A Dissertation on

A STUDY ON PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND USE OF QT_C INTERVAL IN ITS PREDICTION

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032.

In partial fulfilment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE

KILPAUK MEDICAL COLLEGE

CHENNAI – 600 010

APRIL 2017

CERTIFICATE

This is to certify that Dr. **ANJU SURENDRAN .S**, Post -Graduate Student (JULY 2014 TO JUNE 2017) in the Department of General Medicine, **KILPAUK MEDICAL COLLEGE**, Chennai- 600 010, has done this dissertation on "**STUDY ON PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND USE OF QT_C INTERVAL IN ITS PREDICTION**" under my guidance and supervision in partial fulfilment of the regulations laid down by the Tamilnadu Dr.M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2017.

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DECLARATION

I, Dr.ANJU SURENDRAN .S declare that I carried out this work on "**STUDY ON PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN DIABETES MELLITUS AND USE OF QT_C INTERVAL IN ITS PREDICTION**" at Department of Medicine, Government Kilpauk Medical College Hospital during the period of April 2016 to September 2016. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, and diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M.D. Degree examination in General Medicine.

DR.ANJU SURENDRAN .S

ACKNOWLEDGMENTS

I am very much thankful to Prof. **Dr.R.NARAYANA BABU**, THE DEAN, Govt Kilpauk Medical College, Chennai for granting me permission to utilize the facilities of the hospital for the study

I express my profound thanks to my esteemed Professor and Teacher Prof. **Dr.S.Ushalakshmi, MD**.,Professor and HOD of medicine, Govt Kilpauk Medical College Hospital, for encouraging and extending invaluable guidance to perform and complete this dissertation.

I immensely thank our unit chief Prof**.Dr.R.MUTHUSELVAN, M.D.,** Professor of Medicine, Kilpauk Medical College for his constant encouragement and guidance throughout the study.

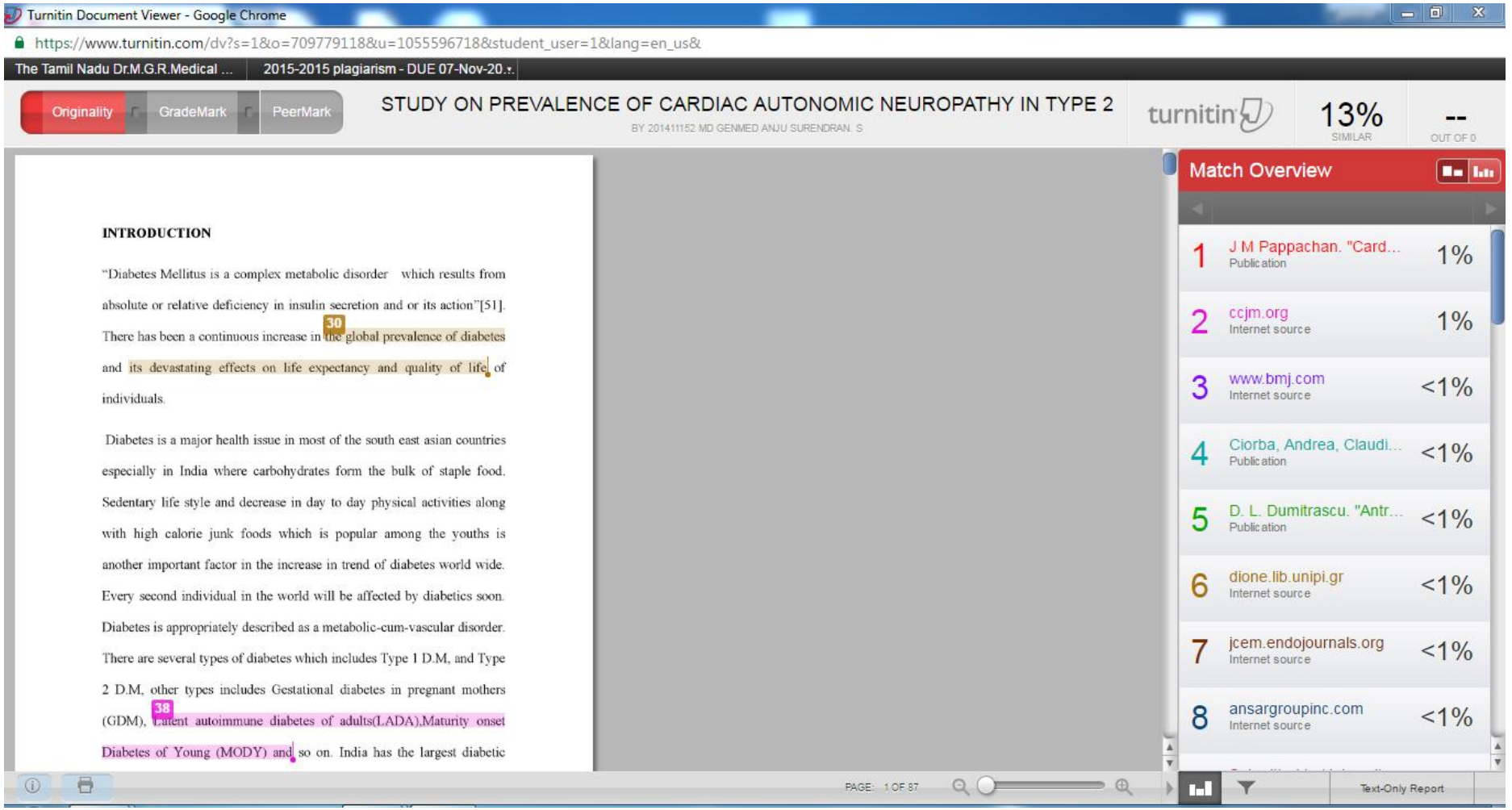
I am also immensely grateful to Prof**. Dr.K.DHANANJAYAN, M.D.,D.C.H.,**Assistant professor of our unit, Department of medicine, Kilpauk Medical College for his valuable suggestion and constant support , encouragement and advice doing this study.

I wish to thank **Dr.KUMARAVEL,M.D.,D.C.H.,**Asssistant Professor of our unit, Department of Medicine, Kilpauk Medical College for guiding and supporting me in doing this study

I sincerely thank the members of Institutional Ethics Committee, Kilpauk Medical College, for approving my dissertation topic. I also

thank Mr.VENKATESAN, statistician for his guidance in analysing the study.

I thank all our Postgraduates, House surgeons and Staff of our Hospital for their contribution in this study. I express my gratitude to all the patients without whose cooperation this study would not have been successful.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INTRODUCTION
"Diabetes Mellitus is a complex metabolic disorder which results from absolute or relative deficiency in insulin secretion and or its action"[51]. There has been a continuous increase in the global prevalence of diabetes and its devastating effects on life expectancy and quality of life of individuals.
Diabetes is a major health issue in most of the south east asian countries especially in India where carbohydrates form the bulk of staple food. Sedentary life style and decrease in day to day physical activities along with high calorie junk foods which is popular among the youths is another important factor in the increase in trend of diabetes world wide. Every second individual in the world will be affected by diabetics soon. Diabetes is appropriately described as a metabolic-cum-vascular disorder. There are several types of diabetes which includes Type 1 D.M, and Type 2 D.M, other types includes Gestational diabetes in pregnant mothers (GDM), Latent autoimmune diabetes of adults(LADA),Maturity onset Diabetes of Young (MODY) and so on. India has the largest diabetic
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CONTENTS

ABBREVIATIONS

ANS	-	Autonomic Nervous System
CAN	-	Cardiac Autonomic Neuropathy
DAN	-	Diabetic Autonomic Neuropathy
DCCT	-	Diabetes Control and Complication Trial
DPP	-	Di Peptidyl Peptidase
ECG	-	Electrocardiogram
E:I	-	Expiration to Inspiration
SBP	-	Systolic Blood Pressure
DBP	-	Diastolic Blood Pressure
GI	-	Gastro Intestinal
HR	-	Heart Rate
HRV	-	Heart Rate Variation
LVDD	-	Left Ventricular Diastolic Dysfunction
MI	-	Myocardial Infraction
PSA	-	Power Spectral Analysis
QSART	-	Quantitative Sudomotor Axon Reflex Test

INTRODUCTION

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Diabetes is a major health issue in most of the South East Asian countries, especially in India where carbohydrates form the bulk of staple food. Sedentary life style and decrease in day to day physical activities along with high calorie junk foods which is popular among the youth is another important factor in the increase in trend of diabetes world wide. Every second individual in the world will be affected by diabetics soon.

Diabetes is appropriately described as a " Metabolic-Cum-Vascular" disorder. There are several types of diabetes which includes Type 1 D.M, and Type 2 D.M, other types includes Gestational diabetes in pregnant mothers (GDM), Latent autoimmune diabetes of adults(LADA),Maturity Onset Diabetes of Young (MODY) and so on.

India has the largest diabetic population in the world and is infamously dubbed as "The Diabetic capital" of the world. According to Indian council of Medical Research (ICMR), India is faced with

galloping diabetes epidemic, approximately more than 70 million patients are affected with diabetes in India and this number is projected to cross beyond hundred million by the year 2030

Diabetic neuropathy is a common complication of diabetes, specifically diabetic autonomic neuropathy, which can affect many systems. Though autonomic dysfunction is common in diabetes, symptomatic autonomic disturbances are less common. Cardiac dysautonomia is associated with resting tachycardia, orthostatic hypotension, painless myocardial ischemia or infarction, cardiac arrhythmias and even sudden cardiac death.

Among all diabetes, Type 2 Diabetes Mellitus accounts for more than 80 percent of diagnosed cases of diabetes cardiac autonomic neuropathy. Cardiovascular autonomic neuropathy (CAN) is one of the serious complications among diabetics. CAN contributes to poor prognosis of coronary artery disease in diabetes .

Early recognition of asymptomatic cardiac dysautonomia helps in delaying or arresting its progression. The autonomic function tests are mostly non invasive and do not require sophisticated equipments Therefore, it has very important clinical and prognostic relevance.

Diabetic patients having regional sympathetic imbalance and QTc interval prolongation are greater risk for arrhythmias[5]. Early in 1980s[5],various studies revealed an association of prolonged QTc interval and cardiovascular autonomic neuropathy. These led to finding the possibility of using simple rapid objective tests for earlier detection of patients having cardiac autonomic neuropathy.

This study was performed to estimate the prevalence of CAN among diabetics in our hospital using simple bedside tests and to study the usefulness of corrected qt interval in diagnosing it.

AIMS AND OBJECTIVES

1. To study the prevalence of Cardiac Autonomic Neuropathy among Type 2 Diabetes Mellitus patients in Government Kilpauk Medical College Hospital,Chennai.

2. To study the use of QTc prolongation in the prediction of cardiac autonomic neuropathy in Type 2 diabetes mellitus (DM) patients in Government Kilpauk Medical College Hospital.

REVIEW OF LITERATURE

Type 2 diabetes is one of the major distressing non-communicable diseases worldwide ,which shows an increasing prevalence especially in developing countries like India. Diabetes is a "Metabolic cum Vascular disorder" causing long term damage and dysfunction, which leads to failure of various organs like kidneys, eyes, heart and blood vessels.

Even after decades of insulin discovery, diabetic patients still have a considerably reduced life expectancy despite a significant decrease in incidence of acute metabolic events like ketoacidosis. This is mainly due to long term macrovascular and microvascular complications. Among non-communicable diseases, growth of diabetes appears to dramatic and worrisome.

"One of the most neglected and underdiagnosed among complications related to diabetes mellitus is cardiovascular autonomic neuropathy. It is a chronic complication of diabetes which involves damage to sympathetic and parasympathetic fibres of heart which results in alteration in control of heart rate and blood pressure"[52]. The clinical symptoms include high heart rate in resting state, fall in BP during standing, decreased tolerance to exercise, altered sweating response , loss of heart rate variation during deep breathing, painless and symptomless

heart attack and even sudden cardiac death..Thus, autonomic dysfunction not only affects daily activities of diabetic individuals , but it may even cause potentially life threatening outcomes.

CHRONIC COMPLICATIONS OF DIABETES

1. **Microvacular**

   A. Eye disease

      - Retinopathy (non proliferative/proliferative)
      - Macular disease

   B. Neuropathy

      - Sensory and motor neuropathy
      - Autonomic neuropathy

   C. Nephropathy

2. **Macrovascular**

   A. Coronary heart didease

   B. Peripheral arterial disease

   C. Cerebrovascular disease

Other complications are gastrointestinal, genitourinary, dermatological, cheiroarthropathy, periodontal disease etc.

DIABETIC NEUROPATHY

Diabetic Neuropathy is heterogenous in its clinical presentation. It is the commonest complication of diabetes and is associated with significant morbidity. When there are signs and symptoms of peripheral nerve involvement in diabetes patients, a diagnosis of diabetic neuropathy is made after excluding other causes. This condition poses a therapeutic challenge to the treating physician . It has multifactorial pathogenic mechanism and varied clinical presentations. Hence treating these patients and curing them is difficult and the effectiveness of therapy given is mostly not satisfying to the patient. Syndrome of diabetic neuropathy and its panaroma of clinical manisfestations has been studied in greater detail with respect to pathogenesis and ultrastructural changes in peripheral nerves. Hyperglycemia contributes a major role in its pathogenesis.

Risk factors for diabetic neuropathy

1. Poor glucose control
2. Long duration of DM
3. Damage to blood vessels

4. Genetic susceptibility
5. Autoimmune factors
6. Lifestyle factors
7. Smoking
8. Alcohol

Classification of Diabetic Neuropathy[8]:

- **Rapidly reversible**

  Hyperglycemic neuropathy

- **Generalised symmetric polyneuropathy**

  A. Acute sensory neuropathy

  B. Chronic sensorimotor neuropathy

  (i) Small fibre neuropathy

  (ii) Large fibre neuropathy

  C.Autonomic neuropathy

- **Focal and multifocal neuropathies**

  A.Focal-limb neuropathy

  B.Cranial neuropathy

  C.Proximal motor neuropathy(amyotrophy)

  D.Truncal radiculoneuropathy

E.Coexisting chronic inflammatory demyelinating

Neuropathy

Autonomic neuropathy is further classified as-

a. Sudomotor

b .Gastrointestinal

c .Cardiovascular

d .Genitourinary

"Diabetic autonomic neuropathy (DAN) is deleterious and now a days a usual complication of diabetes. Inspite of its ability of to cause sudden painless heart attacks and death in patients due to cardiac autonomic instability , it is presumably under rated and untreated "[7]

DAN and other peripheral neuropathies mostly occurs along with other complications of diabetes but rarely can be isolated, sometimes precedes other complications[7]. Major clinical manifestations of DAN include increased heart rate in resting state, intolerance to exercise , diarrhea, unawareness to hypoglycemia, gustatory sweating , impaired temperature regulation, altered sweating, and sexual dysfunctions[7,27]. Almost all organ systems are affected by DAN (e.g., gastrointestinal [GI], genitourinary, and cardiovascular)[7]. GI disturbances are frequent complications among these .

Clinical manifestations of Diabetic Autonomic Neuropathy

Cardiovascular –

Resting tachycardia ,exercise intolerance,orthostatic hypotension,silent myocardial ischemia,intraoperative cardiovascular lability.

Gastrointestinal-

Esophageal dysmotility,gastroparesis,diarrhea,constipation,gall bladder stasis

Genitourinary-

Neurogenic bladder ,erectile dysfunction,retrograde ejaculation

Sudomotor –

Anhidrosis,hypohidrosis,gustatory sweating

Hypoglycaemia counter regulatory-

Hypoglycaemia unawareness,hypoglycaemia associated autonomic failure

CARDIOVASCULAR AUTONOMIC NEUROPATHY

CAN is an impairment of autonomic control of the cardiovascular system in the setting of diabetes mellitus after exclusion of other causes.CAN is usually detected at a subclinical stage by means of several cardiovascular autonomic reflex tests[9].

Hyperinsulinemia due to insulin resistance can modulate autonomic activities ,inducing hemodynamic changes.Insulin may increase heart rate slightly,as shown in hyperinsulinemic euglycemic clamps in healthy individuals[10,11] .Heart rate elevation occurs as a result of both vagal depression and cardiac sympathetic activation[10,11].

DM patients having CAN carries an increased risk for developing coronary artery disease and is also associated with poor prognosis once they develop CAD.There is no “circardian variation” (morning increase in MI) of acute CVD events in diabetic patients with CAN. “Diabetic patients with CAN are prone for sudden painless death due to ischemic myocardial infraction, rhythm disturbances, heart failure and rapid progression of diabetic nephropathy which cause further more damage to the myocardium by elevated BUN and other parameters”[12].

Parasympathetic fibres are affected at relatively early stages. This leads to a relative increase in sympathetic tone,which causes attenuation

of expected increase in BP and heart rate changes during exercise.Decrease in parasympathetic tone causes exaggerated coronary vasoconstriction,leading to worsening of ischemia.

PATHOGENESIS OF DIABETIC AUTONOMIC NEUROPATHY

In presence of persistent hyperglycemia**, polyol pathway** is activated. Excess intracellular glucose is converted to sorbitol by enzyme aldose reductase. Increase in osmolarity which results due to intracellular sorbitol and fructose accumulation causes Schwann cell damage, leading to deleterious effects on nerve conduction velocities.

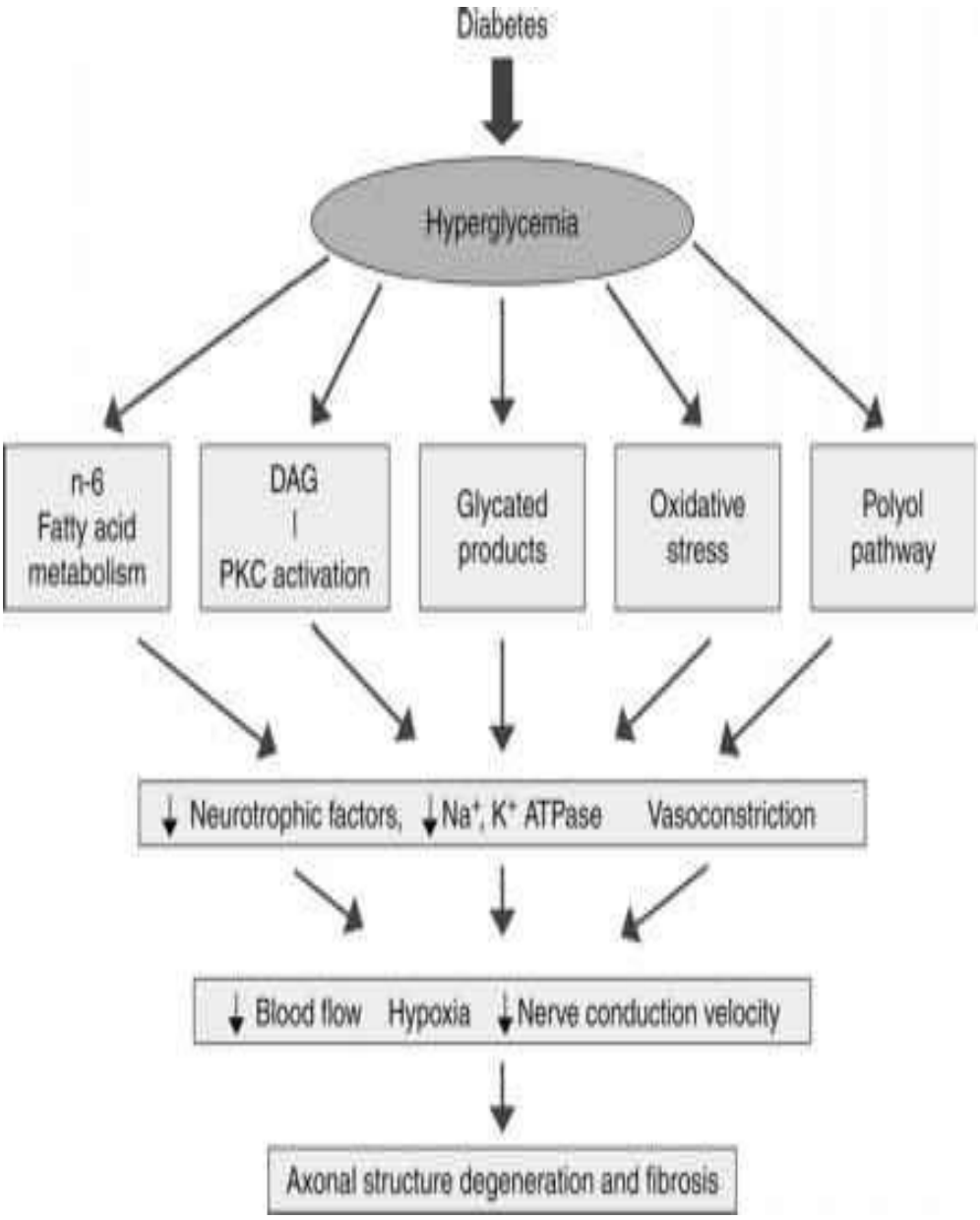
There is increased free radical formation leading to oxidative stress,causing endothelial cell dysfunction and neurotoxic effects.

Microvascular theory is that chronic hypoxia occurring due to decreased endoneural blood flow explains the pathogenesis of structural lesions of nerves.The normal "**Vascular autoregulation**" is said to be lost in chronic hyperglycemia.There is absolute and relative ischemia in the nerves and also decrease in Na^+/K^+ ATPase activity .This reduces nerve conduction velocity by decreasing axonal transport.

Neurotrophic factors like Nerve Growth Factor(NGF),Neurotrophin-3,4/5,Insulin Like Growth Factor(IGF)-1 which are necessary for survival

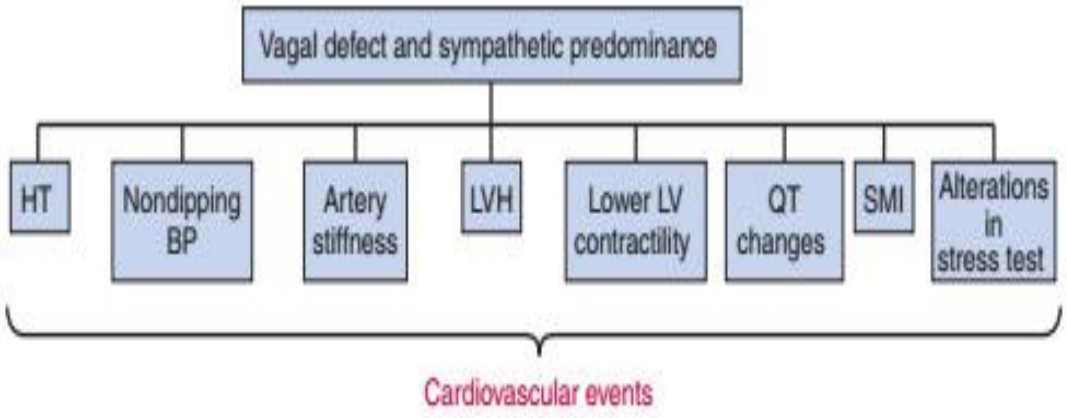
of neurons are deficient in hyperglycaemic individuals.These also causes damage to nerve cells leading to neuropathy.

PATHOGENIC MECHANISMS IN DAN



CARDIOVASCULAR DISORDERS ASSOCIATED WITH CAN

There is an increase in cardiovascular events associated with subclinical CAN and due to sympathetic predominance.



Silent myocardial ischemia(SMI)

SMI may be detected by stress ECG ,Echocardiogram or by stress myocardial scintigraphy. Earlier meta analysis studies have shown higher rate of silent and painless heart attacks in patients with cardiac dysautonomia compared to normal individuals or diabetics without cardiac dysautonomia.

Hypertension

A defect in vagal activity and a relative sympathetic override contributes to hypertension. In patients with T1DM or T2DM ,the prevalence of hypertension increases with CAN severity, which supports the role of CAN contributing to hypertension in diabetics[14].

Left ventricular dysfunction

CAN has been associated with left ventricular dysfunction, particularly diastolic dysfunction.

QT interval prolongation

QT interval prolongation occurs due to loss of balance between sympathetic and parasympathetic innervations in heart, hypertrophy of left ventricle, changes in myocardium caused by electrolye and metabolic abnormalities and diseases affecting coronary arteries .Hyperglycemia and acute hypoglycemia can induce reversible QTc prolongation in healthy and diabetic patients. These all favours the basis for arrhythmias causing “Dead in Bed” syndrome.

Abnormal circadian BP pattern

Non dipping and reverse dipping[15,16] of BP may occur due to CAN.Several studies linked non -dipping to changes in day and night variation of sympathetics and parasympathetic system which consists of decreased rise in vagal activity and a dominance of sympathetic activity[15,16].

Arterial stiffness

Low-frequency peaking of systolic BP variations in standing position using spectral analysis,correlates significantly with pulse pressure measured supine position,suggesting an increase in arterial stiffness associated with higher sympathetic activity[47].

Exercise intolerance

There is a marked decrease in the ability to do strenous activities, in patients with cardiac dysautonomia ,which is also accompanied by decrease in heart rate and variation in cardiac stroke volume with cardiac output variations. The severity of CAN is inversely related to maximal heart rate increase during exercise.CAN testing is a useful tool in identifying patients with potentially poor exercise tolerance ,thus preventing adverse outcomes during stress exercise tests and exercise training programs.

Resting tachycardia

During early stages of CAN abnormalities in HRV is present, where as fixed HR and resting tachycardia are characteristically late findings in diabetics with vagal impairment. Patients who have damage in the vagal system shows higher heart rates at resting states in earlier stages of autonomic neuropathy. In later stages, patients have combined vagal

and sympathetic involvement, causing return of heart rate towards normal but remains elevated.Fixed heart rate unresponsive to exercise,stress,,or sleep indicates complete cardiac denervation.

Postural hypotension

In normal patients, on standing, BP is usually maintained, may have a slight rise or fall, but the drop of systolic BP usually doesn't exceed 10 mm of Hg. Orthostatic hypotension (OH) is referred to as a fall in blood pressure [*i.e.* 30 mm Hg for systolic or 10 mm Hg for diastolic] in response to postural change after 2 minutes, from supine to standing[17]. Symptoms of postural hypotension are giddiness, light headedness, blackouts, disturbances in vision, vomiting, syncope, following sudden position change. It can become distressing but some patients do not have any symptoms[19]. It is due to inactivation of a baro-receptor initiated centrally mediated sympathetic reflex. It reflects failure of vasoconstriction in both systemic and vascular beds . Magnitude of systolic fall of BP on standing has no tight correlation with symptoms of dizziness. Orthostatic hypotension (OH) is often worse on getting out of bed during morning. Administration of insulin (acts as vasodilator),diuretics ,antihypertensives, and tricyclic antidepressants can aggravate OH.

Possible mechanisms of increased morbidity and mortality in diabetic cardiac autonomic neuropathy

1) Silent MI ,impaired angina recognition and infarction

2) Decreased ischemia threshold

  a) Impairment in coronary vasomotor regulation

  b) Increased resting heart rate

  c) Blunted chronotropic response to exercise

3) **QTc** interval prolongation

  a) Increase in lethal arrhythmias

  b) Sudden death with or without MI

4) Abnormal diastolic or systolic function

  a) Contributes to diabetic cardiomyopathy

  b) Affects natural history of congestive heart failure

5) Increased perioperative risk

6) Alteration in normal circardian variation of sympathomimetic activity

Sudomotor and peripheral microvascular manifestations of DAN

Sudomotor involvement is common in DAN.It is usually manifested as loss of sweating and dry skin in extremities accompanied by excessive sweating in trunk. Excessive sweating in trunk may occur as a compensatory phenomenon, as the proximal regions like head and trunk

are spared in dying back neuropathy. Gustatory sweating is less common. Microvascular skin flow is regulated by ANS and the rhythmic contractions of small arteries and arterioles are disordered in DAN. This is manifested as changes in skin texture, nail loss,anhidrosis,callus formation, fissures and cracks.Peripheral edema and venous prominence occur, which are associated with poor wound healing. There is high peripheral blood flow and abnormal local reflex vascular control due to loss of sympathetic vascular innervation.This leads to increased osteoclastic activity,reduction in bone density,susceptibility to fractures and results in Charcot's neuroarthropathy.

Sudomotor tests

- **"QSART (**Quantitative Sudomotor Reflex Test)"
- **TST**(Thermoregulatory Sweat Test)
- **S**weat Imprint
- Sympathetic Skin Response

"QSART measures the axon reflex mediated sudomotor response, thus evaluating post ganglionic sudomotor function using a cholinergic agonist.It uses the principle of iontophoresis of a cholinergic agonist" [54]. "TST is a test which determines distribution of sweat by

colour change of an indicator powder on skin after exposure to infrared light"[54].

Genito-urinary autonomic neuropathy

Neurogenic bladder

Erectile dysfunction

Sexual dysfunction in women

Ultrasound is performed to detect residual volume.micturography, cystometry and urometric studies ar performed.

DIAGNOSIS OF CAN

Subclinical CAN is a frequent condition that can be documented with (Cardiovascular autonomic reflex tests)CARTs, which is the gold standard for clinical diagnosis of CAN .These are safe, clinically relevant, non invasive,easy ,reproducible, and standardized tests.

"Parasympathetic function testing"[55]:

"Heart –rate response to Valsalva manoeuvre"[55]: "During the strain period of Valsalva manoeouvre, BP falls and heart rate rises after release, Bp rises, overshooting the resting value and the heart rate slows down'[55].Though these reflex changes are complex," the heart rate

response can be abolished by atropine, but remains unaffected by propranolol, which suggests that it is mediated by the vagus nerve"[55]. Patients with autonomic damage have slow fall in the blood pressure during the strain phase and it slowly returns to normal after release, with no overshot rise in BP and no change in HR.

"In healthy people the Valsalva maneouvre has a four phased response"[48].

• **Phase I: "**There is at transient rise in BP and a fall in heart rate mainly due aorta compression and propulsion of blood into the peripheral circulation. These hemodynamic changes mostly occurs due mechanical factors"[48].

• **Phase II: "**There is an early fall in BP followed by normalization of blood pressure. The change in BP is associated with rise in heart rate. Impaired venous return results decreased cardiac output, causing a increased peripheral resistance and rise in sympathetic activity"[48].

•**PhaseIII:**With cessation of expiration,there is a fall in BP with rise in heart rate

• **Phase IV[48]: "**There is an overshoot of BP value from the resting rate.This occurs because due to venous return and cardiac output is restored with residual vasoconstriction"[48].

The test is performed by the patient blowing into a mouthpiece connected to a modified sphygmomanometer and holds it at a pressure of 40 mm Hg for 15 seconds during which a continuous ECG is recorded. this test is performed 3 times with one minute interval between each.Patients with proliferative retinopathy should not undergo Valsalva because of the risk of retinal haemorrhage"[55]."The result of Valsalva test is expressed as the ratio of the longest R-R interval[55] after the manoeuvre(overshoot bradycardia following release) to the shortest R-R interval during the manoeuvre(tachycardia during the phase of strain),measured using a ruler from the electrocardiogram tracing..The mean of the three valsalva ratios is taken as the final value "[55

" HR variation with breathing" [29]

"Normally the heart rate varies continually depending on an intact parasympathetic nerve supply"[29, 55]. "At slow HR, deep respiration and in adolescent patients and children, it becomes more evident. There is total abolition of HRV or considerable decrease in this response, in diabetic patients with cardiac dysautonomia. HRV can be assessed by different types of breathing. quiet breathing. Deep inspiration and expiration at 6 times a minute is usually used. The patient is asked to do the above for 60 seconds, 5 seconds taking deep inspiration and 5 seconds deep doing deep exhalation. sits quietly and breathes deeply at a rate of

six breaths a minute . An ECG is recorded all along the manoeuvere taken throughout the period of deep breathing, and beginning of inhalation and exhalation tracings are marked". The values of longest and shortest between two R waves is measured during each respiratory cycle and is measured with the help of a scale and converted to heart rate per minute. The longest and shortest RR interval is measured and its mean is taken. This bedside method is objective, comparatively easier when compared to other methods . "HRV can also be expressed as the ratio of the HR at expiration to heart rate at inspiration, the so-called E:I ratio"[29,55].

"Heart-rate response to standing"[18] :

During change from lying to standing position, there is an immediate rapid increase in heart rate which occurs maximally at about the 15th beat following standing position. At about 30th beat there is a relative overshoot bradycardia[18.] This is a vagus nerve mediated response. In diabetic patients with CAN, heart rate either shows minimal response or no response at all to standing position .Continuous ECG recordings are taken with patient lying comforatably in supine position. The patient is then asked to stand up without help and the point at which he begins to stand is noted in ECG.

Using a ruler, the shortest distance between two R waves at about 15 th beat and the longest R-R interval at about 30 th beat post standing is noted[18]. " The typical HR response to postural change is represented as 30:15 ratio. With little patient cooperation, this test is simple and reproducible and donot depend other confounding factors"[18].

Sympathetic Autonomic Function Test:

"BP response to standing position"[21]:

"Usually during standing there is stagnation of blood in lower limbs which causes drop in BP, which is normally rectified by peripheral vasoconstriction"[21]. In diabetic patients with dysautonomia the drop in BP persists and continues to be at a lower level than that of lying position.

"This test is performed by recording patient's blood pressure using a sphygmomanometer, with the patient lying comfortably and then two minutes after standing position .. The difference between the systolic BP in supine position and the systolic BP in standing position is calculated as the postural drop in BP"[21].

Blood pressure variation to sustained handgrip[21]:

Isometric exercises mostly are associated with increase in BP. Hand grip is one among the isometric exercises, which cause elevation of BP due to HR dependent increase in cardiac output with unaltered peripheral vascular resistance[21].

In patients with CAN, the normal reflex pathways are damaged and this is associated with extensive sympathetic abnormalities. As a result, there is significant reduction in rise of BP during hand grip. Using hand grip dynamometer, initial maximum voluntary contraction is estimated. Hand grip is sustained at 30% of initial maximum contraction for long as possible upto 5minutes. BP is recorded 3 times before and after hand grip. The mean of three diastolic BPs before hand grip is calculated. Result is expressed as a difference between highest DBP recorded during sustained hand grip and the mean diastolic BP before the hand grip

Summary of cardiovascular autonomic tests

Test	Posture	Appropriate test time	Apparatus required
Heart rate response to valsalva	Sitting	5 min	Sphygmomanometer,ECG
Heart rate variation to deep breathing	Sitting	2 min	ECG
BP to sustained hand grip	Sitting	5 min	Sphygmomanometer
Heart rate response standing	Lying to standing	3 min	ECG
BP response to standing	Lying to standing	3 min	sphygmomanometer

BATTERY OF AUTONOMIC TESTS-EWING AND CLARKE[22]

Five simple, non invasive cardiovascular reflex tests based on works of Ewing et al [22] is used to assess autonomic function.

Score	Deep breathing	Heart rate ratio during Valsalva	Heart rate variability to standing	BP variabilty to hand grip	BP change to standing
0	≥15	≥1.21	≥1.04	≥16	≤10
1	11- 14	1.11 -1.20	1.01 -1.03	11-15	11- 29
2	≤10	<1.20	≤1	≤10	≥30 mm

For grading of cardiovascular autonomic function, a battery of 5 tests using heart rate and BP responses are used.

A score of 0-2 was assigned to each of these tests. Total score out of 10 is calculated.

1.Postural fall in systolic blood pressure (BP)[20]

Systolic BP was measured with the patient in supine position and 2 minutes after standing.

A fall of systolic BP more than 30 mm Hg considered abnormal -Score 2

11-29mm Hg fall is BP is considered as borderline-Score 1

Less than or equal to 10 mm Hg is taken as normal -Score 0

2. Increase in diastolic pressure during hand grip[20]

Hand grip is sustained at 30% of the maximum for 5 minutes.

A rise in diastolic BP in the opposite upper limb is measured.

Rise in diastolic BP ≥16mmHg considered Normal-Score 0

11-15mmHg considered Borderline-Score1

<10 mm Hg considered Abnormal -Score-2

3. Heart rate response to Valsalva manoeuvre-

The patient is made to exhale forcefully into manometer after closing the nostrils to raise the pressure to 40 mmHg for 15 seconds. Ratio of longest RR interval to the shortest RR interval is measured and is expressed as Valsalva ratio.

Value ≥1.21 is considered as Normal and score of 0 is given. Value 1.11-1.20 is considered Borderline and score of 1 is given.Value ≤1.10 considered as Abnormal and a score of 2 is given

4. Heart rate response to deep breathing

Patient in lying down position, breathes in and out 6 times per minute. The differences in maximum and minimum heart rate during each cycle of breathing is being accurately calculated for accurate results.

≥15 beats per minute considered Normal Score 0

11-14 beats per minute considered Borderline Score 1

≤10 beats per minute considered Abnormal Score 2

5. Heart rate response to standing

The RR interval is measured at 15 th and 30 th beat after standing from supine position

A ratio of 30^{th} beat :15 th beat is being precisely measured and a Value of ≥1.04 is considered as Normal and as Score 0 Value of 1.01-1.03 is considered as Borderline and as Score 1 Value of ≤1.00 is considered as Abnormal and as Score 2

CAN SCORING

Total score out of 10 is calculated.

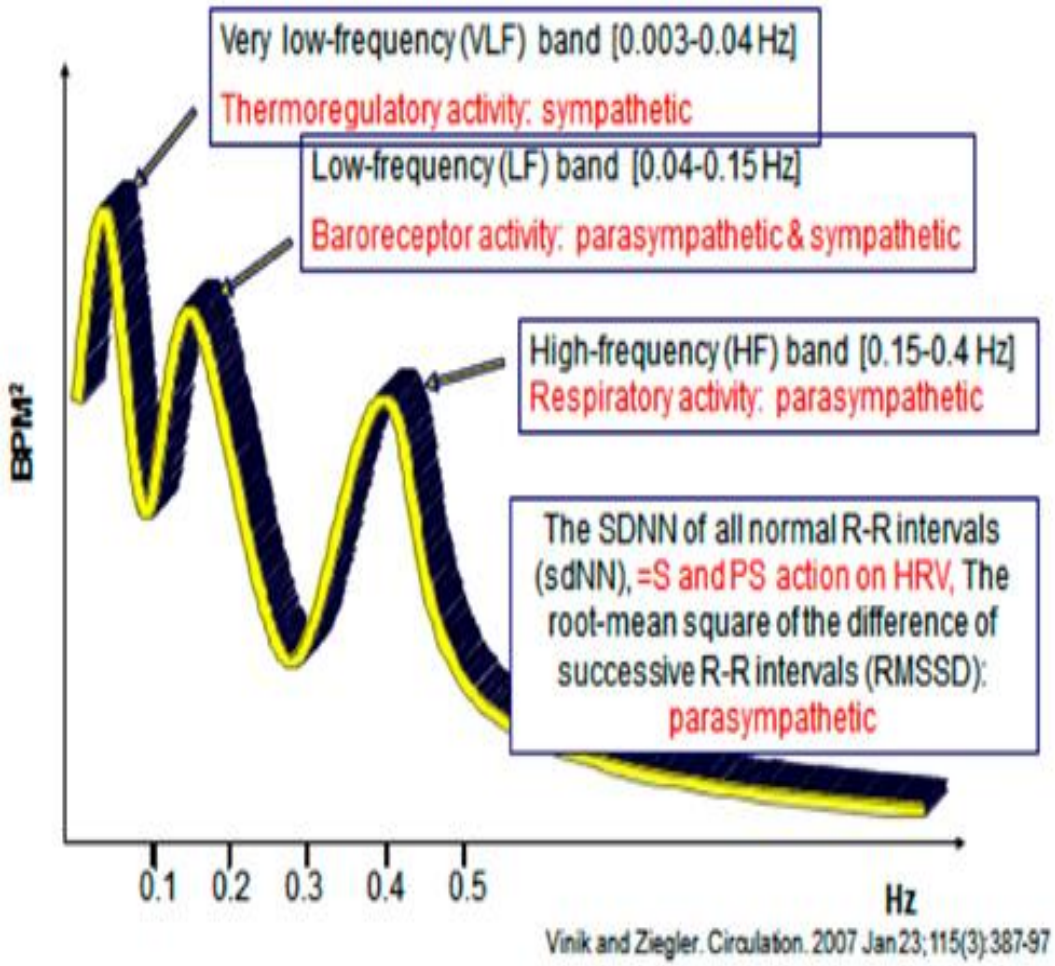
1. An overall score of '0' or '1' is considered normal
2. A score 2,3,4 are considered borderlines
3. A score ≥5 is judged is abnormal autonomic function

CARTs (cardiovascular autonomic reflex testing) are done after avoiding confounding factors. Patients are advised to avoid strenuous exercises in the preceding 24hours of tests. Caffeine, alcoholic beverages, smoking, and alcohol are avoided at least 2 hours before testing. Testing are done at fasting or after 2 hours after a light meal. In patients who are on insulin therapy, tests are done at least 2 hours after taking short-acting insulin , and not during time of hypoglycemia or hyperglycemia.

These test results are to be cautiously interpreted in patients having chronic respiratory illness, obstructive sleep apnea ,cardiac diseases, in particularly in heart failure. Medications like diuretics, sympatholytics ,antipsychotics which interfere with the test result should be advised to withdraw before performing these tests or the patients who needed these drugs for their survival should not be included in this study.

Power Spectral Analysis

Heart rate variability can be determined by frequency domained spectral analysis of R-R intervals. A 7 minute ,short R-R interval or a twenty four hour ECG recording can be used[30]. "HRV can be measured over various frequency distribution with very minimal cooperation of patient"[30]. "The high-frequency region(0.15-0.4 Hz) of power spectral band is usually denotes vagal activity. The lower frequency range (0.04-0.15 Hz) denotes both sympathetic and vagal activity"[31].

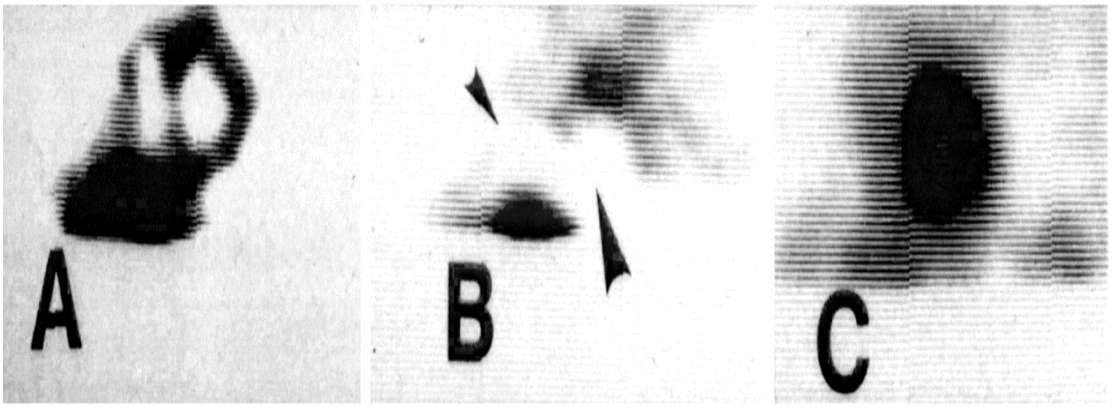


Cardiac Radionuclide Imaging

Cardiac sympathetic innervations could be quantified using imaging using radionucleotides. MIBG is used in these techniques. It is an unmetabolized noradrenaline analogue. “cardiac dysautomia shows reduction in MIBG uptake in patient’s myocardium”[**32].**

However these methods are highly expensive and not done in our day to day clinical practices.

Maldistribution of Sympathetic Innervation in Cardiac Autonomic Neuropathy (MIBG)



MUGA MIBG Thallium

MANAGEMENT OF AUTONOMIC DYSFUNCTION

Cardiac autonomic reflex tests can detect CAN at early stages in asymptomatic patients. Also, later stages have poor prognostic implications..Early detection aids in early initiation of therapies to limit or halt the progression of CAN, thus reducing the morbidity and mortality.

Evidence from the DCCT [33] suggests that near normal levels of glycemic status is "the best method to delay the occurrence of cardiac dysautonomia"[33]. Autonomic neuropathy progression may be influenced by proper treatment measures in early weeks[34,55], Tight glycemic control can delay in progression of neuropathy, whereas reversal of the condition is less likely[34].

Autonomic neuropathy and hypoglycaemia has an overlap and autonomic neuropathy can lead to hypoglycaemic unawareness. So there should be caution in exercising very strict glycemic controls.patients should be educated about the chance of hypoglycaemic episodes[36,37].

Several mechanisms have been attributed to the pathogenesis of diabetic neuropathy. These includes polyol pathway,neurotrophic factors, advanced glycated end products,oxidative stress etc .Timely identification of neuropathy in diabetics enables the use of as the use of prophylactic

treatments such as ACE inhibitors and aspirin along with other pharmacological and non pharmacological methods.

Nonpharmacological measures

- Cessation of smoking, tailored exercise programs

  These are shown to improve autonomic functions

- Body stockings and gravity suits

  Useful in patients with orthostatic hypotension- aimed at improvement in peripheral vascular resistance

- High sodium diet,,elevation of head end while sleeping-may give symptomatic relief

- "Staged" posture changing

- Standing on crossed legs.

- Dorsiflexing the feet or doing handgrip exercises before standing

Pharmacological measures

Strict glycemic control,good blood pressure control and lipid reduction can slow down the progression of CAN

Some studies have shown the use of antioxidant,alpha lipoic acid in slowing or reversing progression of neuropathies.

Angiotensin converting enzyme(ACE) inhibitors,especially,quinapril has been shown to cause improvement in parasympathetic activity after 3 months of treatment.

Cardioselective beta blockers(Atenolol) or propranolol can block central or peripheral sympathetic stimuli.This helps in restoration of parasympathetic-sympathtic balance.

Orthostatic hypotension may be treated with fludrocortisone (0.1-0.4 mg per day).This acts by increasing plasma volume..Pindolol,fluoxetine and intranasal or oral desmopressin have also been tried.

QTc INTERVAL AND CARDIAC AUTONOMIC NEUROPATHY

QT interval is the time interval measured between the beginning of the Q wave and the end of the T wave in the ECG. The QT interval represents the total duration of the ventricular activity,that is the electrical depolarisation and repolarisation of ventricles[23].QT interval may vary in different parts of the ventricles.

1. The QT decreases with tachycardia,that is, with a diminution of R-R interval.
2. The QT lengthens with bradycardia

For a meaningful evaluation, the QT interval cannot be viewed in absolute terms and must be corrected for the effect of associated heart rate.

QT interval measurement

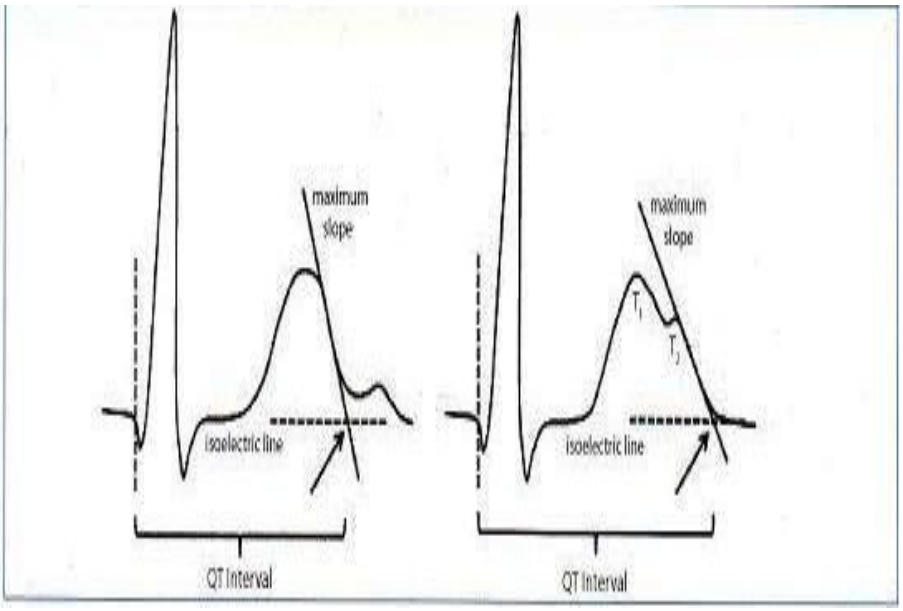
Measurement of QT interval may present some difficulty at times.This happens because,it may be difficult to determine the exact beginning and end of the interval

1) "Measured in either lead I,II or V5 ,V6.the beginning of QRS complex is best appreciated in leads with an initial q wave"[50].

2) "The end of the T wave may be obscured by a superimposed U wave. Larger U waves are taken into consideration for measurement"[50]

3) The end of T WAVE is determined by the ***maximum slope intercept method*** **[50].**

Maximum slope intercept method



Corrected QT interval[49,23]

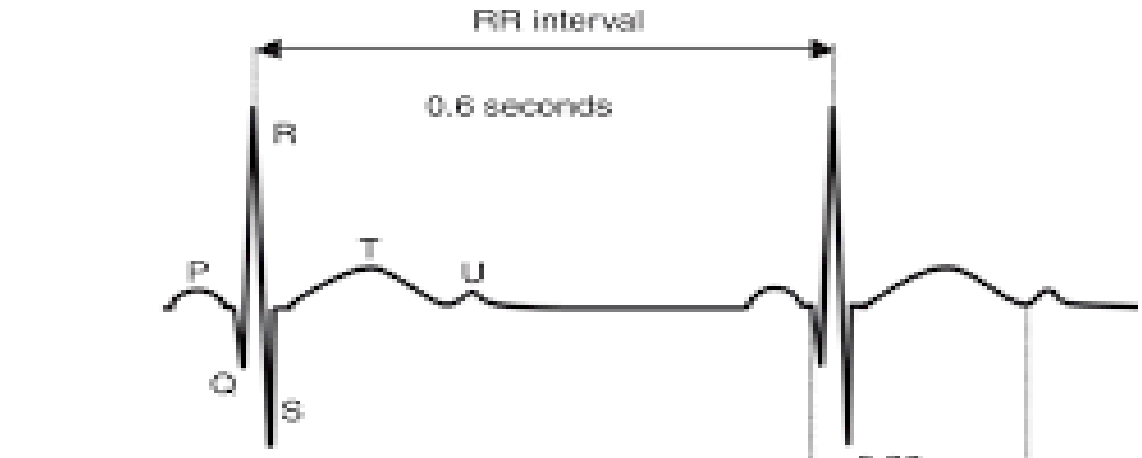
QTc interval is corrected for a theoretically heart rate of sixty beats /min

Bazett's formula:

$QT_C = QT / \sqrt{RR}$.

The RR interval measured between two consecutive R waves is expressed in seconds.

- **Bazett's formula** is the most commonly used as it is simplest among all.
- It under-corrects at heart rates less than 60
- It over corrects at heart rates more than 60
- provides an adequate correction for heart rates between 60 – 100 bpm.



$$\text{QTc interval} = \frac{\text{QT interval}}{\sqrt{\text{RR interval}}}$$

$$\text{QTc interval} = \frac{0.32 \text{ sec}}{\sqrt{0.6 \text{ sec}}} = \frac{0.32 \text{ sec}}{0.77 \text{ sec}} = 0.41 \text{ seconds}$$

Causes of a prolonged QTc (>440ms)[23]

1. During sleep-longer during sleep
2. Hypokalemia
3. Acute myocarditis from any cause, particularly rheumatic carditis

4. Hypocalcemia-mainly due to prolongation of ST segment
5. Hypothermia
6. MI-are more likely to develop complex arrhythmias
7. Post-cardiac arrest
8. Raised intracranial pressure
9. Certain drugs-quinidine,procainamide,tricyclic antidepressants
10. Congenital long QT syndrome

An association between cardiac autonomic neuropathy and QT interval prolongation was demonstrated in many studies and it may predispose to sudden death in diabetes[24,25].Increased QT dispersion was also suggested as a marker of diabetic autonomic neuropathy[26].

METHODOLOGY

Study Design:

A Cross sectional study was conducted to evaluate the prevalence of cardiac autonomic neuropathy among Type 2 Diabetes Mellitus patients and to find the use of QTc interval in predicting it.

Sample size

Sample size = $Z^2*(p)(1-p)/c^2$

p=60%

(prevalence of CAN in type 2 DM, according to previous studies, (Pappachan et al.))

c= absolute precision taken as 10% ,keeping 95% confidence interval

sample size = 1.96*1.96*0.6*0.4/0.1*0.1=92

(rounded to 100)

Study Population:

100 Type 2 diabetic patients, both male and female, who satisfy all inclusion and exclusion criteria, from the outpatient department and

inpatients of Medicine department of Government Kilpauk Medical College, Chennai, will be included in this study

DATA COLLECTION METHODS

CRITERIA

Inclusion criteria

- ✓ Type 2 diabetes diagnosed according to WHO criteria, already on treatment
- ✓ Both male and female are included in the study group.

Exclusion criteria :

- ✓ Systemic hypertension
- ✓ Coronary Artery disease
- ✓ Documented Valvular disease
- ✓ Cardiac failure
- ✓ Age above 60 yrs
- ✓ Electrolyte imbalance(hypocalcemia, hypokalemia)
- ✓ Patients who are on any drugs that would interfere with the autonomic functions.

STUDY PERIOD:

6months of study from March 2016 to September 2016

DATA COLLECTION:

All the patients are evaluated by detailed history including duration of diabetes , symptoms of autonomic neuropathy and relevant basic blood investigations

Battery of five autonomic function tests done in all cases (as described by Ewing and Clarke et al). Autonomic neuropathy testing using simple bed side tests was done in op department and medical ward with the use of 12 lead ECG monitor, Pulse oxymeter and BP apparatus .The same 100 patients were tested after obtaining proper informed consent, with 10 minutes interval after each manoeuvre.

The following 5 tests for detecting Cardiac Autonomic Neuropathy will be :

BLOOD PRESSURE FOR POSTURAL OR ORTHOSTATIC HYPOTENSION

"Bloodpressure recording is done when the subject is made to lie down and again 2 minutes after standing up. The difference in systolic pressure from lying to standing is a measure of orthostatic hypotension"[46].

“CHANGE IN HEART RATE TO VALSALVA MANOEUVRE”[46]:

This test can be performed using a modified b.p apparatus. Patient blows in to the rubber tubing to raise the pressure to 40 mm of Hg, a long strip ECG in lead II is taken. Ratio of longest to shortest R-R interval is measured and mean ratio is obtained

“DEEP BREATHING ASSOCIATED CHANGES IN HEART RATE”[46]:

ECG is recorded continuously while patient is taking breath at a regular rate of 6-12 breaths/min.A difference of in heart rate <15 beats/min between expiration and inspiration is taken as abnormal

“BLOOD PRESSURECHANGES DURING SUSTAINED HAND GRIP”[46]

“Subject is given a ball and is asked to press the ball in his or her left hand for about 5 minutes Failure to rise the diastolic blood pressure more than 15 mm of Hg is considered as an abnormal finding and graded accordingly.

HEART RATE RESPONSE TO STANDING

R-R interval is measured at beats 15 and 30.

A 30:15 ratio is calculated

EWING'S AUTONOMIC FUNCTION TESTS AND SCORING

Score	Deep breathing	Heart rate response to Valsalva ratio	Heart rate variability to standing	BP variability to hand grip	BP change during standing
0	≥15	≥1.21	≥1.04	≥16	≤10
1	11- 14	1.11 -1.20	1.01 -1.03	11-15	10- 29
2	≤10	<1..20	≤1	≤10	≥30 mm

Each test is graded as

- Score 0 – normal
- Score 1- borderline
- Score 2 – abnormal

1. An overall score of '0' or '1' is considered normal
2. Score 2,3,4 are considered borderlines
3. Score ≥5 is judged is abnormal autonomic function

QTc INTERVAL: QT interval is determined on a 12 lead ECG taken at rest and correction for cardiac cycle is made

The QTc is determined by using **Bazetts** formula :

QTc = QT/√RR interval

QTc>440 ms is taken as abnormal

Apart from these cardiac autonomic reflex testing,,symptoms suggestive of autononomic dysfunction like light headedness, vertigo, palpitations, sweating abnormalities, diarrhea, constipation etc.were asked .,using detailed questionnaire.

BENEFIT TO THE PATIENTS

They will be explained that having high blood glucose levels for many years may damage nerves through out body and CAN interferes with body's ability to adjust blood pressure and heart rate. So keeping blood sugars under control is important. Exercises with gradual prolonged warm up and cool down periods is encouraged .Avoid sudden changes in postures, isometric exercises and straining. Avoid large,high carbohydrate meals, as it may cause sudden fall in bp.

DATA ANALYSIS

Prevalence of cardiac autonomic neuropathy in diabetes mellitus was calculated.

Difference in mean QTc interval between patients with CAN and without CAN is analysed

Specificity and sensitivity of QT interval in diagnosing diabetic autonomic neuropathy ,is calculated using Ewing's cardiac autonomic dysfunction scoring as gold standard

The collected data were analysed with IBM.SPSS statistics software 23 Version. For analysis of frequency of data in descriptive statistics continuous variables were analysed using mean and standard deviation and categorical variables were analysed as percentage.

For the Multivariate analysis Oneway ANOVA with Tukey's Post-Hoc test was used.

The Receiver Operator Characteristic (ROC) curve analysis was utilized to determine the Sensitivity ,Specificity ,PPV and NPV on comparison of QTc with CAN Score.

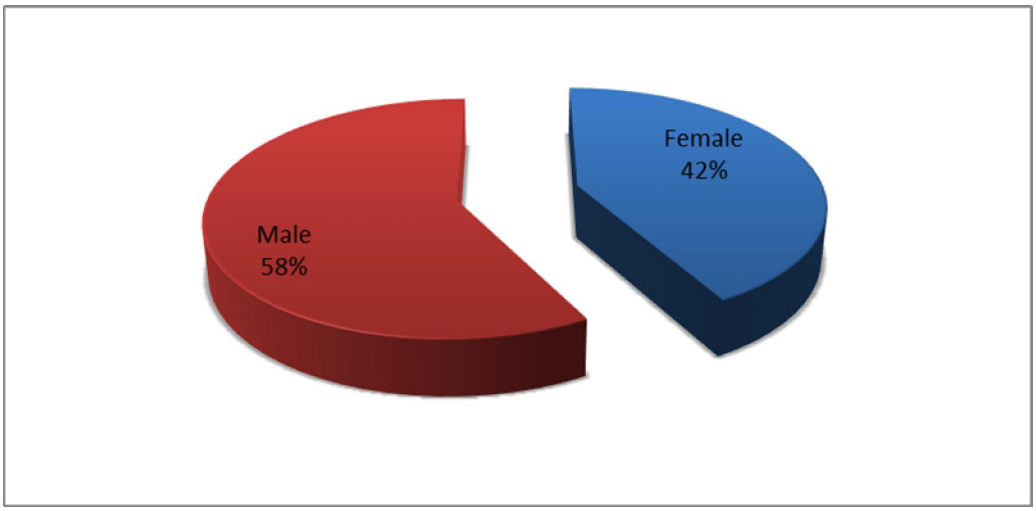
chi-square test was used to find association among categorical variables. In all both the above statistical tools the p value of 0.05 is considered as significant level.

FREQUENCY TABLES

SEX DISTRIBUTION

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	F	42	42.0	42.0	42.0
	M	58	58.0	58.0	100.0
	Total	100	100.0	100.0	

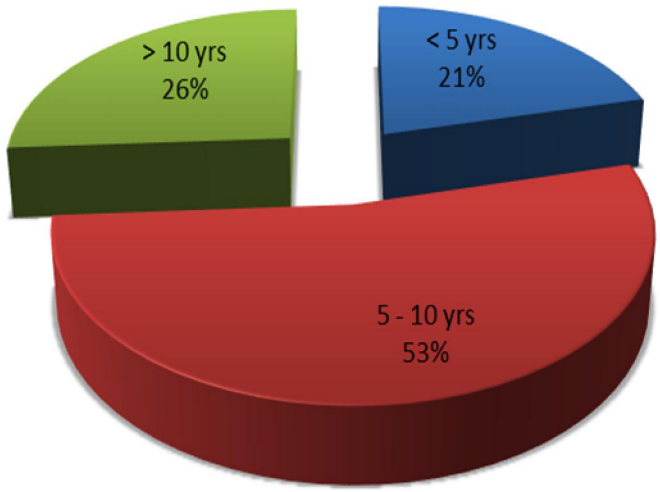
Among the study population of 100 diabetic patients included in the study,from KMCH,58 were males and 42 females..



DURATION OF DIABETES

Duration of DM(yrs)	Frequency	Percent	Valid Percent	Cumulative Percent
< 5 yrs	21	21.0	21.0	21.0
5 - 10 yrs	53	53.0	53.0	74.0
> 10 yrs	26	26.0	26.0	100.0
Total	100	100.0	100.0	

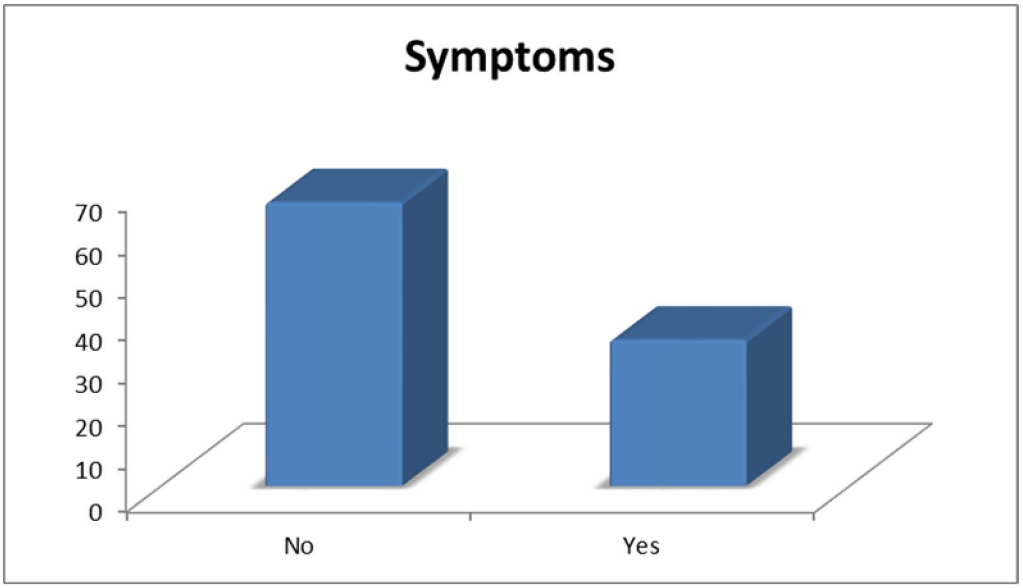
Among 100 patients from the study group, 21people had duration of diabetes less than 5 yrs,53 had duration 5-10 yrs, 26 had duration more than 10 yrs



SYMPTOMS OF CARDIAC AUTONOMIC NEUROPATHY

Symptoms	Frequency	Percent	Valid Percent	Cumulative Percent
No	66	66.0	66.0	66.0
Yes	34	34.0	34.0	100.0
Total	100	100.0	100.0	

Among 100 patients,34 were symptomatic and rest 66 were asymptomatic

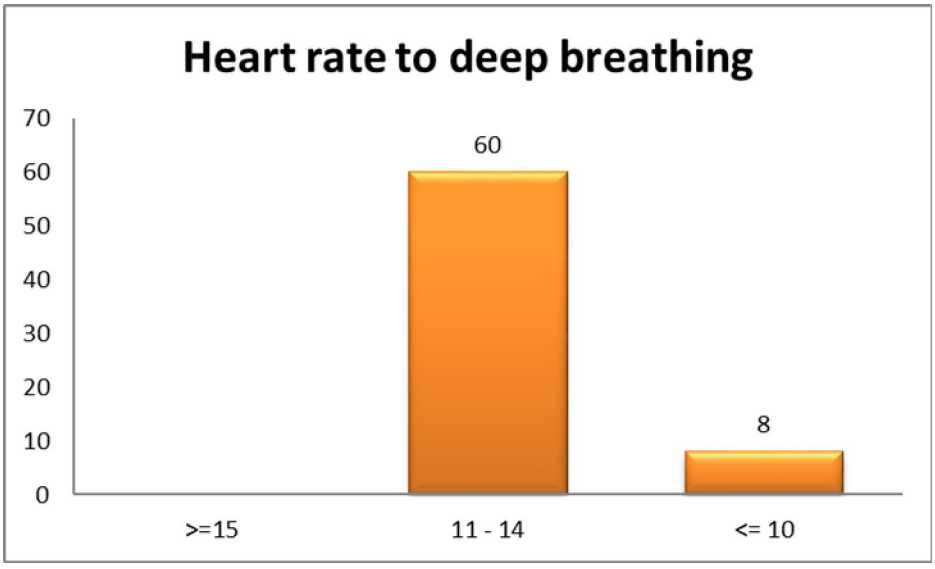


CARDIAC AUTONOMIC REFLEX TESTS

Heart rate response to deep breathing

Heart rate difference	Frequency	Percent	Valid Percent	Cumulative Percent
≥15	32	32.0	32.0	32.0
11 - 14	60	60.0	60.0	92.0
≤10	8	8.0	8.0	100.0
Total	100	100.0	100.0	

Among 100 patients, for heart rate response to deep breathing testing,8 had abnormal scores,60 had border line scores and 32 were normal

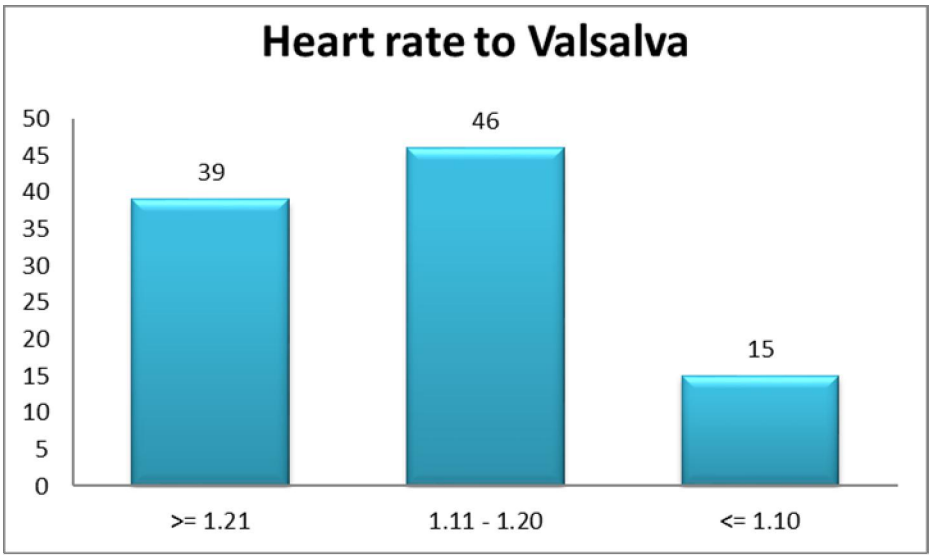


HEART RATE RESPONSE

Heart rate response to Valsalva

Heart rate ratio	Frequency	Percent	Valid Percent	Cumulative Percent
≥ 1.21	39	39.0	39.0	39.0
1.11 - 1.20	46	46.0	46.0	85.0
≤1.10	15	15.0	15.0	100.0
Total	100	100.0	100.0	

Heart rate response to Valsalva tests showed,normal score for 39 patients,borderline scores for 46 people,abnormal scores for 15 people

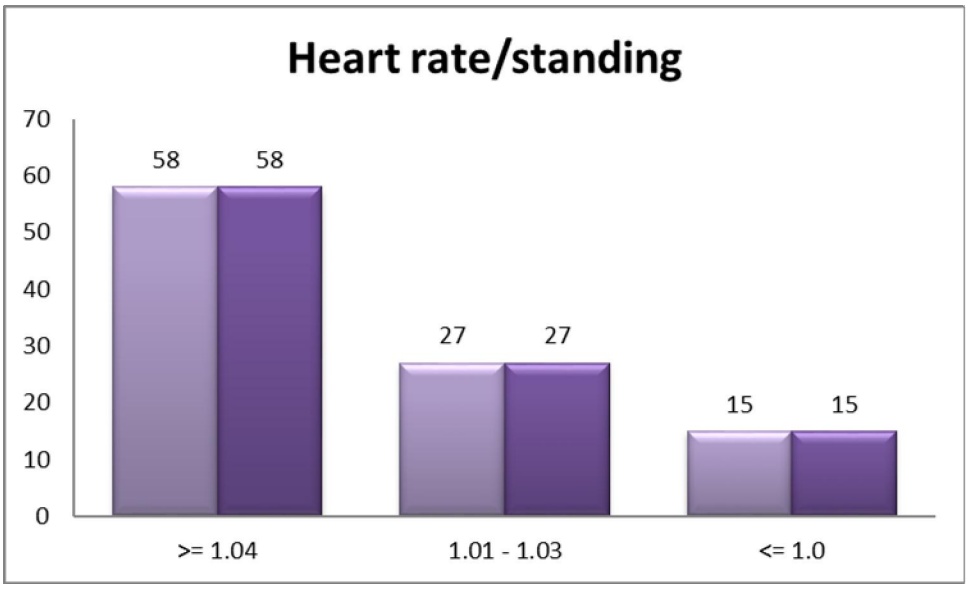


HEART RATE RESPONSE TO STANDING

Heart rate response to standing

Heart rate ratio	Frequency	Percent	Valid Percent	Cumulative Percent
≥1.04	58	58.0	58.0	58.0
1.01 - 1.03	27	27.0	27.0	85.0
≤ 1.0	15	15.0	15.0	100.0
Total	100	100.0	100.0	

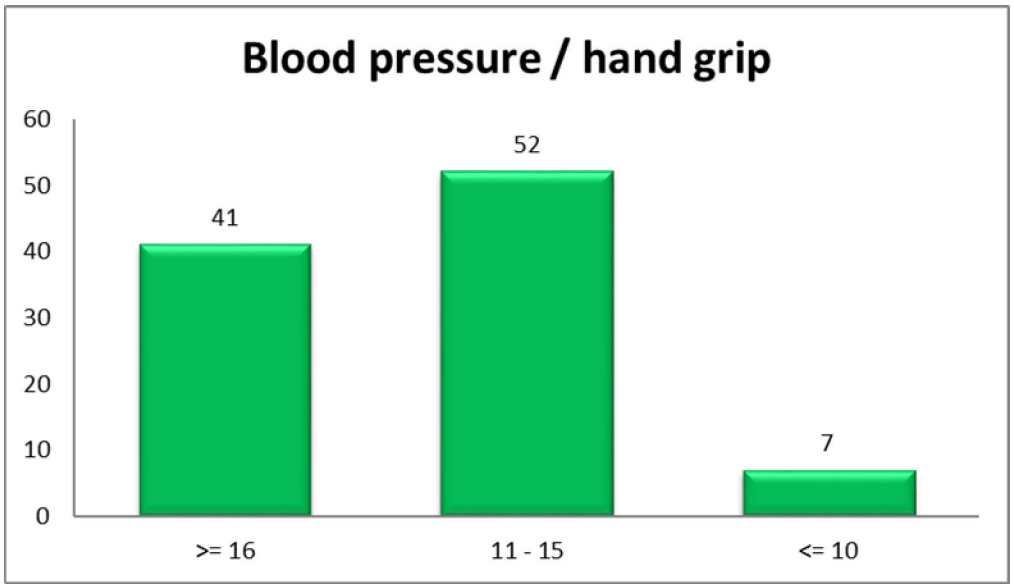
Out of 100 study population,15 had abnormal heart rate response to standing,27 had borderline scores, and 58 were normal.



BP RESPONSE TO HAND GRIP

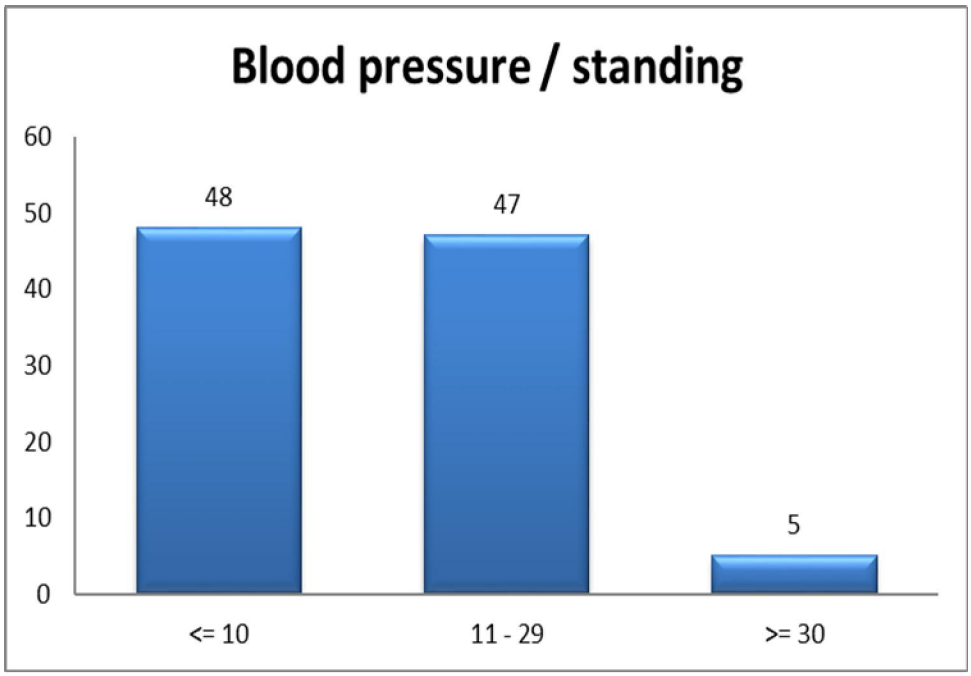
BP Response	Frequency	Percent	Valid Percent	Cumulative Percent
≥ 16	41	41.0	41.0	41.0
11 - 15	52	52.0	52.0	93.0
≤10	7	7.0	7.0	100.0
Total	100	100.0	100.0	

41 patients had normal BP response to had grip,52 were borderline and 7 were abnormal.



BP RESPONSE TO STANDING

BP Response/standing	Frequency	Percent	Valid Percent	Cumulative Percent
≤10	48	48.0	48.0	48.0
11 - 29	47	47.0	47.0	95.0
≥ 30	5	5.0	5.0	100.0
Total	100	100.0	100.0	



Summary of CAN test results

Overall, among 100 patients in the study group**, 8** people had abnormal results(score 2) for heart rate variability to deep breathing**, 15** had abnormal results for heart rate response to valsalva**, 15** showed abnormal results for heart rate response to standing, **7** had abnormal results for BP response to hand grip,**5** had abnormal BP response to standing respectively,

CAN SCORE- FREQUENCY DISTRIBUTION

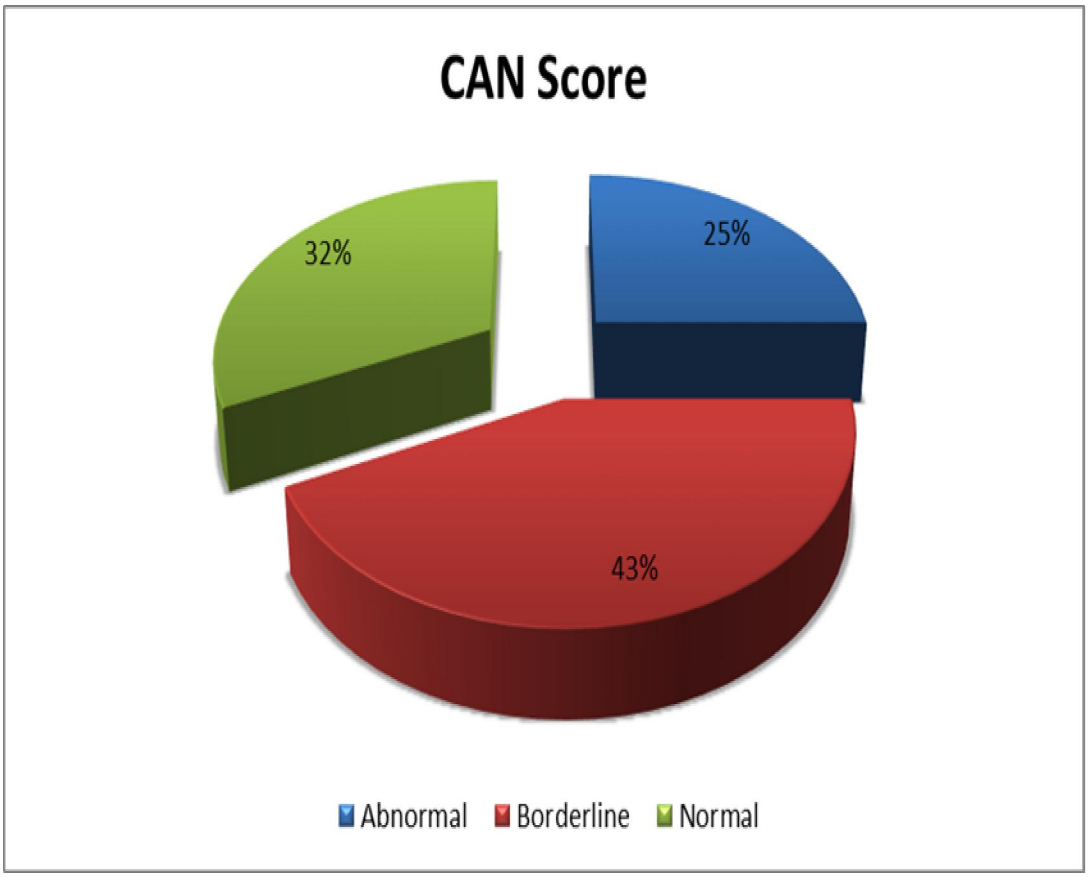
CAN Score	Frequency	Percent	Valid Percent	Cumulative Percent
Abnormal	25	25.0	25.0	25.0
Borderline	43	43.0	43.0	68.0
Normal	32	32.0	32.0	100.0
Total	100	100.0	100.0	

Among 100 patients,25 had an abnormal CAN Score,

43 had borderline and

32 had normal CAN Scores

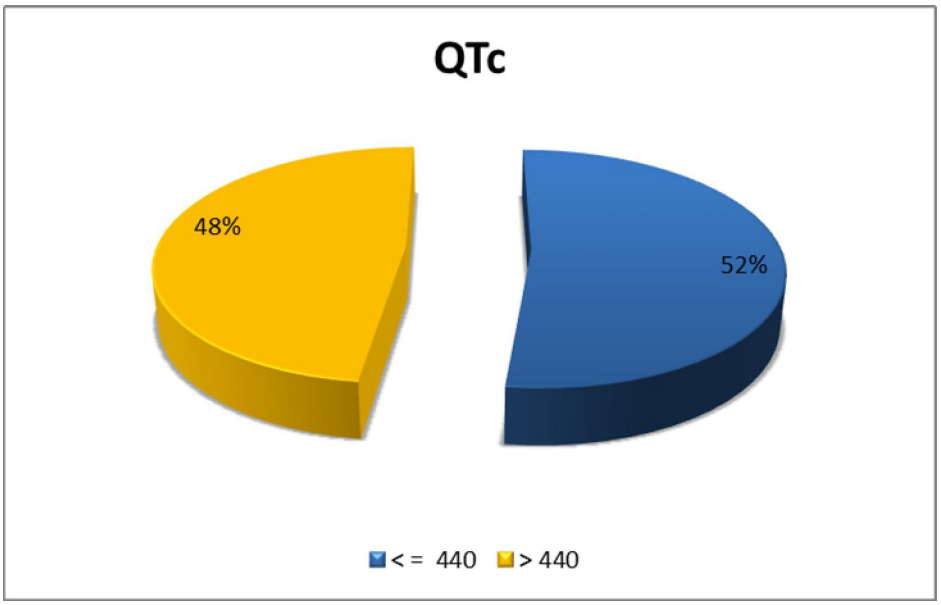
DISTRIBUTION OF CAN SCORE AMONG STUDY GROUP



QTc INTERVAL AMONG THE STUDY GROUP

QTc(ms)	Frequency	Percent	Valid Percent	Cumulative Percent
≤ 440	52	52.0	52.0	52.0
> 440	48	48.0	48.0	100.0
Total	100	100.0	100.0	

Among our study group of 100 diabetics,48 people showed a prolongation in corrected QTc(more than 440 milliseconds)

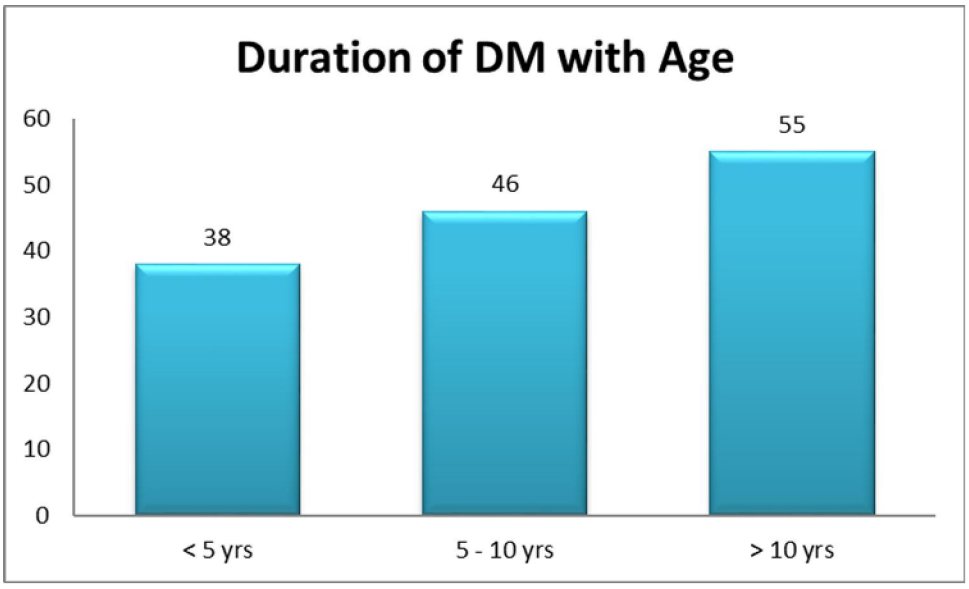


ONE WAY ANALYSIS

DURATION OF DM AND AGE

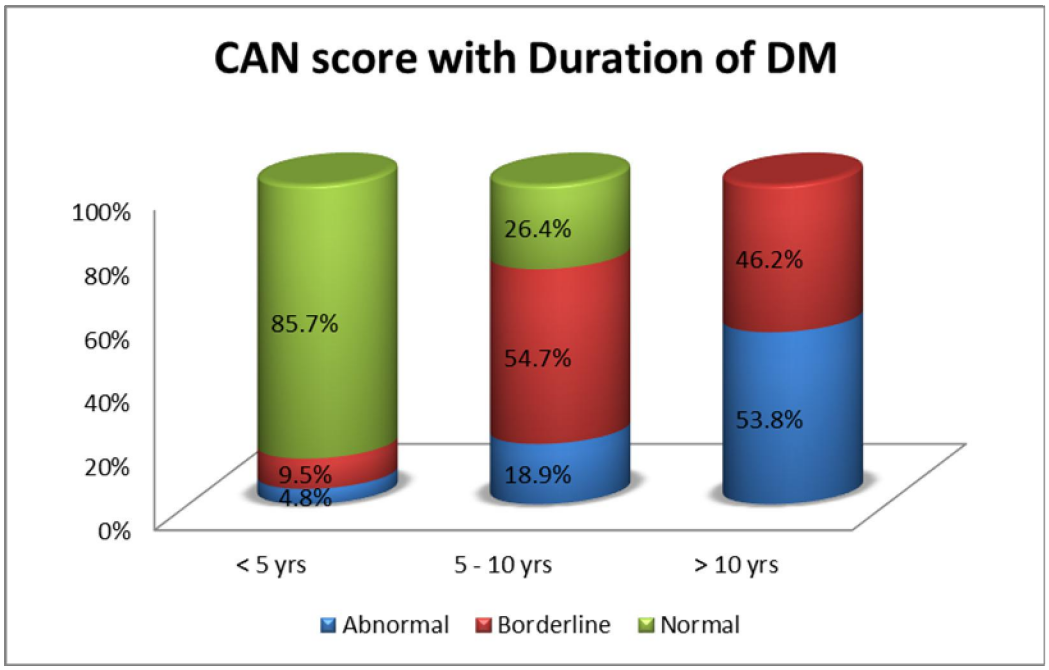
Duration of DM	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
< 5 yrs	21	38	3.130	.683	36.58	39.42	32	44
5 - 10 yrs	53	46	5.000	.687	44.98	47.74	35	56
> 10 yrs	26	55	2.591	.508	53.88	55.97	50	59
Total	100	46.83	7.118	.712	45.42	48.24	32	59

Among the study group of 100 people,21 had less than 5 yrs DM ,and the mean age was 38yrs (min-32,max-44).53 people had 5-10 yrs of DM and the mean age of the group was 46yrs(min-35,max-56).26 people had more than 10 yrs DM,with mean age 55 yrs(min-50,max-59)



CROSS TABS-CAN SCORE AND DURATION OF DM

			Duration of DM(yrs)			
			< 5 yrs	5 - 10 yrs	> 10 yrs	Total
CAN Score	Abnormal	Count	1	10	14	25
		% within Duration of DM(yrs)	4.8%	18.9%	53.8%	25.0%
	Borderline	Count	2	29	12	43
		% within Duration of DM(yrs)	9.5%	54.7%	46.2%	43.0%
	Normal	Count	18	14	0	32
		% within Duration of DM(yrs)	85.7%	26.4%	0.0%	32.0%
Total		Count	21	53	26	100
		% within Duration of DM(yrs)	100.0%	100.0%	100.0%	100.0%



Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	47.888[a]	4	.000
Likelihood Ratio	52.284	4	.000
Linear-by-Linear Association	36.830	1	.000
N of Valid Cases	100		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.25.

Among the study group of 100,4.8% of <5yrs diabetics,18.9% of 5-10 yrs diabetics and 53.8% of >10yrs diabetics showed abnormal CAN.Chi square tests showed there is a significant relation between duration of DM and CAN scores.

QTc AND DURATION OF DIABETES

One way analysis

qtc(ms)	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
< 5 yrs	21	428.29	11.217	2.448	423.18	433.39	408	452
5 - 10 yrs	53	438.75	16.391	2.251	434.24	443.27	400	483
> 10 yrs	26	454.27	15.803	3.099	447.89	460.65	432	500
Total	100	440.59	17.682	1.768	437.08	444.10	400	500

ANOVA

qtc(ms)	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	8222.978	2	4111.489	17.546	.000
Within Groups	22729.212	97	234.322		
Total	30952.190	99			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: qtc(ms)

Tukey HSD

(I) Duration of DM(yrs)	(J) Duration of DM(yrs)	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
< 5 yrs	5 - 10 yrs	-10.469*	3.947	.025	-19.86	-1.07
	> 10 yrs	-25.984*	4.491	.000	-36.67	-15.29
5 - 10 yrs	< 5 yrs	10.469*	3.947	.025	1.07	19.86
	> 10 yrs	-15.515*	3.665	.000	-24.24	-6.79
> 10 yrs	< 5 yrs	25.984*	4.491	.000	15.29	36.67
	5 - 10 yrs	15.515*	3.665	.000	6.79	24.24

*. The mean difference is significant at the 0.05 level.

Homogeneous Subsets

qtc(ms)

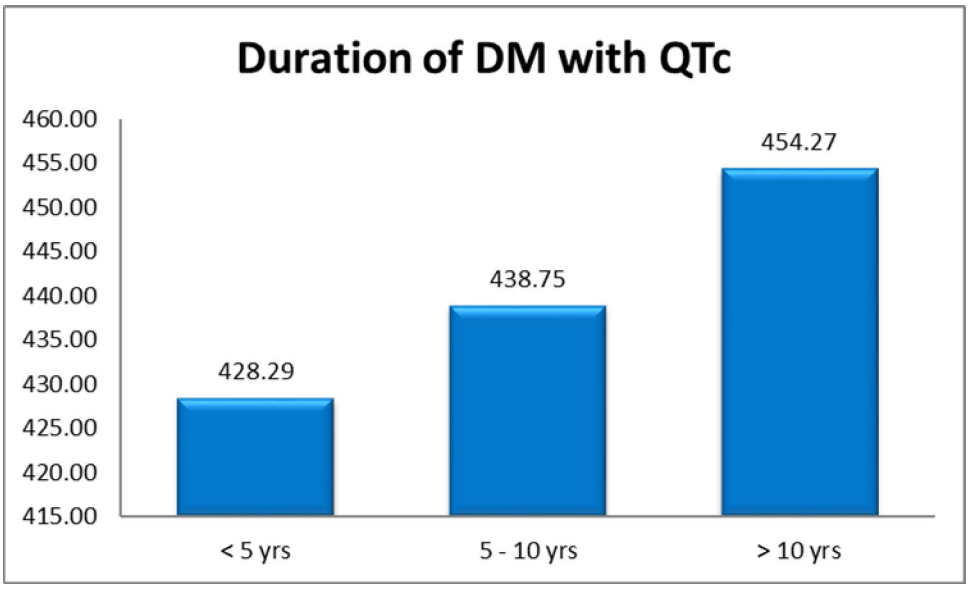
Tukey HSD[a,b]

Duration of DM(yrs)	N	Subset for alpha = 0.05		
		1	2	3
< 5 yrs	21	428.29		
5 - 10 yrs	53		438.75	
> 10 yrs	26			454.27
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 28.585.

b. The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.



Among patients with duration of diabetes <5 yrs,mean QTc interval was428.29,among 5-10 yrs group,mean QTc interval was 438.75,and >10 yrs group mean QTc was 454.27.There was prolongation of QTc interval as duration of Diabetes increases.

QTc and CAN SCORE

qtc * CAN Score Crosstabulation

			CAN Score			Total
			Abnormal	Borderline	Normal	
qtc	> 440	Count	21	24	3	48
		% within CAN Score	84.0%	55.8%	9.4%	48.0%
	< = 440	Count	4	19	29	52
		% within CAN Score	16.0%	44.2%	90.6%	52.0%
Total		Count	25	43	32	100
		% within CAN Score	100.0%	100.0%	100.0%	100.0%

QTc and Can score cross tabulation and comparison was done,which showed statistical significance. Pearson Chi –Square value was 33.150,and likelihood ratio of 37.546 with p value of <0.05

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	33.159[a]	2	.000
Likelihood Ratio	37.546	2	.000
Linear-by-Linear Association	32.023	1	.000
N of Valid Cases	100		

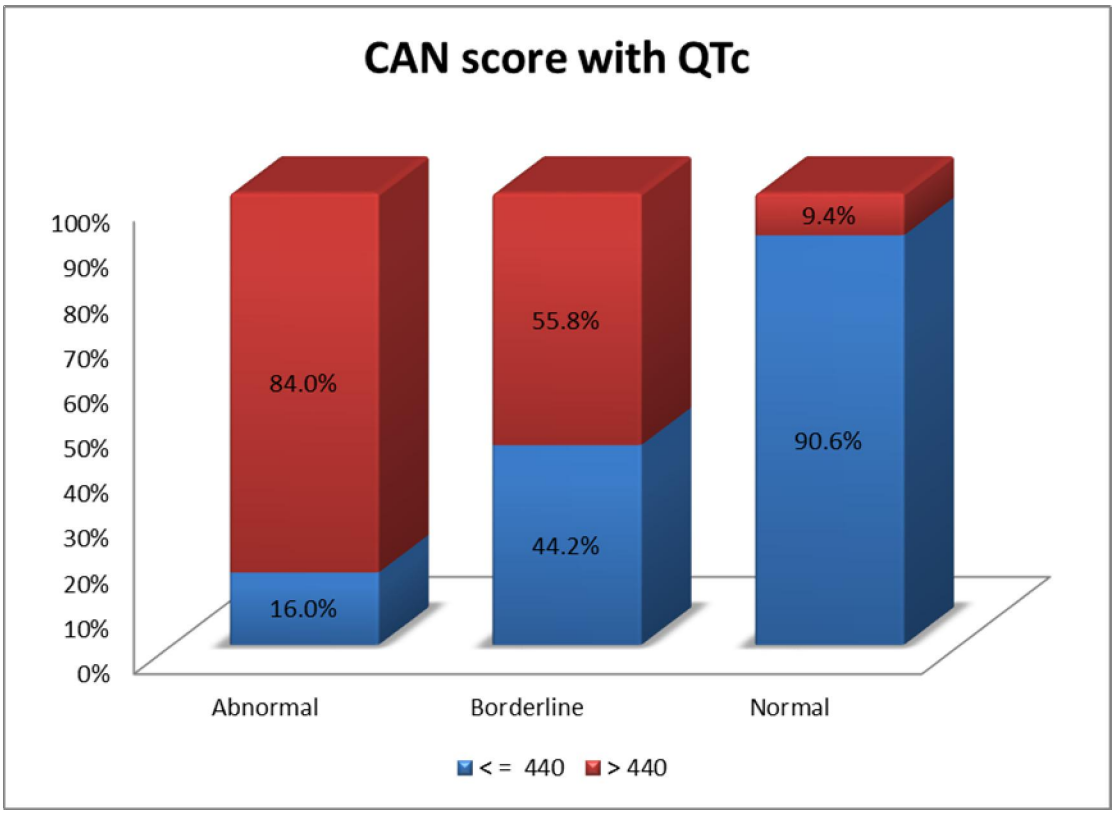
a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 12.00.

QTc * CAN Crosstabulation

Qtc interval		CAN		Total
		Abnormal	Normal	
Qtc	> 440	45	3	48
	≤ 440	23	29	52
Total		68	32	100

Sensitivity %	66.2
Specificity %	90.6
PPV %	93.8
NPV %	55.8
Accuracy %	74.0

QTc prolongation had 66.2% sensitivity and 90.6% specificity in diagnosing CAN in Diabetes Mellitus patients,with a 93.8 %positive predictive value,55.8% negative predictive value and an accuracy of 74%



In patients with CAN score abnormality, there was an increase in QTc interval

ROC Curve

Case Processing Summary

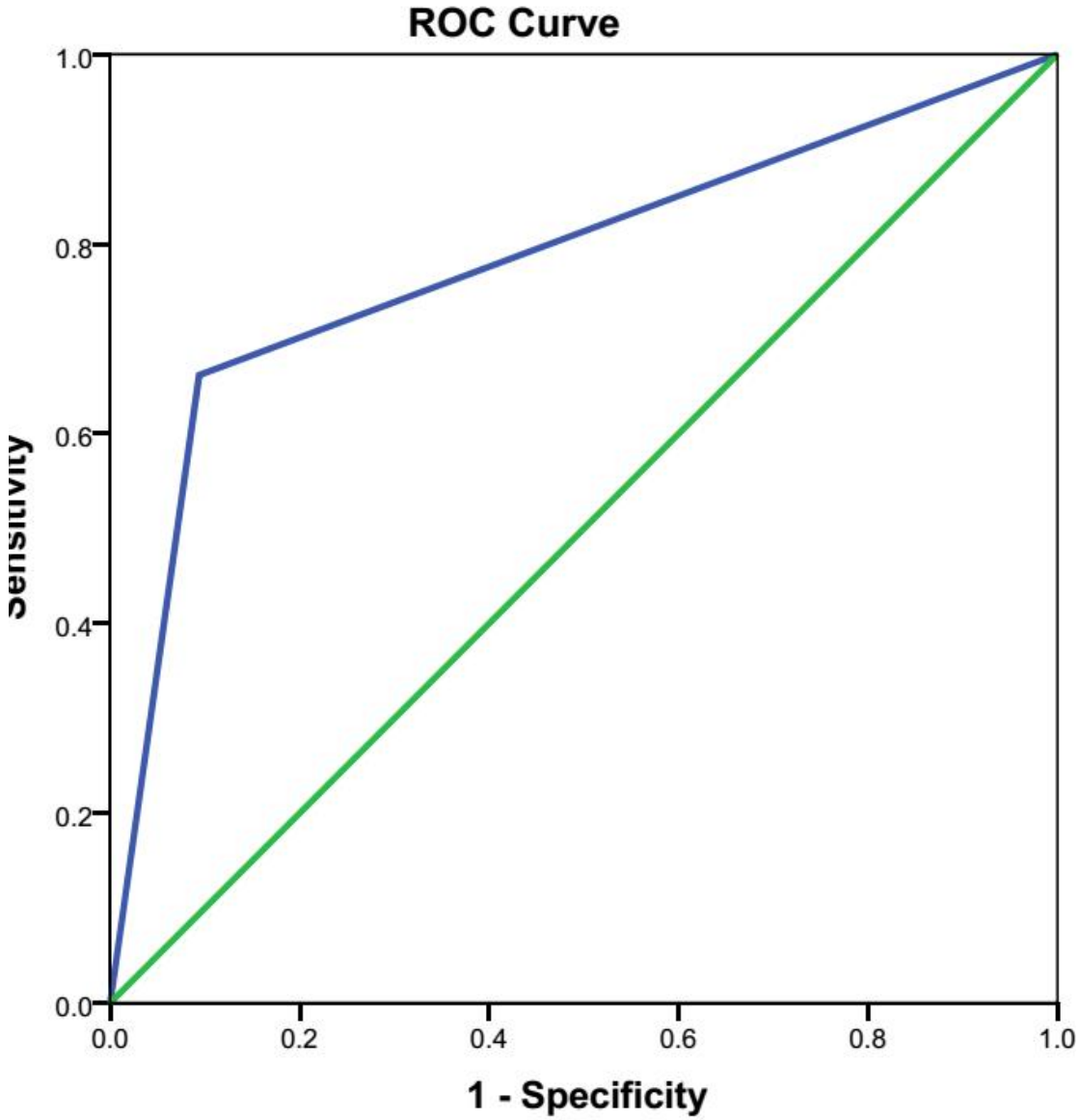
CAN	Valid N (listwise)
Positive[a]	68
Negative	32

Smaller values of the test result variable(s) indicate stronger evidence for a positive actual state.

a. The positive actual state is Abnormal.

ROC Curve is an excellent way to compare diagnostic tests in statistics. its draws on the power of statistical tests.the curve is drawn between sensitivity on X –axis and 1-specificity on Y axis.

Area	Accuracy
0.9-1	Excellent
0.8-0.9	Good
0.7-0.8	Fair
0.6-0.7	Poor
0.5-0.6	Fail


ROC Curve
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s): qtc

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.784	.047	.000	.691	.877

The test result variable(s): qtc has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

From the above ROC curves,area under curve was calculated for QTc.was .It came as 0.754.Thus QTc is fair in diagnosing CAN score.

DISCUSSION

Various previous studies demonstrated that cardiac dysfunction is common in Type 2 DM patients, and shows an increase in prevalence as the duration of diabetes mellitus increases[42-45].

Our study among 100 diabetics in kilpauk medical college showed significant cardiac autonomic dysfunction among diabetes patients.42 females and 58 males were included in our study ,selected after considering exclusion and inclusion criteria. Among 100 patients 21 had duration of diabetes less than 5 yrs,53 patients had duration 5-10 yrs, 26 had duration more than 10 yrs . Among 100 patients,34 were symptomatic and rest 66 were asymptomatic.

Among 100 patients in the study groups, 8 people had abnormal results(score 2) for heart rate variability to deep breathing, 15 had abnormal results for heart rate response to valsalva, 15 showed abnormal results for heart rate response to standing, 7 had abnormal results for BP response to hand grip,5 had abnormal BP response to standing respectively,

Among 100 patients,25 had an abnormal CAN Score,43 had borderline and 32 had normal CAN Scores..CAN score of 0,1 was taken as normal,2 to 4 was considered as borderline and $\geq$ 5 was considered as

abnormal.

Among our study group of 100 diabetics,48 people showed a prolongation in corrected QTc(more than 440 milliseconds).

Among the study group of 100,4.8% of <5yrs diabetics,18.9% of 5-10 yrs diabetics and 53.8% of >10yrs diabetics showed abnormal CAN.Chi square tests showed there is a significant relation between duration of DM and CAN scores.

Out of 100 patients, mean QTc interval in patients with ≤5yrs of diabetes was 428.29(min-408 and max-452),5-10 yrs was 438.75(min-400 ,max-483)and >10 yrs was 454.27(min-432 ,max-500).there was a statistically significant relation between QTc and diabetes.

Post Hoc tests done for multiple comparisons between duration of DM and QTc as dependent variable also showed statistical significance with p value <0.05

Among 48 patients with prolonged QTc interval,21 had abnormal CAN score, 24 had borderline score.Only 4 patients with abnormal CAN score had normal QTc

Mohan et al [42] study from India ,studied can in 336 patients,which showed an increase in prevalence of CAN and duration of diabetes.

Pappachan J M et[46] al studies evaluated the usefulness ofl (QTc) in the Electrocardiogram to diagnose Cardiac autonomic neuropathy in patients with diabetes. Sensitivity and specificity of QTc prolongation in diagnosing CAN were 77% and 62.5% in type 1 diabetes mellitus and 76.5% and 75% in type 2 diabetes.. The study concluded that QTcinterval can be used to diagnose CAN with reasonable sensitivity and specificity[46].

In our study,QTc prolongation had 66.2% sensitivity and 90.6% specificity in diagnosing CAN in Diabetes Mellitus patients,with a 93.8 %positive predictive value,55.8% negative predictive value and an accuracy of 74%.

Thus, prevalence of CAN among diabetic patients in our hospital is fairly high comparable to previous similar study and QTC interval prolongation can be used as a relatively easier diagnostic tool

CONCLUSION

The conclusions from our study are

1. Prevalence of CAN among type 2diabets patients in our hospital is fairly high, 58%
2. There is a relation between prevalence of CAN and duration of diabetes..prevalence of cardiac autonomic neuropathy increases with duration of diabetes
3. QT c interval prolongation increases with increasing duration of diabetes and CAN
4. QTc prolongation can be used as a diagnostic tool in evaluating cardiac autonomic neuropathy with fair specificity and sensitivity

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PROFORMA

NAME: AGE: SEX:

SMOKING/ALCOHOL STATUS:

DURATION OF DIABETES:

HISTORY SUGGESTIVE OF AUTONOMIC NEUROPATHY:

BLOOD PRESSURE: PULSE RATE:

EXAMINATION OF CARDIOVASCULAR SYSTEM:

TEST FOR CARDIOVASCULAR AUTONOMIC FUNCTION:

	TEST 1	TEST 2	TEST3	MEAN
VALSALVA RATIO				
DEEP BREATHING TEST (HEART RATE VARIABILITY)				
SUPINE TO STANDING HEART RATE RESPONSE				
BP RESPONSE TO STANDING				
BP RESPONSE TO SUSTAINED HAND GRIP				

CAN SCORING:

EXAMINATION OF R.S:

EXAMINATION OF GIT:

EXAMINATION OF CNS:

ECG FINDING WITH QTc INTERVAL

INVESTIGATIONS:

HEAMOGLOBIN:

TOTAL COUNT : DIFFRENTIAL COUNT:

COMPLETE RFT :

SERUM POTASSIUM: SERUM CALCIUM:

ECHOCARDIOGRAM

ETHICS COMMITTEE APPROVAL

INSTITUTIONAL ETHICS COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No. 04/2016 Dt: 20.06.2016
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "STUDY ON PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND USE OF QTC INTERVAL IN ITS PREDICTION"- For Project Work submitted by Dr.S.Anju Surendran, Post Graduate in MD (General Medicine), Govt. Kilpauk Medical College, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

8/8/16

DEAN
Govt.Kilpauk Medical College,
Chennai – 10.

8/8/16

சுயஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு:

இடம்: பொது மருத்துவத்துவ துரை

அரசு கீழ்பாக்கம் மருத்துவ கல்லூரி மருத்துவமனை

சென்னை

பங்குபெறுபவரின் பெயர் :

பங்குபெறுபவரின் வயது : **பங்குபெறுபவரின் எண் :**

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்டசிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக்கொள்ளல்லாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில்பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக்கொள்ள மறுக்க மாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ஆய்வாளரின் கையொப்பம்

இடம் :

தேதி

PATIENT CONSENT FORM

Study detail: **"STUDY ON PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND USE OF QTc INTERVAL IN ITS PREDICTION"**

Study centre : KILPAUK MEDICAL COLLEGE, CHENNAI

Patients Name :

Patients Age :

Identification Number :

Patient may check ( ) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any

information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests.

Signature/thumb impression:

Patients Name and Address: place date

Signature of investigator :

Study investigator's Name : place date

MASTER CHART

A	Name	Age	Sex	Duration of DM(yrs)	Symptoms	Heart rate to deep breathing	Heart rate to Valsalva	Heart rate/standing	Bp/hand grip	Bp/standing	CAN Score	A
1	govindhan	50	M	8	y	12	1.1	1	14	25	7	483
2	kamala	45	F	7	n	16	1.11	1.05	17	25	2	430
3	angammal	38	F	5	y	13	1.15	1.04	13	30	5	436
4	krishnan	52	M	12	n	9	1.05	1	14	20	8	476
5	seetha	54	F	11	y	13	1.05	0.93	14	25	7	460
6	vimala	40	F	5	Y	15	1.15	1.05	14	20	3	436
7	Velu	55	M	13	y	9	1.05	0.93	9	28	9	487
8	chandran	52	M	10	n	14	1.15	1.04	14	10	3	449
9	shanthi	43	F	5	n	11	1.1	1	14	15	7	430
10	anbalagan	35	m	3	n	11	1.04	0.94	12	25	7	449
11	chelladurai	53	m	12	y	14	1.1	1.05	15	26	4	449
12	kannappan	50	m	18	y	9	1.05	0.94	8	30	10	500
13	ramasamy	54	m	10	n	12	1.05	1.05	8	25	6	476
14	sasikala	35	f	5	n	15	1.2	1.05	17	8	1	432
15	parvathy	40	f	6	n	14	1.15	1.04	15	12	4	400
16	muniyammal	50	f	8	y	14	1.2	1.05	14	20	5	430
17	pandiyan	35	m	5	n	12	1.15	1.04	10	14	4	460
18	arivoli	52	m	14	y	9	1.14	1	12	30	8	476
19	nazeer	50	m	5	n	11	1.2	1.04	10	15	5	438
20	thangamma	49	f	5	n	16	1.21	1.05	16	15	1	400
21	mani	43	m	4	y	14	1.14	1.05	14	15	4	434
22	siva	32	m	2	n	15	1.23	1.06	16	6	0	426

23	shakthivel	35	m	3	n	16	1.15	1.04	15	10	2	443
24	amirtham	58	f	20	y	10	1.12	1	14	20	7	449
25	sekar	53	m	8	n	16	1.22	1.04	16	14	1	442
26	anjalai	45	f	9	y	14	1.15	1.02	14	15	5	448
27	shanmugam	44	m	7	n	13	1.12	1.05	16	14	4	460
28	manogaran	50	m	14	y	14	1.15	1.02	9	20	6	452
29	srinivasan	40	m	3	n	18	1.21	1.05	17	6	0	416
30	amsa	41	f	9	y	13	1.16	1.04	14	18	4	432
31	sivagami	50	f	10	n	14	1.1	1.02	14	16	7	448
32	santhi	34	f	4	y	16	1.21	1.04	15	8	1	420
33	marimuthu	41	m	7	n	16	1.22	1.04	14	8	1	436
34	amudham	40	f	6	n	12	1.22	1.05	16	5	1	436
35	sasindar	39	m	4	n	15	1.22	1.06	15	6	1	432
36	babu	55	m	18	y	14	1.18	0.94	12	30	7	468
37	annamalai	57	m	12	n	12	1.11	1.04	16	18	4	446
38	pandian	40	m	6	n	13	1.22	1.05	17	4	1	438
39	gopal	49	m	7	n	15	1.15	1.04	14	16	3	420
40	mariyappan	58	m	14	y	9	1.09	1.02	15	24	8	452
41	velu	52	m	9	n	14	1.19	1.03	16	8	4	442
42	jagan	40	m	2	n	17	1.24	1.07	17	4	0	424
43	dhanapal	46	m	5	n	14	1.21	1.04	14	8	2	412
44	revathy	37	f	4	n	15	1.2	1.05	16	10	1	438
45	leelavathy	56	f	8	y	14	1.22	1.02	14	15	4	438
46	prem	46	m	5	n	14	1.23	1.05	17	8	1	432
47	ambiga	35	f	4	n	16	1.24	1.06	16	4	0	426
48	pushpa	56	f	12	y	13	1.18	1.02	14	8	4	442

49	muthu	52	m	8	n	14	1.21	1.04	14	20	3	456
50	kaniappan	52	m	12	y	13	1.18	1.02	12	15	3	448
51	palani	38	m	4	n	16	1.2	1.04	16	4	1	438
52	jeevamma	50	f	8	y	14	1.22	1.04	16	16	2	442
53	rammaih	47	m	6	n	14	1.24	1.05	18	4	1	428
54	ravi	40	m	5	n	16	1.23	1.04	16	6	0	438
55	sheik	42	m	7	n	13	1.19	1.02	17	8	3	432
56	rosy	45	f	6	y	12	1.1	1.01	14	16	6	446
57	gowri	57	f	11	y	13	1.2	1.04	14	18	4	448
58	mariamma	59	f	16	y	14	1.09	0.98	14	30	8	456
59	kannan	50	m	8	n	14	1.2	1.03	16	8	3	456
60	amal	35	m	2	n	17	1.23	1.06	17	4	0	424
61	shantha	56	f	11	n	14	1.18	1.04	12	12	4	438
62	manoranjan	45	m	7	n	14	1.2	1.03	14	8	4	450
63	yuvarani	39	f	3	n	13	1.22	1.04	16	6	1	430
64	siddiq	40	m	5	n	14	1.23	1.04	14	8	2	438
65	surya	42	m	6	n	12	1.18	1.01	16	10	3	436
66	sankar	37	m	3	n	14	1.24	1.06	18	2	1	428
67	radha	55	f	12	y	12	1.16	1.02	14	20	5	448
68	asiya	50	f	10	y	12	1.21	1.02	16	16	3	442
69	suganthi	49	f	8	n	16	1.16	1.02	14	14	4	442
70	sathish	40	m	4	n	14	1.23	1.05	16	6	1	452
71	srinivasan	58	m	12	n	12	1.17	1.05	12	13	4	432
72	shanmugam	56	m	11	n	14	1.21	1.01	14	8	3	438
73	mahesh	39	m	4	n	16	1.2	1.06	17	6	1	424
74	thilaka	51	f	5	y	12	1.21	1.04	14	9	2	442
75	govindhan	56	m	16	y	9	1.1	1.01	11	10	8	459

76	kamala	45	f	6	n	16	1.25	1.04	16	12	1	424
77	ayisha	54	f	10	y	13	1.19	1.02	16	8	3	438
78	karthik	36	m	2	n	14	1.24	1.05	17	4	1	428
79	yamuna	39	f	4	n	16	1.22	1.01	16	6	1	408
80	krishnan	59	m	15	y	12	1.18	0.93	14	18	5	449
81	jaya	52	f	12	n	12	1.19	1.04	16	14	3	444
82	gopi	50	m	9	y	16	1.16	1.01	14	12	4	456
83	anita	38	f	4	n	14	1.23	1.05	16	4	1	412
84	padma	48	f	8	n	16	1.22	1.04	14	10	1	410
85	daisy	45	f	6	n	16	1.21	1.01	16	14	2	436
86	varadhan	55	m	11	y	14	1.18	1.01	14	10	4	448
87	amal	48	m	8	n	16	1.19	1.02	11	9	3	439
88	ganga	54	f	12	n	14	1.21	0.93	16	12	4	442
89	devan	56	m	14	y	10	1.14	0.93	9	20	8	460
90	arumugam	45	m	5	n	16	1.22	1.01	14	10	2	446
91	sekar	40	m	5	n	16	1.19	1.05	17	6	1	442
92	emrose	44	f	4	n	12	1.22	1.04	16	4	1	422
93	jancy	48	f	5	n	14	1.24	1.05	16	8	1	400
94	noorjahan	50	f	8	n	16	1.22	1.04	14	10	1	435
95	balan	48	m	9	n	17	1.16	1.01	14	8	3	452
96	selvam	52	m	8	n	14	1.08	0.93	13	22	7	468
97	ramesh	43	m	4	n	17	1.18	1.06	16	6	1	420
98	murugan	48	m	9	n	16	1.24	1.01	14	10	2	436
99	rose	49	f	8	n	14	1.23	1.05	16	14	2	440
100	savithri	53	f	12	y	14	1.16	1.04	13	14	4	444