Dissertation on

A STUDY OF QTd AS AN INDICATOR OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS

Submitted in partial fulfillment of requirements of

MASTER OF MEDICINE DEGREE

BRANCH – I – (GENERAL MEDICINE)

GOVERNMENT RAJAJI HOSPITAL

MADURAI MEDICAL COLLEGE

MADURAI- 20

THE TAMILNADU

Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI

2017

Madurai 20, 28.09.2016

CERTIFICATE

This is to certify that this dissertation entitled ***"A STUDY OF QTd AS AN INDICATOR OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS"*** *is the bonafide work of* ***Dr.VRINDA.V*** *in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for* ***M.D General Medicine Branch I*** *examination to be held in* ***April 2017***

Dr.M.R.VAIRAMUTHURAJU .MD. GM

THE DEAN,

Madurai Medical College and

Government Rajaji Hospital,

Madurai.

CERTIFICATE FROM THE HEAD OF THE DEPARTMENT

This is to certify that this dissertation entitled ***"A STUDY OF QTd AS AN INDICATOR OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS"*** *is the bonafide work of* ***Dr.VRINDA.V*** *in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for* ***M.D General Medicine Branch I*** *examination to be held in* ***April 2017.***

Dr.V.T.PREMKUMAR, M.D,

Professor and Head of the Department,

Department of General Medicine,

Government Rajaji Hospital,

Madurai Medical College,

Madurai.

CERTIFICATE FROM THE GUIDE

This is to certify that this dissertation entitled ***"A STUDY OF QTd AS AN INDICATOR OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS"*** *is the bonafide work of* ***Dr.VRINDA.V*** *in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for* ***M.D General Medicine Branch I*** *examination to be held in* ***April 2017.***

Dr.V.T.PREMKUMAR, M.D,

Professor and Head of the Department,

Department of General Medicine,

Government Rajaji Hospital,

Madurai Medical College,

Madurai.

DECLARATION

I, ***Dr.VRINDA.V,*** *declare that, I carried out this work on* ***"A STUDY OF QTd AS AN INDICATOR OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS"*** *at the Department of Medicine, Govt. Rajaji Hospital during the period December 2016 to May 2016. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree or 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 fulfillment of the rules and regulations for the M.D degree examination in General Medicine.*

Place : *Madurai* ***DR.VRINDA.V***

Date:

ACKNOWLEDGEMENTS

I would like to thank our Dean ***Dr.M.R.VAIRAMUTHURAJU.MD.GM,*** *for permitting me to use the facilities of Madurai Medical College and Government Rajaji Hospital to conduct this study. I would like to express my deep sense of gratitude and thanks to my Unit Chief and Head of the Department, Department of Medicine,* ***Prof.Dr.V.T.Premkumar M.D****., for his valuable suggestions and guidance throughout the course of my study.*

I also sincerely express my thanks to our Professors ***Dr.R.Balajinathan.M.D., Dr.M.Natarajan.M.D., Dr.G.Bagialakshmi, M.D., Dr.J.Sangumani.M.D., Dr.C.Dharmaraj.M.D., Dr.Ravindran M.D., Dr.Prabhakaran M.D., Dr.Peer Mohammed*** *for their par excellence in clinical teaching and constant support.*

I express my sincere thanks to ***Prof. Dr.P.Muthukumareshan. MD.,*** *Head of the department of Biochemistry for their constant support, guidance, cooperation in this study.*

I also thank the Assistant Professors of my unit ***Dr.M.Sooriyakumar,MD., Dr.K.Muralidharan,MD., Dr.S.Murugesan.MD., Dr.Sridharan MD*** *for their constant encouragement to complete my study.*

I thank ***Dr.Kumar, Dr.Vijayakumar, Dr.Sujatha, Dr.Ahamed kalil, Dr.Gokul Prasannan, Dr Vinoj , Dr. Renu Raj R*** *for their timely help and encouragement to do my study.*

I express my sincere gratitude and love to my only sister ***Vidya .V*** *who encouraged me throughout this study .*

I thank the patients of our hospital for their extreme patience and cooperation without whom the project would have been a distant dream.

Finally I thank ***GOD ALMIGHTY*** *for all his blessings.*

TABLE OF CONTENTS

ANNEXURES

INTRODUCTION

INTRODUCTION

Diabetes Mellitus is a group of metabolic diseases characterised by chronic hyperglycemia associated with abnormal metabolism of proteins fats and carbohydrates due to absolute or relative insulin deficiency[13].

Diabetes is a modern day epidemic affecting around 366 million people globally as per 2011 statistics. India, our country is the diabetic capital of the world harbouring more than 60 million people[13,14].

As the understanding of Diabetes Mellitus has greatly improved now , patients are living longer ,making them susceptible to long term complications such as neuropathy,nephropathy, retinopathy, and vasculopathy. Each complication need to be addressed specifically in addition to hyperglycemia.

Diabetic neuropathy is one of the commonest complication of diabetes mellitus and is associated with considerable morbidity and mortality. Autonomic neuropathy, often overlooked, is one of the most insidious complications of diabetes mellitus (DM) especially if long standing and poorly controlled. Cardiovascular autonomic neuropathy (CAN), within the context of Diabetic autonomic neuropathy, occurs when there is an impairment of autonomic control of the cardiovascular system after ruling out other causes of dysautonomia[5]. However, symptomatic CAN (CAN) manifests in about 5% of diabetic patients, but when present, it is associated with the increased mortality , predisposing to ventricular arrhythmias, silent ischaemia, and cardiac arrest. Hence, its early detection and early prevention is essential.

Cardiac Autonomic Neuropathy (CAN) is often overlooked both in diagnosis and treatment simply because there is no widely accepted single approach to

its diagnosis. Currently, Cardiovascular autonomic reflex tests (CART) are the gold standard for diagnosing CAN in persons with DM .It include four tests: (i)heart rate variation to deep breathing (ii) heart rate variation to Valsalva, (iii.)heart rate response to standing (30:15), and (iv) orthostatic hypotension (OH)[20]. Maneuvers used in the first three tests induce changes in heart rate variability that primarily assess the parasympathetic ANS. In contrast, Orthostatic hypotension or the variation in systolic BP in supine and standing positions evaluates the function of the sympathetic ANS .But these tests are cumbersome and not easy to perform in every patient. Therefore, there is a need of simple, non-invasive bed side test to detect early autonomic involvement in diabetes.

In 1980 an association of prolonged QT interval with CAN was established .This opened the possibility of rapid objective method to detect cardiac dysautonomia. The QTc interval is considered as a measurement of myocardial depolarisation and repolarisation, which is influenced by central autonomic neural tone and kinetics of myocardial cells. Abnormality of the QT interval which indicates abnormal repolarisation has been linked with the development of potentially fatal arrhythmias which may lead to sudden death . One potential cause may be severe but asymptomatic ischemia, which can induce lethal arrhythmias.

QT is not uniform in all the 12 leads of ECG[9], which leads to the concept of QT dispersion which is the difference between the longest and the shortest QT interval on 12 leads ECG strip. QTd also has been shown to be a reliable detection method for early abnormalities in autonomic imbalance. So keeping in mind the possible role of QTc & QTd on morbidity & mortality in a patient with diabetic CAN,

the present study was done to study the relationship of prolonged QTc & QTd with CAN in Type 2 diabetes.

AIMS AND OBJECTIVES

AIM OF THE STUDY

1. To determine QTc maximum, QTc mean , QTc minimum QTc dispersion in Type2 diabetic patients.
2. Comparison of QTc maximum, QTc minimum, QTc dispersion, QTc mean in both study group and control group.
3. To study the significance of QTd as an indicator of CAN in Type 2 Diabetes mellitus.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

1. DIABETES MELLITUS

Diabetes Mellitus is a chronic disease characterised by fasting and post prandial hyperglycemia with varied clinical features and progression. The underlying basic mechanism of diabetes is either the defect in the production or defect in the action of insulin, which is a hormone that controls metabolism of glucose, fat and amino acids[3]. Chronic hyperglycemia from any cause may lead to many complications which includes both microvascular and macrovascular complications

1.A. ETIOLOGICAL CLASSIFICATION[3]

"The etiological classification of diabetes mellitus currently recommended by World Health Organisation and American Diabetes Association is given below:

1. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)

A. Immune-mediated

B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes

A. Genetic defects of beta cell development or function characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)

2. Glucokinase (MODY 2)

3. HNF-1α (MODY 3)

4. Insulin promoter factor-1 (IPF-1; MODY 4)

5. HNF-1β (MODY 5)

6. NeuroD1 (MODY 6)

7. Mitochondrial DNA

8. Subunits of ATP-sensitive potassium channel

9. Proinsulin or insulin

10. Other pancreatic islet regulators/proteins such as *KLF11, PAX4, BLK, GATA4, GATA6, SLC2A2* (GLUT2), *RFX6, GLIS3*

B. Genetic defects in insulin action

1. Type A insulin resistance

2. Leprechaunism

3. Rabson-Mendenhall syndrome

4. Lipodystrophy syndromes

C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase

D.Endocrinopathies— acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma

E. Drug- or chemical-induced—glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, calcineurin and mTOR

inhibitors, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine

F. Infections—congenital rubella, cytomegalovirus, coxsackievirus

G. Uncommon forms of immune-mediated diabetes—"stiff-person" syndrome, anti-insulin receptor antibodies

H. Other genetic syndromes sometimes associated with diabetes— Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon- Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM)"

1.B. TYPE 1 DIABETES MELLITUS

"Type1 Diabetes Mellitus develops as a result of synergistic effects of genetic , environmental and immunologic factors that ultimately destroys the pancreatic beta cells .Individuals with genetic susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occur over months to years[3]. A number of auto antibodies are described in type 1 diabetes which include anti GAD antibodies, anti islet cell antibodies , anti tyrosine phosphatase antibodies etc . This autoimmune process is proposed to be triggered by environmental or infectious stimulus. Features of diabetes may not become apparent until majority of beta cells are destroyed[3]."

1.C. TYPE 2 DIABETES MELLITUS

"This represents a heterogenous group of conditions which was previously thought to occur in adults, now it is frequently encountered in children and adolescents. This disease is characterised by either disorders of insulin action and secretion, one of which maybe a dominant problem[7]. When diabetes become clinically evident both disorders of insulin action and secretion are present."

" Circulating endogenous insulin is sufficient enough to prevent keto acidosis but is inadequate to prevent hyperglycemia especially in the setting of insulin resistance. So these patients have a relative but not absolute insulin deficiency. They may not require exogenous insulin for their survival but may require insulin for glycemic control."

"Genetic and environmental factors combine to cause insulin resistance

and beta cell loss .Early in the disease process, hyperplasia of pancreatic beta cells occurs and probably accounts for fasting hyper-insulinism and exaggerated insulin and proinsulin responses to glucose and other stimuli. With time chronic deposition of amyloid in islets may combine with inherited genetic defects progressively to impair beta cell function[7]."

"Obesity is the most important factor causing insulin resistance. Visceral obesity , due to accumulation of fat in omentum and mesentry correlates with insulin resistance. Even those who are not obese may have characteristic centripetal fat distribution which confers insulin resistance. Most of Type 2 diabetic patients may remain undiagnosed for a long time, mostly in years, because in them classical

symptoms of diabetes ie polyuria and polydypsia may not be present due to the insidious onset of hyperglycemia[7] . For the same reason these patients may have evidence of neuropathic and cardiovascular complications at the time of diagnosis."

" The risk of type 2 diabetes increases with age ,BMI, and physical inactivity .Type 2 diabetes shows strong familial aggregation and hence should be suspected in people with positive family history . Incidence is also higher in patients with other lifestyle diseases like hypertension and dyslipidemia. Diabetes should be suspected in women with chronic vulvo-vaginal candidiasis and generalised pruritus. Patients with history of gestational diabetes mellitus, with history macrosomia, polyhydramnios, pre-eclampsia, unexplained fetal loss are at high risk for developing diabetes in later life. Males may present with balanoposthitis[3]."

1.D. RISK FACTORS FOR TYPE 2 DIABETES MELLITUS[3]

i. "Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
ii. Obesity (BMI ≥25 kg/m2 or ethnically relevant definition for overweight)
iii. Physical inactivity
iv. Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
v. Previously identified with IFG, IGT, or an hemoglobin A1c of 5.7–6.4%
vi. History of GDM or delivery of baby >4 kg
vii. Hypertension (blood pressure ≥140/90 mmHg) or history of CVD
viii. HDL cholesterol level <35 mg/dL and/or a triglyceride level >250mg/dL
ix. PCOS"

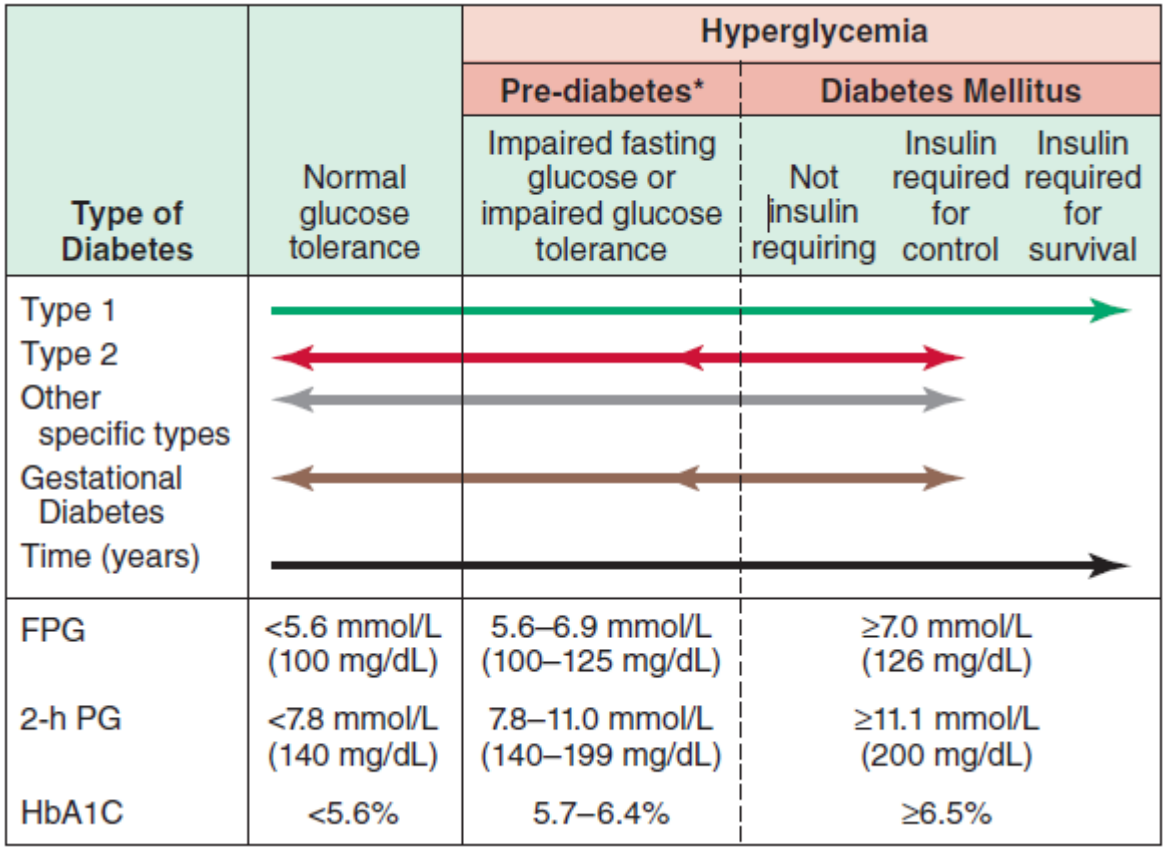


Figure 1.1. Spectrum of glucose homeostasis and diabetes mellitus. In most types of diabetes mellitus individual progresses from normal glucose tolerance to impaired glucose tolerance to overt diabetes[3].

1.E. PATHOGENESIS OF TYPE 2 DIABETES[3,7]

"The pathological sequence of type 2 diabetes mellitus is complex and entails many different elements .There is a strong genetic component. The disease is polygenic and multi-factorial as in addition to genetic factors several environmental factors modulate the phenotype. The genes that predispose to type 2 DM are incompletely identified[15]. Recent genome-wide association studies have identified a

large number of genes that convey a relatively small risk for type 2 DM.. The mechanisms by which these genetic loci increase the susceptibility to type 2 DM are not clear, but most are predicted to alter islet function or development or insulin secretion[3,7]. Although the genetic susceptibility to type 2 DM is under active investigation , it is currently not possible to use a combination of known genetic loci to predict type 2 DM[19]."

" As the blood glucose rises above normal, acquired defects in glucose homeostasis system occurs. It initially impairs beta cell's glucose responsiveness by impairing the first phase of insulin response, thereby causing blood glucose level to rise in the range of impaired glucose tolerance. Hyperglycemia together with increased free fatty acids due to obesity and insulin resistance causes further deterioration in beta cell function along with insulin resistance causes more hyperglycemia ranging to full blown diabetes[3] ."

" Type 2 diabetes is thus characterised by hyperinsulinemia, insulin resistance, increased hepatic glucose output and impaired fat metabolism. In the early stages the blood sugar is maintained normal by hyperinsulinemic response by beta cells.So the insulin resistance in type 2 diabetes is relative as it is overcome by hyperinsulinemic state. As these progress the beta cells get exhausted and will be unable to maintain this hyperinsulinemic state . This leads to decreased peripheral utilisation of glucose by the insulin resistant muscle and adipose tissue leading to post prandial hyperglycemia[3]. As disease progresses , further decline in insulin secretion along with increased hepatic glucose output leads to fasting hyperglycemia and overt diabetes."

The molecular mechanism for resistance to insulin is still not clear. Its postulated that post receptor defects in insulin regulated phosphorylation and dephosphorylation is involved in in resistance . Accumulation of lipid within skeletal myocytes impair insulin stimulated mitochondrial ATP production[3] .This leads to impaired fatty acid oxidation and lipid accumulation within skeletal myocytes leads to generation of reactive oxygen species and lipid peroxides. Hyperinsulinemia induced these effects may be the reason for accelerated atherosclerosis seen in diabetics.

Central obesity plays a central role in insulin resistance. Increased adipocyte mass leads to increased circulating free fatty acids: which contribute to insulin resistance. Adiponectin which is an insulin sensitiser is reduced in obesity adding on to insulin resistance.In addition these adipokines induces an inflammatory state.

The mechanism behind the beta cell failure is not elucidated[3,7]. A second genetic defect in addition to insulin resistance is postulated to cause beta cell failure. Glucotoxicity may add on to this causing further beta cell failure. Increased hepatic glucose output occurs as a result of insulin resistance and hyperinsulinemia leading to decreased glycogen synthesis and storage as well as increased gluconeogenesis .The increased circulating free fatty acids may lead to increased hepatic synthesis of lipids which may lead on to hepatic steatosis and non alcoholic fatty liver disease.

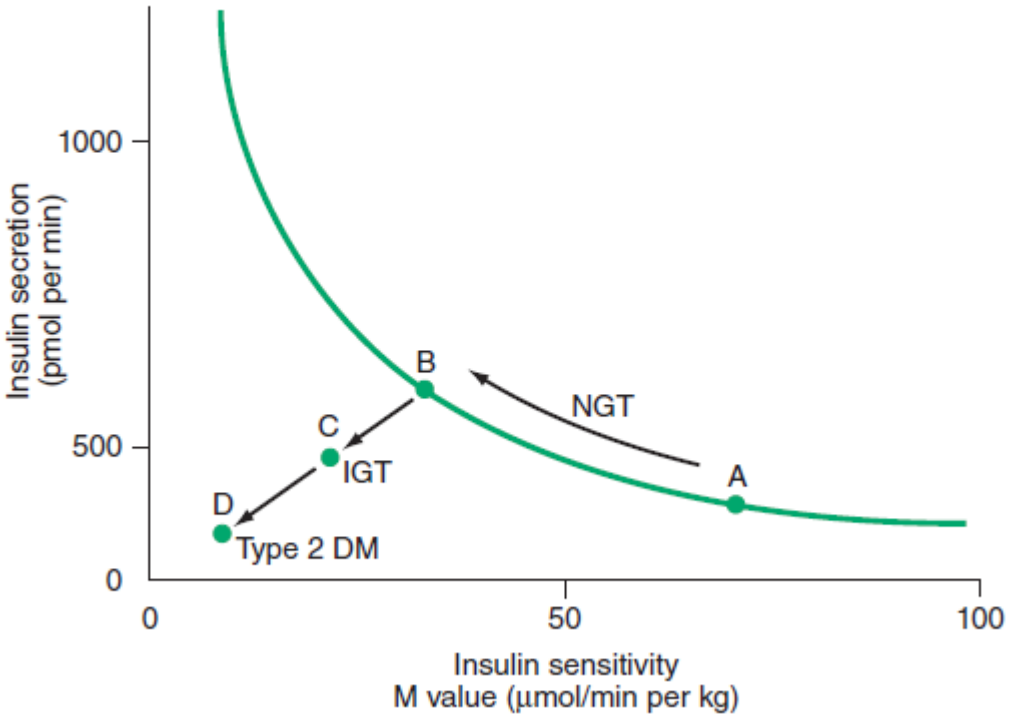


Figure1.2: "Metabolic changes during the development of type 2 diabetes mellitus (DM). Insulin secretion and insulin sensitivity are related, and as an individual becomes more insulin resistant (by moving from point A to point B), insulin secretion increases. A failure to compensate by increasing the insulin secretion results initially in impaired glucose tolerance (IGT; point C) and ultimately in type 2 DM (point D)."

1.F. Prevention of diabetes

Overt diabetes is preceded by a variable period of impaired glucose tolerance[3,7,13]. Life style modifications and pharmacological interventions are suggested to delay the onset of DM. Important considerations are maintaining an adequate BMI and regular physical activity ie 30 minutes a day for 5 days a week. Pharmacological measures to prevent diabetes is controversial due to lack of supporting data. Currently American

Diabetes[3] association suggested the use of metformin in individuals with IFG and IGT and high risk features for development of diabetes like :

i. age <60years
ii. BMI>/=35kg/m2
iii. Family history of diabetes mellitus in first degree relative
iv. Women with history of GDM

1.G . CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS[3,13]

i. Symptoms of diabetes plus random blood glucose concentration >/= 200mg/dl
ii. Fasting plasma glucose >/=126mg/dl
iii. Haemoglobin A1C >/= 6.6%
iv. 2 hour plasma glucose >/= 200mg/dl during an oral glucose tolerance test

1.H .COMPLICATIONS OF DIABETES MELLITUS

ACUTE COMPLICATIONS OF DIABETES MELLITUS[3]

"Hypoglycaemia , Diabetic ketoacidosis, hyperglycaemic hyperosmolar state are acute complications of the disease. Hypoglycemia is seen in both Type 1 and Type 2 diabetes, when the patient skips a meal. In a previously well controlled Type 2 diabetes patient if develops hypoglycaemia the physician should rule out the development of diabetic nephropathy. DKA is primarily seen in individuals with Type 1 diabetes Mellitus as they have absolute insulin deficiency which leads to ketogenesis. HHS is seen in Type 2 Diabetes mellitus patients where they have

enough insulin to prevent ketogenesis but not enough to reduce hyperglycemia . Both are associated with potentially serious complications if not promptly diagnosed and treated".

CHRONIC COMPLICATIONS OF DIABETES MELLITUS[3]

I. "Microvascular

A. Eye disease

i. Retinopathy (nonproliferative/proliferative)

ii. Macular edema

B. Neuropathy

i. Sensory and motor (mono- and polyneuropathy)

ii. Autonomic

C. Nephropathy (albuminuria and declining renal function)

II. Macrovascular

i. Coronary heart disease

ii. Peripheral arterial disease

iii. Cerebrovascular disease

III. Other

i. Gastrointestinal (gastroparesis, diarrhea)

ii. Genitourinary (uropathy/sexual dysfunction)

iii. Dermatologic

iv. Infectious

v. Cataracts

vi. Glaucoma

vii. Cheiroarthropathy

viii. Periodontal disease

ix. Hearing loss”

“Other comorbid conditions associated with diabetes (relationship to hyperglycemia is uncertain): depression, obstructive sleep apnea, fatty liver disease, hip fracture, osteoporosis (in type 1 diabetes), cognitive impairment or dementia, low testosterone in men”.

MECHANISM OF COMPLICATIONS[3]

Three major theories are proposed to explain the emergence of complications.

i. “Increased intracellular glucose via non enzymatic glycosylation of cellular proteins, leads to the formation of advanced glycosylation end products (AGE’s) AGE’s is thought to cause cross linking of proteins , accelerate atherosclerosis ,promote glomerular dysfunction ,reduce nitric oxide synthesis ,induce endothelial dysfunction and alter the extra-cellular matrix composition and structure.

ii. Hyperglycemia increases glucose metabolism via sorbitol pathway, thus converting it to sorbitol by enzyme aldose reductase .Increased sorbitol adversely affects cellular physiology and leads to cellular dysfunction.

iii. Hyperglycemia is also proposed to increase formation of diacylglycerol leading to activation of certain isoforms of protein kinase C which in turn lead to diabetes related complications.

iv. Hyperglycemia increases the metabolism of glucose via hexosamine pathway leading to generation of fructose 6 phosphate. This in turn is a substrate for proteoglycan production and glycosylation of proteins leading to complications."

In addition growth factors like VEGF-A, TGF beta are also implicated in the pathogenesis of diabetes related complications. Its postulated that hyperglycemia leads to increased production of free radicals and reactive oxygen species in the mitochondria which may activate the above 4 pathways. Though hyperglycemia serves as the initial triggering event, the different pathogenetic mechanisms involved in the development of different complications are still not clearly understood.

2. DIABETIC NEUROPATHY

" The clinical impact of diabetes is mainly manifest in the peripheral nervous system though CNS is also involved in long standing diabetes. Diabetic neuropathy causes substantial morbidity and mortality. It is diagnosed on the basis of symptoms and signs, and after the exclusion of other causes of neuropathy as the clinical features of diabetic neuropathy are similar to those of other neuropathies[3]. Depending on the criteria used for diagnosis, it affects between 50 and 90% of patients with diabetes, and of these, 15–30% will have painful diabetic neuropathy

(PDN).Neuropathy occurs secondary to metabolic disturbance, and prevalence is related to the duration of diabetes and the degree of metabolic control. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Additional risk factors are body mass index (BMI) , smoking. , presence of CVD, elevated triglycerides, and hypertension is also associated with diabetic peripheral neuropathy[4].”

2.A . “Classification of diabetic neuropathy[3]

i. Somatic

A. Polyneuropathy

a. Symmetrical, mainly sensory and distal

b. Asymmetrical, mainly motor and proximal (including amyotrophy)

B. Mononeuropathy (including mononeuritis multiplex)

ii. Visceral (autonomic)

a. Cardiovascular

b. Gastrointestinal

c. Genitourinary

d. Sudomotor

e. Vasomotor

f. Pupillary”

“The most common form of diabetic neuropathy is distal symmetric polyneuropathy in which loss of function appears in a glove and stocking pattern and is due to axonal neuropathic process, but up to 50% of patients do not have symptoms of neuropathy.

Longer nerves are vulnerable and hence more impact is on foot. Both motor and sensory nerve conduction is delayed in peripheral nerves and ankle jerk may be absent: Sensory involvement precedes motor involvement .Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Pain typically involves the lower extremities, is usually present at rest, and worsens at night"

" Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness.The asymmetric neuropathies are distinctive and may be due to combination of microvascular, compression and immune mediated mechanisms".

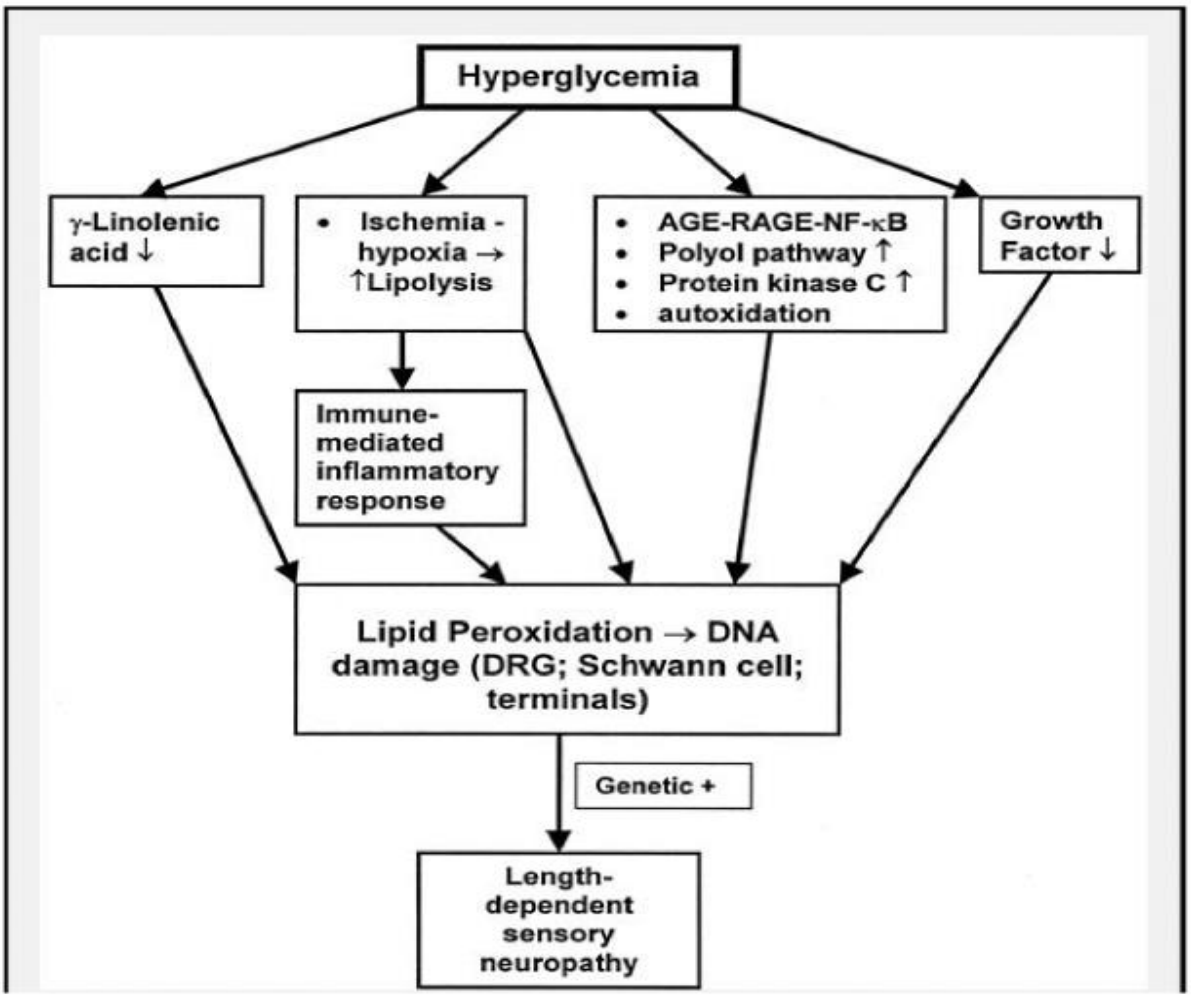


Figure 2.1: Suggested pathogenesis of diabetic neuropathy

2.B . DIABETIC AUTONOMIC NEUROPATHY

“Autonomic neuropathy is one of the serious and common complication of diabetes. DM-related autonomic neuropathy can involve multiple systems, including the Cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. This is not necessarily associated with peripheral somatic neuropathy. Autonomic neuropathy may reduce counter-regulatory hormone release, especially catecholamines , leading to an inability to sense hypoglycemia thereby subjecting the

patient to the risk of severe hypoglycemia .It further complicates the efforts to improve glycemic control. The development of autonomic neuropathy is less clearly related to poor metabolic control than somatic neuropathy. So improved glycemic control rarely results in improved symptoms."

2.C. Clinical features of autonomic neuropathy

I. Cardiovascular

i. Postural hypotension

ii. Resting tachycardia

iii. Fixed heart rate

iv. Exercise intolerance

II. Gastrointestinal

i. Dysphagia, due to oesophageal atony

ii. Abdominal fullness, nausea and vomiting, unstable glycaemia, due to delayed gastric emptying ('gastroparesis')

iii. Nocturnal diarrhoea •

iv. Constipation, due to colonic atony

v. Fecal incontinence

III. Genitourinary

i. Difficulty in micturition

ii. Urinary incontinence

iii. Recurrent infection due to atonic bladder

iv. Erectile dysfunction

v. Retrograde ejaculation

IV. Sudomotor

i. Nocturnal sweats without hypoglycaemia

ii. Gustatory sweating

iii. Heat intolerance

iv. Anhidrosis; fissures in the feet

V. Vasomotor

i. Feet feel cold, due to loss of skin vasomotor responses

ii. Dependent oedema, due to loss of vasomotor tone and increased vascular permeability

iii. Bullous formation

VI. Metabolic

i. Hypoglycaemia unawareness

ii. Hypoglycaemia associated autonomic failure

VII. Pupillary

i. Decreased pupil size

ii. Resistance to mydriatics

iii. Delayed or absent reflexes to light

2.D. CARDIVASCULAR AUTONOMIC NEUROPATHY

"CAN (CAN) is one of the well recognised complication of diabetes which carries high mortality and morbidity but is often overlooked both in diagnosis and treatment simply because there is no widely accepted single approach to its

diagnosis[5]. Cardiovascular autonomic neuropathy occurs when there is an impairment of autonomic control of the cardiovascular system. It is well known that CAN is an early and frequent complication of DM, affecting around 8-15 % of newly diagnosed. In addition, CAN is among one of the most disabling complications of DM in terms of life expectancy and quality. Clinical manifestations of CAN are pleomorphic and appear in late stages. Hence clinical symptoms alone doesn't have enough sensitivity and specificity for diagnosis[11]. Cardiovascular autonomic involvement can manifest clinically as postural hypotension, resting tachycardia, exercise intolerance or may be just silent, detected on autonomic function tests".

"Severity and development of CAN is not all or none phenomenon[5] .It represents a continuous progression of disease .Hence its severity was directly related to the duration and degree of high blood sugar levels. Within a decade of developing manifest autonomic neuropathy, mortality ranges 30–50% , mostly from sudden cardio-respiratory arrest[10]. Patients with postural fall in blood pressure have the highest mortality".

"CAN is associated with a high risk of sudden cardiac death, possibly related to silent myocardial ischemia and fatal arrhythmias. In patients with diabetic autonomic neuropathy there occurs a decrease in parasympathetic tone at night and sympathetic activity predominates during sleep. This may be the reason for cardio vascular events".

2.E. Pathogenesis of CAN

"Most of the proposed mechanisms of neuronal Injury in diabetes mellitus are based on models of somatic rather than autonomic neuropathy[1]. The pathogenesis of CAN is likely involve several mechanisms and pathways that lead ischemia of neurons or direct death or dysfunction of neurons".

i. Hyperglycaemia

"Hyperglycaemia and the adverse metabolic mileu in patients with DM result in increased oxidative and nitrosative stress.It can cause direct neuronal damage as well as neuronal and endothelial dysfunction .The rich mitochondria in neuronal axons makes them particularly susceptible to effects on oxidative and nitrosative stress. Increased oxidative stress results in poly ADP-ribose polymerase activation. This coupled with other activated downstream pathways including the polyol pathway, advanced glycation end products production, protein kinase C and the hexosamine pathway are thought to contribute to glucose toxicity. These pathways in return exacerbate oxidative stress. These can induce changes in gene transcription factors ,gene expression: thus disrupting many cellular functions .This interferes with the communication of cell and the extra cellular matrix all of which leads to neuronal dysfunction and death[16].These pathways also result in impaired microvascular--regulation and endothelial dysfunction by different mechanisms, including increase in plasminogen activator inhibitor-1 and endothelin- 1 production and impairment of endothelial nitric oxide (NO) synthase and NO actions. This can lead to neurovascular dysfunction owing to impaired perfusion, and cellular apoptosis"

ii. Autoimmunity

iii. Genetic factors

a. TCF7L2

b. T393C polymorphism of the gene encoding the Gs-protein-α-subunit (GNAS1)

iv. Obstructive sleep apnoea

Intermittent hypoxia that occurs in OSA could lead to increased oxidative stress, nitrosative stress, and microvascular complications which could lead to CAN.CAN inturn can cause changes in upper airways and respiratory drive thus predisposing patients to OSA.

2.F. NATURAL HISTORY OF CAN

"In DM, autonomic nervous system is affected in an ascending and length dependent manner. The vagus nerve, being the longest autonomic nerve it tends to be involved early in the course of CAN development. Therefore CAN in early stages causes reduced parasympathetic activity, which inturn results in sympathetic dominance. This increased sympathetic tone continues up until the late stages of CAN .Then in later stages of CAN sympathetic system is also involved".

"CAN is arbitarily divided into 2 stages-a sub-clinical stage and a clinical stage. During the sub-clinical stage patient may be asymptomatic and diagnosis of CAN needs evaluation of abnormalities in time and frequency domains of the spectral analysis of HRV and the Baroreflex Sensitivity (BRS) tests:as well as an increased torsion of the left ventricle .Standard autonomic function tests may be normal in this stage"

"CAN progresses over time and parasympathetic denervation occurs which inturn causes compensatory sympathetic overdrive. This results in abnormal CARTs: this stage is followed by development of symptomatic CAN.The time scale required for the progression of subclinical stage to abnormal CART is not clear.It is estimated that most patients with sub-clinical CAN will develop abnormal CARTs and features suggestive of cardiac involvement within almost 5 years of developing abnormal time and frequency domain parameters"

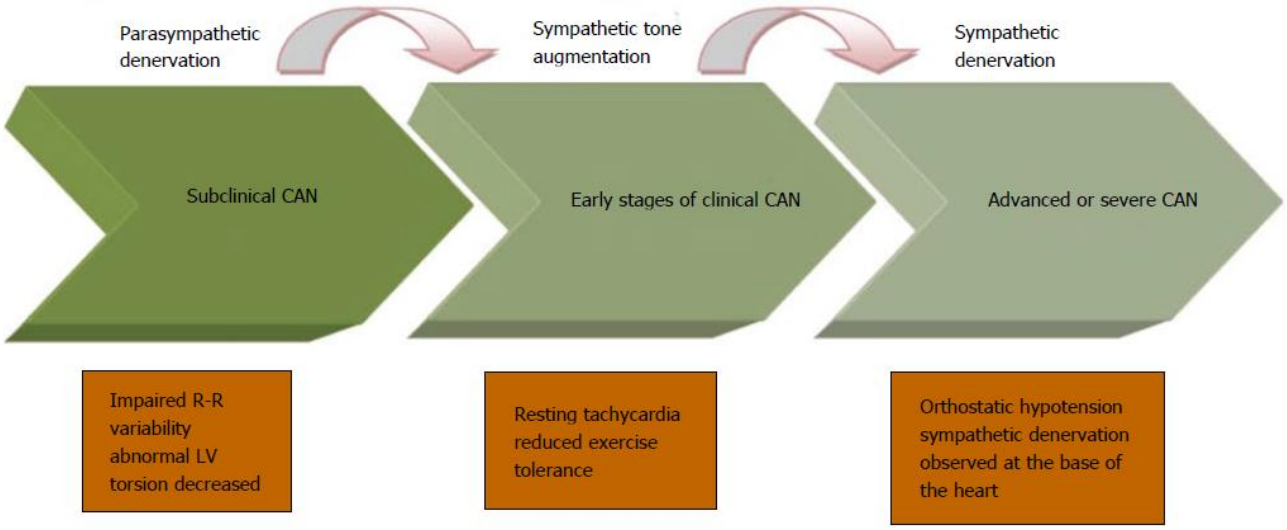


Figure 2.2 : Natural progression of CAN and correlation with clinical signs and symptoms

2.G. CLINICAL MANIFESTATIONS OF CAN[1]

i. Resting tachycardia

"This occurs at a relatively early stage of the disease. A resting heart rate of 90-130 beats per minute is observed which is due to reduced

parasympathetic tone and increased sympathetic activity . A fixed heart rate ,which doesn't change with stress or sleep or physical activity is a sign of complete cardiac denervation".

ii. Exercise intolerance

"CAN causes abnormal blood pressure, heart rate responses to exertion. In later stages ,due to imbalance between parasympathetic and sympathetic system leads to further deterioration of these parameters. This is very important to recognise as exercise testing in such individuals may give false negative results"

iii. Orthostatic hypotension

"Orthostatic hypotension is a manifestation of late stage of CAN; when sympathetic denervation also occurs. This occurs as a result of the impairment of the sympathetic response to postural change: this is secondary to poor norepinephrine response and abnormalities in the baro-receptor sensitivity, resulting in inadequate HR response and peripheral vasoconstriction. Orthostatic hypotension can be aggravated by many medications that are commonly used in patients with DM such as diuretics, vasodilators, tricyclic antidepressants and insulin. Assessment of resting heart rate and orthostatic hypotension carries prognostic significance in patients with autonomic neuropathy".

iv. Silent ischaemia

"Patients with DM and CAN are at high risk for sustaining a major cardiovascular event during exertion owing to the limited perception of ischemic pain which could delay the appropriate and timely response to ischemia.

The mechanism by which CAN causes silent ischemia is not clear. Mechanisms proposed include a) altered pain threshold b) impaired afferent myocardial autonomic pathways c) ischaemic processes not detected by routine electrocardiography".

v. Diabetic cardiomyopathy and LV dysfunction

"The sympathetic- parasympathetic imbalance observed in the early stages of the disease causes a lot of metabolic changes which includes increased myocardial catecholamine levels and catecholamine toxicity, which induces mitochondrial uncoupling . Such alterations lead to programmed cell death and fibrosis ; finally hypertrophy and remodelling of the LV. Important mediators in this process are mitochondrial ROS, insulin resistance and calcium dependent apoptosis. Diastolic dysfunction in CAN is associated with delayed relaxation and increased stiffness thus causing impaired filling of the LV. Sympathetic overdrive stimulates RAAS, resulting in increased heart rate, cardiac output and peripheral vasoconstriction, increased LV wall stress and LV hypertrophy".

vi. Mortality/sudden death

"CAN is considered as an independent predictor of mortality and this persists despite adequate glycemic control . It highlights the importance of preventing the development of CAN. Sudden cardiac death may be due to silent ischemia or fatal arrhythmias" .

Possible factors associated with high mortality are as follows:

i. Silent myocardial ischemia or infarction

ii. Cardio-respiratory arrest/ more peri-operative and peri-intubation risk

iii. Tachycardia at rest

iv. Ventricular arrhythmias/prolonged QT interval

v. Hypertension

vi. Orthostatic hypotension

vii. Flattening of nocturnal decrease of BP and heart rate(non dipper)

viii. Absence of sinus arrhythmia

ix. Exaggerated BP responses on lying down and with exercise

x. Abnormal diastolic or systolic LV function

xi. Poor exercise tolerance

xii. Impaired cardio vascular responsiveness

xiii. Intolerance to heat due to defect in the sympathetic thermo-regulation

xiv. Susceptibility to ulcers of the foot and arteriovenous shunting and sudomotor dysfunction leading to amputations

xv. Hypoglycaemic unawareness

xvi. Increased risk of severe hypoglycaemia

xvii. Obstructive sleep apnoea

vii. Peri-operative and intra-operative complications

viii. Cerebrovascular disease

ix. Diabetic nephropathy

"Sympathetic overactivity is proposed to cause tubule-glomerular dysfunction in diabetic animal models *via* a). indirect –hypertension and angiotensin and b).direct -vascular smooth muscle proliferation,

vasoconstriction, podocytes injury. Nocturnal hypertension causes glomerular hypertension and proteinuria. Also CAN is postulated to cause erythropoietin defiency" .

x. Lower limb complications

"Alterations in microvascular blood flow , impaired sudomotor responses , all contribute to dry skin and increased risk of foot ulcers.In addition lower limb hyperaemia and inflammation ,owing to sympathetic denervation of lower limb vessels contributes to charcot arthropathy".

2. H. DIAGNOSIS OF CAN

i. CARTs

" In early 1970s Ewing *et al* proposed five simple and noninvasive tests to measure cardiac autonomic function based on the heart rate and blood pressure response to certain physiological manoeuvres. These tests include:

(1) HR response to deep breathing

(2)HR response to standing, which is expressed as the 30:15 ratio

(3) HR response to Valsalva manoeuvre

(4) Blood pressure response to standing

(5)Blood pressure response to sustained handgrip

The first two tests defects in the parasympathetic activity ;while last two tests sympathetic function. The autonomic changes that occur during the Valsalva manoeuvre involve both the sympathetic and parasympathetic systems, although the Valsalva ratio mostly represents parasympathetic activity".

ii. ***HRV using spectral analysis of sinus arrhhythmia***

iii. ***Baro-reflex sensitivity***

"This primarily measures changes in HR in response to changes in systolic BP. The test can be performed either with the use of pharmacological methods or non-pharmacological techniques. Even subclinical CAN can detected by BRS . BRS is now considered as a strong independent risk factor for mortality".

iv. Scintigraphy

" The use of Single-photon emission computed tomography: (SPECT) and/or positron emission tomography (PET) and sympathetic neurotransmitter analogues, such as the 123I-metaiodobenylguanide (123I-MIBG) (SPECT), the 11C-metahydroxyephedrine (11C-HED) (PET) and 11C-epinephrine has enabled the quantitative scintigraphic evaluation of cardiac sympathetic innervations. Cost, radiation exposure and lack of standardisation are limiting factors".

v. Muscle nerve sympathetic nerve activity

"MSNA helps in assessing peripheral sympathetic activity and therefore a useful research tool. Cost, time consuming nature and invasiveness are limiting factors".

vi. Other tests

a) Arterial stiffness, expressed as carotid femoral wave velocity (PWV)
b) Catecholamine kinetics
c) Assessment of cutaneous MBF

d) Intra epidermal nerve fibre density (IENFD) using immune-staining

2.I. CRITERIA FOR DIAGNOSIS AND STAGING

"Following the eighth International symposium on diabetic neuropathy held in 2010 , CAN subcommittee of the Toronto consensus panel formulated a criteria for early diagnosis and staging of CAN: According to this panel :

i. Possible or early CAN- A single abnormal CART result
ii. Definite or confirmed CAN- presence of 2 or 3 abnormal test among the seven autonomic cardiovascular indices -5 CARTS, time-domain and frequency-domain HRV tests
iii. Severe or advanced CAN- presence of orthostatic hypotension in addition to the above criteria

These tests are cumbersome to perform which necessitates the need of a simple , easily reproducible, non invasive bed side test to diagnose early CAN".

2. J. SCREENING FOR CAN[1]

"It is very important to recognise CAN at an early stage as its reversible in early stages. But most patients with early CAN may be asymptomatic making this a difficult task. So the Toronto panel has advised routine screening for CAN".

Who all to be screened??

i. Type 2 diabetics at the time of diagnosis
ii. Type 1 diabetics after 5 years
iii. Diabetics with other micro or macrovascular complications

iv. Patients with poor glycemic control

v. Diabetics as a part of peri operative assessment

vi. Diabetics who sustained MI for prognostication

vii. Diabetics on changing their exercise plan as CAN can affect exercise tolerance

2.K. THERAPEUTIC APPROACHES FOR CAN[1]

"Treatment approaches are aimed at slowing or reversing the progression of the disease in early CAN whereas its aimed at symptom relief in symptomatic CAN.

i. Life style modification

Diet modification , moderate degree of aerobic exercise smoking cessation and aggressive management of other comorbid conditions are proven to improve heart rate variability and delay progression of CAN

ii. Intensive glycemic control

iii. Other promising therapies- alpha lipoic acid,GLP 1 agonists , DPP4 inhibitors, vitamin E, C-peptide

iv. Blockers of RAAS- ACEI or ARBs or spironolactone or betablocker

v. Treatment of orthostatic hypotension

Lifestyle measures-avoiding sudden changes in body posture, avoiding precipiting drugs, increased salt and water intake ,physical manoeuvres like crossing legs ,squatting

Pharmacological measures- midodrine, fludrocortisone, somatostatin analogues, erythropoietin"

But none of these measures is satisfactory and management of postural hypotension is still difficult .

2.L. SIGNIFICANCE OF AUTONOMIC FUNCTION TESTING IN TYPE 2 DIABETICS

" Autonomic function testing can contribute to good patient management in the following ways:

i. Assist in emphasizing the need for tight glycemic control

It is observed that early identification and tight glycemic control delays the progression of CAN. This is emphasized in DCCT trial which says that intensive glycemic control may prevent the further deterioration of autonomic neuropathy".

ii. Early initiation of specific treatment

"Timely identification of autonomic dysfunction helps in initiating end organ prophyllaxis such as the use of ACEI, and aspirin and the use of pharmacological and non pharmacological measures to improve blood pressure and lipid control".

iii. Emphasize the importance of adhering to diet and exercise plans

" Early detection of autonomic dysfunction enables and motivates the patient to adhere to diet and exercise plans which help in achieving better glycemic control".

3. ECG IN CAN

"CAN is known to be associated with a variety of ECG changes. ECG changes in early CAN include tall R wave , increases QTc duration , absence of sinus arrhythmia[6]."

"CAN is said to be associated with obesity, hyperglycemia, long duration of diabetes, hypertension, dyslipidemia, micro-vascular complications and smoking. QTc interval prolongation has also been associated with age, sex, blood pressure, BMI, visceral obesity, smoking, the type of diabetes and the duration of diabetes. It is likely to be influenced by OHA , degree of glycemic control and severity of autonomic neuropathy".

" The association of prolonged QT interval with CAN was proposed in early in 1980[17]. This paved way for a simple bedside objective and easily reproducible method to detect CAN. QTc interval is a reflection of myocardial depolarization and repolarization[6]. This in turn is under the influence of central autonomic neural tone".

"More recently it is observed that there is inter lead variation in QT segment duration –QT dispersion. It is said to represent the regional difference in the myocardial recovery from excitability. It is already known that increased QT dispersion associated with long QT syndromes, HOCM, CCF, acute MI etc is a major cause of sudden cardiac death occurring in such conditions".

" In diabetes mellitus the autonomic denervation is regional and irregular. This leads to variability in QT and QT dispersion increases. Hence QT

dispersion along with corrected QT with heart rate is considered as a better marker for CAN" .

"How CAN produces QT prolongation is still not clear. Its proposed that sympathetic overdrive following early parasympathetic involvement is causing QT prolongation."

3.A QTc interval calculation

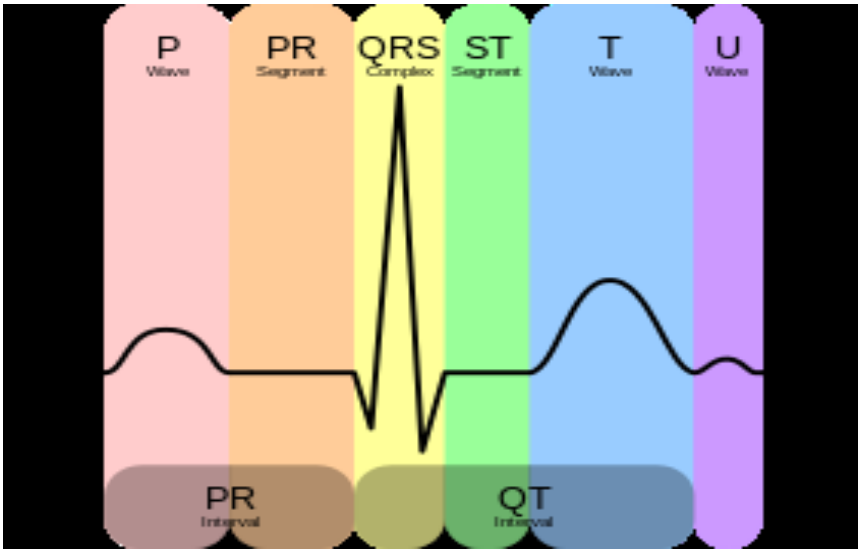


Figure 3.1: Normal ECG

" QT interval represents the total duration of ventricular depolarisation and repolarisation. It is measured from the beginning of the Q wave to the end of the T wave. Usually the lead with the maximum QT interval and T wave amplitude is taken into account[9]".

"Theoritically QT interval should be same in all the standard limb leads but practically it is not so[9,12]. Differences do occur because

ventricular projections on different limb leads are different.In precordial leads too QT interval may be varying because of the differences in the proximity to the heart and also due to local repolarisation duration differences in the sites facing the electrode".

"The changes in the QT interval with RR interval occurs gradually. So the measured QT represents an instantaneous value only when rhythm is regular for several cycles. QT interval includes QRS complex ; but still prolonged QRS comples as occurs in bundle branch block doesn't interfere with QT measurement: but it may interfere with the interpretation .QRS complex duration has to be subtracted from the QT interval to find the JT interval which represents ventricular repolarisation independent of depolarisation".

"The time of QT measurement may also influence its measurement[9]. It is observed that QT interval is longer at night and eve. And maximum QT interval is said to be present shortly after awakening. This diurnal variation with QT is due to the variation in autonomic tone".

Studies also show that QT interval varies between males and females. Studies observed three patterns in QT[9]:

a) Male pattern- j point elevation >0.1mV and ST angle more than 20 degrees
b) Female pattern with j point elevation <0.1mV and ST angle < 20 degrees
c) Indeterminate pattern with j point elevation >0.1mV and ST angle < 20 degrees

"Studies showed that male pattern predominates in males at puberty and by middle age female pattern predominates and there is complete reversal by old age. These changes are attributed to the fall in testosterone levels in males as they grow old. Testosterone causes shortening of QT interval"

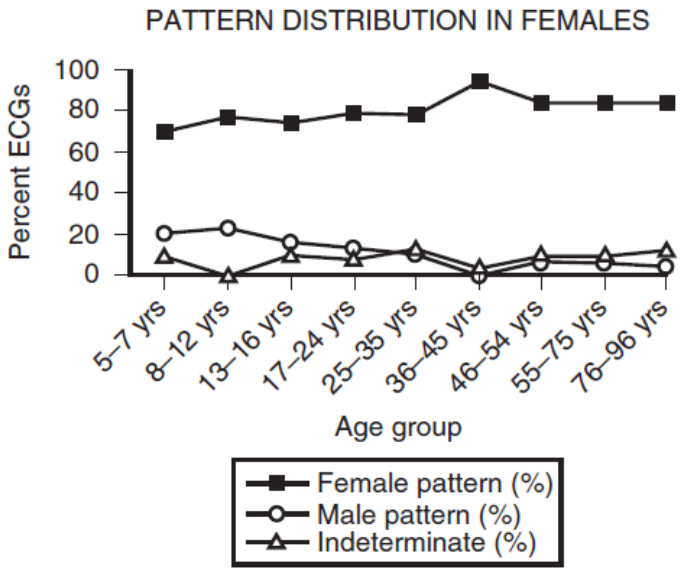


Figure 3.2 . Pattern showing QT distribution in females

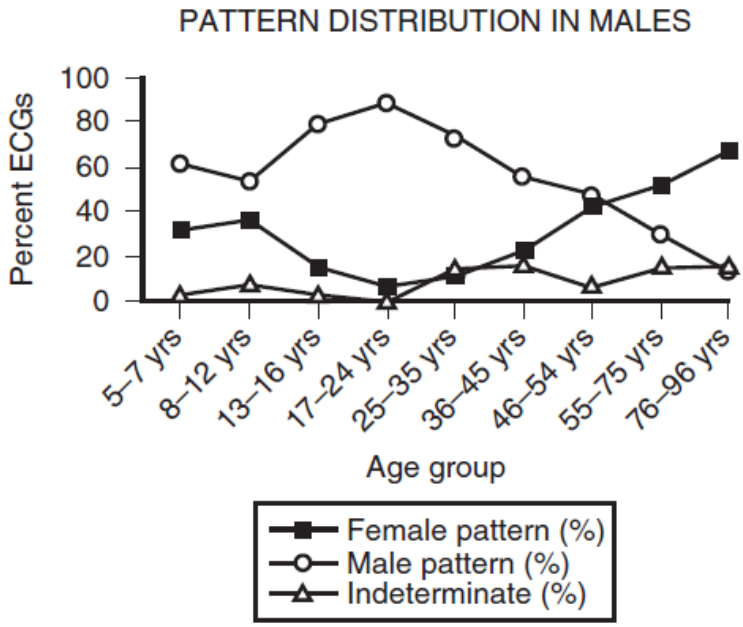


Figure 3 .3 : Pattern showing QT distribution in males and females

"Twelve-lead ECG was carried out in all the patients with paper speed of 25 mm / s by electrocardiography .The QT interval duration was manually calculated from the 'beginning of the Q wave to the end of the T wave' in all 12 leads. The maximal QT interval duration was measured among these 12 leads"

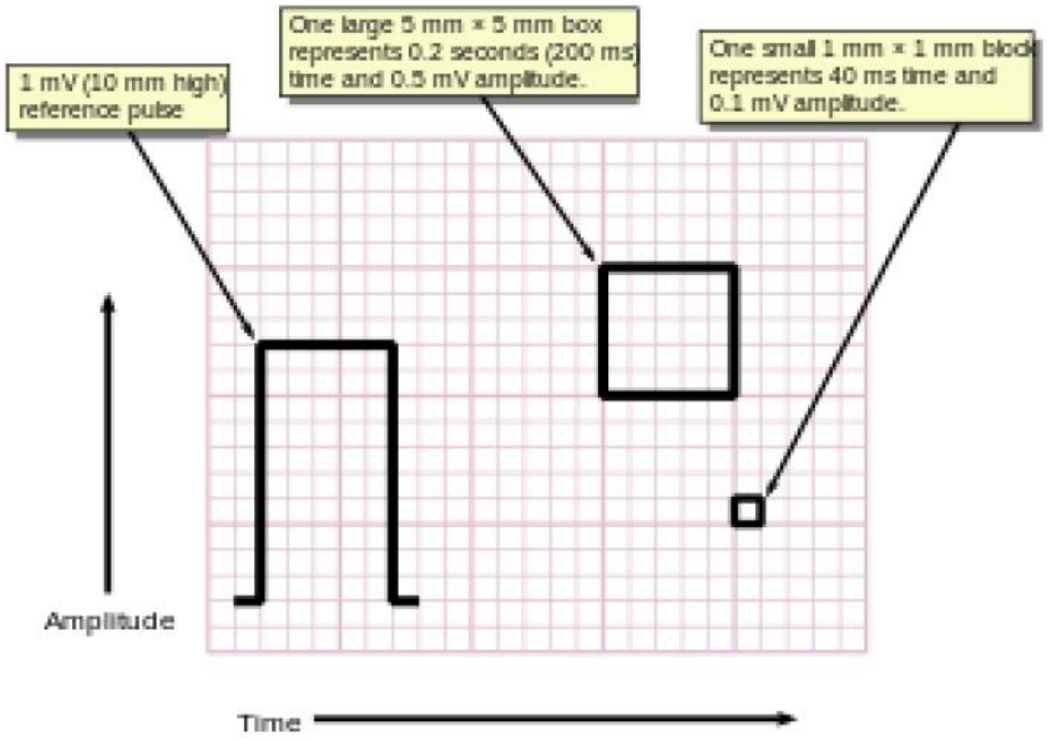


Figure3.4. A normal ECG strip showing the voltage and duration

QT intervals were corrected in accordance with the rate using the 'BAZET' formula:

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

"The corrected QT of 460 milliseconds or more in women and 440 milliseconds or more in men was considered as prolonged QT interval. The QT interval represents

electrical depolarisation and repolarisation of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachy-arrhythmias like torsades de pointes and a risk factor for sudden death[9]".

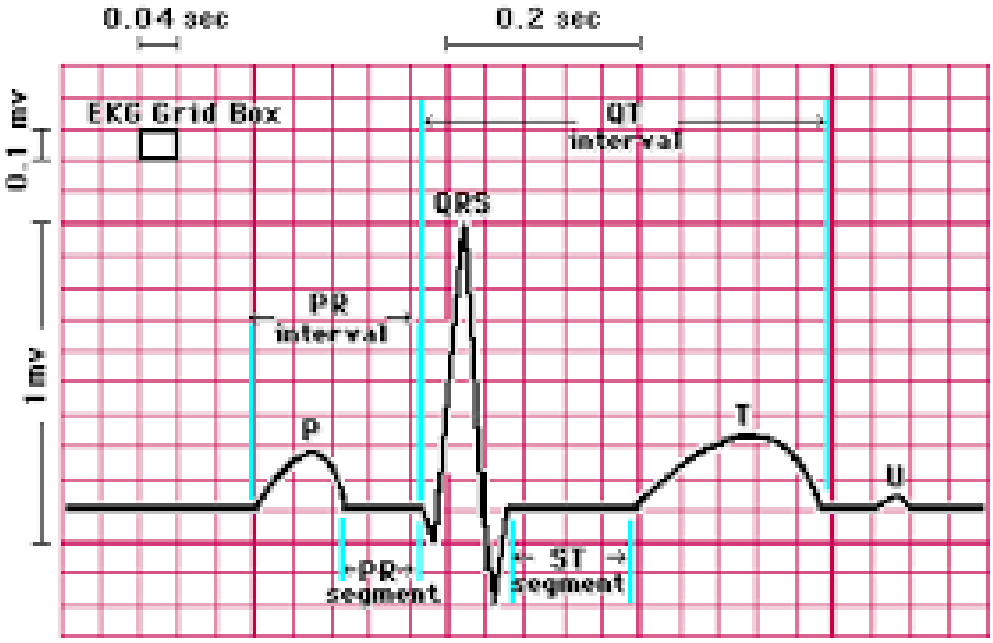


Figure 3.5.. Normal waves in ECG with their duration.

3.B Correction for heart rate

"Both R-R interval, the QT interval are dependent on the heart rate (the faster the heart rate the shorter the R-R Interval and QT interval).Correction of QT interval is necessary to improve the detection of patients at increased risk of ventricular arrhythmia. The standard clinical correction is to use 'Bazett's formula[12]".

$$\mathrm{QTcB} = \frac{\mathrm{QT}}{\sqrt{\mathrm{RR}}}$$

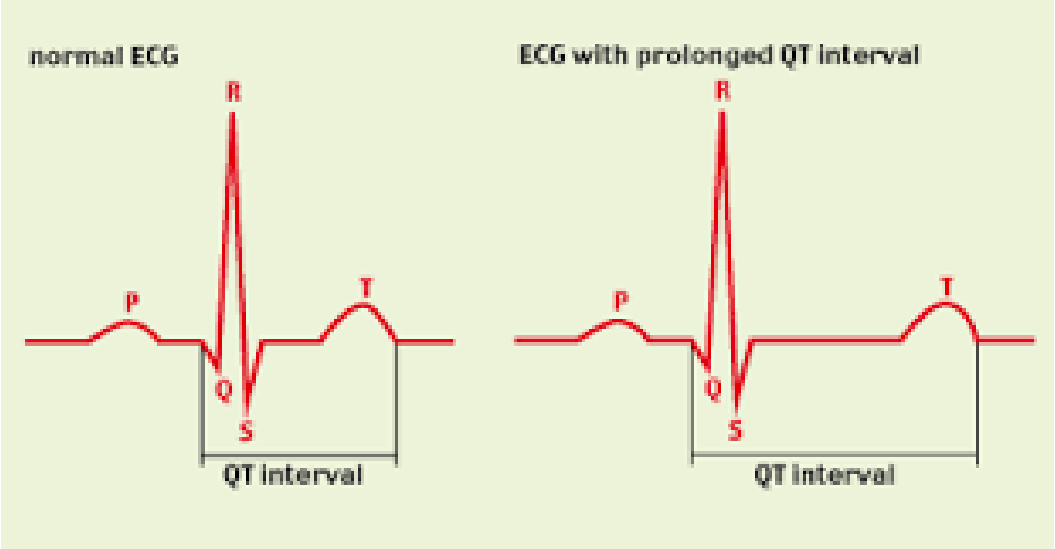
QTcB is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds, QT is measured in milliseconds).

“Fridericia” formula an alternative correction formula using the cube-root of RR.

$$\mathrm{QTcF} = \frac{\mathrm{QT}}{\sqrt[3]{\mathrm{RR}}}$$

“REGRESSION ANALYSIS”

$$QTcL = QT + 0.154(1 - RR)$$



SUMMARY OF PRIOR PUBLICATIONS

SUMMARY OF PRIOR PUBLICATIONS

1. In Heart India, Vol 3 / Issue 1 / Jan-Mar 2015 Pillai and Madhavan published an article on "CAN and QTc Interval in Type 2 diabetes"

This study included fifty patients with Type 2 diabetes mellitus with duration more than 5 years . Thirty age and sex-matched controls without any history of diabetes were also included in the study . Five autonomic function tests were done in all cases and controls to assess CAN. Heart rate, QTc , and QTc dispersion were measured and compared among patients and controls. Diabetics with autonomic neuropathy had significantly higher QTc mean and QTc max values compared to diabetics without autonomic neuropathy and controls. QTc dispersion was significantly more among patients with autonomic neuropathy compared to those without autonomic neuropathy and controls.

2. JIMSA April-June 2011 Vol. 24 No. 2 S.N. Chugh, P. Mittal, S. Kumar, K. Chugh published an article on "QT Dispersion in Patients of Diabetes Mellitus without Manifest Cardiac Dysautonomia"

The objective of this study was to detect the complication in diabetic individuals by measuring QT interval and its dispersion. For this 50 diabetic patients selected for the study. Cardiac dysautonomia was diagnosed in 25 out of 50 patients. Further analysis revealed that severity of CAN correlated with QT interval and dispersion .

3. In JIACM 2006; 7(2): 130-2 ,CP Mathur, Deepak Gupta published an article on "QTc Prolongation in Diabetes Mellitus – An Indicator of CAN"

In this study 50 cases of diabetes with stable clinical cardiac status were subjected to a battery of 5 autonomic function tests to find out the incidence of CAN (CAN). 19 cases out of 50 (38%) were found to have evidence of CAN.QTc prolongation was observed in 15 cases.. The study suggested that QTc prolongation can be taken as an evidence of CAN in diabetics.

4. In The Egyptian Heart Journal (2014) 66, 63–69 , Wael Refaie published an article on the " Assessment of CAN in long standing type 2 diabetic women"

This study was conducted with the background of patients with long standing DM undergoing surgical procedures are put under great stress as they may have occult cardiovascular involvement and/or CAN (CAN).In this study 106 Type 2 diabetic mellitus women scheduled for major surgical procedures were assessed by the cardiac autonomic function tests. Continuous 24 hour holter monitoring was done to evaluate QTc and QTd, arrhythmia ,and ischemia . In the study group CAN was diagnosed in 70 %. QTc prolongation and QT dispersion were found in many cases.

5. In JIMSA Oct. - Dec. 2014 Vol. 27 No. 4; N. S. Neki, Jatinder Kaur published an article on "A study of QTc-Prolongation and QT Dispersion (QTd) as an indicator of CAN (CAN) in type 2 Diabetes Mellitus Patients"

This study was done on hundred cases of type-2 diabetes mellitus patients , out of which fifty cases were diagnosed to have CAN on the basis of standard cardiac autonomic function tests. These reflexes include i). valsalva manoeuver ii). Heart rate response to deep breathing, and iii). Standing to assess parasympathetic function as well as iv). BP response to standing and v). Sustained hand grip to assess sympathetic function. Rest of fifty patients not having CAN served as healthy controls. ECG was taken for all. The QTc interval and QTc dispersion was calculated for patients and controls . The study concluded that QTc prolongation showed positive correlation with the degree of CAN. QTc prolongation in an otherwise healthy looking diabetic patient can be used as a bedside tool for assessment of CAN.

6. In Rev Med Chir Soc Med Nat Iasi.2010 Jan –Mar ;114(1);282-6; Matel D, Chiochină AD, Stratone A; "Utility of QTc interval for the diagnosis of CAN in type 2 diabetes mellitus"

In this study 65 cases of type 2 diabetes with no evidence of cardiac disease clinically were subjected to a set of 5 non-invasive autonomic function tests as recommended by Ewing et al ; these included deep breathing test, heart rate response to standing (30:15 ratio), Valsalva ratio, diastolic

blood pressure rise with sustained hand grip, and orthostatic hypotension on standing. A score of 2 or larger diagnosed CAN. QT interval was calculated from ECG. The corrected QT was determined with Bazett's formula, and a value more than 440 msec was considered as prolonged. Prolongation of QTc was observed in diabetics by comparison with control group . Study showed that QTc was higher in diabetics with CAN compared to diabetics without CAN . Hence it was concluded that QTc prolongation correlated positively with the severity of CAN.

7. In Journal of clinical Endocrinology Metabolism 1987 April ;64(4):751-4;Kahn JK, Sisson JC, Vinik AI; published an article on "QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy".

In this thirty among insulin-dependent diabetes mellitus patients with no evidence of ischemic heart disease, seventeen patients were found to have CAN. The corrected QT interval was measured using Bazett formula at rest and at peak exercise,and was found to be prolonged (greater than 440 msec) in twelve of these patients at rest and in fifteen at peak exercise. QTc prolongation was found in patients with CAN. These data also suggest that diabetic CAN results in parasympathetic-sympathetic imbalance and hence cause QTc interval prolongation, predisposing these patients to sudden arrhythmias and death.

8. Jermendy G, Tóth L, Vörös P, Koltai MZ, Pogátsa G; published an article on

"Cardiac autonomic neuropathy and QT interval length. A follow- up study in diabetic patients."

The objective of this study was to evaluate the clinical significance of QT prolongation in diabetics with CAN , fifty three diabetic patients were followed up for a period of five years or to death. The results of cardiovascular autonomic function tests as well as the QT intervals were determined. It was found that QTc intervals were significantly prolonged in diabetics with definitive CAN compared to those with early and those without signs of CAN and controls. Out of 53, 13 patients died during the follow-up period .Of those 1 was without CAN ;2 with early CAN and 10 patients with definitive signs of CAN; but QTc intervals were not significantly different in patients with cardiac and non-cardiac causes of death.

9. Pourmoghaddas A, Hekmatnia A; published an article on " The relationship between QTc interval and CAN in diabetes mellitus."

This study included two hundred diabetics and 200 non-diabetic patients . QTc was determined in both case and control group. Then the case and control group was compared. It was observed that the prevalence of QTc prolongation was significantly more in cases than controls. Parasympathetic dysfunction was observed to be more common than sympathetic. The prolonged QT in case group predisposed them to ventricular tachyarrhythmias and silent ischemia which causes sudden death. The study thus emphasised the need for early identification of CAN thus preventing such fatal complications

10. Gonin JM , Kadrofske MM, Schmaltz S, Bastyr EJ 3rd, Vinik AI; published an article on “Corrected Q-T interval prolongation as diagnostic tool for assessment of CAN in diabetes mellitus”.

In this study 73 diabetic patients comprising 46 insulin dependent and 27 non-insulin dependent diabetes mellitus patients taken. For study purpose patients were separated into four groups based on the presence and severity of CAN with the help of non-invasive cardiovascular reflex tests. The patients with evidence of ischemic heart disease, chronic kidney disease, or the idiopathic long Q-T-interval syndrome were excluded from the study. ECG was taken to calculate QT and corrected QT interval was with Bazett's formula.It was observed that diabetic patients with more than 2 abnormal CARTs had longer QTc interval compared to those with no evidence of CAN. Diabetic patients with more than one abnormal CARTs had a prolonged QTc interval compared with a control group .

MATERIALS

AND

METHODS;

I. MATERIALS AND METHODS;

STUDY POPULATION:

The study was conducted among patients from General Medicine wards of Government Rajaji Hospital, Madurai during the period of February 2016 to July 2016. The aim of the study was to find out the significance of QTd as an indicator of CAN in Type 2 Diabetes mellitus. The study included 100 cases of diabetes and 100 age and sex matched controls.

STUDY GROUP

The study was conducted among 100 patients of type 2 diabetes mellitus diagnosed according to World Health Organization (WHO) criteria, from the General Medicine wards of Government Rajaji Hospital , Madurai , from February 2016 to July 2016.

INCLUSION CRITERIA:

i. Onset of diabetes after 30 years and
ii. Duration more than or equal to 5 years

EXCLUSION CRITERIA:

i. History of hypertension
ii. History or electrocardiography (ECG) evidence of coronary artery disease
iii. Stroke/transient ischemic attack (TIA)
iv. Electrolyte imbalance like hypokalemia or hypocalcemia

v. History of heart failure

vi. History of renal dysfunction

vii. History of hypothyroidism

viii. Patients on drugs affecting autonomic tone or QT interval

CONTROL GROUP

Age and sex matched 100 controls were selected after getting informed consent. The same exclusion criteria was applied to the control group also.

STUDY DESIGN: Case control study

STUDY PERIOD : February 2016 to July 2016 (6 months)

ETHICAL COMMITTEE CLEARANCE- Obtained

FINANCIAL SUPPORT-Nil

DATA COLLECTION:

A previously designed proforma was used to collect the demographic and clinical details of the patients. History regarding symptoms of autonomic neuropathy like orthostatic hypotension ,palpitations, exercise intolerance, bladder symptoms, diarrhoea, constipation, heat intolerance, sweating, anhydrosis, dry skin, erectile dysfunction and female sexual dysfunction was asked for.

History regarding duration of diabetes and past history of hypertension, stroke, Chronic kidney disease, cardiac disease, history of pregnancy or lactation, history of any chronic drug intake, family history of diabetes mellitus , hypertension, Coronary artery disease were recorded.

Clinical examination of height ,weight , blood pressure, heart rate , pulse rate, was done for all patients. Body mass index was found out with the help of the formula :$BMI = \frac{WEIGHT(kg)}{HEIGHT(m^2)}$. ECG was rewcorded for all patients.

Lab investigations like complete hemogram, Renal function tests, Liver function tests , urine routine examination, FBS, PPBS ,lipid profile were done.

A battery of five autonomic function tests are done in all cases to assess CAN. A score of 0-2 is assigned to each test. The tests conducted were:

1. Postural fall in systolic blood pressure (BP) — Systolic BP was measured when the patient lying down and 3 minutes after standing.

A fall of more than 30 mm Hg was abnormal — Score 2

A fall of 10-29 mmHg was borderline — Score 1

A fall less than 10 mmHg — normal Score 0

2. Increase in diastolic pressure during hand grip — Hand grip was maintained at 30% maximum for 5 minutes. A rise in diastolic BP in the contralateral arm from the value obtained before the test was measured.

Rise >16 mmHg — Normal Score 0

11-15 mmHg — Borderline Score 1

<10 mm Hg — Abnormal Score-2

3. Heart rate response to Valsalva manoeuvre—The patient was asked to forcefully exhale into a manometer after closing the nose to raise the pressure to 40 mmHg for 15 seconds. Ratio of longest RR interval shortly after the manoeuvre to the shortest RR interval during the manoeuvre was then measured. This was expressed as Valsalva ratio.

Value >1.21 — Normal score 0

Value 1.11-1.20 - Borderline score 1

Value ≤1.10 — Abnormal score 2

4. Deep breathing test—Patient was asked to lie supine and breathe 6 times per minute and ECG was recoreded. The mean of the differences in maximum and minimum heart rate during each breathing cycle for three successive breathing cycles was taken to give the maximum minus minimum heart rate.

≥15 beats per minute — Normal Score 0

11-14 beats per minute — Borderline Score 1

≤10 beats per minute — Abnormal Score 2

5. Heart rate response to standing — The RR interval was measured at beats 15 and 30 after the patient assumes erect posture from horizontal. Usually a rapid increase in heart rate to standing that is maximum at about 15 th beat after standing .This is followed by relative bradycardia which is maximum at 30 th beat after standing. ECG

tracings was used to determine the 30:15 ratio , calculated as the ratio of the longest RR interval found at beat 30 to the shortest RR interval found at about beat 15 . Because the maximum and minimum RR intervals may not always occur at exactly the 30 th or 15 th beat after standing , maximum /minimum 30:15 ratio was calculated as the longest RR interval during beats 20-40 divided by the shortest RR interval during beats 5-25. This was according to the redefinition by Zieger et al. Heart rate response to standing was considered abnormal if the patient had orthostatic hypotension.

Value ≥1.04 — Normal Score 0

Value 1.01-1.03 — Borderline Score 1

Value ≤1.00 — Abnormal Score 2

Total score ranged from 0–10. Based on the score obtained from the test, patients are divided in to three groups:

Group 1: Severe autonomic neuropathy — Score >5

Group 2: Early autonomic neuropathy — Score 2-4

Group 3: No autonomic neuropathy — Score 0-1

A 12 lead ECG is taken after 10 minutes rest in all patients at 50 mm/second speed. RR interval, heart rate, QTc interval, QTc maximum, QTc minimum and QTc dispersion are calculated from the ECG.

QTc (second) = QT (second)/√ RR (seconds)

QTc mean is calculated from the QTc intervals of all the leads

QTc dispersion is then calculated by the formula

QTc dispersion = QTc max (longest QTc) — QTc min (shortest QTc)

Comparisons of heart rate, QTc mean, QTc max, QTc min, QTc dispersion are made in various groups and controls and significance assessed by Students t test. Relation between age, sex, and autonomic neuropathy are assessed by Pearson correlation test.

RESULTS AND INTERPRETATIONS

RESULTS AND INTERPRETATIONS

A total of 100 patients were included in the study, from among the patients who got admitted in General Medicine wards at Government Rajaji Hospital Madurai.

I. AGE DISTRIBUTION

Most of the patients belonged to the age group 50-60 years, followed by 40-50 years. The average age for study group was 54 years

The following table (table 1) shows the age distribution of patients included in the study.

Table 1: Age distribution

Age in years	Cases	Controls
30-40 years	0	0
40-50 years	34	36
50-60 years	53	56
60-70 years	11	7
above70 years	2	1
Total	100	100
Range	42-72	40-70
Mean	54.12	53.19

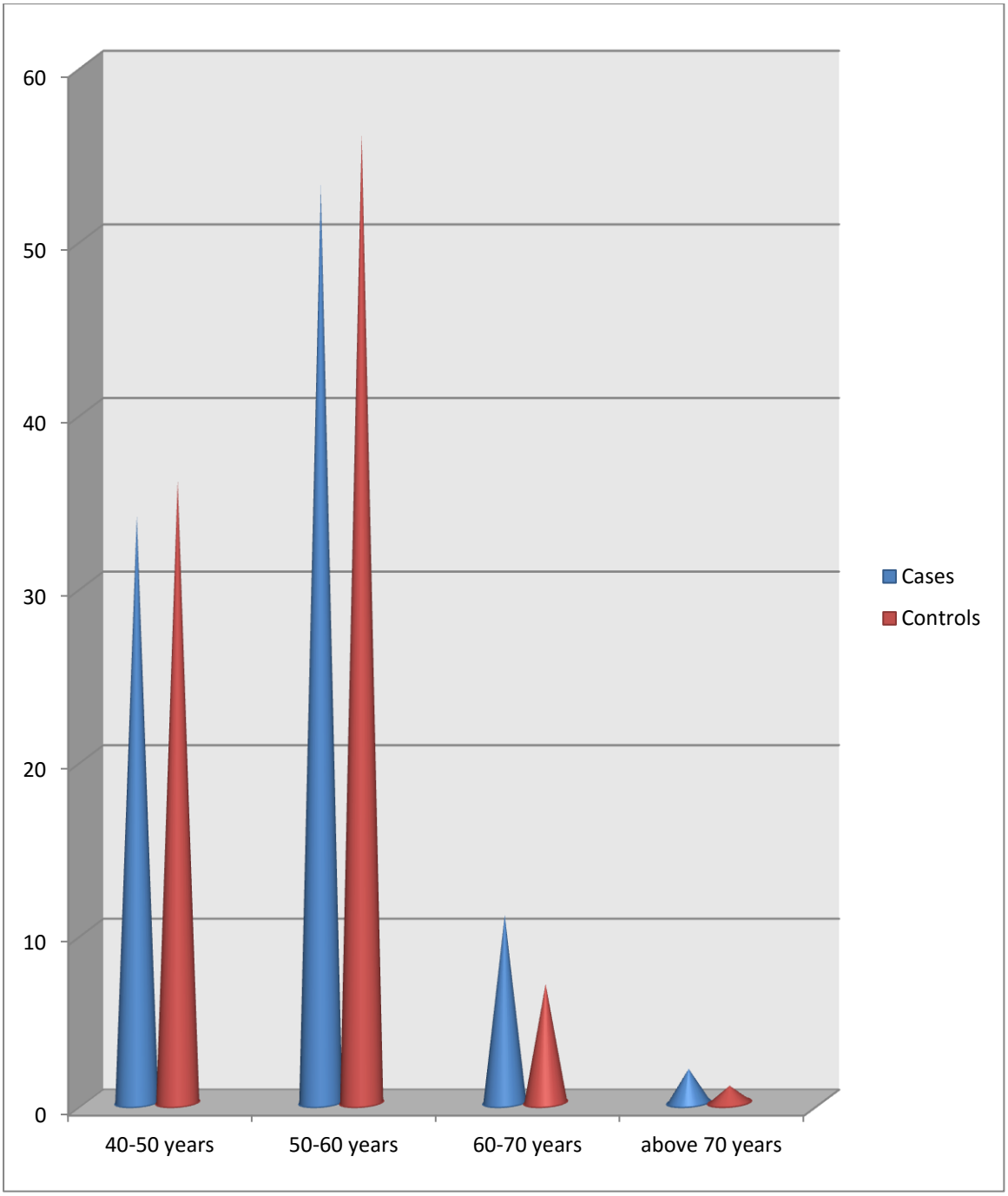


Figure 1 : Diagram showing age distribution of cases . 100 similar ageand sex matched controls were taken for the study.

II. SEX DISTRIBUTION

Among the 100 patients studied 55 were males and 45 females

Table 2:Sex distribution

Sex	Number of cases	Number of controls
Males	55	56
Females	45	44
Total	100	100

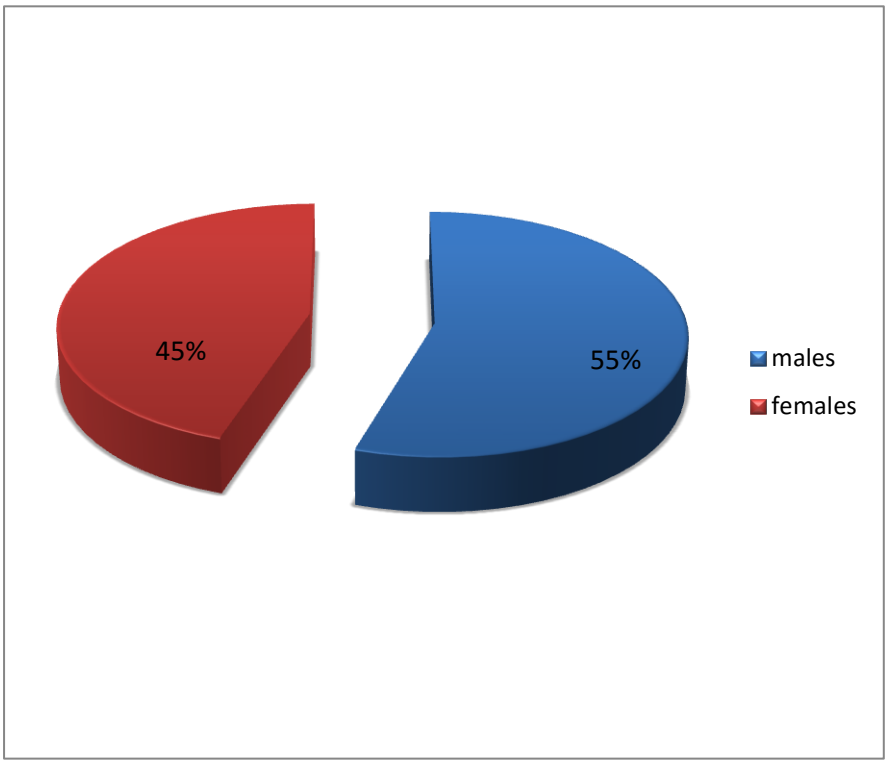


Figure 2: Pie diagram showing sex distribution of cases, 100 similar age and sex matched controls were taken for the study.

III. DURATION OF DIABETES

All the patients in the study group had duration of diabetes more than 5 years.The cases were divided into 3 groups according to the duration of diabetes.

Table 3: Duration of diabetes in study group

Duration in years	Males	Females	total
5-10 years	48	33	81
10-15 years	9	7	16
>15years	1	2	3

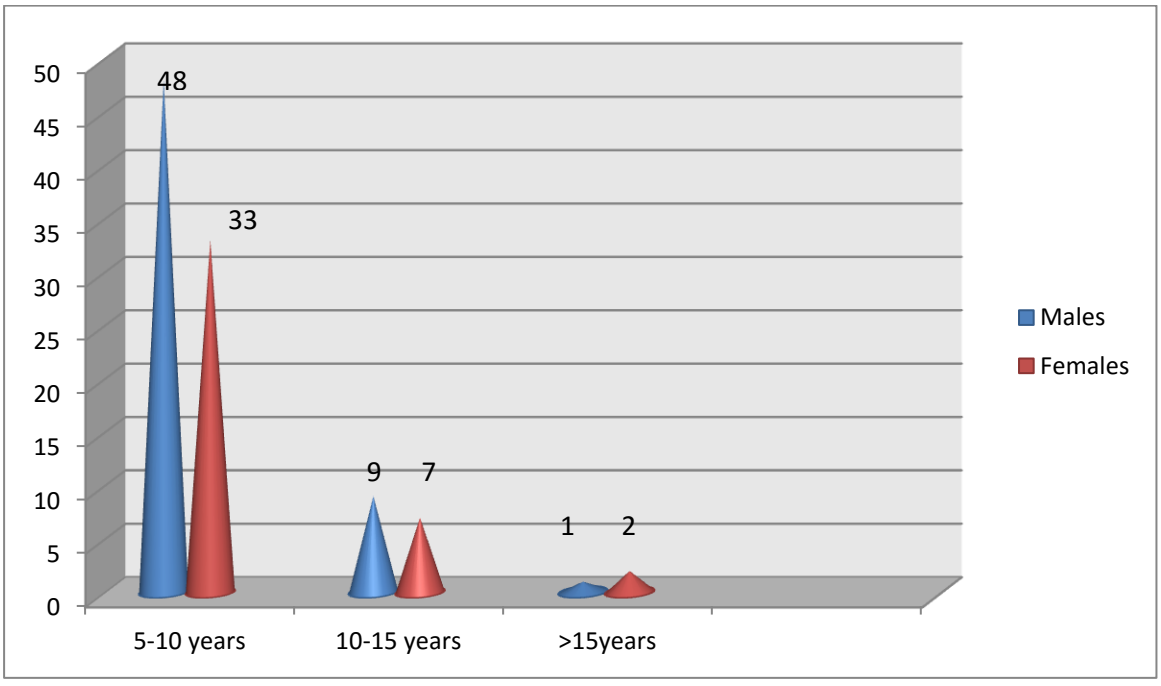


Figure 3:Diagram showing duration of diabetes among cases.

IV. CAN IN T2DM CASES AND CONTROLS

Among the 100 cases studied 62 had CAN .Of these 62, 44 had Grade 2(severe) CAN, 18 had Grade1(early) CAN .In the control group 3 had Grade1 CAN, which can be attributed to their age.

Table 4: CAN in T2DM patients and controls

CAN GRADE	CASES			CONTROLS		
	Males	Females	Total	Males	Females	Total
Grade0	27	11	38	52	44	96
Grade1	8	10	18	2	1	3
Grade2	20	24	44	1	0	1

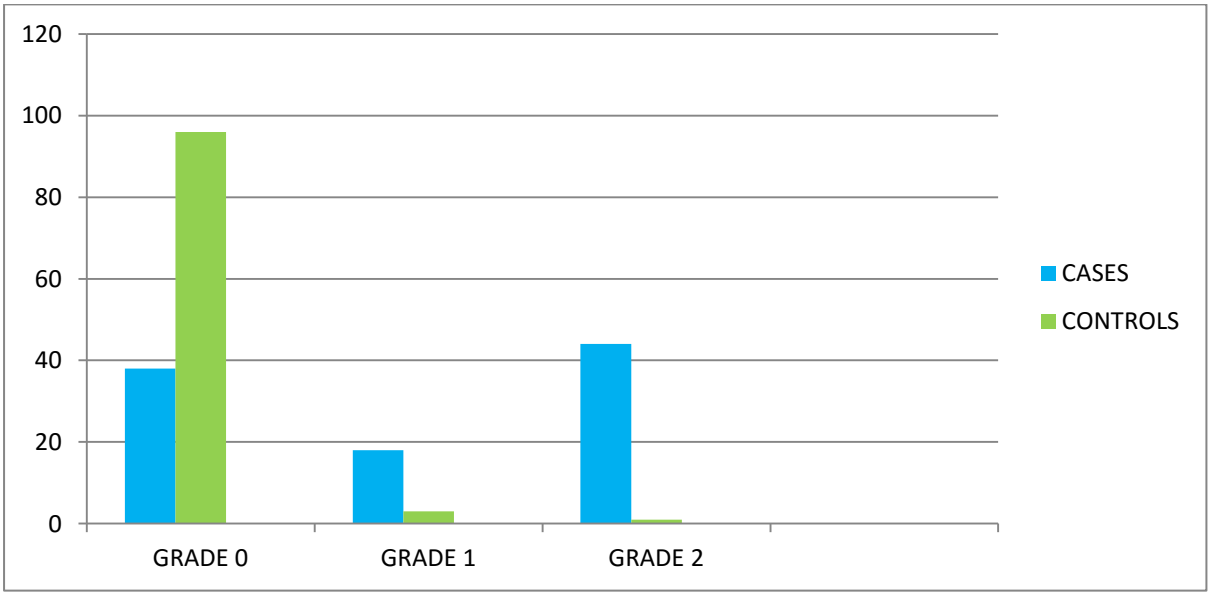


Figure 4: CAN in cases and controls

V. SEVERITY OF DIABETES BASED ON PPBS

The Type 2 Diabetes Mellitus patients were divided into three groups based on the PPBS values as mild ,moderate and severe hyperglycemia.76 patients had mild hyperglycemia with PPBS values less than 250mg% , while 6 had moderate and 18 had severe hyperglycemia with PPBS values between 250-300mg% and more than 300mg% respectively.

Table 5: Severity of diabetes based on PPBS

PPBS (mg/dl)	NUMBER OF CASES
Mild (<250mg/dl)	76
Moderate (250-300mg/dl)	6
Severe (>300mg/dl)	18

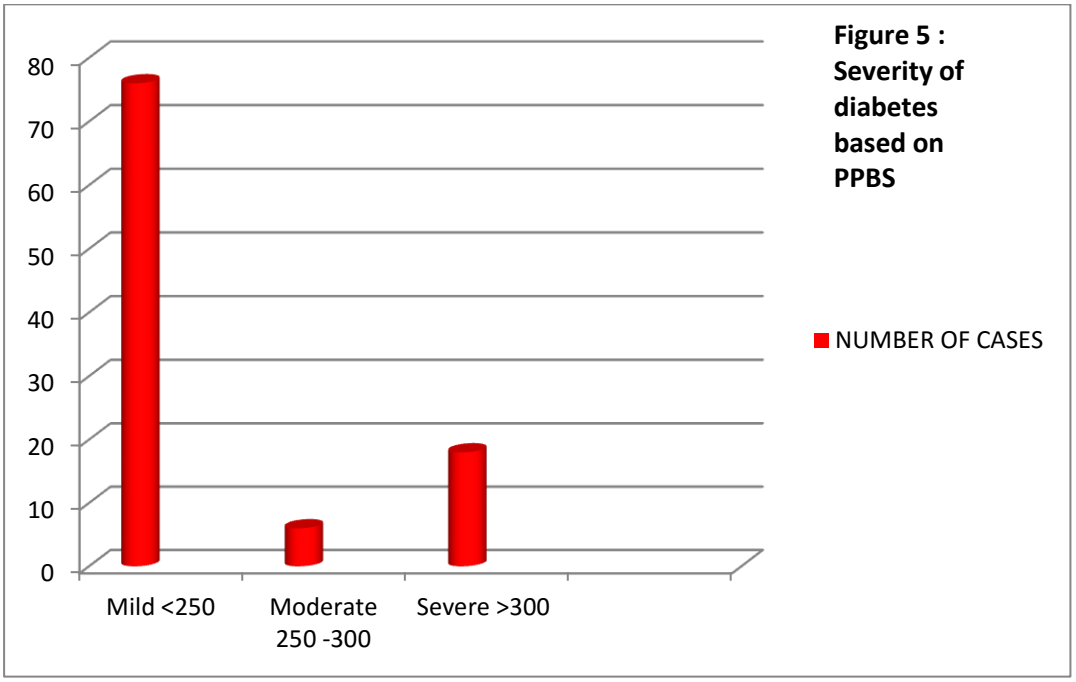


Figure 5 : Severity of diabetes based on PPBS

VI. MEAN HEART RATE IN TYPE 2 DM CASES AND CONTROLS

Mean heart rate was found to be high in diabetic patients compared to controls .Among the cases the heart rate was higher in those with severe CAN . There was no significant difference in mean heart rate between control group and diabetic patients without CAN.

Table 6: Mean heart rate in cases and controls

Group	Number of patients	Mean heart rate
Cases-Grade 2 CAN	44	92.68
Cases-Grade 1 CAN	18	76.78
Cases-Grade 0 CAN	38	72.26
Controls	100	72.56

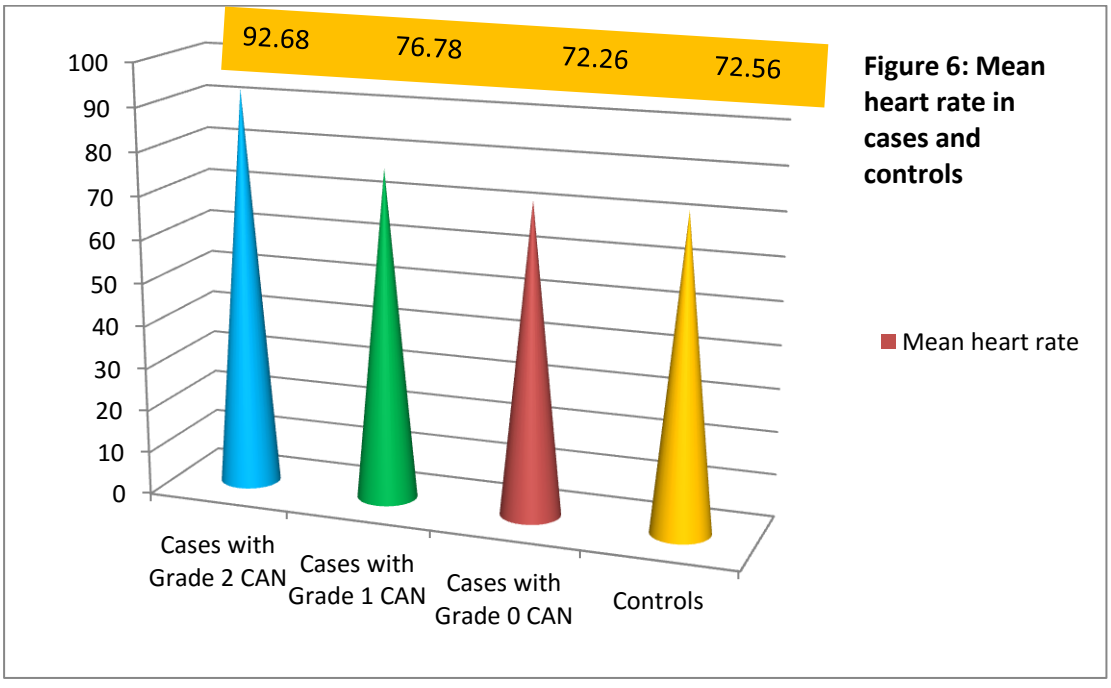


Figure 6: Mean heart rate in cases and controls

VII. QTc MEAN IN TYPE 2 DIABETES MELLITUS PATIENTS AND CONTROLS

Among the Type 2 Diabetes Mellitus patients and controls QTc mean was found to be significantly high in diabetic patients with Grade 2 CAN. There was no significant difference in QTC mean values between diabetics without CAN and healthy controls .

Table 7: QTc Mean in Type 2 Diabetes Mellitus patients and controls

Group	Number of patients	Mean QTc mean
Cases -Grade 2 CAN	44	425.64
Cases- Grade 1 CAN	18	402.22
Cases- Grade 0 CAN	38	390.32
Controls	100	387.57

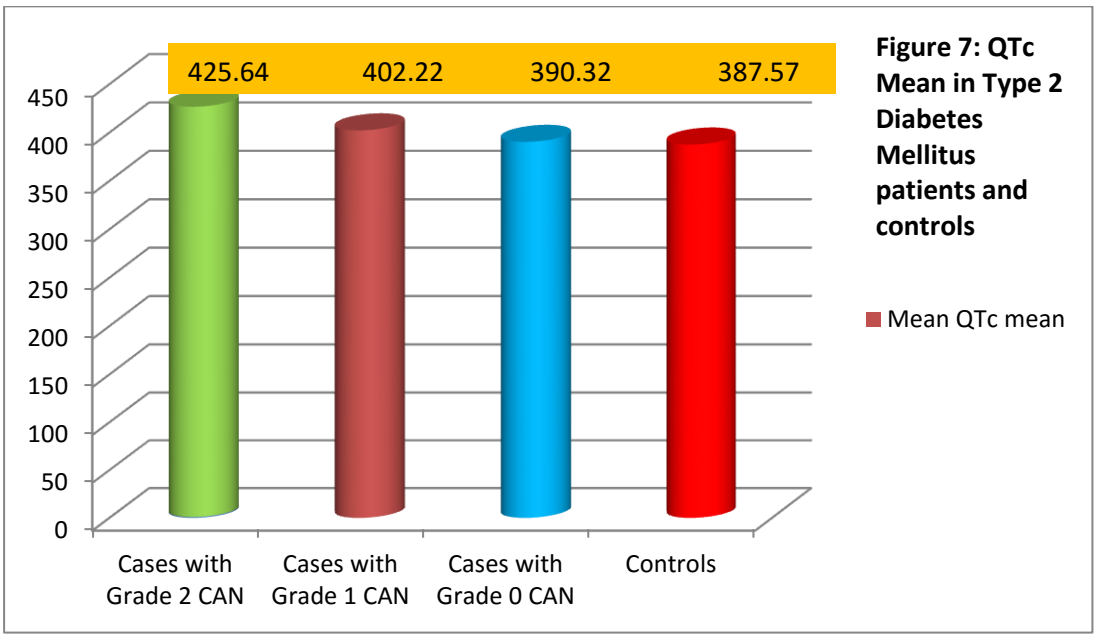


Figure 7: QTc Mean in Type 2 Diabetes Mellitus patients and controls

VIII. QTc MAXIMUM IN TYPE 2 DIABETES MELLITUS PATIENTS AND CONTROLS

Among the Type 2 Diabetes Mellitus patients and controls QTc max was found to be significantly high in diabetic patients with Grade 2 CAN. QTc max was found to be higher in diabetics with Grade 1 or 0 CAN compared to controls

Table 8: QTc Maximum in Type 2 Diabetes Mellitus patients and controls.

Group	Number of patients	Mean QTc maximum
Cases- Grade 2 CAN	44	452.91
Cases- Grade 1 CAN	18	420.89
Cases- Grade 0 CAN	38	406.74
Controls	100	400.80

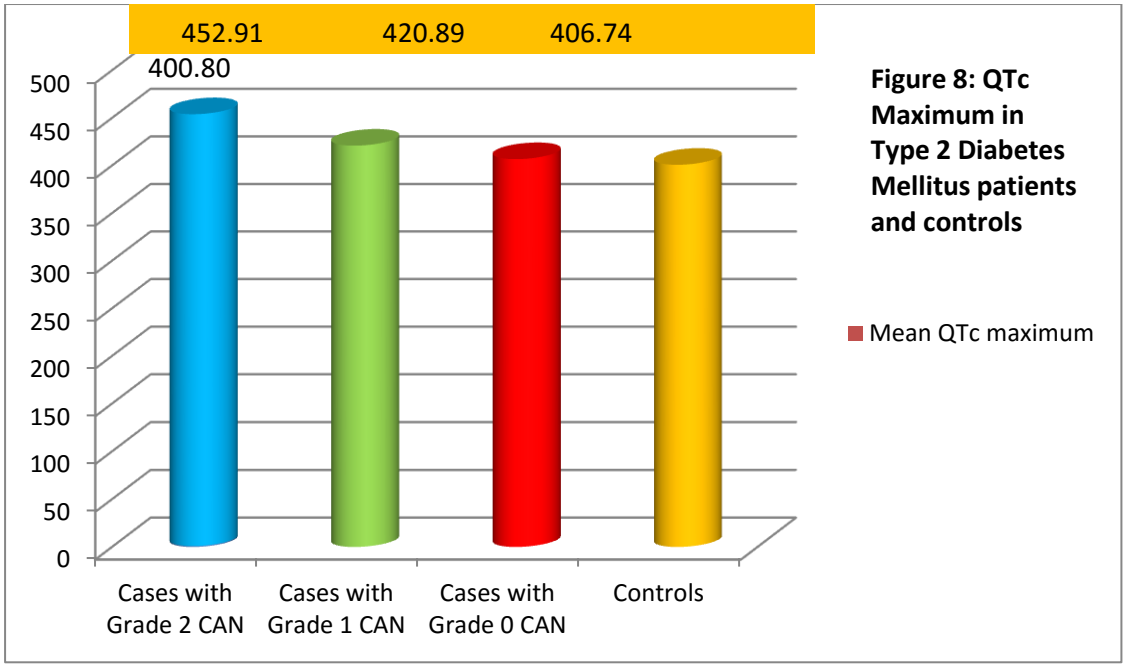


Figure 8: QTc Maximum in Type 2 Diabetes Mellitus patients and controls

IX. QTc MINIMUM IN TYPE 2 DIABETES MELLITUS PATIENTS AND CONTROLS

Among the Type 2 Diabetes Mellitus patients and controls QTc minimum was found to be significantly high in diabetic patients with Grade 2 CAN. There was no significant difference in QTc minimum values between diabetics without CAN and healthy controls .

Table 9: QTc Minimum in Type 2 Diabetes Mellitus patients and controls

Group	Number of patients	Mean QTc minimum
Cases- Grade 2 CAN	44	398.36
Cases- Grade 1 CAN	18	383.56
Cases- Grade 0 CAN	38	373.89
Controls	100	374.58

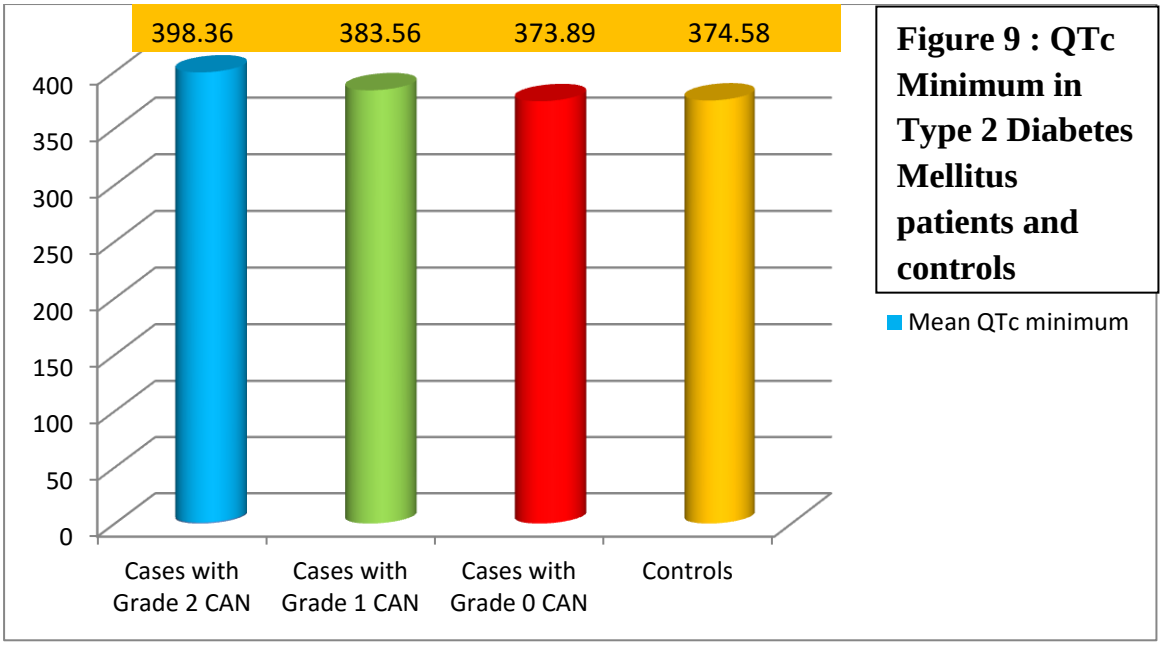


Figure 9 : QTc Minimum in Type 2 Diabetes Mellitus patients and controls

X. QTc DISPERSION IN TYPE 2 DIABETES MELLITUS PATIENTS AND CONTROLS

Among the Type 2 Diabetes Mellitus patients and controls QT dispersion was found to be significantly high in diabetic patients with Grade 2 CAN. QTd was found to be high in diabetics with Grade 1 CAN compared to controls

Table 10: QTd in Type 2 Diabetes Mellitus patients and controls.

Group	Number of patients	Mean QTd
Cases- Grade 2 CAN	44	54.09
Cases- Grade 1 CAN	18	37.11
Cases- Grade 0 CAN	38	33.11
Controls	100	26.48

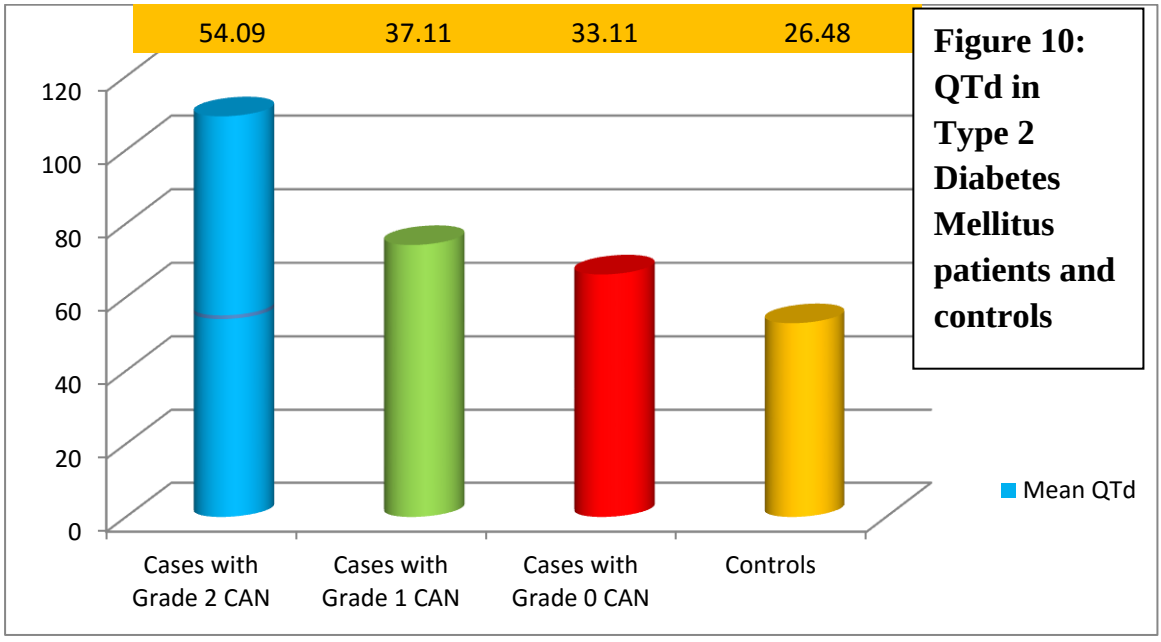


Figure 10: QTd in Type 2 Diabetes Mellitus patients and controls

ANALYSIS OF RESULTS

STATISTICAL ANALYSIS

The information collected regarding all selected cases were recorded in master chart. Data analysis was done with the help of computer using Statistical Package for Social Sciences(SPSS) software developed by IBM Corporation. Using this software percentage, mean, standard deviation and p value were calculated through Pearson correlation and Student t test and p value of < 0.05 was taken as significant.

In this study the association between QTc mean, QTc maximum ,QTc minimum, QTc mean ,QT dispersion and severity of CAN was studied among Type 2 Diabetes Mellitus patients and controls.

.

I. RELATION BETWEEN DURATION OF DIABETES AND CAN

Among 81 patients with Type 2 Diabetes Mellitus with duration of diabetes 5-10 years ,35 patients had no features of CAN. 18 patients had Grade 1 CAN ,28 patients had Grade 2 CAN. Among the study group 16 patients had duration of diabetes 10-15 years.Of these patients, 3 had no features of CAN, 13 had Grade 2 CAN. Among 3 patients with disease duration more than 15 years, 3 had Grade 2 CAN. The incidence of CAN and its severity found to be higher with longer duration of the disease with a correlation coefficient of 0.520.

Table 1: Correlation between duration of diabetes and CAN

Duration in years	No. of cases	Grade 0	Grade 1	Grade 2
5-10 years	81	35	18	28
11-15 years	16	3	0	13
>15 years	3	0	0	3
Correlation coefficient- 0.520 : High Correlation				

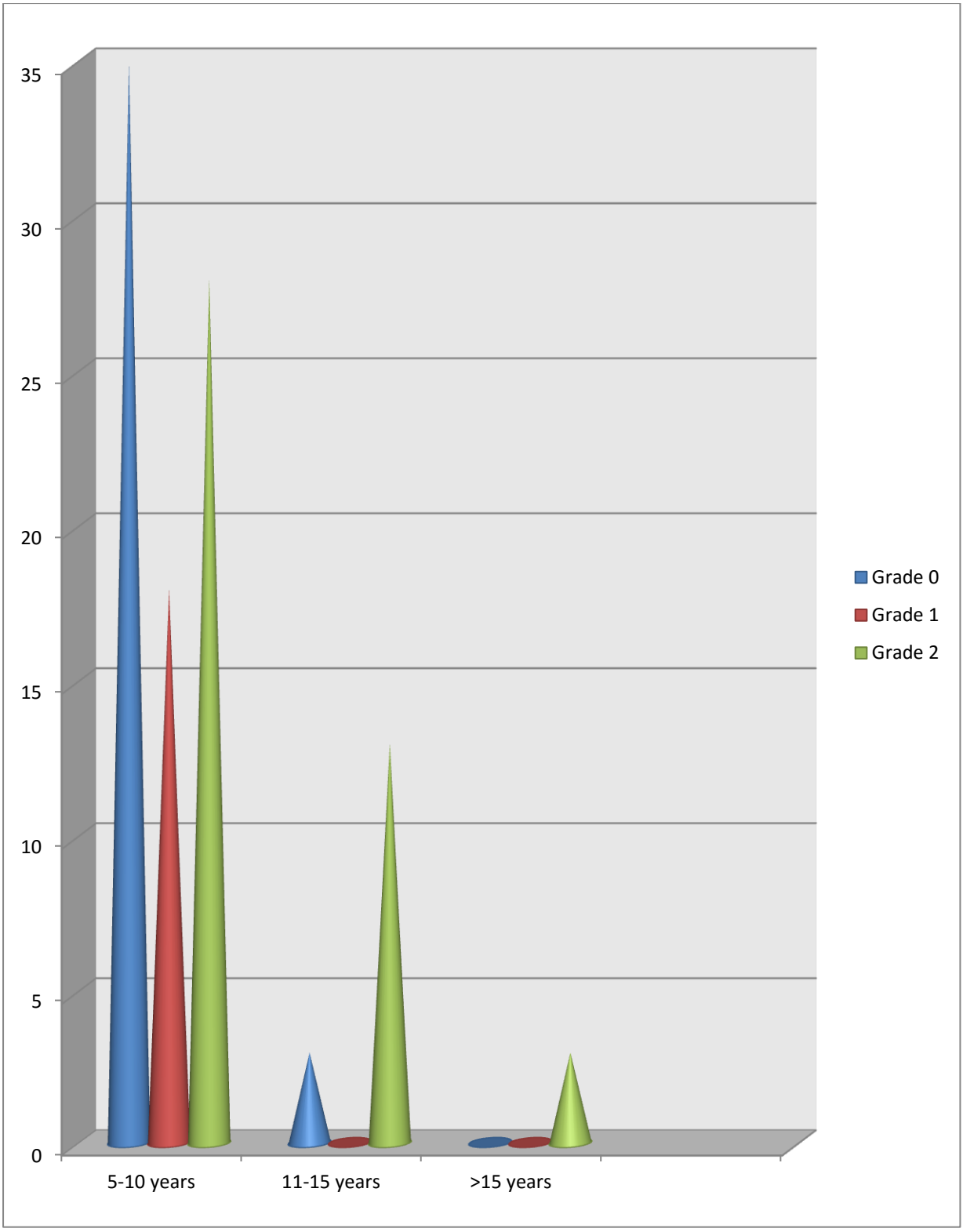


Figure 1: Diagram showing Correlation between duration of diabetes and CAN

II. CORRELATION BETWEEN SEVERITY OF DIABETES AND CAN

Among 76 patients with PPBS <250mg/dl, 20 had Grade2 CAN, 18 had Grade 1 CAN and 38 had no features of CAN. Of 6 patients with PPBS between 250-300 mg/dl , all of them had Grade 2 CAN. Out of 18 patientswith PPBS> 300 mg /dl all of them had Grade 2 CAN.On analysing the data , Pearson correlation coefficient is found to be 0.717 , which indicates high correlation.

Table 2. Correlation between severity of diabetes and CAN

PPBS in mg/dl	No. of cases	Grade 0	Grade 1	Grade 2
<250mg/dl	76	38	18	20
250-300 mg/dl	6	0	0	6
>300 mg/dl	18	0	0	18
Correlation coefficient- 0.717 : High Correlation				

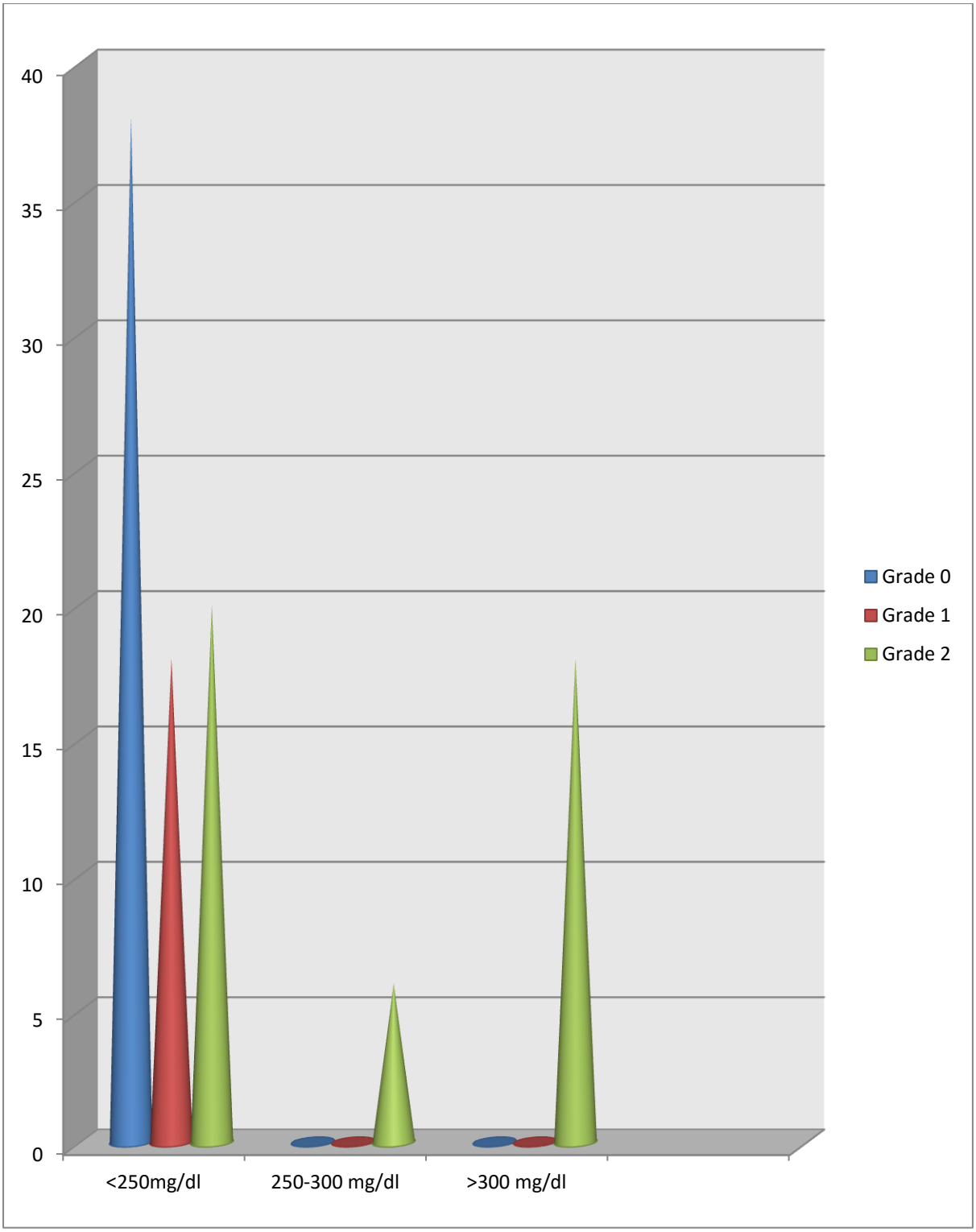


Figure 2 : Diagram showing Correlation between severity of diabetes and CAN

III. COMPARISON OF HEART RATE BETWEEN STUDY GROUP AND CONTROL GROUP

The resting heart rate of Type 2 diabetic patients was compared with healthy controls . It was found that mean resting heart rate was significantly more in study group than control group($p<0.01$). Within the study group mean resting heart rate was found to be significantly more in patients with autonomic neuropathy than in patients without autonomic neuropathy ($p<0.01$). Among those with autonomic neuropathy mean resting heart rate was found to be significantly more in patients with Grade 2 CAN than those with Grade 1 CAN($p<0.01$).There was no significant difference in mean heart rate among diabetic patients without autonomic neuropathy and healthy controls($p=0.110$).

Table 3. Mean Heart rate in study and control groups

Group	Heart rate
Grade 2 CAN	92.68
Grade 1 CAN	76.78
Grade 0 CAN	72.26
Control gp	72.56

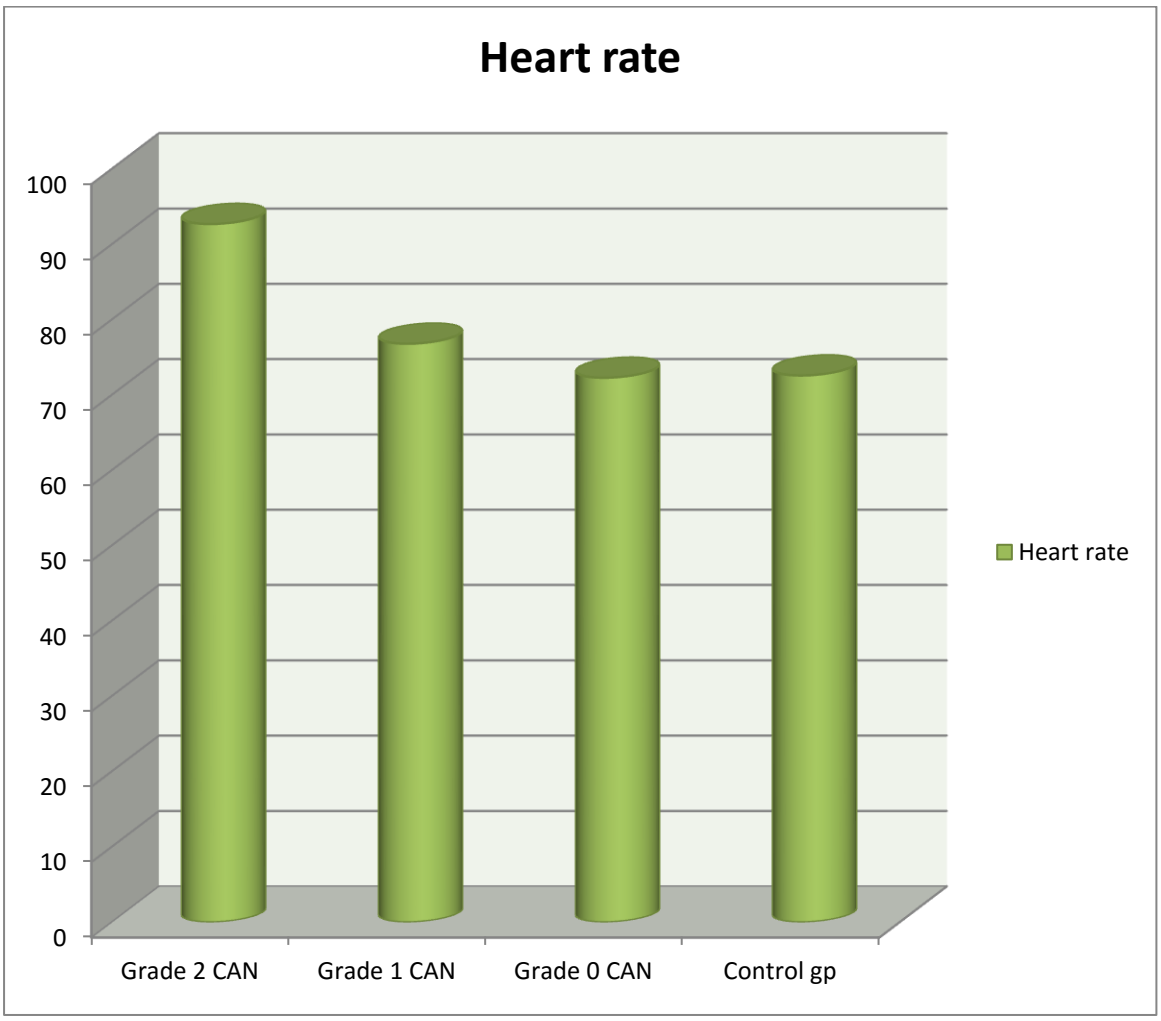


Figure 3: Diagram showing Mean Heart rate in study and control groups. In the study group mean resting heart rate was found to be 92.68 in patients with Grade 2 CAN and 76.78 in those with Grade 1 CAN and 72.78 in diabetic patients without autonomic neuropathy and 72.56 in healthy controls.

IV. COMPARISON OF QTc MAXIMUM BETWEEN STUDY GROUP AND CONTROL GROUP

The QTc maximum of Type 2 diabetic patients was compared with healthy controls . It was found that QTc maximum was significantly more in cases than controls ($p<0.01$). Within the study group QTc maximum was found to be significantly more in patients with CAN than in patients without CAN($p<0.01$). Among those with CAN QTc maximum was found to be significantly more in patients with Grade 2 CAN than those with Grade 1 CAN($p<0.01$).There was no significant difference in QTc maximum among diabetic patients without CAN and healthy controls($p=0.061$).

Table 4. QTc maximum in study and control groups

Group	QTc maximum (ms)
Grade 2 CAN	452.91
Grade 1 CAN	420.89
Grade 0 CAN	406.74
Control gp	400.80

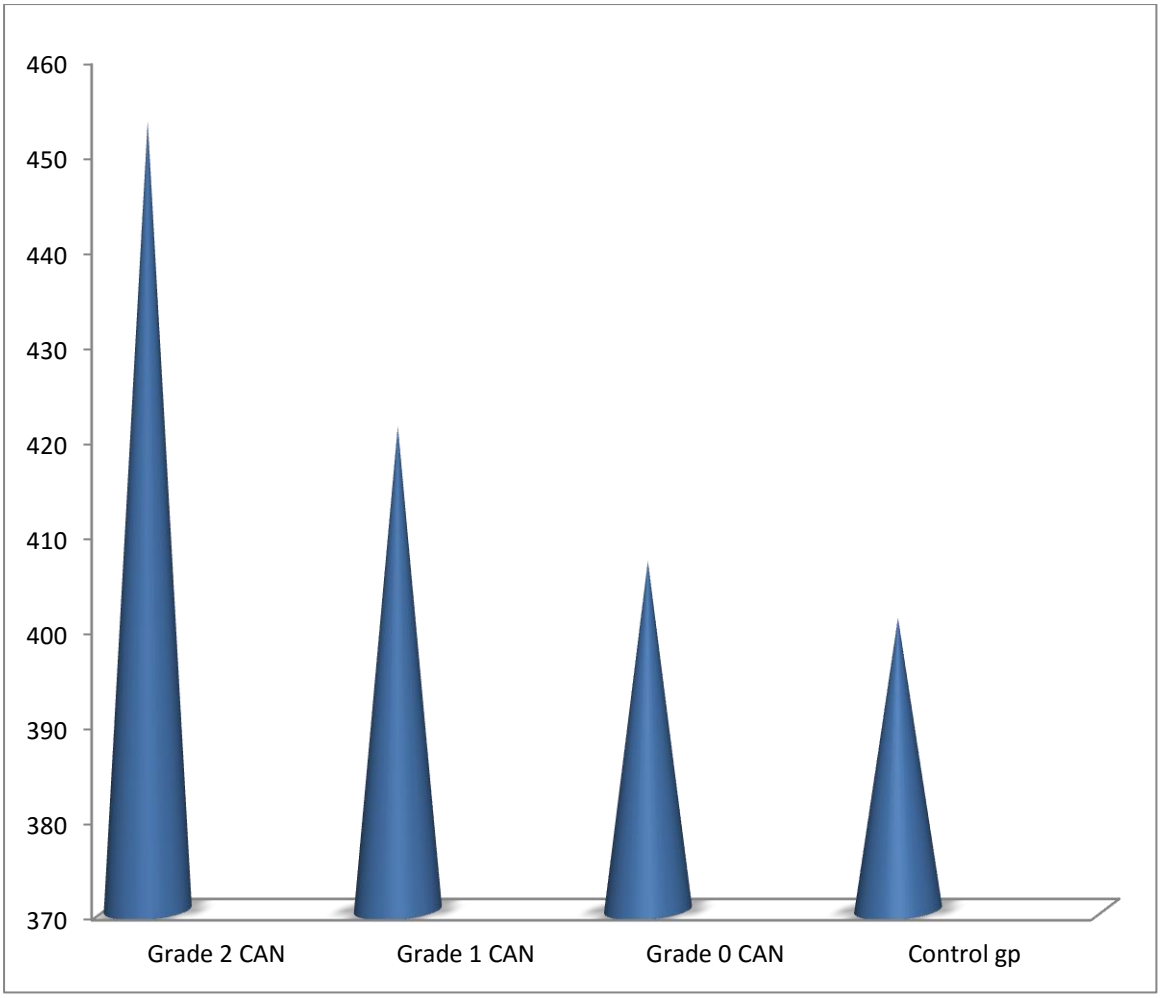


Figure 4 : Diagram showing QTc maximum in study and control groups . QTc maximum values were 452.91 msec, 420.89 msec, 406.74msec and 400.80 msec, respectively in the four groups. Difference between the groups were statistically significant except that there was no statistically significant difference in QTc maximum value among diabetics without autonomic neuropathy and controls .QTc maximum in the severe autonomic neuropathy group (452.91 msec) was significantly more than that in early neuropathy group (420.89 msec).

V. COMPARISON OF QTc MINIMUM BETWEEN STUDY GROUP AND CONTROL GROUP

The QTc minimum of Type 2 diabetic patients was compared with healthy controls . It was found that QTc minimum was significantly more in study group than control group ($p<0.01$). Within the study group QTc minimum was found to be significantly more in patients with CAN than in patients without CAN($p<0.01$). Unlike QT maximum ,QT minimum did not show statistically significantly difference between patients with Grade 2 CAN and those with Grade 1 CAN($p=0.275$).There was no significant difference in QTc minimum among diabetic patients without CAN and healthy controls($p=0.929$).

Table 5. QTc minimum in study and control groups

Group	QTc minimum (ms)
Grade 2 CAN	398.36
Grade 1 CAN	383.56
Grade 0 CAN	373.89
Control gp	374.58

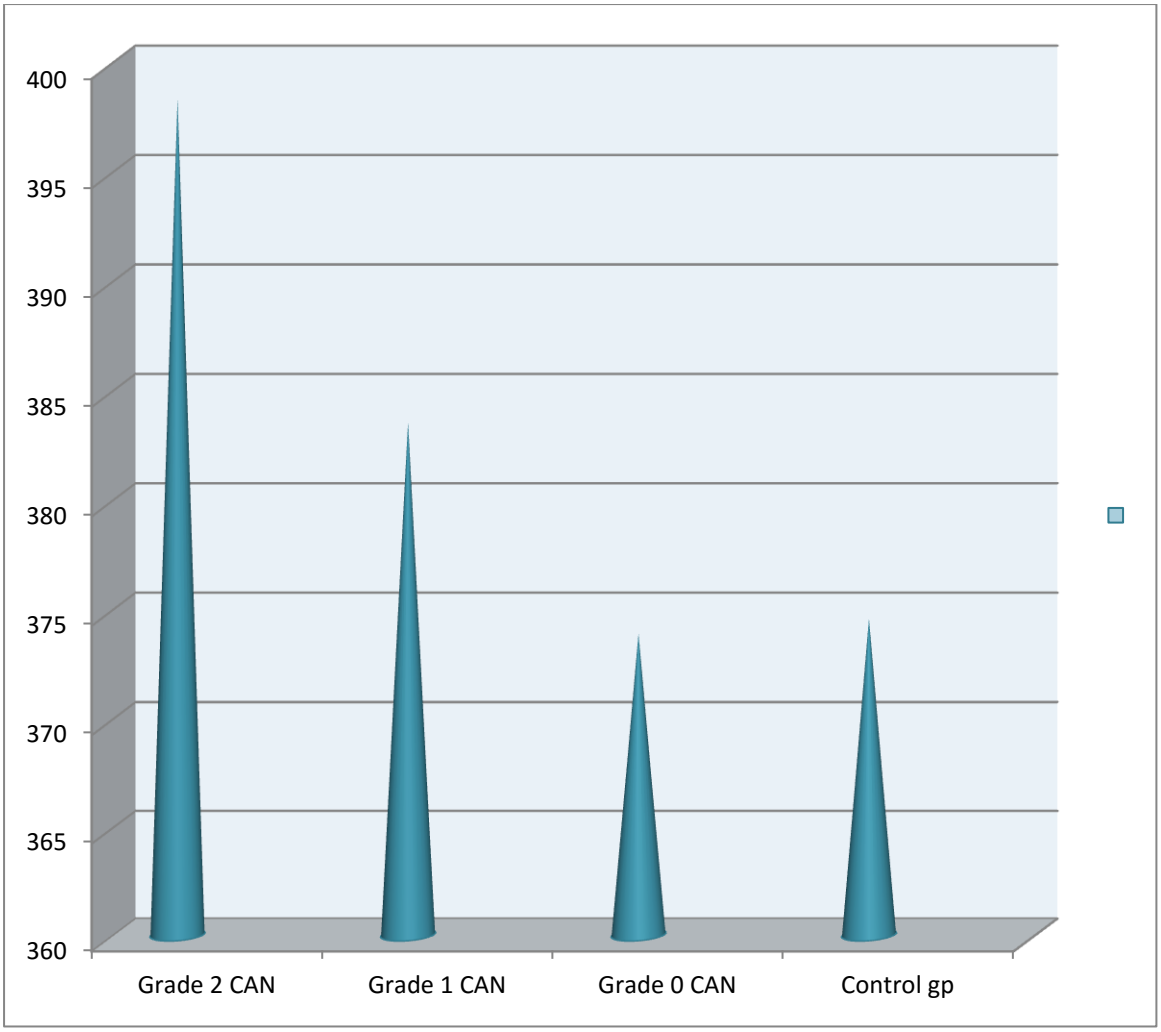


Figure 5 : Diagram showing QTc minimum in study and control groups. QTc minimum values were 398.36 msec, 383.56 msec, 373.89msec and 374.58 msec, respectively in the four groups. Difference between the groups were statistically significant except that there was no statistically significant difference in QTc minimum value among diabetics without autonomic neuropathy and controls. QTc minimum in the severe autonomic neuropathy group (398.36 msec) and in early neuropathy group (383.56 msec).

VI. COMPARISON OF QTc MEAN BETWEEN STUDY GROUP AND CONTROL GROUP

The QTc mean of Type 2 diabetic patients was compared with healthy controls . It was found that QTc mean was significantly more in study group than control group ($p<0.01$). Within the study group QTc mean was found to be significantly more in patients with CAN than in patients without CAN($p<0.01$). Among those with CAN QTc mean was found to be significantly more in patients with Grade 2 CAN than those with Grade 1 CAN($p<0.01$).There was no significant difference in QTc mean among diabetic patients without CAN and healthy controls($p=0.348$).

Table 6. QTc mean in study and control groups

Group	QTc mean (ms)
Grade 2 CAN	425.64
Grade 1 CAN	402.22
Grade 0 CAN	390.32
Control gp	387.57

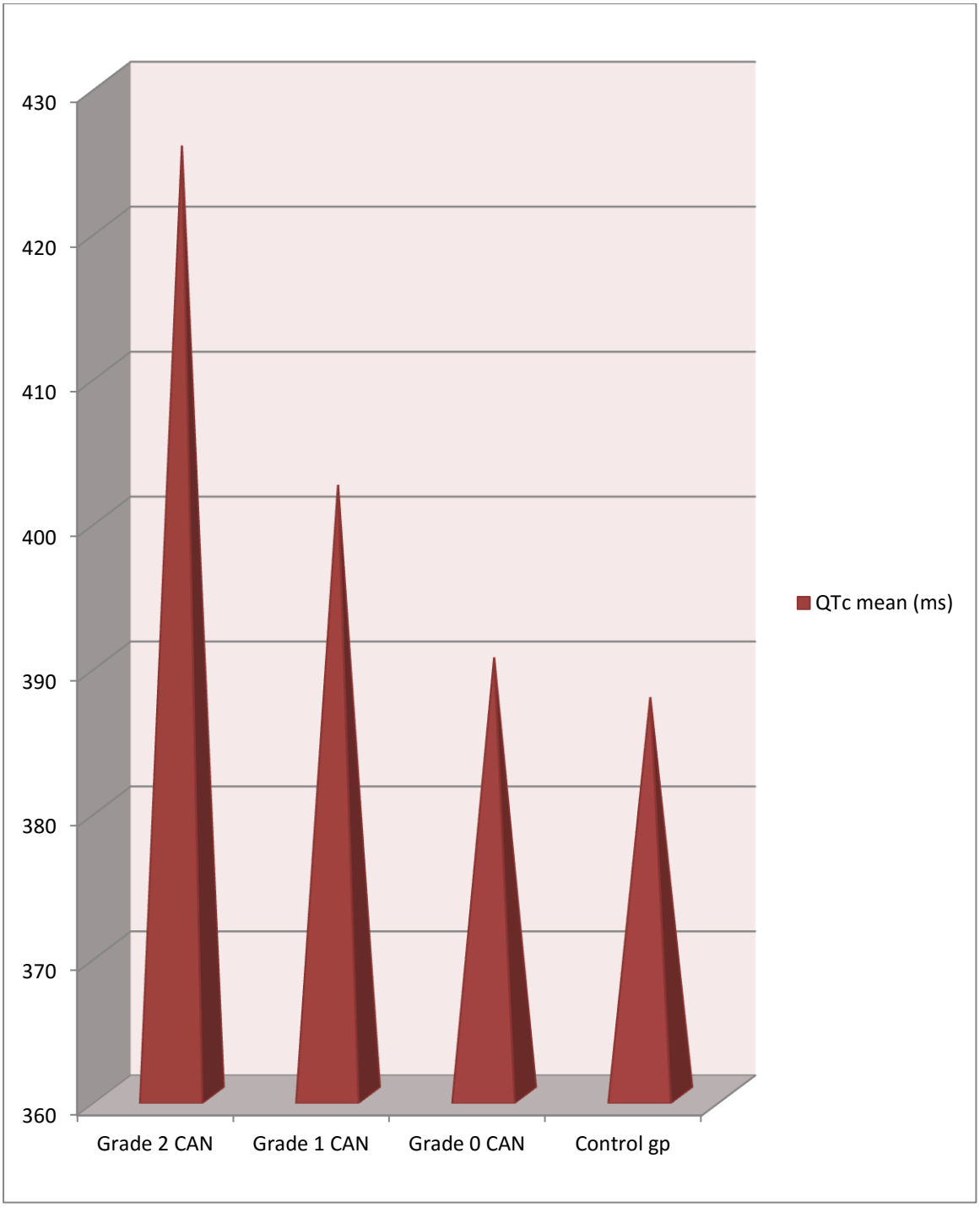


Figure 6: Diagram showing QTc mean in study and control groups. QTc mean in the four groups were 425.64 msec, 402.22 msec, 390.32 and 387.57 msec, respectively. The difference between autonomic neuropathy and no autonomic neuropathy group was statistically significant. But there was no statistically significant difference in QTc mean value among diabetics without autonomic neuropathy and controls.

VII. COMPARISON OF QT DISPERSION BETWEEN STUDY GROUP AND CONTROL GROUP

The QT dispersion of Type 2 diabetic patients was compared with healthy controls . It was found that QT dispersion was significantly more in study group than control group ($p<0.01$). Within the study group QT dispersion was found to be significantly more in patients with CAN than in patients without CAN($p<0.01$). Among those with CAN QT dispersion was found to be significantly more in patients with Grade 2 CAN than those with Grade 1 CAN($p<0.01$). Unlike other parameters QTd showed significant difference between diabetics without autonomic neuropathy and healthy controls(0.024).

Table 7. QT dispersion in study and control groups

Group	QT dispersion (ms)
Grade 2 CAN	54.09
Grade 1 CAN	37.11
Grade 0 CAN	33.11
Control gp	26.48

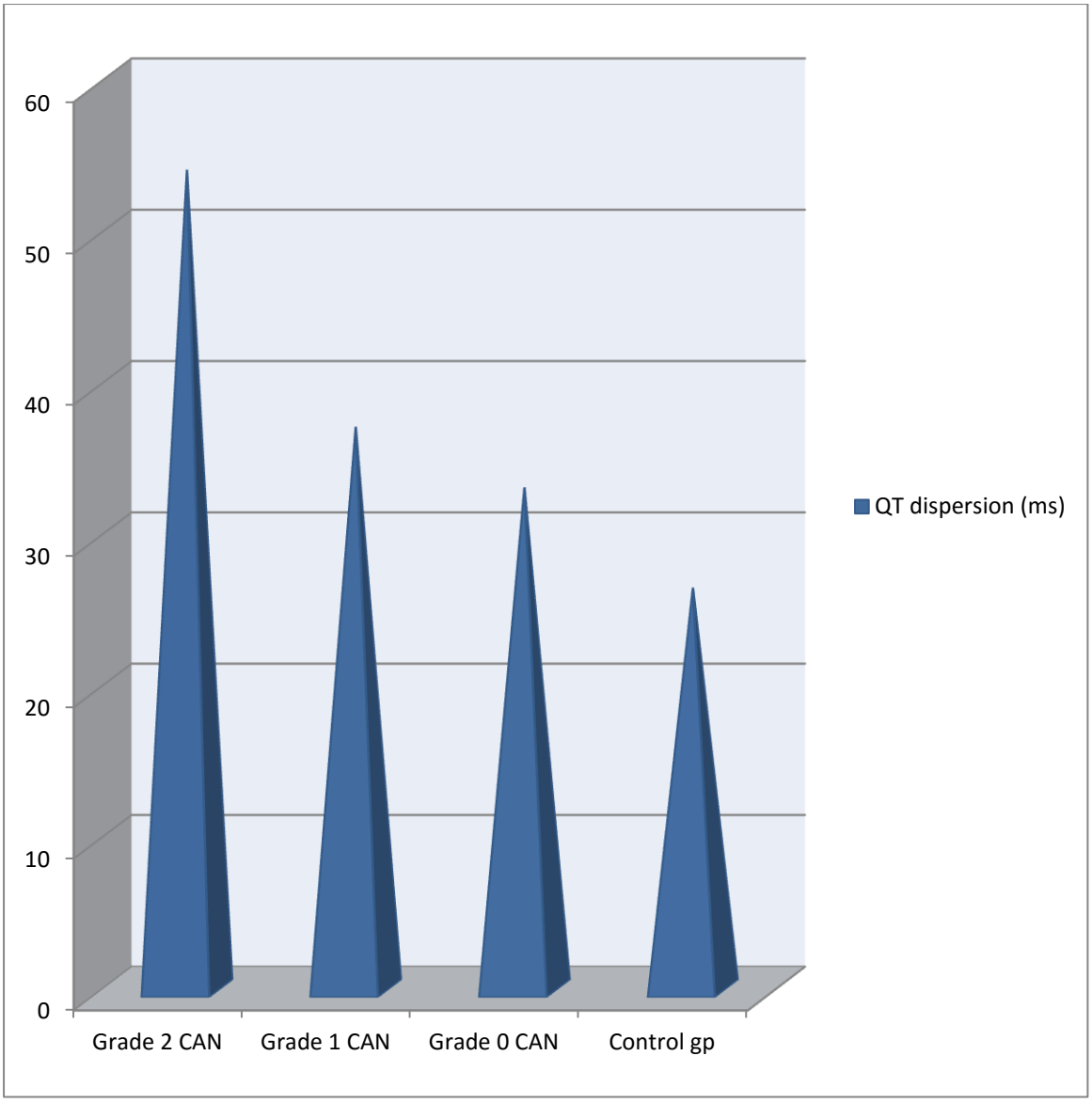


Figure 7 : Diagram showing QT dispersion in study and control groups. QTc dispersion in the case group with severe diabetic autonomic neuropathy was 54.09 msec ,compared to 37.11 msec in diabetics with early autonomic neuropathy ;33.11 msec in diabetics without autonomic neuropathy ;and 26.48 in healthy controls. The difference was statistically very significant. In contrast to other parameters QTc dispersion was found to be significantly more in diabetics without autonomic neuropathy than healthy controls making it an even more sensitive parameter.

DISCUSSION

DISCUSSION

The present study findings are consistent with and correlate those of prior studies documenting that ECG can be used as a bedside tool to assess the presence of CAN in Type 2 diabetes mellitus patients.

In this study QTc mean and QTc maximum, QTc minimum and QTc dispersion values were measured in the severe and early autonomic neuropathy group and compared with no autonomic neuropathy group and controls. QTc mean in the four groups were 425.64 msec, 402.22 msec, 390.32 and 387.57 msec, respectively. The difference between autonomic neuropathy and no autonomic neuropathy group was statistically significant. But there was no statistically significant difference in QTc mean value among diabetics without autonomic neuropathy and controls.

Similarly, QTc maximum values were 452.91 msec, 420.89 msec, 406.74msec and 400.80 msec, respectively in the four groups. Difference between the groups were statistically significant except that there was no statistically significant difference in QTc maximum value among diabetics without autonomic neuropathy and controls .QTc maximum in the severe autonomic neuropathy group (452.91 msec) was significantly more than that in early neuropathy group (420.89 msec). In our study, 79% of severe autonomic neuropathy patients ie 35 patients out of 44 with severe CAN had QTc maximum more than 440 msec. In the previous study by Germandy G *et al.*, QTc intervals in definite CAN was 456msec, and in early-435msec, and without CAN-413msec.

QTc minimum values were 398.36 msec, 383.56 msec, 373.89msec and 374.58 msec, respectively in the four groups. Difference between the groups were

statistically significant except that there was no statistically significant difference in QTc minimum value among diabetics without autonomic neuropathy and controls. Unlike other parameters QTc minimum did not show significant difference between patients with Grade 2(398.36 msec) and Grade 1 CAN(383.56 msec).

Diabetic patients with CAN showed an increase in QTc dispersion in our study that correlates with cardiac adrenergic dysinnervation .Increased QT dispersion was demonstrated in diabetic patients during episodes of hypoglycemia. In our study, QTc dispersion in the case group with severe diabetic autonomic neuropathy was 54.09 msec ,compared to 37.11 msec in diabetics with early autonomic neuropathy ;33.11 msec in diabetics without autonomic neuropathy ;and 26.48 in healthy controls. The difference was statistically very significant. In contrast to other parameters QTc dispersion was found to be significantly more in diabetics without autonomic neuropathy than healthy controls making it an even more sensitive parameter. Normal QT dispersion is <50 msec. 47% of the severe autonomic neuropathy group ie 21 out of 44 patients with severe autonomic neuropathy had QTc dispersion of more than 50 msec. Since all other factors which may cause prolongation of QTc were ruled out in this study group, the prolonged QTc intervals in our group can be considered to be be due to autonomic dysfunction.

In addition ,in the early stages of autonomic neuropathy , when the patient is asymptomatic and diagnosis of autonomic neuropathy can be made out only by doing cumbersome autonomic function tests, our study showed that QT dispersion, QT minimum, QT maximum and QT mean helped in the identification of such patients . The present study showed that QT dispersion, QT minimum, QT maximum

and QT mean was significantly more in diabetics with early diabetic neuropathy and controls.

Diagnosing patients with early autonomic neuropathy is very important ,since aggressive management by lifestyle modification and strict glycemic control helps in delaying the progression of CAN in such patients. QT dispersion was found to be a even more sensitive indicator, as it was found to be higher in diabetic patients without CAN compared to healthy controls.

LIMITATIONS OF THE STUDY

i. Lack of clinical follow-up data so the influence of CAN on mortality of diabetic patients with severe CAN including sudden cardiac death were not assessed

ii. Ischemic heart disease was not ruled out by coronary angiography

CONCLUSIONS

CONCLUSIONS

Diabetics with CAN had significantly higher QTc mean, QTc maximum ,QTc minimum values compared to diabetics without CAN and controls .

QTc dispersion was significantly more among patients with CAN compared to those without CAN and controls .

QTc mean, QTc maximum ,QTc dispersion values were significantly more among patients with severe CAN compared to early CAN.

QTc minimum values were not significantly different among patients with Severe vs. Early CAN.

QTc dispersion values were significantly different among patients without CAN and controls.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Gerasimos Dimitropoulos, Abd A Tahrani, Martin J Stevens; Cardiac autonomic neuropathy in patients with diabetes mellitus; *World J Diabetes* 2014 February 15; 5(1): 17-39 ISSN 1948-9358
2. Jayaprasad Narayana Pillai, Suresh Madhavan; CAN and QTc Interval in Type 2 diabetes Heart India, Vol 3 / Issue 1 / Jan-Mar 2015
3. Kasper, Fauci, Hauser, Longo, Jameson, Loscalzo; Principles of medicine; Harrison – 19th edition; Pages 2399-2430
4. S.N. Chugh, P. Mittal, S. Kumar, K. Chugh; QT Dispersion in Patients of diabetes Mellitus without Manifest Cardiac dysautonomia; JIMSA April-June 2011 Vol. 24 No. 2
5. Wael Refaie; Assessment of cardiac autonomic neuropathy in long standing type 2 diabetic women; The Egyptian Heart Journal (2014) 66, 63–69
6. Christina Voulgari,1, 2 Nicholas Tentolouris,1 and Christodoulos Stefanadis; The ECG Vertigo in Diabetes and Cardiac Autonomic Neuropathy; Experimental Diabetes Research Volume 2011, Article ID 687624, 17 pages doi:10.1155/2011/687624
7. Brian.R.Walker, Nicki R Colledge, Stuart.H Ralston, Ian D Penman; Davidsons Principles and practice of medicine 22nd edition pages 800-834
8. Lucianne Righeti MonteiroTannus*, Karla Rezende Guerra Drummond, Eliete Leão da Silva Clemente, Maria de Fátima Bevilacqua da Matta and Marilia Brito Gomes on behalf of the BrazilianType 1 Diabetes Study Group (BrazDiab1SG); Predictors of cardiovascular autonomic neuropathy in patients

with type 1 diabetes;frontiers in Endocrinology published: 25 November 2014 doi: 10.3389/fendo.2014.00191

9. Surawicz knilans;Chou's Electrocardiography in clinical practice 6th edition pages 19-23
10. N. S. Neki, Jatinder Kaur; A study of QTc-Prolongation and QT Dispersion (QTd) as an indicator of Cardiac Autonomic Neuropathy (CAN) in type 2 Diabetes Mellitus Patients; JIMSA Oct. - Dec. 2014 Vol. 27 No. 4
11. CP Mathur, Deepak Gupta; QTc Prolongation in Diabetes Mellitus – An Indicator of Cardiac Autonomic Neuropathy; JIACM 2006; 7(2): 130-2
12. Romulo F Balthazar;Basic and Bedside Echocardiography;pages 12-20
13. American diabetes association ; Standards of medical care in diabetes ; Diabetes care 34:S11,2011
14. Chan J C et al :Diabetes in Asia :Epidemiology ,risk factors, and pathophysiology :JAMA 301:2129,2009(PMID 19470990)
15. Grant R W et al :Genetic architecture of type 2 diabetes :Recent progress and clinical implications: Diabetes Care 32:1107,2009
16. Marton MM; Diabetic neuropathy; a clinical study of 150 cases ;Brain 1953;76:594-624
17. Gonin JM , Kadrofske MM, Schmaltz S, Bastyr EJ 3rd, Vinik AI; ;Corrected Q-T interval prolongation as diagnostic tool for assessment of CAN in diabetes mellitus

18. Matel D, Chiochină AD, Stratone A;Rev Med Chir Soc Med Nat Iasi.2010 Jan –Mar ;114(1);282-6; Utility of QTc interval for the diagnosis of CAN in type 2 diabetes mellitus

19. Kahn JK, Sisson JC, Vinik AI Journal of clinical Endocrinology Metabolism 1987 April ;64(4):751-4;; QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy

19. Mann, Zipes ,Libby,Bonow: Braunwalds heart disease tenth edition

LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS

DM	-DIABETES MELLITUS
CAN	-CARDIAC AUTONOMIC NEUROPATHY
CART	-CARDIAC AUTONOMIC REFLEX TESTS
MODY	-MATURITY ONSET DIABETES OF YOUNG
HNF	-
BMI	-BODY MASS INDEX
PCOS	-POLYCYSTIC OVARIAN SYNDROME
HDL	-HIGH DENSITY LIPOPROTEIN
GDM	-GESTATIONAL DIABETES MELLITUS
IFG	-IMPAIRED FASTING GLUCOSE
IGT	-IMPAIRED GLUCOSE TOLERANCE
CVD	-CARDIOVASCULAR DISEASE
PG	-PLASMA GLUCOSE
DKA	-DIABETIC KETOACIDOSIS
HHS	-HYPEROSMOLAR HYPERGLYCEMIC STATE
AGE’s	-ADVANCED GLYCOSYLATION END PRODUCTS
BRS	-BAROREFLEX SENSITIVITY
HRV	-HEART RATE VARIABILITY
LV	-LEFT VENTRICLE
HR	-HEART RATE
MSNA	-MUSCLE NERVE SYMPATHETIC NERVE ACTIVITY

MBF	-MEAN BLOOD FLOW
MI	-MYOCARDIAL INFARCTION
RAAS	-RENIN ANGIOTENSIN ALDOSTERONE SYSTEM
GLP	-GLUCAGON LIKE PEPTIDE
DPP	-DIPEPTIDYL PEPTIDASE
ACEI	-ANGIOTENSIN CONVERTING ENZYME INHIBITOR
QTd	-QT DISPERSION
QTc	-CORRECTED QT

PROFORMA

PROFORMA

Name:

Age / Sex:

IP no:

Occupation:

Presenting complaints:

Past History:

Personal history

alcoholic/ non alcoholic

smoker/ nonsmoker

Clinical Examination:

General Examination: Consciousness, orientation,febrile/afebrile, Pallor, jaundice, Clubbing, Lymphadenopathy, pedal edema.

Vitals:

PR

BP

MEAN RESTING HEART RATE

RR

SPO2

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations: FBS, PPBS, Urine albumin,Serum Creatinine

CAN GRADE:

ECG: QT interval, QTc, QT maximum, QT minimum, QT mean, QT dispersion

MASTER CHART

CASE GROUP

Sl.no.	Age	Sex	Duration of diabetes	Heart rate	FBS	PPBS	CAN grade	QTc mean	QT max	QT min	QTd
1	72	M	12	98	160	340	severe	440	464	416	48
2	62	M	10	96	189	320	severe	436	460	412	48
3	45	M	6	66	122	187	nil	396	404	388	16
4	48	M	7	76	140	220	early	400	412	388	24
5	65	F	9	92	140	220	severe	428	452	404	48
6	55	F	15	96	180	340	severe	424	444	404	40
7	50	M	6	72	116	168	nil	384	396	372	24
8	60	M	6	76	112	200	nil	412	428	396	32
9	45	F	6	88	142	200	severe	408	440	376	64
10	48	F	10	90	200	340	severe	392	424	360	64
11	52	F	5	70	132	188	early	400	412	388	24
12	55	M	7	70	110	132	nil	408	416	400	16
13	42	M	5	70	120	148	nil	392	400	384	16
14	56	M	8	96	180	340	severe	404	448	360	68
15	58	F	9	98	132	198	severe	416	460	372	88
16	49	M	5	94	180	360	severe	420	436	404	32
17	44	F	5	70	134	200	early	388	420	356	64
18	65	F	10	102	180	320	severe	428	464	392	72
19	45	M	5	66	112	160	nil	376	396	356	40
20	66	F	12	88	112	180	severe	432	468	396	72
21	62	M	11	80	90	130	nil	376	396	356	40
22	65	M	12	70	110	140	nil	380	400	360	40
23	56	M	8	88	160	220	severe	428	456	400	56
24	55	F	9	72	124	200	early	392	424	360	64
25	54	M	15	96	180	240	severe	432	456	408	48
26	54	M	8	70	130	180	nil	388	404	372	32
27	53	F	8	92	160	340	severe	420	460	380	80
28	50	F	6	72	120	160	nil	388	400	376	24
29	46	F	5	70	130	200	early	400	412	388	24
30	66	M	20	106	120	320	severe	440	468	412	56
31	45	M	5	72	112	180	nil	400	416	384	32
32	50	M	5	66	120	180	nil	380	408	352	56
33	55	M	7	110	150	240	severe	396	436	356	80
34	52	M	6	88	112	148	nil	412	420	404	16
35	50	M	6	88	140	180	early	416	428	404	24
36	53	M	9	98	180	240	severe	416	448	384	64
37	54	F	11	100	190	320	severe	428	468	388	80
38	57	F	6	70	112	140	nil	396	400	392	8

39	47	F	5	70	96	150	nil	380	396	364	34
40	55	M	8	98	160	220	severe	432	452	412	40
41	58	M	9	102	230	320	severe	436	464	408	56
42	45	F	6	80	110	146	nil	376	396	356	40
43	54	F	6	80	128	200	early	392	412	372	40
44	48	M	7	78	120	200	nil	388	400	376	24
45	44	M	5	76	110	130	nil	404	408	400	8
46	60	M	11	88	130	200	severe	436	452	420	32
47	56	F	8	82	140	180	early	412	424	400	24
48	58	M	7	78	150	200	nil	376	396	356	40
49	60	F	10	70	130	180	early	392	412	372	40
50	48	F	8	90	220	340	severe	424	468	380	88
51	44	M	5	70	130	260	nil	392	404	380	24
52	48	F	7	92	160	240	severe	416	452	380	72
53	48	M	5	66	140	200	nil	400	412	388	24
54	56	F	10	90	220	360	severe	420	444	396	48
55	52	M	8	82	120	156	early	404	420	388	32
56	54	F	10	88	156	220	severe	432	448	416	32
57	59	F	7	70	112	136	nil	408	416	400	16
58	49	M	6	76	130	180	early	408	420	396	24
59	55	F	5	66	100	140	nil	380	396	364	32
60	67	F	15	88	190	280	severe	436	460	412	48
61	56	M	7	60	160	200	nil	376	392	360	32
62	86	F	22	90	242	292	severe	432	460	404	56
63	58	F	8	76	112	156	nil	384	400	368	32
64	60	M	9	78	132	180	early	404	424	384	40
65	57	F	8	88	140	200	early	408	428	388	40
66	60	M	12	98	148	240	severe	428	456	400	56
67	58	M	14	96	240	360	severe	432	464	400	64
68	56	M	12	100	200	240	severe	436	460	412	48
69	54	F	9	78	212	292	severe	420	440	400	40
70	64	F	16	72	200	220	severe	440	468	412	56
71	60	M	6	70	140	190	nil	392	396	388	16
72	46	M	5	88	180	240	severe	416	436	396	40
73	44	M	5	80	100	160	nil	400	416	384	32
74	60	M	7	76	220	240	nil	376	396	356	40
75	56	F	8	74	240	360	severe	432	448	416	32
76	55	M	8	70	116	140	nil	380	400	360	40
77	54	M	6	78	140	156	early	404	432	376	56
78	45	F	5	72	160	200	early	408	432	384	48
79	48	F	5	92	160	200	severe	432	452	412	40
80	56	M	8	96	100	180	severe	416	436	396	40
81	56	F	7	70	130	180	nil	400	440	360	80
82	52	M	8	92	200	320	severe	428	452	404	48

83	54	M	9	90	180	260	severe	436	464	408	56
84	67	F	12	88	280	360	severe	416	440	392	48
85	61	M	10	66	160	240	nil	380	404	356	48
86	49	F	5	68	140	200	early	392	412	372	36
87	52	F	6	66	140	180	nil	392	404	380	24
88	54	M	5	70	112	168	nil	376	396	356	40
89	56	F	9	88	190	320	severe	420	440	400	40
90	48	M	6	92	160	280	severe	428	452	404	48
91	48	M	8	90	140	180	early	408	424	392	32
92	48	M	9	92	160	220	nil	404	412	396	16
93	55	F	12	98	200	268	severe	436	456	416	40
94	52	F	15	88	180	240	severe	440	464	416	48
95	50	F	8	94	160	200	severe	420	448	392	56
96	56	M	5	72	132	176	early	412	428	396	32
97	58	M	6	70	112	148	nil	396	416	376	40
98	48	M	6	70	140	180	nil	400	428	372	56
99	45	F	6	72	130	180	nil	384	412	356	56
100	46	F	7	76	110	140	nil	400	436	364	72

CONTROL GROUP

Sl.no.	Age	Sex	Duration of diabetes	Heart rate	FBS	PPBS	CAN grade	QTc mean	QT max	QT min	QTd
1	58	M	0	72	82	120	0	422	424	420	24
2	45	F	0	76	90	100	0	414	428	400	28
3	54	F	0	80	78	90	0	362	384	352	32
4	48	M	0	66	88	110	0	378	396	360	36
5	44	M	0	56	100	120	0	382	392	372	20
6	60	M	0	72	96	114	0	388	400	376	24
7	56	F	0	66	92	112	0	384	400	368	32
8	58	M	0	64	78	90	0	370	384	356	28
9	60	F	0	62	88	130	0	380	392	368	24
10	48	F	0	70	100	120	0	402	416	388	28
11	44	M	0	80	78	112	0	408	424	392	32
12	52	F	0	88	80	114	0	370	388	352	36
13	50	F	0	92	78	116	0	382	392	372	20

14	56	M	0	56	98	118	0	384	396	372	24
15	58	M	0	68	96	110	0	392	408	376	32
16	48	M	0	62	68	104	0	418	428	408	20
17	45	F	0	80	84	98	0	372	384	360	24
18	46	F	0	70	82	96	0	380	396	364	32
19	72	M	0	76	90	110	2	372	392	364	28
20	62	M	0	74	92	100	0	388	400	376	24
21	45	M	0	58	98	90	0	386	400	372	28
22	48	M	0	60	96	120	0	372	384	360	24
23	65	F	0	76	86	130	1	378	392	364	28
24	65	M	0	72	94	120	0	400	416	384	32
25	56	M	0	70	84	140	0	374	392	356	36
26	55	F	0	80	86	126	0	406	416	396	20
27	54	M	0	86	88	110	0	412	424	400	24
28	54	M	0	84	100	120	0	370	388	352	36
29	53	F	0	58	96	114	0	382	392	372	20
30	50	F	0	56	92	112	0	384	396	372	24
31	46	F	0	60	78	90	0	392	408	376	32
32	66	M	0	60	88	130	1	418	428	408	20
33	56	F	0	66	100	120	0	372	384	360	24
34	55	M	0	64	78	112	0	386	396	376	20
35	54	M	0	68	80	114	0	380	392	368	24
36	45	F	0	72	78	116	0	380	396	364	32
37	48	F	0	64	98	118	0	380	392	368	28
38	56	M	0	62	68	104	0	388	400	376	24
39	56	F	0	68	84	98	0	386	400	372	28
40	52	M	0	86	82	96	0	368	384	352	32
41	54	M	0	80	90	110	0	374	392	356	36
42	56	F	0	90	92	100	0	406	416	396	20
43	48	M	0	74	98	90	0	412	424	400	24
44	48	M	0	72	96	120	0	372	388	356	32
45	50	M	0	72	86	130	0	382	392	372	20
46	55	M	0	70	94	120	0	384	396	372	24
47	52	M	0	66	84	140	0	394	408	380	28
48	50	M	0	76	86	126	0	412	428	396	32
49	53	M	0	74	88	110	0	371	392	350	36
50	54	F	0	72	96	120	0	386	396	376	20
51	57	F	0	88	86	130	0	396	408	384	24
52	47	F	0	80	94	120	0	410	428	392	36
53	55	M	0	84	84	140	0	374	384	364	20
54	45	M	0	76	86	126	0	384	396	372	24
55	48	M	0	66	88	110	0	376	392	360	32
56	65	F	0	64	100	120	0	390	400	380	20
57	55	F	0	68	96	114	0	388	400	376	24

58	50	M	0	86	92	112	0	374	384	364	20
59	60	M	0	74	78	90	0	380	392	368	24
60	45	F	0	72	88	130	0	404	416	392	24
61	48	F	0	70	100	120	0	376	392	360	32
62	52	F	0	70	90	110	0	410	424	396	28
63	55	M	0	66	92	100	0	416	428	404	24
64	42	M	0	64	98	90	0	370	384	356	28
65	56	M	0	80	96	120	0	380	396	364	32
66	45	M	0	78	86	130	0	374	392	356	36
67	50	M	0	84	94	120	0	390	400	380	20
68	55	M	0	82	84	140	0	388	400	376	24
69	52	M	0	80	86	126	0	368	384	352	32
70	50	M	0	66	88	110	0	382	392	372	20
71	53	M	0	76	96	120	0	404	416	392	24
72	54	F	0	64	86	130	0	410	424	396	28
73	57	F	0	62	90	110	0	372	388	356	32
74	47	F	0	90	92	100	0	374	392	356	36
75	55	M	0	88	98	90	0	386	396	376	20
76	58	M	0	82	96	120	0	396	408	384	24
77	45	F	0	58	86	130	0	418	428	408	20
78	60	F	0	66	94	120	0	372	384	360	24
79	48	F	0	64	84	140	0	380	396	364	32
80	44	M	0	66	86	126	0	382	392	372	20
81	48	F	0	80	88	110	0	388	400	376	24
82	48	M	0	88	96	120	0	390	400	380	20
83	56	F	0	74	86	130	0	384	396	372	24
84	52	M	0	76	94	120	0	404	416	392	24
85	54	F	0	82	84	140	0	408	424	392	32
86	59	F	0	80	86	126	0	374	388	360	28
87	49	M	0	76	88	110	0	382	392	372	20
88	58	F	0	74	100	120	0	384	396	372	24
89	60	M	0	70	96	114	0	396	408	384	24
90	57	F	0	66	86	126	0	411	428	394	32
91	60	M	0	68	88	110	0	370	384	356	28
92	58	M	0	90	96	120	0	384	396	372	24
93	56	M	0	64	86	130	0	378	392	364	28
94	54	F	0	66	90	110	0	384	400	368	32
95	64	F	0	80	92	100	0	382	400	364	36
96	60	M	0	78	98	90	0	382	392	372	20
97	46	M	0	80	96	120	0	404	416	392	24
98	46	F	0	66	88	110	0	410	420	400	20
99	52	M	0	68	96	120	0	377	384	370	24
100	66	M	0	70	86	130	1	386	396	376	20

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.VRINDA.V
Course	:	PG in MD GENERAL MEDICINE
Period of Study	:	2014-2017
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A STUDY OF QTD AS AN INDICATOR OF CARDIAC AUTOMATIC NEUROPATHY IN TYPE 2 DIABETES
Ethical Committee as on	:	11.01.2016

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

R. Parameswari
Member Secretary

Chairman

Dean / Convenor
DEAN
Madurai Medical College
Madurai-20

11 JAN 2016

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201411124 Md Genmed VRINDA.V
Assignment title:	2015-2015 plagiarism
Submission title:	A STUDY OF QTD AS AN INDICAT…
File name:	DR._VRINDA_GENERAL_MEDICINE..
File size:	2.44M
Page count:	85
Word count:	11,425
Character count:	63,088
Submission date:	17-Sep-2016 10:32PM
Submission ID:	706337253

I. INTRODUCTION

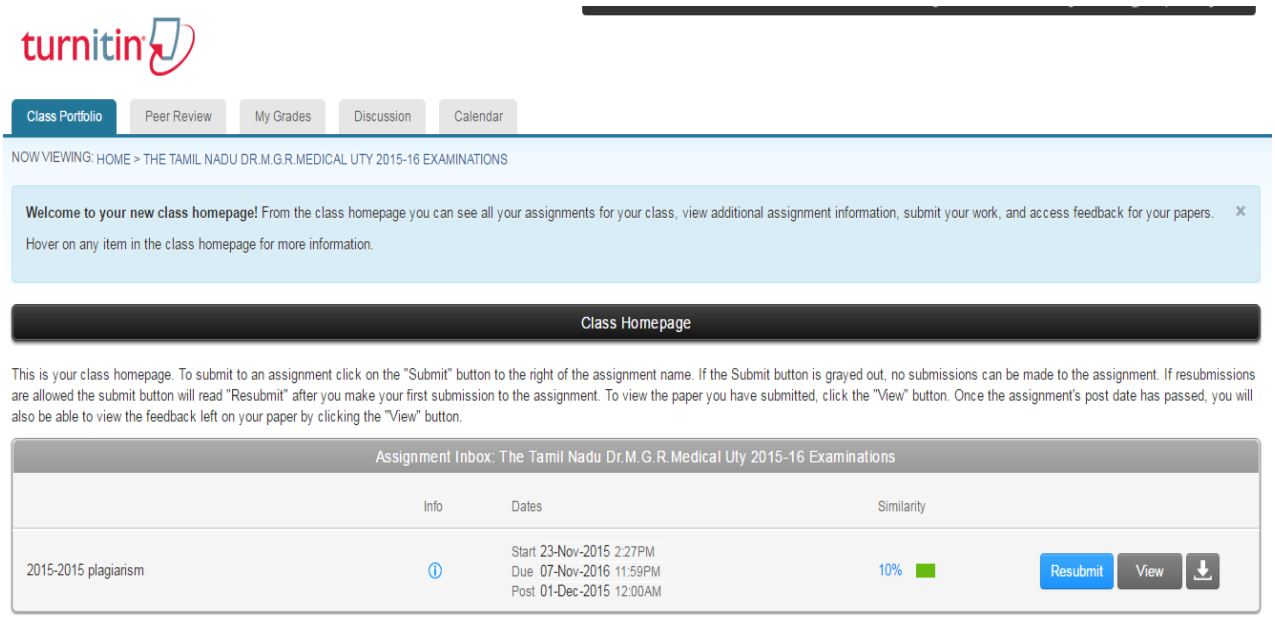
Diabetes Mellitus is a group of metabolic diseases characterised by chronic hyperglycemia associated with abnormal metabolism of proteins fats and carbohydrates due to absolute or relative insulin deficiency.

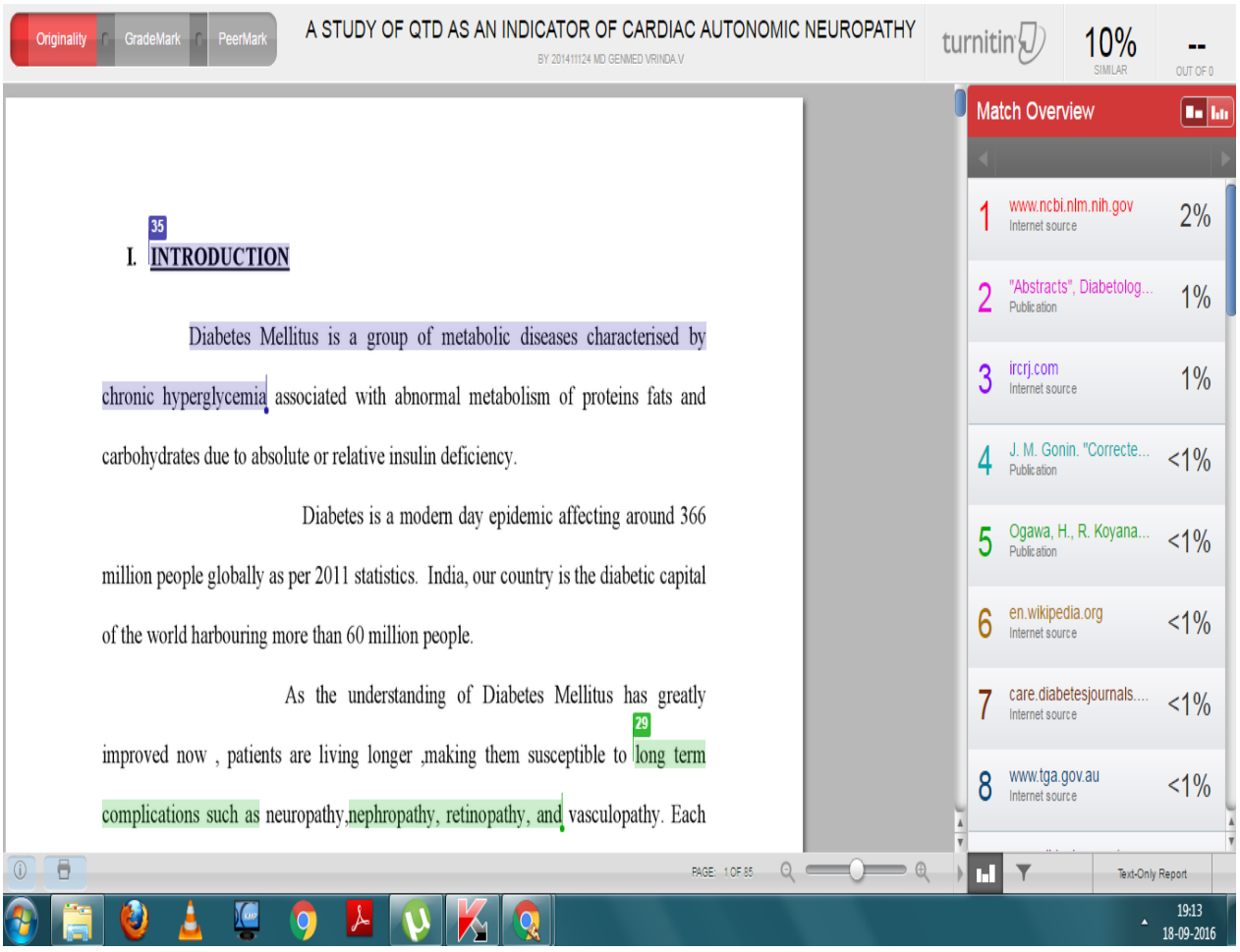
Diabetes is a modern day epidemic affecting around 366 million people globally as per 2011 statistics. India, our country is the diabetic capital of the world harbouring more than 60 million people.

As the understanding of Diabetes Mellitus has greatly improved now , patients are living longer ,making them susceptible to long term complications such as neuropathy,nephropathy, retinopathy, and vasculopathy. Each complication need to be addressed specifically in addition to hyperglycemia.

Diabetic neuropathy is one of the commonest complication of diabetes mellitus and is associated with considerable morbidity and mortality. Autonomic neuropathy, often overlooked, is one of the most insidious complications of diabetes mellitus (DM) especially if long standing and poorly controlled. Cardiovascular autonomic neuropathy (CAN), within the context of Diabetic autonomic neuropathy, occurs when there is an impairment of autonomic control of the cardiovascular system after ruling out other causes of dysautonomia. However, symptomatic CAN (CAN) manifests in about 5% of diabetic patients, but when present, it is associated with the increased mortality , predisposing to ventricular arrhythmias, silent ischaemia, and cardiac arrest. Hence, its early detection and early prevention is essential.

"Cardiac Autonomic Neuropathy (CAN) is often overlooked both in diagnosis and treatment simply because there is no widely accepted single approach to


turnitin
Class Portfolio
Peer Review
My Grades
Discussion
Calendar
NOW VIEWING: HOME > THE TAMIL NADU DR.M.G.R.MEDICAL UTY 2015-16 EXAMINATIONS
Welcome to your new class homepage! From the class homepage you can see all your assignments for your class, view additional assignment information, submit your work, and access feedback for your papers.
Hover on any item in the class homepage for more information.
Class Homepage
This is your class homepage. To submit to an assignment click on the "Submit" button to the right of the assignment name. If the Submit button is grayed out, no submissions can be made to the assignment. If resubmissions are allowed the submit button will read "Resubmit" after you make your first submission to the assignment. To view the paper you have submitted, click the "View" button. Once the assignment's post date has passed, you will also be able to view the feedback left on your paper by clicking the "View" button.
Assignment Inbox: The Tamil Nadu Dr.M.G.R.Medical Uty 2015-16 Examinations
Info
Dates
Similarity
2015-2015 plagiarism
Start 23-Nov-2015 2:27PM
Due 07-Nov-2016 11:59PM
Post 01-Dec-2015 12:00AM
10%
Resubmit
View


Originality
GradeMark
PeerMark
A STUDY OF QTD AS AN INDICATOR OF CARDIAC AUTONOMIC NEUROPATHY
BY 201411124 MD GENMED VRINDA.V
turnitin
10%
SIMILAR
--
OUT OF 0
I. INTRODUCTION
Diabetes Mellitus is a group of metabolic diseases characterised by chronic hyperglycemia associated with abnormal metabolism of proteins fats and carbohydrates due to absolute or relative insulin deficiency.
Diabetes is a modern day epidemic affecting around 366 million people globally as per 2011 statistics. India, our country is the diabetic capital of the world harbouring more than 60 million people.
As the understanding of Diabetes Mellitus has greatly improved now , patients are living longer ,making them susceptible to long term complications such as neuropathy,nephropathy, retinopathy, and vasculopathy. Each
Match Overview
1 www.ncbi.nlm.nih.gov Internet source 2%
2 "Abstracts", Diabetolog... Publication 1%
3 ircrj.com Internet source 1%
4 J. M. Gonin. "Correcte... Publication <1%
5 Ogawa, H., R. Koyana... Publication <1%
6 en.wikipedia.org Internet source <1%
7 care.diabetesjournals.... Internet source <1%
8 www.tga.gov.au Internet source <1%
PAGE: 1 OF 85
Text-Only Report
19:13
18-09-2016