A STUDY ON PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS PATIENTS AND ITS CORRELATION WITH OTHER MICROVASCULAR COMPLICATIONS

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CERTIFICATE

This is to certify that **"A Study on Prevalence of Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus Patients and its Correlation with other Microvascular Complications"** is bonafide work done by **Dr.G.Sathya,** post graduate student, **Department of Internal Medicine, Kilpauk Medical College, Chennai - 10** under my guidance and supervision in partial fulfillment of regulations of **The Tamilnadu Dr.M.G.R. Medical University** for the award of **M.D. Degree Branch I, Part II (General Medicine)** during the academic period from May 2005 to March 2008.

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CONTENTS

INTRODUCTION

Type 2 Diabetes Mellitus is a major health problem all over the world. It forms more than 90% of the diabetic population[1]. The WHO has highlighted that India would lead the world in the prevalence of Diabetes mellitus and would become diabetic capital of the world and contribute more than 20% of the world diabetic population by the year 2025.[2]

The impact of the worldwide explosion of type 2 diabetes mellitus (which accounts for approximately 85 to 95% of all cases of diabetes) will remain centered in the developing countries, since by the year 2025, 75 % of all the people with diabetes will be in the developing countries, a majority in the Indian subcontinent (59 %). By 2025, there will be a 170% increase from 84 – 228 million , in the developing countries.[3] India already faces a grave problem with the largest number of subjects with diabetes approximately 33 million in 2003 and it is expected to escalate further with the number increasing to 57.2 million in the year 2025 [3,4]and by the year 2030 it may be 80.9 million.[5]

Langley coined the term autonomic nervous system in 1898.[6] Cardiac autonomic neuropathy was noted nearly 100 years ago by Eichhorst (1882). The autonomic nervous system, through the sympathetic and parasympathetic pathways influences every organ of the body. It closely integrates vital processes such as heart rate, blood

pressure, myocardial contractility and as a consequence plays a vital role in the regulation of the cardiovascular system. Autonomic dysfunction is common (40%) in diabetics but in sharp contrast symptomatic autonomic neuropathy is rare .[7]

Diabetes is the most common cause of autonomic neuropathy and autonomic damage to the heart occurs as a part of the wider spectrum of the autonomic neuropathy which affects most organs of the body. It is in the cardiovascular system that autonomic neuropathy is most noticeable and most easily assessed. With advent of newer methods of assessment of cardiac autonomic dysfunction, it is now well known that autonomic neuropathy could occur quite early in the course of diabetes mellitus.

It is also generally assumed that cardiac autonomic neuropathy is responsible for an altered perception of myocardial ischaemia, painless myocardial ischaemia and silent acute myocardial infarction. In a recently published study cardiac autonomic neuropathy was independently associated with asymptomatic coronary artery disease in patients with type 2 diabetics. Autonomic neuropathy is significantly associated with diabetic retinopathy or nephropathy. Autonomic neuropathy usually coexists with a small fibre peripheral neuropathy [8]

The diabetes control and complications trial showed that intensive control of the blood sugar over a 7 year study interval reduced the progression of diabetic neuropathy, retinopathy and nephropathy.[9]

Diabetes complicates every organ and is the fourth major cause of mortality and morbidity worldwide. The relationship between control and complications in type 2 diabetes mellitus was evaluated in UKPDS.[10] The study concluded that for every 1% decrease in HbA1c there was 35% reduction in the risk of microvascular complications.

The availability of sensitive, specific and reproducible noninvasive tests of autonomic function has enhanced our understanding of the prevalence, pathophysiology and clinical manifestations of this disorder.[11] Estimates of the prevalence of diabetic autonomic neuropathy are dependent on the criteria used for diagnosis and the specific population under study.

This study is aimed at detecting the autonomic functions in a group of randomly selected type 2 diabetic patients, by simple bed side tests. Our better understanding on clinical and prognostic importance of autonomic neuropathy was closely related to the widespread use of simple non-invasive reflex tests. Recognizing cardiac dysautonomia earlier can help us to prevent many dreadful complications like sudden death and to start on various measures to prevent its progression.

AIMS OF THE STUDY

The aims of the study are:

1. To assess the prevalence of Cardiac Autonomic Neuropathy in a group of Type 2 Diabetes mellitus patients using a comprehensive series of standardized tests by using a cardiac autonomic nervous system analyzer CANS 504

2. Attempt to correlate Cardiac Autonomic dysfunction with duration of Diabetes mellitus and other microvascular complications like Peripheral neuropathy, Nephropathy and Retinopathy.

REVIEW OF LITERATURE

Diabetes mellitus is a heterogenous group of metabolic disorders characterized by chronic hyperglycemia. The effect of diabetes mellitus include long term damage, dysfunction and failure of various organs especially the eyes, kidneys, heart and blood vessels.[1]

The worldwide prevalence of DM has risen dramatically over the past 2 decades. There is considerable geographic variation in the incidence of both type 1 and type 2 DM. The results of the prevalence studies of DM in India were systematically reviewed with emphasis on those utilizing the standard WHO criteria for diabetes diagnosis. The prevalence of diabetes in adults was found to be 2.4 % in rural and 4.0 – 11.6 % in urban dwellers. High frequencies of impaired glucose tolerance, shown by these studies, ranging from 3.6 – 9.1% indicate the potential for further rise in prevalence of diabetes mellitus in the coming decades.[12] Recently the WHO in consultation with an expert committee of the American Diabetes Association has approved a new diagnostic criteria for DM.

DIAGNOSTIC CRITERIA

CATEGORY	FPG	PPG
Normal	< 100mg/dl (5.6 mmol / L)	< 140 mg/dl (< 7.8 mmol / L)
IFG	100 – 125 mg / dl (5.6 – 6.9 mmol / L)	_
IGT	_	140 – 199 mg / dl (7.8 – 11.0 mmol / L)
DIABETES	≥ 126 mg / dl (7.0 mmol/ L)	≥ 200 mg / dl (11.1 mmol / L)

Fasting : No caloric intake for atleast 8 hours.

When the diagnosis of diabetes is made, it is confirmed by a repeat testing done on a different day.

Diabetic neuropathy is the commonest diabetic complication. The nervous system is frequently involved in diabetes mellitus, irrespective of the type of diabetes mellitus. Diabetes mellitus can affect the nervous system in the following ways:

1) Affection of the nerves (neuropathy)- motor, sensory, autonomic or mixed.

2) Affection of the brain and spinal cord indirectly by potentiating atherosclerosis and thereby vasculopathy (ischeamia/infarction)

3) Coma as a result of diabetic ketoacidosis, nonketotic hyperosmolar state or hypoglycemia causing damage to the brain .[13]

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM [8,14]

The most remarkable features of the autonomic nervous system (also called the visceral vegetative, or involuntary nervous system) is that a major part of it is located outside the cerebrospinal system, in proximity to the visceral structures that it innervates.

In the autonomic nervous system there are always two efferent neurons serving this fucntion - one (preganglionic) arising from its nucleus in the brainstem or spinal cord and the other (postganglionic) arising from specialized nerve cells in peripheral ganglia. The autonomic nervous system is divided into two parts the craniosacral, or parasympathetic and the thoracolumbar, or sympathetic.

Parasympathetic Nervous system

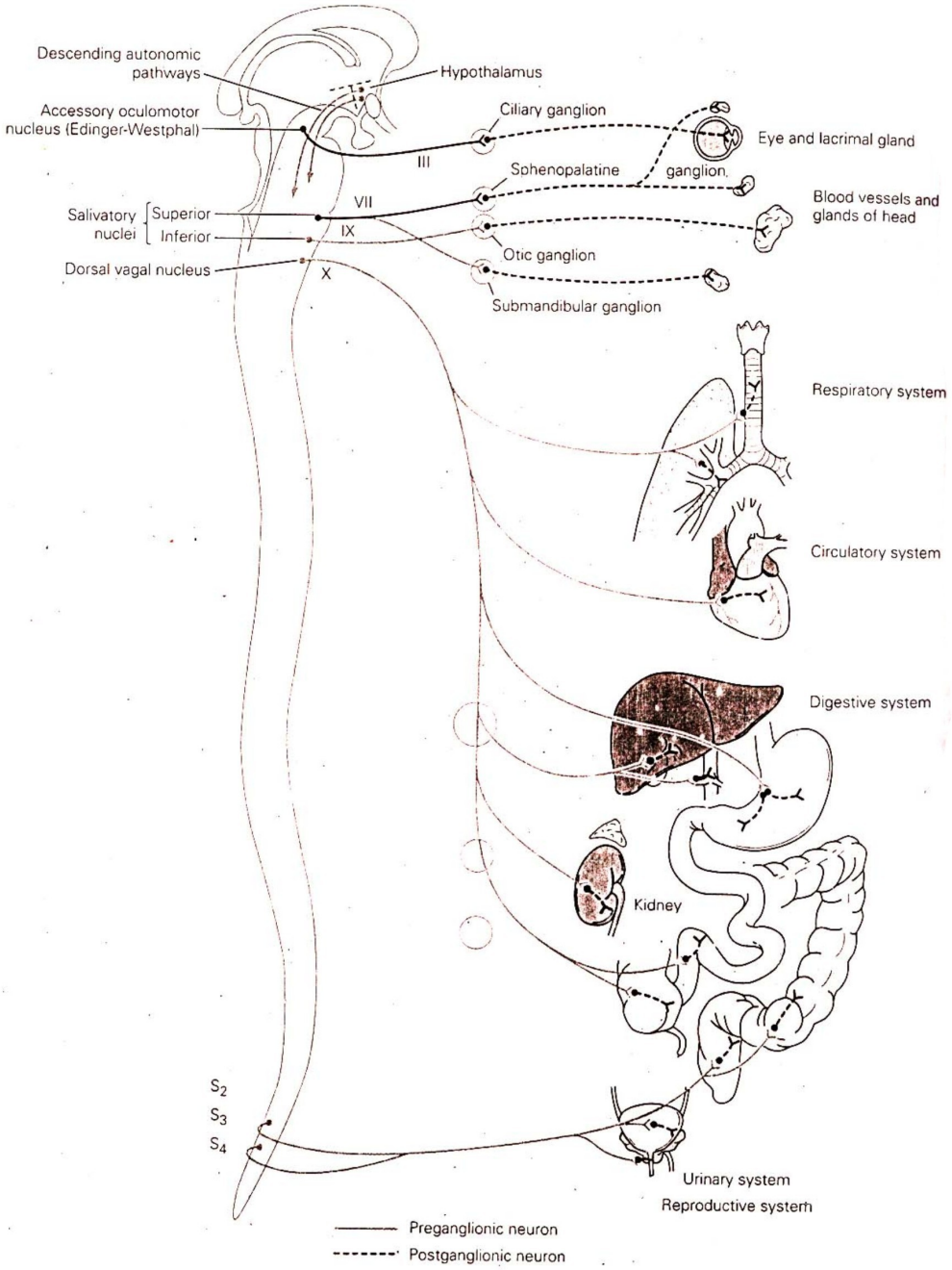
There are two divisions of the parasympathetic nervous system - cranial and sacral.

Cranial division

It originates in the visceral nuclei of the midbrain, pons and medulla. These nuclei lie in close proximity to the somatic afferent nuclei and induce the Edinger - Westphal pupillary nucleus, superior

and inferior salivatory nuclei, dorsal motor nucleus of the vagus, and adjacent reticular nuclei.

The parasympathetic (craniosacral) division of the autonomic nervous system



The preganglionic fibers of the visceral cranial nuclei course through the oculomotor, facial, glassopharyngeal and vagus nerves. The preganglionic fibers from the Edinger - Westphal nucleus traverse the oculomotor nerve and synapse in the cilliary ganglion in the orbit & axons of the cilary ganglion cells innervate the ciliary muscle and papillary sphincter.

The preganglionic fibers of the superior salivatory nucleus enter the facial nerve and form the greater superficial petrosal nerve, through which they reach the spheno - palatine ganglion, psotganglionic fibers from the cells of this ganglion innervate the lacrimal gland. Other fibers of the facial nerve traverse the tympanic cavity as the chord tympani and eventually join the submandibular ganglion, cells of this ganglion innervate the submandibular and sublingual glands.

Axons of the inferior salivatory nerve cells enter the glossopharyngeal nerve and reach the otic ganglion through the tympanic plexus and lesser superficial petrosal nerve, cells of the otic ganglion send fibers to the parotid gland.

Preganglionic fibers, derived from the dorsal motor nucleus of the vagus and adjacent visceral nuclei in the lateral reticular formation, enter the vagus nerve and terminate in ganglia situated in the walls of many thoracic and abdominal viscera. The short post-ganglionic fibers that activate smooth muscle and glands of the pharynx, esophagus and gastrointestinal tract (up to of the descending colon) and of the heart, pancreas, liver, gallbladder, kidney and ureter.

Sacral division:

It originates in the lateral horn cells of the second, third, and fourth sacral segments. Axons of these sacral neurons, constituting the preganglionic fibers, traverse the sacral nerves and synapse in ganglia that lie within the walls of the distal colon, bladder and other pelvic organs. Thus, the sacral autonomic neurons, like the cranial ones, have long preganglionic and short postganglionic fibers - a feature that permits a circumscribed influence upon the target organ.

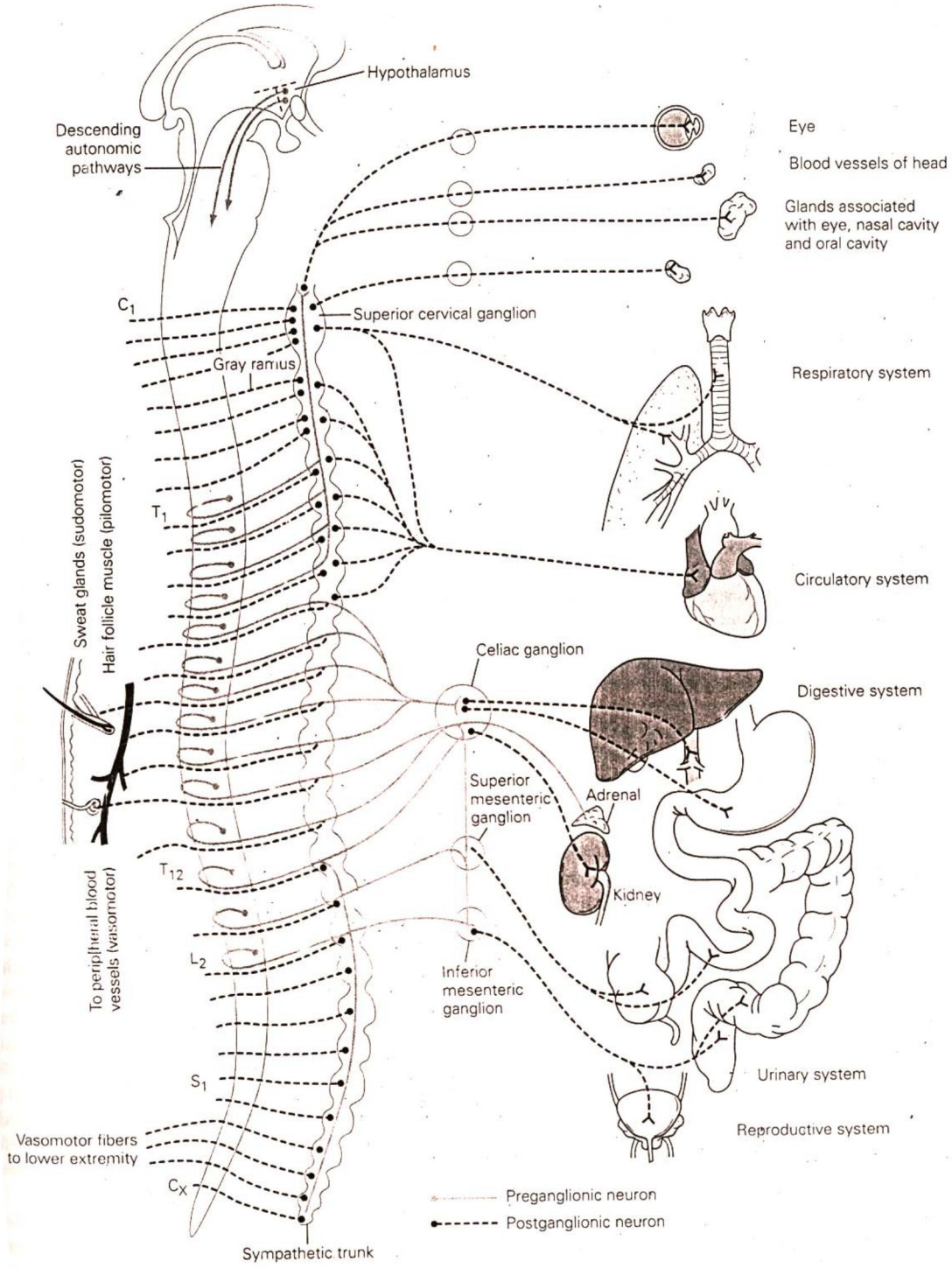
Sympathetic Nervous system

The preganglionic neurons of the sympathetic division originate in the intermedio-lateral cell column of the spinal gray matter, from the eighth cervical to the second lumbar segments.

Axons of the nerve fibers originating in the intermedio-lateral column are of small calibre and are myelinated; when grouped, they form the white communicating rami. These preganglionic fibers synapse with the cell bodies of the postganglionic neurons, which are collected into two large ganglionated chains or cords, one on each side of the vertebral column (paravertebral ganglia), and several single paravertebral ganglia.

Axons of the sympathetic ganglion cells are also of small caliber but are unmyelinated. Most of the postganglionic fibers pass via gray communicating rami to spinal nerves of T_5 to L_2, they supply blood

The sympathetic (thoracolumbar) division of the autonomic nervous system



vessels, sweat glands, and hair follicles and also form plexuses that supply the heart, bronchi, kidneys, intestines, pancreas, bladder and sex organs. The postganglionic fibers of the prevertetral ganglion (located in the posterior abdomen rather than paravertebrally), form the hypogastric, splanchnic, and mesenteric plexuses, which innervate the glands, smooth muscle and blood vessels of the abdominal and pelvic viscera.

There are three cervical (superior, middle and inferior or stellate), eleven thoracic, and four to six lumbar sympathetic ganglia. The head receives its sympathetic innervation from the eighth cervical and first two thoracic cord segments, the fibers of which pass through the inferior to the middle and superior cervical ganglia. Postganglionic fibers from cells of the superior cervical ganglion follow the internal and external carotid arteries and innervate the blood vessels and smooth muscle as well as the sweat, lacrimal and salivary glands of the head. The arm receives its postganglionic innervation from the inferior cervical ganglion and uppermost thoracic ganglia (the two are fused to form the stellate ganglion). The cardiac plexus and other thoracic sympathetic nerves are derived from the upper thoracic ganglion and the abdominal visceral plexuses, from the fifth to the ninth or tenth thoracic ganglia. The lowermost thoracic ganglia have no abdominal visceral

connections; the upper lumbar ganglia supply the descending colon, pelvic organs and legs.

PHYSIOLOGY OF CARDIOVASCULAR REGULATION [15]

Cardiovascular regulation is generally mediated through changes in vascular resistance and cardiac output by the following

1) ARTERIAL BARORECEPTORS:

Arterial baroreceptors in the adventitia of the aortic arch and the carotid bifurcations are activated by mechanical deformation due to the stretching of the vessel wall, secondary to high blood pressure. The increased baroreceptor discharge inhibits the tonic discharge of the vasoconstrictor nerves and excites the vagal innervation of the heart, producing vasodilation, venodilation, a drop in the blood pressure, bradycardia, and a decrease in cardiac output.

2) ARTERIAL CHEMORECEPTORS:

The aortic and carotid bodies (Torrance 1968) are highly vascular, with a flow of 20 ml/g/mt. The chemoreceptors act as a emergency system in contrast to baroreceptors which have an ongoing regulatory function. Stimulation of these leads to bradycardia, vasoconstriction in the major vascular beds and an increase in the arterial pressure.

3) CARDIAC RECEPTORS:

Cardiac receptors are present in the coronary vessels and within each of the four chambers of the heart.

i) Complex unencapsulated endings located mainly at the junctions of the pulmonary veins and the atria.

ii) Atrial stetch receptors: The stretch receptors in the atria are of two types: those that discharge primarily during atrial systole (type A), and those that discharge primarily late in diastole (type B). The reflex circulatory adjustment initiated by increased discharge from these receptors include vasodilation and a fall in blood pressure. However, heart rate is increased rather than reduced.

iii) Free nerve endings of unmyelinated vagal C fibres which are distributed throughout the heart and pericardium.These receptors especially those located in the ventricles are responsible for the Bezold-Jarisch reflex, the reflex bradycardia and hypotension seen after the injection of veratridine derivatives into the heart.

iv) Sympathetic afferent fibres have a role in myocardial ischeamia. They have an exicitatory action on sympathetic

efferent discharge, thus eliciting a tachycardia and increasing cardiac contractility.

4) LUNG STRETCH RECEPTORS:

The majority of afferent fibres running in the vagus arise from stretch receptors in the lung parenchyma, which are activated by pulmonary inflation (Hering-Bruer reflex). Lung inflation leads to reflex vasodilation in the skin, muscle and splanchic beds due to decrease in the sympathetic efferent activity.

5) Several interconnected structures located throughout the rostro-caudal brain axis have important role to play in cardiovascular regulation.

Cardio-inhibitory centre in the medulla is responsible for the tonic vagal discharge and the Nucleus of Tractus Solitarius projects directly to the intermediolateral cell column of the spinal cord.

CENTRAL NEUROTRANSMITTERS INVOLVED IN CARDIOVASCULAR REGULATION:[15]

1) Catecholamines – Adrenaline
Noradrenaline
2) Serotonin
3) GABA
4) Peptides: Angiotensin
Opioid peptides

Substance P
Neuropeptide Y
Vasopressin
Kinins
Corticotrophin releasing factor
Bombesin
Somatostatin

DIABETIC AUTONOMIC NEUROPATHY [16]

Diabetic autonomic neuropathy (DAN) can affect virtually all systems of the body. The DANMAN is an unhappy person whose symptoms are often nonspecific and vary from clinically unimportant (eg:pupillary abnormalities) to great disability (eg:Postural hypotension). DAN, a subtype of the peripheral polyneuropathies that accompany diabetes, can involve the entire autonomic nervous system. DAN is a serious and common complication of diabetes. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple systems and impairment, the significance of DAN has not been fully appreciated. DAN may be either clinically evident or subclinical. It is manifested by dysfunction of one or more organ systems (cardiovascular, gastrointestinal, genitourinary, ocular).[17]

Subclinical autonomic dysfunction can occur within a year of diagnosis in type 2 diabetics and within 2 years in type 1 diabetics.[18,19,20] Based even on asymptomatic subjects with abnormality only in

autonomic function tests, the overall mortality rate may be as high as 25% to 45% over 10 years [21]

CLASSIFICATION OF DIABETIC NEUROPATHY [1]

A) SYMMETRIC NEUROPATHIES

1) Distal symmetric sensorimotor polyneuropathy
2) Autonomic neuropathy
3) Acute painful neuropathy
4) Hyperglycemic neuropathy
5) Treatment-induced neuropathy
6) Symmetric proximal lower extremity neuropathy

B) FOCAL AND MULTIFOCAL NEUROPATHY

1) Cranial neuropathy
2) Thoracoabdominal neuropathy
3) Focal limb neuropathy
4) Diabetic amyotrophy

DIABETES AND HEART [22]

Diabetes involves heart in the following ways

1) Coronary artery disease
2) Small vessel disease
3) Diabetic cardiomyopathy
4) Heart failure

5) Cardiac autonomic neuropathy

NATURAL HISTORY OF CARDIAC AUTONOMIC NEUROPATHY[23]

Diabetes is a known disease of complications. Over 50% of either sex, above 65 years of age, die from disorders of the heart. Although cardiac autonomic neuropathy was first envisaged by Eichorst[24] way back in 1892 and more comprehensively dealt with by Rundles in 1945,[25] its impact in clinical cardiology was not generally appreciated until emphasized by Wheeler and Watkins[26] as well as by Ewing and co-workers[27] in 1973. Since then (1980 onwards), diabetes related cardiac disorders have been generally classified as due to

1) Premature and more extensive atherosclerotic coronary artery disease

2) Cardiomyopathy

3) Cardiac autonomic neuropathy

These play a role in modification of the clinical characters and the progress of the major manifestations of ischemic heart disease.

Autonomic damage in diabetics is not an ALL or NONE phenomenon and it is not well established in which order symptoms develop although postural hypotension and gastroparesis occur relatively late in the course of disease indicating poor prognosis. There is a great variation in the tendency of individuals to develop symptoms and it is striking that some patients who have severe abnormality of

autonomic function may have no symptoms. Observations are also made of the intermittent nature of features such as postural hypotension and diarrohea. Tests of autonomic function often remain normal during many years of diabetes mellitus and it is not uncommon for many long standing diabetics to remain free from autonomic symptoms. Gradual detoriation has been observed in some patients whose tests may decline from normal to abnormal in five years. A uniform sequence of cardiac autonomic damage occurs in diabetics, with early cardiac parasympathetic and later sympathetic involvement. It is possible to have cardiac parasympathetic damage without sympathetic damage but never the vice versa and once damage has occurred it does not reverse.

The high mortality of diabetics with established autonomic symptoms has been well described by Ewing et al (1980). In many of these patients, autonomic problems are associated with other diabetic complications .As many as 37% of the patients with diabetes mellitus suffer from at least one microvascular complication and atleast 13% have more than one. The occurrence of sudden and otherwise unexplained deaths amongst autonomic neuropathy patients have been described by the Edinburgh group, Ewing et al (1980) and Page and Watkins (1978).[28]

PATHOGENESIS OF NEUROPATHY [29,30,31]

Diabetic neuropathies have multifactorial mechanisms and varied clinical presentations. Length dependent symmetrical nerve damage, primarily affecting the small unmyelinated fibres of sensory and autonomic systems, is common in both type 1 and type2 diabetes (= 50% after 20 yrs of diabetes). The evolution of the vagal damage indicates that the autonomic neuropathies are also distal, symmetrical and length dependent. Moreover, autonomic neuropathy coincides with small-fibre somatosensory neuropathy.In autonomic neuropathy ,presence of small fibre involvement and absence of small vessel involvement are the hallmark. Unmyelinated C fibres are predominantly involved and the quantum of involvement is high probably indicating the irreversibility of autonomic dysfunction. Prevalence is similar to IDDM and NIDDM patients, suggesting that the metabolic consequences of hyperglycemia, rather than the type of diabetes lead to autonomic damage.

Microvascular complications in diabetes have traditionally included retinopathy, nephropathy, and neuropathy. In each of these complications, pathologic changes and cellular changes are seen in nonvascular tissues at early stages itself and cannot be explained by circulatory changes alone. Thus in retinopathy and neuropathy dysfunction of neurons develops in parallel with microvascular pathology.

Multiple abnormalities in diabetic states, including the activation of protein kinase C, enhanced oxidative stress, formation of advanced glycosylation end products in neuronal tissues and altered expression of neurotrophic factors such as nerve growth factor and IGF-1 all have been reported to be important determinants for the pathogenesis of diabetic neuropathy. [32,33] Vascular etiology in diabetic neuropathy is supported by multiple abnormalities in the microvasculature, including the deposition of AGE in the perineuronal vascular wall, basement membrane thickening, endothelial cell swelling and loss of pericytes, reduced endothelial nitric oxide activity and capillary occlusion and degeneration of blood vessels supplying neuronal tissues.[34]All the changes eventually contribute to hyperglycemia induced decrease in neurovascular blood flow and the subsequent hypoxia-ischemic damage.[35]

METABOLIC THEORY

i) POLYOL PATHWAY:

Hyperglycemia leads to excess intracellular accumulation of glucose. This excess glucose gets converted to sorbitol by enzyme aldose reductase. The accumulation of sorbitol has deleterious effects on nerve conduction velocity and also depletes the myoinositol content.Inhibition of aldose reductase has been shown to prevent experimental cataracts and retinopathy. It thus seems possible that

neuropathy and retinopathy are primarily due to activation of the polyol pathway.

ii) MYO-INOSITOL METABOLISM:

Hyperglycemia causes increased intracellular concentrations of glucose, resulting in increased activity of polyol pathway and inhibits myoinositol uptake. Decreased myoinositol results in abnormal phosphoinositide metabolism, decreased diacylglycerol release and therefore decreased protein kinase C activation leading to reduced Na^+ K^+ ATPase. This leads to increased intra axonal sodium accumulation in the paranodal regions, axonal swelling and axoglial dysjunction ie: separation of the terminations of the myelin lamellae from the axon and further structural changes. The reduction in electrogenic Na^+ K^+ ATPase, acutely reduces nerve conduction velocity. In addition, altered inositol phospholipid metabolism affects other membrane bound proteins and voltage dependent sodium channels.

iii) ADVANCED GLYCOSYLATION END PRODUCTS:

In the setting of prolonged hyperglycemia, nonenzymatic glycosylation of proteins occurs, which results in structural changes to the components of the extracellular matrix. These structural changes may lead to functional neural and vascular abnormalities. AGE also may quench nitric oxide, thereby attenuating endothelium mediated vasodilatation.

iv) PROTEINKINASE C ACTIVATION:

Hyperglycemia leads to increased synthesis of diacylglycerol, which leads to activation of protein kinase C .It may also be activated by oxidative stress and AGE products. Protein kinase C activation causes increased vascular permeability, impaired nitric oxide synthesis, and changes in blood flow. It may also contribute to reduced Na^+ K^+ ATPase activity.

v) OXIDATIVE STRESS[36]

It is well recognized that reactive oxygen species (ROS) may be important mediators of diabetes and its macro and microvascular complications. In fact, oxidative stress has been proposed as a unifying hypothesis linking various molecular disorders of type 2 DM. Recent studies implicate that hyperglycemia induced superoxide generation seems to be the key event in the activation of all other pathways in the pathogenesis of diabetic complications. These include increased polyol pathway flux, increased AGE products, activation of protein kinase C and NF_kB, and increased hexosamine pathway flux. DNA damage is an obligatory stimulus for the activation of the nuclear enzyme PARP, which in turn depletes intracellular NAD^+, thus slowing the rate of glycolysis, electron transport, ATP formation and produces ADP ribosylation of many proteins. These processes result in acute endothelial dysfunction in diabetic blood vessels that contributes to the development of diabetic complications.

vi) NEUROTROPHIC FACTORS:

Nerve growth factor (NGF), the prototypical growth factor, is necessary for the growth maintenance and survival of the sympathetic and small sensory nerve fibres. NGF also regulates the expression of the neuropeptides, substance P and calcium gene-related peptides in dorsal root ganglion sensory neurons and sympathetic nerves. There is evidence that failure of neurotrophic support is in part responsible for the pathogenesis of diabetic polyneuropathy.

VASCULAR THEORY:

Hypoxia, which occurs due to decreased endoneural blood flow is sufficient to produce nerve dysfunction. The normal vascular auto regulation is said to be lost. The decreased blood flow leads to endoneural hypoxia and also decreases the $Na^+ K^+$ ATPase. This reduces the nerve conduction velocity by decreasing axonal transport and leads on to axonal atrophy.

THOUGH VASCULAR AND METABOLIC HYPOTHESIS FOR THE PATHOGENESIS OF DIABETIC NEUROPATHY HAS BEEN POSTULATED, THE DIVISION IS ARTIFICIAL.MORE OFTEN THERE IS OVERLAY OF METABOLIC AND VASCULAR EVENTS.

PATHOLOGY[1]

The pathologic basis of diabetic autonomic neuropathy is not completely understood. A number of investigators have identified abnormalities in paravertebral sympathetic ganglia, including neurons distended by lipid rich material, vacuolar degeneration of neurons produced by dilation of endoplasmic reticulum, and mononuclear cell infiltration of autonomic nerve bundles and ganglia. Loss of myelinated nerve fibres has been described in sympathetic communicating rami, vagus nerves, splanchic nerves and nerves to the bladder wall.

CLINICAL PRESENTATION OF CARDIAC AUTONOMIC NEUROPATHY

CARDIAC DENERVATION

Cardiac dysautonomia refers to autonomic dysfunction of heart. It appears to be the most frequent complication of diabetes mellitus. There are two terms

1) Autonomic neuropathy

Refers to combined clinical and objective evidence of autonomic involvement

2) Autonomic dysfunction

Refers to abnormal cardiovascular tests in the absence of clinical symptoms.

Cardiac autonomic neuropathy occurs in about 17% of patients with type 1 DM and 22% of those with type 2 DM. An additional 9% of type 1 patients and 12% of type 2 patients have borderline dysfunction.[37] Using cardiovascular reflex tests, the prevalence is reported to be 17 % to 40%[38,39].The prevalence is associated with both duration [40] of diabetes and with age and is equal to or higher in type 2 than in type 1 DM.[41] Diabetic autonomic neuropathy is usually accompanied by peripheral neuropathic disturbances.[22] Estimates of the mortality associated with Cardiac autonomic neuropathy range from 27% to 56% over 5 to 10 years.[1]

Autonomic nerves provide the heart with very fine control mechanism, variations in parasympathetic (vagal) tone very rapidly alter heart rate on a beat to beat basis while stimulation of sympathetic tone has a more gradual cardioaccelerator effect. Both parasympathetic and sympathetic denervation occur in diabetics, parasympathetic impairment occurs first, followed by sympathetic denervation. Loss of heart rate variation both at rest and during deep breathing and loss of immediate heart rate acceleration and overshoot on standing are also result of vagal impairment and commonly occur in diabetic cardiac autonomic neuropathy.

Sympathetic denervation occurs later in the disease and always follows vagal damage. Complete sympathetic denervation is rare, but occasionally the heart is totally denervated of its parasympathetic and sympathetic nerve supply.[42]

Ewing et al found that 40 % of all diabetics have some impairment of cardiac autonomic neuropathy. Mackay et al found that 7 % of diabetics without peripheral neuropathy and 80 % of those with peripheral neuropathy have autonomic dysfunction. For unknown reason the incidence is said to be much higher in non-caucasians (70-80%).

The onset of symptoms is usually insidious with no typical pattern in the early stages. Autonomic damage may be asymptomatic and thus be detected incidentally, even if asymptomatic they are mostly unnoticed due to the vagueness of early symptoms. The autonomic nervous system, through the sympathetic and parasympathetic pathways, supplies and influences every organ in the body. It closely integrates vital processes such as heart rate, blood pressure, myocardial contractility and body temperature and as a consequence plays a pivotal role in the regulation of the cardiovascular system. Cardiac autonomic neuropathy (CAN) represents a serious complication.

The features of cardiac autonomic neuropathy include

1) RESTING TACHYCARDIA

2) EXERCISE INTOLERANCE

3) POSTURAL HYPOTENSION

4) FIXED HEART RATE

5) PAINLESS (OR) SILENT MYOCARDIAL INFARCTION

Although insidious in onset, autonomic neuropathy may be associated with substantial morbidity. CAN is associated with a high risk of unexpected and sudden death. There is increased susceptibility to fatal ventricular arrythmias. Any diabetic with CAN is at a considerable anaesthetic risk.

EXERCISE INTOLERANCE:

Exercise intolerance is due to impaired sympathetic and parasympathetic responses that normally augment cardiac output and redirect peripheral blood flow to skeletal muscles. Diminished cardiac acceleration may also play a role.

RESTING TACHYCARDIA:

It is an early sign. There are several reports of resting heart rate in excess of 95 bpm in diabetics with autonomic damage and sometimes more rapid rates upto 130 bpm. The tachycardia may be followed by a decrease in heart rate and ultimately, a fixed heart rate due to the progressive dysfunction of the cardiac sympathetic nervous system.

POSTURAL HYPOTENSION:

The most incapacitating manifestation of autonomic failure, is a common feature of diabetic cardiovascular neuropathy. It is a fall in systolic blood pressure of more than 30 mmHg upon standing from supine position.

In 1945,RUNDLES[43] first linked postural hypotension with autonomic neuropathy in diabetes. Maintenance of BP on standing depends on afferent impulses from baroreceptors in the carotid sinus and on efferent sympathetic impulses to the heart and blood vessels. In normal people there is a 20% fall in cardiac output on standing, (about 700 cc of blood). Compensatory mechanisms prevent a fall in BP. If one or more of the pathways in this system are impaired, postural hypotension occurs. Postural hypotension is an essential complication of diabetic autonomic neuropathy (MARTIN 1953) and is chiefly due to efferent sympathetic vasomotor denervation (MOORHOUSE et al 1966, BENNETT et al 1975). It occurs in patients with advanced neuropathy as a sympathetic defect is usually a late feature.

Failure of cardiac acceleration and reduced cardiac output both contribute to the problem. Noradrenaline levels are generally reduced in diabetics with postural hypotension. Insulin is known to have its own effects.[44] It causes a reduction in plasma volume, an increase of peripheral blood flow from vasodilation and an increase in heart rate. In

patients with autonomic neuropathy, insulin may cause an exacerbation of postural hypotension.

Though many patients may be asympotamatic inspite of significant postural hypotension, typically patients complain of light headedness, weakness, visual changes and palpitations. These symptoms can be mistaken for hypoglycemia. Both hypotension and it symptoms fluctuate spontaneously to a remarkable degree and may persist for many years without necessarily deteriating.[45]

FIXED HEART RATE:

Heart rate show less diurnal variation with increasing autonomic damage. The loss of the normal cardiac slowing at night results from vagal damage. With severe damage there is loss of minute to minute and second to second variation in heart rate, resulting in relatively fixed heart rate.

PAINLESS (OR) SILENT MYOCARDIAL INFARCTION:

Autonomic neuropathy reduces the perception of cardiac ischaemic pain. Diabetic patients admitted to hospital with myocardial infarction have been reported to suffer from less intense pain than nondiabetic patients. Margolis et al reviewed the ECG of all patients in Framingham heart study and found that 23% of myocardial infarction were silent.

ASSESSMENT OF CARDIOVASCULAR AUTONOMIC DYSFUNCTION [11,41,46,47- 51]

Objective measurement of autonomic nerve damage is based on parasympathetic and sympathetic cardiovascular reflexes. The abnormalities in cardiovascular reflexes is assumed to reflect autonomic damage elsewhere and the evidence suggests that it does. This is aided by screening tests, although indirect, are widely used because they are simple, non- invasive, reproducible and give a clear distinction between normal and abnormal. Symptoms such as lack of sweating on the feet and impotence may antedate abnormal cardiovascular tests.

TESTS FOR PARASYMPATHETIC FUNCTION

1) HEART RATE RESPONSE TO DEEP BREATHING
2) HEART RATE RESPONSE TO STANDING
3) HEART RATE RESPONSE TO VALSALVA MANOEUVRE

TESTS FOR SYMPATHETIC FUNCTION

1) BLOOD PRESSURE RESPONSE TO STANDING

2) BLOOD PRESSURE RESPONSE TO SUSTAINED HAND GRIP

HEART RATE RESPONSE TO DEEP BREATHING:

This test is a sensitive and specific index of autonomic function. It is the best noninvasive test to assess cardiac vagal innervation. The normal acceleration and deceleration of the heart rate during normal respiration (sinus arrthymia) is reduced early in the course due to cardiac vagal involvement.Sinus arrthymia is very commonly absent in diabetics with autonomic neuropathy, and is the most easy bedside test.

The patient breathes deeply and evenly at the rate of six breaths per minute ie: five seconds each for inspiration and five seconds for expiration, a rate, which produces maximum variation in heart rate.

The heart rate is measured by an instantaneous heart rate monitor or more simply from an ECG.RESULT: Maximum and minimum heart rates during each breathing cycles are measured and the mean of the differences during three successive cycles taken to give the maximum – minimum heart rate expressed as E/I ratio.

HEART RATE RESPONSE TO STANDING:

This test evaluates the cardiovascular response elicited by a change from a horizontal to vertical position. The subject is asked to stand abruptly from a supine position once the BP and HR are stable after atleast a 10-min period of quite supine rest. In healthy subjects, there is a characteristic and rapid increase in heart rate in response to standing that is maximal at approximately the 15^{th} beat after standing and followed by slowing, maximal after the 30^{th} beat. This is expressed as the 30:15 ratio, the ratio of the longest R-R interval around the 30^{th} beat to the shortest around the 15^{th} beat.

In patients with diabetic autonomic neuropathy, there is only a gradual increase in heart rate. The changes in heart rate are largely due to the withdrawal of parasympathetic drive.

HEART RATE RESPONSE TO VALSALVA MANOEUVRE:

In the standard valsalva manoeuvre, the patient exhales into a manometer or against a closed glottis for 10 to 15 sec, creating a markedly positive intrathoracic pressure.

The response to performance of the valsalva manoeuvre has four phases and in healthy individuals can be observed as follows. The phases of valsalva manoeuvre were defined by (Hamilton et al., 1936)

PHASE 1: Transient rise in blood pressure and a fall in heart rate due to compression of the aorta and propulsion of the blood into the peripheral circulation.

PHASE 2: Early fall in blood pressure with a subsequent recovery of blood pressure later in the phase. The blood pressure changes are accompanied by an reflex 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 3: Abrupt, transient decrease in blood pressure and rise of heart rate with cessation of straining.

PHASE 4: Blood pressure increases above the baseline value (overshoot) because of residual vasoconstriction and restored normal venous return and cardiac output and reflex bradycardia is seen.

The responses are mediated through alternating activation of parasympathetic and sympathetic nerve fibres. In patients with autonomic damage from diabetes, the reflex pathways are damaged. This is seen as a blunted heart rate response and sometimes as a lower than normal decline in blood pressure during strain, followed by a slow recovery after release.

The Valsalva ratio is determined from the ECG tracings by calculating the ratio of the longest R – R interval after the manoeuvre to the shortest R-R interval during the manoeuvre. The ratio is usually expressed as the mean ratio of three successive tests.

SYSTOLIC BLOOD PRESSURE RESPONSE TO STANDING:

The most frequently performed cardiovascular test for assessing sympathetic function is the blood pressure response to postural change. Blood pressure normally changes only slightly on standing from a supine position. In healthy subjects, there is an immediate pooling of blood in the dependent circulation resulting in a fall in blood pressure that is rapidly corrected by baroreflex mediated peripheral vasoconstriction and tachycardia. In normal individuals, the systolic blood pressure falls by $\leq$ 10 mmHg in 30 sec. In diabetic patients with autonomic neuropathy, baroreflex compensation is impaired. Several recordings of BP and HR responses within first 5 minutes (usually within the first 2 minute) are sufficient to detect orthostatic hypotension and whether the heart rate response is normal. Recently , the Consensus Committee of the American Autonomic Society and the American Academy of Neurology (1996) has defined orthostatic hypotension as fall in systolic BP of $\geq$ 20 mmHg or diastolic BP of $\geq$ 10 mmHg within 3 minutes of standing.

DIASTOLIC BLOOD PRESSURE RESPONSE TO SUSTAINED HANDGRIP:

Sustained (isometric) muscle contraction as measured by a handgrip dynamometer causes a rise in systolic and diastolic blood pressure and heart rate. The efferent fibres innervate the heart and muscle, resulting in increased cardiac output, blood pressure and heart rate. Blood pressure is measured with 30% of maximum voluntary contraction using a hand grip dynamometer for 5 minutes. The normal response is a rise of diastolic blood pressure of > 16mmHg, whereas a response of < 10mmHg is considered abnormal. Patients with DAN are more likely to exhibit only a small increase in diastolic blood pressure.

Values in tests of cardiovascular autonomic function

TESTS REFLECTING PARASYMPATHETIC FUNCTION	**Normal**	**Borderline**	**Abnormal**
Heart rate variation during deep breathing (E/I) ratio	> 1.1	-	≤ 1.1
Heart rate response to standing (30:15) ratio	≥ 1.04	1.01- 1.03	≤ 1.00
Heart rate response to valsalva manoeuvre	≥ 1.21	1.11- 1.20	≤ 1.10
TESTS REFLECTING SYMPATHETIC FUNCTION			
Blood pressure response to standing	≤ 10 mmHg	11-29 mmHg	≥ 30 mmHg
Blood pressure response to sustained hand grip	≥ 16mmHg	11-15 mmHg	≤ 10 mmHg

The classification of the tests as parasympathetic or sympathetic, though useful, is not physiologically precise because the cardiovascular reflexes are complex and involve both sympathetic and parasympathetic fibres to a great or lesser extent. Therefore, the tests are better defined as normal, early, definite and severe.

EWINGS AND CLARKES Classification according to severity:

1) Normal – All five tests are normal or one borderline.

2) Early involvement- One of the three heart rate tests are abnormal or two borderline

3) Definite involvement – Two or more of the heart rate tests are abnormal

4) Severe involvement – Two or more of the heart rate tests are abnormal plus one or both blood pressure tests abnormal, or both borderline

5) Atypical pattern – Any other combination of abnormal tests. In Ewings experience only about 6% of the patients tested were atypical.

An alternative to this classification is to give each individual a score of 0, 1 or 2 depending on whether they are respectively normal,

borderline or abnormal. An overall autonomic test score of 0-10 can then be used.

NORMAL: 0 and 1

EARLY: 2, 3 and 4

DEFINITE: 4, 5, 6 and 7

SEVERE: 7, 8, 9 and 10

Lloyd-Mostyn and Watkins [42] found that cardiac parasympathetic function could be impaired but not the reverse, while Wieling et al[52] concluded that sympathetic lesions occurred only in diabetics with longstanding disease with extensive cardiac vagal damage.

The early parasympathetic involvement may be more apparent than real because heart rate based tests are much more sensitive than BP based tests. However the detailed physiological studies show unequivocally that parasympathetic fibres are damaged earlier than sympathetic fibres possibily because they are longer and therefore more liable to damage, as also suggested by computer stimulated models of random nerve damage in which longer fibres were affected first.

MANAGEMENT

MANAGEMENT OF PATHOGENIC MECHANISMS:

STRICT GLYCEMIC CONTROL:

Management of diabetic neuropathy begins with the treatment of hyperglycemia. Strict glycemic control has shown to decrease the risk of developing neuropathy and to slow the progression of established

neuropathy. The Diabetes Control and Complications Trial (DCCT) in 1993 unquestionably established the necessity of meticulous control of hyperglycemia.

TREATMENT OF METABOLIC ABNORMALITIES:

ALDOSE REDUCTASE INHIBITORS

Aldose reductase inhibitors reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol and fructose and preventing reduction of redox potentials.

Alrestatin

Sorbinil

Tolrestat

Zenarestat

Trials with these class of agents are still in progress.

MYOINOSITOL:

There are several studies suggesting that myoinositol supplements in the diet improves neuropathy, but the treatment may have to be prolonged for atleast six months for significant results to be achieved.

TRENDS FOR THE FUTURE

INHIBITORS OF GLYCATION

AMINOGUANIDINE – an inhibitor of non-enzymatic glycation is under trial. They have shown some beneficial effects. Its precise mechanism of action remains obscure.

GAMMA LINOLEIC ACID

Linoleic acid, an essential fatty acid is metabolized to gamma linolenic acid, which serves as an important constituent of neuronal membrane phospholipids, and also serves as a substrate for prostaglandin E formation which is vital for preserving nerve blood flow.

ALPHA LIPOIC ACID

The effects of the alpha lipoic acid were studied. This is a derivative of octanoic acid and is shown to be effective in ameliorating both somatic and autonomic neuropathy in diabetes.

NEUROTROPHINS

NGF is the most widely studied neurotrophin. Nerve growth factor binds to high and low affinity nerve growth factor receptors present on small, unmyelinated fibres of the sensory neurons of the peripheral nervous system, on sympathetic neurons in the autonomic nervous system, and in the regions of the central nervous system. This

therapy is under trial and is directed towards regeneration of the damaged nerves.

PROTEIN KINASE C INHIBITION

Trials are currently under progress using specific protein kinase c inhibitor ROBOXISTAURIN. This has found to reduce the symptoms and signs of peripheral neuropathy.

MANAGEMENT AIMED AT SYMPTOMS

CARDIOVASCULAR[53]

The resting tachycardia and heart rate variation do not require treatment.

Postural hypotension can be managed as follows:

1) Stop any drugs which may exacerbate hypotension eg: hypotensive agents, diuretics, tricyclic antidepressants and nitrates.

2) Postural changes of blood pressure on getting up in the morning can be prevented by sleeping in as nearly vertical position as possible.

3) Antigravity suits as worn by astronauts can completely cure postural hypotension but are hardly practical.

4) Full length elastic stockings which must come up to and preferably above the waist may be effective.

5) DRUGS :

a) 9-alpha-fluorohydrocortisone (fludrocortisone) a potent mineralocorticoid promotes renal sodium reabsorption and increases sensitivity of arterioles to norepinephrine. Dose 0.1 mg once or twice per day

b) Midodrine is an alpha 1 agonist, started at a dose of 2.5 mg per day and increased to 30 mg per day in 2 to 3 divided doses.

c) Other sympathomimetics such as ephedrine, pseudoephedrine, phenylephrine, phenylpropan-olamine have been used.

NUTRITIONAL SUPPLEMENTS

ANTIOXIDANTS

Antioxidants play a pivotal role in preventing the progression of diabetic neuropathy. Their role in autonomic neuropathy is validated through many trials; eg. Ziegler et al proved the efficacy of antioxidants in CAN. The following agents are recommended.

Vitamin A

Vitamin C

Vitamin E

Selenium

N Acetyl cysteine

Gingko Biloba Extract

OTHERS

Chromium, Biotin, Niacin, Inositol, Taurine, Magnesium have also been tried and is recommended for prevention of DAN.

MATERIALS AND METHODS

Cardiac Autonomic Neuropathy System Analyser model CANS 504 is an important tool to measure and diagnose Autonomic dysfunction using ECG R-R interval and automatic BP measurement with various manoeuvre.

FEATURES:

1. Analyses both sympathetic and parasympathetic autonomic function
2. Simple test procedures
3. Upgradable to future development
4. Two page comprehensive report for easy interpretation
5. Accurate and repeatable values

CONTROLS:

ECG INPUT:

A 3 lead ECG patient cable is connected to this connector. The colour coding of the patient with lead details are indicated on the respective leads. Plug the cable and tighten the screws provided in the plug.

QRS: A red LED blinks for every QRS detected.

BP CUFF:

An automatic BP measurement cuff is to be connected to the unit for measuring the BP. The cuff has to be connected correctly to the patient. The arrow mark on the cuff should be placed on or near the brachial artery of the patient.

VALSALVA:

This control is used for detecting the ECG response due to valsalva manoeuvre. A pressure sensor is used by the unit to detect the blowing pressure of the patient. The patient is asked to blow through the mouthpiece of the control and as he /she blows the pressure, value in mmHg is varied and displayed on the computer. The patient has to blow and maintain 40mmHg of pressure for 20 sec. If the patient goes less than the prescribed value the test is terminated automatically. Again the patient is asked to perform the test without going below the value. However we cannot expect every patient to blow and hold the value for 20 sec. A begin and end mark is displayed during the one minute ECG performed.

HAND GRIP:

This spring loaded accessory is used for finding out the sustained handgrip function. The patient is asked to apply the maximum grip and the system measures it and finds the 30% of the maximum grip of the patient. Then the patient has to hold the grip for the 30% value indicated for 5 minutes before the BP measurement is enabled.

MATERIALS:

STUDY GROUP:

We undertook the study in a randomly selected 40 Type 2 diabetic patients attending the out patient department of Ambedkar Institute of Diabetology, KMC, Chennai.

Period of Study: April 2007 - August 2007.

These subjects were selected after scrutinizing them for exclusion criteria.

METHODS:

All patients were subjected for thorough physical examination. Blood samples were drawn and subjected to estimation of plasma glucose and renal function tests.

EXCLUSION CRITERIA:

1. Symptomatic coronary artery disease.
2. Drug intake including antidepressants, antihistaminics, diuretics, aspirin, anticholinergics, β agonists and β blocker.
3. End organ failure.
4. Other concomitant diseases.
5. Exercise, smoking and caffeine intake.
6. Chronic obstructive pulmonary disease.
7. Treatment for Parkinsonism.
8. Hypothyrodism.

Autonomic dysfunction was assessed using following parameters

TESTS FOR PARASYMPATHETIC FUNCTION

1) Heart rate response to deep breathing

2) Heart rate response to standing

3) Heart rate response to valsalva manoeuvre

TESTS FOR SYMPATHETIC FUNCTION:

1) Systolic blood pressure response to standing

2) Diastolic blood pressure response to sustained handgrip

After connecting all the accessories to the unit, prepare the patient. The patient is explained of all the procedures in detail .After instructing the patient, attach the ECG electrodes. The patient should not touch the metal part. Ensure proper earth before starting the test.

HEART RATE RESPONSE TO DEEP BREATHING:

Select the resting ECG option. The ECG waveform will be displayed on the screen and continue to run for a minute. After finishing resting ECG select deep breathing test. The patient has to inhale strongly for 5 seconds and exhale for 5 seconds. This test is done for a minute and during this time the patient would have done 6 cycles of breathing. Patient should be in supine position.

HEART RATE RESPONSE TO STANDING:

The patient after a rest of 4 to 5 minutes, one minute supine ECG is taken. Then the patient is asked to stand unaided on a nonconducting plastic floor mat and the ECG is recorded in the standing position.

HEART RATE RESPONSE TO VALSALVA MANOEUVRE:

The patient should be in supine position. Ask the patient to hold the valsalva probe tightly and keep the mouthpiece in the mouth tightly. The patient should blow hard and the value will increase. Normally the

value will be indicated as green colour and when they reach 40 mmHg or more it turns into green in colour. Once they reach the range they should not reduce the blow since the test will be terminated immediately after the pressure is less than 40 mmHg. The patient should blow and maintain this value for 20 sec.

SYSTOLIC BLOOD PRESSURE RESPONSE TO STANDING:

Select BP SUPINE, automatically the BP cuff is inflated to measure the systolic and diastolic BP. Then the patient is asked to stand immediately. Select BP STANDING for measuring the BP. This procedure takes about 40 sec. BP is taken automatically 60 sec after the first BP measurement.

DIASTOLIC BLOOD PRESSURE RESPONSE TO SUSTAINED HANDGRIP:

Ask the patient to get the maximum grip from the grip meter and the value is displayed on the system. After getting the maximum grip it detects the 30% of the grip value and it is displayed. The patient has to hold this 30% value for 5 minutes continuously and at the end of 5 minutes, BP after grip is applied and BP value is taken.

The values for various tests are interpreted and print out of the waveforms is taken.

DETECTION OF PERIPHERAL NEUROPATHY:

10 g monofilament was used to check the presence or absence of sensation in the foot. Vibration perception threshold (VPT) was checked in the foot using a biothesiometer (6 sites were examined –great toe, 1st, 3rd, 5th metatarsal heads, instep, heel).

Peripheral neuropathy if present was graded as mild, moderate and severe. (VPT 11-15 V mild, 16 – 25 V moderate, > 25 V severe)

DETECTION OF NEPHROPATHY:

History of diabetic nephropathy was taken. Early morning urine sample was analysed for albumin using dip stick method. Two samples were analysed. Urine for microscopic examination was done to exclude active urinary sediments. Patients having urine albumin positive for 2 sample using dipstick method, were considered to have diabetic nephropathy.

DETECTION OF RETINOPATHY:

Ocular fundus was examined by ophthalmologist after proper dilatation of the pupil using mydriatic. Direct opthalmoscopy method was used. Levels of diabetic retinopathy were noted.

Statistical Analysis

The statistical methods used for analysis were

1. Two sample `t' test
2. Chi-Square test
3. Fisher exact 2 tailed test.

RESULTS AND ANALYSIS

Total No of subjects included in the study = 40

Males = 25 (62%)

Females = 15 (38%)

Mean age of individuals studied = 46.8 yrs

DURATION OF TYPE 2 DM	MALE	FEMALE	TOTAL
0 -5 YRS	21	9	30
6 -10 YRS	3	4	7
> 10 YRS	1	2	3
	25	15	40

Mean duration of diabetes = 6.03 yrs

No of cases of diabetes less than 5 yrs = 30

Males = 21

Females = 9

No of cases of diabetes between 6 to 10 yrs = 7

Males = 3

Females = 4

No of cases of diabetes greater than 10 yrs = 3

Males = 1

Females = 2

12 out of the 40 cases (30%) had postural giddiness.

8 out of the 40 patients were found to be smokers.

5 out of the 40 patients were found to be alcoholics.

Resting tachycardia of 100/mt and above were seen in 5 out of the 40 patients (12%).

Cardiac Autonomic Function Tests were found to be

Normal = 14 (35%) Total = 40

Early = 12 (30%) Normal = 14

Definite = 6 (15%) Abnormal = 26

Severe = 4 (10%)

Atypical = 4 (10%)

Heart Rate Variability to Deep Breathing(E/I Ratio)

E/I RATIO	NORMAL FOR AUTONOMIC FUNCTION TESTS	ABNORMAL FOR AUTONOMIC FUNCTION TESTS	TOTAL
NORMAL	14	11	25
ABNORMAL	0	15	15
	14	26	40

P = 0.000325 SIGNIFICANT

Out of the 26 patients with abnormal cardiac autonomic function tests, 15 patients were found to have abnormal E/I ratio i.e 57%. P value is significant (P = 0.000325).

Heart Rate Response to Standing (30/15 Ratio)

30/15 RATIO	NORMAL FOR AUTONOMIC FUNCTION TESTS	ABNORMAL FOR AUTONOMIC FUNCTION TESTS	TOTAL
NORMAL	14	11	25
ABNORMAL	0	15	15
	14	26	40

P = 0.000325 SIGNIFICANT

Out of the 26 patients with abnormal cardiac autonomic function tests, 15 patients were found to have abnormal 30/15 ratio i.e 57%. P value is significant (P = 0.000325).

Valsalva Ratio

VALSALVA RATIO	NORMAL FOR AUTONOMIC FUNCTION TESTS	ABNORMAL FOR AUTONOMIC FUNCTION TESTS	TOTAL
NORMAL	14	20	34
ABNORMAL	0	6	6
	14	26	40

P = 0.051225 NON SIGNIFICANT

Out of the 26 patients with abnormal cardiac autonomic function tests, 6 patients were found to have abnormal valsalva ratio i.e 26%.

P value is non significant (P = 0.051225).

Fall in Systolic BP

FALL IN SYSTOLIC BP	NORMAL FOR AUTONOMIC FUNCTION TESTS	ABNORMAL FOR AUTONOMIC FUNCTION TESTS	TOTAL
NORMAL	14	24	38
ABNORMAL	0	2	2
	14	26	40

P = 0.53333 NON SIGNIFICANT

Out of the 26 patients with abnormal cardiac autonomic function test, only 2 patients had fall in systolic BP. P value is non significant (P = 0.53333).

Increase in Diastolic BP with hand grip

INCREASE IN DIASTOLIC BP	NORMAL FOR AUTONOMIC FUNCTION TESTS	ABNORMAL FOR AUTONOMIC FUNCTION TESTS	TOTAL
NORMAL	14	23	37
ABNORMAL	0	3	3
	14	26	40

P = 0.30000 NON SIGNIFICANT

Out of the 26 patients with abnormal cardiac autonomic function tests, only 3 patients had increase in diastolic BP with hand grip.

P value is non significant (P = 0.3000).

Other Microvascular complications

Peripheral Neuropathy

PERIPHERAL NEUROPATHY	NORMAL FOR AUTONOMIC FUNCTION TESTS	ABNORMAL FOR AUTONOMIC FUNCTION TESTS	TOTAL
YES	1	21	22
NO	13	5	18
	14	26	40

P = 0.000008 SIGNIFICANT

Total No of Cases with Peripheral Neuropathy = 22

Mild = 11

Moderate = 11

Abnormal cardiac autonomic neuropathy is seen in 21 of these patients with Peripheral Neuropathy and 1 patient had no cardiac autonomic dysfunction.

5 patients with CAN did not have peripheral neuropathy. Significant correlation was found between CAN and peripheral neuropathy with P value of 0.000008.

Retinopathy

RETINOPATHY	NORMAL FOR AUTONOMIC FUNCTION TESTS	ABNORMAL FOR AUTONOMIC FUNCTION TESTS	TOTAL
YES	1	9	10
NO	13	17	30
	14	26	40

P = 0.1157 NON SIGNIFICANT

Total No of Cases with fundus abnormality = 10

Out of the 10 patients, 9 patients had abnormal CAN and 1 patient had normal cardiac autonomic function. Out of the 26 patients with abnormal CAN only 9 patients had fundus involvement. Their correlation was statistically non significant with P = 0.1157.

Nephropathy

NEPHROPATHY	NORMAL FOR AUTONOMIC FUNCTION TESTS	ABNORMAL FOR AUTONOMIC FUNCTION TESTS	TOTAL
YES	1	10	11
NO	13	16	29
	14	26	40

P = O.O613 NON SIGNIFICANT

Total No of cases with nephropathy = 11

Out of the 11 patients, 10 patients had abnormal CAN and 1 patient had normal cardiac autonomic function. Out of the 26 patients with abnormal CAN only 10 patients had abnormal kidney function.

Others are found to be normal. Their correlation was statistically non significant with P = 0.0613.

Correlation between Microvascular Complications

1. Peripheral Neuropathy, Retinopathy, Nephropathy were associated with CAN in 3 patients.

2. Two microvascular complications (either of the 3) were found associated with CAN in 10 patients.

3. At least one microvascular complication was found to be associated with CAN in 9 patients.

4. 3 patients with CAN had no other microvascular complications.

DISCUSSION

Cardiac Autonomic Neuropathy is a easily detectable dysfunction among other involved systems of the body.

Symptoms attributable to CAN was obtained in about 12 patients (30%). It was mainly postural giddiness. Rundles (1945)[43] study showed a prevalence of 6% and Balachander & Chandrasekar study (1984)[54] showed a prevalence of 46%. Present study showed a prevalence of about 30%.

Cardiac Autonomic Function Tests

The results of autonomic function tests in this study are compared to that by EWING & CLARKE (1985)[55] as follows

Category	EWING & CLARKE	Present Study
Normal	39%	25%
Early	15%	30%
Definite	18%	15%
Severe	22%	10%
Atypical	6%	10%

However the study by Ewing & Clarke was on a Caucasian population of 543 diabetics in contrast to this study on south Indian population of 40 Type 2 diabetics. So the variations observed may be due to either a small sample size or the Non-caucasian population which has been studied.

Correlation between CAN and

1. Duration of DM

In the present study, it was found that with increasing duration of DM, the incidence of autonomic dysfunction increases.

CAN	NO	MEAN OF DURATION OF DM	95% CONFIDENCE INTERVAL	
			LCL OF MEAN	UCL OF MEAN
NORMAL FOR AUTONOMIC FUCNTION TEST	14	1.75	1.286569	2.21343
ABNORMAL FOR AUTONOMIC FUCNTION TEST	26	6.038462	4.330617	7.746306

It is found that as the duration of diabetes increases over 6 yrs, they are more prone to develop CAN. The Diabetes Control and Complications Trial(DCCT)[46] found that 1.6% of patients with a 5 years history of diabetes had lack of heart rate variability during deep breathing. The rate rose to 6.2% of those with a 5 years to 9 years history of diabetes and to 12% in those who had the disease for more than 9 years.

2. AGE OF THE PATIENT:

CAN	NO	MEAN OF AGE	95% CONFIDENCE INTERVAL	
			LCL OF MEAN	UCL OF MEAN
NORMAL FOR AUTONOMIC FUNCTION TEST	14	39.35714	34.41823	44.29605
ABNORMAL FOR AUTONOMIC FUNCTION TEST	26	50.88462	47.04034	54.72889

P = 0.000539 SIGNIFICANT

A significant correlation was seen between the increasing age of the patient and development of cardiac autonomic neuropathy.

3. Obesity

We found no significant difference in the BMI/WHR among those patients with normal autonomic function tests compared to abnormal autonomic function tests. P value is found to be non significant.

CAN	NO	MEAN OF BMI	S.D	S.E
NORMAL FOR AUTONOMIC FUNCTION TEST	14	23.85	4.071	1.088
ABNORMAL FOR AUTONOMIC FUNCTION TEST	26	25.75	4.581	0.898

P = 0.201642 NON SIGNIFICANT

4. Metabolic Control of DM

The correlation between metabolic control and autonomic dysfunction was not studied since with a single value of FBS & PPBS done at the time of examination, the metabolic control of the patient could not be assessed correctly. Metabolic control is also influenced by many factors.

5. Resting Tachycardia

Increased heart rate of 90 to 100 beats per minute have been seen in diabetic patients with autonomic neuropathy and sometimes more rapid rates of up to 130/mt occur (Clarke et al - 1982)[56]. Ewing et al – 1981,[57] found that those with no detectable autonomic damage had slower heart rates and those with cardiac parasympathetic damage had faster rates and those with additional sympathetic damage had slightly slower rates.

In this study, resting tachycardia (heart rate > 90/mt) was observed in 8 out of 40 patients (20%). Watkins PJ et al[58] in their study involving 13 diabetics, observed resting tachycardia in 3 of them (23%).

The cut-off value for the resting tachycardia differs in various studies. Page and Watkins reported resting tachycardia in 100% of the subjects studied in their studied when heart rate > 82/mt was taken as

abnormal. Applying that criteria in this study 17 patients (42.5%) of diabetics had resting tachycardia.

The clinical utility of the knowledge that resting heart rate is often higher in diabetics due to parasympathetic damage is that such patients need to be studied in great detail for CAN since they are prone to develop sudden unexpected cardiac arrest more so during procedures like anaesthesia. Mangoni AA, Microti L,[59] showed that resting tachycardia decreases the distensibility of the vascular wall and increases the risk of atherosclerosis, all favouring coronary artery disease.

6. Heart Rate Variability to Deep breathing was abnormal in 37% of study subjects. Decreased HRV is considered the earliest indication of CAN and its often the most frequent finding in symptomatic CAN. The demonstration of the loss of HRV during deep breathing indicates the presence of vagal denervation of the heart and is also associated with increased rate of progression of coronary atherosclerosis. Decreased vagal activity limits exercise tolerance making these individual prone to syncope and predisposition to sudden cardiac death.

7. Abnormal heart rate tests were more often found than the BP tests, which is in concordance with the findings of Watkin's, Ewing and others who postulated that parasympathetic fibers were involved earlier

than sympathetic fibres. They were found to have significant P value correlation with CAN.

Abnormal BP response to standing was found only in 2 (5%) patients & abnormal heart rate on standing in 15(37%) of patients. In contrast, according to study conducted by R.C. Gupta M.D, Chittora et al (1995),[60] these tests were abnormal in 64%, 56% of patients respectively.

The most common abnormal tests in the present study was heart rate response to deep breathing and heart rate response to standing, 37% each. According to Bergstorm, Sundkuist, et al 1990, the most frequent disturbance was an impaired heart rate on deep breathing(E/I ratio) 72% & there was no correlation between autonomic neuropathy & duration of diabetes, peripheral neuropathy or retinopathy. But the present study has showed a significant correlation beween CAN & duration of diabetes and with peripheral neuropathy with P values of 0.000611and P value of 0.000008 respectively. In our study no significant statistical correlation was found between CAN and retinopathy & nephropathy. Probably this might be due to different sample size of the population used in their study and different modes used to detect them.

8. Peripheral Neuropathy

An increased incidence of autonomic dysfunction has been observed in patients with evidence of peripheral neuropathy (80%). This

is in agreement with the findings of other workers like Bhatia,[61] Tandon[62] etc.

9. Diabetic Retinopathy

The propensity to develop Diabetic Retinopathy is lower in south India compared to other population. This may be due to the facts that Indians develop type 2 DM at an earlier age than the western population, hence more resistance to the development of the Retinopathy at a younger age and also the type of diet in south India which includes much vegetables, less fat and perhaps antioxidants and anti-inflammatory agents like curcummin. Diabetic Retinopathy may be present even at the time of diagnosis of type 2 DM due to the insidious onset of the disease. Virtually all studies carried out in different parts of India have shown an increased prevalence of Diabetic Retinopathy as the duration of diabetes increased.[63,64,65] Dandona et al[63] reported that 87.5% of those with > 15 yrs duration of diabetes had Diabetic Retinopathy compared with 18.9% of those who had < 15 yrs duration. It has been demonstrated by the CURES eye study that severity of retinopathy proportionally increased with longer duration of diabetes and that for every five year increase in duration of diabetes the risk for Diabetic Retinopathy increased by 1.89 times. In our study the fundus abnormality has been found in only 10 patients probably this might be

due to the sample size and different tests used for the detection of retinopathy.

10. Diabetic Nephropathy

In type 2 DM, renal disease is often well-established at diagnosis of diabetes and the progression to end stage renal disease occurs faster. Persistent microalbuminuria is the earliest sign of diabetic kidney disease. It has also been found to be an independent predictor of cardio vascular morbidity and mortality[66]. Mohan et al,[67,68] in his study in a diabetic centre in South India, observed a prevalence rate of 36.3% microalbuminuria among type 2 diabetic patients. In our study microalbuminuria was found in 11 patients (27.5%) which is in concordance with the study mentioned above.

11. In UKPDS[69] study group it has been found that as many as 37% of patients with DM suffer atleast 1 micro vascular complication and atleast 13% have more than. In our study it has been found in 28 patients(70%).

12. In a study of 3010 diabetics by Ramachandran A[70], the prevalence of microvascular complications were Retinopathy – 23.7%, Nephropathy – 5.5%,Neuropathy – 27.5%.In our study the prevalence of Retinopathy – 25%, Nephropathy – 27% and Neuropathy – 55%.

CONCLUSION

1. The determination of incidence and prevalence of autonomic nervous system involvement in DM using non-invasive simple tests is quite feasible and should be done in all diabetics registering in diabetic clinics to study the natural history of diabetic autonomic neuropathy.

2. These tests can be used in young asymptomatic DM and should be used for future reference during surgery or intercurrent infections of these patients.

3. This study shows the high prevalence of cardiac dysautonomia. Most of these patients remain asymptomatic. The incidence of cardiac autonomic neuropathy has also been found in recently detected type 2 diabetics.

4. There is a significant correlation between duration of DM and occurrence of cardiac autonomic neuropathy. In this study it has been found that the prevalence of CAN increases as the duration of DM is greater than 6 yrs.

5. Significant correlation has been found between CAN and age of the patient.

6. There is a significant correlation between cardiac autonomic neuropathy and peripheral neuropathy as compared to other microvascular complications like nephropathy and retinopathy.So these microvascular complications should be screened as early as possible to avoid major morbidity and mortality.

It can be recommended that a baseline determination of cardiac autonomic function be performed upon diagnosis in type 2 DM followed by a yearly repeat test.

ANNEXURES

CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER

ECG **Normal Cardiac Autonomic Function**

CANS 504 — CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER

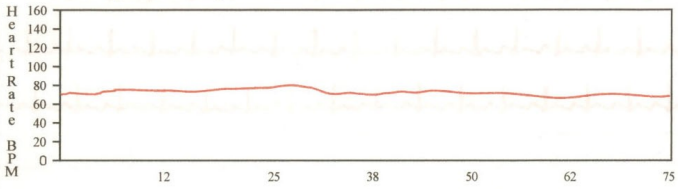
Name : V.Vaithialingam
ID : 44
Age : 49 Sex : Male
Referal : Dr. ANANDMOSES

Confidential Patient Information
Test Date : 31 - 05 - 2007 10:38:54

PARASYMPATHETIC FUNCTION

1. Resting Heart Rate : **70 BPM** **Normal**

2. Deep Breathing

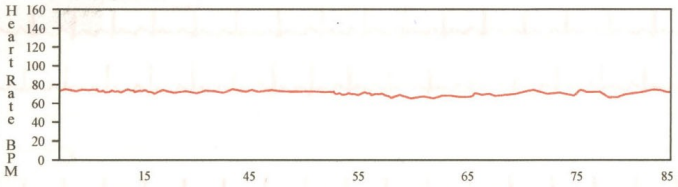


1. E/I Ratio = 1.30

(Normal Value ≥ 1.1)

Normal

3. Standing

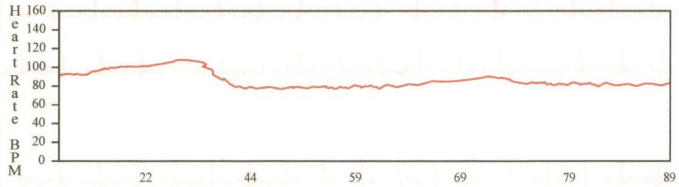


30 : 15 Stand Ratio = 1.27

(Normal Value ≥ 1.04)

Normal

4. Valsalva



Valsalva Ratio = 1.40

(Normal Value ≥ 1.21)

Normal

SYMPATHETIC FUNCTION

1. Postural Hypotention

BP :Supine	:	135/88 mmHg
BP Standing imediate	:	131/87 mmHg
After 60 Second	:	130/87 mmHg
Change in Systolic BP	:	5 mmHg

Normal

2. Sustained Hand Grip

Before Grip	:	135/88 mmHg
After	:	136//104 mmHg
Increase in Diastolic BP	:	16 mmHg

Normal

Impression

Normal Parasympathetic function
Normal sympathetic function
Normal CAN Study
This may be clinically co-related

aa
CONSULTANT PHYSICIAN

Early Cardiac Autonomic Neuropathy

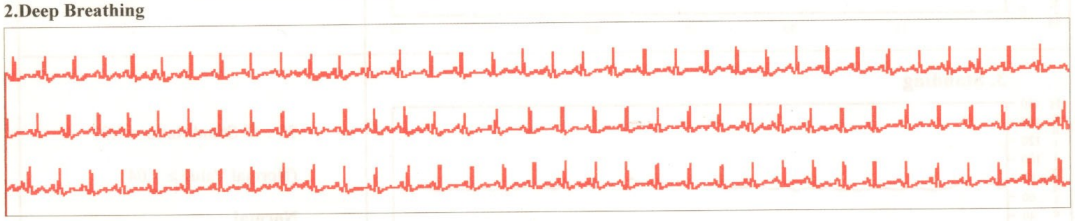
CANS 504 **CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER**

Name : j.doss
ID : 53
Age : 51 Sex : Male
Referal DR.ANANDMOSES

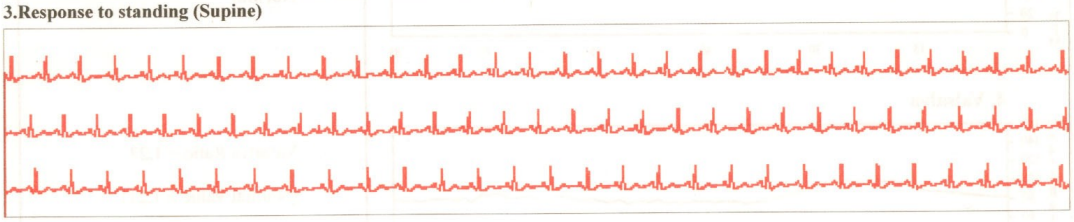
Confidential Patient Information
Test Date : 14-06-2007 10:39:38

1.Resting HR

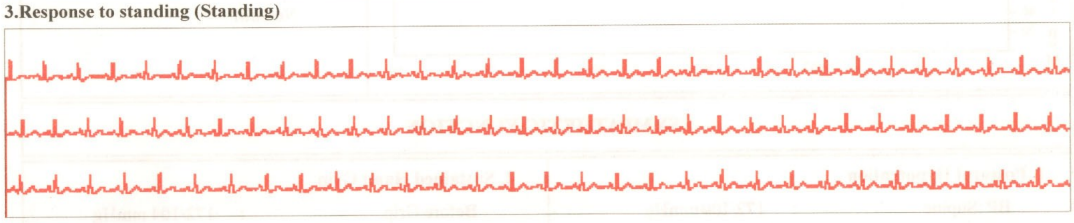
2.Deep Breathing



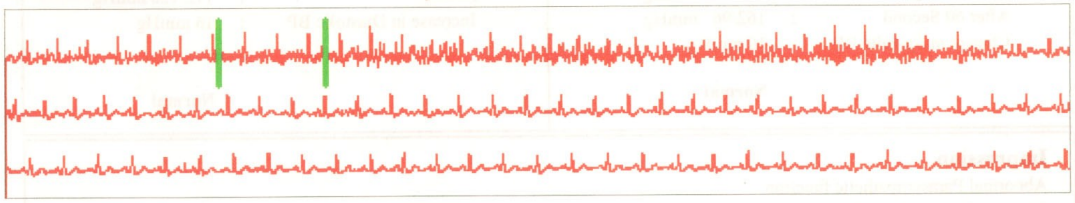
3.Response to standing (Supine)



3.Response to standing (Standing)



4.Valsalva Maneuver



CANS 504 **CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER**

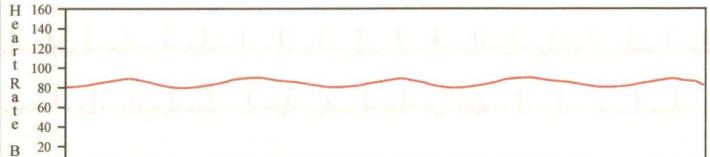
Name : **J. Doss**
ID : 53
Age : 51 Sex : Male
Referal : Dr. ANANDMOSES

Confidential Patient Information
Test Date : 14 - 06 - 2007 10:39:38

PARASYMPATHETIC FUNCTION

1. Resting Heart Rate : **86 BPM** **Normal**

2. Deep Breathing



1. E/I Ratio = 1.06

(Normal Value ≥ 1.1)

Abnormal

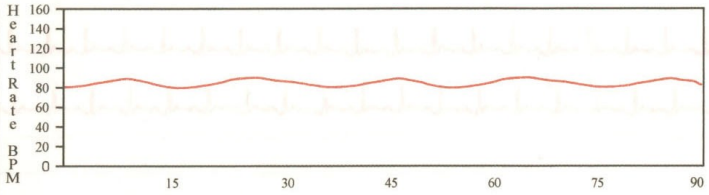
CANS 504 — CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER

Name : **J. Doss**	**Confidential Patient Information**
ID : 53	**Test Date : 14 - 06 - 2007 10:39:38**
Age : 51 Sex : Male	
Referal : Dr. ANANDMOSES	

PARASYMPATHETIC FUNCTION

1. Resting Heart Rate : **86 BPM** **Normal**

2. Deep Breathing

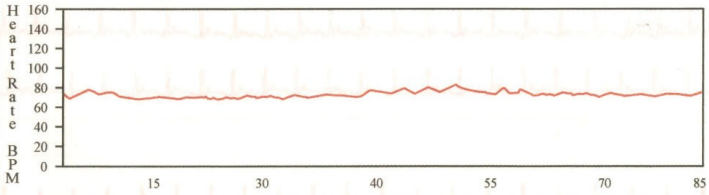


1. E/I Ratio = 1.06

(Normal Value ≥ 1.1)

Abnormal

3. Standing

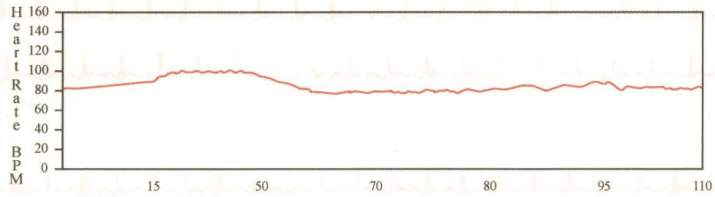


30 : 15 Stand Ratio = 1.07

(Normal Value ≥ 1.04)

Normal

4. Valsalva



Valsalva Ratio = 1.27

(Normal Value ≥ 1.21)

Normal

SYMPATHETIC FUNCTION

1. Postural Hypotention

BP :Supine	:	172/100 mmHg
BP Standing imediate	:	170/98 mmHg
After 60 Second	:	162/96 mmHg
Change in Systolic BP	:	10 mmHg

Normal

2. Sustained Hand Grip

Before Grip	:	172/104 mmHg
After	:	172/120 mmHg
Increase in Diastolic BP	:	16 mmHg

Normal

Impression

Abnormal Parasympathetic function
Abnormal sympathetic function
Abnormal CAN Study
This may be clinically co-related

aa

CONSULTANT PHYSICIAN

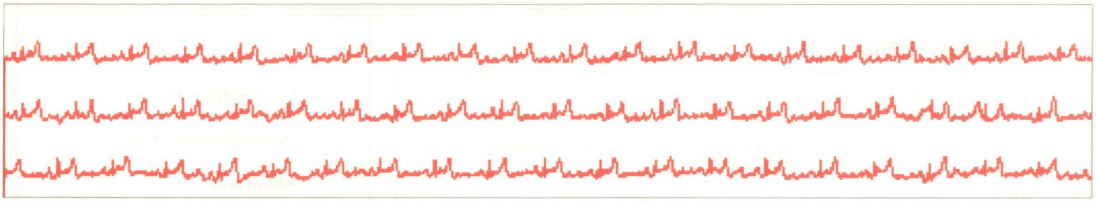
Definite Cardiac Autonomic Neuropathy

CANS 504 **CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER**

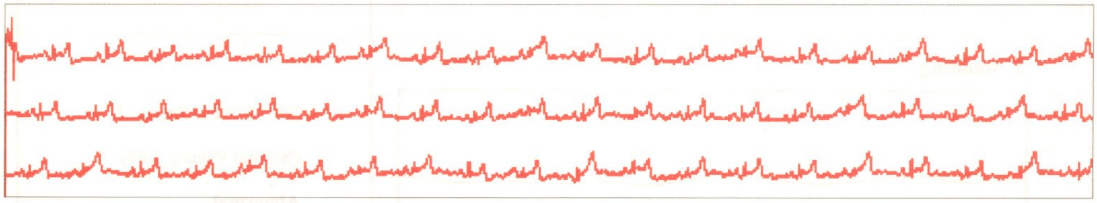
Name : MR.T.KARUPPAIAH
ID : 30
Age : 65 Sex : Male

Confidential Patient Information
Test Date : 22-05-2007 12:16:58

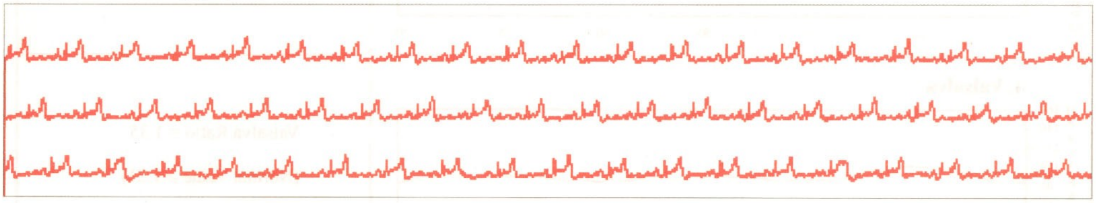
1.Resting HR



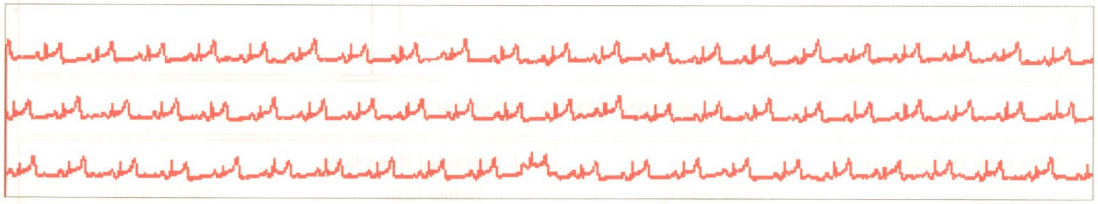
2.Deep Breathing



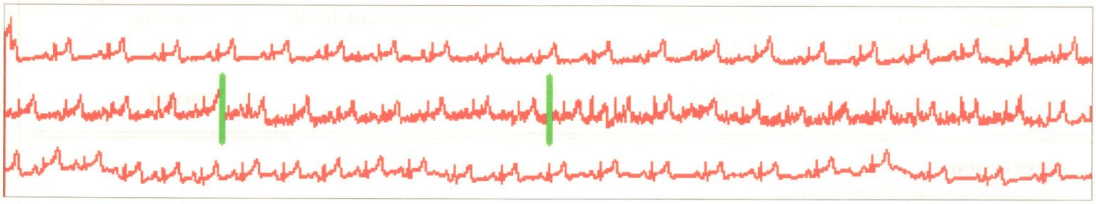
3.Response to standing (Supine)



3.Response to standing (Standing)



4.Valsalva Maneuver



CANS 504 — CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER

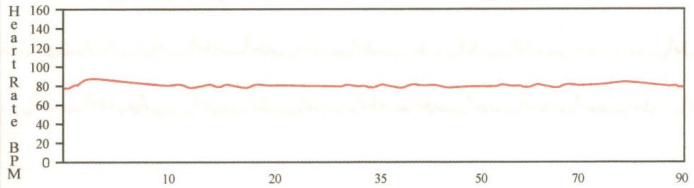
Name : **T. Karuppaiah**
ID : 30
Age : 65 Sex : Male
Referal : Dr. ANANDMOSES

Confidential Patient Information
Test Date : 22 - 05 - 2007 12:16:58

PARASYMPATHETIC FUNCTION

1. Resting Heart Rate : **104 BPM** **Abnormal**

2. Deep Breathing

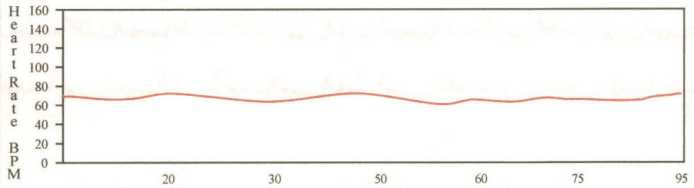


1. E/I Ratio = 1.0

(Normal Value ⩾ 1.1)

Abnormal

3. Standing

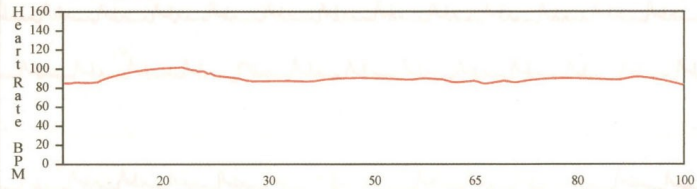


30 : 15 Stand Ratio = 1

(Normal Value ⩾ 1.04)

Abnormal

4. Valsalva



Valsalva Ratio = 1.35

(Normal Value ⩾ 1.21)

Normal

SYMPATHETIC FUNCTION

1. Postural Hypotention

BP :Supine	:	134/64 mmHg
BP Standing imediate	:	132/62 mmHg
After 60 Second	:	124/62 mmHg
Change in Systolic BP	:	10 mmHg

Normal

2. Sustained Hand Grip

Before Grip	:	134/64 mmHg
After	:	140/80 mmHg
Increase in Diastolic BP	:	16 mmHg

Normal

Impression

Abnormal Parasympathetic function
Normal sympathetic function
Abnormal CAN Study
This may be clinically co-related

aa

CONSULTANT PHYSICIAN

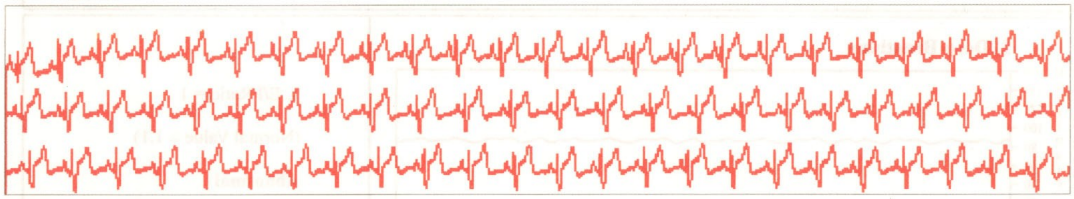
Severe Cardiac Autonomic Neuropathy

CANS 504 **CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER**

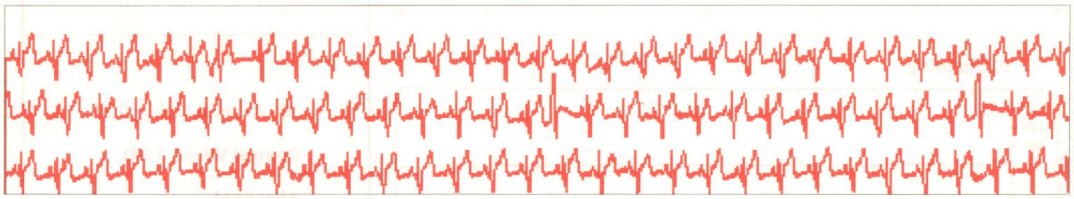
Name : a.peter
ID : 17
Age : 70 Sex : Male
Referal DR.ANANDMOSES

Confidential Patient Information
Test Date : 14-05-2007 12:11:13

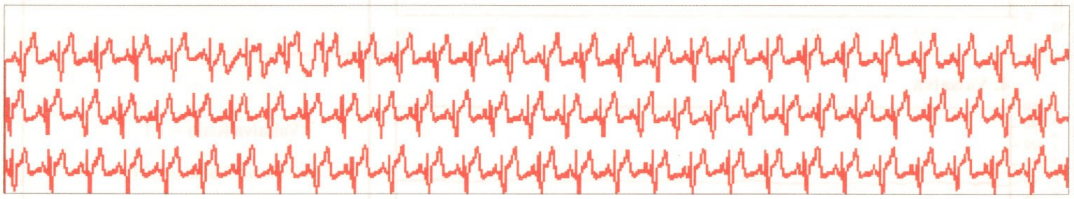
1.Resting HR



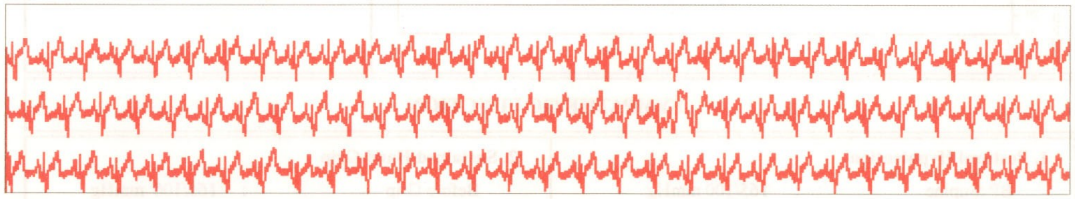
2.Deep Breathing



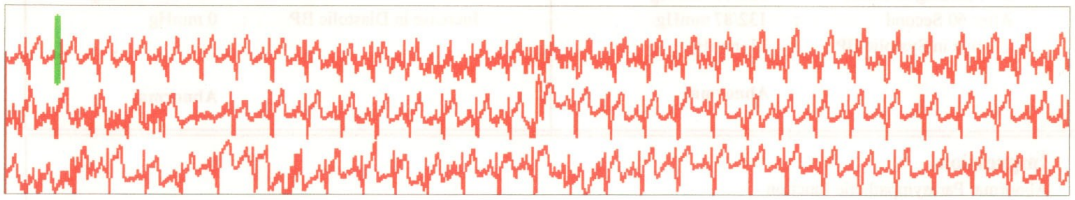
3.Response to standing (Supine)



3.Response to standing (Standing)



4.Valsalva Maneuver



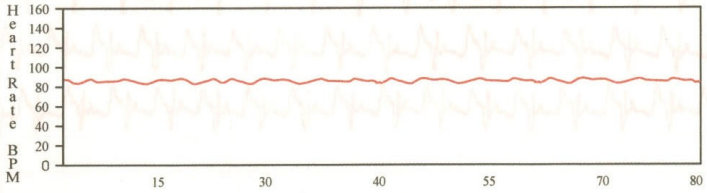
CANS 504 — CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER

Name : **A. Peter**	**Confidential Patient Information**
ID : 17	**Test Date : 14 - 05 - 2007 12:11:13**
Age : 70 Sex : Male	
Referal : Dr. ANANDMOSES	

PARASYMPATHETIC FUNCTION

1. Resting Heart Rate : **110 BPM** **Abnormal**

2. Deep Breathing

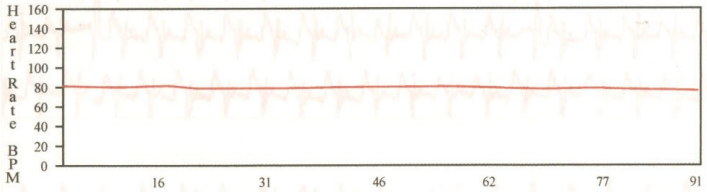


1. E/I Ratio = 1

(Normal Value ⩾ 1.1)

Abnormal

3. Standing

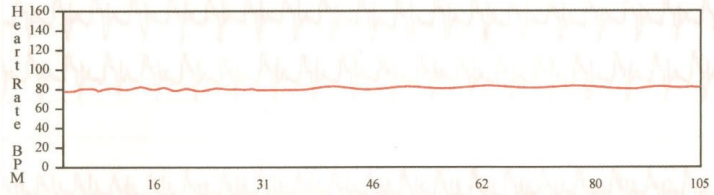


30 : 15 Stand Ratio = 0.8

(Normal Value ⩾ 1.04)

Abnormal

4. Valsalva



Valsalva Ratio = 1.1

(Normal Value ⩾ 1.21)

Abnormal

SYMPATHETIC FUNCTION

1. Postural Hypotention

BP :Supine	:	165/100 mmHg
BP Standing imediate	:	152/78 mmHg
After 60 Second	:	132/87 mmHg
Change in Systolic BP	:	33 mmHg

Abnormal

2. Sustained Hand Grip

Before Grip	:	165/100 mmHg
After	:	160/100 mmHg
Increase in Diastolic BP	:	0 mmHg

Abnormal

Impression

Abnormal Parasympathetic function
Abnormal sympathetic function
Abnormal CAN Study
This may be clinically co-related

aa

CONSULTANT PHYSICIAN

Atypical Cardiac Autonomic Neuropathy

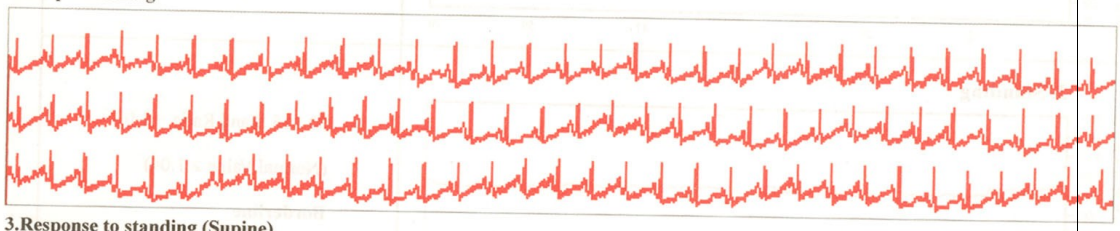
CANS 504 **CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER**

Name : r.lakshmi
ID : 41
Age : 48 Sex : Female
Referal DR.ANANDMOSES

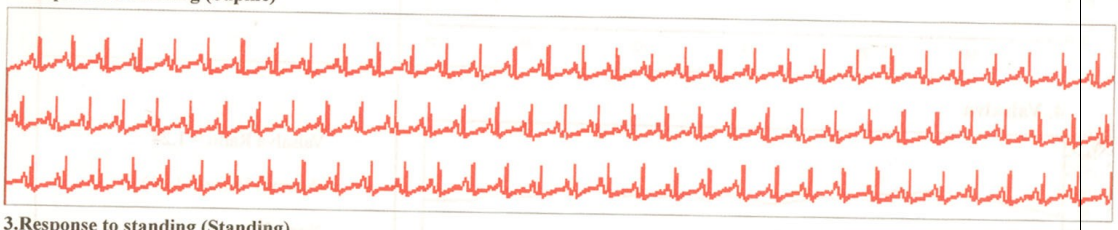
Confidential Patient Information
Test Date : 28-05-2007 11:41:57

1.Resting HR

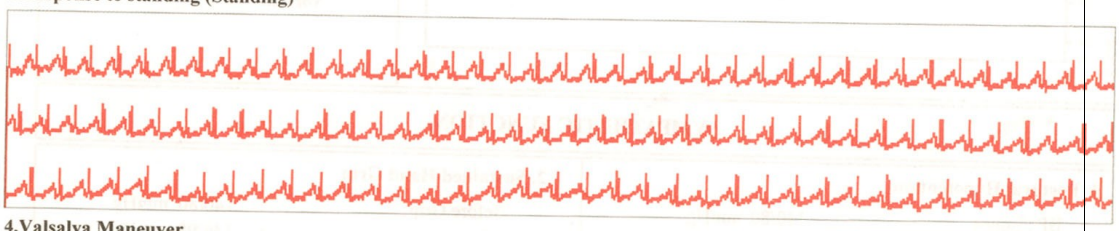
2.Deep Breathing



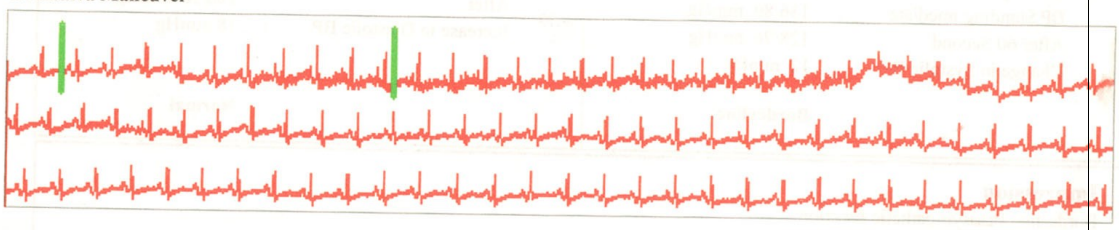
3.Response to standing (Supine)



3.Response to standing (Standing)



4.Valsalva Maneuver



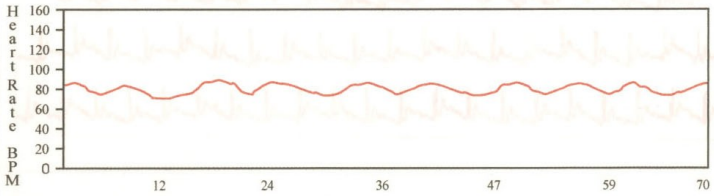
CANS 504 — CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER

Name : **R. Lakshmi**	**Confidential Patient Information**
ID : 41	**Test Date : 28 - 05 - 2007 11:41:57**
Age : 48 Sex : Female	
Referal : Dr. ANANDMOSES	

PARASYMPATHETIC FUNCTION

1. Resting Heart Rate : **76 BPM** **Normal**

2. Deep Breathing

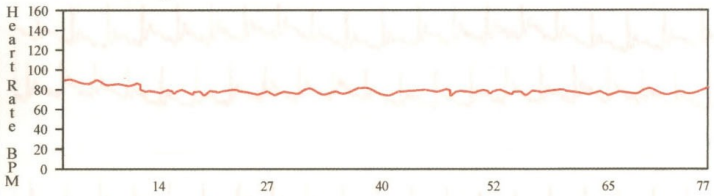


1. E/I Ratio = 1.28

(Normal Value ≥ 1.1)

Normal

3. Standing

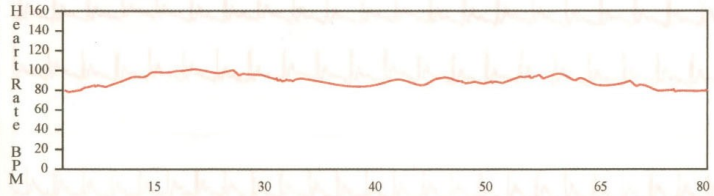


30 : 15 Stand Ratio = 1.03

(Normal Value ≥ 1.04)

Borderline

4. Valsalva



Valsalva Ratio = 1.24

(Normal Value ≥ 1.21)

Normal

SYMPATHETIC FUNCTION

1. Postural Hypotention

BP :Supine	:	140/80 mmHg
BP Standing imediate	:	136/80 mmHg
After 60 Second	:	128/76 mmHg
Change in Systolic BP	:	12 mmHg

Borderline

2. Sustained Hand Grip

Before Grip	:	140/80 mmHg
After	:	146/98 mmHg
Increase in Diastolic BP	:	18 mmHg

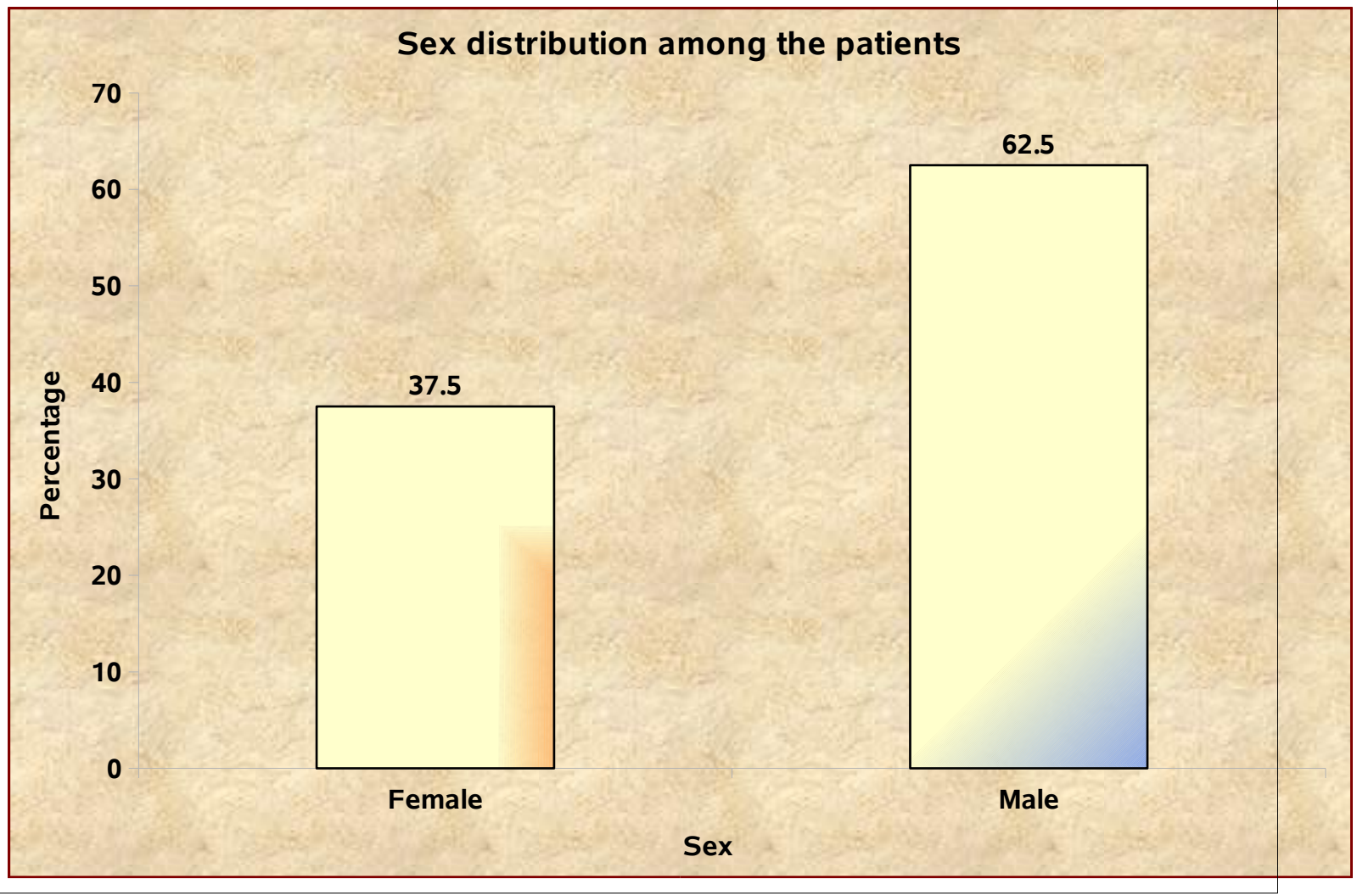
Normal

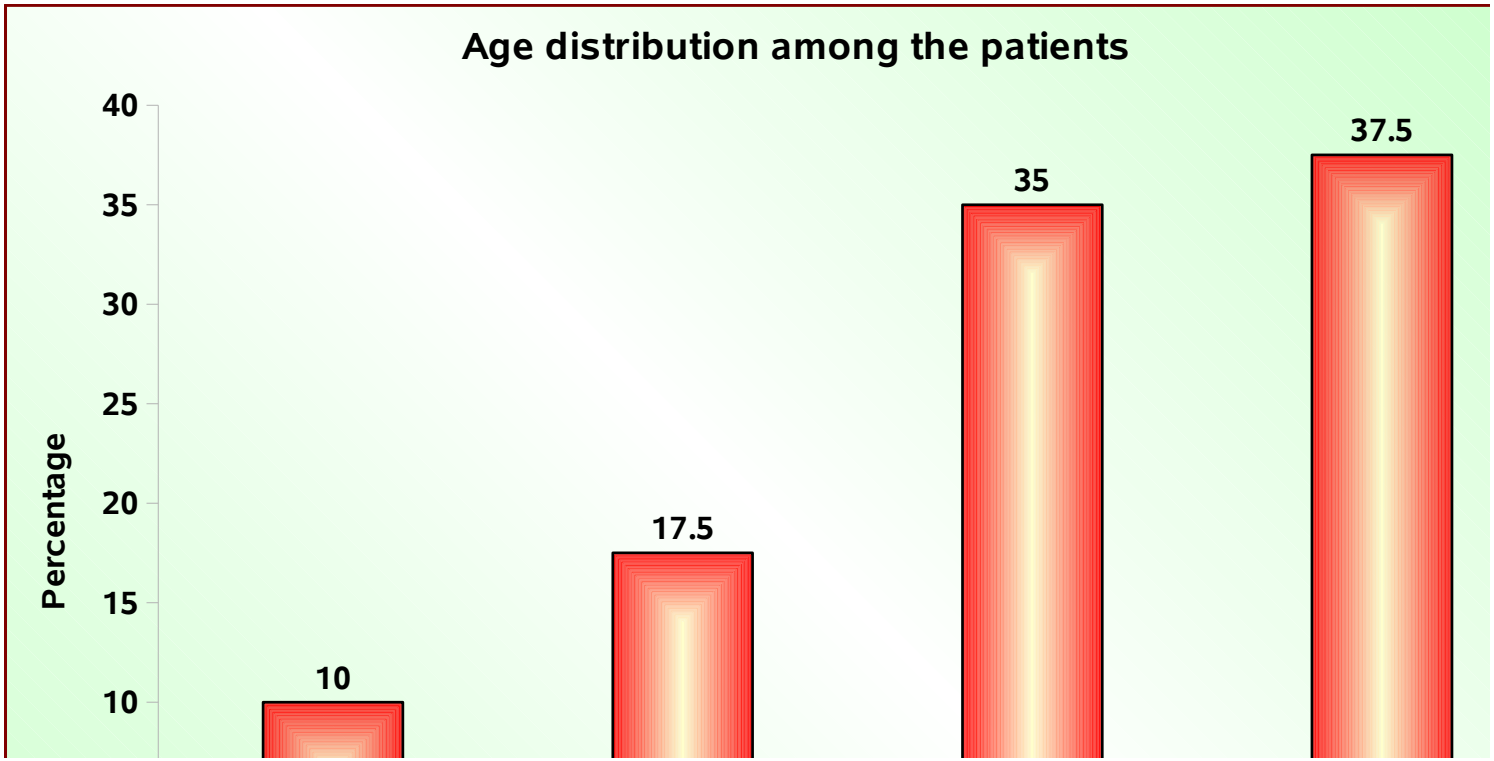
Impression

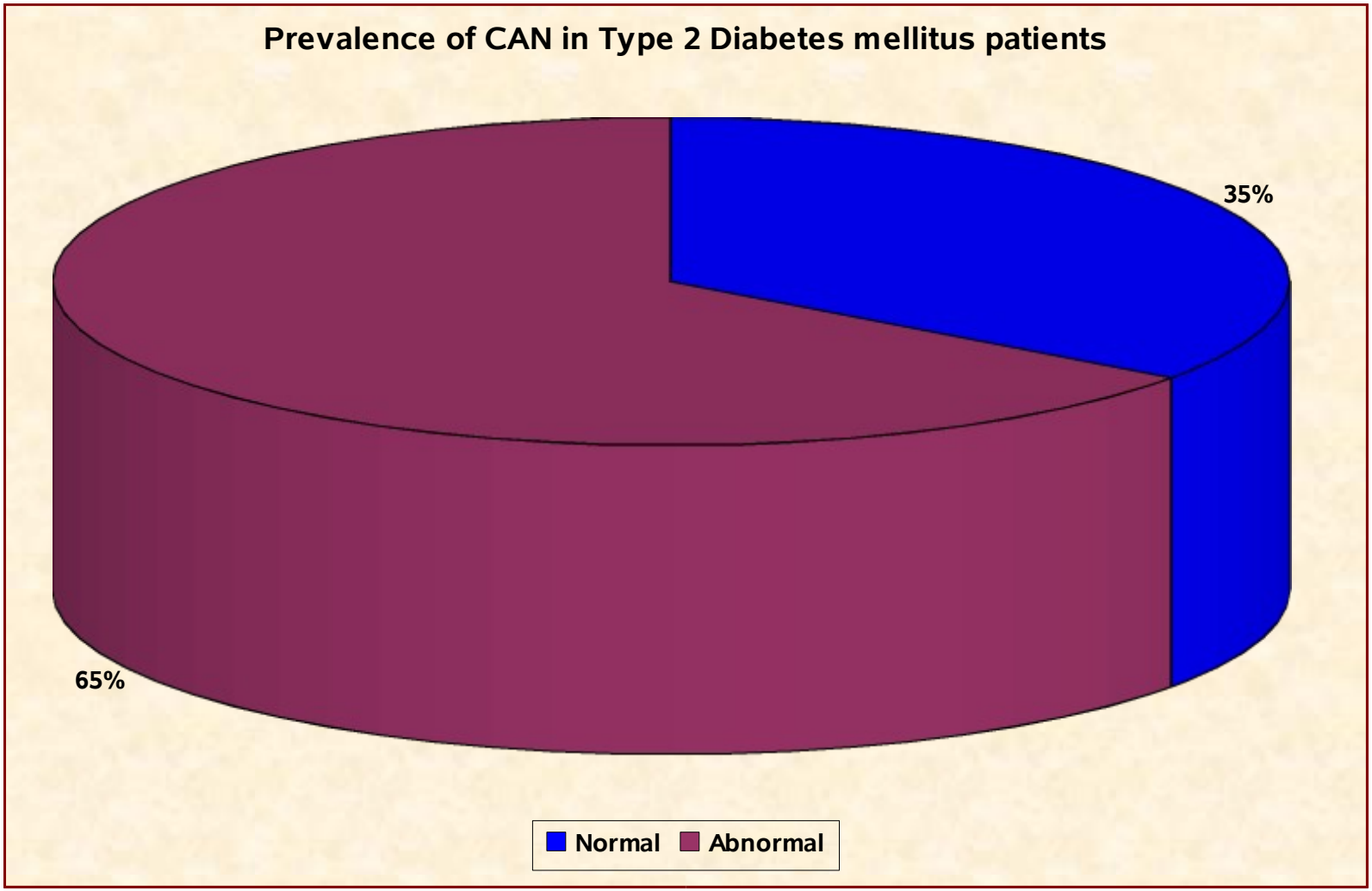
Borderline Parasympathetic function
Borderline sympathetic function
Abnormal CAN Study
This may be clinically co-related

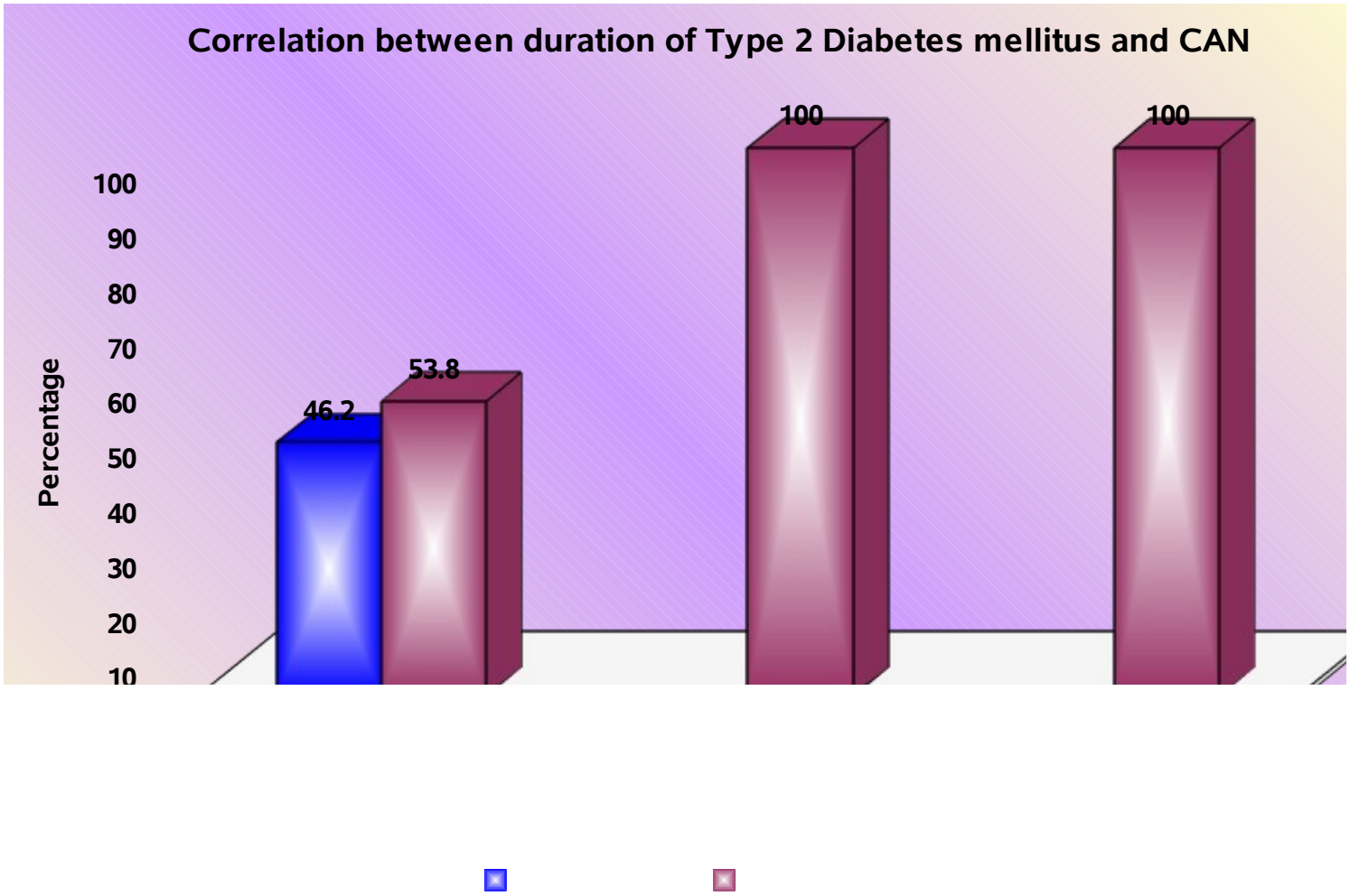
aa
CONSULTANT PHYSICIAN

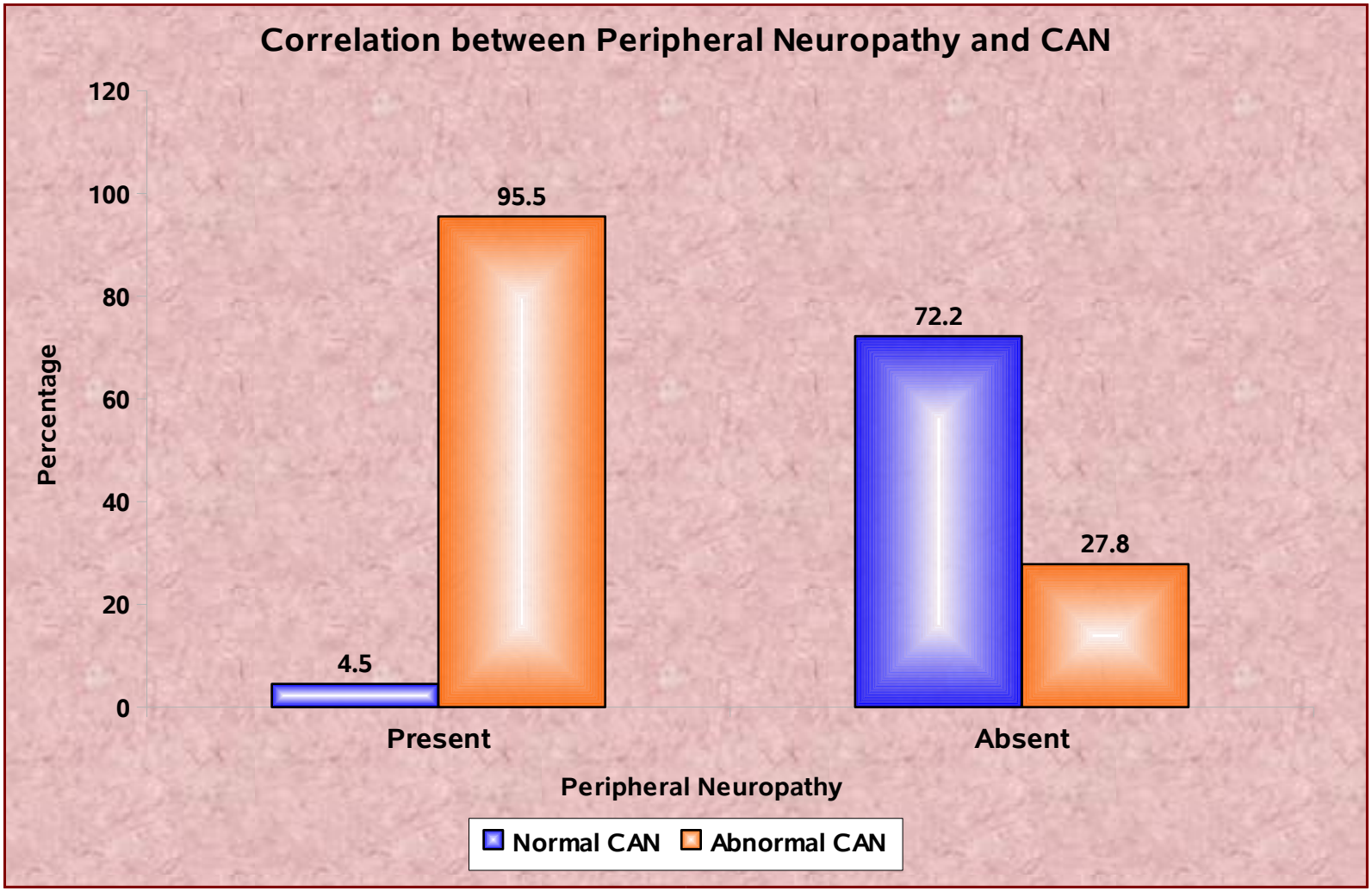
Charts

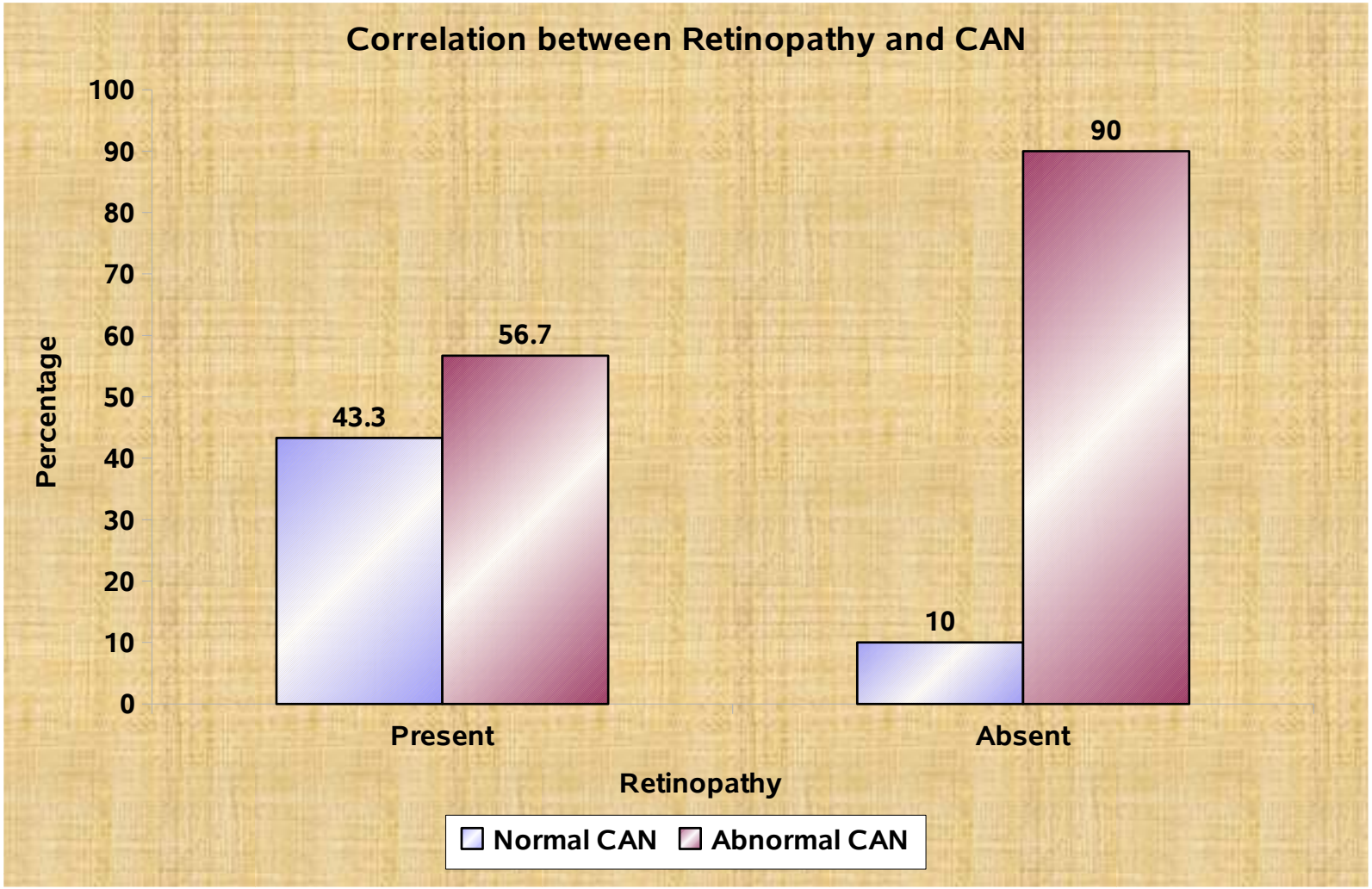

Sex distribution among the patients
70
60
50
40
30
20
10
0
Percentage
37.5
62.5
Female
Male
Sex

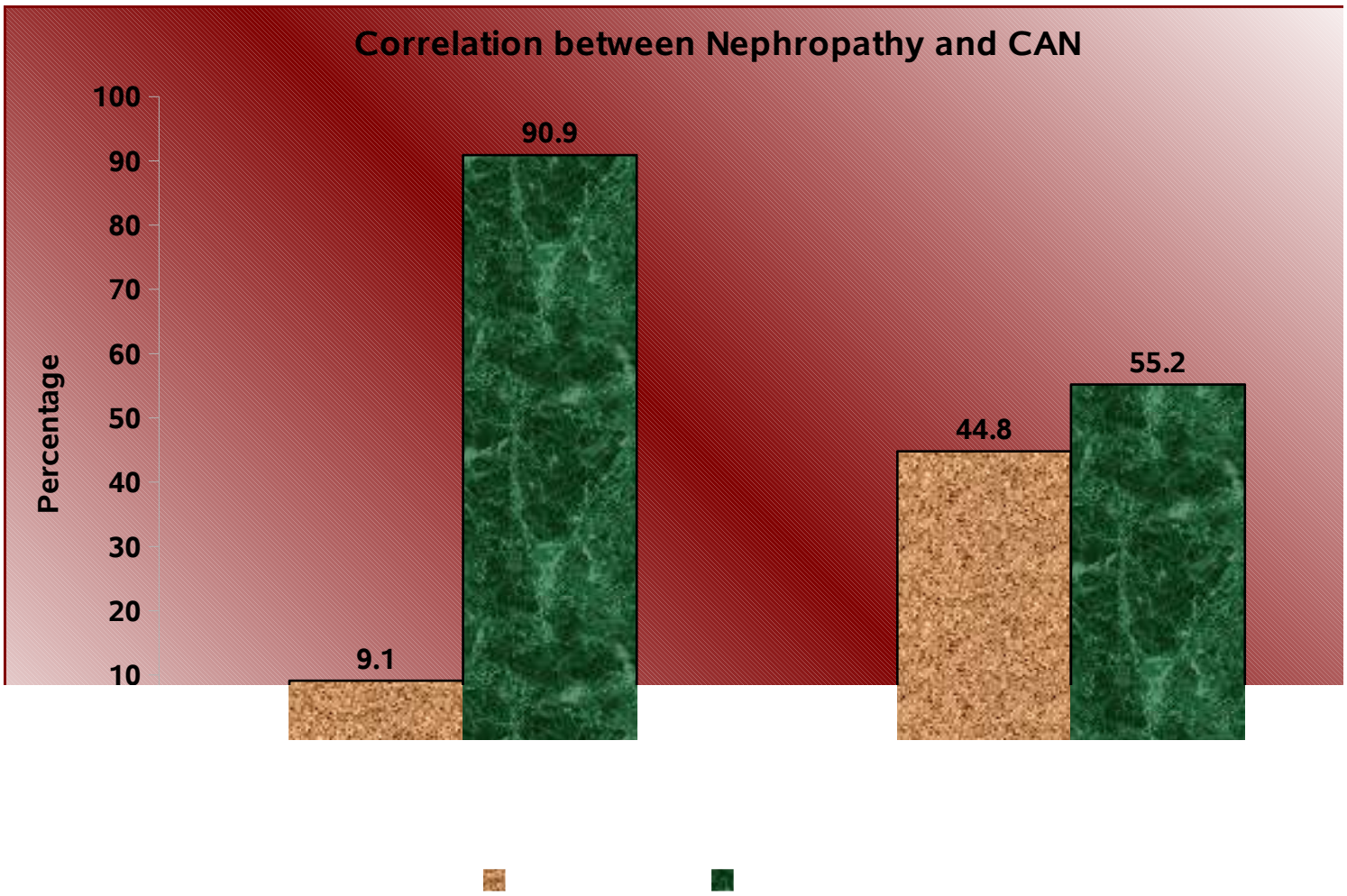

Age distribution among the patients
Percentage
40
35
30
25
20
15
10
10
17.5
35
37.5


Prevalence of CAN in Type 2 Diabetes mellitus patients
35%
65%
Normal
Abnormal


Correlation between duration of Type 2 Diabetes mellitus and CAN
Percentage
100
90
80
70
60
50
40
30
20
10
46.2
53.8
100
100


Correlation between Peripheral Neuropathy and CAN
120
100
80
60
40
20
0
Percentage
95.5
72.2
27.8
4.5
Present
Absent
Peripheral Neuropathy
Normal CAN
Abnormal CAN


Correlation between Retinopathy and CAN
Percentage
100
90
80
70
60
50
40
30
20
10
0
43.3
56.7
10
90
Present
Absent
Retinopathy
Normal CAN
Abnormal CAN


Correlation between Nephropathy and CAN
Percentage
100
90
80
70
60
50
40
30
20
10
9.1
90.9
44.8
55.2

PROFORMA

Name:	OP NO:
Age:	Ht:
Sex:	Wt:
	BMI:
Address:	WHR:

Occupation:

Duration of DM:

Clinical Data: Autonomic Neuropathy

1) Light headedness on standing

2) Visual Disturbances on standing

3) Syncope on standing

Peripheral Neuropathy

H/O Numbness

H/O Paraesthesias

H/O Hyperaesthesia

H/O Lighting pains

Retinopathy

H/O diminished vision

H/O double vision

Past His:

HT duration: Tt

IHD

STD

TB

BR.ASTHMA

TREATMENT HISTORY : OHA

Insulin

Diet : Vegetarian/non-vegetarian

Family History:

Personal History : Smoker Alcohol

G/E : Pulse BP - supine:

Standing:

Anaemia	Lymphadenopathy
Jaundice	Pedal edema
Cyanosis	Skin
Clubbing	

Systemic Examination

Pulse : RR:

CVS : Peripheral pulse, Carotid, Radial, Brachial ,Femoral, Popliteal, Dorsalis pedis.

JVP

Apical impulse

LVH-

MURMUR-

S3 or S4

RS:

Abdomen: organomegaly

Briut- Renal/Abdominal Aorta

Tests of Autonomic function

-when was the last medication

-time of waking up

-consumption of Tobacco/Alcohol in last 72 hrs

-consumption of drugs in last 24 hrs

INVESTIGATIONS

Hb%

TC

DC

ESR

Urine R/E

BLOOD SUGAR FBS PPBS

Hb A1C

BLOOD UREA

SRUM CREATININE

SERUM ELECTROLYTES

ECG

MASTER CHART

TABLE 1

Name	Age	Sex	Ht cms	Wt kgs	WHR	BMI kg / m^2	NIDDM Durn	Tt	Postural Giddiness	Smoking
Manisekaran	53	M	173	75	0.9	25	5 Yrs	T.GB	-	-
Vaithialingam	49	M	173	70	0.9	23.4	2 Yrs	T.GB	-	-
Joseph Mani	57	M	165	79	0.8	29	3 Yrs	T.GB	-	-
Ashokan	39	M	161	56	0.9	21.6	4 Yrs	T.GB	-	-
Ravi	40	M	166	78	0.9	28	8 Yrs	T.GB, MF	+	+
Ruban	57	M	171	73	0.84	24.9	3 Yrs	T.GB	+	-
Rathnam	60	M	155	57	0.8	24	2 Yrs	T.GB	-	-
SenthilKumar	30	M	149	50	0.76	22.5	6 mon	MNT	+	+
Sathish	23	M	153	44	0.9	18.8	3 mon	MNT	-	-
Jambulingam	55	M	166	78	0.9	28	7 Yrs	T. GB, MF	+	+
Anandhan	33	M	148	45	0.78	20.54	1 Yr	T.GB	-	-
Koteeshwaran	42	M	161	60	0.98	23.14	2 Yrs	T.GB	-	-
Doss	51	M	162	55	0.96	20.9	5 Yrs	T.GB, MF	-	-
Vijayalakshmi	45	F	140	67	0.84	34.1	3 Yrs	T.GB	-	-
Kaveri	40	F	152	54	0.8	23.3	3 Yrs	T.GB	-	-
Fathimabee	55	F	151	65	0.9	28.5	13Yrs	T.GB, MF	+	-
M. Pramila	30	F	152	57	0.84	24.67	3 mon	MNT	-	-
Johenan	60	F	153	50	0.9	21	18 Yrs	T.GB, MF	+	-
Sakuntala	57	F	146	68	0.8	31.9	10 Yrs	T.GB, MF	-	-
Gouthaman	47	M	157	55	0.9	22.3	5 Yrs	T.GB	-	+
Mallika	46	F	155	47	0.91	19.5	7 Yrs	T.GB, MF	-	-
Premavathy	58	F	156	63	0.83	25.8	8 Yrs	T.GB, MF	+	-
C. Kala	28	F	149	50	0.86	22.5	2 Yrs	T.GB	-	-
Karuppiah	65	M	165	72	0.95	26.6	1.5Yrs	T.GB	+	+
Sekar	32	M	157	58	0.98	23.5	3 Yrs	T.GB	-	-
Janarthanan	49	M	164	82	0.85	30.4	5 Yrs	T.GB	+	+
Dhanasekaran	42	M	167	71	0.9	25.4	2 Yrs	T.GB	-	-
Manisekaran	43	M	160	63	1.0	24.6	3 Yrs	T.GB, MF	-	+
Ravi	50	M	161	58	1.0	22.3	3 Yrs	T.GB	+	-
Rajasekar	43	M	157	60	0.95	24.3	1 Yr	MNT	-	-
Lingamma	48	F	155	90	0.82	37.4	6 Yrs	T.GB, MF	-	-
Ramamoorthi	58	M	164	70	0.97	26	3 Yrs	T.GB	-	-
Pandian	51	M	161	60	0.98	23.16	2 Yrs	T.GB	-	+
Kamatchi	37	F	159	41	0.84	16.41	1 Yr	T.GB	-	-
R. Lakshmi	48	F	140	67	0.84	34.1	4 Yrs	T.GB, MF	+	-

Name	Age	Sex	Ht cms	Wt kgs	WHR	BMI kg / m^2	NIDDM Durn	Tt	Postural Giddiness	Smoking
T. Lakshmi	45	F	171	57	0.89	19.4	2 Yrs	T.MF	-	-
Isaac Madhava Rajan	35	M	157	64	0.83	25.9	1.5Yrs	T.GB, MF	-	-
Lakshmi	43	F	158	76	0.9	30.4	1 Yr	MNT	-	-
Delci Fathima	50	F	157	83	0.9	33.6	5 Yrs	T.GB	-	-
A. Peter	70	M	167	63	0.9	22.5	10 Yrs	T.GB, MF	+	-

TABLE - 2

S.No	Name	RHR per min.	Cardiac Autonomic Function Tests					Result of CAN	
			E/I Ratio	30/15 Ratio	Valsalva Ratio	Fall in Sys BP	Inc in dias BP		
1	Manisekaran	78	1.87	1.03	2.11	19	16	Atypical	M
2	Vaithialingam	70	1.30	1.27	1.40	5	16	Normal	
3	Joseph Mani	70	1.2	1.01	1.21	10	18	Normal	
4	Ashokan	80	1.23	1.06	1.12	4	13	Atypical	
5	Ravi	72	1.0	1.75	1.08	2	19	Definite	M
6	Ruban	76	1.16	1.04	1.07	6	17	Early	M
7	Rathnam	81	1.05	1.04	1.26	8	20	Early	
8	SenthilKumar	100	1.44	0.99	1.31	4	18	Early	M
9	Sathish	76	2.42	1.19	1.24	2	20	Normal	
10	Jambulingam	81	1.08	0.96	1.00	10	20	Definite	M
11	Anandhan	83	1.54	1.24	1.37	3	11	Normal	
12	Koteeshwaran	75	1.29	1.06	1.36	5	20	Normal	
13	Doss	86	1.06	1.07	1.27	10	16	Early	M
14	VijayaLakshmi	83	1.34	0.87	2.08	3	17	Early	M
15	Kaveri	90	1.22	1.06	1.67	10	18	Normal	
16	Fathimabee	94	1.05	0.96	1.07	30	10	Severe	M
17	M. Pramila	81	1.52	1.21	2.00	5	16	Normal	
18	Johenan	112	1.04	1.00	1.10	16	12	Severe	M
19	Sakuntala	95	1.01	1.00	1.12	14	8	Severe	M
20	Gouthaman	80	1.08	1.04	1.74	10	18	Early	M

Contd...

S.No	Name	RHR per min.	Cardiac Autonomic Function Tests					
			E/I Ratio	30/15 Ratio	Valsalva Ratio	Fall in Sys BP	Inc in dias BP	
21	Mallika	100	1.12	1.04	1.14	3	12	Aty
22	Premavathy	96	1.00	0.88	1.13	3	16	Def
23	C. Kala	82	1.32	0.91	1.56	2	20	Ear
24	Karuppiah	104	1.00	1.00	1.34	10	16	Def
25	Sekar	74	1.26	1.04	1.53	2	18	Nor
26	Janarthanan	90	1.04	0.99	1.21	10	20	Def
27	Dhanasekaran	83	1.27	1.05	1.25	4	18	Nor
28	Manisekaran	75	1.35	0.95	1.37	10	18	Ear
29	Ravi	76	1.06	1.06	1.28	3	16	Ear
30	Rajasekar	86	1.67	1.04	1.38	6	12	Nor
31	Lingamma	86	1.01	0.98	1.29	10	16	Def
32	Ramamoorthi	85	1.20	1.00	2.23	10	20	Ear
33	Pandian	80	1.22	1.00	1.26	4	18	Ear
34	Kamatchi	70	1.49	1.06	1.3	8	16	Nor
35	R. Lakshmi	76	1.28	1.03	1.24	12	18	Aty

36	T. Lakshmi	71	2.16	1.04	1.26	9	17	Nor
37	Isaac Madhava Rajan	79	2.03	1.08	2.9	12	18	Nor
38	Lakshmi	82	1.48	1.06	2.8	4	14	Nor
39	Delci Fathima	84	1.05	1.06	1.25	10	20	Ear
40	A. Peter	110	1.00	0.8	1.1	33	0	Sev

TABLE - 3

S.No	FBS mg/dl	PPBS mg/dl	Sr Urea mg/dl	Sr Creatinine mg/dl	Urine Albumin
1	230	288	23	0.8	+
2	115	200	22	0.9	-
3	120	214	20	0.7	-
4	141	205	44	2.8	+
5	150	212	40	2.5	+
6	130	160	22	0.8	-
7	152	240	24	0.8	-
8	170	210	21	0.7	-
9	110	160	19	0.6	-
10	240	280	20	0.8	-
11	118	192	20	0.75	-
12	92	210	22	0.73	-
13	192	226	26	0.8	-
14	164	200	42	1.7	+
15	120	180	22	0.8	-
16	167	378	38.5	1.6	+
17	119	182	20	0.9	-
18	140	180	22	0.8	-
19	92	214	46	1.9	++
20	166	214	22	0.92	-

Contd..

S.No	FBS mg/dl	PPBS mg/dl	Sr Urea Mg/dl	Sr Creatinine mg/dl	Urine Albumi
21	140	167	20	0.7	-
22	240	288	42	1.9	+
23	180	260	20	0.8	-
24	190	270	26	0.9	-
25	126	244	21	0.7	-
26	154	219	24	0.9	-
27	125	215	23.5	0.8	-
28	124	200	44	1.9	++
29	142	188	24	0.8	-
30	100	260	22	0.9	-
31	167	230	42	1.7	+
32	110	210	20	0.9	-
33	140	260	21	0.8	-
34	90	170	19	0.8	-

35	116	180	46	1.7		++
36	86	120	20	0.9		-
37	136	166	44	1.9		+
38	120	180	26	0.8		-
39	146	216	42	0.7		-
40	110	246	19	0.9		-

ABBREVIATIONS

DM	-	Diabetes Mellitus
WHO	-	World Health Organization
UKPDS	-	United Kingdom Prospective Diabetes Study
CANS	-	Cardiac Autonomic Neuropathy System Analyzer
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance
CNS	-	Central Nervous System
GABA	-	Gamma Amino Butyric Acid
DAN	-	Diabetic Autonomic Neuropathy
IDDM	-	Insulin Dependent Diabetes Mellitus
NIDDM	-	Non Insulin Dependent Diabetes Mellitus
IGF	-	Insulin like Growth Factor
AGE	-	Advanced Glycosylation End Products
DNA	-	Deoxy Ribonucleic Acid
PARP	-	Poly ADP - Ribose Polymerase
NAD+	-	Nicotine Adenine Dinucleotide
ATP	-	Adenosine Triphosphate
ADP	-	Adenosine Diphosphate
NGF	-	Nerve Growth Factor
CAN	-	Cardiac Autonomic Neuropathy
bpm	-	beats per minute
BP	-	Blood Pressure
ECG	-	Electrocardiogram
min	-	Minute
mmHg	-	mm of Mercury

sec	-	Seconds
VPT	-	Vibration Perception Threshold
V	-	Voltage
DCCT	-	Diabetes Control and Complications Trial
Yr	-	Year
BMI	-	Body Mass Index
WHR	-	Waist Hip Ratio
HRV	-	Heart Rate Variability
ROS	-	Reactive Oxygen Species
CURES	-	Chennai Urban Rural Epidemiological Study
RHR	-	Resting Heart Rate
Inc	-	Increase
N	-	Normal
Sys BP	-	Systolic Blood Pressure
dias BP	-	Diastolic Blood Pressure
+	-	Positive
-	-	Negative
Sr	-	Serum
Ht	-	Height
Wt	-	Weight
H/O	-	History of
HT	-	Hypertension
IHD	-	Ischemic Heart Disease
STD	-	Sexually Transmitted Disease
TB	-	Tuberculosis
BR.Asthma	-	Bronchial Asthma
OHA	-	Oral Hypoglycemic Agent

G/E	-	General Examination
RR	-	Respiratory Rate
JVP	-	Jugular Venous Pulse
LVH	-	Left Ventricular Hypertrophy
RS	-	Respiratory System
Hrs	-	Hours
Hb%	-	Haemoglobin
TC	-	Total Count
DC	-	Differential Count
ESR	-	Erythrocyte Sedimentation Rate
R/E	-	Routine Examination
g	-	Grams
MNT	-	Medical Nutritional Therapy
GB	-	Glibenclamide
MF	-	Metformin
NF_kB	-	Nuclear factor $_k$ B

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