CARDIAC AUTONOMIC NEUROPATHY IN TYPE2 DIABETES MELLITUS PATIENTS

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CONTENTS

INTRODUCTION

India is frequently referred to as the diabetic capital of the world. Diabetes mellitus is widely prevalent in our country and its incidence is rising in alarming proportions. The worldwide prevalence of diabetes has risen dramatically over past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, more than 360 million individuals world wide will have diabetes by the year 2030. Although the prevalence of both type 1 and type 2 diabetes is increasing worldwide, the prevalence of type 2 diabetes is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized. Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be 45-64 years of age.

According to the Diabetes Atlas published by the International Diabetes Federation, there are an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people in 2025 by which time every fifth diabetic subject in the world would be an Indian. Diabetes is a major cause of mortality, but several studies indicate that diabetes is likely underreported as a cause of death. A recent estimate suggested that diabetes was the fifth leading cause of death

worldwide and was responsible for almost 3 million deaths annually (1.7-5.2% of deaths worldwide).

The real burden of the disease is however due to its micro and macro vascular complications which lead to increased morbidity and mortality. Diabetic autonomic neuropathy is a serious and common complication of diabetes. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of diabetic autonomic neuropathy has not been fully appreciated. Diabetic autonomic neuropathy frequently co-exists with other peripheral neuropathies and other diabetic complications.

Most serious consequences of autonomic neuropathy have been due to cardiac sympathetic and para sympathetic denervation and prolongation of QTc interval which may lead to arrhythmias, silent cardiac ischemia, and abnormal response to hypoxia during surgical procedures and anesthesia.

Cardiovascular autonomic neuropathy is the most studied and clinically important form of diabetic autonomic neuropathy. Determination of the presence of cardiac autonomic neuropathy is usually based on a battery of autonomic function tests rather than just one test. Other forms of autonomic neuropathy can be evaluated with specialized tests but these are less standardized and less available.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus (DM) refers to a group of metabolic disorders which have common denominator namely hyperglycemia. Factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization and increased glucose production. The metabolic deregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

CLASSIFICATION

DM is classified on the basis of the pathogenic process that leads to hyperglycemia. The two broad categories of DM are designated type 1& type 2.

- Type 1 is the result of complete or near-total insulin deficiency.

- Type 2 DM is a heterogeneous group of disorders characterized by variable degree of insulin resistance, impaired insulin secretion, and increased glucose production. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) impaired glucose tolerance (IGT).

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

I 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 secretary defect with insulin resistance).

III Other specific types of diabetes.

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

1. Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1)
2. Glucokinase (MODY 2)
3. HNF-1(MODY 3)
4. Insulin promoter factor -1 (IPF-1;MODY 4)
5. HNF -1 (MODY 5)
6. NeuroD1 (MODY 6)
7. Mitochondrial DNA
8. Subunits of ATP- sensitive potassium channel
9. Proinsulin or insulin conversion

B. **Genetic defects in insulin action**

1. Type A insulin resistance
2. Leprechaunism
3. Rabson- mendenhall syndrome
4. Lipodystrophy syndrome

C. Diseases of the exocrine pancreas-pancreatitis, pancreatectomy, neoplasia, cysticfibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase.

D.Endocrinopathies- Acromegaly, Cushing's Syndrome, Glucagonoma, Phenochromocytoma, Hyperthyroidism, Somatostatinoma, Aldosteronoma.

E.Drug-or chemical induced-vacor , pentamidine nicotinic acid , glucocorticoids, thyroid hormone, diazoid, beta-adrenergic agonists, thiazides, phenytoin, protease inhibitors, clozapine.

F.Infections –congenital rubella, cytomegalovirus, coxsackie

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

H.Other gentic syndromes sometimes associated with diabetes :

Down Syndrome, Klinefelter'sSyndrome, TurnersSyndrome' Wolframs'syndrome Friedreich's Ataxia, Hunington'sChorea,Laurence Moon Biedl Syndrome,Myotonic Dystrophy, Porphyria, Prader –Willi Syndrome.

IV. Gestational diabetes mellitus(GDM)

Glucose intolerance may develop during pregnancy. Insulin resistance is related to the metabolic changes of late pregnancy and the increased insulin requirements may lead to IGT. GDM occurs in 4% of pregnancies in the United states. Most women revert to normal glucose tolerance post-partum but have a substantial risk (30-60%) of developing DM later in life.

Diagnosis of diabetes mellitus

The national diabetes data group and World Health Organization (WHO) have issued certain diagnostic criteria:

- Symptoms of diabetes plus random blood glucose concentration 11.1mmol/L (200mg /dL)[a]or
- Fasting plasma glucose 7.0 mmol/L(126 mg/dL)[b] or
- Two –hour plasma glucose 11.1 mol/L(200mg/dL) during an oral glucose tolerance test.[c]

[a]Random is defined as without regard to time since last time meal .

[b]Fasting is defined as no caloric intake for at least 8 hours.

[c]The test should be performed using a glucose load containing the equivalent of 75 gms anhydrous glucose dissolved in water ; not recommended for routine clinical use.

Glucose tolerance is classified into three categories based on the FPG:

(1) FPG<5.6mmol/L(100-125mg/dL) is considered normal

(2) FPG=5.6-6.9mmol/L(100-125mg/dL)is defined as IFG

(3) FPG=7.0mmol/L(126mg/dL) warrants the diagnosis of DM.

Based on the OGTT,IGT is defined a plasma glucose levels between 7.8 ad 11.1 mmol/L (140 and199 mg/dL)and diabetes is defined as a glucose >11.1 mmol/L (200mg/dL)2 h after a 75-g oral glucose load. Some individuals have both IFG and IFG and IGT individuals with IFG and/or IGT . Recently designated 'pre –diabetes ' by the American Diabetes association (ADA) are at substantial risk for developing type 2DM (25-40% risk over the next 5 years) and have an increased risk of cardiovascular disease.[2]

Risk factors for type 2 diabetes mellitus

1. Family history of diabetes (i.e, parent or sibling with type 2 diabetes)
2. Obesity (BMI>25kg/m^2)
3. Habitual physical inactivity
4. Race/ethnicity(e.g.,African, American, Latino, NativeAmerican, Asian American, Pacific Islander)
5. Previously identified IFG or IGT
6. History of GDM or delivery of baby>4 kg(>9lb)
7. Hypertension (blood pressure>140/90mmHg)
8. HDL cholesterol level <35 mg/dL(0.90mmol/L) and/or a triglyceride level >250mg/dL (2.82mmol/L)
9. Polycystic ovary syndrome or acanthosis nigricans
10. History of vascular disease

Pathophysiology

Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. Obesity ,particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2DM in the early stages of the disorder .Glucose tolerance remains near-normal, despite insulin resistance , because the pancreatic beta cells compensate

by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately Beta cells failure may ensure.

COMPLICATION OF DM

Acute Complications:

Diabetic ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS) are acute complications of diabetes[1].DKA is primarily seen in patients with type 1 DM, and HHS is seen in patients with type 2DM.Both disorders are associated with absolute and relative insulin deficiency, volume depletion, and altered mental status. Both are associated with potentially serious complications if not promptly diagnosed and treated[1,2]

Chronic complications:

Chronic complications of DM affect many organ systems and are responsible for majority of morbidity and mortality.

Microvascular

Eye disease: Retinopathy

Macular edema

Cataract

Glaucoma

Neuropathy:

sensory and motor

Autonomic

Nephropathy

Macrovascular

Coronary artery disease

Peripheral vascular disease

Cerebrovascular disease

Others

Gastrointestinal

Genitourinary

Dermatological

The risk of complications of type 1 and type 2 increase as a function of the duration of hyperglycemia .They usually become apparent in the second decade of hyperglycemia.[1,2]

MECHANISM OF COMPLICATIONS

Three major theories have been proposed to explain the emergence of complications.[2,1]

1. Increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via non enzymatic glycosylation of cellular proteins. AGEs have been shown to cross link proteins, accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, induce endothelial dysfunction and alter the extra cellular matrix composition and structure.

2. Hyperglycemia increases glucose metabolism by sorbitol pathway. Increased intracellular glucose is converted to sorbitol by the enzyme aldose reductase.Increased sorbitol concentration affect several aspects of cellular physiology and may lead to cellular dysfunction.

3. Hyperglycemia increases the formation of diacyl glycerol leading to activation of certain isoforms of protein kinase which in turn ,affect a variety of cellular events that leads to diabetes mellitus related complications .

Finally, oxidative stress and free radical generation may also promote the development of complications

DIABETIC RETINOPATHY

Diabetic retinopathy is the most common cause of blindness in adults. Hyperglycemia increases retinal blood flow and metabolism and has direct effect on retinal endothelial cells and pericytes, loss of which impairs vascular autoregulation. The resulting uncontrolled blood flow increases production of vasoactive substances and endothelial proliferations resulting in capillary closure. This causes chronic retinal hypoxia and stimulates production growth factors, including vascular endothelial growth factor(VEGF) to stimulate endothelial cell growth causing new vessel formation and increased vascular permeability causing exudative damage.

Diabetic retinopathy includes microaneurysms, intraretinal hemorrhage, exudates, macular edema, macular ischemia, neovascularization, vitreous hemorrhage, and traction retinal detachment. Symptoms may not develop until late in the disease. The degree of retinopathy is highly correlated with, duration of diabetes, blood glucose levels, blood pressure.

Pathophysiology.

Nonproliferative Retinopathy: (also called background retinopathy) develops first and causes increased capillary permeability, micro aneurysms, hemorrhages, exudates, macular ischemia, and macular edema (thickening of the retina caused by fluid leakage from capillaries).

Proliferative retinopathy: develops after nonproliferative retinopathy and is more severe; it may lead to vitreous hemorrhage and traction retinal detachment. Proliferative retinopathy is characterized by abnormal new vessel formation (neovascularization), which occurs on the inner (vitreous) surface of the retina and may extend into the vitreous cavity and cause vitreous hemorrhage. The neovascularization is often accompanied by preretinal fibrous tissue, which, along with the vitreous humor, can contract, resulting in a traction retinal detachment. Neovascularization may also occur in the anterior segment of the eye on the iris, which can result in neovascular membrane growth in the angle of the eye at the peripheral margin of the iris, leading to neovascular glaucoma. Vision loss with proliferative retinopathy may be severe.

Clinically significant macular edema can occur with nonproliferative or proliferative retinopathy and is the most common cause of vision loss due to diabetic retinopathy.

Symptoms and Signs

Nonproliferative Retinopathy: Vision symptoms accompany macular edema or macular ischemia. However, patients may be unaware of vision loss. The first signs of nonproliferative retinopathy are

- Capillary micro aneurysms
- Dot and blot retinal hemorrhages
- Hard exudates
- Cotton-wool spots (soft exudates)

Cotton-wool spots are areas of micro infarction that lead to retinal opacification; they are fuzzy-edged and white and obscure underlying vessels. Hard exudates are discrete, yellow, and generally deeper than retinal vessels and suggest retinal edema.

Signs in later stages are macular edema (seen on slit-lamp biomicroscopy as elevation and blurring of retinal layers), Venous dilation and intraretinal microvascular abnormalities.

Proliferative Retinopathy: Symptoms may include blurred vision, black spots or flashing lights in the field of vision, and sudden, severe painless vision loss. Some of these symptoms may be caused by vitreous hemorrhage or traction retinal detachment.

Proliferative retinopathy, unlike nonproliferative retinopathy, causes fine preretinal capillaries (newly developed capillaries) to appear on the optic nerve or retinal surface. Macular edema or retinal hemorrhage may be visible on funduscopy.

Diagnosis is by funduscopy; further details are elucidated by fluorescein angiography and optical coherence tomography. Treatment includes control of diabetes and BP and ocular laser photocoagulation, intravitreal injection of drugs, vitrectomy, or a combination.

DIABETIC NEPHROPATHY

Diabetic nephropathy is the leading cause of end stage renal disease in many countries.

Mechanism of hyperglycemia to ESRD involve

1. Interaction of soluble factors (AT II,AGEs, Endothelin)
2. Hemodynamic alterations in renal microcirculation.
3. Structural charges in glomerulus

DIABETIC NEUROPATHY

"A descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic includes manifestations in the somatic and autonomic parts of the peripheral nervous system.

AETIOPATHOGENESIS

Hypotheses concerning the multiple etiologies of diabetic neuropathy include a metabolic insult to nerve fibres, neurovascular insufficiency, autoimmune damage, and neurohormonal growth factor deficiency. Several different factors have been implicated in this pathogenic process. 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(Greene et al,1983). Activation of protein kinase C includes vasoconstriction and reduces neuronal blood flow(Verves et al,2001) increased oxidative stress, with increased free radical production, causes vascular endothelium damage and reduces nitric oxide bioavailability(Cameron et al.1997) Alternatively, excess nitric oxide production may result in formation of peroxynitrate and damage endothelium and neurons, a process referred to as nitrosative stress. In a subpopulation of individuals with neuropathy, immune mechanism may also be involved. Reduction in neurotropic growth factors, deficiency of essential fatty acids, and formation of advanced glycosylation end products (localized in endoneurial blood vessels(Brownlee,1992) also result in reduced endoneurial blood flow and nerve hypoxia with altered nerve function. The result of this multifactorial process may be activation of genes involved in neuronal damage.

DIABETIC AUTONOMIC NEUROPATHY

A subtype of the peripheral polyneuropathies that accompany diabetes, diabetic autonomic neuropathy can involve the entire autonomic nervous system(ANS).Diabetic autonomic neuropathy may be either clinically evident or subclinical. It is manifested by dysfunction of one more organ systems (eg: Cardiovascular, Git, Genitourinary, Sudomotor, or Ocular). Indeed ,because the vagus nerve (the longest of the ANS nerves, accounts 75% of the all parasympathetic activity),and the diabetic autonomic neuropathy manifests in longer nerves. Symptoms suggestive of autonomic dysfunction may be common, they may frequently be due to other causes rather than to true autonomic neuropathy. Subclinical autonomic dysfunction can ,however occur within a year of diagnosis of type 2 diabetes patients(Pfeier et al,1984).Because of its association with a variety of adverse outcomes including cardiovascular deaths, cardiovascular autonomic neuropathy(CAN) is the most clinically important and well studied form of diabetic autonomic neuropathy.

EPIDEMIOLOGY

The reported prevalence of diabetic autonomic neuropathy varies, depending on whether studies have been carried out in community, clinic, or tertiary referral center .In a community based population study of diabetic neuropathy in Oxford, the prevalence of autonomic neuropathy as defined by one or more abnormal heart rate variability(HRV) test result was 16.7%.(Neil et al.).

In a further study, Ziegler[18] et al evaluated the prevalence of CAN in 1,171 diabetic patient(647 type 1 diabetes patients,524 type 2 diabetes) randomly recruited from 22 diabetes centres in Germany, Austria and Switzerland. The study found that 25.3% of patients with type 1 diabetes and 34.3% of patients with type 2 diabetes had abnormal findings in more than two of six autonomic function tests(Zieglar,1992[9]).Vernotti rt al. found that 47 out of 110 diabetic children and adolescents showed one or more abnormal test for cardiac autonomic dysfunction.(Ziegler[9] et al.1992).Verotti et al found that 47of 110 diabetic children and adolescents showed one or more abnormal test for cardiac autonomic dysfunction. Overt signs and symptoms of autonomic disease fall in to one or more of the following categories.

Cardiovascular

- Resting tachycardia
- Exercise intolerance
- Orthostatic hypotension
- Silent myocardial infarction

Gastrointestinal

- Esophageal dysmotility
- Gastroparesis diabeticorum
- Constipation
- Diarrhea
- Fecal incontinence

Genitourinary

- bladder(diabetic cystopathy)
- Erectile dysfunction
- Retrograde ejaculation
- Female sexual dysfunction(eg: loss of vaginal lubrication)

Metabolic

- Hypoglycemia unawareness
- Hypoglycemia associated autonomic failure

Sudomotor

- Anhidrosis
- Heat intolerance
- Gustatory sweating
- Dry skin

Pupillary

- Pupillomotor function impairment(eg: decreased diameter of dark adapted pupil)
- Argyll Robertson pupil

CARDIAC AUTONOMIC NEUROPATHY

Cardiovascular autonomic neuropathy (CAN), a common form of autonomic dysfunction found in patients with diabetes mellitus, causes abnormalities in heart rate control, as well as defects in central and peripheral vascular dynamics. Individuals with parasympathetic dysfunction have a high resting heart rate most likely because of vagal neuropathy that results in unopposed increased sympathetic outflow. Persons with a combined parasympathetic/sympathetic dysfunction have slower heart rates. With advanced nerve dysfunction, heart rate is fixed. Thus, it is apparent that the determination of heart rate itself is not a reliable diagnostic sign of CAN. Reduction in variability of heart rate is the earliest indicator of CAN. Clinical

manifestations of CAN include exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension (OH), asymptomatic ischemia, painless myocardial infarction (MI), and increased risk of mortality

An increased resting heart rate has frequently been observed in diabetic patients. With progression of disease, some patients display a fixed heart rate that responds only minimally to physiologic stimuli.

Orthostatic hypotension occurs in diabetes mellitus as a consequence of efferent sympathetic vasoconstriction of the splanchnic and other vascular beds(Helsted et al 1981)

Other CVS abnormalities have included a cardiomyopathy in patients without ischemic heart disease manifesting as impaired myocardial contractility and decreased left ventricular diastolic filling observed by radio nuclear ventriculography. Silent cardiac ischemia and prolongation of QT has been observed.(Kahn et al 1987)

There is increased frequency of sudden death in patients with autonomic neuropathy . Proposed etiologies include cardio respiratory arrest caused by cardiac arrhythmias, silent cardiac ischemia, sleep apnoea, and a with an abnormal response to hypoxia, particularly in pulmonary infections.(Page et al 1978). Abnormal measures of cardiac autonomic function also have correlated with abnormal autonomic functions in other

organ systems including abnormal pupillomotor, gastrointestinal infections. Ewings[4] et al reported a 2.5 –year mortality rate of 27.5% that increased to 53%after 5 years in diabetic patients with abnormal autonomic function tests ,compared with a mortality of only 15% over the 5 year period among diabetic patients with normal autonomic function tests(Ewings[4] et al 1980)

CLINICAL MANIFESTATIONS OF CARDIOVASCULAR AUTONOMIC DYSFUNCTION

Exercise intolerance

In diabetic individuals with CAN, exercise tolerance is limited as a result of impaired parasympathetic/sympathetic responses that would normally enhance cardiac output and result in directing peripheral blood flow to skeletal muscles . Reduced ejection fraction, systolic dysfunction, and decreased diastolic filling, potentially as a result of CAN, also limit exercise tolerance

Intraoperative cardiovascular lability.

There is a 2- to 3-fold increase in cardiovascular morbidity and mortality intra operatively for patients with diabetes [19].Studies have demonstrated that the induction of anesthesia causes greater degree of decline in heart rate and blood pressure in diabetic patients compared with non

diabetic individuals [20]and that hemodynamic stability, in the intraoperative period, depends on the severity of autonomic dysfunction [21]. Patients with severe autonomic dysfunction have a high risk of blood pressure instability [21, 22], and intraoperative blood pressure support is needed more often in those with greater impairment[20]. Intraoperative hypothermia [23], which may decrease drug metabolism and affect wound healing, and impaired hypoxic-induced ventilatory drive [24] have also been shown to be associated with the presence of CAN.

Orthostatic hypotension

A change from lying to standing normally results in activation of a baroreceptor-initiated, centrally mediated sympathetic reflex, resulting in an increase in peripheral vascular resistance and cardiac acceleration [19]. OH is characterized by a defect in this reflex arc, resulting in signs and symptoms such as weakness, faintness, dizziness, visual impairment, and syncope .Although the absolute fall in blood pressure is arbitrary, OH is usually defined as a fall in blood pressure [*i.e.*>20–30mm Hg for systolic or >10 mm Hg for diastolic [26, 27]] in response to postural change, from supine to standing.

Painless myocardial ischemia

Inability to detect ischemic pain can impair the recognition of myocardial ischemia or MI. The mechanisms of painless myocardial ischemia are, however, complex and not fully understood. Altered pain thresholds, sub threshold ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms [(28)].A recent investigation that used positron emission tomography to measure regional cerebral blood flow as an index of regional neuronal activation has shown that impaired afferent signaling resulting from autonomic dysfunction is associated with failed signal transmission from the thalamus to the frontal cortex[(29)] A meta-analysis of 12 studies also demonstrated a consistent association between CAN and the presence of painless myocardial ischemia[12]. The Mantel-Haenszel estimate for the pooled prevalence rate risk for silent myocardial ischemia was 1.96, with a 95% confidence interval of 1.53–2.51 ($P < 0.001$; n = 1468 total subjects) [(12)]. Thus, patients with CAN warrant more careful attention. Cardiovascular autonomic function testing may be an important component in the risk assessment of diabetic patients with coronary artery disease [(21)].

Increased risk of mortality

Impaired autonomic control of heart rate is linked to increased risk of mortality. Reduced parasympathetic function or increased sympathetic activity may provide the propensity for lethal arrhythmias [32]

Treatment interventions :non pharmacological methods:

Nonpharmacological measures, such as increasing consumption of water [95] and wearing lower-extremity stockings, can be used to reduce symptoms (*e.g.* dizziness, dyspnea) [96].It is well known that exercise plays an important role in the treatment of diabetes. The role of exercise in the improvement of cardiovascular autonomic function is not as clear. Numerous studies both in diabetic and non diabetic populations have tried to determine whether HRV can be improved by exercise. For example, chronic endurance exercise training in sedentary adult males [81] and a single bout of submaximal endurance exercise in healthy males [82] were associated with increased HRV with a shift toward parasympathetic influence on cardiovascular function. Endurance training was also shown to improve vagal activity in non diabetic patients who had a MI [83] and in insulin-requiring diabetic individuals with early CAN [84]. Other studies showed no benefit or only minimal benefit for healthy men [85] and individuals with type 2 diabetes [86]. The discordant findings are most likely due to differences in patient populations, lack of

randomization, differences in length and type of exercise, and various measurements of autonomic function. Thus, more intervention studies are needed to determine the best exercise protocol that results in improved autonomic function for diabetic persons with CAN. In addition, it will be important to evaluate whether beneficial effects in autonomic function result in favorable effects on the clinical outcome (*e.g.* better exercise tolerance, decreased mortality) of these patients.

Treatment interventions :pharmacological agents:

Interventions to ameliorate reduced HRV are being evaluated in clinical trials based on theories of the pathogenesis of diabetic neuropathy. Development of diabetic neuropathy is the result of a multifactorial process including metabolic insult to nerve fibers, neurovascular insufficiency, increased oxidative stress, reduction in neurotropic growth factors, deficiency of essential fatty acids, formation of advanced glycosylation end products, and autoimmune damage [(12)]. When treating OH due to autonomic dysfunction, pharmacological therapies must balance an increase in standing blood pressure against prevention of supine hypertension [(96).] In addition, OH can be aggravated by different forms of therapy [*e.g.* tricyclic antidepressant (amitriptyline)] used for the treatment of other complications (*e.g.* painful

sensory neuropathy). Therefore, careful attention to other medications that may aggravate OH in these patients is necessary ([97]).

Various pharmacological agents that are directed at components of the pathogenic process are described below.

Glycemic control

The results of the Diabetes Control and Complications Trial showed that intensive treatment prevented the development of abnormal RR variation and slowed the deterioration of autonomic dysfunction over time [(39)]. Eighteen years of follow-up of a group of type 1 diabetic individuals demonstrated that fair long-term glycemic control (*i.e.* glycosylated hemoglobin <8.4%) was associated with preserved cardiovascular autonomic function, whereas lack of fair glycemic control was associated with dysfunction [(40)]. For persons with type 2 diabetes, intensive insulin therapy showed a small tendency for improved autonomic function, whereas deterioration was noted in the conventionally treated group [(41)].

Antioxidants

During chronic hyperglycemia, the metabolism of glucose also results in the generation of free radicals. Although free radicals of superoxide and hydrogen peroxide are essential for normal cell function, excessive

accumulation of free radicals is detrimental and has a direct neurotoxic effect [42]. α -Lipoic acid, an antioxidant that reduces free radical formation, appears to slow progression of CAN [43, 44]. For persons with type 2 diabetes, the improvement in CAN was seen after 4 months of treatment with an oral dosage of 800 mg/d [44]. For persons with type 1 diabetes, the effect on autonomic function was seen after 10 d of 600 mg daily iv α -lipoic acid followed by 600 mg given orally for 50 d [43].It should be noted that many herbal manufacturers are promoting α -lipoic acid for use by patients with diabetes, but studies evaluating the effectiveness of these products have not been performed. Vitamin E has been shown to improve the ratio of cardiac sympathetic to parasympathetic tone for persons with type 2 diabetes [45]. In light of a recent meta-analysis that found that 400 IU/d or more may increase all-cause mortality, high doses of vitamin E should be avoided [46].

Angiotensin converting enzyme (ACE) inhibitors

Micro vascular insufficiency has also been proposed as a potential component in the pathogenesis of diabetic neuropathy. Results of animal studies have suggested that impaired ganglion blood flow in diabetes could be responsible for neuro degenerative changes in autonomic postganglionic cell bodies .[47] In human diabetic neuropathy, impaired nerve blood flow has

been demonstrated[48]. Given that vascular dysfunction may be part of the pathogenesis of diabetic neuropathy, ameliorating this abnormality may positively benefit nerve function. ACE inhibitors promote vasodilation by preventing the generation of angiotensin II and by preventing the breakdown of bradykinin. Angiotensin II, in addition to its role as a vasoconstrictor, stimulates aldosterone release and promotes sympathetic outflow, thus ACE inhibitors may provide additional benefits as a result of the inhibition of angiotensin-II. With regard to changes in HRV, the use of ACE inhibitors in patients with CAN has resulted in conflicting outcomes. Of the ACE inhibitors studied, 12 months of use of quinapril showed some degree of success in treating CAN [49], whereas no improvement of cardiovascular autonomic function was shown after 12 months of treatment with trandolapril [50]. Conflicting results from various studies are disappointing, but it is important to remember that the effect of medications might not be homogeneous, even within the same class, and the beneficial response of an ACE inhibitor may depend on the degree of tissue penetration [51].

Angiotensin type 1 blockers

Angiotensin type 1 (AT_1) receptor mediates all potentially deleterious effects of angiotensin II [52]. AT_1 antagonists block the AT_1receptor, thus blocking the harmful effects of angiotensin II. Raelene[3] et al conducted a 1-

yr clinical trial in 44 diabetic individuals to determine the effect of losartan on HRV. Raelene et al[3] hypothesized that losartan would improve nerve function by increased nerve blood flow and inhibition of angiotensin II-induced facilitation of sympathetic neuro transmission. Although 50 mg of losartan appeared to slow the expected decline in RR variation, there was no significant improvement [53]. Improved cardiovascular autonomic function was, however, shown in another study, in which 23 diabetic individuals were treated with 100 mg of losartan for 1 year [54]. Twelve weeks of treatment of losartan (50–100mg/d) was also shown to reduce muscle sympathetic activity and improve cardiac baroreceptor sensitivity for 10 non diabetic males with hypertension [55]. In contrast, a 7-d trial in non diabetic males treated with eprosartan was shown to lower HRV [56].

Aldosterone blockers

Aldosterone has been shown to affect the autonomic nervous system with sympathetic activation and parasympathetic inhibition [57]and impair the baro reflex response [58]. Other dysfunctions associated with aldosterone include the blockage of myocardial uptake of norepinephrine in animal models [59] and decreased arterial and venous compliance, leading to vascular organ damage[60]. Spironolactone, an aldosterone-receptor blocker, has been used to reduce the morbidity and mortality for patients with severe heart

failure [57]. Mechanisms thought to promote the beneficial effect of spironolactone include blocking the effect of aldosterone on the loss of potassium and magnesium and improved HRV [61, 62, 63]. For example, acute administration of an aldosterone antagonist given iv has been shown to improve HRV and baroreflex sensitivity in healthy subjects, suggesting that aldosterone exerts a tonic inhibitory effect on cardiac vagal control [64].In disease-specific studies, the use of spironolactone improved HRV and survival for patients with congestive heart failure[61, 62, 63]. In contrast, however, one study of individuals with type 2 diabetes administered spironolactone 50 mg/d for1 month demonstrated a small but significant worsening in HRV[65]. It is possible that the effects of spironolactone maybe disease specific.

Calcium-channel blockers

Calcium-channel blockers prevent the flow of calcium ions into cardiovascular cells by binding to the α_1 subunit of the L-type voltage-gated calcium channel [66]. The drug class is heterogeneous, however, with reflex sympathetic activation after blood pressure reduction occurring more frequently after blockade with dihydropyridines than phenylalkylamines [66]. In studies of hypertensive individuals, verapamil depressed sympathetic activity [66], and slow release diltiazem had favorable effects on autonomic

function [67].Verapamil also decreased norepinephrine excretion in persons with stable angina pectoris [68] and improved parasympathetic function in non diabetic patients after an acute MI [69]. Although the mechanism by which verapamil influences HRV is not clear ,it may be due to specific properties of the drug that have a suppressive effect on sympathetic outflow of catecholamines[69]. Calcium-channel blockers may not, however, have a beneficial effect on HRV in persons with diabetes. For example, verapamil had no effect on HRV in diabetic subjects post-MI [69], where as long-acting calcium antagonists enhanced, rather than reduced, sympathetic activity in patients with type 2 diabetes [70].

ß-Blockers

The use of ß-blockers in diabetic patients has been questioned because these agents may mask signs and symptoms of hypoglycemia and interfere with insulin release. Nonetheless, in the Cooperative Cardiovascular Project, post-MI diabetic patients treated with ß-blockers had a 36% reduction in mortality [71]. In addition, ß-blockers were associated with a lower 1-yr mortality rate for elderly diabetic patients[72]. The exact reason for the reduction in mortality may or may not be related to the effect on CAN. In the ß-blocker Heart Attack Trial, propranolol improved recovery of parasympathetic tone and decreased morning sympathetic predominance for

post-MI patients [73]. The addition of metoprolol to ramipril-treated type 1 diabetic patients with abnormal albuminuria was also shown to improve autonomic dysfunction. [74].

Metformin

Free fatty acids (FFAs) interfere with glucose metabolism [75].Under normal circumstances; FFAs are the main fuel source for the heart [76]. Recently, it has been shown that the combination of TNF-α and hyperglycemia stimulated lipolysis with a consequential increase in FFAs and induced insulin resistance [77]. Decreased activation of the parasympathetic nervous system increases lipolysis, thus resulting in an increased concentration of FFAs in the plasma [76]. An increase in FFAs has been shown to affect the cardiovascular system through activation of the sympathetic nervous system in healthy subjects [78], as well as in individuals with type 2 diabetes [79]. Recently, it was demonstrated that overweight type 2 diabetic patients had metformin-related decreases in FFAs and insulin resistance that were associated with improved sympatho-vagal balance[80].

Other Drugs: those that supplement α adrenergic activity (midodrine) Medications that expand the plasma volume (fludrocortisone)), Enhancement of ganglionic transmission via the use of pyridostigmine (inhibitor of acetylcholinesterase) Octreotide- an somatotropin release-inhibiting hormone analog).

AIM OF THE STUDY

1. To determine the prevalence of cardiac autonomic neuropathy in type 2 diabetes mellitus patients.
2. To examine the relationship between autonomic dysfunction and age, sex, known duration of the disease, glycemic control and body mass index.
3. To establish the relation between diabetic retinopathy, peripheral neuropathy and diabetic cardiac autonomic neuropathy.

MATERIALS AND METHODS

MATERIALS:

The study included fifty patients with type 2 diabetes mellitus attending the outpatients department of Medicine and Diabetology of Government Rajaji hospital .Thirty age and sex matched healthy volunteers were chosen as controls. Informed consent was obtained from each patient and control subject.

A careful history was taken from each persons and stress was laid on duration of illness as well as the symptoms suggestive of autonomic nervous systems dysfunction, diabetic retinopathy, and peripheral neuropathy

Detailed examination of both control and cases were done to find out the presence of peripheral neuropathy, diabetic retinopathy and other factors enabling them to include or exclude in this study.

SELECTION OF CASES

Cases included in this study were selected as per the records available with them with treatment particulars. Duration the disease, body mass index ,current blood sugar values were taken in to consideration.

Duration of the study : 1 year

EXCLUSION CRITERIA FOR CASES

1.Presence of coronary artery disease, cardiomyopathy, arrhythmias, patients on drugs like beta blockers, anti arrhythmics.

2.Presence of diabetic kidney disease, chronic renal failure.

3.Presence of liver disease.

4.Presence of chronic obstructive pulmonary disease.

5.Presence of central or peripheral nervous system disease other than due to diabetes mellitus like CVA, leprosy.

6.Presence congestive cardiac failure, severe volume overload

7.Presence of electrolyte abnormality like hypokalemia, hyponatremia

8.Presence of any other disease that affects the ANS like hypothyroidism, amyloidosis, systemic lupus erythematosis, multiple myeloma..etc

SELECTION OF CONTROLS

Age and sex matched healthy controls who were non diabetic, normotensive with normal blood sugar and renal function tests having normal resting electrocardiogram were selected for the study.

METHODS

Five standard cardio vascular autonomic reflex tests (Ewings et al,1970)[4] which assess the integrity of autonomic nervous systems were done using continuous ECG monitoring with **8-CHANNEL PSYCO-PHYSIOPAC.** First three tests assessed parasympathetic system and the rest two assessed sympathetic function.

1.HEART RATE RESPONSE TO DEEP BREATHING

The patient is made sit quietly and breathe at the rate of six breaths per minute for one minute. An ECG is recorded throughout the period of deep breathing, with marker to indicate the onset of each inspiration and expiration using **8-CHANNEL PSYCO-PHYSIOPAC**. The maximum and minimum heart rate during each breathing cycle is measured. The results is then expressed as the mean of the difference between maximum and minimum heart rate for the six measured cycles.

2. HEART RATE RESPONSE TO VALSALVA MANOEUVRE

The patient is asked to blow in to the rubber tubing of the sphygmomanometer and hold it at pressure of 40 mm of mercury for 15seconds while continuous ECG was recorded. Then the patient was asked to breathe normally with continuous ECG monitoring. The maneuver is

performed thrice ,with one minute interval in between them. The result in the valsalva ratio, which is calculated as the ratio of the maximum heart rate during the release phase to the minimum heart rate during the straining phase

.3. IMMEDIATE HEARTRATE RESPONSE TO STANDING

The test is performed with the patient lying quietly, while a continuous ECG is being recorded. The patient is asked to standup and the point at the start of standing is marked on the ECG paper. The shortest RR interval at or around the 15^{th} beat and the longest RR interval at or around the 30^{th} beat after standing are measured .The result is expressed as the ratio of RR interval of thirtieth to fifteenth beat (30:15 ratio)

4.BLOOD PRESSURE RESPONSE TO STANDING

Measuring patient's blood pressure twice, once is at lying posture and the second is at standing posture performs this test. The standing blood pressure is taken after an interval of three minutes of standing. The blood pressure response is the difference in systolic pressure on lying and on standing. The test is repeated thrice and the average of 3 values is taken into account.

5. BLOOD PRESSURE RESPONSE TO SUSTAINED HANDGRIP

The maximum voluntary contraction of hand is determined and the hand grip is maintained at one third of the maximum up to three minutes using dynamometer. The result is expressed as the difference between the highest diastolic blood pressure during the hand grip and the normal diastolic blood pressure before the hand grip.

The results of each of the above five tests are classified into three separate groups based on the severity of abnormality detected, and each of them is given a definite point as described by Bellavere et al.[116]

The total points from each of these five tests are added together and the cardiac autonomic neuropathy score, (CAN score) categorized as follows: CAN score 0 (total points 0), CAN score 1 (points 0.5–1.5), CAN score 2 (points 2–3), and CAN score 3 (points >3.5). CAN is considered absent, early, definite or severe if the CAN scores are 0, 1, 2 or 3, respectively.

TABLE:1 DETERMINATION OF CAN SCORE	
Autonomic function test	**Points**
1 Heart rate variability on deep breathing	
>15 beats/min	0
11-15 beats/min	1/2
<11 beats/min	1
2. Postural hypotension (fall in systolic blood pressure)	
<10 mm Hg	0
11-29 mm Hg	1/2
>30 mm Hg	1
3. Valsalva ratio (longest RR interval: shortest RR interval)	
>1.2	0
1.2–1.10	1/2
<1.10	1
4. Heart rate variability on standing(30:15)	
>1.04	0
1.01-1.03	1/2
<1	1
5. Increase in diastolic blood pressure during sustained handgrip	
>15 mm Hg	0
15–10 mm Hg	1/2
<10 mm Hg	1

OTHER TESTS DONE ON THE PATIENTS

Each participant is examined for the presence or absence of peripheral neuropathy during the neurological examination by testing for abnormal pin-prick sensations in the limbs using monofilament (10 gms/5.07), abnormality of vibration sense in the foot and hands using tuning fork-128Hz and the Achille's tendon reflex. All patients were examined for diabetic retinopathy using indirect ophthalmoscope.

BIOCHEMICAL INVESTIGATIONS

Blood is drawn from all patients under recommended ideal conditions to determine the fasting and post prandial blood sugar ,serum electrolyte, blood urea, serum creatinine and lipid profile. Urine of the patients was tested for presence of microalbuminuria and patients with elevated renal parameters or with albuminuria were excluded from the study

STATISTICAL ANALYSIS

Statistical analysis of data was done using SPSS Statistics Software version 17.0

DEFINITIONS

Known Duration of The Diseases

Patients with known duration of diabetes up to 5 years and those with duration of disease more than 5 years were classified in to two groups for study purposes.

Body Mass Index

The cut off value of Body Mass Index was taken as 25 kg /m^2 .Those with BMI above 25 and those with BMI below 25 are classified separately.

Glycemic Control

Patients whose blood sugar values of either fasting blood sugar more than 130 mg/dl or postprandial blood sugar more than 180 mg/dl considered as having poor glycemic control[(1)]. Others are considered to be having good glycemic control.

Peripheral neuropathy

Absence of both ankle reflexes taken as absent and abnormality of any one of the each monofilament test in six sites in each foot taken as abnormal. Impaired vibration sense in any of the foot or hand taken as absent vibration sense.

Retinopathy

Patients are classified in to having normal fundus,non proliferative retinopathy, and proliferative retinopathy on examining the dilated fundus depends on the appearance of the fundus on indirect ophthalmoscopy.

CAN SCORE: a patient/control is considered to be having cardiac autonomic neuropathy if he/she scores two or more than two. If they score less than two ,they are considered to be having no cardiac autonomic neuropathy.

RESULTS AND ANALYSIS

Composition of Study Population

The study population consists of 50 cases and 30 age and sex matched healthy controls.

Cases:

Among 50 cases ,27 (54%) were females and 23(46%) were males.

Controls:

Among controls 15(50%) were males and 15(50%) were females.

1.Prevalence of Cardiac autonomic neuropathy

In the present study, 31 (62%)out of 50 type 2 Diabetic patients having evidence of cardiac autonomic neuropathy.

2.CAN and age

The present study population included patients between age groups of 41 and 71.In this study CAN was more common in the age group of 61-70. Nintey one percentage (91.7%) of the age group of 61-70 showed CAN, but only 47.4%of the age group 41-50 showed the evidence of CAN. Prevalence of the cardiac autonomic neuropathy increased with age group in this study population.

TABLE NO: 2 CAN SCORE AND AGE

Age	CAN SCORE			
		Negative	Positive	Total
41-50	Count	10	9	19
	%	52.6%	47.4%	100.0%
51-60	Count	8	11	19
	%	42.1%	57.9%	100.0%
61-70	Count	1	11	12
	%	8.3%	91.7%	100.0%
TOTAL	Count	19	31	50
	%	38.0%	62.0%	100.0%
Pearson chi-square	value	Df	Asymp. Sig. (2-sided)	
	6.345	2	0.042	

3.SEX DISTRIBUTION AND CAN SCORE

TABLE NO:3 SEX DISTRIBUTION AND CAN SCORE.

SEX		CAN SCORE		
		Negative	Positive	Total
MALE	Count	11	16	27
	%	40.7%	59.3%	100%
FEMALE	Count	8	15	23
	%	34.8%	65.2%	100.0%
TOTAL	Count	19	31	50
	%	38.0%	62.0%	100.0%
Pearson chi-square	value	Df	Asymp. Sig. (2-sided)	
	6.345	2	0.665	

In the present study, 16 out of 27 (59.3%) males and 15 of 23 (65.2%) females showed evidence of cardiac autonomic neuropathy, which was not significant. (p=0.665). 11 out of 27 (40.7%)males and 8 out of 23 (34.8%)females did not have cardiac autonomic neuropathy. This showed sex was not a major determinant for the prevalence of cardiac autonomic neuropathy.

4. CAN AND KNOWN DURATION OF THE DISEASE

There were 23 cases of more than 5 years of diabetes, of which 20 cases having cardiac autonomic neuropathy. Out of 27 cases of less than 5 years of diabetes only 11 cases showed cardiac autonomic neuropathy, which was significant.(p= 0.001)

TABLE NO4:CAN SCORE AND KNOWN DURATION OF THE DISEASE

DURATION	CAN SCORE			
		Negative	Positive	Total
<=5	Count	16	11	27
	%withinDuration	59.3%	40.7%	100%
>5	Count	3	20	23
	%withinDuration	13.0%	87.0%	100.0%
TOTAL	Count	19	31	50
	%withinDuration	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	11.260	1	0.001

5. BMI and CAN:

TABLE NO:5.BMI AND CAN SCORE

BMI	CAN SCORE			
		Negative	Positive	Total
NORMAL	Count	9	9	18
	%withinBMI	50.0%	50.0%	100%
OBESE	Count	10	22	32
	%withinBMI	31.3%	68.8%	100.0%
TOTAL	Count	19	31	50
	%withinBMI	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	1.719	1	.190

In the present study, 9 of out 18 patients(50%) of having BMI less than 25 and 22 out of 32 patients (68.8%) of having BMI more than 25 showed presence of cardiac autonomic neuropathy, which was not significant (p= .190).

6. CAN AND GLYCEMIC CONTROL

This study showed 6 of 27 patients (35.3%) having good glycemic control had CAN and 25 of 33 patients (75.8%) having poor glycemic control had evidence of CAN, which was significant (p= .005)

TABLE NO:6 CAN AND GLYCEMIC CONTROL

glycemic control	CAN SCORE			
		Negative	Positive	Total
GOOD	Count	11	6	17
	%within Gly_Cont	64.7%	35.3%%	100%
POOR	Count	8	25	33
	%within Gly_Cont	24.2%%	75.8%%	100.0%
TOTAL	Count	19	31	50
	%withinGly_Cont	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	7.719	1	.005

7.FUNDUS AND CAN

TABLE NO7:FUNDUS AND CAN SCORE

FUNDUS	CAN SCORE			
		Negative	Positive	Total
NORMAL	Count	17	14	31
	% within Fundus	54.8%	45.2%	100%
NPDR	Count	2	9	11
	% within Fundus	18.2%	81.8%	100.0%
PDR	Count	0	8	8
	% within Fundus		100.0%	100.0%
TOTAL	Count	19	31	50
	%withinGly_Cont	38.0%	62.0%	100.0%
Pearson chi-square	value	Df	Asymp. Sig. (2-sided)	
	10.468	2	.005	

8 out of 8 patients (100%)having proliferative retinopathy showed cardiac autonomic neuropathy, while 9 out of11 patients (81.8%)of non proliferative retinopathy showed presence of cardiac autonomic neuropathy. Only 14 of 31 patients having normal fundus showed cardiac autonomic neuropathy.(45.2%),which was statistically significant(p = .005).

8. ANKLE REFLEX and CAN SCORE

This study showed 29 out of 42 patients (69%) having absent ankle reflexes had cardiac autonomic neuropathy. Only two patients out of 8(25%) having ankle reflexes had cardiac autonomic neuropathy. Six out of eight patients(75%)having ankle reflexes did not have cardiac autonomic neuropathy, which was statistically significant.(p=0.019)

TABLE NO:8 ANKLE REFLEX AND CAN SCORE

ANK_REF	CAN SCORE			
		Negative	Positive	Total
ABSENT	Count	13	29	42
	% within Ank_Ref	31.0%	69.0%	100%
PRESENT	Count	6	2	8
	% within Ank_Ref	75.0%	25.0%	100.0%
TOTAL	Count	19	31	50
	%withinAnk_Ref	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	5.534	1	.019

9.VIBRATION SENSE AND CAN SCORE

TABLE NO:VIBRATION SENSE AND CAN SCORE

VIBRATION TEST	CAN SCORE			
		Negative	Positive	Total
ABSENT	Count	1	16	17
	% within Vibr_Test	5.9%	94.1%	100%
PRESENT	Count	18	15	33
	% within Vibr_Test	54.5%	45.5%	100.0%
TOTAL	Count	19	31	50
	% within Vibr_Test	38.0%	62.0%	100.0%
Pearson chi-square	value	Df	Asymp. Sig. (2-sided)	
	11.278	1	.001	

This study showed 16 patients of 17 (94.1%) of absent perception of vibration sense had cardiac autonomic neuropathy, and only 15 of 33 patients(45.5%) with perception of vibration sense had cardiac autonomic neuropathy, which was statistically significant($p = .001$)

11. MONOFILAMENT TEST AND CAN SCORE

This study showed 5 out of 21 (23.8%)patients with normal monofilament tests had cardiac autonomic neuropathy. 26 of 29 (89.7%) patients with abnormal monofilament tests showed evidence of cardiac autonomic neuropathy, which was statistically significant(p=0 .0001)

TABLE NO:10 MONOFILAMENT TEST AND CAN SCORE

MONOFILAMENT	CAN SCORE			
		Negative	Positive	Total
NORMAL	Count	16	5	21
	% within Mon_Fila	76.2%	23.8%	100%
ABNORMAL	Count	3	26	33
	% within Mon_Fila	10.3%	89.7%	100.0%
TOTAL	Count	19	31	50
	% within Mon_Fila	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	11.278	1	.0001

11.RESTING HEART RATE AND CAN SCORE

TABLE NO:11 RESTING HEART RATE AND CAN SCORE

Resting heart rate	CAN SCORE			
		Negative	Positive	Total
<100	Count	19	30	49.0%
	% within restin heart rate	38.8%	61.2%	100%
ABNORMAL	Count	0	1	1
	% within resting heart rate	0%	100%	100%
TOTAL	Count	19	31	50
	% within resting heart rate	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	.625	1	.429

Thirty (30) out of 49patients (61.2%) having resting heart rate less than 100 showed presence of cardiac autonomic neuropathy. Only one patients with resting heart rate more than 100 showed presence of cardiac autonomic neuropathy, which was statistically insignificant **(p=0.429)**

12.VALSALVA RATIO AND CAN SCORE

TABLE NO:12 VALSALVA RATIO AND CAN SCORE

VALSALVA RATIO	CAN SCORE			
		Negative	Positive	Total
<1.10	Count	0	16	16
	% within Vals_Ratio	0	100 %	100%
1.10-1.20	Count	6	15	21
	% within Vals_Ratio	28.6%	71.4%	100.0%
>1.20	Count	13	0	13
	% within Vals_Ratio	100.0%	.0%	100.0%
Total	Count	19	31	50
	% within Vals_Ratio	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	11.278	1	.0001

In this study 16 of 16 (100%) patients having valsalva ratio less than 1.10 showed presence of cardiac autonomic neuropathy.15 of 21 patients(71.4%) having valsalva ratio between 1.10 and 1.20 showed evidence of cardiac autonomic dysfunction.13 patients having ratio more than 1.2 showed no evidence of cardiac autonomic neuropathy. So valsalva ratio appeared to be a good predictor of cardiac autonomic neuropathy.(**$p_{=}$ 0.0001).**

13.DIASTOLIC BLOOD PRESSURE DIFFERENCE AND CAN SCORE

TABLE NO:14.DIASTOLIC BP DIFFERENCE AND CAN SCORE

DIASTOLIC BP DIFFERENCE	CAN SCORE			
		Negative	Positive	Total
<10	Count	3	4	7
	% within DBP_Diff	17.6%	82.4%	21%
10-15	Count	7	14	21
	% within DBP_Diff	33.3%	66.7%	100.0%
>15	Count	9	3	12
	% within DBP_Diff	75.0%	25.0%	100.0%
Total	Count	19	31	50
	% within DBP_Diff	38.0%	62.0%	100.0%
Pearson chi-square	value	Df	Asymp. Sig. (2-sided)	
	10.156	2	.006	

This study showed 14 of 17 patients (82.4%) of having diastolic blood pressure difference less than 10 during isometric exercise showed presence of cardiac autonomic neuropathy.14 of 21 patients (66.7%) with diastolic rise in blood pressure between 15-10 showed the presence of cardiac autonomic neuropathy. Only 3 of 12 patients (25%) having diastolic blood pressure rise more than 15 during isometric exercise showed evidence of cardiac autonomic neuropathy. It showed rise of diastolic blood pressure during isometric exercise was a good predictor of cardiac autonomic neuropathy.(**p=0 .006)**

14. HEART RATE VARIABILITY AND CAN SCORE

TABLE NO:14. HEART RATE VARIABILITY AND CAN SCORE

HEART RATE VARIABILITY	CAN SCORE			
		Negative	Positive	Total
<10	Count	2	21	23
	% within HR_Diff	8.7%	91.3%	21%
10-15	Count	15	8	23
	% within HR_Diff	65.2%	34.8%	100.0%
>15	Count	2	2	4
	% within HR_Diff	50.0%	50.0%	100.0%
Total	Count	19	31	50
	% within HR_Diff	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	15.860	2	.0001

This study showed 21 of 23 patients (91.3%) having heart rate variability less than 10 during deep breathing had evidence of cardiac autonomic neuropathy which is significant.(**p=.0001**). 8 out of 23 patients (34.8%) having heart rate variability between 10-15 showed evidence of cardiac autonomic neuropathy. Only two of four patients (50%) having heart rate variability more than 15 showed presence of cardiac autonomic neuropathy.

15. 30:15 RR INTERVAL RATIO AND CAN SCORE.

TABLE NO: 16 30:15 RR INTERVAL RATIO AND CAN SCORE

RR INTERVAL RATIO(30:15 ratio)	CAN SCORE			
		Negative	Positive	Total
ABNORMAL (≤ 1)	Count	0	14	14
	% within RR_Ratio	0%	100.0%	100.0%
NORMAL (> 1.04)	Count	19	17	36
	% within RR_Ratio	52.8%	47.2%	100.0%
Total	Count	19	31	50
	% within RR_Ratio	38.0%	62.0%	100.0%

Pearson chi-square	value	Df	Asymp. Sig. (2-sided)
	11.918	1	.001

In this study 14 patients of 14 (100%) having abnormal (≤1) 30:15 ratio showed presence of cardiac autonomic neuropathy. Only 17 of 36 patients having normal (>1.04) 30:15 ratio showed presence of cardiac autonomic neuropathy. So the presence of abnormal 30:15 ratio was statistically significant in predicting cardiac autonomic neuropathy. (**p= is .001**)

16. SBP fall and CAN SCORE

TABLE NO:17. SYSTOLIC BP FALL AND CAN SCORE

SYSTOLIC BP FALL	CAN SCORE			
		Negative	Positive	Total
<= 10	Count	17	16	33
	% within SBP_Fall	51.5%	48.5%	100.0%
11-30	Count	2	15	17
	% within SBP_Fall	11.8%	88.2%	100.0%
Total	Count	19	31	50
	% within SBP_Fall	38.0%	62.0%	100.0%
Pearson chi-square	value	Df	Asymp. Sig. (2-sided)	
	7.525	1	.006	

This study showed 16 of 33 patients(48.5%) with systolic blood pressure fall less than 10 during standing had cardiac autonomic neuropathy.15 of 17 patients(88.2%) with systolic blood pressure fall between 11-30 showed evidence of cardiac autonomic neuropathy, which was statistically significant**(p=0.006).** In the study group nobody showed a systolic BP fall of more than 30mm of mercury during standing.

DISCUSSION

The present study includes 50 patients of type 2 diabetes mellitus, with 30 controls whose age and sex is matched that of study group .

Takebayashi et al, studied 60 patients and Pourmoghaddas[104] et al studied 200 patients.

1.Prevalence of Cardiac autonomic neuropathy

In the present study, Cardiac autonomic neuropathy is observed in 31 patients of type 2 diabetes mellitus **(62%).**

Jeyarajah [102]R et al observed 46.2% prevalence and Ziegler et al observed 34.3% prevalence. Depending on the tests and criteria used, and on the patients cohorts studied, the prevalence shows variation between the studies. In 2008 Pappachan et al[(6)] found that the prevalence of cardiac autonomic neuropathy among type 2 DM patients was 60% in South Indian population. Mehta[(7)] et al published an Indian study showing 57.5% of prevalence of cardiac autonomic neuropathy in type 2 DM patients.

2. Cardiac Autonomic neuropathy and age

In this study CAN is more common in the age group of 61-70. Ninteyone percentage (91.7%) of patients of the age group of 61-70 shows CAN, but only 47.4%of the age group 41-50 shows the evidence of CAN.

Prevalence of the cardiac autonomic neuropathy increases with age group in this study population. The same observation was made by Valensi[5] and Jeyarajah[102] et al. Advancing age is a strong risk factor for diabetic neuropathy, independent of the duration of diabetes mellitus and glycemic control. The prevalence of diabetes mellitus increases markedly with age. Furthermore, several biological changes occurring during the aging process may account for the facilitating effect of age on diabetic neuropathy. These include an increase in the production of advanced glycosylation end-products (AGEs), a defect in the polyol pathway, nerve vascular alterations and impaired resistance to oxidative stress. The clinical diagnosis of diabetic neuropathy is often difficult in elderly patients. The relationship between symptoms and neuropathy and that between neuropathy and diabetes mellitus are more difficult to ascertain in elderly patients due to age-related changes in the peripheral and autonomic nervous system and associated diseases frequently encountered in this population. Clinical complications of diabetic neuropathy in the elderly are often severe. Early detection is required, as it is the most effective way to avoid or postpone debilitating complications. Belmin J, Valensi P[5] et al also found that severity of cardiac autonomic neuropathy increases with advancing age.In 1989 Nobutoshi Kuroda[117] et al published a study proving the autonomic function is related to age. They

proved that autonomic function of young diabetic patient corresponds to that of old non diabetic in terms of cardiac beat to beat variation.

3. Cardiac Autonomic Neuropathy And Sex

In the present study, 16 0f 27 (59.3%) females and 15 of 23 (65.2%) males show evidence of cardiac autonomic neuropathy, which is insignificant.(p=0.665). This shows sex is not a major determinant for the prevalence of cardiac autonomic neuropathy. In the DCCT[38] trial presence of autonomic neuropathy correlated with male sex. Jaffe [8] et al showed male sex to be predominantly affected in cardiac autonomic neuropathy. May et al showed significant association of female sex with autonomic neuropathy. Hence larger numbers of trial are needed to determine the prevalence of cardiac autonomic neuropathy among either sex particularly in relation to Indian ethnicity.

4.Cardiac autonomic neuropathy and Duration of the disease

There are 23 cases with more than 5 years of diabetes of which 20(87%) cases have cardiac autonomic neuropathy. Out of 27 cases with less than 5 years of diabetes ,only 11 cases (40.7%) show cardiac autonomic neuropathy, which is significant. (p=.001). Valensi[5] et al found that autonomic abnormality tests correlated significantly with duration of the disease. In 2008 Pappachen[6] et al established a significant correlation

between cardiac autonomic neuropathy and duration of the disease.(odds ratio-7.2).

5.Cardiac autonomic neuropathy and BMI

Present study shows 9 out of 18 patients (50%) having BMI less than 25 and 22 of 32 patients (68.8%) having BMI more than 25 show evidence cardiac autonomic neuropathy, which is insignificant. (p=0.190). Hence our study does not show any correlation between BMI and cardiac autonomic neuropathy. This is in accordance with the study reports of Chen H.T et al in 2008.

6.Cardiac autonomic neuropathy and Glycemic control

This study shows 6 out of 27 patients (35.3%)having good glycemic control have CAN and 25out of 33 patients (75.8%) having good glycemic control have CAN, which is significant (p=0.005). Mustonen() et al reported the similar results in 4 year follow up study of 32 individuals with poor glycemic controls. In 1990, Vegilo.M et al published a study proving autonomic neuropathy correlated with metabolic control of diabetes. The results from the DCCT Trial showed that intensive glycemic treatment can prevent the development of abnormal heart rate variation and slow the deterioration of autonomic dysfunction over time(Ziegler 1994).

7.Cardiac autonomic neuropathy and FUNDUS

In this study all patients having proliferative retinopathy show presence of cardiac autonomic neuropathy, while 9 of 11 patients (81.8%)of non proliferative retinopathy show presence of cardiac autonomic neuropathy, which is statistically significant(p=0 .005).Only 14 of 31 patients having normal fundus show cardiac autonomic neuropathy.(45.2%) Thus severity of retinopathy correlated with the degree of cardiac autonomic dysfunction. The study result establishes the important association between cardiac autonomic neuropathy and diabetic retinopathy. S.E SMITH et[(9)] al, and HELENA SCHMID[(10)] et al showed similar correlation between grade of diabetic retinopathy and cardiac autonomic dysfunction in their studies .

8.Cardiac Autonomic Neuropathy And Peripheral Neuropathy.

This study shows 29 out of 42(69%). patients having absent ankle reflexes had cardiac autonomic neuropathy. Only 2 out of 8 patients (25%) having ankle reflexes show presence of cardiac autonomic neuropathy, which is statistically significant (p=0.019). Six of eight patients (75%) having ankle reflexes do not show evidence cardiac autonomic neuropathy. Hence it is a good predictor of severity of cardiac autonomic neuropathy.

In this study, 16 patients out of 17 (94.1%) having absent perception of vibration sense show cardiac autonomic neuropathy, and only 15 of 33

patients(45.5%) with perception of vibration sense show cardiac autonomic neuropathy, which is statistically significant(p-value is .001).

This study also shows 5 out of 21 (23.8%)patients with normal monofilament tests have cardiac autonomic neuropathy. 26 out of 29 (89.7%)patients with abnormal monofilament tests have cardiac autonomic neuropathy, which is again statistically significant (p=0 .0001).

Thus patient diagnosed to have peripheral neuropathy by clinical examination should be screen for cardiac autonomic neuropathy. NEVZAT [(110)] et al in 2006 found that severity of cardiac autonomic neuropathy is associated with increased prevalence of other micro vascular complications. NEVZAT et[(110)] al in their study showed that there was no significant difference regarding the prevalence of peripheral neuropathy diagnosed by neurological examination and scintigraphic measurement of gastric and bladder emptying time ,or by EMG .In 2008 Pappachan[(6)] et al published a study establishing significant association between cardiac autonomic neuropathy and peripheral neuropathy(p<.001).

9.Cardiac autonomic neuropathy and Autonomic function tests

In this study, 30 out of 49patients (61.2%) having resting heart rate less than 100 show presence of cardiac autonomic neuropathy. Only one patient with resting heart rate more than 100 shows presence of cardiac autonomic neuropathy. This study shows that resting tachycardia is not a

good predictor of cardiac autonomic dysfunction. S.E SMITH, S.A.SMITH [9] and P.M BROWN reported that resting tachycardia is an unreliable marker of cardiac autonomic neuropathy.

There were five non invasive cardiovascular reflex tests used to assess the cardiac autonomic neuropathy. They were heart rate variation to deep breathing, heart rate variation to valsalva maneuver, postural tachycardia index, systolic blood pressure response to standing and diastolic blood pressure response to hand grip. First 3 tests used to assess the parasympathetic system and 2 tests for the sympathetic system. In this study heart rate variation to deep breathing (p=0.0001),heart rate variation to valsalva maneuver expressed by valsalva ratio (p=0.0001) are the better predictors of assessing cardiac autonomic neuropathy compared to other tests. Jeyarajah[102] et al reported that of all the tests performed ,heart rate response to deep breathing was the commonest to become abnormal. Strobescue[109] et al in 2002 showed that changes in heart rate during deep inspiration–expiration remains the preferable tests according to its sensitivity, specificity and predictive value.

Diabetes Mellitus is an old disease of human being and autonomic dysfunction involving virtually all the body system is an established complication. Cardiac autonomic neuropathy is the most frequent and clinically important form of diabetic autonomic neuropathy. .Cardiovascular

dysfunction assumes maximum importance because it leads to silent infarction, intractable arrhythmias and sudden cardiac death. Cardiac autonomic neuropathy is associated with increased frequency of other micro vascular complications.

A group of non invasive tests have been used for the diagnosis of cardiac autonomic neuropathy. These tests although sensitive and reproducible, are time consuming and are not practical screening methods in crowded diabetic clinics. As cardiac autonomic neuropathy is common in diabetes, and it is associated with known duration of the disease, control of hyperglycemia. So early detection of diabetes and assessing the risk factors and controlling modifiable risk factors are important cornerstone of preventing its complication.

The severity of other micro vascular complications like diabetic retinopathy and peripheral neuropathy parallel the severity of cardiac autonomic neuropathy. Examination of dilated fundus, ankle reflexes, monofilament tests, vibration tests are simple tests performed in routine out patient clinics. This study showed that patients with proliferative retinopathy, and peripheral neuropathy also had cardiac autonomic neuropathy.

So fundus examinations, clinical tests like checking ankle reflexes, monofilament tests, vibration tests are predictors of the severity of cardiac autonomic neuropathy.

SUMMARY

The study "Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus patients" was a case control study conducted on patients visiting outpatient department of Diabetes clinic of Government Rajaji Hospital Maduari.50 patients with type 2 Diabetes Mellitus and 30 healthy controls were included in this study. Selected patients and controls underwent clinical and biochemical evaluation including Ewing's Reflex Tests using 8 Channel PSYCOPHYSIOPAC. They were also subjected to clinical examination for peripheral neuropathy, fundus examination, fasting and postprandial blood sugar estimation, and BMI calculation. It was observed that prevalence of cardiac autonomic neuropathy is correlated with age, known duration of the disease, and glycemic control. There is no correlation of cardiac autonomic neuropathy with sex and body mass index. There is a significant correlation between the severity of retinopathy and degree of cardiac autonomic neuropathy. Presence of peripheral neuropathy is associated with increasing severity of cardiac autonomic neuropathy. Simple neurological examination like ankle reflexes, vibration sense and monofilament test helps to predict the presence and severity of cardiac autonomic neuropathy.

CONCLUSIONS

- The prevalence of cardiac autonomic neuropathy is 62% in patients with type 2 Diabetes Mellitus.
- The presence of cardiac autonomic neuropathy is directly related to the age, known duration of the disease and glycemic control.
- There is no direct correlation between cardiac autonomic neuropathy, sex and body mass index.
- The degree of diabetic retinopathy is associated with degree of cardiac autonomic neuropathy.
- The prevalence of peripheral neuropathy increases as the severity of cardiac autonomic neuropathy increases in patients with type 2 Diabetes Mellitus.
- This study emphasizes the need for an early screening for peripheral neuropathy, retinopathy and other micro vascular complications in Type 2 diabetes patients and it reflects the severity of cardiac autonomic neuropathy.

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PROFORMA

CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS

CASE NO: DATE:

OP :

NAME:-

AGE: SEX:

ADDRESS: OCCUPATION:

PHONE:

SOCIO ECONOMIC STATUS:

HISTORY OF ILLNESS:

1KNOWN DURATION

TYPE II DM ☐

2.PRESENT SYMPTOMS

3.TREATMENT HISTORY

PAST H/O:-

HTN	TB	ASTHMA	LIVER DISEASE
CAD	CVA	DYSLIPIDEMIA	RENAL DISEASE

FAMILY H/O:-

DM	HTN	CAD	DYSLIPIDEMIA

OTHER RELEVENT HISTORY

MENSTRUAL H/O:-

GENERAL EXAMINATION:-

BUILT: NOURISHMENT

PALLOR ICTERUS CLUBBING EDEMA

CYANOSIS LYMPHADENOPATHY

RESTING PULSE RATE:-

BLOOD PRESSURE: SUPINE

STANDING

DIASTOLIC BP: Before isometric exercise:

After isometric exercise:

RESPIRATORY RATE:

TEMPERATURE:

OTHER SYSTEMS:-

CVS:

RESPIRATORY SYSTEM:

Dilated fundus	
right	left

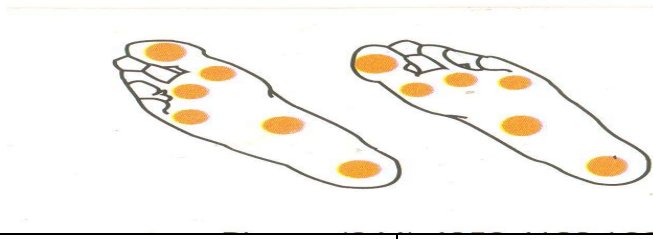
Ankle reflex	
right	left

CNS:

Vibration sense-128Hz		
	right	left
Hand		
Foot		

HMF

CRANIAL NERVES

MONOFILAMENT TEST	
right	left
	

INVESTIGATIONS:-

CBC:

Hb TC

DC

ESR

PLT.COUNT

URINE R/E

ALB SUG

CASTS

RBC

RBS: Blood urea: S.Creatinine: S.E- Na+

K+

FLP: Total chol LDL HDL VLDL TG

LFT: TBb/DBb T.pro S.ALB/GLOB

SGPT/SGOT ALP

HBA1C

ECG

QTc:

CXR:

CONTINOUS ECG MONITORING

1. R-R INTERVAL IN VALSALVA MANOUVRE

On straining:

After straining:

Ratio:

2. HEART RATE IN DEEP BREATHING:

Resting heart rate before deep breathing:

Heart rate during deep breathing:

3.HR RESPONSE TO STANDING

RR INTERVAL AT 30th beat:

RR INTERVAL AT 15th beat: 30:15 Ratio:

OTHERS: (if any)

CAN SCORE: ABSENT (0) EARLY (1) DEFINITE (2) SEVERE ($\geq$3)

Autonomic function test	Points	Pt'point
1 Heart rate variability on deep breathing		
>15 beats/min	0	
11-15 beats/min	1/2	
<11 beats/min	1	
2. Postural hypotension (fall in systolic blood pressure)		
<10 mm Hg	0	
11-29 mm Hg	1/2	
>30 mm Hg	1	
3. Valsalva ratio (longest RR interval: shortest RR interval)		
>1.2	0	
1.2–1.10	1/2	
<1.10	1	
4. Heart rate variability on standing(30:15)		
>1.04	0	
1.01-1.03	1/2	
<10 beats/min	1	
5. Increase in diastolic blood pressure during sustained handgrip		
>15 mm Hg	0	
15–10 mm Hg	1/2	
<10 mm Hg	1	

FIG:1 PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS

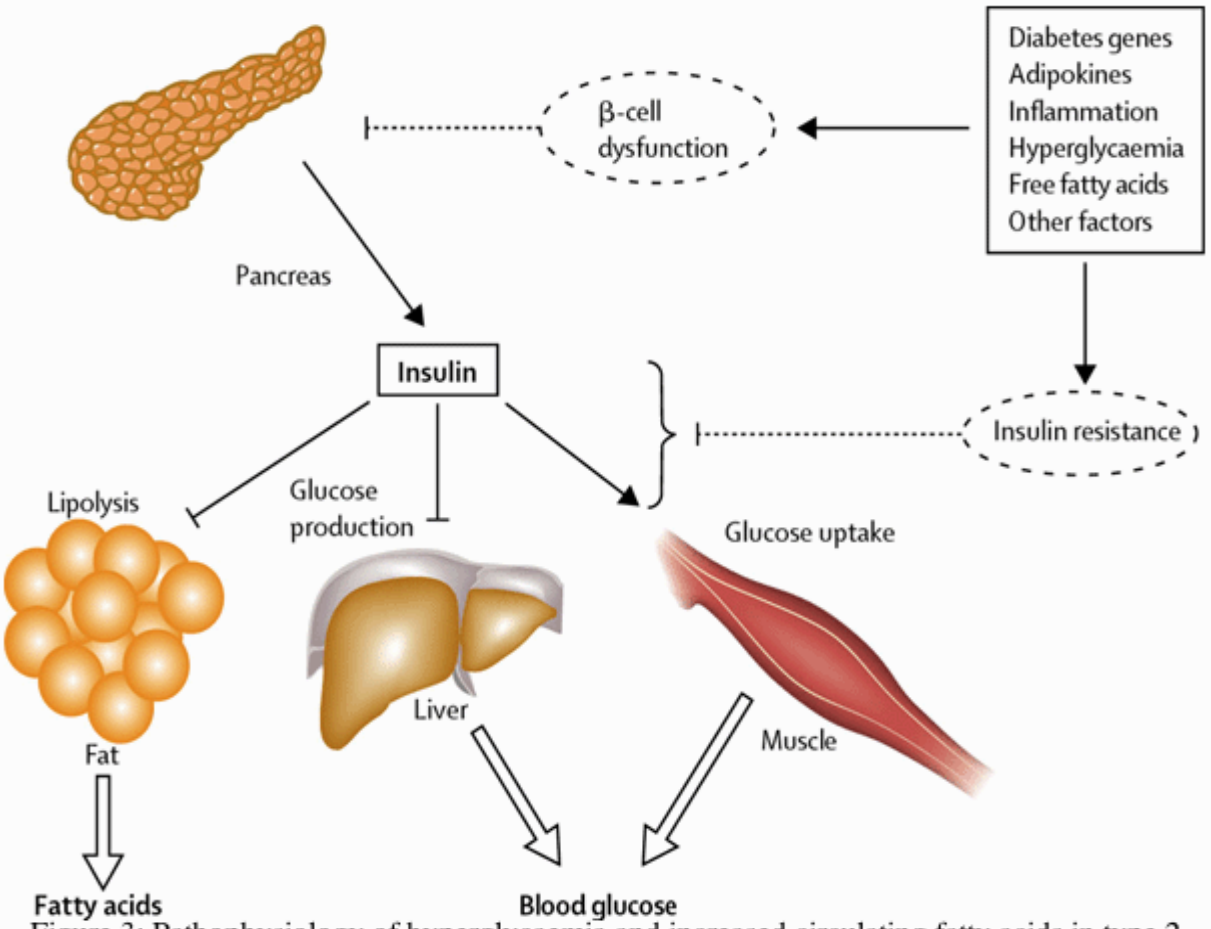
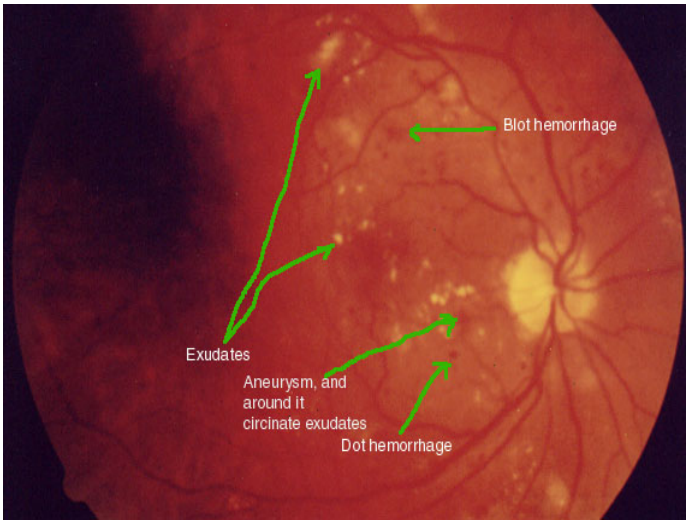


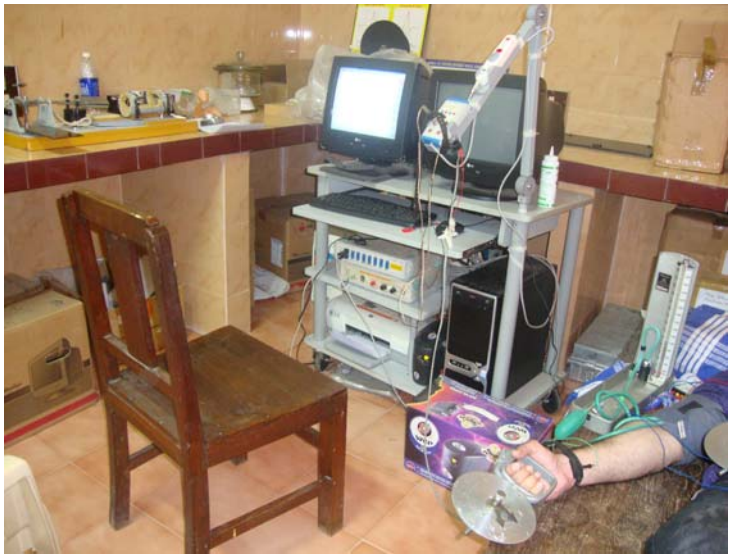
Figure 3: Pathophysiology of hyperglycaemia and increased circulating fatty acids in type 2 diabetes

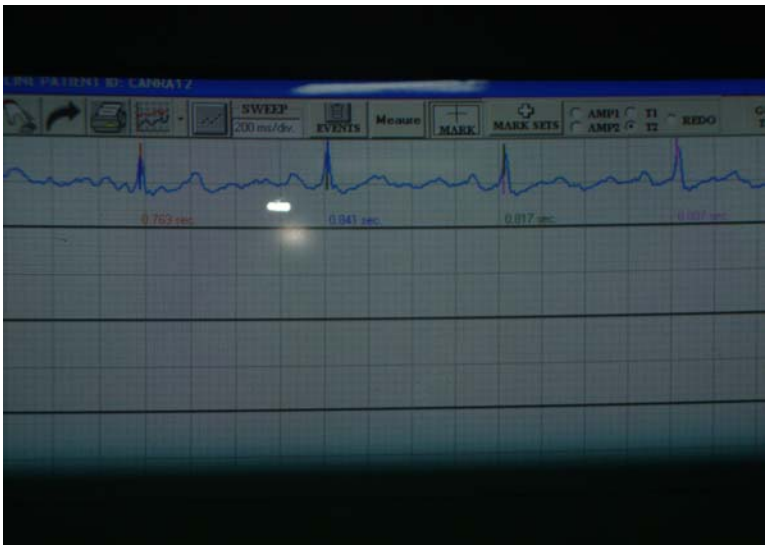
FIG:2. NON PROLIFERATIVE DIABETIC RETINOPATHY

FIG:3 PROLIFERATIVE DIABETIC RETINOPATHY

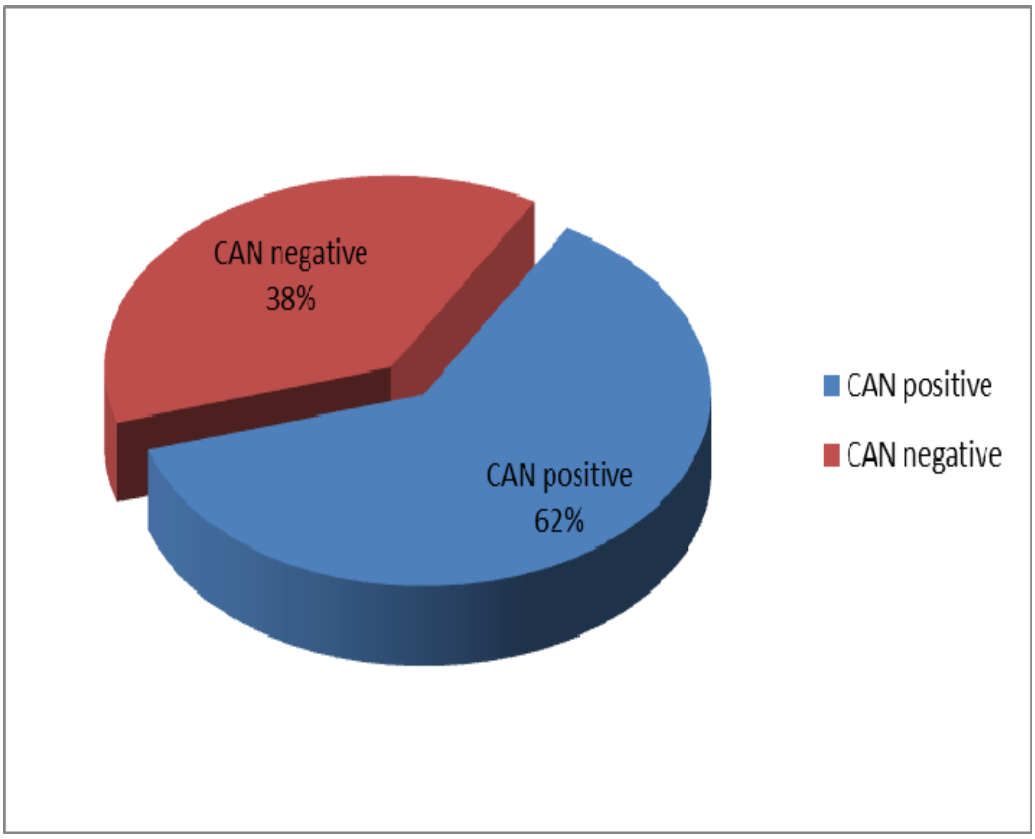


ECG MONITORING WITH 8-CHANNEL PSYCO PHYSIOPAC

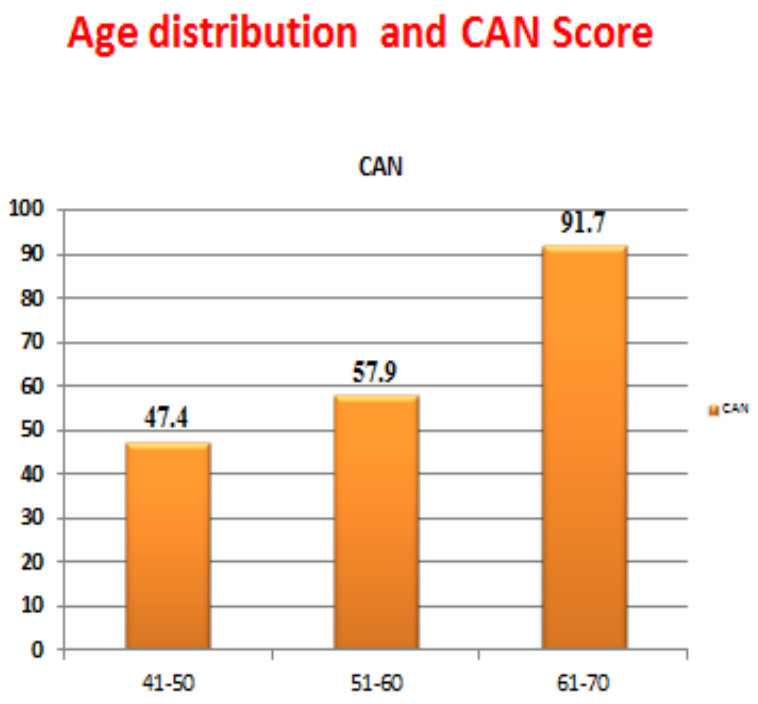




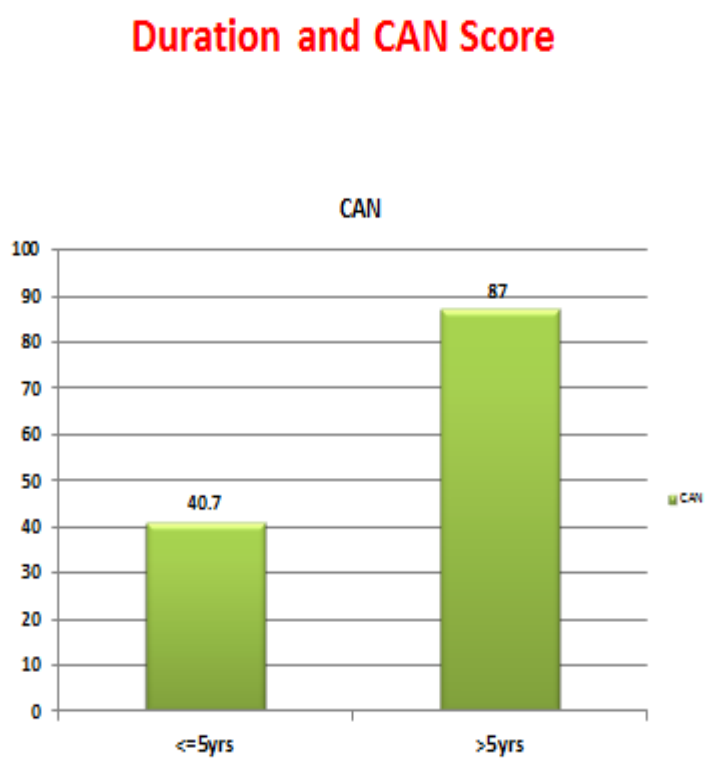
GRAPH-1 Prevalence of Cardiac Autonomic Neuropathy



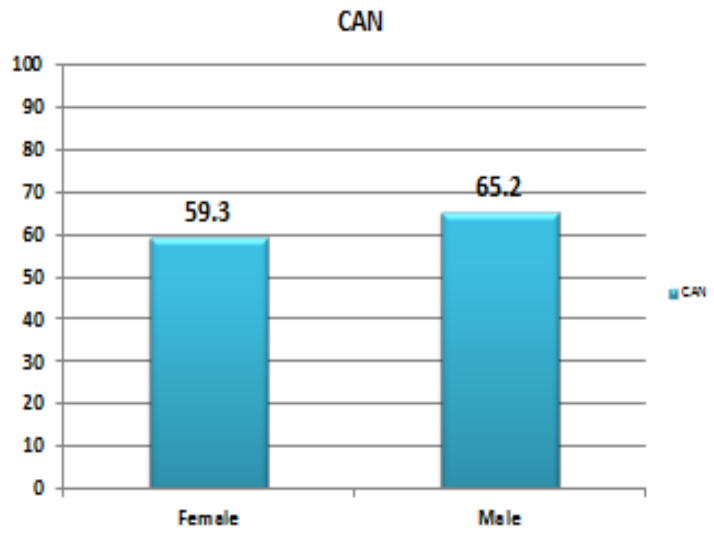
GRAPH-2 Age distribution and Cardiac Autonomic Neuropathy score



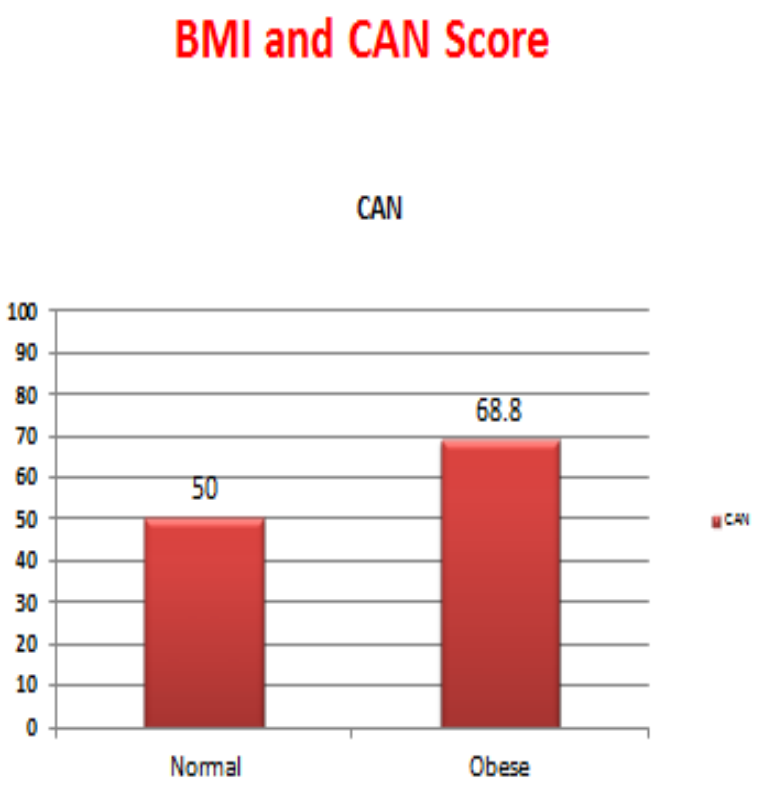
GRAPH-4 Duration and cardiac autonomic neuropathy score



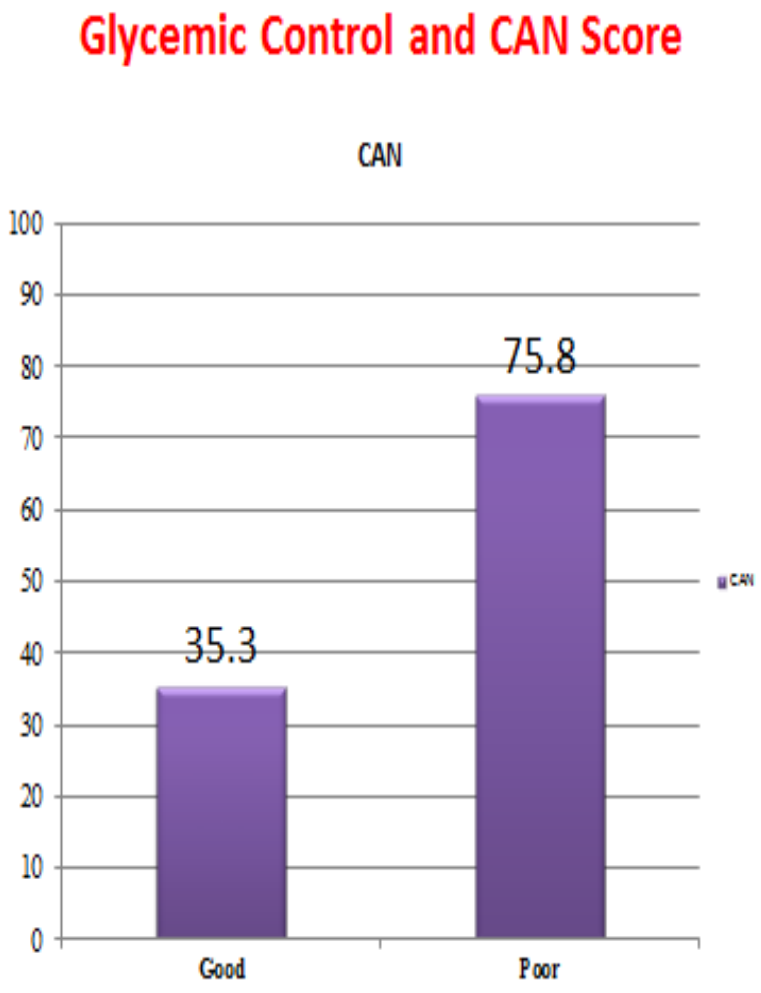
GRAPH-3 Sex Distribution And Can



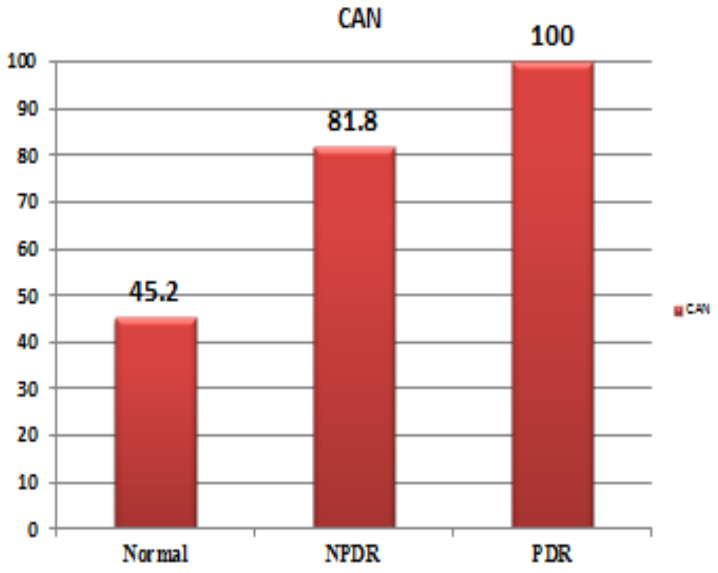
GRAPH-5 :BMI and Cardiac Autonomic Neuropathy Score



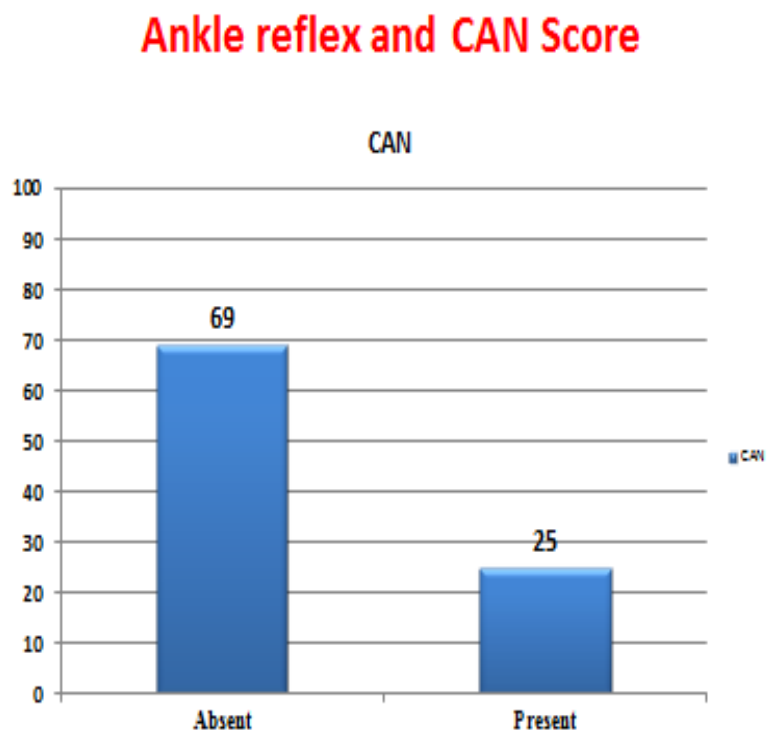
GRAPH-6: Glycemic Control and Cardiac Autonomic Neuropathy Score



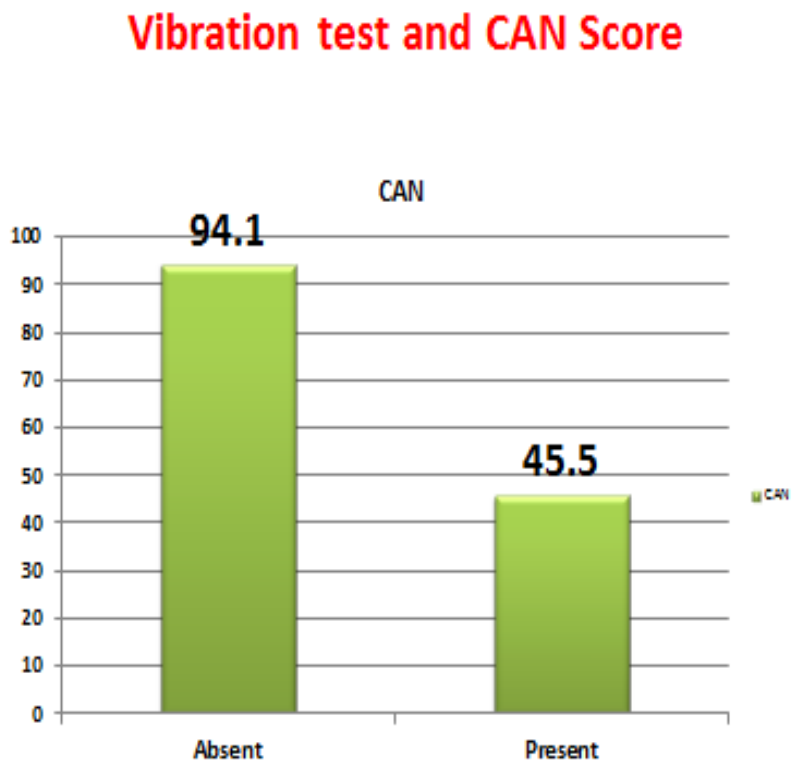
GRAPH-7: FUNDUS and Cardiac Autonomic Neuropathy Score



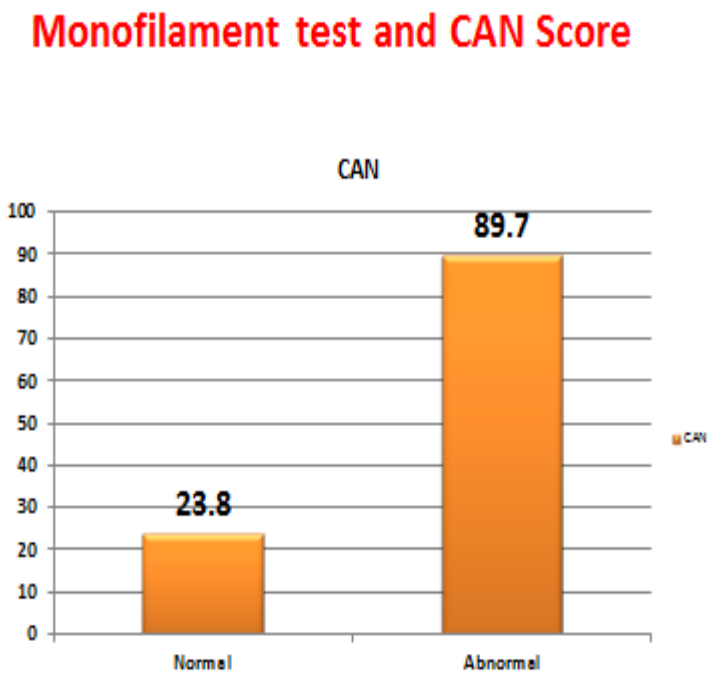
GRAPH-8:Ankle Reflexes and Cardiac Autonomic Neuropathy Score



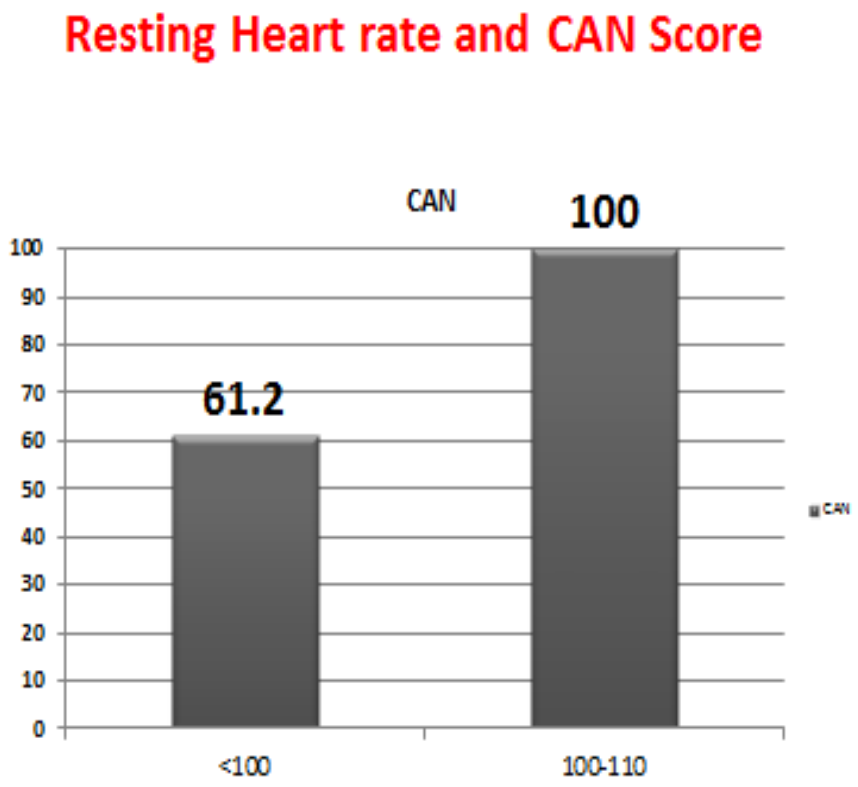
GRAPH-9: Vibration Sense and Cardiac Autonomic Neuropathy Score



GRAPH-10:.Monofilament Tests and Cardiac Autonomic Neuropathy Score

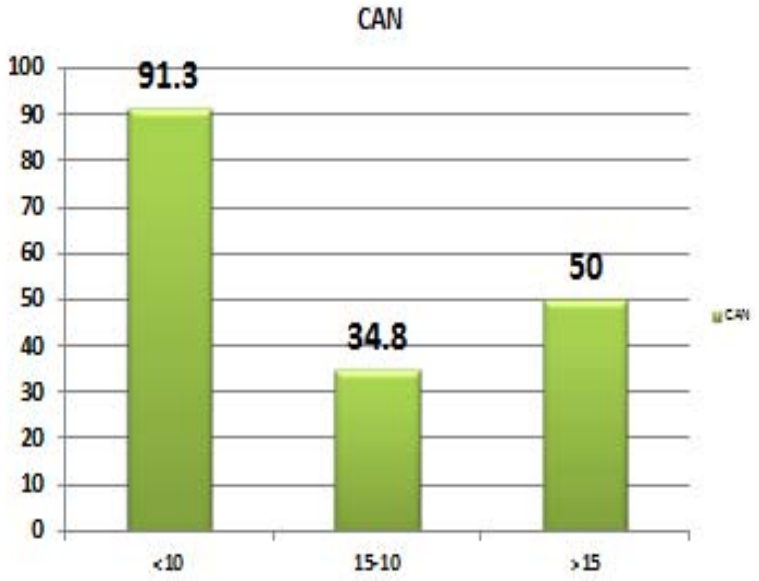


GRAPH-11 :resting heart rate and Cardiac Autonomic Neuropathy Score

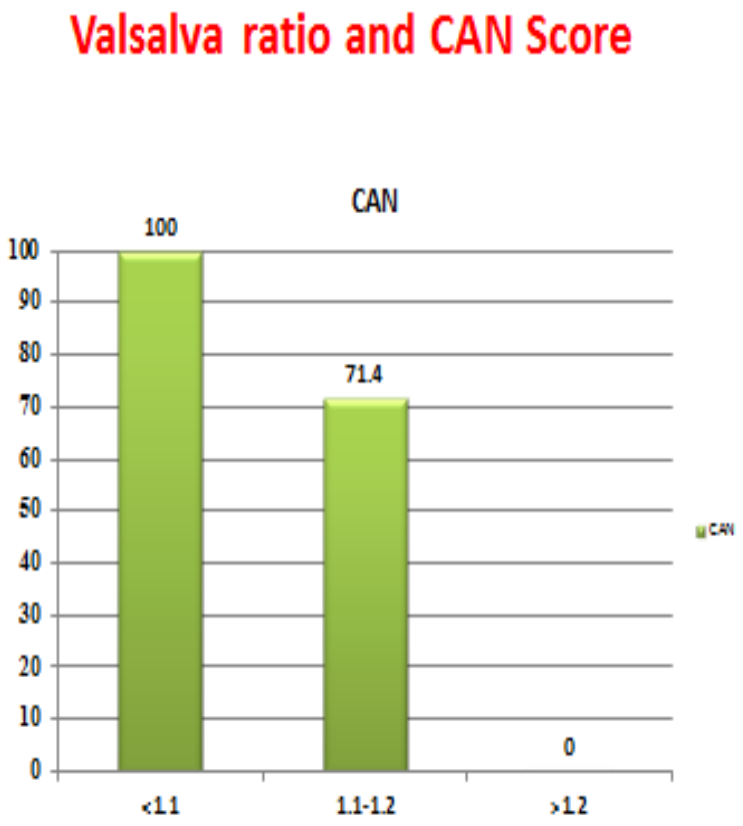


GRAPH-12: Heart Rate variability and Cardiac

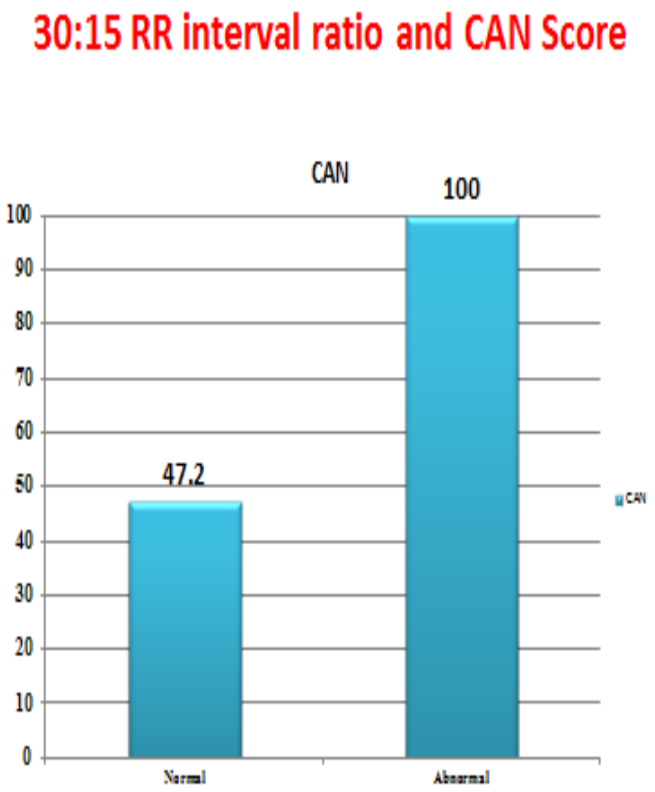
Autonomic Neuropathy Score



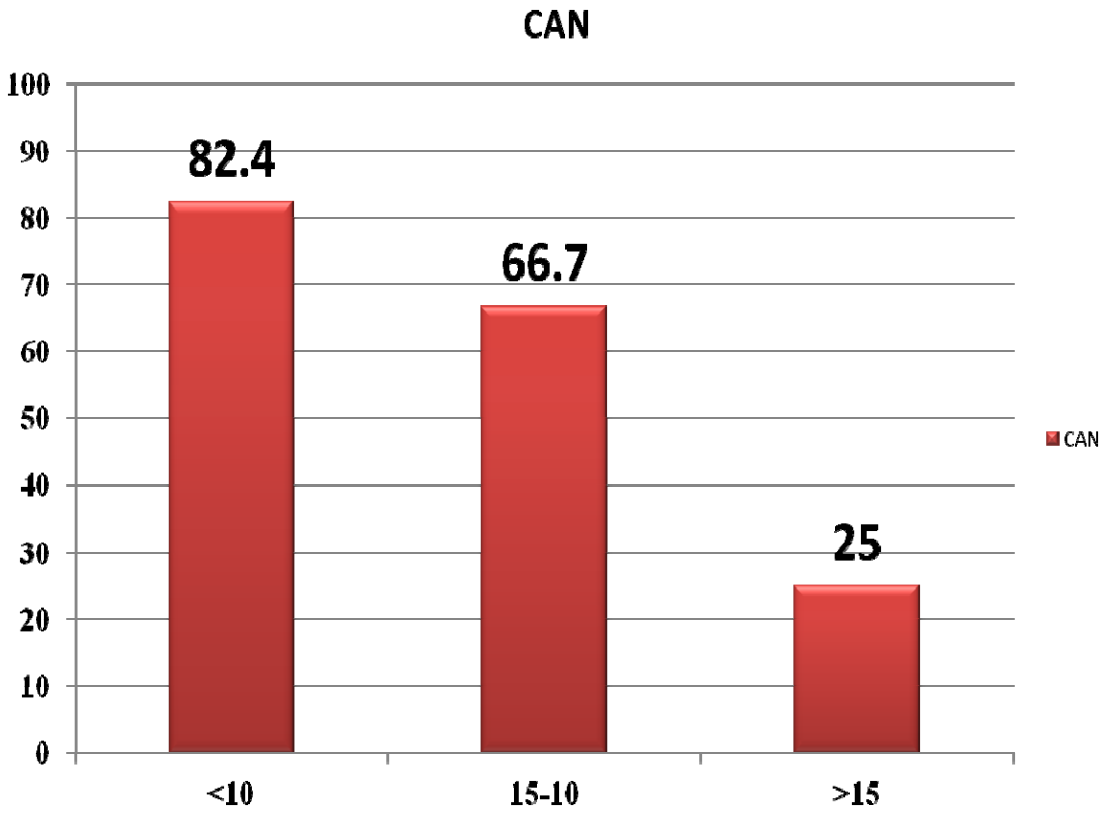
GRAPH-13 :Valsalva ratio and Cardiac Autonomic Neuropathy Score



GRAPH-15: 30:15 RR interval ratio and Cardiac Autonomic Neuropathy Score



GRAPH-14: DBP difference and Cardiac Autonomic Neuropathy Score



GRAPH-16: Systolic BP fall and Cardiac Autonomic Neuropathy Score