A STUDY ON

"CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS-CORRELATION WITH QTc INTERVAL AND DURATION OF DIABETES-A CROSS SECTIONAL STUDY IN A TERTIARY CARE CENTRE IN SOUTH INDIA."

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CERTIFICATE

This is to certify that this dissertation entitled **"CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS-CORRELATION WITH QTc INTERVAL AND DURATION OF DIABETES-A CROSS SECTIONAL STUDY IN A TERTIARY CARE CENTRE IN SOUTH INDIA."** submitted by **Dr. S. JAYASREE** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of the requirement for the award of M.D Degree Branch-I (General Medicine) is a bonafide research work carried out by her under direct supervision and guidance.

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I solemnly declare that the dissertation titled **"CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS-CORRELATION WITH QTc INTERVAL AND DURATION OF DIABETES-A CROSS SECTIONAL STUDY IN A TERTIARY CARE CENTRE IN SOUTH INDIA."** is a bonafide work done by me at Government Stanley Hospital, Chennai between March 2021 and September 2021 under the guidance and supervision of **Prof. I. Rohini M.D.** I also declare that this bonafide work or a part of this work was not submitted by me or any other forward degree or diploma to any other university, board either in India or abroad. This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree (Branch – I) in General Medicine.

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CERTIFICATE – II

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ABBREVIATIONS

DM	-	Diabetes Mellitus
CAN	-	Cardiac Autonomic neuropathy
QTc interval	-	Corrected QT interval
ECG	-	Electrocardiogram
HR	-	Heart Rate
BP	-	Blood Pressure
SBP	-	Systolic Blood Pressure
DBP	-	Diastolic Blood Pressure
HbA1c	-	Hemoglobin A1 c
FBS	-	Fasting Blood Sugar
PPBS	-	Post Prandial Blood Sugar
DAN	-	Diabetic Autonomic neuropathy
CAD	-	Coronary Artery Disease
CKD	-	Chronic Kidney Disease
COPD	-	Chronic Obstructive Pulmonary Disease
LVDD	-	Left Ventricular Diastolic Dysfunction

SCD	-	Sudden Cardiac Death
MI	-	Myocardial Infarction
QSART	-	Quantitative Sudomotor Axon Reflex Test
OHA	-	Oral Hypoglycemic Agents
SGLT-2	-	Sodium-Glucose co-transporter 2
DPP-4	-	Dipeptidyl Peptidase 4
GIP	-	Glucose Dependent Insulinotropic Polypeptide
GLP-1	-	Glucagon-Like Peptide 1
PPAR-γ	-	Peroxisome Proliferator-Activated Receptor Gamma

CONTENTS

S.No	CONTENT	PG No
1	**INTRODUCTION**	**1**
2	AIMS AND OBJECTIVES	4
3	REVIEW OF LITERATURE	5
4	MATERIALS AND METHODS	43
5	OBSERVATION AND RESULTS	46
6	DISCUSSION	75
7	CONCLUSION	77
8	LIMITATION	78
9	BIBLIOGRAPHY	79
10	ANNEXURES	
1	PROFORMA	
II	ETHICAL COMMITTEE APPROVAL CERTIFICATE	
III	INFORMED CONSENT	
IV	MASTER CHART	

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Introduction

INTRODUCTION

Diabetes mellitus encompasses disorders of carbohydrate and lipid metabolism. It is considered to be a state of absolute or relative impairment in insulin secretion associated with even insulin resistance.

Globally, aproximately 346 million people have diabetes. 75 % of the people with diabetes live in low- and middle-income countries. The South-East Asian Region has nearly 71 million living with diabetes. 3.4 million people globally and 1 million in the south east Asian Region die from consequences of hyperglycemia annually[(1).]

India rightly called as the “diabetic capital” has around 77 million people with diabetes, which makes it the second most affected country in the world, after China. One in six people in the world with diabetes are from our country. The number is expected to grow by 2045 to become 134 million per the International Diabetes Federation [(2)]

The term "Diabetes Mellitus" comprises of a metabolic disorder of multifactorial etiology consisting of chronic hyperglycemia along with disturbances of carbohydrate, fat (dyslipidaemia) and protein metabolism due to defects in insulin secretion, insulin action, or both[(3)]. The principal symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger).

The widespread metabolic dysfunction in type 2 diabetes results in various systemic complications. Cardiovascular diseases are one of the most dreaded and fatal complications of this disease.

The cardiovascular complications can be in the form of Coronary Artery Disease, diabetic cardiomyopathy or Cardiovascular autonomic neuropathy (CAN).

CAN is the causative factor for sudden cardiac deaths and myocardial infarction in the diabetic patients. It causes defective heart rate regulation as well as defective central and vascular dynamics[4].

It can remain asymptomatic in the earlier stages and hence lead on to numerous cardiovascular complications. Therefore, recognition of cardiac dysautonomia in the early stages can arrest its progression and thereby prevent further complications.

CAN assessment allows for management of its manifestations, cardiac risk stratification, and tailoring therapeutic targets.

Diabetic Autonomic Neuropathy (DAN) is one of the most common complications of diabetes mellitus. It co-exists with other complications like peripheral neuropathy, nephropathy but can also be isolated. Despite being associated with an increased risk of cardiovascular mortality and morbidity, DAN remains underdiagnosed till today.

The tests for assessing autonomic dysfunction are simple bedside, non-invasive tests that need no specialised equipment. It just requires a sphygmomanometer, heart rate monitor and an ECG machine.

The risk factors for CAN are mainly glycaemic control, hypertension, dyslipidaemia, and obesity in type 2 diabetes mellitus (T2DM). Glycaemic control prevents CAN in T1DM, whereas multifactorial intervention would prove to be effective in T2DM. Lifestyle intervention improves autonomic function even in pre-diabetic patients[5].

Prolongation of QT interval was observed in diabetic autonomic neuropathy by many investigators as early as 1980s. Recent studies have even shown a positive correlation between QTc dispersion, QTc max in diabetic patients with CAN.

This study aims to determine the correlation of CAN with QTc interval and the duration of diabetes mellitus.

Aim & Objectives

AIMS AND OBJECTIVES

1. To determine the correlation of cardiac autonomic neuropathy with QTc interval.

2. To determine the correlation of cardiac autonomic neuropathy with the duration of diabetes mellitus and glycemic control.

Review of Literature

REVIEW OF LITERATURE

Diabetes has been affecting many lives for thousands of years. A disease similar to diabetes was recognized by the Egyptians in manuscripts dating to approximately 1500 B.C.

According to a study, ancient Indians (circa 400–500 A.D.) were very well aware of the condition, and had even identified two types of the disease. They tested for the presence of diabetes — which they called "honey urine" — by determining if ants were attracted to a person's urine.

The term "diabetes"

Diabetes in Greek means "to go through" and mellitus in Latin means honey (referring to sweetness). It was named by a Greek physician Apollonius of Memphis in view of its top symptom: the excessive passage of urine through the body's system.

Many historical documents show that Greek, Indian, Egyptian doctors were aware of the condition, but they could not determine its cause. In earlier times, a diagnosis of diabetes was most likely a death sentence.

Insulin deficiency

In the beginning of 20th century, medical professionals took the first step towards identifying a cause and treatment mode for diabetes. In 1926, Edward Albert Sharpey-Schafer found out that the pancreas of a patient with diabetes was not able to produce what he termed “insulin,” a chemical that the body uses to break down sugar. Thus, according to him, the excess sugar ended up in the urine.

It was in 1921 that scientists experimenting with dogs had a breakthrough in treating the effects of diabetes. Two Canadian medical professionals, Frederick Grant Banting and Charles Herbert Best, successfully extracted insulin from a healthy dog. They then injected it into the dogs that had diabetes to manage their condition.

It was found that some diabetic patients were unresponsive to insulin treatment. Harold Himsworth was the pioneer in distinguishing between the two types of diabetes in 1936. He classified them as “insulin-sensitive” and “insulin-insensitive.” now, these classifications are commonly referred to as “type 1” and “type 2” diabetes.

Subsequent studies showed that diabetes can result in a wide variety of complications both macrovascular and microvascular.

Diabetic autonomic neuropathy (DAN) is a very common and debilitating form of neuropathy. It may be detected in the majority of patients with diabetes by neurophysiologic or clinical testing and is classified as subclinical or clinical based upon the presence or absence of symptoms. A wide variety of manifestations affecting many organ systems can occur, including the cardiovascular, gastrointestinal, genitourinary, pupillary and neuroendocrine systems.

Cardiovascular autonomic neuropathy (abbreviated as CAN) is the impairment of autonomic control of the cardiovascular system [(6)]. It is associated with defects in autonomic cardiovascular function. Sub clinically, the disease is diagnosed by cardiovascular reflex testing, which has a lot of prognostic implications. Clinically, dysautonomia consists of resting tachycardia, orthostatic hypotension, syncope, exercise intolerance, cardiovascular instability, silent myocardial infarction and increased morbidity and mortality.

The prevalence of cardiovascular autonomic neuropathy varies widely, which depends upon the tests used, diagnostic criteria, and the population studied. Some studies have reported an annual incidence of cardiovascular autonomic neuropathy of 1.8 percent in individuals with well-controlled diabetes.[7] This reflects improvements due to early detection and reduction in risk factors.

CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS[7]

- Symptoms of diabetes plus random blood sugar concentration >200mg/dl or
- Fasting plasma sugar > 126mg/dl or
- Haemoglobin A1C >6.5% or
- Two hour plasma glucose > 200 mg/dl during oral glucose tolerance test.

CAN encompasses widespread damage to the autonomic nerve fibres that supply the heart and blood vessels, ultimately resulting in abnormalities of heart rate control and vascular dynamics.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system carries sensory impulses from the blood vessels, the heart, abdomen and pelvis to brain, mainly the medulla, pons and hypothalamus. These impulses elicit largely automatic or reflex responses through the efferent autonomic nerves, thereby eliciting appropriate reactions of the heart, the vascular system and all the organs of the body.

The autonomic nervous system is a complex neuronal circuit for maintaining internal homeostasis and proper systemic functioning. A thorough assessment of the autonomic nervous system is essential for proper evaluation of the peripheral and central nervous sythestem.

ANATOMY

The autonomic nervous system consists of 2 opposing systems, sympathetic and parasympathetic nervous system.

SYMPATHETIC NERVOUS SYSTEM

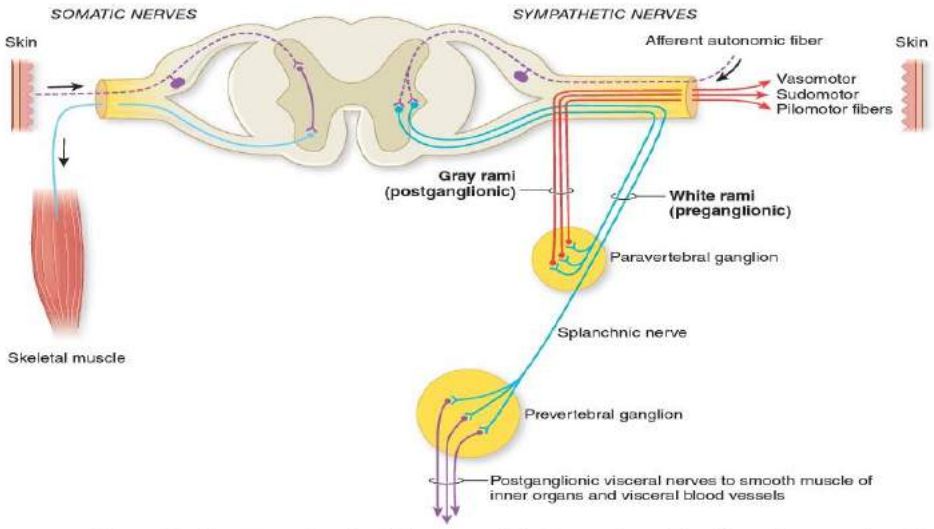


Figure 25-1. Sympathetic outflow from the spinal cord and the course and distribution of sympathetic fibers. The preganglionic fibers are in blue; postganglionic fibers are red and purple. (From Pick.)

The sympathetic nervous system has its exit from the thoracolumbar region of the spinal cord and it synapses at the prevertebral and paravertebral ganglia[8].

Its preganglionic neurons originate in the intermediolateral column of the gray mater of the spinal cord, from the eigth segment of the cervical

cord till the second lumbar segments. The axons of this intermediolateral column are small and unmyelinated. They are grouped to form the white communicating rami. The preganglionic fibres connect with the cell bodies of the postganglionic neurons which are consolidated into two large ganglionated chains on either side of the vertebral column, to form the paravertebral ganglia and it also forms several single prevertebral ganglia. The post ganglionic fibers pass through the grey rami communicans to the spinal nerves of T5 to L3 to supply the blood vessels, hair follicles, sweat glands, and also form plexuses that innervate the bronchi, heart, intestines, kidneys, bladder and the sex organs.

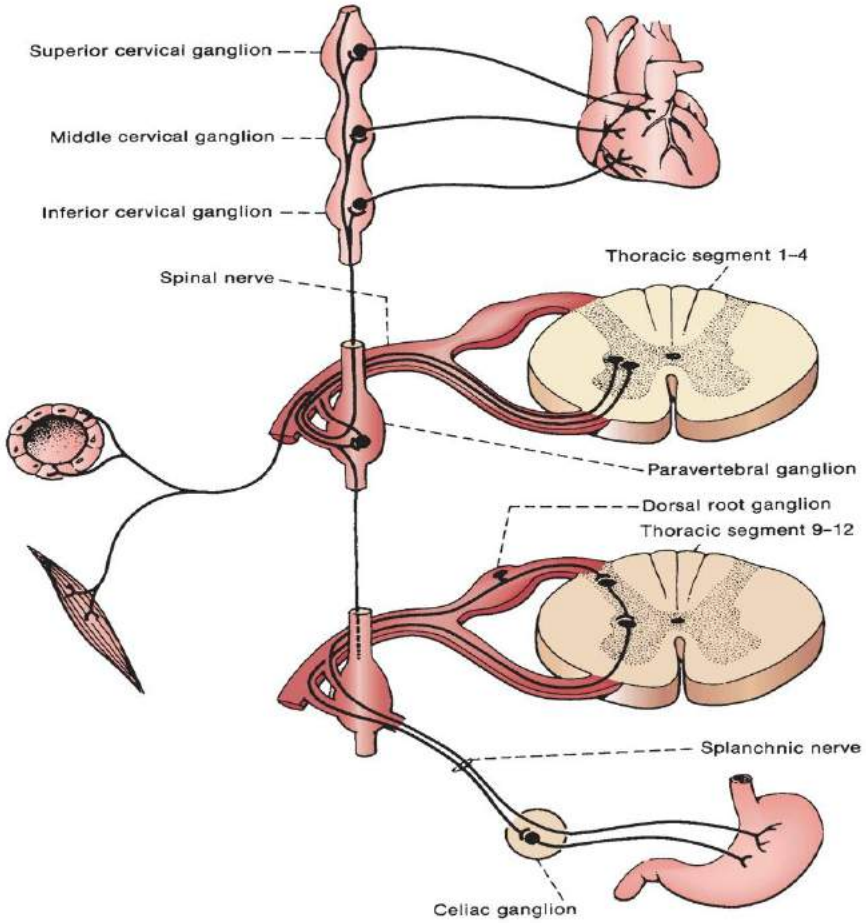


FIGURE 45.3 The sympathetic outflow, showing connections with the paravertebral ganglionic chain, splanchnic nerves, and collateral ganglia.

PARASYMPATHETIC NERVOUS SYSTEM

The parasympathetic nervous system has two divisions; cranial and sacral. The cranial division has its origin from the visceral nuclei of the brainstem.

Edinger-Westphal nucleus, dorsal motor nucleus of vagus, superior and inferior salivatory nuclei are the nuclei of the cranial division of the parasympathetic system. The preganglionic parasympathetic fibres course through the occulomotor, vagus, facial, glossopharyngeal and vagus

nerves. The sacral division has its origin from the lateral horn cells of the second, third and fourth sacral segments. These nerve roots pass through the cauda equina and supply the smooth muscles of the bladder.

APPROACH TO AUTONOMIC NERVOUS SYSTEM EXAMINATION

A detailed history along with clinical examination of the autonomic nervous system is an important area in clinical neurophysiology. Andersen ST, Witte DR et al assessed the risk factors and the course of progression of cardiac autonomic neuropathy in type 2 diabetes[9].

The history should include features of orthostatic hypotension like dizziness, presyncope or syncope, weakness, postprandial angina, palpitations, tremulousness, etc.

History of excess sweating and also decreased or absent sweating must also be elicited. History of urinary retention, urinary incontinence, impotence, must be asked for. Features of gastrointestinal dysautonomia like constipation, postprandial fullness, anorexia, diarrhoea, fecal urgency and incontinence must be elicited.

CARDIOVASCULAR AUTONOMIC TESTING

The symptoms and signs of cardiovascular autonomic dysfunction may be subtle in the initial stages and may occur late in the course of

diabetes. The symptoms include abnormal exercise-induced cardiovascular performance, cardiac denervation syndrome and postural hypotension. Autonomic nervous system examination involves a comprehensive evaluation of the responses of complex reflex pathways. There are many bedside examination to look for dysautonomia

Sympathetic Failure	Parasympathetic Failure	ENS Failure
Orthostatic hypotension	Dry mouth	Anorexia
Widespread anhidrosis	Dry eyes	Early satiety
	Impaired pupillary light response	Postprandial abdominal pain
	Fixed heart rate	Vomiting
	Urinary retention	Diarrhea
	Sexual dysfunction	Constipation
		Intestinal pseudo-obstruction

CARDIAC AUTONOMIC NEUROPATHY AND CAD

CAN may often be associated with abnormalities in left ventricular (LV) systolic and particularly diastolic function in the absence of cardiac disease in diabetic patients. Echocardiographic studies have revealed a significant correlation of the severity of CAN with reduced peak diastolic filling rate and with an augmented atrial contribution to diastolic filling as assessed by Doppler echocardiography. It is difficult to judge, however, whether CAN is an independent contributor to these abnormalities, because other factors such as interstitial myocardial fibrosis and microangiopathic

or metabolic changes (discussed in the pathogenesis of diabetic heart muscle disease) may also be responsible for LV dysfunction.

CAN is associated with LV diastolic dysfunction (LVDD) at rest, both in patients with long-term type 1 or type 2 diabetes. LVDD may progress to heart failure, mainly with preserved LV systolic function (diastolic heart failure), which is also related to high morbidity and mortality rates[4]. The pathophysiology of LVDD includes delayed relaxation, impaired LV filling, and/or increased stiffness of the ventricles. Diabetes mellitus can produce functional, biochemical, and morphological myocardial abnormalities independent of coronary atherosclerosis and hypertension, contributing to heart failure with normal LV systolic function.

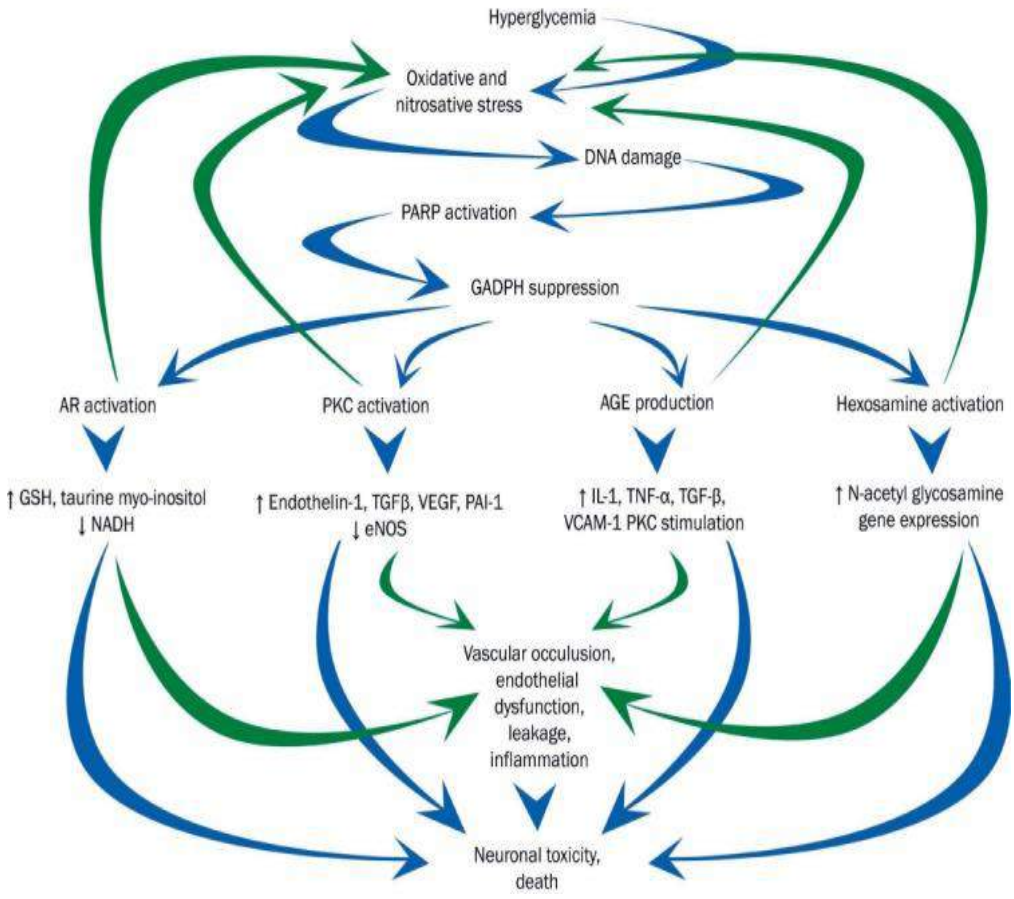
Silent myocardial ischemia/cardiac denervation syndrome

The perception of angina is severely impaired in the diabetic patients, allowing these individuals to exercise longer after the onset of myocardial ischemia[10]. The delay in perception of angina was associated with the presence of cardiovascular autonomic dysfunction. Studies revealed that the neuropathic damage to the myocardial sensory afferent fibres in the autonomic nerve supply reduced the diabetic individual's sensitivity to regional ischemia by interrupting pain transmission. The presence of CAN does not exclude painful myocardial infarction (MI)

among individuals with diabetes(11). Chest pain in any location in a patient with diabetes should be considered to be of myocardial origin until proven otherwise; but of equal importance, unexplained fatigue, confusion, tiredness, oedema, haemoptosis, nausea, vomiting, diaphoresis, arrhythmias, cough, or dyspnoea should alert the clinician to the possibility of silent MI.

PATHOPHYSIOLOGY OF AUTONOMIC NEUROPATHY

Autonomic dysfunction due to diabetes has been extensively studied and the pathogenic mechanisms have been explained.



Many different factors have been implicated in the pathophysiology of DAN. The activation of the polyol pathway due to hyperglycemia causes direct neuronal damage and the alteration in the NADH:NAD ratio also decreases the nerve blood supply, mediating nerve damage(12).

Activation of Protein Kinase C also stimulates vasoconstriction and decreased the neuronal blood flow. Increased free radical production due to oxidative damage mediated by chronic hyperglycemia also causes vascular endothelial damage and decreases the bioavailability of nitric oxide.

Deficiency of essential fatty acids, decrease in the neurotrophic factors and formation of advanced glycolsylation end products, also cause reduced endoneural blood flow and hypoxia of the nerve fibres and alters the nerve function.

These processes result in the depletion of ATP and causing cell necrosis and activation of genes involved in neuronal damage. Duchen et al reported that vacuolisation of the sympathetic ganglionic nerve fibres, inflammation of the nerve cells, and loss of myelinated nerve fibres are implicated in the autonomic neuropathy.

CLINICAL FEATURES OF DYSAUTONOMIA

Cardiovascular symptoms:

Postural hypotension, vertigo, syncope, dizziness, neck pain and weakness

GIT symptoms:

Dysphagia, nausea, early satiety, bloating, nocturnal diarrhoea, constipation, and feeling of incomplete evacuation.

Urological symptoms:

Dysuria, involuntary micturition, prolonged dribbling of urine, incomplete bladder emptying, erectile dysfunction.

Tests of cardiovascular autonomic dysfunction

It is based on the changes in blood pressure and heart rate in response to change in posture and breathing. It has been stated that a fall of more than 30 mm Hg systolic and 15 mm Hg diastolic from recumbent to standing position is significant(13).

Multiple factors have been found to influence autonomic function – emotional state, body position, ingested food and medicines, etc. Caffeine and nicotine should be avoided for at least 3-4 h before testing and alcohol intake should be avoided for 8 h. Sympathomimetic drugs should be

withheld for 24-48 h before testing, and anticholinergics for 48 h. Standardization of the testing conditions is important in order to make them comparable.

Most of the tests are based on evaluating the cardiovascular reflexes stimulated by performing specific provocative manoeuvres(14). Triggers that raise blood pressure, like isometric exercise, cold pressor test or mental arithmetic, activate mainly the sympathetic outflow. Blood pressure responses to orthostatic testing and Valsalva manoeuvre are considered in a large part to be a reflection of the sympathetic activity.

TABLE 3.40 Important tests used for evaluation of autonomic functions

A. Tests of cardiac and vascular autonomic regulation
   - Cardiovascular response to standing and 30th to 15th R–R ratio
   - Head-up tilt-table testing
   - Heart rate variation with respiration (sinus arrhythmia; R–R interval analysis)
   - Valsalva maneuver and Valsalva ratio
   - Miscellaneous tests

B. Tests of thermoregulatory function
   - Sympathetic skin response
   - Quantitative sudomotor axon reflex test
   - Thermoregulatory sweat test
   - Sweat imprint test

C. Miscellaneous tests
   - Tests of exocrine and pupillary regulation
   - Tests of gastrointestinal autonomic regulation
   - Tests of genitourinary autonomic regulation

HEART RATE VARIATION WITH RESPIRATION:

The extent of variation of heart rate with respiration is an indicator of the integrity of the parasympathetic and cholinergic functions(15). The term sinus arrhythmia is used to denote the variation of the heart rate with respiration. The heart rate is increased during inspiration and decreased during expiration. The vagal innervation of the heart is responsible for mediating this change.

Sinus arrhythmia is inhibited by parasympathetic blockage by atropine but not by sympathetic blockers. Cardiac mechanoceptors, stretch receptor in the pulmonary vasculature and also baroreceptors contribute to the sinus arrhythmias.

This phenomenon decreases with age increases with slower respiratory rates, attaining a maximum around 5-6 breaths/minute. It also decreases with increase in heart rate as in the resting tachycardia found in autonomic neuropathy, pulmonary disease, CNS depression, cardiac failure and hyperventilation.

Most of the methods for determining heart rate variability with respiration require the patient to take deep breaths at 5-6 per minute. There is maximum variation of the heart rate at this respiratory rate. The

inspiratory to expiratory ratio or index is calculated as the average of six ratios of the longest R-R intervals.

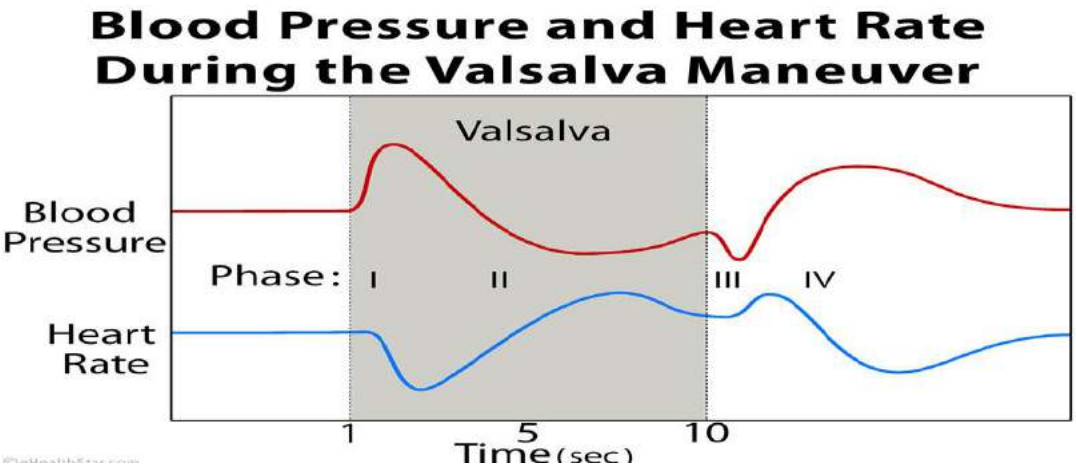
VALSALVA MANUEVRE

Like the heart rate variability with respiration, the heart rate changes during Valsalva maneuver also reflects the parasympathetic system functioning. The respiratory strain due to the manoeuvre increases the intra-abdominal and the intra-thoracic pressures and alters the cardiac hemodynamics(16).

The Valsalva manoeuvre has the following 4 phases:

Phase I:

It occurs at the onset of the strain. It is characterised by a transient increase in BP lasting for a few seconds which is mainly due to the intrathoracic pressure increase and the mechanical force on the great vessels. But the heart rate does not vary during this phase.



Phase II:

It occurs at during the straining process. In the initial part of phase II, the venous return decreases, thereby reducing the stroke volume, cardiac output. This lasts for 3-4 seconds. The BP returns to the baseline in the later part of the phase II. This recovery occurs because of the sympathetic system activation leading to increase in the peripheral resistance due to vasoconstriction. The heart rate increases steadily during this phase due to the sympathetic activity.

This can be pharmacologically inhibited by atropine in the early part and propranolol in the later part. Phase II is a sensitive indicator of sympathetic adrenergic functioning.

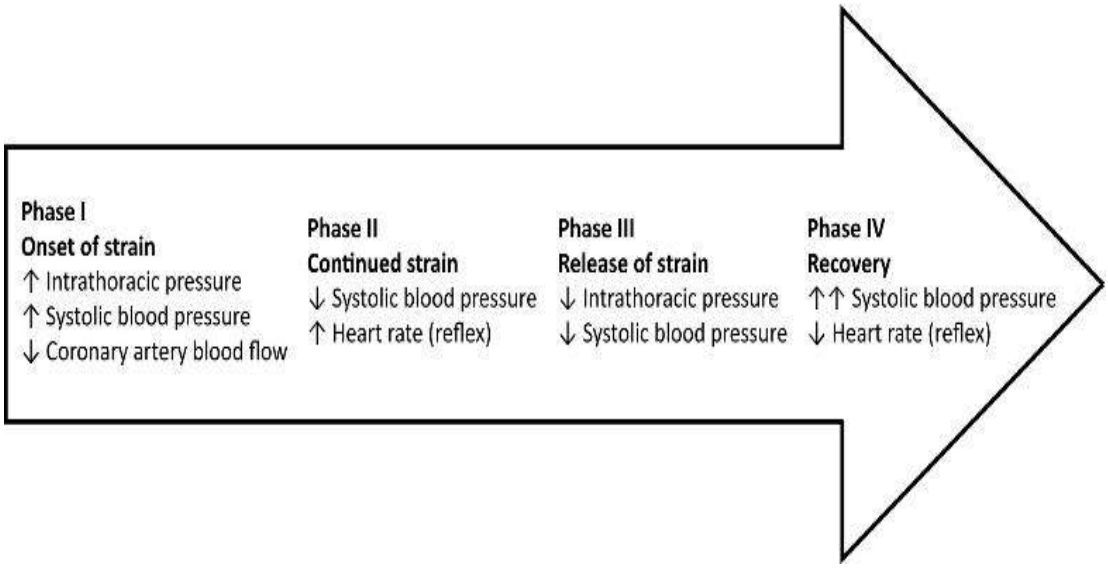
Phase III:

It occurs following the release of strain which results in a transient decrease in the blood pressure lasting for s few seconds. It is due to the increase in the intrathoracic pressure and there is no change in heart rate at this phase.

Phase IV:

It occurs with further cessation of the straining. BP slowly increases and the heart rate slowly goes down. This is called as the overshoot phase as both the heart rate and the blood pressure falls and rises with respect to

the baseline respectively. It happens following 15-20 seconds following the strain cessation and may last for upto one minute. This phenomenon is due to the increase in the venous return, stroke volume and cardiac output. Valsalva ratio is the maximum heart rate in phase II to the minimal heart rate in phase IV. Factors like age, gender, position of the patient, force of the strain influence the Valsalva ratio.



Head up tilt test:

The tilt table test is used in testing the integrity of the autonomic cardiovascular and neurogenic reflexes. It has also been used to demonstrate the presence of vasovagal syncope in patients with unexplained syncope(17).

The patient is asked to fast for 4-6 hours prior to the testing. The patient is made to lie in a special type of table. ECG monitor and the BP cuff are attached. The patient is kept in a supine pre-tilt phase for 5 minutes.

The table is then tilted at an angle of 60-80 degrees. The patient is maintained in this angle for 45 minutes. The passive phase in the initial 20 minutes where IV cannula is established. If the passive phase is negative, sublingual nitroglycerin in the dose of 400 micrograms is used. The drug challenge phase is about 15-20 minutes. The end point of the test is the occurrence of syncope or a progressive decline in BP for atleast 3 minutes or a systolic BP value of 60 mm Hg.

Cardiovascular response to standing

The BP response to standing are used to determine the proper functioning of the sympathetic and the heart rate response to standing are used to assess the parasympathetic system functioning. Normally, standing causes mechanical effects of arterial resistance and venous capacitance and also gravitational changes. The venous return increases due to the squeezing of the capacitance vessels by the calf muscles.

The baroreceptors are activated which in turn reduce the sympathetic outflow, release the vasoconstrictor tone, and reduces the peripheral resistance up to 40 percent. This causes a drop of BP of about 20 mm Hg for about 6-8 seconds.

The heart rate raises immediately upon standing and it continues to rise for about 20 seconds. The initial increase in the heart rate is an exercise

reflex, which is mediated by the sympathetic activation and the withdrawn parasympathetic tone. Most of the heart rate variations are due to the inhibition of the parasympathetic action.

A steady state is achieved subsequently which is controlled by humoral mechanisms, autonomic reflexes and the capillary fluid shift.

Technique of measurement:

The heart rate and the blood pressure are measured after the patient is in a resting state for 20 minutes. Baseline BP and heart rate are measured and then serial recordings are taken at 1-3 minutes after standing.

The 30^{th} to the 15^{th} R-R ratio is determined from the ECG. It is the longest R-R interval that occurs 30 beats after standing divided by the shortest R-R interval that occurs 15 beats after standing.

A fall of atleast 20 mm systolic or 10 mm Hg of diastolic BP on standing is considered orthostatic hypotension[13].

When there is a sustained increase in the heart rate of more than 25 beats per minute or a resting heart rate exceeding 110/ minute, it is called as orthostatic tachycardia. The 30^{th} to 15^{th} R-R ratio is considered normal if its >1.04 and abnormal if <1.0.

These clinical methods of testing are not complex, easily accessible and quantitative but have less sensitivity.

In orthostatic hypotension due to dysautonomia, there will be a striking absence of the compensatory tachycardia indicating the defective functioning of both the cardiac and vascular reflexes.

Blood pressure response to sustained handgrip:

There is an increased blood pressure in response to sustained muscle contraction due to exercise reflex causing reduced parasympathetic and increased sympathetic activity. The changes in blood pressure are regulated by sympathetic adrenergic vascular function and the changes in heart rate are regulated parasympathetic cholinergic function. The patient is asked to maintain a hand grip of 30 % of maximum activity for upto 3-5 minutes. Normally, the diastolic BP should rise more than 15 mm Hg. A rise of 11-15 mm Hg is borderline.

According to Ewing et al, this test is relatively independent of age[18].

The following tests have been suggested by Ewing and Clarke for the assessment of autonomic function.

Test	Normal	Borderline	Abnormal
1. Heart rate response to standing (BPM)	≥ 1.04	1.01–1.03	≤ 1.00
2. Blood pressure response to standing (mmHg)	≤ 10	11–29	≥ 30
3. Heart rate response to deep breathing (mmHg)	≥ 15	11–14	≤ 10
4. Valsalva maneuver and heart rate response (BPM)	≥ 1.21	1.11–1.20	≤ 1.10
5. Blood pressure response to sustained handgrip (mmHg)	≥ 16	11–15	≤ 10

Resting Tachycardia

Abnormalities in Heart Rate Variability are early findings of cardiac autonomic neuropathy[19]. Resting tachycardia and an absence of heart rate variability are characteristic late findings in diabetic patients with impairment of the parasympathetic system. The highest resting heart rates have been seen in patients with parasympathetic damage, occurring earlier than sympathetic system dysfunction.

A fixed heart rate that is not responsive to moderate exercise, stress, or sleep denotes almost complete cardiac denervation.

Parasympathetic neuropathy can be present early in the course of type 2 diabetes due to subclinical atherosclerosis. Hence, early detection of autonomic neuropathy can facilitate the detection of atherosclerosis earlier in T2DM and prevent adverse cardiac events.

Exercise Intolerance

Autonomic dysfunction affects exercise tolerance, reduces the response in heart rate and blood pressure (BP) and blunts increase in cardiac output in response to exercise[20]. Diabetic patients who are most likely to have CAN should be tested for cardiac stress before undertaking an exercise program. Patients with CAN need to rely on their perceived exertion, not heart rate, to avoid hazardous levels of intensity of exercise. At present, there is not adequate evidence to recommend routine screening

of asymptomatic diabetic patients with an exercise ECG test. Upcoming data supports the utility of stress imaging tests to identify diabetic patients with pre-clinical coronary artery disease. Patients with high-risk features, and co morbidities such as long-standing diabetes, CAN, multiple chronic renal failures, resting ECG abnormalities, and peripheral artery disease.

Abnormal sweating

This is a common but frequently neglected, symptom of diabetic autonomic neuropathy. Gustatory sweating, precipitated by eating cheese and other foods, is characteristic. Sweating is often profuse over the face and sometimes upper chest, corresponding to the area supplied by the superior cervical ganglion.

Some patients find this socially debilitating. Other abnormalities of sweating include the dry neuropathic foot, which allows cracking of the skin and the entry of infection and episodic nocturnal sweating that cannot be attributed to hypoglycemia.

Sudomotor function

SUDOSCAN is a novel device that detects sweating dysfunction by measuring the skin conductance response. It tests integrity of the efferent sympathetic pathway. In sympathetic or galvanic skin- resistance test, a set of electrodes are placed on the skin. This test measures the resistance to passage of weak current in the skin. The change in electric potential is due to an ionic current within the sweat glands. The result mainly depends upon

the sympathetic response to sweat glands. The SUDOSCAN allows the quick quantitative assessment of sudomotor function. It can be used for early detection of CAN in everyday clinical practice before applying the more sophisticated and specific, but more time-consuming, Ewing tests. It can be done if equipments and resources are avalaible. It has a sensitivity and specificity of 88% and 54% respectively[21].

The QSART (Quantitative Sudomotor Axon Reflex Test) is a more quantitative and reproductive method for the examination of postganglionic sudomotor function[22]. It involves iontophoresis of a cholinergic agonist to determine the axon reflex mediated sudomotor responses to evaluate postganglionic sudomotor function. Four sites are used and studied with the patient supine. The test, typically done by recording from the forearm and three lower extremity skin sites, has high sensitivity, specificity, and reproducibility. The test is not generally available and warrants the purchase of expensive specialized equipment.

The QT interval and Cardiac Autonomic Neuropathy

QT intervals taken from the onset of QRS complex to end of the 'T' wave and corrected for heart rate give the corrected QT interval (QTc). A QTc interval of more than 440 millisecond is considered prolonged. It is the total duration of ventricular myocardial depolarization and repolarization in the ECG.

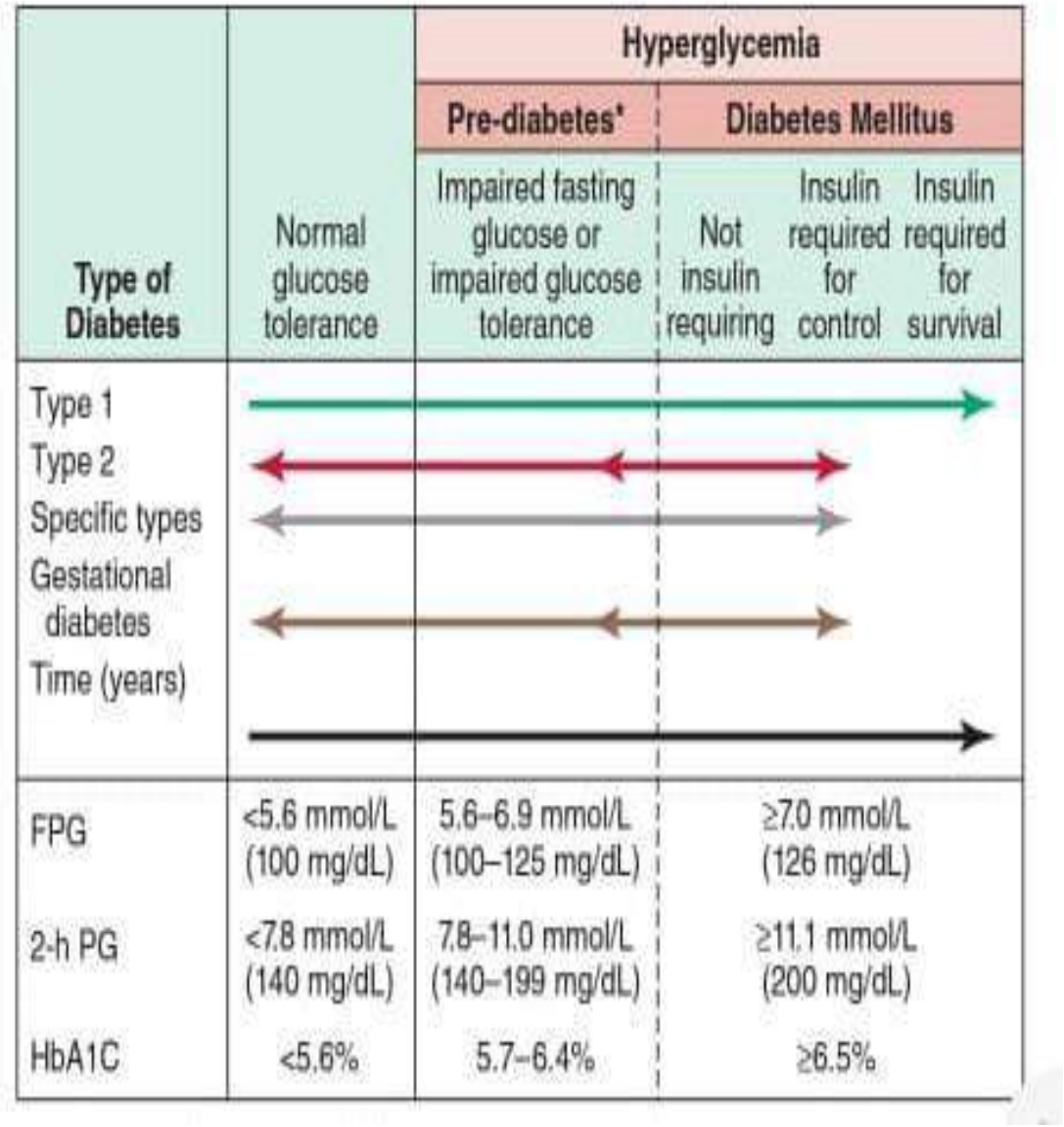
It is usually corrected for heart rate by Bazett formula, where

QTc = QT / √RR interval.

QTc prolongation in ischemic heart disease carries an increased risk (2-5 times) of sudden cardiac death. The exact mechanism of QTc prolongation is not clearly defined. It has been suggested that some non-quantifiable sympathetic imbalance is responsible for QTc prolongation. A prolonged QTc interval and QT dispersion (the difference between the longest and shortest QT interval) indicates an imbalance between right and left sympathetic innervation.

QTc interval in the ECG can be used to diagnose CAN with reasonable sensitivity, specificity and positive predictive value[23]. QT interval prolongation is an irregularity of the electrical activity of the heart that places patients at risk for ventricular arrhythmias[24]

Diabetes mellitus



Classification

Diabetes mellitus is classified on the basis of the pathogenic process causing hyperglycemia, instead of the earlier criteria like age of onset or type of treatment. There are two categories of DM, type 1and type 2 DM.

Type 1 diabetes mellitus

Type 1 DM occurs as a result of autoimmunity against the insulin-producing pancreatic beta cells, resulting in absolute insulin deficiency. It is the result of complex interactions of genetic, environmental, and immunologic factors that finally lead to the immune-mediated destruction of the pancreatic beta cells and absolute insulin deficiency. It can develop at any age, but most commonly occurs before 20 years of age. Most of the individuals with this disease have evidence of islet-directed autoimmunity. However, some individuals lack immunologic markers reflective of an autoimmune process involving the beta cells. These patients are thought to develop insulin deficiency by nonimmune mechanisms and may be prone to ketosis. This mainly affects the individuals of African American or Asian heritage. The autoimmune process is thought to be initiated by an infectious or environmental stimuli. In most of the patients, autoantibodies against beta cell antigens occur after this triggering event, followed by rapid and progressive loss of insulin secretion. The rate of loss in beta cell function differs widely among individuals, with some patients progressing

very rapidly to clinical diabetes and other patients evolving to diabetes more slowly and over a period of time.

Type 2 diabetes mellitus

Insulin resistance and abnormal insulin secretion are pivotal to the development of type 2 DM. Type 2 DM encompasses a range of disorders with the common aspect of chronic hyperglycemia.

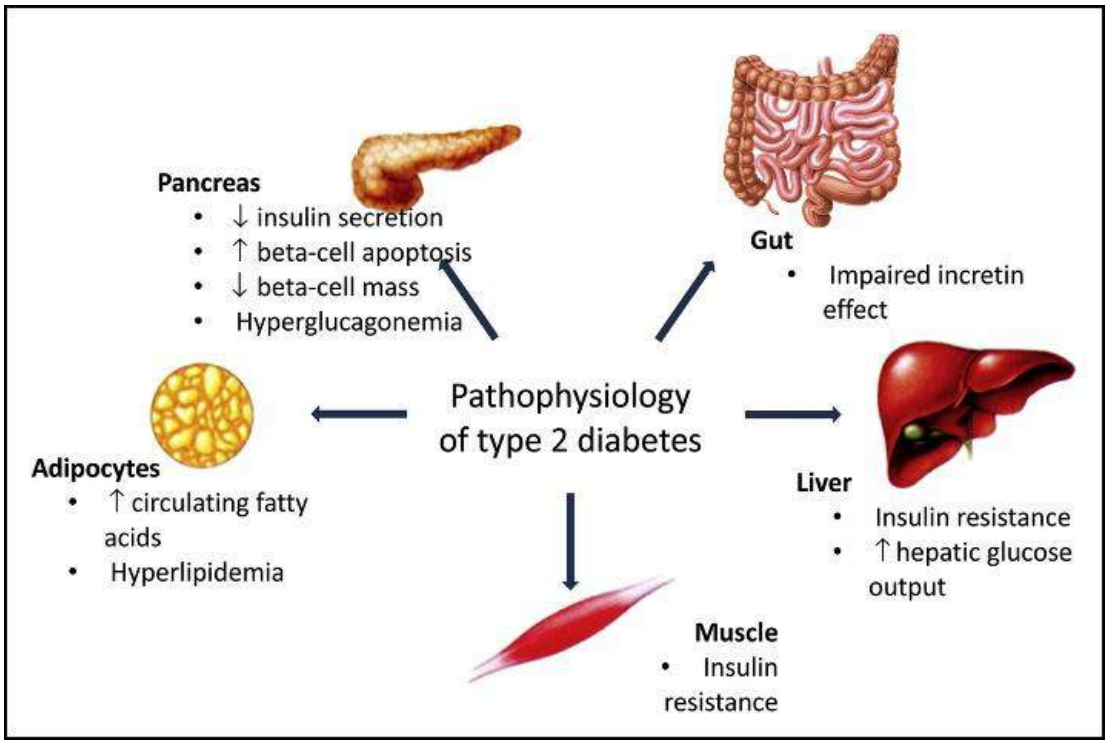
Genetic risk factors

Type 2 DM has a very strong genetic component. The occurrence of type 2 DM in identical twins is between 70 and 90%. Individuals with a parent with type 2 DM have a greater risk of diabetes; if both parents have type 2 DM, the risk is about 40%. Insulin resistance, as shown by reduced glucose utilization in skeletal muscle, is found in many nondiabetics, first-degree relatives of individuals with type 2 DM. The disease is polygenic and multifactorial, as in addition to genetic susceptibility, environmental factors such as obesity, poor nutrition, and physical inactivity also contribute to the disease process. Increased or reduced birth weight increases the risk of type 2 DM in adult life. Children of pregnancies complicated by gestational diabetes also exhibit an elevated risk of type 2 DM. The following are the risk factors for type 2 diabetes mellitus

Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
Overweight or obese (BMI ≥25 kg/m², ≥23 kg/m² in Asian Americans, or other ethnically relevant definition for overweight)
Physical inactivity
Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
Previously identified with IFG, IGT, or an hemoglobin A_{1c} of 5.7–6.4%
History of GDM
Hypertension (blood pressure ≥140/90 mmHg)
HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
Polycystic ovary syndrome or acanthosis nigricans
History of cardiovascular disease

Pathophysiology

Type 2 DM is manifested by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, abnormal fat metabolism, and systemic low-grade inflammation.



Central obesity is very common in type 2 DM. In the early stages of the disease, glucose tolerance is near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output causing a state of hyperinsulinemia. As the insulin resistance and compensatory hyperinsulinemia progresses, the pancreatic islets in some individuals are not able to maintain the hyperinsulinemic state. Impaired glucose tolerance, characterized by elevations in postprandial glucose, then develops. A further decrease in insulin secretion and an increase in hepatic glucose production leads to overt diabetes with fasting hyperglycemia. Lastly, beta cell failure ensues. Due to inadequate insulin suppression, glucagon is relatively overproduced and secreted, thereby augmenting hepatic glucose production. Although both insulin resistance and impaired insulin secretion contribute to the pathogenesis of type 2 DM, the relative contribution of each varies from individual to individual.

Metabolic Abnormalities

ABNORMAL MUSCLE AND FAT METABOLISM

Insulin resistance, the reduced ability of insulin to act effectively on target tissues mainly muscle, liver, and fat is a very prominent feature of type 2 DM and occurs from a combination of genetic susceptibility and obesity. However, the insulin resistance is relative, because supranormal levels of circulating insulin will tend to normalize the plasma glucose.

Insulin dose-response curves show a rightward shift, indicating reduced sensitivity, and a reduced maximal response, indicating an overall decrease in maximum glucose utilization (30–60% lower than in normal individuals).

Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output; both effects contribute to the hyperglycemia. Increased hepatic glucose output predominantly accounts for increased FPG levels, whereas decreased peripheral glucose utilization results in postprandial hyperglycemia.

In skeletal muscle, there is a greater impairment in non oxidative glucose usage than in oxidative glucose metabolism through glycolysis. Glucose metabolism in insulin-independent tissues is not altered in type 2 DM.

Insulin receptor levels and tyrosine kinase activity in skeletal muscle are reduced, but these alterations are most likely secondary to hyperinsulinemia and are not a primary defect. Therefore, “postreceptor” defects in insulin-regulated phosphorylation/dephosphorylation appear to play the predominant role in insulin resistance. Abnormalities include the accumulation of lipid intermediates within skeletal myocytes, which may impair mitochondrial oxidative phosphorylation and reduce insulin-stimulated mitochondrial ATP production.

IMPAIRED INSULIN SECRETION

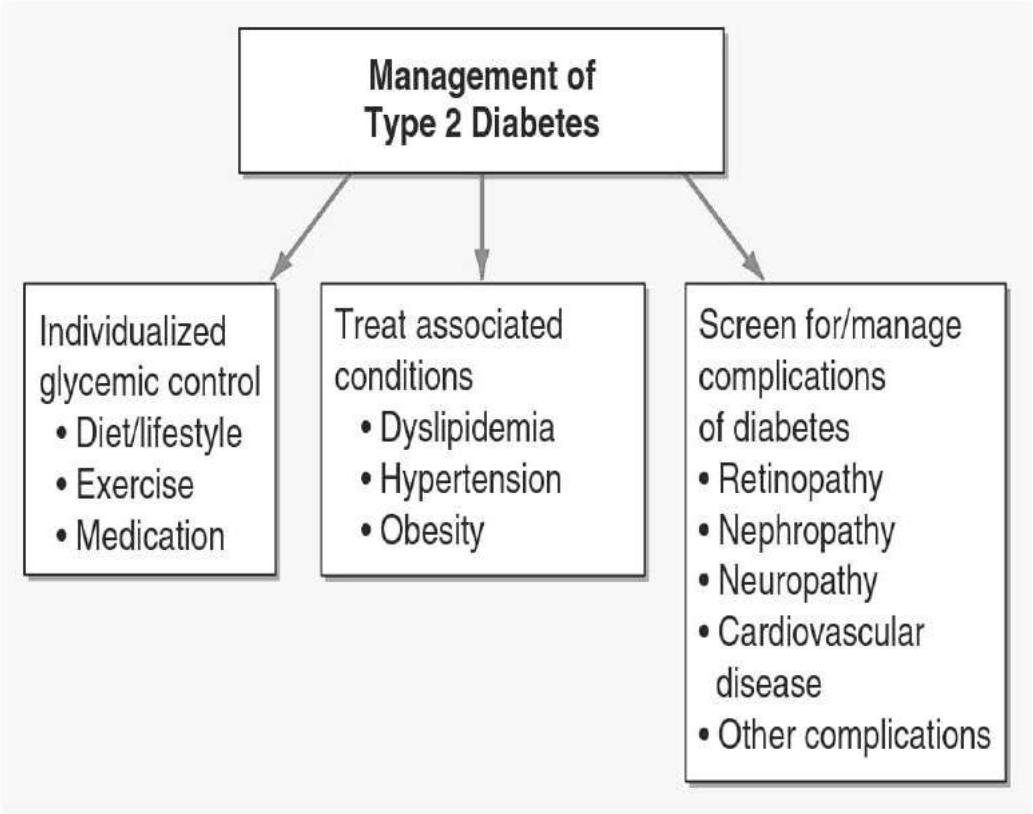
Insulin secretion and sensitivity are interrelated. In type 2 DM, insulin secretion initially increases in response to insulin resistance to maintain normal glucose tolerance. Initially, the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion, including a greatly reduced first secretory phase. The response to other nonglucose secretagogues, such as arginine, is preserved, but overall beta cell function is reduced by as much as 50% at the onset of type 2 DM. Abnormalities in pro insulin processing are reflected by increased secretion of proinsulin in type 2 DM. Eventually, the insulin secretory defect is progressive. The reasons for the decline in insulin secretory capacity in type 2 DM is unclear. The assumption is that a second genetic defect that is superimposed upon insulin resistance leads to defects in beta cell function, mass, and potentially cellular identity and differentiation status. Beta cell mass is decreased by ~50% in individuals with long-standing type 2 DM. Islet amyloid polypeptide or amylin, co-secreted by the beta cell, forms amyloid fibrillar deposits found in the islets of individuals with long-standing type 2 DM. Whether such islet amyloid deposits are a primary or secondary event is not known.

The metabolic environment of diabetes also negatively impacts islet function. For example, chronic hyperglycemia paradoxically impairs islet

function and leads to a worsening of hyperglycemia. Improvement in glycemic control is often associated with improved islet function.

In addition, elevated levels of free fatty acids, and systemic and local elevations in pro-inflammatory cytokines from increased numbers of islet-associated macrophages, may also worsen islet function. Reduced GLP-1 action may contribute to the reduced insulin secretion.

DIABETES MELLITUS; MANAGEMENT



Medical nutrition therapy

MNT is defined as nutritional diagnostic, therapy, and counseling services for the purpose of disease management, which are furnished by a registered dietician or nutrition professional[25]**.**

MNT comprises dietary, nutritional and culinary advice. It includes both the home-made food and medical-grade formulations. As well as diet-related content, MNT also encompasses style of communication and counselling.[26] MNT aims to manage both dysglycemia and adiposity through nutritional intervention**.**

Oral hypoglycemic agents[27]

- Sulfonylureas (glipizide, glyburide, gliclazide, glimepiride)
- Meglitinides (repaglinide and nateglinide)
- Biguanides (metformin)
- DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin)
- SGLT2 inhibitors (dapagliflozin and canagliflozin)
- Thiazolidinediones (rosiglitazone, pioglitazone)
- α-Glucosidase inhibitors (acarbose, miglitol, voglibose)

Sulfonylureas

These drugs bind to the adenosine triphosphate-sensitive potassium channels (K-ATP channels) in the pancreatic beta cells.

This leads to the inhibition of the channels and changes the resting membrane potential of the cell, causing an entry of calcium into the cell and insulin secretion is stimulated. Hence these drugs are also called insulin secretagouges.

Meglitinides

These drugs exert their effects through a different pancreatic beta-cell receptor, but they act similarly to sulfonylureas by controlling adenosine triphosphate-sensitive potassium channels in pancreatic beta cells, hence causing an increase in insulin secretion.

Biguanides -Metformin

Metformin is a very commonly used drug which increases the hepatic adenosine monophosphate-activated protein kinase activity, threby decreasing the hepatic gluconeogenesis and lipogenesis and stimulating insulin-mediated uptake of glucose in muscles.

Thiazolidinediones

Thiazolidinediones activate peroxisome proliferator-activated receptor gamma (PPAR-γ). It is a nuclear receptor, which increases the sensitivity of insulin and stimulates the peripheral uptake of glucose. It also increases the level of adiponectin, an adipose tissue-secreted cytokine, that increases not only the number of insulin-sensitive adipocytes but also promotes fatty acid oxidation.

Alpha-glucosidase inhibitors

These drugs act on the intestinal brush border cells and competitively inhibit alpha-glucosidase enzymes that digest the dietary starch, thereby inhibiting the reabsorption of polysacchrides and the metabolism of sucrose to glucose and fructose.

DPP-4 inhibitors

The DPP-4 inhibitors inhibit the enzyme dipeptidyl peptidase 4 (DPP- 4). These in turn inhibit the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). Hence, these drugs regulate glucose control through multiple effects, such as decreasing glucagon release and increasing glucose dependent release of insulin, and also decreasing gastric emptying, and increasing satiety.

SGLT2 inhibitors

These novel group of inhibit sodium-glucose co-transporter 2 (SGLT-2) in the proximal tubules of the glomeruli, causing inhibition of about 80-90% glucose reabsorption and resulting in glycosuria which in turn lowers the plasma glucose levels.

Insulin

Insulin is used in patients with type 1 diabetes and those with type 2 diabetes with a high Hba1c or not responding to OHAs. In India we get insulin in the formulation of U-40(40 Units/ml)).Insulin can be classified into Short acting, Long acting and also in combinations. Short acting insulin have a complete biological activity but less tendency for self aggregation. Hence they have shorter duration of action and less hypoglycemic episodes. Long acting insulin have less frequency of administration but more hypoglycemic episodes. Nowadays combination therapy is being used in many patients as they mimic the physiologic release of insulin with food. Also no separate dose adjustments for long and short acting insulins are required.

PREPARATION	TIME OF ACTION		
	ONSET, h	PEAK, h	EFFECTIVE DURATION, h
Short-acting[b]			
Aspart	<0.25	0.5–1.5	2–4
Glulisine	<0.25	0.5–1.5	2–4
Lispro[f]	<0.25	0.5–1.5	2–4
Regular[g]	0.5–1.0	2–3	3–6
Inhaled human insulin	0.5–1.0	2–3	3
Long-acting[g]			
Degludec	1–9	—[c]	42[d]
Detemir	1–4	—[c]	12–24[d]
Glargine[f]	2–4	—[c]	20–24
NPH	2–4	4–10	10–16
Examples of insulin combinations[e]			
75/25–75% protamine lispro, 25% lispro	<0.25	Dual[f]	10–16
70/30–70% protamine aspart, 30% aspart	<0.25	Dual[f]	15-18
50/50–50% protamine lispro, 50% lispro	<0.25	Dual[f]	10–16
70/30–70% NPH, 30% regular	0.5–1	Dual[f]	10–16
Combination of long-acting insulin and GLP-1 receptor agonist	See text		

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MATERIALS AND METHODS

This study was conducted in the medicine OPD and wards of Government Stanley Medical College and Hospital. The study was conducted in 150 patients over a period of 6 months from March 2021 to September 2021.

Written consent was obtained from all the patients participating in the study after clearly explaining the study procedure. The patients were grouped into three according to the duration of diabetes. Autonomic neuropathy testing by 5 bed side tests was done in Medical ward using ECG monitor, pulse oxymeter and sphygmomanometer. Each group was compared with one another with the available statistical data.

Study setting- Medicine wards and OPDs of Government Stanley Medical College

Study population- Patients with type 2 diabetes mellitus attending general medicine OPD and admitted in medicine wards.

Study design- Cross sectional study to find out the correlation between cardiac autonomic neuropathy and the QTc interval and the duration of diabetes.

Inclusion criteria

Type 2 diabetics (already on treatment and newly diagnosed)

Exclusion criteria

- Type 1 diabetics.
- Pregnant women.
- Age>65 years.
- CAD, valvular heart diseases.
- COPD, CKD patients
- Patients with psychiatric disorders
- Dyselectrolytemia

Sample size

Based on the reference study done done by Jayaprasad et al , Kerala

Formula:

$n = Z^2pq / d^2$

Where Z = 1.96 (statistical significant constant for 95% CI)

p =66 % (Incidence of Cardiac Autonomic Neuropathy among type 2 Diabetes Mellitus patients from previous study.)

q = 34 % (100-p)

d = 12 % relative precision (ie 12% of 66 = 8)

On substituting, in the formula

n = 3.84 x 66 x 34 / 64

n = 134

Adding 10% non response rate (ie 10% of 134 = 13)

n = 147 (minimum sample size)

Therefore Sample size **n = 150 (1 group).**

Statistical analysis

For our study, data entry was done in Microsoft Excel. Data analysis was performed using SPSS software. Results were analysed using Chi-square test with p-value as a measure of significance

Observation and Results

OBSERVATION AND RESULTS

The mean age of the participants in our study was 54.5 years (S.D=4.8).

Majority of them were males (n=88, 58.7%). Remaining were females Comparison of age with severity of Cardiac Autonomic Neuropathy shows that the mean age was higher in severe than early autonomic neuropathy (57.2 years vs 55.7 years) [$p<0.001$, statistically highly significant]. This could be attributed to the increased duration of diabetes in old age.

Gender had no impact on the severity of cardiac autonomic neuropathy ($p>0.05$)

Comparison of duration of DM with severity of Cardiac Autonomic Neuropathy showed that longer duration is associated with higher severity of neuropathy ($p<0.001$). The prevalence of CAN was around 50 % in the subjects.

Out of 150 patients, 46% (n=69) did not have cardiac autonomic neuropathy whereas 54% (n=81) had cardiac autonomic neuropathy. Out of those 81 subjects, 54 had severe autonomic neuropathy and 27 had early autonomic neuropathy. In the early vs severe autonomic neuropathy, postural giddiness was a prominent symptom. 8 out of 27 in the early

autonomic neuropathy group and 31 out of 54 in the severe CAN group. Postural giddiness was found in about 57 % of the CAN patients.

The incidence of gastroparesis was higher in severe than early autonomic neuropathy group (28 vs 4) [$p<0.001$, statistically highly significant].

Abnormalities in sweating was very uncommon only about 5 %. The incidence of nocturnal diarrhoea was also only about 4%

It was found that the incidence of erectile dysfunction was higher in severe than early autonomic neuropathy group (18 vs 6) [$p<0.001$, statistically highly significant]. In 46 of the 81 patients, the resting heart rate was found to be more than 100. Resting tachycardia was found to be higher in severe than early autonomic neuropathy group (34 vs 12) [$p<0.001$, statistically highly significant].

It was also found that Hba1c was higher in the group with severe CAN. 37 of the 54 patients in the severe group vs 8 out of 27 in the early cardiac autonomic neuropathy group

The presence of elevated FBS (>130) was higher in severe than early autonomic neuropathy group (44 vs 14) [$p<0.001$, statistically highly significant].

PPBS was found to be (>200) higher in severe than early autonomic neuropathy group (40 vs 16) [p<0.001, statistically highly significant]. The incidence of QTc prolongation (>440 msec) was higher in severe than early autonomic neuropathy group (43 vs 9) [p<0.001, statistically highly significant]. Heart rate variability in standing was lower in severe than early autonomic neuropathy (34 vs 0) [p<0.001, statistically highly significant].

In deep breath test, severe autonomic neuropathy had lesser beats/ min. [p<0.001, statistically highly significant]. In HR response to Valsalva, severe autonomic neuropathy has lesser response than early neuropathy [p<0.001, statistically highly significant].

In DBPV during hand grip, severe autonomic neuropathy has lesser diastolic blood pressure than early neuropathy [p<0.001, statistically highly significant].

In score of fall in SBP, severe autonomic neuropathy had higher fall than early neuropathy [p<0.001, statistically highly significant].

In 81 cases of CAN, 52 of them had QT prolongation. In 54 cases of severe CAN, 43 of them had QT prolongation. QT prolongation is 82.7% sensitive and 62.1% specific in detecting severity of CAN.

Age distribution of the participants

The mean age of the participants in 54.5 years (S.D=4.8).

AGE		
N	Valid	150
	Missing	0
Mean		54.573
Median		55.000
Std. Deviation		4.8596
Minimum		44.0
Maximum		64.0

Table 1: Age distribution of the participants

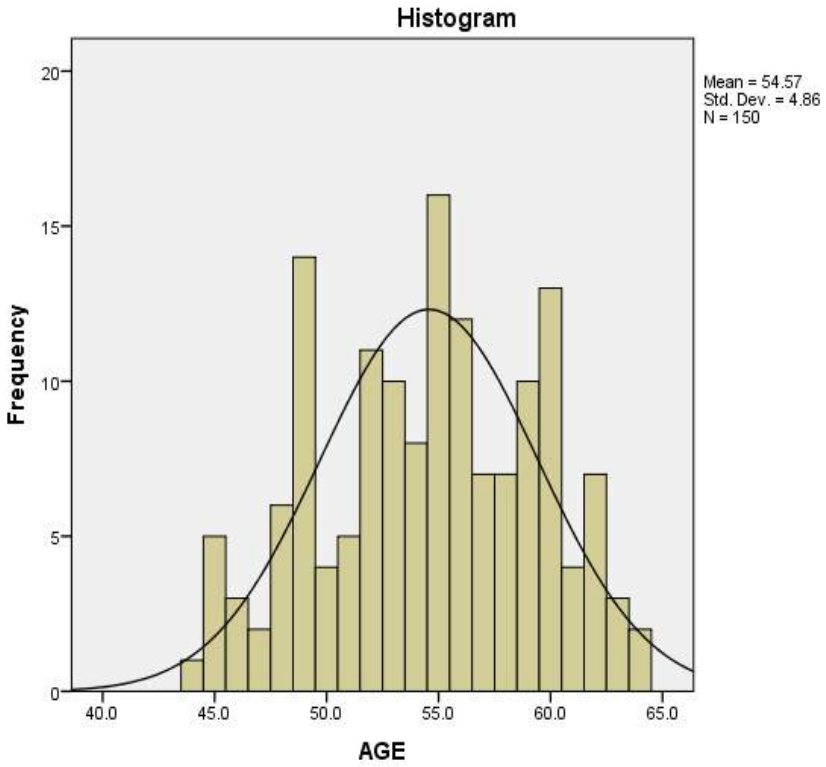

Figure 1: Age distribution of the participants

Gender distribution of the participants

Majority of them were males (n=88, 58.7%).

SEX		Frequency	Percent
	Female	62	41.3
	Male	88	58.7
	Total	150	100.0

Table 2: Gender distribution of the participants

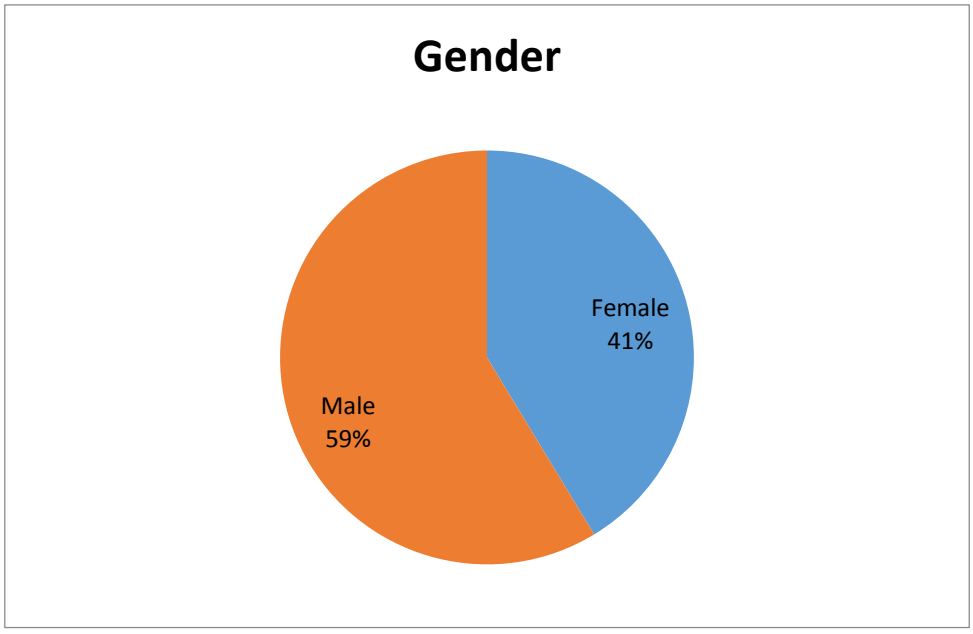

Figure 2: Gender distribution of the participants

Out of 150 patients, 46% (n=69) did not have cardiac autonomic neuropathy whereas 54% (n=81) had cardiac autonomic neuropathy. Out of those 81 subjects, 54 had severe autonomic neuropathy and 27 had early autonomic neuropathy.

Cardiac Autonomic Neuropathy	Frequency	Percent
No Autonomic Neuropathy	69	46.0
Early Autonomic Neuropathy	27	18.0
Severe Autonomic Neuropathy	54	36.0
Total	150	100.0

Table 3: Incidence of Cardiac Autonomic Neuropathy

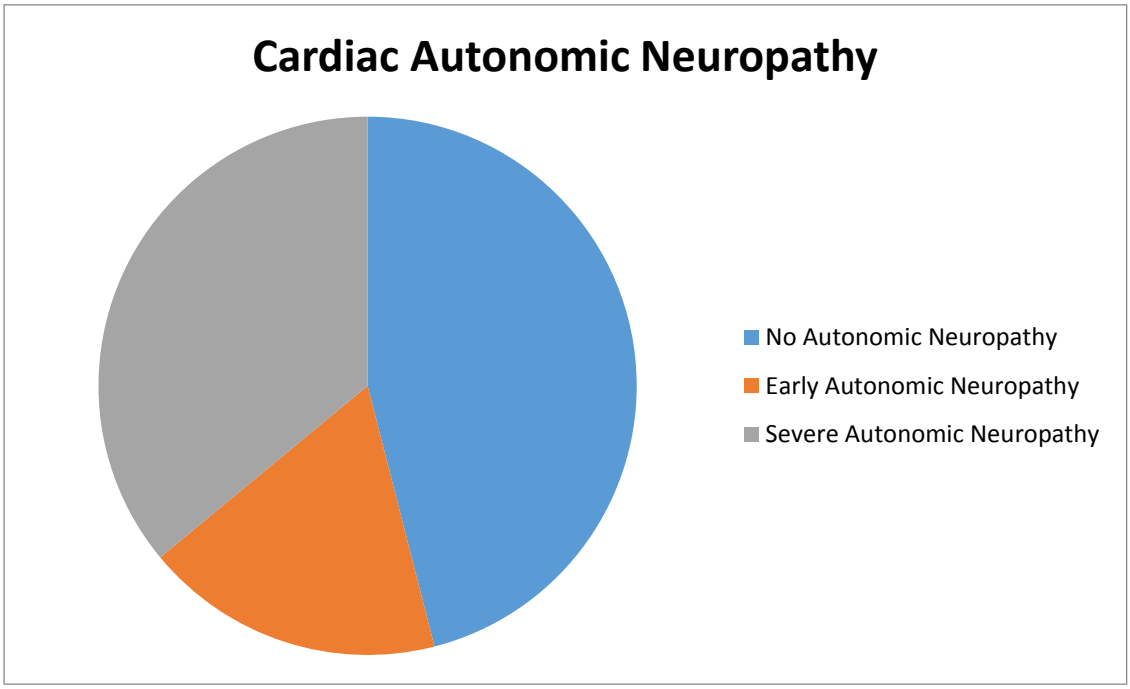

Figure 3: Incidence of Cardiac Autonomic Neuropathy

Comparison of age with severity of Cardiac Autonomic Neuropathy

Comparison of age with severity of Cardiac Autonomic Neuropathy shows that the mean age was higher in severe than early autonomic

neuropathy (57.2 years vs 55.7 years) [p<0.001, statistically highly significant].

	Cardiac Autonomic Neuropathy	N	Mean	Standard Deviation
AGE	No Autonomic Neuropathy	69	52.014	4.8704
	Early Autonomic Neuropathy	27	55.704	3.5390
	Severe Autonomic Neuropathy	54	57.278	3.6312
	Total	150		

Kruskal-Wallis Test	
	AGE
Chi-Square	35.889
df	2
Asymp. Sig.	.000

Table 4: Comparison of age with severity of Cardiac Autonomic Neuropathy

Comparison of gender with severity of Cardiac Autonomic Neuropathy

Gender had no impact on the severity of cardiac autonomic neuropathy (p>0.05)

		Cardiac Autonomic Neuropathy			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
SEX	Female	27	10	25	62
	Male	42	17	29	88
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	.892[a]	2	.640
Likelihood Ratio	.890	2	.641
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 11.16.			

Table 5: Comparison of gender with severity of Cardiac Autonomic Neuropathy

Comparison of duration of DM with severity of Cardiac Autonomic Neuropathy

Comparison of duration of DM with severity of Cardiac Autonomic Neuropathy showed that longer duration is associated with higher severity of neuropathy ($p<0.001$).

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
Duration of Diabetes Mellitus	Less Than 5 Years	45	3	3	51
	5-10 Years	15	15	22	52
	More Than 10 Years	9	9	29	47
Total		69	27	54	150

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	60.113[a]	4	.000
Likelihood Ratio	64.884	4	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 8.46.			

Table 6: Comparison of duration of DM with severity of Cardiac Autonomic Neuropathy

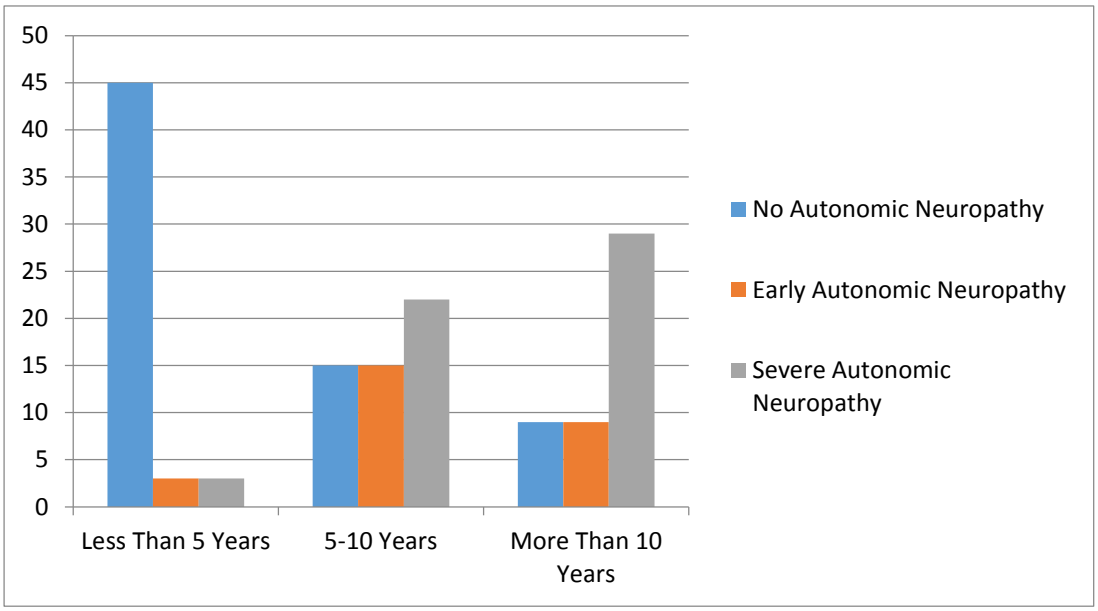

Figure 4: Comparison of duration of DM with severity of Cardiac Autonomic Neuropathy

Comparison of postural giddiness with severity of Cardiac Autonomic Neuropathy

The incidence of postural giddiness was higher in severe than early autonomic neuropathy group (31 vs 8) [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
H/O POSTURAL GIDDINESS	NO	69	19	23	111
	YES	0	8	31	39
Total		69	27	54	150

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	52.114[a]	2	.000
Likelihood Ratio	65.431	2	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 7.02.			

Table 7: Comparison of postural giddiness with severity of Cardiac Autonomic Neuropathy

Comparison of gastro paresis with severity of Cardiac Autonomic Neuropathy

The incidence of gastro paresis was higher in severe than early autonomic neuropathy group (28 vs 4) [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
GASTROPARESIS	Absent	69	23	26	118
	Present	0	4	28	32
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	49.364[a]	2	.000
Likelihood Ratio	58.064	2	.000
No of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.76.			

Table 8: Comparison of gastroparesis with severity of Cardiac Autonomic Neuropathy

Comparison of sweating abnormalities with severity of Cardiac Autonomic Neuropathy

The incidence of sweating abnormalities was higher in severe than early autonomic neuropathy group (6 vs 1) [p>0.05, statistically not significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
SWEATING ABNORMALITES	Absent	69	26	48	143
	Present	0	1	6	7
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	8.475[a]	2	.614
Likelihood Ratio	10.346	2	.006
N of Valid Cases	150		
a. 3 cells (50.0%) have expected count less than 5. The minimum expected count is 1.26.			

Table 9: Comparison of sweating abnormalities with severity of Cardiac Autonomic Neuropathy

Comparison of nocturnal diarrhoea with severity of Cardiac Autonomic Neuropathy

The incidence of nocturnal diarrhea was higher in severe than early autonomic neuropathy group (6 vs 0) [p>0.05, statistically not significant].

		CAN SCORE			**Total**
		No Autonomic Neuropathy	**Early Autonomic Neuropathy**	**Severe Autonomic Neuropathy**	
NOCTURNAL DIARRHOEA	Absent	69	27	48	144
	Present	0	0	6	6
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	13.054[a]	4	.511
Likelihood Ratio	14.921	4	.005
N of Valid Cases	150		
a. 6 cells (66.7%) have expected count less than 5. The minimum expected count is .18.			

Table 10: Comparison of nocturnal diarrhoea with severity of Cardiac Autonomic Neuropathy

Comparison of erectile dysfunction with severity of Cardiac Autonomic Neuropathy

The incidence of erectile dysfunction was higher in severe than early autonomic neuropathy group (18 vs 6) [p<0.001, statistically highly significant].

		CAN SCORE			**Total**
		No Autonomic Neuropathy	**Early Autonomic Neuropathy**	**Severe Autonomic Neuropathy**	
H/O ERECTILE DYSFUNCTION	Absent	69	21	36	126
	Present	0	6	18	24
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	25.992[a]	2	.000
Likelihood Ratio	34.553	2	.000
N of Valid Cases	150		
a. 1 cells (16.7%) have expected count less than 5. The minimum expected count is 4.32.			

Table 11: Comparison of erectile dysfunction with severity of Cardiac Autonomic Neuropathy

Comparison of resting tachycardia with severity of Cardiac Autonomic Neuropathy

The incidence of resting tachycardia was higher in severe than early autonomic neuropathy group (34 vs 12) [p<0.001, statistically highly significant].

		CAN SCORE			**Total**
		No Autonomic Neuropathy	**Early Autonomic Neuropathy**	**Severe Autonomic Neuropathy**	
Pulse	Less than 100	63	15	20	104
	More than 100	6	12	34	46
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	59.420[a]	2	.000
Likelihood Ratio	76.638	2	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 8.28.			

Table 12: Comparison of pulse with severity of Cardiac Autonomic Neuropathy

Comparison of Hba1C levels with severity of Cardiac Autonomic Neuropathy

The incidence of poor glycemic control (Hba1C> 7.5) was higher in severe than early autonomic neuropathy group (37 vs 8) [p<0.001, statistically highly significant].

		CAN SCORE			**Total**
		No Autonomic Neuropathy	**Early Autonomic Neuropathy**	**Severe Autonomic Neuropathy**	
HBA1C	5.5-6.5	49	4	1	54
	6.-7.5	17	15	16	48
	>7.5	3	8	37	48
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	89.341[a]	4	.000
Likelihood Ratio	101.871	4	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 8.64.			

Table 13: Comparison of HBa1C levels with severity of Cardiac Autonomic Neuropathy

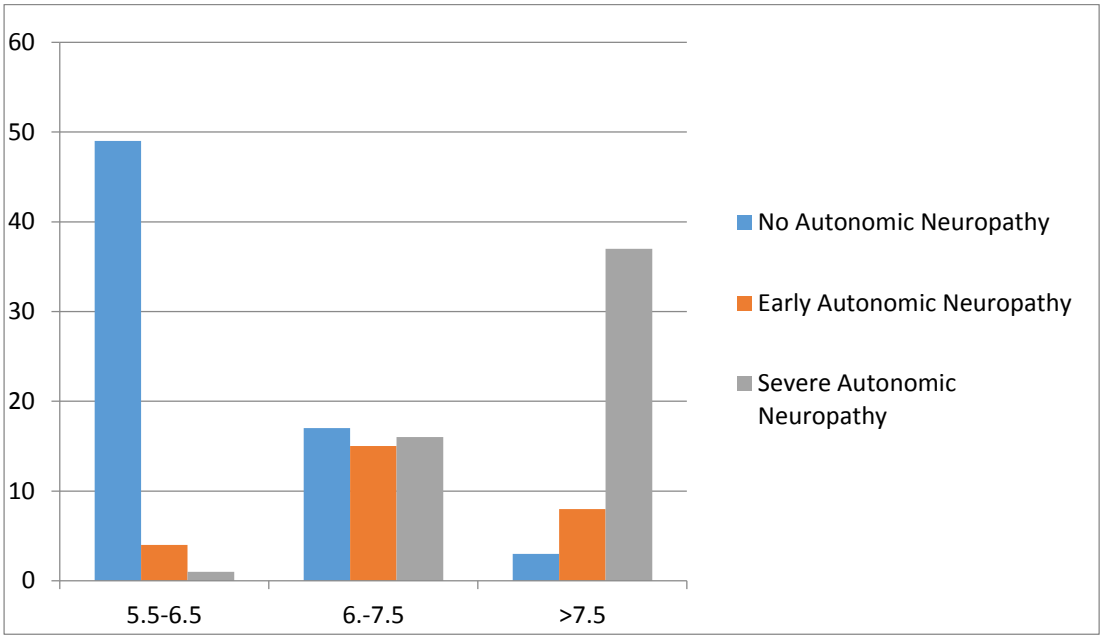

Figure 4: Comparison of Hba1C levels with severity of Cardiac Autonomic Neuropathy

Comparison of FBS levels with severity of Cardiac Autonomic Neuropathy

The incidence of elevated FBS (>130) was higher in severe than early autonomic neuropathy group (44 vs 14) [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
FBS (mg/dl)	<130	57	13	10	80
	>130	12	14	44	70
Total		69	27	54	150

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	50.349[a]	2	.000
Likelihood Ratio	54.373	2	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 12.60.			

Table 14: Comparison of FBS levels with severity of Cardiac Autonomic Neuropathy

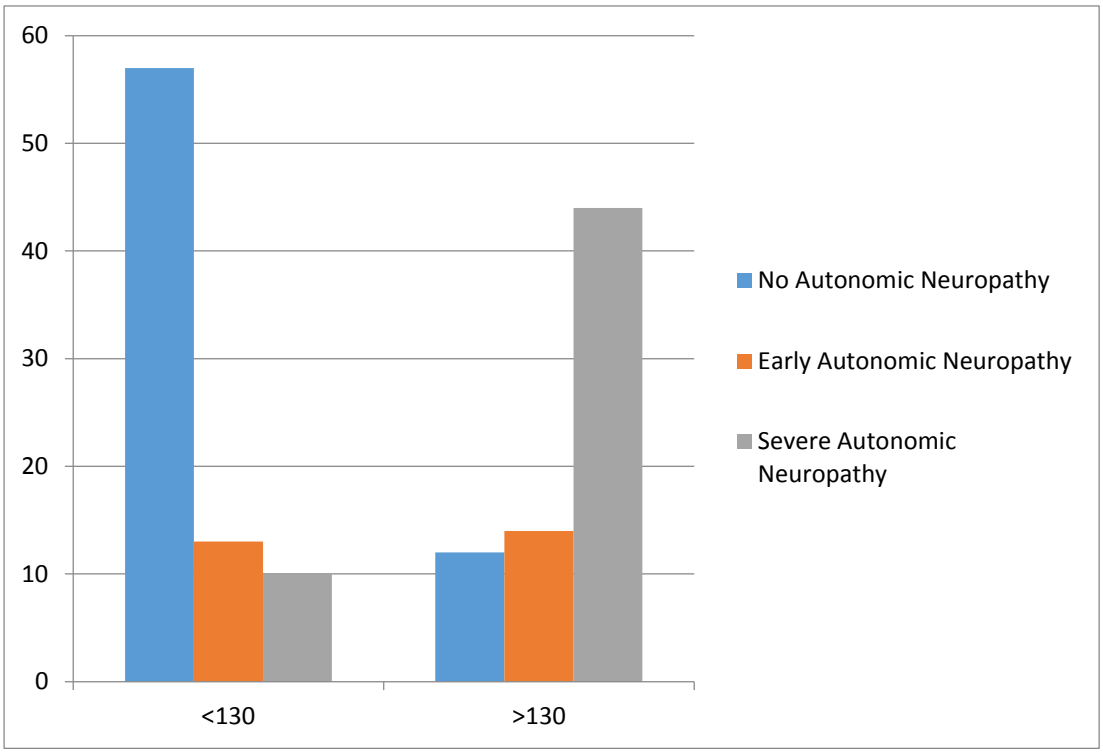

Figure 5: Comparison of FBS levels with severity of Cardiac Autonomic Neuropathy

Comparison of PPBS levels with severity of Cardiac Autonomic Neuropathy

The incidence of elevated PPBS (>200) was higher in severe than early autonomic neuropathy group (40 vs 16) [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
PPBS (mg/dl)	<200	48	11	14	73
	>200	21	16	40	77
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	23.920[a]	2	.000
Likelihood Ratio	24.731	2	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 13.14.			

Table 15: Comparison of PPBS levels with severity of Cardiac Autonomic Neuropathy

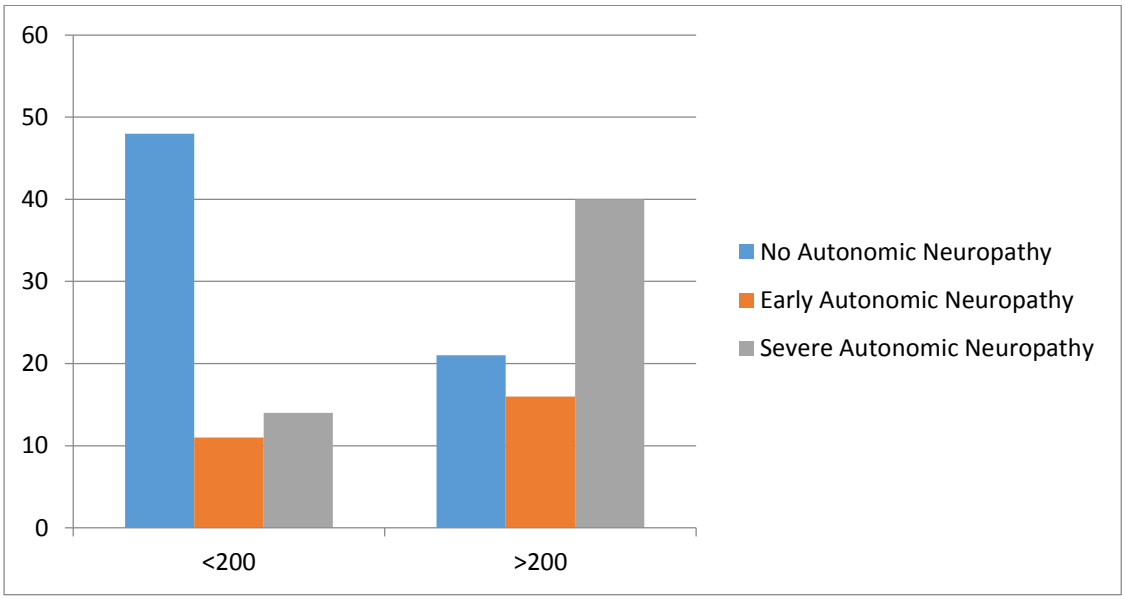

Figure 6: Comparison of PPBS levels with severity of Cardiac Autonomic Neuropathy

Comparison of QTc Interval with severity of Cardiac Autonomic Neuropathy

The incidence of QTc prolongation (>440 msec) was higher in severe than early autonomic neuropathy group (43 vs 9) [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
QTC INTERVAL	<440 msec	67	18	11	96
	>440 msec	2	9	43	54
Total		69	27	54	150

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	84.835[a]	2	.000
Likelihood Ratio	104.642	2	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 9.36.			

Table 16: Comparison of QTc Inteval with severity of Cardiac Autonomic Neuropathy

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
HR IN STANDING	>=1.04	69	8	0	77
	1.01-1.03	0	19	20	39
	<=1	0	0	34	34
Total		69	27	54	150

Comparison of HR in standing with severity of Cardiac Autonomic Neuropathy

Heart rate in standing was lower in sever than early autonomic neuropathy (34 vs 0) [p<0.001, statistically highly significant].

Chi-Square Tests			
	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	163.392[a]	4	.000
Likelihood Ratio	204.690	4	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.12.			

Table 17: Comparison of HR in standing with severity of Cardiac Autonomic Neuropathy

Comparison of Deep Breath Test with severity of Cardiac Autonomic Neuropathy

In deep breath test, severe autonomic neuropathy had lesser beats/ min. [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
DEEP BREATH TEST	>15 beats per minute	69	10	4	83
	11-14 beats per minute	0	17	22	39
	<10 beats per minute	0	0	28	28
Total		69	27	54	150

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	135.347[a]	4	.000
Likelihood Ratio	164.597	4	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.04.			

Table 18: Comparison of Deep Breath Test with severity of Cardiac Autonomic Neuropathy

Comparison of HR response to Valsalva with severity of Cardiac Autonomic Neuropathy

In HR response to Valsalva, severe autonomic neuropathy has lesser response than early neuropathy [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
HR RESPONSE TO VALSALVA	>1.21	69	15	6	90
	1.11-1.20	0	12	38	50
	<=1.10	0	0	10	10
Total		69	27	54	150

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	104.000[a]	4	.000
Likelihood Ratio	132.074	4	.000
N of Valid Cases	150		

a. 3 cells (33.3%) have expected count less than 5. The minimum expected count is 1.80.

Table 19: Comparison of HR response to Valsalva with severity of Cardiac Autonomic Neuropathy

Comparison of DBPV during hand grip to Valsalva with severity of Cardiac Autonomic Neuropathy

In DBPV during hand grip, severe autonomic neuropathy has lesser presure than early neuropathy [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
DBPV DURING HAND GRIP	>16 mm Hg	68	16	3	87
	11-15 mm Hg	1	11	51	63
Total		69	27	54	150

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	107.564[a]	2	.000
Likelihood Ratio	133.963	2	.000
N of Valid Cases	150		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 11.34.			

Table 20: Comparison of DBPV during hand grip to Valsalva with severity of Cardiac Autonomic Neuropathy

Comparison of fall in SBP score during hand grip to Valsalva with severity of Cardiac Autonomic Neuropathy

In score of fall in SBP, severe autonomic neuropathy had higher fall than early neuropathy [p<0.001, statistically highly significant].

		CAN SCORE			Total
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
SCORE OF FALL IN SBP	<10 mm Hg	61	2	0	63
	10-29 mm Hg	8	24	27	59
	>30 mm Hg	0	1	27	28
Total		69	27	54	150

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	142.189[a]	4	.000
Likelihood Ratio	166.378	4	.000
N of Valid Cases	150		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.04.

Table 21: Comparison of fall in SBP score during hand grip to Valsalva with severity of Cardiac Autonomic Neuropathy

Comparison of fall in QT prolongation with incidence of Cardiac Autonomic Neuropathy

In 81 cases of CAN, 52 of them had QT prolongation.

	CAN present	CAN absent	Total
QT prolonged	52	0	52
QT normal	29	69	98
Total	81	69	150

Table 22: Comparison of fall in QT prolongation with incidence of Cardiac Autonomic Neuropathy

CAN score severity with QT prolongation

	CAN Severe	CAN Non severe	Total
QT prolonged	43	9	52
QT normal	11	18	29
Total	54	27	81

In 54 cases of severe CAN, 43 of them had QT prolongation. QT prolongation is 82.7% sensitive and 62.1% specific in detecting severity of CAN

Table 23: CAN score severity with QT prolongation

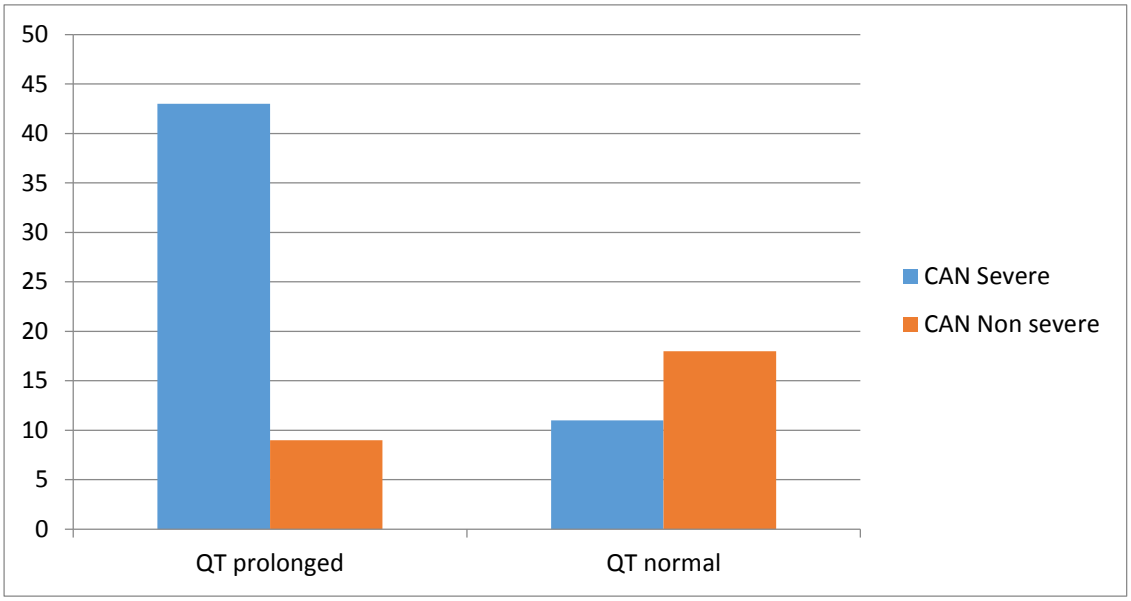

Figure 8: CAN score severity with QT prolongation

Sensitivity and specificity of QT prolongation in predicting severity of Cardiac Autonomic Neuropathy

	Disease				
Test	**Present**	**n**	**Absent**	**n**	**Total**
Positive	True Positive	a= 43	False Positive	c= 11	a + c = **54**
Negative	False Negative	b= 9	True Negative	d= 18	b + d = **27**
Total		a + b = **52**		c + d = **29**	

Statistic	Value	95% CI
Sensitivity	82.69%	69.67% to 91.77%
Specificity	62.07%	42.26% to 79.31%
Positive Likelihood Ratio	2.18	1.35 to 3.53
Negative Likelihood Ratio	0.28	0.14 to 0.54
Disease prevalence (*)	64.20%	52.77% to 74.55%
Positive Predictive Value (*)	79.63%	70.71% to 86.36%
Negative Predictive Value (*)	66.67%	50.86% to 79.44%
Accuracy (*)	75.31%	64.47% to 84.22%

Table 24: Sensitivity and specificity of QT prolongation in predicting severity of Cardiac Autonomic Neuropathy

Discussion

DISCUSSION

The results of this study illustrate the fact that cardiac autonomic dysfunction is common in diabetic patients and its prevalence increases with duration of diabetes. Similar results have been reported in previous studies conducted in India and other countries.

Jayaprasad Narayana Pillai et al reported in their study the association between cardiac autonomic neuropathy and QTc interval. They found that prolongation of QTc interval correlated with the severity of CAN. In this study, among the study population, 42% had severe autonomic neuropathy and 24% had early autonomic neuropathy. Mean heart rate was significantly more in patients with autonomic neuropathy than those without neuropathy. The results of this study are comparable to our study with 18 % of patients with early cardiac autonomic neuropathy and 36% of the patients had severe autonomic neuropathy.

Pappachan J M et al studied the prevalence the CAN among 100 type 1 and type 2 diabetes mellitus, in south India assessed by the five autonomic function tests by Ewing's methodology. The prevalence of CAN was 60% which is comparable to the results obtained in this study (54%).

Pop Busui R et al reported in their study that CAN predisposes to sudden cardiac death and cardiac arrhythmias in diabetics.

Andersen ST, Witte DR et al assessed the risk factors and the course of progression of cardiac autonomic neuropathy in type 2 diabetes.

Benichou T, Pereira et al studied the effects of heart rate variability in type 2 diabetics. Heart Rate Variability was found to be decreased in patients with CAN.

Bhati P, Shenoy S reported that exercise training leads to positive improvements in autonomic function of type 2 diabetes patients.

The association between prolonged QT interval and sudden cardiac death was reported by Ninkovic VM et al in their study.

M Veglio et al stated that QT interval is a simple method in predicting cardiac autonomic dysfunction in diabetes.

Conclusion

CONCLUSION

Cardiac autonomic neuropathy is a dreaded complication of diabetes mellitus predisposing to sudden cardiac death and myocardial infarction. In this study, following were concluded;

1. The presence of cardiac autonomic neuropathy is independent of gender. It was found that the prevalence of CAN increases with increase in age.

2. Cardiac autonomic neuropathy was highest in the group with diabetes more than 10 years duration. So we can conclude that there is a positive correlation between the duration of diabetes and the occurrence of CAN.

3. Postural giddiness was the most common symptom of CAN in our patients. Nocturnal diarrhoea and sweating abnormalities were the least common.

4. Patients with poor glycemic control had higher incidence of CAN. There was a positive correlation between the FBS, PPBS and the Hba1c levels.

5. In 81 cases of CAN, 52 of them had QT prolongation. In 54 cases of severe CAN, 43 of them had QT prolongation. QT prolongation is 82.7% sensitive and 62.1% specific in detecting severity of CAN.

Limitations

LIMITATIONS

1. Newer techniques for measuring autonomic functions like the computer aided power spectral analysis of heart-rate variability could not be done because of limitations in resources and cost.

2. Serum Magnesium and Serum Calcium which may alter QT interval could not be done as they would add to the cost factor.

3. The patients could not be assessed by Holter monitoring at assess the risk of arrhythmias.

4. Patients could not be followed up to assess the risk of adverse cardiac events.

5. The study was done in a single centre in a single geographic area

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Annexures

PROFORMA

Name: Age/Sex:

I.P. No.: Date of admission:

Age of onset of DM:

Duration of diabetes mellitus:

History of smoking

History of alcohol consumption:

Other comorbidities:

Medications, if any:

History of postural hypotension (giddiness on posture change):

History of erectile dysfunction

History of nocturnal diarrhoea

History of sweating abnormalities

History of previous angina:

General examination:

Pulse

Blood Pressure:

Supine-

Standing-

Cardiovascular autonomic Reflexes testing:

Tests done	**TEST 1**	**TEST 2**	**TEST 3**	**Mean**
Heart rate variability during deep breathing				
Heart rate variability during Valsalva Manuever				
Heart rate response to standing				
BP response to standing				
BP response to sustained hand grip				

Investigations:

- Fasting blood glucose
- Post prandial blood glucose
- Hba1c

Electrocardiogram

- Heart rate
- QRS axis
- QRS duration
- QTc interval

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,CHENNAI -01

INSTITUTIONAL ETHICS COMMITTEE

TITLE OF THE WORK	:	"CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND CORRELATION WITH QTC INTERVAL AND DURATION OF DIABETES - CROSS SECTIONAL STUDY IN A TERTIARY CARE CENTRE IN SOUTH INDIA"
PRINCIPAL INVESTIGATOR	:	DR. S. JAYASREE
DESIGNATION	:	PG IN GENERAL MEDICINE
DEPARTMENT	:	DEPARTMENT OF GENERAL MEDICINE

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 17.02.2021 at the Council Hall, Stanley Medical College, Chennai-1 at 10am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI.

CONSENT FORM

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001
INFORMED CONSENT

"Cardiac autonomic neuropathy in Type 2 Diabetes Mellitus- correlation with the QTc interval and the duration of diabetes-A cross sectional study in a tertiary care centre in South India"

AT GOVERNMENT STANLEY MEDICAL COLLEGE HOSPITAL, CHENNAI.

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/sputum if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer: Name and address Signature/thumb impression: Date:	Witness: Name and address Signature/thumb impression Date:

Investigator Signature and date

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

‘‘Cardiac autonomic neuropathy in Type 2 Diabetes Mellitus- correlation with the QTc interval and the duration of diabetes-A cross sectional study in a tertiary care centre in South India’’.

நான் இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

ஆய்வில் பங்கு எடுத்து போது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களை பற்றி நான் அறிந்துள்ளேன்.

நான் எந்தவொரு வேளையிலும் ஆய்வில் இருந்து திரும்ப முடியும், அதன் பின்னர், நான் வழக்கம் போல் மருத்துவ சிகிச்சை பெற முடியும் என்று புரிந்துகொள்கிறேன்

நான் ஆய்வில் பங்கு எடுத்து பணம் எதையும் பெற முடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை, என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்க கூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்ய போகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்	சாட்சி
பெயர் மற்றும் முகவரி	பெயர் மற்றும் முகவரி
கையொப்பம் / விரல் ரேகை:	கையொப்பம் /
விரல் ரேகை:	

ஆராய்ச்சியாளராக
கையொப்பம் மற்றும் தேதி

Master Chart

S.NO	AGE	SEX	DURATION OF DM	H/O POSTURAL GIDDINESS	GASTROPARESIS	SWEATING ABNORMALITES	NOCTURNAL DIARRHOEA	H/O ERECTILE DYSFUNCTION	PULSE	BP(SUPINE)	BP(STANDING)	SCORE OF FALL IN SBP	DBPV DURING HAND GRIP	HR RESPONSE TO VALSALVA	DEEP BREATH TEST	HR IN STANDING	QTC INTERVAL	CAN SCORE	HBA1C	FBS	PPBS
1	52	M	A	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	1	1	1
2	58	F	C	YES	B	A	A	A	B	130/80	100/70	3	2	3	3	3	2	C	3	2	2
3	44	M	A	NO	A	A	A	A	A	110/70	110/65	1	1	1	1	1	1	A	1	1	1
4	56	M	B	NO	B	A	A	A	B	110/70	100/60	2	1	2	2	1	1	B	3	2	2
5	50	F	A	NO	A	A	A	A	A	120/80	110/80	1	1	1	1	1	1	A	1	1	1
6	62	M	C	NO	A	A	A	A	A	130/80	110/80	2	1	1	1	1	1	A	1	1	2
7	55	F	C	YES	B	B	A	A	B	130/90	100/70	3	2	2	2	3	2	C	2	2	2
8	48	M	B	NO	A	A	A	A	A	110/70	100/70	1	1	1	1	1	1	A	1	1	1
9	60	M	A	NO	B	A	A	B	B	120/80	100/60	2	2	2	3	3	2	C	3	2	2
10	55	F	B	NO	A	A	A	A	A	110/70	110/60	1	1	1	1	1	1	A	2	1	2
11	53	F	B	NO	A	A	A	A	A	110/80	110/70	1	1	1	1	1	1	A	1	1	1
12	59	M	B	YES	A	B	B	B	B	120/80	100/60	2	2	2	1	3	2	C	3	2	2
13	45	M	A	NO	A	A	A	A	A	110/70	110/65	1	1	1	1	1	1	A	1	1	1
14	56	F	C	YES	B	B	A`	A	B	130/90	100/65	3	2	2	2	3	2	C	3	2	2
15	59	M	C	NO	A	A	A	B	A	120/70	100/70	2	2	1	1	2	2	C	2	2	1
16	48	M	A	NO	A	A	A	A	A	120/70	120/80	1	1	1	1	1	1	A	1	1	1
17	55	M	A	YES	A	A	B	B	B	130/90	100/70	3	2	2	1	2	2	C	3	2	2
18	49	F	A	NO	A	A	A	A	A	120/80	110/70	1	1	1	1	1	1	A	1	1	2
19	52	F	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	2	1	2
20	50	F	A	NO	A	A	A	A	A	110/70	100/70	2	1	1	1	1	1	A	1	1	1
21	58	F	B	YES	B	B	A	A	A	120/70	100/70	2	1	2	1	2	2	B	3	2	2
22	49	F	B	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	1	1	1
23	52	M	B	YES	B	A	A	B	A	120/70	100/70	2	2	2	2	2	2	C	2	2	1
24	46	M	B	NO	A	A	A	A	A	120/70	115/70	1	1	1	1	1	1	A	1	1	1
25	53	F	B	NO	A	A	B	A	B	120/80	100/70	2	2	3	3	3	1	C	3	2	2
26	61	F	C	YES	A	A	A	A	B	130/80	100/70	3	2	3	2	3	2	C	3	2	2
27	59	M	C	NO	A	A	A	A	A	120/80	115/70	1	2	1	1	1	1	A	1	1	1
28	55	F	C	NO	A	A	A	A	A	130/80	110/80	2	1	1	2	2	1	B	3	2	2
29	60	M	C	YES	B	A	A	B	B	120/80	90/60	3	2	3	3	3	2	C	3	2	1
30	59	M	C	NO	B	A	A	B	A	120/80	100/70	2	2	2	2	2	1	C	3	2	1
31	49	F	A	NO	A	A	A	A	A	120/80	100/70	2	1	2	1	2	1	B	2	1	2
32	53	M	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
33	45	F	A	NO	A	A	A	A	A	120/80	110/80	2	1	1	1	1	1	A	1	1	1
34	59	M	A	YES	A	A	A	B	B	130/90	100/70	3	2	3	2	3	1	C	3	2	2
35	52	F	A	NO	A	A	A	A	A	120/80	100/70	2	2	2	1	1	2	B	2	1	2

36	55	M	B	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	1	1	1
37	58	M	B	NO	A	A	A	A	B	130/80	110/80	2	2	1	2	1	1	B	2	2	1
38	49	F	B	NO	A	A	A	A	A	130/80	120/80	2	1	1	1	1	1	A	1	1	1
39	57	M	B	YES	B	A	A	B	B	120/70	90/60	3	2	2	3	3	2	C	2	1	2
40	60	M	B	NO	B	A	A	A	A	120/80	100/70	2	1	2	2	2	1	C	3	2	2
41	49	M	B	YES	B	A	A	A	B	120/80	100/70	2	1	2	2	2	2	C	3	2	2
42	55	F	B	NO	A	A	A	A	B	110/70	90/60	2	1	1	2	2	1	B	2	1	1
43	54	M	B	YES	B	A	A	A	A	120/80	100/70	2	2	1	2	2	2	C	3	2	1
44	60	F	B	YES	A	A	A	A	B	130/80	100/70	3	2	3	3	3	2	C	3	2	2
45	52	F	B	NO	B	B	A	A	B	120/70	90/60	3	2	2	3	3	2	C	2	1	2
46	63	M	C	YES	B	A	A	A	B	130/80	100/70	3	2	2	3	3	2	C	3	2	2
47	58	M	C	NO	A	A	A	B	A	120/80	100/70	2	2	2	3	3	2	C	2	2	1
48	60	M	C	NO	B	A	A	B	B	130/80	110/80	2	2	2	2	2	1	C	2	1	1
49	55	M	C	NO	A	A	A	A	A	120/70	110/70	2	1	1	1	1	1	A	1	1	1
50	62	M	C	YES	A	A	A	A	A	110/70	90/60	2	2	2	1	1	1	B	2	1	2
51	55	M	C	NO	A	A	A	B	B	110/70	100/60	2	2	2	1	1	2	B	3	2	2
52	59	F	C	YES	A	A	A	A	B	120/70	90/60	3	2	2	2	3	2	C	3	2	1
53	53	F	C	NO	B	A	A	A	A	110/70	95/60	2	2	3	2	2	2	C	1	1	1
54	59	F	C	YES	A	A	A	A	B	120/80	90/60	3	2	2	3	3	2	C	3	2	2
55	58	F	C	YES	B	A	A	A	A	130/80	100/70	3	2	3	3	3	2	C	3	2	2
56	62	M	C	NO	A	A	A	A	A	120/80	100/60	2	1	1	2	2	2	B	2	2	1
57	60	M	C	NO	A	A	A	A	A	110/70	100/70	2	1	1	1	1	1	A	1	1	1
58	62	F	C	NO	A	A	A	A	A	130/80	125/80	1	1	1	1	1	1	A	1	1	1
59	57	F	C	YES	B	A	A	A	B	120/80	100/70	2	2	2	1	2	1	B	2	1	2
60	55	F	C	NO	A	A	A	A	A	110/70	90/60	2	2	1	1	2	2	C	3	2	1
61	45	M	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	2	1	2
62	53	M	A	NO	A	A	A	A	A	100/70	100/70	1	1	1	1	1	1	A	1	1	1
63	49	M	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	1	1	1
64	60	M	A	NO	A	A	A	A	A	110/80	110/70	1	1	1	1	1	1	A	1	1	1
65	50	M	A	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	3	2	2
66	51	M	A	NO	A	A	A	A	A	120/80	110/80	1	1	1	1	1	1	A	2	1	2
67	49	M	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
68	55	M	A	NO	A	A	A	A	A	120/70	110/70	2	1	1	1	1	1	A	2	2	2
69	47	M	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
70	62	M	A	NO	A	A	A	A	A	120/70	115/70	1	1	1	1	1	1	A	1	1	1
71	56	F	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	2	2	2
72	48	F	A	NO	A	A	A	A	A	120/70	115/70	1	1	1	1	1	1	A	1	1	2
73	54	F	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
74	46	F	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	1	2	1
75	48	F	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
76	52	F	A	NO	A	A	A	A	A	120/70	115/70	1	1	1	1	1	1	A	2	2	1

77	60	M	B	YES	B	A	A	B	B	135/80	110/70	2	2	1	3	3	2	C	3	2	2
78	53	M	B	NO	A	A	A	A	A	120/80	100/70	2	1	2	3	3	1	C	2	2	1
79	55	M	B	NO	A	A	A	B	B	110/70	90/60	2	2	3	3	3	2	C	3	2	2
80	62	M	B	NO	B	A	A	B	A	120/80	90/60	3	2	2	3	3	2	C	3	2	2
81	53	M	B	YES	B	A	A	A	B	110/70	90/60	2	2	2	3	2	1	C	3	1	2
82	52	M	B	YES	A	A	B	B	B	120/80	100/70	2	2	2	3	3	2	C	2	1	2
83	56	F	B	NO	A	A	A	A	B	130/80	100/70	3	2	1	2	2	2	C	3	2	2
84	52	F	B	YES	B	A	A	A	A	120/80	100/70	2	2	2	3	3	1	C	2	2	2
85	64	F	B	YES	B	A	A	A	A	130/80	100/70	3	2	2	2	2	2	C	2	1	2
86	56	F	B	NO	A	A	A	A	B	120/80	100/60	2	2	2	3	3	2	C	3	1	2
87	54	F	B	YES	A	A	A	A	A	130/80	100/70	3	2	2	2	2	2	C	3	2	2
88	61	F	B	YES	A	B	A	A	B	130/70	100/70	3	2	2	2	3	2	C	3	1	2
89	52	F	B	NO	A	A	B	A	B	120/80	90/60	3	2	2	3	3	2	C	3	2	2
90	54	M	B	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	1	1	2
91	55	M	B	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	2	1	2
92	49	M	B	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	1	1	2
93	57	M	B	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
94	59	F	B	YES	B	A	A	A	B	130/70	110/70	2	1	1	2	2	2	B	3	2	2
95	51	F	B	NO	A	A	A	A	A	110/70	90/60	2	2	1	2	1	1	B	2	2	1
96	49	F	B	NO	A	A	A	A	B	110/80	95/60	2	1	1	2	2	2	B	2	2	1
97	51	M	B	NO	A	A	A	B	A	120/80	100/70	2	2	1	2	2	1	B	3	2	2
98	56	M	B	YES	A	A	A	A	B	110/70	90/60	2	1	2	1	2	1	B	2	1	2
99	61	M	B	YES	A	A	A	B	A	120/70	90/60	3	1	1	1	2	1	B	3	2	2
100	54	M	B	NO	A	A	A	A	A	110/70	90/60	2	1	1	2	2	2	B	2	1	1
101	57	M	B	NO	A	A	A	B	B	120/70	100/70	2	2	1	2	1	1	B	1	1	1
102	55	M	B	NO	A	A	A	B	A	120/80	100/70	2	2	1	2	2	1	B	3	2	2
103	56	M	B	YES	A	A	A	A	B	110/70	90/60	2	1	2	1	2	1	B	2	1	1
104	45	M	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	2	2	1
105	53	M	A	NO	A	A	A	A	A	100/70	100/70	1	1	1	1	1	1	A	1	1	2
106	49	M	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	1	1	1
107	60	M	A	NO	A	A	A	A	A	110/80	110/70	1	1	1	1	1	1	A	1	1	1
108	50	M	A	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	3	2	2
109	51	M	A	NO	A	A	A	A	A	120/80	110/80	1	1	1	1	1	1	A	2	2	1
110	49	M	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
111	55	M	A	NO	A	A	A	A	A	120/70	110/70	2	1	1	1	1	1	A	2	1	2
112	47	M	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
113	62	M	A	NO	A	A	A	A	A	120/70	115/70	1	1	1	1	1	1	A	1	1	1
114	56	F	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	2	1	2
115	48	F	A	NO	A	A	A	A	A	120/70	115/70	1	1	1	1	1	1	A	1	1	1
116	54	F	A	NO	A	A	A	A	A	110/70	90/60	2	1	1	2	2	1	B	1	1	1
117	46	F	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	1	1	1

118	48	F	A	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
119	52	F	A	NO	A	A	A	A	A	120/70	115/70	1	1	1	1	1	1	A	2	2	1
120	45	F	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	2	1	2
121	53	F	A	NO	A	A	A	A	A	100/70	100/70	1	1	1	1	1	1	A	1	1	1
122	49	F	A	NO	A	A	A	A	A	110/70	105/70	1	1	1	1	1	1	A	1	1	1
123	60	F	A	NO	A	A	A	A	A	110/80	110/70	1	1	1	1	1	1	A	1	1	1
124	54	M	B	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	1	1	1
125	55	M	B	YES	A	A	A	A	A	110/70	90/60	1	1	1	2	2	1	B	2	2	1
126	49	M	B	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	1	1	1
127	57	M	B	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	1	1	1
128	49	M	B	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	2	2	1
129	63	M	C	YES	B	A	A	B	B	130/80	100/70	3	2	2	3	3	2	C	3	2	2
130	58	M	C	NO	B	A	A	A	A	120/80	100/70	2	2	2	3	3	2	C	2	2	2
131	60	M	C	NO	A	B	A	A	B	130/80	110/80	2	2	2	2	2	1	C	3	2	2
132	55	M	C	NO	A	A	A	A	A	120/80	115/80	1	1	1	1	1	1	A	1	1	1
133	59	M	C	NO	A	A	A	A	A	110/80	110/80	1	1	1	1	1	1	A	2	2	2
134	53	M	C	NO	A	A	A	A	B	120/80	100/70	2	1	2	2	1	2	B	2	2	2
135	57	M	C	NO	A	A	A	B	A	110/80	100/70	2	2	1	2	2	1	B	1	1	1
136	56	F	C	NO	A	A	A	A	A	110/70	110/70	1	1	1	1	1	1	A	2	1	2
137	51	F	C	NO	A	A	A	A	A	120/70	115/70	1	1	1	1	1	1	A	3	2	2
138	57	F	C	YES	B	A	A	A	B	130/80	100/70	3	2	2	3	3	2	C	3	2	2
139	56	F	C	NO	B	A	A	A	B	130/80	100/70	3	2	1	2	2	2	C	3	2	2
140	52	F	C	YES	A	A	A	A	A	120/80	100/70	2	2	2	3	3	1	C	2	1	2
141	64	F	C	YES	A	A	A	A	A	130/80	100/70	3	2	2	2	2	2	C	2	2	2
142	56	F	C	NO	A	A	A	A	B	120/80	100/60	2	2	2	3	3	2	C	3	2	2
143	54	F	C	YES	B	A	A	A	A	130/80	100/70	3	2	2	2	2	2	C	3	2	2
144	63	M	C	YES	B	A	A	A	B	130/80	100/70	3	2	2	3	3	2	C	3	2	1
145	58	M	C	NO	A	A	A	B	A	120/80	100/70	2	2	2	3	3	2	C	2	2	1
146	60	M	C	NO	B	A	A	B	B	130/80	110/80	2	2	2	2	2	1	C	2	2	1
147	60	M	C	YES	A	A	B	A	B	120/80	90/60	3	2	3	3	3	2	C	3	2	2
148	59	M	C	NO	A	A	A	A	A	120/80	100/70	2	2	2	2	2	2	C	3	2	2
149	61	M	C	NO	A	A	A	A	A	110/70	90/60	2	2	2	1	2	2	B	2	1	2
150	56	M	C	NO	A	A	A	A	B	130/70	120/80	1	1	2	2	2	1	B	1	1	2

DURATION OF DM	**H/O POSTURAL GIDDINESS**	**GASTROPARESIS**	**SWEATING ABNORMALITES**	**NOCTURNAL DIARRHOEA**
A-LESS THAN 5 YEARS	A-ABSENT	A-ABSENT	A-ABSENT	A-ABSENT
B-5-10 YEARS	B-PRESENT	B-PRESENT	B-PRESENT	B-PRESENT
C-MORE THAN 10 YEARS				
H/O ERECTILE DYSFUNCTION	**PULSE**	**BP(SUPINE)**	**BP(STANDING)**	**SCORE OF FALL IN SBP**
A-ABSENT	A-LESS THAN 100			>30 mm Hg-3
B-PRESENT	B-MORE THAN 100			10-29 mm Hg-2
				<10 mm Hg-1
DBPV DURING HAND GRIP	**HR RESPONSE TO VALSALVA**	**DEEP BREATH TEST**	**HR IN STANDING**	**QTC INTERVAL**
<10 mm Hg-3	<=1.10-3	<10 beats pe	<=1-3	<440 msec-A
11-15 mm Hg-2	1.11-1.20-2	11-14 beats	1.01-1.03-2	>440 msec-B
>16 mm Hg-1	>1.21-1	>15 beaats p	>=1.04-1	
CAN SCORE	**HBA1C**	**FBS**	**PPBS**	
SEVERE AUTONOMIC NI	5.5-6.5-1	<=130 -1	<=200-1	
EARLY AUTONOMIC NEU	6.-7.5-2	>=130-2	>=200-2	
NO AUTONOMIC NEURO	>7.5-3			