Dissertation on

A STUDY ON PREVALENCE OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES AND UTILITY OF CORRECTED QT INTERVAL FOR ITS DIAGNOSIS

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1

CERTIFICATE

This is to certify that the dissertation titled **"PREVALENCE OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES AND UTILITY OF CORRECTED QT INTERVAL FOR ITS DIAGNOSIS"** is the bonafide original work of **Dr.G.VIGNESH** in partial fulfillment of the regulation for M.D. Branch–I (General Medicine) Examination of the Tamilnadu Dr. M.G.R Medical University to be held in MARCH 2009. The Period of study was from May 2007 to August 2008.

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DECLARATION

I, **Dr G.VIGNESH,** solemnly declare that dissertation titled "**PREVALENCE OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES AND UTILITY OF CORRECTED QT INTERVAL FOR ITS DIAGNOSIS"** is a bonafide work done by me at Madras Medical College and Govt. General Hospital from May 2007 to August 2008 under the guidance and supervision of my unit chief **PROF.R.SUKUMAR,MD**, Professor of medicine.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of regulation for the award of M.D. Degree (Branch – I) in General Medicine.

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CONTENT

ABBREVIATION

ANS - Autonomic Nervous System

CAN - Cardiovascular Autonomic Neuropathy

DAN - Diabetic Autonomic Neuropathy

DCCT - Diabetes Control and Complications Trial

DPP - Dipeptidyl Peptidase

ECG - Electrocardiogram

ED - Erectile Dysfunction

E:I - Expiration-to-Inspiration

GI - Gastrointestinal

HDL – High Density Lipoprotein

HRV - Heart Rate Variability

LDL – Low Density Lipoprotein

LVDD – Left Ventricle Diastolic Dysfunction

MI - Myocardial Infarction

PSA - Power Spectral Analysis

QSART - Quantitative Sudomotor Axon Reflex Test

TGL – Triglyceride

STS – Supine to Standing

INTRODUCTION

Diabetes Mellitus is a heterogenous group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both[1]. Type 2 Diabetes is one of the major health problems all over the world.[1] WHO recently reported that total diabetics in India in 2000 was 31.7 million and this number likely to increase to 79.4 million by 2030[2].

Autonomic dysfunction is common in diabetics but symptomatic autonomic neuropathy is not that common. Presence of Cardiac Autonomic Neuropathy(CAN) is responsible for silent myocardial infarction and sudden death in diabetics. Hence recognizing cardiac dysautonomia early, which is asymptomatic will helpful to delay or arrest its progression.

Diabetic neuropathy is one of the common complications of diabetes and specifically autonomic neuropathy can affect several systems[2]. Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. DAN frequently coexists with other peripheral neuropathies and other diabetic complications, but DAN may be isolated, frequently preceding the detection of other complications. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of DAN has not been fully appreciated[3]. The autonomic

function tests are now widely used for the assessment of autonomic function. These tests are non-invasive and do not require sophisticated equipment. All that required is an electrocardiogram machine, Heart rate monitor and sphygmomanometer. This highlights the importance of simple non-invasive tools like ECG and sphygmomanometer in diagnosing asymptomatic cardiac autonomic neuropathy.

Type 2 diabetic patients with abnormal CVR tests may have increased mortality, and those combined with postural hypotension have higher mortality than those without [4].

In 1980, for the first time, an association of prolonged QTc interval with cardiac autonomic neuropathy was given, thereby opening the possibility of a rapid objective method for detecting cardiac autonomic neuropathy. Further studies demonstrated an association of prolonged QTc interval with cardiac dysautonomia in diabetes mellitus[5].

This study is performed to estimate the Prevalence of Cardiovascular Autonomic Neuropathy with relation to duration of diabetes in our GGH and to check the utility of corrected QT interval in diagnosing it.

AIMS AND OBJECTIVES

1. To evaluate the prevalence of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes patients in our hospital.

2. To correlate the prevalence of Cardiovascular Autonomic Neuropathy with duration of diabetes.

3. To investigate the relationship between Cardiac Autonomic Neuropathy and QTc interval prolongation.

REVIEW OF LITERATURE

The Diabetic pandemic is rapidly spreading and mostly affects developing countries like India. Indeed, India presently has the largest number of diabetic patients in the world and has been infamously dubbed as the 'Diabetic capital of the world'. Although by definition, diabetes is characterized by elevated glucose concentrations, the impact of diabetes on both the health of individuals and on the health care systems, resides almost entirely in the long term complications of diabetes affecting almost every system in the body including eyes, kidneys, heart, feet and nerves.[2]

Neuropathy occurs more or less with the same frequency in both type 1 and type 2 diabetes, suggesting a common etiological mechanism based on chronic hyperglycemia .[2]

One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. The clinical manifestations are resting tachycardia, orthostasis, exercise intolerance, intra-operative cardiovascular liability, silent myocardial infarction [MI], and increased risk of mortality in the presence of CAN. It also demonstrates that autonomic dysfunction can

affect daily activities of individuals with diabetes and may invoke potentially life-threatening outcomes.[4,5]

Autonomic nervous system

The autonomic nervous system conveys sensory impulses from the blood vessels, the heart and all of the organs in the chest, abdomen and pelvis through nerves to other parts of the brain (mainly the medulla, pons and hypothalamus). These impulses often do not reach our consciousness, but elicit largely automatic or reflex responses through the efferent autonomic nerves, thereby eliciting appropriate reactions of the heart, the vascular system and all the organs of the body to variations in environmental temperature, posture, food intake, stressful experiences and other changes to which all individuals are exposed.   There are two major components of the autonomic nervous system, the sympathetic and the parasympathetic systems. The afferent nerves sub-serving both systems convey impulses from sensory organs, muscles, the circulatory system and all the organs of the body to the controlling centers in the medulla, pons and hypothalamus.

The impulses of the parasympathetic system reach the organs of the body through the cranial nerves 3, 7, 9, & 10, and some sacral nerves - to the eyes, the gastrointestinal system, and other organs. The sympathetic   nerves   reach their   end-organs through more devious pathways down the spinal cord to clusters of sympathetic nerve bodies

(ganglia) along the side of spine where the messages are relayed to other nerve bodies (or neurons) that travel to a   large extent with the blood vessels to all parts of the body. Through these nervous pathways, the autonomic nerves   convey stimuli resulting in largely unconscious reflex, bodily adjustments such as in the size of the pupil, the digestive functions of the stomach and intestines, the rate and depth of respiration and dilatation or constriction of the blood vessels.

The function of Autonomic nervous system in its regulation of the internal organ is highly independent. When the autonomic nervous are interrupted, these organ continue to function, but they are no longer as effective in maintaining homeostasis and adapting to the demands of changing internal condition and external stress.

Autonomic dysfunction

Impairment of Autonomic function may occur as part of the more common acute or chronic peripheral neuropathies (e.g: Diabetic, alcoholic-nutritional, Amyloidosis, Gullain-Barre syndrome, infections, heavy metal toxic and porphyrias). Diseases of the peripheral nervous system may affect the circulation in two ways: the nerves from baroreceptors may be affected, interrupting normal homeostatic reflexes on the afferent side or post ganglionic efferent sympathetic fibres may be involved in the spinal nerves. The severity of the autonomic failure need not parallel the degree of motor weakness.

PATHOGENESIS OF DAN

Autonomic dysfunction that accompanies diabetic neuropathy is the one that has extensively evaluated.[6,7,8] Several different factors have been implicated in this pathogenic process[3]. Hyperglycemic activation of the polyol pathway leading to accumulation of sorbitol and potential changes in the NAD:NADH ratio may cause direct neuronal damage and/or decreased nerve blood flow. Activation of protein kinase C induces vasoconstriction and reduces neuronal blood flow. Increased oxidative stress, with increased free radical production, causes vascular endothelium damage and reduces nitric oxide bioavailability. Alternately, excess nitric oxide production may result in formation of peroxynitrite and damage endothelium and neurons, a process referred to as nitrosative stress. In a subpopulation of individuals with neuropathy, immune mechanisms may also be involved. Reduction in neurotrophic growth factors, deficiency of essential fatty acids, and formation of advanced glycosylation end products (localized in endoneurial blood vessels) also result in reduced endoneurial blood flow and nerve hypoxia with altered nerve function. The result of this multifactorial process may be activation of polyADP ribosylation depletion of ATP, resulting in cell necrosis and activation of genes involved in neuronal damage.

Duchen and Coworkers[9] attributed the autonomic disorder to vacuolization of sympathetic ganglionic nervous, cell nervous and inflammation, loss of myelinated fibres in the vagi and white rami

communicantes and loss of lateral horn cells in the spinal cord. They believe the later changes to be secondary.

Clinical features of Autonomic Dysfunction can be divided as follows[10]

(i)   **Cardiovascular symptoms:** Postural hypotension, vertigo, syncope, dizziness, blurring of vision, neck pain, weakness.

(ii)   **Upper GI symptoms**: Dysphagia, nausea, emesis, early satiety, bloating.

(iii)   **Lower GI symptoms**: Nocturnal Diarrhea, constipation involuntary loss of stools and incomplete evacuation.

(iv)   **Urological symptoms**: Dysuria, involuntary dribbling of urine, prolonged dribbling, incomplete bladder emptying, Erectile dysfunction(ED).

(v)   **Others**: Hypohydrosis, Gustatory sweating.

Physiological basis for testing Abnormalities of Autonomic Nervous System

(i)   Responses of Blood pressure and Heart Rate to changes in posture and breathing.

McLeod and Tuck[11] state that in changing from recumbent to standing position a fall of more than 30mmHg systolic and 15 mmHg diastolic is abnormal; others give figures of 20 and 10mmHg. This excessive drop in Blood pressure indicates inadequate sympathetic vasoconstrictor activity. In response to the induced drop in blood pressure, the pulse rate normally increases. The failure of rise in heart rate in response to drop in blood pressure withstanding is a good indication of vagal nerve dysfunction[12]. In addition the pulse after rising initially in response to upright posture slows after about 15 beats to reach a stable rate by the 30th beat. The ratio of R-R interval in the ECG, corresponding to the 30th and the 15th beats is an even more sensitive measure of the integrity of Vagal inhibition the sinus node. A ratio in nonelderly of less than 1.05 is usually abnormal, indicating loss of vagal tone[12].

Another simple procedure for quantification of vagal function consists of measuring the variation in heart rate during deep breathing. Normally heart rate varies by as many as 15 beats per minute or even more, between expiration and inspiration; differences of less than 10 beats per minute may be abnormal[12]. Measurement of HRV at the time of diagnosis of type 2 diabetes serves to establish a baseline, with which 1-year interval tests can be compared. Regular HRV testing provides early detection and thereby promotes timely diagnostic and therapeutic interventions. HRV testing may also facilitate differential diagnosis and the attribution of the symptoms (e.g., erectile dysfunction, dyspepsia, and

dizziness) to autonomic dysfunction. In Valsalva maneuver, the subject exhales into a manometer or against a closed glottis for 15 seconds. Creating a markedly positive intra- thoracic pressure.

The response to performance of the Valsalva maneuver has four phases[3] and in healthy individuals can be observed as follows:

- **Phase I:** Transient rise in blood pressure and a fall in heart rate due to compression of the aorta and propulsion of blood into the peripheral circulation. Hemodynamic changes are mostly secondary to mechanical factors.

- **Phase II:** Early fall in blood pressure with a subsequent recovery of blood pressure later in the phase. The blood pressure changes are accompanied by an increase in heart rate. There is a fall in cardiac output due to impaired venous return causing compensatory cardiac acceleration, increased muscle sympathetic activity, and peripheral resistance.

- **Phase III:** Blood pressure falls and heart rate increases with cessation of expiration.

- **Phase IV:** Blood pressure increases above the baseline value (overshoot) because of residual vasoconstriction and restored normal venous return and cardiac output.

The response is mediated through alternating activation of parasympathetic and sympathetic nerve fibers. Failure of the heart rate to rise during positive intra thoracic pressure indicates sympathetic dysfunction and failure of the heart rate to slow during blood pressure overshoot indicates parasympathetic dysfunction. In patients with autonomic failure, the fall in BP is not aborted during the last few seconds of increased intra thoracic pressure and there is no over shoot of BP when breath is released [12].

Vasomotor reactions

Measurement of the skin temperature is a useful index of vasomotor function. The integrity of sympathetic reflex arc which includes baroreceptors of the aorta and carotid sinus, their afferent pathways, the vasomotor centers and the sympathetic and parasympathetic outflow, can be tested in a general way by the cold pressor test, grip test, mental arithmetic test and Valsalva maneuver.

Vasoconstriction induces an elevation in Blood pressure. Similarly the sustained isometric contraction of a group of muscles for say 5 minutes normally increases the heart rate and the systolic and diastolic pressure by at least 15mmHg [34]. The response to both tests is impaired, particularly with lesion of the efferent fibers of the sympathetic reflex arc[12].

Sudomotor function

Test for integrity of efferent sympathetic pathway. In sympathetic or galvanic skin- resistance test, a set of electrodes placed on the skin measures the resistance to passage of weak current in skin, the change in electric potential is the result of a ionic current within sweat glands. The response depends on sympathetic response to sweat glands (Gutrecht)[13]. A more quantitative and reproductive method is examination of postganglionic sudomotor function termed QSART (quantitative sudomotor axon reflex test)[14]. The QSART involves iontophoresis of a cholinergic agonist to measure axon reflex-medicated sudomotor responses quantitatively to evaluate postganglionic sudomotor function. Four sites are used and studied simultaneously with the patient supine. The test, typically done by recording from the forearm and three lower-extremity skin sites, has high sensitivity, specificity, and reproducibility, with a coefficient of variation of 20% if performed by trained personnel. The test is not generally available and requires the purchase of expensive specialized equipment.

Assessing Pupillary function

Patients with DAN show delayed or absent reflex response to light and diminished hippus due to decreased sympathetic activity and reduced resting pupillary diameter[15]. Pupillary measurements are usually only performed in a research setting.

Cardiac autonomic neuropathy (CAN)

CAN probably contribute to the poor prognosis of CHD and CHF in diabetes. The majority of patients with CAN come to clinical attention with complaints of postural hypotension, resting tachycardia, exercise intolerance (or) prior myocardial ischemia (or) infarction. The risk for CAN depends on the duration of diabetes and the degree of glycemic control and leads to parallel the development of other end organ disease related to diabetes such as retinopathy, nephropathy and vasculopathy. Symptoms and signs of CAN often occur relatively late in the natural history of this complication. [1]

Simple bedside tests for cardiac autonomic neuropathy diagnosis[16]:

Score	Heart rate variability test			Blood pressure test	
	Deep breathing	Valsalva ratio	Response to standing	Response to handgrip	Response to standing
0	>15	>1.20	>15	>15	≤ 10
1	11-15	1.11-1.20	12-15	11-15	11-29
2	≤ 10	≤1.10	<12	≤ 10	>30

For grading of cardiovascular autonomic function, results are classified into normal, borderline and abnormal (scores 0,1,2 respectively). An overall score of '0' or '1' was considered normal, score 2,3,4 were considered borderlines and score ≥5 were judged was abnormal autonomic function[16].

Prevalence of Cardiac autonomic neuropathy (CAN) [17]

The reported prevalence of CAN varies with the population studied and methods used. Regarding of these variations CAN appears to be common in diabetes. A summary of 15 reports on CAN suggests that the prevalence is in between 2.6 and 90% in diabetic population. The average incidence is about 30%.

Pathology of Autonomic neuropathy in Diabetes[9]

Pathologic changes in the autonomic nervous syndrome were studied postmortem in many diabetic cases. All had clinical evidence of peripheral sensory motor neuropathy and developed disturbances of autonomic function that included postural hypotension, diarrhea, bladder dysfunction and signs of cardiac denervation. In celiac and other sympathetic ganglia there were many distended (Giant) or vacuolated nervous as well as enlarged club shaped neural processes. The vagus nerve and sympathetic trunks showed severe loss of myelinated fibers[9].

There were inflammatory changes in autonomic ganglia in all cases and in (or) around bundles of unmyelinated nerve fibers in many. These findings suggest that there may be several different pathogenetic mechanisms involved in the development of autonomic neuropathy in diabetes. [9]

Diabetic patients have a high rate of Coronary Artery disease, which may be asymptomatic owing to autonomic neuropathy. Silent ischemia is significantly more frequent in patients with autonomic neuropathy than in those without autonomic neuropathy (38% versus 5%). [18]

It is clear however that a reduced appreciation of ischemic pain can impair timely recognition of myocardial ischemia (or) infarction and there by delay in initiating appropriate therapy. [18]

In non-diabetic patients, acute myocardial infarction has a circadian variation with a significant morning peak. The characteristic diurnal variation in the occurrence of myocardial infarction is altered in diabetic patients with a lower morning peak and higher percentage of infarction during evening hours. The blunted morning surge of incidence of myocardial infarction results from altered sympatho-vagal balance in patients with cardiac autonomic neuropathy. Mortality rates after a myocardial infarction are also higher for diabetic patients than for non-diabetic patients. This may be due to autonomic insufficiency, increasing

the tendency for development of ventricular arrhythmia and cardiovascular events after infarction.[18]

Autonomic manifestations

Abnormal autonomic function tests are often found in patients with clinical features of sensory neuropathy, and almost any aspect of autonomic function can be affected. However, symptoms of autonomic neuropathy are not always present and are commonest in patients with poorly controlled type I diabetes. In all of the autonomic syndromes described below, symptoms may be chronic or strikingly intermittent.[19]

Most longitudinal studies point to a common sequence of autonomic involvement in patients with diabetic autonomic neuropathy. In the cardiovascular system, the earliest abnormality detected by systematic and sensitive testing is a decrease in heart- rate variability during deep breathing, followed by alterations in the heart rate on standing and then the Valsalva maneuver. Postural hypotension is a relatively late event. This progression suggests that parasympathetic (vagal) fibers are damaged first, followed by the sympathetic outflow. Abnormal autonomic function tests are much more common than significant autonomic symptoms.[19]

Symptomatic, but not asymptomatic, autonomic neuropathy has been associated with a poor prognosis. But there is dispute as to whether

this is related to the neuropathy itself or to coexistent macrovascular disease or other complications. [19]

Resting Tachycardia

Whereas abnormalities in HRV are early findings of CAN, resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients with vagal impairment[5]. Resting heart rates of 90 to 100 bpm and occasional heart rate increments up to 130 bpm occur. The highest resting heart rates have been found in patients with parasympathetic damage, occurring earlier in the course of CAN than sympathetic nerve function; in those with evidence for combined vagal and sympathetic involvement, the rate returns toward normal but remains elevated. A fixed heart rate that is unresponsive to moderate exercise, stress, or sleep indicates almost complete cardiac denervation[5]. Thus, heart rate may not provide a reliable diagnostic criterion of CAN in the absence of other causes unless it is increased by more than 100 bpm.

Exercise Intolerance

Autonomic dysfunction impairs exercise tolerance[20], reduces response in heart rate and blood pressure (BP) and blunts increases in cardiac output in response to exercise[21]. Diabetic patients who are likely to have CAN should be tested for cardiac stress before undertaking an exercise program[22]. Patients with CAN need to rely on their perceived exertion, not heart rate, to avoid hazardous levels of intensity of exercise.

Presently, there is inadequate evidence to recommend routine screening of asymptomatic diabetic patients with an exercise ECG test. Emerging data support the utility of stress imaging testing in identifying diabetic patients with preclinical coronary artery disease, particularly patients with high-risk features, and comorbidities such as long-standing disease, CAN, multiple chronic renal failures, resting ECG abnormalities, and peripheral artery disease.

Abnormal sweating

This is one of the commonest, but frequently neglected, symptoms of diabetic autonomic neuropathy. Gustatory sweating, precipitated by eating cheese and other foods, is characteristic. Sweating is often profuse over the face and sometimes upper chest, corresponding to the area supplied by the superior cervical ganglion. Some patients find this socially debilitating.

Other abnormalities of sweating include the dry neuropathic foot, which allows cracking of the skin and the entry of infection and episodic nocturnal sweating that cannot be attributed to hypoglycemia.[19]

Cardiovascular changes

These include abnormalities of the cardiovascular reflexes related to changes in posture and respiration, with severe postural hypotension in extreme cases.[19]

Postural hypotension

This is due to the impairment of the increase in cardiac output and of the sympathetically mediated vasoconstrictor response in the lower limbs, which normally follow standing upright. In diabetic neuropathy, this is a common manifestation of sympathetic denervation. It can be exacerbated by administration of insulin (which acts as a vasodilator at pharmacological concentrations) and of diuretics, antihypertensives and tricyclic antidepressants (which also have vasodilator activity). On standing, blood pressure is normally maintained, may rise slightly or may fall, but the systolic drop does not usually exceed 10 mmHg; a significant drop is generally taken as > 30 mmHg, although the magnitude of the systolic fall on standing does not correlate tightly with symptoms of dizziness.[19] Postural hypotension is often worse on getting out of bed in the morning, but often varies substantially with time. The diagnosis is made simply by measuring the blood pressure with the patient lying and then standing for up to 2 min (some patients show a delayed fall).[19]

Autonomic Cardiopathy[5]

CAN may be associated with abnormalities in LV systolic and particularly diastolic function in the absence of cardiac disease in diabetic patients. A review of diabetic cardiopathy other than that ascribed to CAN has recently been published[23] and is beyond the scope of this review. Echocardiographic studies have shown a significant correlation of

the severity of CAN with reduced peak diastolic filling rate and with an augmented atrial contribution to diastolic filling as assessed by Doppler echocardiography. It is difficult to judge, however, whether CAN is an independent contributor to these abnormalities, because other factors such as interstitial myocardial fibrosis and microangiopathic or metabolic changes (discussed in the pathogenesis of diabetic heart muscle disease) may also be responsible for LV dysfunction. CAN is associated with LV diastolic dysfunction (LVDD) at rest, both in patients with long-term type 2[25] or type 1 diabetes[24]. LVDD may progress to heart failure, mainly with preserved LV systolic function (diastolic heart failure), which is also related to high morbidity and mortality rates.[26,27] The pathophysiology of LVDD includes delayed relaxation, impaired LV filling, and/or increased stiffness[28]. Diabetes mellitus can produce functional, biochemical, and morphological myocardial abnormalities independent of coronary atherosclerosis and hypertension, contributing to heart failure with normal LV systolic function[29].

Silent myocardial ischemia/cardiac denervation syndrome

The perception of angina was severely impaired in the diabetic patients, allowing these individuals to exercise longer after the onset of myocardial ischemia. The delay in perception of angina was associated with the presence of cardiovascular autonomic dysfunction. The investigators suggested that the neuropathic damage to the myocardial sensory afferent fibers in the autonomic nerve supply reduced the diabetic

individual's sensitivity to regional ischemia by interrupting pain transmission [30]. The presence of CAN does not exclude painful myocardial infarction (MI) among individuals with diabetes [31]. Chest pain in any location in a patient with diabetes should be considered to be of myocardial origin until proven otherwise; but, of equal importance, unexplained fatigue, confusion, tiredness, edema, hemoptysis, nausea and vomiting, diaphoresis, arrhythmias, cough, or dyspnea should alert the clinician to the possibility of silent MI [32].

Association of cerebrovascular disease and CAN

The frequency of ischemic cerebrovascular events is increased in individuals with type 2 diabetes. The impact of autonomic dysfunction on the risk of the development of strokes was examined by Toyry et al. Abnormalities of parasympathetic and sympathetic autonomic function were found to be independent predictors of stroke in this cohort [33].

Cardiac Radionuclide Imaging [3]

Radionuclide techniques for cardiac mapping have recently been used to directly quantify cardiac sympathetic innervation in various diseases, including CAN. The nonmetabolized norepinephrine analogue MIBG participates in norepinephrine uptake in postganglionic sympathetic neurons. Several studies have demonstrated decreased myocardial MIBG uptake in patients with CAN as assessed by autonomic reflex tests. There is evidence to suggest that scintigraphic assessment

using MIBG and single–photon emission computed tomography is more sensitive in detecting CAN than indirect autonomic reflex testing, because MIBG uptake is reduced in patients with normal autonomic tests[3]. The MIBG uptake defects are localized predominantly in the LV posterior and inferior segments. In advanced CAN, completely absent MIBG uptake may be observed.

Cardiovascular autonomic neuropathy and increased cardiovascular morbidity and mortality in diabetes mellitus possible mechanisms[17]

1.   Impaired angina recognition, Silent ischemia and infarction.

2.   Decreased threshold for ischemia

-    Increased resting heart rate and blunted chronotropic response to exercise.

-    Impaired coronary vasomotor regulation.

3.   Prolonged QT interval

-    Increased lethal arrhythmias and sudden death (with or without myocardial ischemia)

4.   Abnormal diastolic and systolic function

-    Contributes to diabetic cardiomyopathy. Increased cardiac mass adversely affects the natural history of congestive heart failure

5.   Increased peri-operative risk

-       Increased need for hemodynamic support

-       Reduced hypoxia-induced respiratory drive.

6.   Alteration of normal circadian variation of sympatho-vagal activity

-       Lack of normal nighttime decrease in blood pressure

-       Loss of night time protection against myocardial infarction

7.   Increased prevalence of other cardiovascular risk factors and other
        Complications

        Increased microvascular complication

        Increased rate of progression of glomerulopathy

        Increased prevalence of hypertension and dyslipidemias[17]

**PHARMACOLOGIC   MANAGEMENT   FOR   CONTROL
DIABETES**

Sulfonylureas

        Sulfonylureas are the preferred therapy for lean patients with type 2
diabetics and are used in combinations with other agents in obese type 2
patients. Sulfonylureas bind to a receptor on the beta cells and inhibit the

sodium-adenosine triphosphate (Na-ATP) channel and cause an increase in intracellular calcium results in insulin exocytosis.

Some experts point to a possible risk of increased myocardial damage in patients with known CAD who use sulfonylureas at the time of an ischemic event. Prevention of protective ischemic preconditioning of the heart by inhibition of the potassium (K)-ATP channel is the putative mechanism. The UKPDS data do not support this concern. The authors agree and use sulfonylureas in appropriate patients with CAD. [3]

Repaglinide

This newer insulin secretagogue binds to a different receptor site than do the sulfonylureas on the K-ATP channel. The half-life of this agent is 3.7h, which makes it effective for postprandial rather than preprandial hyperglycemia, for use in the elderly and for diabetic patients with chronic renal failure.

Metformin

Metformin is a biguanide drug that has been in use for over 30 years. The main mode of action of metformin is decreasing hepatic glucose output primarily by inhibiting gluconeogenesis, typically without hypoglycemia. Metformin is effective alone or in combination with insulin, sulfonylureas, and thiazolidinediones. The drug usually results in weight loss as a result of decreased appetite for up to 1 year after the

inititation of therapy. Significant decrease in LDL cholesterol and triglycerides occur. The incidence of lactic acidosis with metformin is 9 per 100,000 person-years. Contraindications to its use include an elevated creatinine level (>1.4 in women, >1.5 in men), congestive heart failure, severe pulmonary disease, or any hypoxic state.

Thiazolidinediones

Thiazolidinediones promote insulin-stimulated glucose transport in muscles and adipocytes through a mechanism of action involving peroxisome proliferators activated receptor-gamma (PPAR-γ) ligands. Binding to the nuclear receptor promotes differentiation of adipocytes and increased expression of glucose transporter. Thiazolidinediones has been shown to be effective both as monotherapy and in combination with insulin, sulfonylureas, and metformin.

Rosiglitazone monotherapy results in a decrease of Hb A1c of 0.8 to 1.5 percent greater than that seen with placebo, with the greatest reduction seen when it was given in two divided doses. Combination studies of rosiglitazone with metformin for 26 weeks resulted in a 1.0 to 1.2 percent placebo-adjusted decrease in HbA1c. Although rosiglitazone is currently approved for use as monotherapy and in combination therapy with metformin, it also is expected to be efficacious with sulfonylureas or insulin. Rosiglitazone has been reported to result in an increase in LDL

and HDL cholesterol concentrations between 12 and 19 percent, with changes in serum triglycerides similar to those seen with placebo.

Pioglitazone, the newest thiazolidinedione, has been approved for use as monotherapy and in combination with metformin, sulfonylureas, and insulin. Weight gain(20%), ankle edema and fluid overload are the common side effects. Hepatotoxicity can occur. Contraindicated in Volume overload states, Hepatitis, Ischemic heart disease and macular edema.

Alpha-Glucosidase Inhibitors

Acarbose and miglitol work in the intestine to reversibly inhibit brush border alpha-glucosidases, resulting in a delay in carbohydrate absorption. These agents are poorly absorbed from the gastrointestinal tract. These drugs cause a 30 percent decrease in postprandial glucose in contrast to a 10 percent decrease in fasting glucose levels. They are adjuncts to other oral agents and rarely are potent enough to be used as mono therapy.

GLP Analogues and Di peptidylpeptidase inhibitors[1]

Incretin hormones potentiate glucose mediated insulin response and is chiefly caused by two peptide hormones – Glucose dependent insulin releasing polypeptide(GIP) and glucagon-like peptide(GLP-1). GLP-1 is mainly produced by the enteroendocrine L cells located in the

distal intestine. GIP and GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-IV (DPP – IV). Newer therapeutic candidates for the treatment of type 2 diabetes are those drugs that enhance glucose dependent insulin secretion called Incretin mimetics. The use of DPP-IV inhibitors to improve the duration of endogenous GLP-1 ativity to target post-prandial glucose excursions along with effects on fasting glucose levels. They do not demonstrate any hypoglycemic effects. Sitagliptin is the first approved drug which can be used as monotherapy or combination therapy. Reduced hypoglycemic effect and reduced weight gain are the advantages over Sulphonylureas.

Insulin

The natural history of type 2 diabetes is one of progressive beta-cell failure. Therefore, after approximately 10 years of the use of oral hypoglycemic agents, insulin may be required in combination with oral agents as the sole therapy. Although endogenous hyperinsulinemia is clearly associated with atherogenesis, there is no compelling evidence of increased risk of cardiovascular disease or increased mortality from exogenous insulin therapy.

Treatment for Autonomic Dysfunction[3]

Identifying individuals at risk is only the first step in managing patients and ultimately affecting outcomes. After identification, effective management must be provided. Proactive measures are required, because

if those patients at high risk or those shown to be in early stages are not treated until advanced symptomatology is present, little has been achieved.

Unfortunately, information presented at the fifth Regenstrief conference on the intensive management of type 2 diabetes indicated that physicians may feel that screening is not of value because treatment options for identified complications are limited[34]. Such a view does not take into account the clinical research advances that have been made in the treatment of diabetes. Tests that provide evidence of further health consequences may bring patients to medical attention before other signs of diabetic end-organ injury emerge, making proactive treatment, particularly the establishment of intensive diabetes care, possible. The results of autonomic function testing can contribute to good patient management in the following ways.

To assist in the establishment (or reestablishment) of tight glycemic control

Early observations by researchers that near-normal glycemic control seems to be the most effective way to delay the onset of CAN in type 1 diabetes has been confirmed by evidence from the DCCT [35]. Intensive insulin therapy has been shown to be effective at preventing multiple complications in patients with type 1 diabetes and is postulated

to be effective for patients with type 2 diabetes, although clinical studies are underway in the latter.

In its earliest stages, there has been some clinical demonstration that autonomic dysfunction may be influenced within a few days to a few weeks with effective treatment[36,37]. Delay in instituting appropriate interventions can only increase the likelihood of developing advanced neuropathies. Stabilization of the neuropathies (generally considered to be any delays in further progression) through tight glycemic control seems possible, whereas reversal of the condition may be less likely[36]. Again, the results from the DCCT show that intensive glycemic treatment can prevent the development of abnormal heart rate variation and slow the deterioration of autonomic dysfunction over time [38].

Although the relationship between features of autonomic neuropathy and hypoglycemic unawareness is complex and there is overlap, it is recognized that autonomic neuropathy may cause or contribute to the development of hypoglycemic unawareness. In most individuals with hypoglycemic unawareness, raising the target may be necessary to prevent repeat episodes. Thus, emphasizing tight control for individuals with autonomic dysfunction should also include increased vigilance in glycemic monitoring and reeducation of the patient with regard to hypoglycemia.

To facilitate the decision to initiate treatment for cardiovascular autonomic dysfunction[3]

Several different factors have been implicated in the potential metabolic-vascular pathogenic process of diabetic neuropathy (e.g., activation of the polyol pathway, increased oxidative stress, reduction in neurotrophic growth factors, deficiency of essential fatty acids, and formation of advanced glycosylation end products). Thus, timely identification of autonomic dysfunction in diabetic patients may expedite end-organ prophylaxis such as the use of ACE inhibitors and Aspirin and the use of pharmacological and non-pharmacological interventions to improve blood pressure and lipid control. Improved nutrition and reduced alcohol and tobacco consumption are additional options available to patients with diabetes who are identified with autonomic nerve dysfunction. Interventions to modulate reduced heart rate variation currently being studied in clinical trials are based on theories of the pathogenesis of CAN.

Evidence from clinical trials evaluating the use of antioxidants is promising. Early identification of CAN permits timely initiation of therapy with the antioxidant Alpha-lipoic acid (thioctic acid), which appears to slow or reverse progression of neuropathies in some studies. Other antioxidants such as vitamin E have been shown to improve the ratio of cardiac sympathetic to parasympathetic tone in type 2 diabetic

individuals with CAN but may mitigate the effects of statins and niacin in treating or preventing macrovascular disease.

Studies using ACE inhibitors as a means to improve heart rate variation have resulted in conflicting results. Whereas quinapril significantly increased parasympathetic activity after 3 months of treatment, cardiovascular autonomic function did not change significantly after 12 months of treatment with trandolapril.

Non-pharmacological measures like adequate intake of salt and fluids, in the range of 10 to 20g, of salt / day and 2-3 litres of fluid / day. Sleeping with the head end elevated will minimize the effects of supine nocturnal hypertension. Patients are advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand. Other maneuvers like leg–crossing, contraction of leg muscles for 30 seconds. Such measures compress leg vein and increase systemic resistance. Compression stocking may be helpful. Anemia should be corrected.

Fludrocortisone at dose 0.1 mg/day and 0.3 mg bid orally will effectively reduce OH, but aggravate supine hypertension. Potassium supplements are necessary with chronic administration of fludrocortisone. Postprandial OH can be reduced by frequent small meals. Prostaglandin inhibitors taken with meals or midodrine can be used. Somatostatin analogue octreotide in dose of 25 μg bid to 100-200 μg tid acts by

inhibiting gastrointestinal peptides prevent the vasodilation and hypotension effects.

The use of cardioselective (e.g., atenolol) or lipophilic (e.g., propranolol) ß-blockers may also modulate the effects of autonomic dysfunction.[32] By opposing the sympathetic stimulus, they may restore the parasympathetic-sympathetic balance. Recently, the administration of metoprolol to ramipril-treated diabetic patients with abnormal albuminuria has been shown to improve autonomic dysfunction[40].

Because the pathogenesis of CAN is most likely a multifactorial process, a combination of therapies directed simultaneously at different parts of the pathogenic pathway may be needed. In addition, the goal of these interventions should be directed at the prevention of further deterioration of cardiovascular autonomic dysfunction rather than expecting to realize improved function.

To emphasize the importance of adherence to diet and exercise interventions

It is again emphasized that lifestyle interventions (e.g., adherence to diet and exercise) can reduce the incidence of type 2 diabetes. Recently, a report indicated that impaired glucose tolerance may be associated with the development of diabetic neuropathy (i.e., sensory polyneuropathy)[41]. This would put even greater emphasis on the

importance of lifestyle interventions and screening at or soon after diagnosis.

Motivation to adhere and remain compliant with non-pharmacological interventions is difficult. Current research suggests that preventive measures (glycemic control, diet, and exercise) introduced to the general diabetic population are difficult to sustain and consequently less than effective. This is due, in part, to the long-term commitment that must be made to the practice of preventive measures. Although individuals with diabetes are faced with the immediate pressures of disease management on a day-to-day basis, it is the long-term risks of micro- and macrovascular complications that pose the most serious risks[42]. The ability to determine early stages of autonomic dysfunction could intensify the salience of measures such as diet and exercise that directly affect efforts to establish tight glycemic control and delay the development of autonomic dysfunction. Colloquial patient management strategies could be introduced to a now potentially motivated patient.

As mentioned previously, clinicians must be careful when giving recommendations with regard to exercise for individuals with CAN. This does not mean, however, that exercise is inappropriate for individuals with CAN. In fact, Howorka et al.[43] showed that physical training improved heart rate variation in insulin-requiring diabetic individuals with early CAN. Thus, careful testing to evaluate cardiovascular autonomic function and its degree of development is extremely important.

Clinicians working together with the patient can develop an appropriate exercise program that will yield a plan for reaping maximum benefits.

QTc – Interval and prolongation

QT interval taken from the onset of QRS complex to end of the 'T' wave and corrected for heart rate give the corrected QT interval (QTc). A QTc interval of more than 440 millisecond is considered prolonged [44]. It reflects the total duration of ventricular myocardial depolarization and repolarization in the ECG. It is usually corrected for heart rate by Bazett formula, where QTc = QT √RR interval. The Bazett formula gives a slight over correction of QT interval at higher heart rates. Hodges et al[57] also gave a formula to get corrected QT as follows:

QTc = QT + 1.75 (rate-60) and is gaining more acceptance. QTc prolongation in ischemic heart disease carries an increased risk (2-5 times) of sudden cardiac death.

The exact mechanism of QTc prolongation is not clearly defined. It is generally agreed that parasympathetics have little influence on QTc

Modulation[45]. Recently, it has been suggested that some non-quantifiable sympathetic imbalance is responsible for QTc prolongation[46]. A prolonged corrected QT interval and QT dispersion (the difference between the longest and shortest QT interval) indicates an imbalance between right and left sympathetic innervation. QTc interval in the

ECG can be used to diagnose CAN with reasonable sensitivity, specificity and positive predictive value.

QT interval prolongation is an irregularity of the electrical activity of the heart that places patients at risk for ventricular arrhythmias[39]. Patients with QT- prolongation are at high risk of serious ventricular arrhythmias usually, TdP, although monomorphic ventricular tachycardia may also develop[41].Alterations in cardiac sympathetic innervation may result in QTc prolongation and predispose to arrythmias and sudden death.

MATERIALS AND METHODS

STUDY POPULATION

A total of 150 patients satisfying all the inclusion and exclusion criteria were enrolled for the study from the population of Type 2 Diabetes patients who attended the out patient clinics and Inpatients of Institute of Internal Medicine, Government General Hospital . Written consent was obtained from all the patients participating in the study after clearly explaining the study procedure.

The patients were grouped into three according to the duration of diabetes. Autonomic neuropathy testing by simple bet side tests was done in op department and Medical ward using ECG monitor, Pulseoxymeter and BP apparatus for the same 150 patients. Each groups were compared with one another with the available statistical data.

STUDY DURATION

This study was conducted for a period from May 2007 to August 2008.

STUDY DESIGN

A Cross-sectional study to evaluate the Prevalence of Cardiovascular Autonomic Neuropathy in Type 2 diabetes and correlate it

with duration of Diabetes. To investigate the relationship between cardiac autonomic dysfunction and corrected QT interval.

METHODS

Detailed clinical history was taken from each patients and a completes review of their case notes performed. A complete clinical examination of the cardiovascular system was done for each patient.

Tests for autonomic functions

On the day of testing patients were instructed not to ingest caffeine containing products. All recordings the done 5-8 hours post prandially. Blood pressure was recorded manually using standard sphygmomanometer. The heart rate variation was calculation using standard Heart rate monitor, Pulseoxymeter and continous ECG recording. A baseline ECG was taken with a Standard ECG machine for calculation of QTc interval.

The simple bedside tests for assessing the autonomic nervous system were described by Ewing and Clarke[47]. All patients were subjected to a battery of five tests as described below:

Heart rate response to valsalva maneuver

The subject was seated quietly and then asked to blow into the empty barrel of a 20ml syringe attached to a mercury

sphygmomanometer, to maintain a pressure of 40 mm Hg for 10 seconds The ratio of the maximum heart rate during blowing to the minimum during the compensatory bradycardia after stopping is calculated. The maneuver was repeated three times with one minute interval in between and results were expressed as

Valsalva ratio = Max heart rate ÷ Minimum heart rate.

The mean of the three-valsalva ratios was taken as the final value.

Heart rate variation during deep breathing

The subject was asked to breathe deeply at six breaths / min (Five seconds "in" and five seconds "out") for one minute. The average heart rate difference (maximum minus minimum during the respiratory cycle) is calculated while the patient breaths deeply for 1 min. The results were expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats / min.

Immediate heart rate response to standing

The test was performed with the subject lying quietly on a couch. The heart rate increase is recorded 15 seconds after standing from lying position. Alternatively, the ratio of the R-R interval of the 30th beat after standing to that of the 15th beat ('30:15') can be calculated.

Blood pressure response to standing

This test measured the subject's blood pressure with a sphygmomanometer while he was lying quietly. Then he was made to stand up and the blood pressure again after one minute. The postural fall in blood pressure was taken as the difference between the systolic pressure lying and the systolic pressure standing. The test was in repeated three times and the mean systolic blood pressure was calculated.

Blood pressure response to sustained hand grip

The blood pressure of the patient was taken three times before the maneuver. A modified sphygmomanometer was used to sustain handgrip. The patient was asked to grip the inflatable rubber and apply maximum voluntary pressure possible. A reading from the attached mercury manometer was taken during maximum voluntary contraction. There after, the patient was asked to maintain 30% of maximum voluntary contraction for as long as possible up to five minutes. Blood pressure was measured at one minute intervals during the handgrip. The result was expressed as the difference between the highest diastolic blood pressure during the handgrip exercise and the mean of the three diastolic blood pressure readings before the handgrip began.

Apart from the tests cardiac autonomic imbalance was also tested by detailed history. In the history symptoms suggestive of **orthostatic intolerance** like

H/o light headedness

H/o weakness or tiredness

H/o vertigo

H/o anxiety

H/o palpitations

H/o sweating abnormality

H/o diarrhea

H/o constipation

Since cardiac autonomic neuropathy is usually associated with other features of autonomic neuropathy this questionnaire was useful in assessing the patients along with the bed side tests.

INTERPRETATION OF THE TEST WAS BASED ON THE WORKS OF EWING AND CLARKE[16].

Score	Heart rate variability test			Blood pressure test	
	Deep breathing	Valsalva ratio	Response to standing	Response to handgrip	Response to standing
0	>15	>1.20	>15	>15	≤ 10
1	11-15	1.11-1.20	12-15	11-15	11-29
2	≤ 10	≤1.10	<12	≤ 10	>30

For grading of cardiovascular autonomic function, results are classified into normal, borderline and abnormal (scores 0,1,2 respectively). An overall score of '0' or '1' was considered normal, score 2,3,4 were considered borderlines and score ≥5 were judged was abnormal autonomic function[56].

QT interval was taken from the onset of QRS complex to the end of T wave. QT was then corrected for heart rate using the Bazette's formule[44].

QTc interval = QT / $\sqrt{(R - R)}$. A QTc interval more than 440 Millisecond is considered prolonged.

INCLUSION CRITERIA

1)   Type 2 diabetes already on treatment and newly diagnosed patients.

EXCLUSION CRITERIA

1)   Age above 60 years

2)   Documented ischaemic heart disease

3)   Documented valvular or congenital heart disease

4)   Hypertension

5)   COPD

6)   Uraemia

7)   Parkinsonism

STATISTICAL ANALYSIS

Statistical analysis was carried out for 150 patients after categorizing each variable – Age, sex, duration of diabetes, autonomic function tests, autonomic dysfunction score, interpretation results and QTc interval were analyzed. One way Analysis of variance (ANOVA) was performed for comparison of means of more than two groups. The significance of difference between the proportions was indicated by the chi-square (x^2) statistic. The significance of difference in mean between

the groups was calculated by student t-test. Variables were considered to be significant if (P<0.05). Intervariate analysis was done by using Pearson's r- value correlation.

OBSERVATION AND RESULTS

POPULATION CHARACTERISTICS

The study group consists of 150 patients with Type 2 diabetes. The following tables lists the information about the age variation and sex distribution of the study group. The patients in the groups <5yrs, 5-10 yrs and >10 yrs were taken as group A, B and C respectively.

TABLE – 1   AGE VARIATION AMONG STUDY GROUPS

Duration of DM	N	Mean age	SD
<5 years	50	50.08	4.251
5-10 years	50	52.76	3.217
>10 years	50	55.16	2.881

TABLE – 2   SEX DISTRIBUTION AMONG STUDY GROUPS

Duration of DM		<5 years		5-10 years		>10 years	
		n	%	n	%	n	%
SEX	Male	27	54	29	58	28	56
	Female	23	46	21	42	22	44
Total		50	100	50	100	50	100

Among 150 patients, 84 patients were men accounting for 56% of total patients. The remaining 66(44%) patients were women. Mean age of patients   in the groups A, B and C   were 50.8, 52.76 and 55.16 respectively. This shows there is no significant variation in age among the three groups.

CARDIOVASCULAR AUTONOMIC DYSFUNCTION IN THE STUDY GROUP

TABLE -3   FREQUENCY DISTRIBUTION OF NORMAL (0-1), BORDERLINE (2-4), ABNORMAL (≥5)

CAN		Group						Significance
		<5YRS		5-10YRS		>10YRS		
		n	%	n	%	n	%	
Score	0-1	36	72	24	48	13	26	
	2-4	10	20	14	28	8	16	P<0.001
	≥5	4	8	12	24	29	58	Significant
Total		50	100.0	50	100.0	50	100.0	

In the study population, the prevalence of definite CAN was 8%, 24% and 58% in group A, B and C respectively. The prevalence of definite CAN increases with increase in duration of diabetes. P value <0.001 significant.

TABLE – 4   MEAN QTc IN THREE STUDY GROUPS

Duration of DM	n	Mean	SD
<5YRS	50	416.84	4.251
5-10YRS	50	426.55	3.217
>10YRS	50	441.64	2.881

TABLE – 5   QTc RESULT WITH DIAGNOSIS

Screening test results	Interpretation		Total
	Definite CAN+	CAN-	
≤440	9	57	66
>440	36	16	52
Total	45	73	118

Sensitivity = 36 / 45 x 100 = 80% Specificity = 57 / 73 x 100 = 78.08%

The QTc values are correlated with the interpretation obtained from the Cardiac autonomic function tests. From the table the Sensitivity (i.e) the True positives is calculated as 80% and the Specificity (i.e) the True negatives is calculated as 78.08% .

TABLE - 6

CORRELATION BETWEEN AUTONOMIC NEUROPATHY (AN) AND QTc PROLONGATION IN TOTAL DIABETIC PATIENTS

| QTc in msec	Definite CAN	%	Borderline CAN	%	No CAN	%	p Value
≤440	9	20	22	68.8	58	79.5	<0.001
>440	36	80	10	31.2	15	20.5	significant

From the table, QTc interval prolongation occurs with development of CAN. Prolongation of QTc interval is well correlated with Cardiac Autonomic Neuropathy. P value <0.001.

DISTRIBUTION OF SYMPTOMS OF CAN

AMONG CAN+ve PATIENTS

Asymptomatic
CAN, 58%
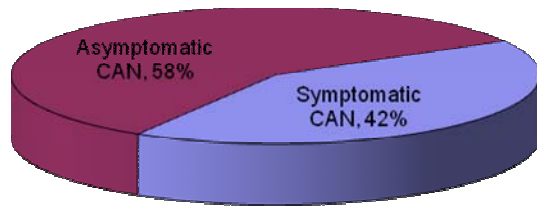
Symptomatic
CAN, 42%

☐ Symptomatic CAN ☐ Asymptomatic CAN

DURATION OF DIABETES AND PREVALENCE OF DEFINITE

CARDIOVASCULAR AUTONOMIC NEUROPATHY
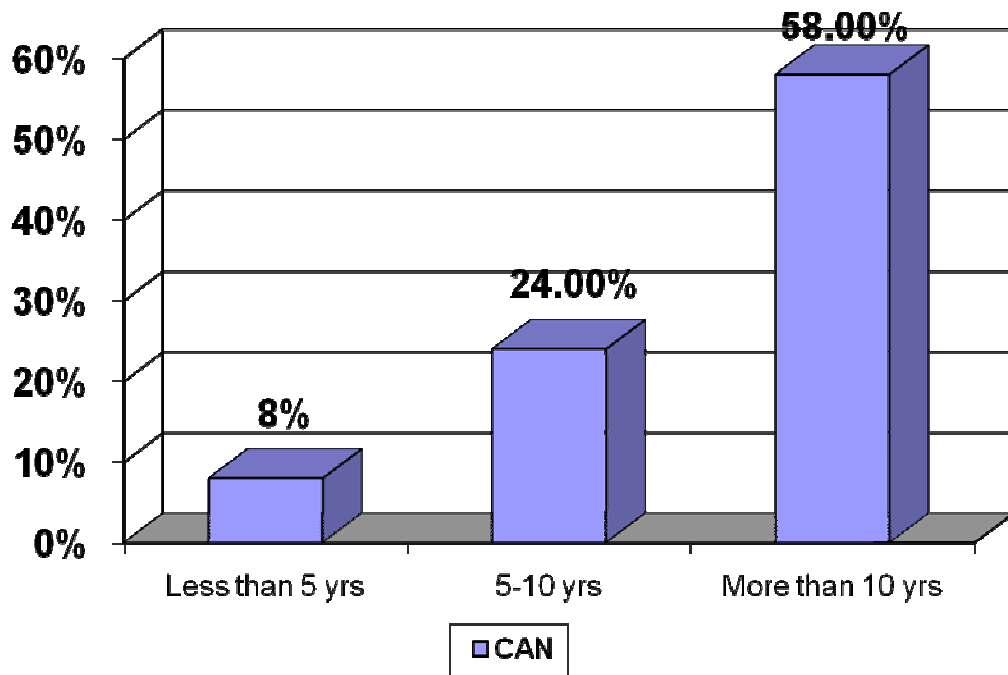
DISCUSSION

The results of this study on native Indian population illustrate the fact that cardiac autonomic dysfunction is common in Diabetic patients and its prevalence increases with duration of diabetes. Similar results have been reported in previous studies conducted in India and other countries[48-51]. This study demonstrated significant abnormalities in autonomic function using basic cardiovascular autonomic function tests, which have well been validated.

Vinik et al [3] studied and published a data of sensitivity of Autonomic function tests done on a population of 3516 patient with type 1 and type 2 Diabetes. The calculated sensitivity of HRV during deep breath testing and valsalva was 98% and 93% respectively. In our study, Heart rate variability during deep breathing is abnormal in 44 out of 45 patients with definite CAN giving a sensitivity of 97.7% and valsalva is abnormal in 42 of 45 patients with CAN giving a sensitivity of 93% which correlates with given values. Abnormal HRV in one test is indicative of early autonomic neuropathy[3]. Meta-analyses of published data demonstrate that reduced cardiovascular autonomic function as measured by heart rate variability (HRV) is strongly (i.e., relative risk is doubled) associated with an increased risk of silent myocardial ischemia and mortality[3].

Mohan et al[51] studied the prevalence of CAN in 336 patients with NIDDM in south India. There was an increase in prevalence of CAN with duration of diabetes. In 0-5 years group the prevalence of autonomic dysfunction was 28.2%. In our study, the prevalence of autonomic dysfunctin in 0-5yrs group is 28% of which 8% had definite CAN and 20% had evidence of borderline/early CAN.

Toyry J P et al[48] studied the clinical significance of autonomic neuropathy in NIDDM. A total of 133 patients with newly diagnosed NIDDM (70 men) and 144 control subjects (62 men) were examined at baseline and after 5 and 10 years of follow-up. The frequency of autonomic dysfunction at baseline, at 5 yrs and 10yrs was 4.9%, 19.6% and 65% respectively. In our study, the prevalence of definite CAN at <5yrs, 5-10yrs and >10yrs is 8%, 24% and 58% respectively which is comparable to the above study. Also, the prevalence of cardiovascular autonomic neuropathy increases with increase in duration of diabetes ($p<0.001$).

Pappachan J M et al[52] studied the prevalence the CAN among 100 type 1 and type 2 diabetes mellitus, in south India assessed by the five autonomic function tests by Eving's methodology. The prevalence of CAN was 60% which is comparable to the results obtained in this study.

Vinik et al[5] found that parasympathetic damage occurs earlier than sympathetic damage in diabetic cardiovascular autonomic neuropathy.

Hence the autonomic tests that assess the parasympathetic system which include Heart Rate Variability(HRV) to deep breath, valsalva, lying to standing becomes abnormal before the blood pressure tests. In our study, the patients with borderline CAN almost everyone have abnormalities in Heart Rate Variability(HRV) with only few have blood pressure abnormalities. This again emphasis the importance of Heart Rate Variability testing as screening for early autonomic dysfunction in diabetes.

The symptoms of Autonomic dysfunction was present only in 19 out of 45(42.22%) patients with definite CAN. Almost 58% of patients with definite CAN were asymptomatic. This clearly shows the importance of screening for autonomic dysfunction even in asymptomatic diabetics. Patients with severe cardiac autonomic dysfunction have high risk of developing silent myocardial infarction and sudden death[53].

Also, in our study, 14 out of 73(19.1%) patients without CAN had symptoms suggestive of autonomic dysfunction. Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes. Whereas symptoms suggestive of autonomic dysfunction may be common they may frequently be due to other causes rather than to true a autonomic neuropathy[3].

Chen H S et al[4] determined the 8-year survival rate for patients with abnormal CVR tests which was 63.6% in males and 76.4% in females,

compared with 80.9 and 93.3% for patients with normal CVR test. He concluded that Type 2 diabetic patients with abnormal CVR tests may have increased mortality, and those combined with postural hypotension have higher mortality than those without. Abnormal CVR tests may be important predictors of mortality in Type 2 diabetes mellitus. Subclinical autonomic dysfunction can, however, occur within a year of diagnosis in type 2 diabetes patients and within two years in type 1diabetes patients.[3] Massin et al[54] demonstrated that early puberty is a critical period for the development of CAN and suggested that all type 1 diabetic patients should be screened for CAN beginning at the first stage of puberty.

Vinik et al[3] proposed the measurement of HRV at the time of diagnosis of type 2 diabetes and within 5 years after diagnosis of type 1 diabetes (unless an individual has symptoms suggestive of autonomic dysfunction earlier) serves to establish a baseline, with which 1-year interval tests can be compared. Regular HRV testing provides early detection and thereby promotes timely diagnostic and therapeutic interventions. The knowledge of early autonomic dysfunction can encourage patient and physician to improve metabolic control and to use therapies such as ACE inhibitors and ß-blockers, proven to be effective for patients with CAN.

There were patients with borderline or early autonomic dysfunction. Out of 150 patients studied total of 32(21.33%) patients had borderline dysfunction, of which 10(20%), 14(28%) and 16(32%) were

present in groups representing <5yrs, 5-10yrs and >10yrs duration respectively. Identifying these individuals at risk is only the first step in managing patients and ultimately affecting outcomes. After identification, effective management must be provided. Proactive measures are required, because if those patients at high risk or those shown to be in early stages are not treated until advanced symptomatology is present, little has been achieved. Early observations by researchers that near-normal glycemic control seems to be the most effective way to delay the onset of CAN and arrest its progression. Hence it is important in emphasizing tight glycemic control for individuals with autonomic dysfunction with reeducation of the patient with regard to need for regular monitoring and hypoglycemia. Thus, timely identification of autonomic dysfunction in diabetic patients may expedite end-organ prophylaxis such as the use of ACE inhibitors and aspirin and the use of pharmacological and non-pharmacological interventions to improve blood pressure and lipid control. Improved nutrition and reduced alcohol and tobacco consumption are additional options available to patients with diabetes who are identified with autonomic nerve dysfunction.[3] Early identification of CAN permits timely initiation of therapy with the antioxidant alpha-lipoic acid (thioctic acid) and Vitamin E, which appears to slow or reverse progression of neuropathies in some studies.[55]

In the ECG, out of 45 patients with definite CAN, corrected QT interval (QTc) is prolonged in 36(80%) patients, which gives a sensitivity

and specificity of 80% and 78.08%. respectively. There was significant correlation (p<0.001) between CAN and QTc prolongation in this study group.

Pappachan J M et al[52] studied the utility of prolongation of corrected QT interval (QTc) in the ECG to diagnose CAN in patients with diabetes. They calculated the sensitivity and specificity of QTc prolongation for the diagnosis of CAN were 77% and 62.5% in type 1 and 76.5% and 75% in type 2, respectively. They concluded that QTc interval in ECG can be used to diagnose CAN with reasonable sensitivity and specificity. This value of sensitivity and specificity correlates with our study.

C P Mathur et al[56] studied 50 patients with diabetes with 20 normal controls to understand the relationship to CAN with QTc interval. There were 15 (78.94%) cases with QTc prolongation out of 19 diabetics with CAN. None of the diabetics without CAN or control subjects had QTc prolongation.It was observed to have sensitivity o9f 82.6% and specificity of 100%. This value of sensitivity matches the with our study but it does not correlates with specificity value.

There were certain limitations in this study:

Newer techniques for measuring autonomic functions like the computer aided power spectral analysis of heart-rate variability could not be done because of limitations in resources and cost. There was no facility for measuring Serum Magnesium and Calcium which may alter QT interval. No Holter monitoring facility was available to assess the risk of ventricular tachycardia in patients with QTc prolongation. It was not possible to rule out the possibility of congenital long QT syndrome.

CONCLUSION

The following are the conclusions from this study:

1. The Prevalence of Cardiovascular Autonomic Neuropathy is high in type 2 diabetics in our hospital.

2. The prevalence of CAN will increase with increase in the duration of diabetes. About half of the patients with type 2 diabetes have autonomic dysfunction after ten years.

3. A significant correlation is present between Cardiovascular autonomic dysfunction and QTc prolongation. QTc interval in the ECG can be used to diagnose Cardiovascular autonomic neuropathy with a reasonable sensitivity and specificity.

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PROFORMA

- Name :   • Age   • Sex

- Smoking / Alcohol Status:

- Duration of Diabetes:

- History Suggestive of Autonomic Neuropathy :

- Examination:

  Vital Signs: HR: BP:

- Examination of cardio vascular system:

[TESTS FOR CARDIO VASCULAR AUTONOMIC FUNCTION		Test 1	Test 2	Test 3	Mean
I	Valsalva Ratio				
ii	Deep Breathing Test				
iii	Supine to standing				
iv	BP Response to standing				
v	BP Response to sustained Hand grip				

- Examination of RS,GIT &CNS:

- ECG: QTc
- Blood Sugar:
  Urea
  Creatinine