – 1080	701.6 ± 72.96519
Control	600 – 1000	794 ± 92.25077

P = 0.0000

Inference

The R – R interval of study group (701.6) is significantly lower than that of control group (794).

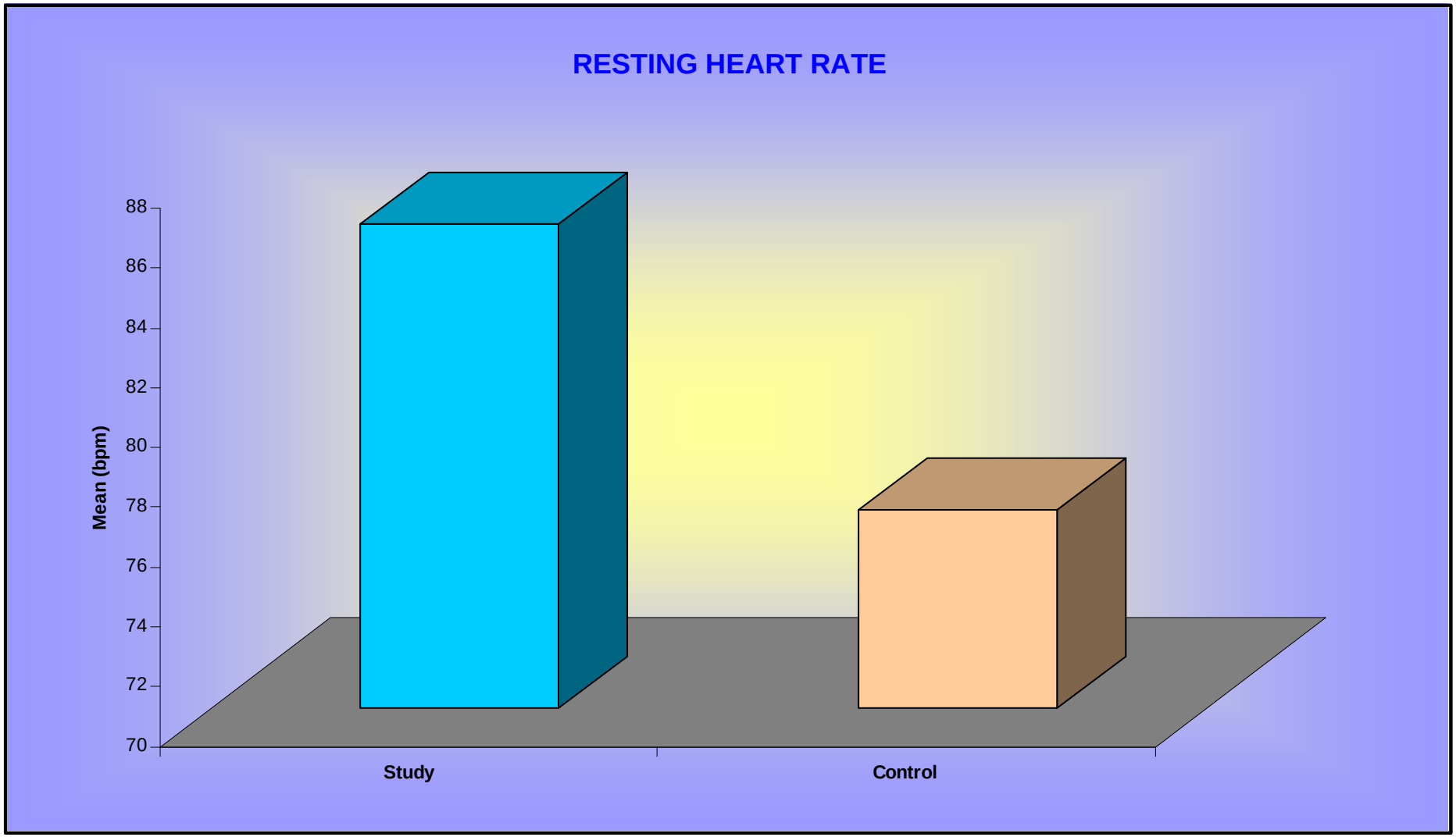

RESTING HEART RATE
Mean (bpm)
88
86
84
82
80
78
76
74
72
70
Study
Control

TABLE – 11

PR INTERVAL

Group	Range	Mean(msec)±SD
Study	120 - 300	163 ± 32.84
Control	120 - 180	136 ± 19. 79487

P = 0.00003

Inference

PR interval of study population (163) is significant higher than that of control (136) group (P<0.05).

TABLE - 12

QRS DURATION

Group	Range (m sec)	Mean (m sec) ± SD
Study	40 – 120	57.2 ± 17.61725
Control	40 - 100	53.6 ± 16. 87408

P = 0.2 99285

Inference

There is no statistically significant (P>0.05) difference in QRS duration of study and control groups.

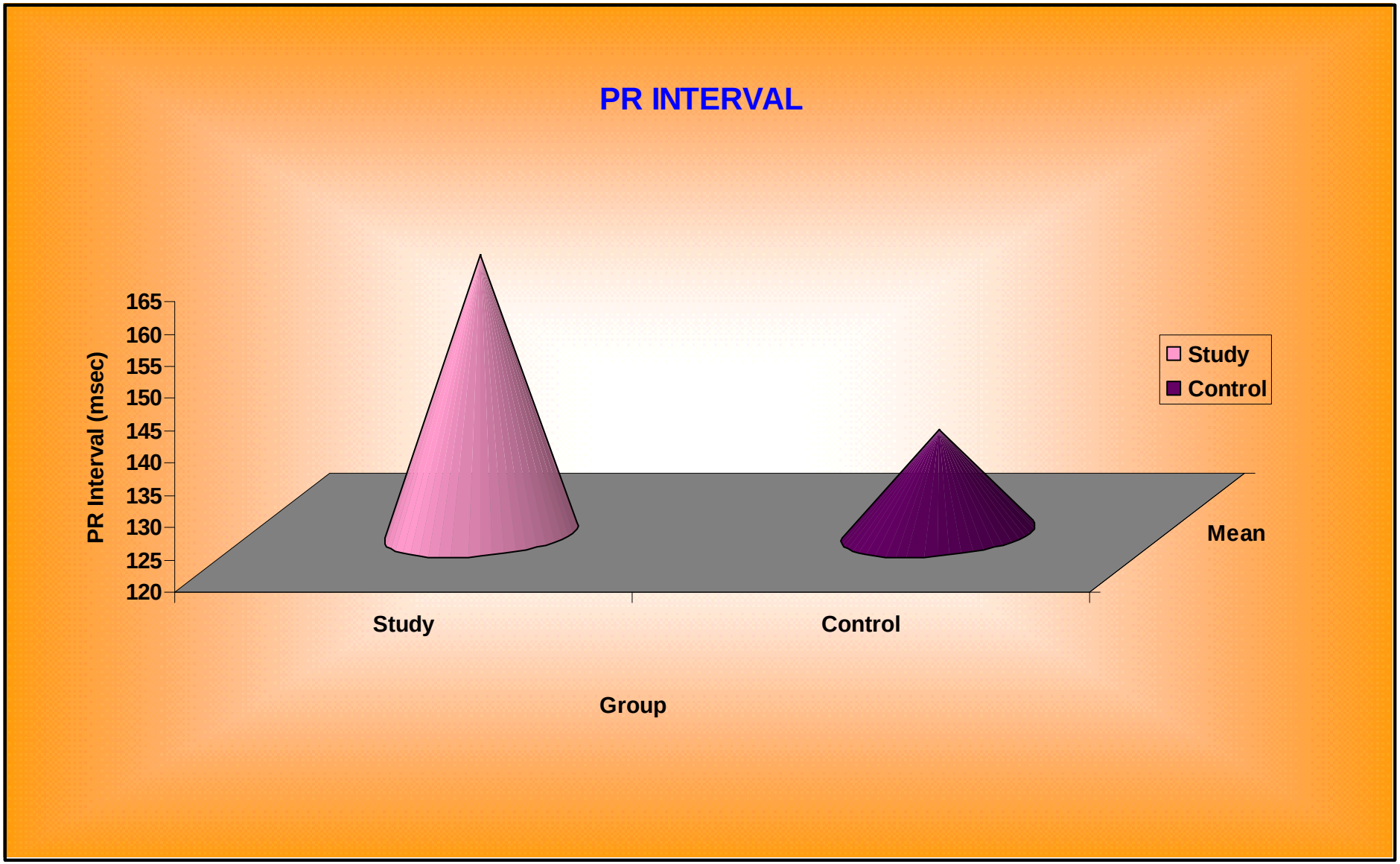

PR INTERVAL
PR Interval (msec)
165
160
155
150
145
140
135
130
125
120
Study
Control
Mean
Group

TABLE - 13

QRS AXIS

Group	Range (degree)	Mean (degree) ± SD
Study	- 30 to +90	31.6 ± 34.36657
Control	0 to 100	54 ± 35. 74285

P = 0.001885

Inference

The QRS axis of study group is more towards leftward (31.6°) compared to control group (54°) which is statistically significant (P<0.05).

TABLE - 14

ECG CHANGES OF ISCHEMIA AND INFARCTION

Group	Evidence of Ischemia		Evidence of infarction	
	No.	%	No.	%
Study	14	28	5	10
Control	5	10	2	4

Inference

28% had evidence of ischemia in the study population and 10% had evidence of infarction suggesting that silent infarction had occurred.

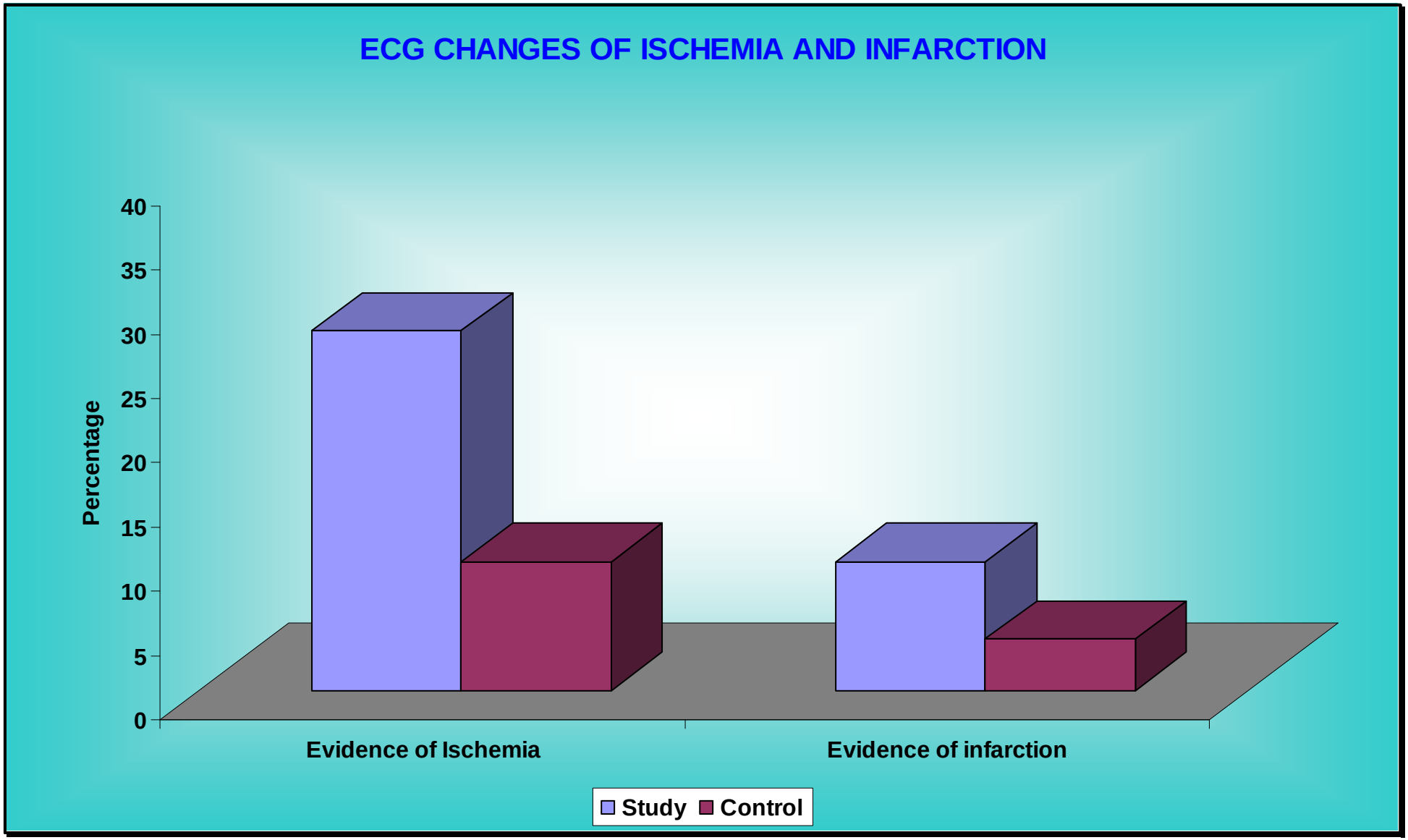

ECG CHANGES OF ISCHEMIA AND INFARCTION
Percentage
40
35
30
25
20
15
10
5
0
Evidence of Ischemia
Evidence of infarction
Study
Control

TABLE - 15

CORRELATION BETWEEN ECG AND SYMPTOMS OF IHD

Group	ECG changes	Symptomatic		Asymptomatic	
		No.	%	No.	%
Study	19	12	63.15	7	36.84
Control	7	6	85.71	1	14.28

Inference

Study group population has more number of patients with asymptomatic heart disease (36.8%) when compared to the control group (14.28%).

TABLE - 16

INCIDENCE OF INTRAVENTRICULAR CONDUCTION DEFECTS

Group	IVCD	Percent
Study	3	6%
Control	-	-

Inference

IVCD is present in 6% of the study populations.

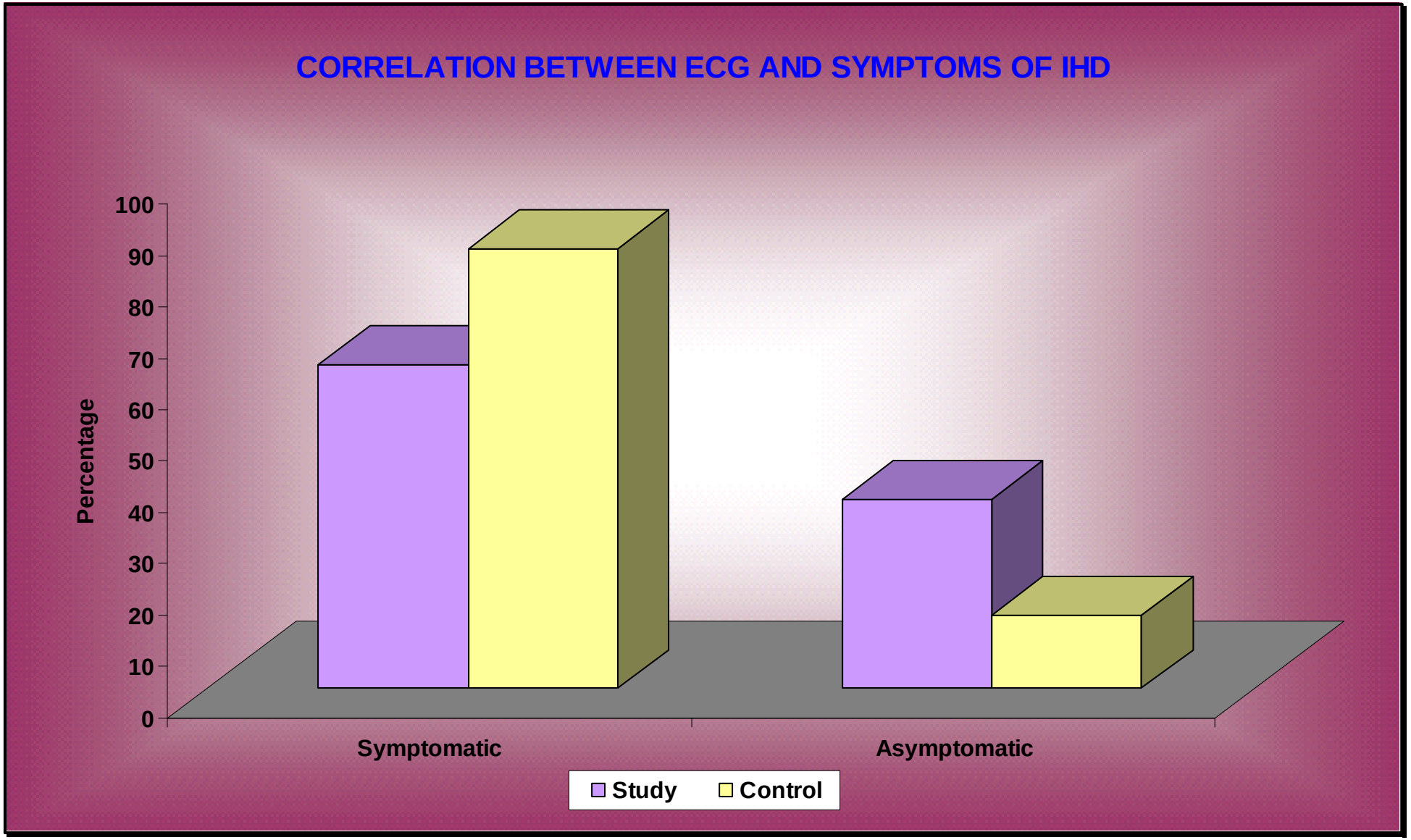

CORRELATION BETWEEN ECG AND SYMPTOMS OF IHD
Percentage
100
90
80
70
60
50
40
30
20
10
0
Symptomatic
Asymptomatic
Study
Control

TABLE - 17

QTc INTERVAL

Group	QTc Interval	
	Range (msec)	**Mean (msec) ± SD**
Study	353 - 487	400.62 ± 32.18942
Control	319 - 410	361.10 ± 22.3828

P = 0.0000

Inference

QTc of the diabetic population (400.6msec) was significantly (P =0.0000) prolonged when compared to that of the control population(361msec).

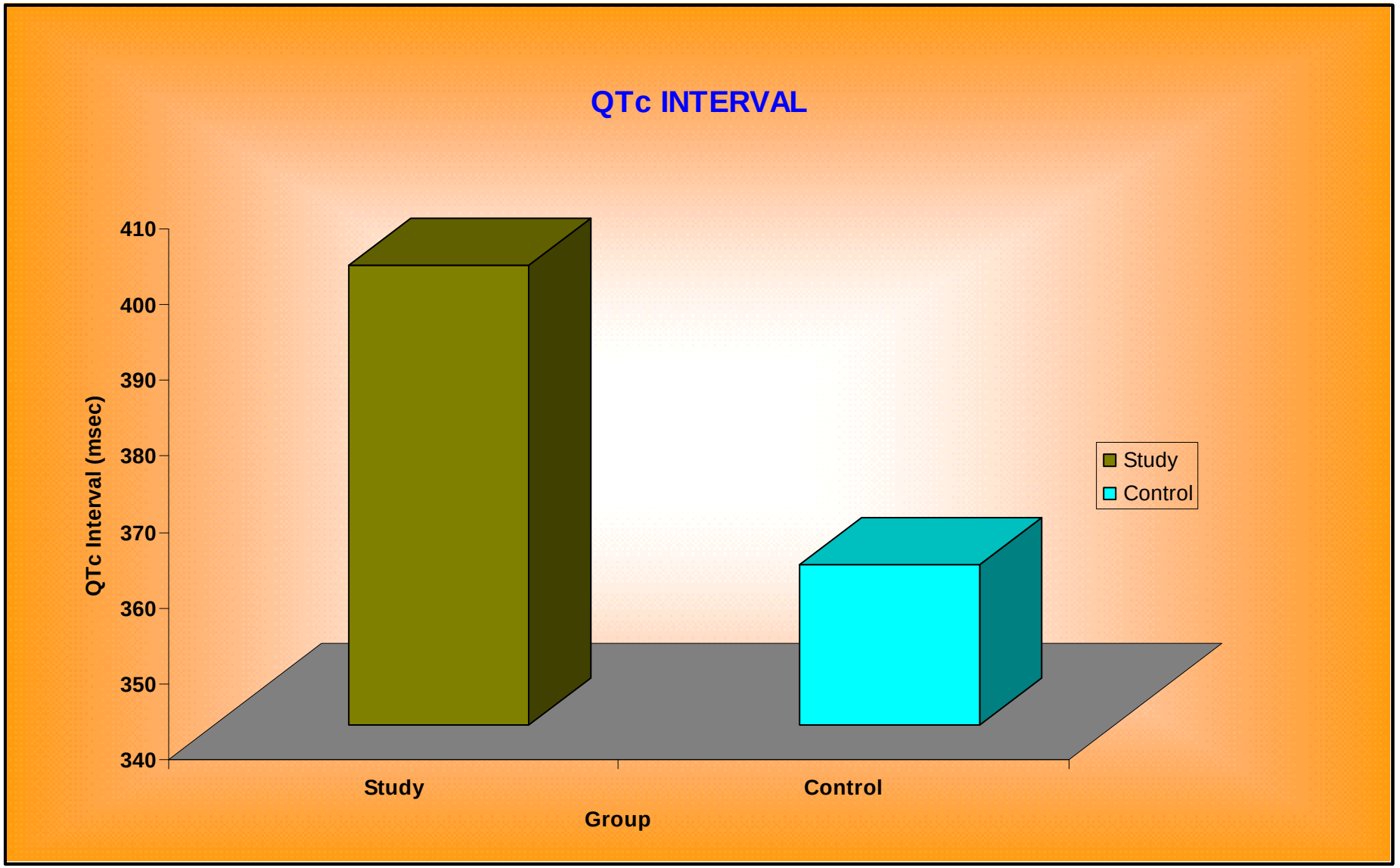
TABLE - 18

E: I RATIO

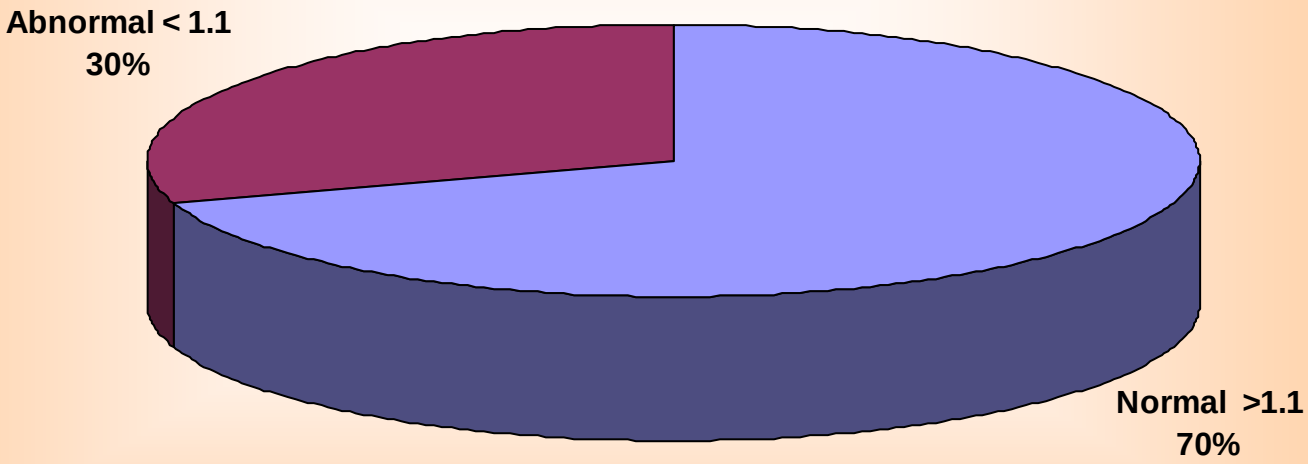
E:I Ratio	Number	Percent (%)
Normal > 1.1	35	70
Abnormal ≤ 1.1	15	30

Inference

30% of study group population have abnormal E:I ratio suggesting early parasympathetic dysfunction.


QTc INTERVAL
410
400
390
380
370
360
350
340
QTc Interval (msec)
Study
Control
Group
Study
Control

E : I RATIO



Discussion

DISCUSSION

The diabetic population had a mean resting heart rate that was (86.16 bpm) higher than that of the control population (76.64 bpm). This difference was statistically significant implying higher resting heart rate in diabetic population. This is probably due to cardiac autonomic dysfunction, more specifically parasympathetic damage. Ewing et al. found that the parasympathetic nerves are the earliest to be involved followed by sympathetic nerves in autonomic neuropathy.

The clinical utility of the knowledge that the resting heart rate is often higher in diabetics due to parasympathetic damage is that such patients need to be studied in great detail for cardiac autonomic neuropathy, since they are prone to develop sudden and unexpected cardiac arrest more so during procedures like anaesthesia. Mangoni AA, Mircoti L. showed that resting tachycardia decreases the distensibility of the vascular wall, and increases the risk of atherosclerosis, all favouring coronary artery disease.

That the resting heart rate is higher in diabetics when compared to non diabetics is reaffirmed by the fact that R-R interval is lower in study group (701.6msec) than that of the non diabetic group (794msec).

Freeman R, Saul P et al. in their spectral analysis of heart rate in DAN; Arch, Neurol; 1991 established that R-R interval analysis served as a means for early assessment of CAN.

The PR interval was significantly prolonged in diabetics suggesting a delayed conduction across atrioventricular node paving way for conduction abnormalities. This evidence of first degree heart block could be the cause for syncope. It has been established in studies that some cases of PR prolongation associated with CAN can predispose to atrial fibrillation.

The leftward axis (31.6°) is also indicative of bundle branch blocks. There is an increased incidence of intraventricular conduction blocks in diabetics (6%).

Conduction blocks at various levels and in varying degrees makes patients with CAN prone to symptoms of heart block and sudden cardiac death as was shown by Erickson et al. in his Primary Prevention study which asserted the fourfold risk of higher atrio ventricular block in patients with RBBB.

A prolonged corrected QT interval, as evidenced in this study, where the QTc in study population is 400.62 msec as against 361.10 msec of the control population, indicates an imbalance between right and left sympathetic innervations. JM Cronin, MM Kadrifrek, EJ Bastyr University of Michigan; Diabetes Care; Vol.13, showed that as a group, diabetic patients with greater than or equal to 2 abnormalities of cardiac autonomic function had a longer QTc interval than those with no evidence of cardiac autonomic neuropathy.

Diabetic patients with a regional sympathetic imbalance and QTc interval prolongation may be at greater risk for arrhythmias predisposing them to sudden cardiac death. Eric A. Witset, Pentittii M. Rautaharju, Sheila A. Veinmami. Diabetes Care; 28:20415 – 20417 in a population based study examined the risk of primary cardiac arrest associated with QTc prolongation and concluded that diabetic patients in the upper quartile of QT index distribution had a three fold risk of primary cardiac arrest.

Kahn et al. demonstrated that prolongation of the QTc interval increased the risk of intractable ventricular arrhythmias and sudden death.

Diabetic study population showed (38%) significant ECG changes of ischemia and infarction proving that diabetic patients have a higher rate of coronary artery disease; significantly these patients remain asymptomatic (36.84%) owing to autonomic neuropathy. This is in concurrence with the results of Valensi P, Sashs R N et al who conducted a study on predictive value of CAN in diabetic patients with or without silent myocardial ischemia.

Silent ischemia is significantly more frequent in diabetic patients with than in those without autonomic neuropathy. A reduced appreciation of ischemic pain can impair early recognition of myocardial ischemia or infarction and delay appropriate therapy making it necessary to screen diabetic patients for ischemia and CAN frequently.

Heart rate variability to deep breathing was abnormal in 30% of study subjects. Decreased HRV is considered the earliest indication of CAN and is often the most frequent finding in symptomatic CAN. The demonstration of loss of HRV during deep breathing indicates the presence of vagal denervation of the heart and is also associated with increased rate of progression of coronary atherosclerosis. Decreased vagal activity limits exercise tolerance making these individuals prone to syncope and predisposed to sudden cardiac death.

10% of the diabetic study group showed orthostatic hypotension, which is usually due to damage to efferent sympathetic vasomotor fibers, particularly in splanchnic vasculature. Diminished cardiac acceleration and cardiac output, particularly in association with exercise may also be important in the presentation of this disorder. Some of these patients presented with light headedness and presyncopal symptoms, while some were asymptomatic. Apart from the pain of peripheral neuropathy, symptoms of orthostatic hypotension is the most troublesome to treat in diabetic patients.

CAN can occur as early as one year after diagnosis of type 2 DM. In this study 54% of population had diabetes for 5 years and the age at diagnosis was between 40-50 years of age for most indicating late diagnosis and hence higher prevalence of CAN.

Conclusion

CONCLUSION

The following ECG parameters were abnormal in Diabetic study group as compared to control population.

- The resting heart rate (86.16±7.6) was significantly (P<0.05) higher than that of non diabetic controls (76.64±9.18).
- The RR interval was narrow in diabetic (701.6 ± 72.9 msec) as compared to control subjects (794 ± 92.25 msec) which was statistically significant.
- The PR interval in diabetics (163 ± 32.84 msec) was prolonged as compared to control (136 ± 19.794) and was statistically significant (P= 0.0003).
- There was a leftward deviation of QRS axis among diabetics (31.6°) as compared to controls (54°).
- QTc interval was prolonged (400.62 ± 32.18 msec) in diabetic study population which was significant (P=0.0000).
- There was an increased prevalence of ischemia and infarction in diabetics as was evidenced by ECG changes (38%).
- Asymptomatic ischemic heart disease was more common (36.84%) among diabetics as compared to control subjects.
- Varying degrees of conduction blocks were prevalent in diabetics (6%).

Cardiac dysautonomia was demonstrated in the study population using the following parameters.

- Abnormal E:I ratio (≤ 1.1) (30%).
- Prolonged QTc interval (> 460 msec) (6%)
- Postural fall in systolic blood pressure (> 30 mmHg) (10%).

This study shows the high prevalence of cardiac dysautonomia in type 2 diabetics. Most of these patients remain asymptomatic. Some of the patients with CAN had diabetes for only as few as 5 years proving the DCCT result that the disease process begins early and it may remain asymptomatic until later stages.

It can be recommended that a baseline determination of cardiac autonomic function be performed upon diagnosis in type 2 diabetes followed by a yearly repeat test.

Proforma

PROFORMA

Name

OP No.

Age

Sex

Age of onset of DM

Duration of DM

Treatment History

Dietary Habits

History of Angina

History of Postural hypotension: (Faintness / Dizziness)

History of Smoking

History of Alcohol consumption

Body Mass Index

Pulse (bpm)

Blood pressure (mm Hg)

Supine :

Standing :

System Examination

Cardio Vascular System

Respiratory System

INVESTIGATIONS

a) Blood Sugar Fasting

Post prandial

b) Blood Urea

c) Serum creatinine

d) Hemoglobin A_1 C

e) Hemoglobin

f) S. Cholesterol

ELECTROCARDIOGRAM

a) Heart rate

b) R-R interval

c) PR interval

d) QRS axis

e) QRS duration

f) QTc Interval

g) E:I ratio

h) ST-T changes

i) Conduction abnormalities

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ABBREVIATIONS

ADA	-	American Diabetes Association
AGE	-	Advanced Glycosylation End products
ANS	-	Autonomic Nervous System
BMI	-	Body Mass Index
BP STN	-	Blood Pressure Standing
BP SUP	-	Blood Pressure Supine
BP	-	Blood Pressure
CAD	-	Coronary Artery Disease
CAN	-	Cardiac Autonomic Neuropathy
CNS	-	Central Nervous System
D	-	Diagnosis
DAN	-	Diabetic Autonomic Neuropathy
DCCT	-	Diabetes Control and Complications Trial
DM	-	Diabetes Mellitus
DUR DM	-	Duration of Diabetes Mellitus
DUR	-	Duration
ECG	-	Electro cardiogram
FPG	-	Fasting Plasma Glucose
H/O A	-	History of Alcohol Intake
H/O ANG	-	History of Angina
H/O PH	-	History of Postural Hypotension
H/O S	-	History of Smoking

HR	-	Heart Rate
HRV	-	Heart Rate Variability
IDDM	-	Insulin Dependent Diabetes Mellitus
IFG	-	Impaired Fasting Glucose
IGF	-	Insulin like Growth Factor
IGT	-	Impaired Glucose Tolerance
IVCD	-	Intra Ventricular Conduction Defects
LBBB	-	Left Bundle Branch Block
NGF	-	Nerve Growth Factor
NIDDM	-	Non Insulin Dependent Diabetes Mellitus
OGTT	-	Oral Glucose Tolerance Test
P	-	Pulse
PNS	-	Peripheral Nervous System
PPG	-	Post Prandial Glucose
RBBB	-	Right Bundle Branch Block
SCD	-	Sudden Cardiac Death
VEGF	-	Vascular Endothelial Growth Factor
WHO	-	World Health Organisation
ROS	-	Reactive Oxygen Species
PKC	-	Protein Kinase C
NOS	-	Nitric Oxide Synthetase

STUDY GROUP

S.No.	Age	Sex	BMI	H/o S.	H/o A.	Dur of DM	Age at D	H/o ANG	H/o PH	Pulse	BP SUP	BP STN	ECG								ST/T		
													HR	RR	PR	QRS Axis	QRS DUR	QTC	E : I	IVCD	ST	T	Q
1	40	M	23	-	+	3	37	-	-	110	140/80	142/86	88	680	160	30	40	390	1.2	-	-	-	-
2	57	M	23.5	+	+	13	44	+	+	90	130/70	120/70	85	700	160	50	40	382	0.9	-	+	+	-
3	55	M	22	+	-	10	45	+	-	86	132/80	126/72	83	720	140	60	40	380	1.7	-	-	-	-
4	55	M	22	-	-	7	48	-	+	110	120/70	80/70	81	740	120	-30	60	395	1.3	-	-	-	-
5	53	F	21	-	-	5	48	-	-	90	120/70	100/70	85	700	160	0	40	440	0.62	-	+	-	-
6	47	F	20	-	-	7	40	-	-	100	100/70	90/70	100	600	180	0	60	415	1.0	-	-	-	+
7	40	F	21	-	-	8	32	+	+	90	92/70	90/70	81	740	200	30	40	373	1.6	-	+	-	-
8	38	F	21	-	-	1	37	-	-	114	110/70	100/70	83	720	160	30	40	353	1.2	-	-	-	-
9	40	M	23	+	-	5	35	+	-	118	144/90	112/72	81	740	120	60	60	418	1.1	-	-	-	-
10	57	F	22	-	-	5	52	-	-	110	134/72	112/74	75	800	120	30	60	382	1.26	-	-	-	-
11	50	F	21	-	-	10	40	+	-	86	134/80	120/72	73	820	160	60	80	376	1.46	+	-	-	-
12	48	F	20	-	-	20	28	-	-	80	124/72	110/70	94	640	120	50	40	400	0.8	-	-	+	-
13	40	F	21	-	+	8	32	+	-	88	140/90	142/90	100	600	160	40	60	390	1.5	-	-	-	-
14	50	F	22	-	-	9	41	-	-	84	100/80	90/70	88	680	120	80	40	440	0.82	-	-	-	-
15	55	F	21.5	-	+	8	47	-	-	94	110/70	100/70	85	700	140	0	60	361	1.76	-	-	-	-
16	53	F	22	-	+	10	43	-	-	92	110/70	90/70	94	640	200	30	80	425	0.8	-	-	-	-
17	50	M	23	+	-	3	47	+	-	106	110/70	114/72	83	720	180	30	60	380	1.3	-	-	-	+
18	50	M	23.5	+	+	1	49	-	-	105	130/80	120/70	94	640	160	0	40	375	1.32	-	-	-	-
19	42	F	21	-	-	5	37	-	-	90	140/70	130/72	85	700	160	90	50	382	1.46	-	-	-	-
20	45	F	21	-	-	2	43	+	-	84	124/94	100/90	85	700	140	60	60	361	1.26	-	-	-	-
21	54	M	23	+	+	6	48	-	-	94	124/72	120/70	80	750	160	-30	80	375	1.6	-	-	-	-
22	36	M	24	+	+	6	30	+	-	90	100/74	110/74	94	640	200	40	60	450	0.6	-	-	-	-
23	47	F	22.5	-	-	7	40	+	-	86	110/70	120/70	88	680	120	60	40	439	0.7	-	+	-	-
24	52	F	22	-	-	6	46	+	-	88	100/64	90/60	90	670	140	60	40	420	1.3	-	+	-	-
25	54	M	23	+	-	20	34	-	-	110	132/40	120/64	95	630	160	40	60	405	1.3	-	-	-	+
26	54	F	22	-	-	2	52	+	-	104	142/70	110/60	94	640	130	0	80	425	0.5	-	+	+	-
27	55	F	22	-	-	5	50	-	-	85	140/84	140/60	100	600	120	-30	40	390	1.62	-	-	-	-
28	35	F	21	-	-	1	34	-	-	88	138/72	140/90	87	720	200	0	60	353	1.4	-	-	-	-

STUDY GROUP

S.No.	Age	Sex	BMI	H/o S.	H/o A.	Dur of DM	Age at D	H/o ANG	H/o PH	Pulse	BP SUP	BP STN	ECG								ST/T		
													HR	RR	PR	QRS Axis	QRS DUR	QTC	E : I	IVCD	ST	T	Q
29	50	F	21.5	-	-	2	48	-	-	98	130/80	138/72	95	630	160	-40	80	380	1.6	-	-	-	-
30	54	M	24	+	-	2	52	-	-	100	110/70	110/70	100	600	180	60	60	415	1.6	-	-	-	-
31	55	M	23	+	+	3	52	-	-	91	134/70	110/70	83	720	160	30	40	428	1.36	-	-	-	-
32	50	F	22.5	-	-	3	47	+	-	85	130/72	120/64	88	680	140	40	120	403	1.36	+	+	+	-
33	58	M	23	-	-	18	40	-	-	89	124/68	110/70	88	680	160	40	40	439	0.6	-	-	-	-
34	45	F	22	-	-	2	43	+	-	99	110/70	90/62	87	690	180	30	60	386	1.4	-	-	+	-
35	53	M	23.5	-	-	2	51	-	-	106	132/70	100/62	85	700	180	40	40	382	1.36	-	-	-	+
36	45	M	23	+	+	6	39	+	-	110	110/70	100/70	87	690	160	70	60	362	0.92	-	+	-	-
37	40	F	22	-	-	4	36	-	-	84	134/70	120/70	85	700	160	60	80	361	1.42	-	-	-	-
38	48	F	21	-	-	3	45	+	-	74	130/80	126/70	88	680	160	40	60	487	0.7	-	+	-	-
39	59	F	21	-	-	5	54	-	-	94	124/68	120/60	83	720	140	30	60	380	1.2	-	-	-	-
40	43	F	23	-	-	2	41	-	-	75	110/72	90/70	85	700	200	0	40	361	1.6	-	-	-	-
41	30	F	21	-	-	4	26	-	-	98	110/74	100/78	81	740	160	0	40	372	1.32	-	-	-	-
42	43	F	22	-	-	5	38	-	-	94	132/80	124/60	79	760	200	30	80	413	1.3	-	-	+	-
43	56	F	22.5	-	-	1	55	-	-	89	130/80	110/74	88	680	300	90	80	463	0.9	-	-	-	-
44	54	F	22	-	-	10	44	-	-	106	110/74	100/90	81	740	140	30	80	395	1.42	+	-	+	-
45	40	M	22	+	-	15	25	+	-	109	134/82	110/74	81	740	160	30	60	395	1.46	-	+	-	-
46	50	M	23	+	+	10	40	+	-	110	132/78	124/70	88	680	160	90	40	440	1.62	-	-	-	+
47	58	M	23	+	-	15	43	-	+	89	140/74	100/68	85	700	160	60	60	382	1.5	-	-	-	-
48	54	F	23.5	-	-	6	48	-	-	88	124/70	110/64	83	720	240	0	40	476	0.9	-	-	-	-
49	48	M	22	+	+	1	47	-	-	96	134/72	124/70	81	740	180	90	40	418	1.7	-	-	-	-
50	47	F	21	-	-	5	42	-	-	64	118/72	102/64	56	1080	180	30	60	418	1.2	-	-	-	-

CONTROL GROUP

S. No.	Age	Sex	H/o S.	H/o A.	H/o ANG	H/o PH	Pulse	BP SUP	BP STN	ECG							ST/T		
										HR	RR	PR	QRS Axis	QRS DUR	QTC	IVCD	ST	T	Q
1	52	F	-	-	-	-	88	124/70	120/72	88	680	120	60	40	365	-	-	-	-
2	53	F	-	-	+	-	80	132/80	130/84	83	720	100	60	40	357	-	+	-	-
3	54	M	-	+	+	-	72	130/80	128/74	71	840	120	60	40	340	-	-	-	-
4	45	M	+	+	-	-	74	130/72	130/70	75	800	140	30	60	382	-	-	-	-
5	55	M	+	-	-	-	60	124/68	120/64	68	880	120	90	60	344	-	-	-	-
6	46	M	-	-	+	-	60	130/70	120/70	63	960	160	40	40	330	-	-	-	-
7	42	M	-	+	-	-	82	120/78	120/70	79	760	120	90	40	368	-	-	-	-
8	56	M	-	+	-	-	81	100/70	110/70	83	720	120	60	60	357	-	-	-	-
9	44	M	-	-	-	-	74	110/78	110/70	75	800	120	60	40	360	-	-	-	-
10	58	F	-	-	-	-	66	120/82	120/70	71	840	140	60	40	362	-	-	-	-
11	55	F	-	-	-	-	72	138/74	130/70	94	640	120	60	60	408	-	-	-	-
12	50	F	-	-	-	-	60	130/70	134/70	68	880	140	30	80	344	-	-	-	-
13	46	F	-	-	-	-	72	130/70	130/70	70	860	160	50	40	345	-	-	-	-
14	50	M	+	-	-	-	84	110/70	110/70	88	680	120	80	40	341	-	-	-	-
15	60	M	-	-	-	-	66	110/80	100/70	68	880	160	0	40	387	-	-	-	-
16	47	M	-	-	-	+	70	140/70	150/80	79	760	160	90	80	344	-	-	-	-
17	48	F	-	-	-	-	70	110/76	110/70	88	680	180	60	100	340	-	-	-	-
18	60	F	-	-	+	-	90	110/70	100/70	100	600	160	90	40	375	-	-	-	+
19	54	M	+	-	-	-	80	130/70	128/70	81	740	120	30	40	372	-	-	-	-
20	48	M	-	-	-	-	60	140/80	130/70	60	1000	120	90	60	320	-	-	-	-
21	53	M	-	+	-	-	86	130/70	128/70	73	820	120	30	40	360	-	-	-	-
22	46	M	-	-	-	-	84	120/70	110/70	79	760	140	40	60	344	-	-	-	-
23	48	M	+	-	+	+	90	128/72	120/70	75	800	160	60	60	360	-	-	-	+
24	51	F	-	-	+	-	76	134/74	130/70	71	840	120	80	40	340	-	-	+	-
25	60	F	-	-	-	-	58	128/70	132/74	68	880	120	90	80	340	-	-	-	-
26	55	F	-	-	-	-	74	120/70	110/74	60	1000	160	90	40	320	-	-	-	-
27	51	F	-	-	-	-	92	130/70	128/80	75	800	160	60	80	360	-	-	-	-
28	60	F	-	-	+	-	88	124/70	120/70	88	680	120	60	40	365	-	-	-	-
29	48	M	+	-	-	+	90	132/70	130/74	70	860	120	60	80	410	-	-	-	-
30	54	F	-	-	-	-	68	130/74	132/74	75	800	140	30	60	382	-	-	-	-

CONTROL GROUP

S. No.	Age	Sex	H/o S.	H/o A.	H/o ANG	H/o PH	Pulse	BP SUP	BP STN	ECG							ST/T		
										HR	RR	PR	QRS Axis	QRS DUR	QTC	IVCD	ST	T	Q
31	58	M	-	-	-	-	70	128/70	132/70	68	880	160	60	60	366	-	-	-	-
32	43	M	+	-	+	-	72	126/70	120/70	75	800	120	50	80	382	-	+	-	-
33	29	M	+	+	-	-	88	130/84	120/80	88	680	120	90	40	341	-	-	-	-
34	45	F	-	-	-	-	70	130/80	120/70	71	840	140	0	40	362	-	-	-	-
35	48	M	-	-	-	-	90	134/70	130/72	79	760	120	90	60	344	-	-	-	-
36	57	M	+	-	+	-	84	128/80	120/74	88	680	120	90	40	365	-	+	-	-
37	55	F	-	-	-	-	72	132/70	130/72	68	880	160	80	60	344	-	-	-	-
38	51	M	+	-	-	+	70	128/70	120/70	70	860	120	30	40	388	-	-	-	-
39	46	F	-	-	-	-	64	124/72	120/70	68	880	140	60	40	387	-	-	-	-
40	50	M	+	+	+	-	70	110/70	110/70	79	760	160	90	40	368	-	-	-	-
41	23	M	-	+	+	-	90	110/10	114/70	85	700	120	30	80	390	-	-	-	-
42	55	M	+	-	-	-	80	120/70	110/70	68	880	140	50	80	366	-	-	-	-
43	60	M	-	-	-	+	80	134/72	130/70	83	720	160	60	60	404	-	-	-	-
44	46	M	+	+	-	-	82	128/74	120/70	79	760	180	30	40	368	-	+	-	-
45	58	M	+	-	-	-	70	132/70	130/80	75	800	120	0	40	382	-	-	-	-
46	40	F	-	-	-	-	72	128/80	120/80	71	840	120	90	40	340	-	-	-	-
47	37	M	-	-	-	-	84	132/80	130/70	91	660	160	90	40	369	-	-	-	-
48	47	M	+	-	-	-	89	132/70	130/74	94	640	120	80	60	400	-	-	-	-
49	53	F	-	-	-	-	70	134/70	130/72	67	900	120	60	80	319	-	-	-	-
50	46	M	+	-	-	-	70	128/70	124/74	79	760	140	30	40	344	-	-	-	-