

**“PREVELANCE OF CARDIAC AUTONOMIC  
NEUROPATHY IN TYPE II DIABETES MELLITUS”**

**By**

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Dissertation submitted to



**BLDE University, Bijapur**

In partial fulfillment of the  
Requirements for the degree of

**MD**

**In**

**General Medicine**

Under the guidance of

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**2014**

**BLDE University**

**Bijapur, Karnataka State**

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## AKNOWLEDGEMENT

*It is with deep sense of gratitude and respect, I take this opportunity to thank my teacher and guide **Dr.R.M.HONNUTAGI** (Professor Department of Medicine, Shri BM Patil Medical College,Bijapur) for his constant inspiration, able guidance and kind help,which he rendered in preparing this dissertation and in pursuit of my post graduate studies.*

*I also thank him for being my well-wisher and giving encouragement over the last 3 years. It is my honor to have such a punctual, down to earth and helping person as my teacher.*

*My sincere and special thanks goes to **Dr.M.S.MULIMANI** (Professor and Head, Department of Medicine, Shri BM Patil Medical College, Bijapur) for his able guidance, valuable contribution and timely advice over the last three years of my post-graduate study.*

*It gives me an immense pleasure to express my deep sense of gratitude and sincere thanks to my esteemed teacher and beloved Principal **DR.M.S.BIRADAR**(Professor and Unit Head, Department of Medicine, Shri BM Patil Medical College, Bijapur), a man of great knowledge, spirit and dedication to the field of medicine, for his masterly guidance, worthy advice, constant inspiration and noble suggestions throughout my studies.*

*My sincere and hearty thanks to **Dr.P.G.MANTUR** (PROFESSOR) **Dr. Shankaragouda.Patil** (Asst .prof), for spending their valuable time for methodology of training and they made my study to run smoothly in a right pathway and reach the destiny.*

*I am forever grateful to Dr.R.C.Bidri (Prof), Dr.S.S.Devaramani (Prof),DR.Sharan Badiger(Prof) Dr.L.S.Patil (Prof),, Dr.S.N.Bentoor (Prof),Dr.A.P.Ambali (Prof) , Dr.V.G.Warad (Prof , Dr.S.G.Balaganur(prof), Dr.S.M.Biradar ( AssocProf), Dr.G.S.Mahishale( Assoc Prof), Dr.S.Y.Hanjagi (Asst Prof), Dr.S.B.Nadagowda (Asst. Prof), Dr.Anand.Choudhri( Asst. Prof), for their valuable help and guidance during my study.*

*I am thankful to my seniorsDr.Archana,Dr.Nijora, Dr.Vinayak, Dr.Manish, Dr.Sainath,Dr.Sheetal Desai,Dr.Srinivas,Dr.Ayaz,Dr.Harish pujari,Dr.Harish.N.S for their suggestions and advice.*

*I would like to express my gratitude to the statistician who helped me in my dissertation work Mrs. Vijaya Sorganvi*

*I express my hearty gratitude and thanks to all my colleagues, interns and friends who have worked with me during my post-graduate days. I sincerely thank all the patients who have helped me in my study without them this study would not have been possible.*

## LIST OF ABBREVIATIONS

ADA	-	American Diabetes Association
ATP	-	Adenine dinucleotide Tri Phosphate
AGE	-	Advanced Glycosylation End product
ANOVA	-	Analysis of variance
ANS	-	Autonomic Nervous System
BP	-	Blood Pressure
CAN	-	Cardiovascular Autonomic Neuropathy
CNS	-	Central Nervous System
CV	-	Coefficient of Variation
CVS	-	Cardiovascular System
DAN	-	Diabetic Autonomic Neuropathy
DBD	-	Deep Breathing Difference
DBP	-	Diastolic Blood Pressure
DCCT	-	Diabetes Control Complication Trial
DM	-	Diabetes Mellitus
DMV	-	Dorsal Motor nucleus of Vagus
ECG	-	Electrocardiogram
GHb	-	Glycosylated Hemoglobin
HbA	-	Hemoglobin A
HbA1c	-	Hemoglobin A1c
HRV	-	Heart Rate Variability
IDDM	-	Insulin Dependent Diabetes Mellitus
MAP	-	Mitogen Activated Protein
MI	-	Myocardial Infarction

NADH/NAD	-	Nicotinamide Dehydrogenase
NE	-	Nor epinephrine
NIDDM	-	Non Insulin Dependent Diabetes Mellitus
NO	-	Nitric Oxide
NTS	-	Nucleus Tractus Solitarius
OGTT	-	Oral Glucose Tolerance Test
OHT	-	Orthostatic Hypotension
PDGF	-	Platelet Derived Growth Factor
PKC	-	Protein Kinase C
PTI	-	Postural Tachycardia Index
RAGE	-	Receptor for Advanced Glycosylation End product
RHR	-	Resting Heart Rate
SD	-	Standard Deviation
SBP	-	Systolic Blood Pressure
SHG	-	Sustained Hand Grip
VEGF	-	Vascular Endothelium Derived Growth Factor
VLM	-	Ventro Lateral Medulla
VR	-	Valsalva Ratio

# **ABSTRACT**

## **INTRODUCTION:**

One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, and causes denervation resulting in abnormalities in heart rate control and vascular dynamics. The present report discusses the clinical manifestations resting tachycardia, orthostasis, exercise intolerance, dizziness in the presence of CAN. It also demonstrates that autonomic dysfunction can affect daily activities of individuals with diabetes and may invoke potentially life-threatening outcomes. Advances in technology, built on decades of research and clinical testing, now make it possible to objectively identify early stages of CAN with the use of careful measurement of autonomic function and to provide therapeutic choices that are based on symptom control and that might abrogate the underlying disorder.

## **AIM OF THE STUDY:**

TO find out the prevalence of cardiac autonomic neuropathy in type 2 Diabetes Mellitus.

## **METHODS:**

The study group comprised of 96 type 2 diabetic mellitus patients within the age group of 35-70 years attending Shri.B.M.Patil Hospital. they were further classified in to Normal, borderline, Abnormal based on their on their response to various autonomic function teststwo sub-groups, and with the values of HbA1c < 7 normal and HbA1c > 8 abnormal glycemic level was detected by Cat-ion exchange resin method.

Parasympathetic function tests were based on heart rate variation:

1. Deep breathing test ( Deep breathing difference).
2. Valsalva maneuver ( Valsalva ratio)
3. Supine to standing ( Postural tachycardia index).

Sympathetic function tests were based on Blood pressure responses:

1. BP responses on standing (Orthostatic test).
2. BP response to sustained handgrip.

## **RESULTS:**

The results obtained were treated statistically by One-way ANOVA, Chi Square tests and multiple comparisons to compare the variables between groups. ANS function was decreased in type 2 diabetes patients, Parasympathetic and sympathetic cardiovascular responses were significantly decreased in type 2 diabetes, Parasympathetic autonomic tests showed more sensitivity and significant compared to Sympathetic tests. Correlation of HbA1c in relation to various autonomic function tests showed significant in Patients with HbA1c > 8 and decline in the Performance of the tests.

## **CONCLUSION:**

In this study CAN is found in 75% of the patients, in significance to Parasympathetic activity found in 65% of patients and Sympathetic activity in 35 % of patients, and the conclusions of this study showed that Prevalence of CAN in relation to division of groups into Normal, border line, Abnormal groups showed that the study groups and its Correlation with HbA1c showed significant decline cardiac function.

## **Key words:**

Parasympathetic, Sympathetic, Cardiovascular autonomic function tests, denervation, HbA1c.

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## INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both, chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidney, nerves, heart, and blood vessels.<sup>1</sup>

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk can often be identified by serological evidence of an autoimmune pathologic process occurring in pancreatic islets and by genetic markers.<sup>1</sup>

In the other, prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response, and a degree of hyperglycemia causes pathologic and functional changes in various target tissues, but can be without clinical symptoms, for a long period of time before diabetes is detected.<sup>1</sup>

Diabetes mellitus is the single, most important metabolic disease recognized worldwide as one of the leading causes of death and disability<sup>2</sup>, Prevalence of diabetes in the adults worldwide was estimated to be 4.0% in 1995 and expected to be 5.4% by the year 2025. Its incidence is higher in developing countries than developed countries<sup>3</sup>.

Today, India leads in the world with its largest number of diabetic subjects as compared with any given country. It has been estimated that presently 19.4 million individuals are affected by diabetes and these numbers are expected to increase to 57.2 million by the year 2025<sup>4</sup>.

World Health Organization (WHO) has already declared India as the global capital of diabetes. In 1970s, the prevalence of diabetes among urban Indians was

reported to be 2.1%, and this has now risen to 12.1%<sup>5</sup>, countries and wealthier being not healthier in developing countries, WHO has revised the predicted number of diabetics in India to be nearly 80 million by 2030.<sup>6</sup>

**Table no 1. CLASSIFICATION OF DIABETES MELLITUS<sup>1</sup>**

Type	Alternative name
Ia	Insulin-dependent diabetes (IDDM) Juvenile onset diabetes
Ib	As for type Ia
II(non-obese)	Non-insulin-dependent diabetes (NIDDM) Maturity onset diabetes of the young
II(obese)	As for type II
III	Malnutrition-related diabetes Tropical diabetes
Other types	Asymptomatic diabetes Borderline diabetes Chemical diabetes Sub clinical diabetes Gestational diabetes

Diabetes mellitus is well known for chronic complications particularly the triad of neuropathy, retinopathy, and nephropathy, which have a close correlation with the metabolic abnormalities a characteristic of diabetes<sup>7</sup>.

Neuropathy is the most common complication of diabetes especially autonomic neuropathy which is not investigated so frequently, One of the earliest manifestations of diabetic autonomic neuropathy is denervation of cardiovascular system and assesment of cardiovascular reflexes affords a satisfactory evaluation, prescence of symptoms along with abnormal cardiovascular function tests suggest, poor prognosis, increased incidence of silent myocardial infarction, cardiac arrest, sudden death.<sup>7</sup>

Prevalence of DAN varies widely with asymptomatic individuals with diabetes, 20% had abnormal cardiovascular autonomic function, frequently coexists with other peripheral neuropathies and other diabetic complications,Least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life in people with diabetes.<sup>8,9</sup>

## **AIMS AND OBJECTIVES OF THE STUDY**

1. To determine the prevalence of cardiac autonomic neuropathy in type 2 Diabetes Mellitus by doing cardiac autonomic function tests.
2. To correlate Cardiac autonomic neuropathy in type 2 Diabetes mellitus with glycosylated haemoglobin and other complications like retinopathy and microalbuminuria.

## REVIEW OF LITERATURE

### HISTORICAL REVIEW OF LITERATURE<sup>11-15</sup>

The earliest known record of diabetes was mentioned on the 3rd Dynasty Egyptian papyrus (1552 BC) by physician Hesy-Ra; it mentions polyuria as a symptom. The first described cases are believed to be of type 1 diabetes. Indian physicians around the same time identified the disease and classified it as *madhumeha* or *honey urine* noting that the urine would attract ants<sup>11</sup>.

The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Appollonius of Memphis. The first complete clinical description of diabetes was given by the Ancient Greek physician Aretaeus of Cappadocia during 1st century AD, who noted the excessive amount of urine which passed through the kidneys and gave the disease the name "diabetes." He described it as "the melting down of flesh and limbs into urine" during 1st century AD. In 164 AD, the Greek physician Galen of Pergamum mistakenly diagnoses diabetes as an ailment of the kidneys<sup>11</sup>.

Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400-500 AD with type 1 associated with youth and type 2 with being overweight. Diabetes mellitus appears to have been a death sentence in the ancient era. Hippocrates makes no mention of it, which may indicate that he felt the disease was incurable.

In medieval Persia, Avicenna (980–1037) provided a detailed account on diabetes mellitus in *The Canon of Medicine*, "describing the abnormal appetite and the collapse of sexual functions," and he documented the sweet taste of diabetic urine. Avicenna recognized primary as well as secondary diabetes. He also described diabetic gangrene, and treated diabetes using a mixture of lupine,

Up to the 11th century, diabetes was commonly diagnosed by "water tasters," who drank the urine of those suspected of having diabetes as the urine of people with diabetes was thought to be sweet-tasting.

In the 15th century, Paracelsus identified diabetes as a serious general disorder. The term "mellitus" or "from honey" was added by the Britian John Rolle in the late 1700s to separate the condition from diabetes insipidus which is also associated with frequent urination. It was in 1776 that Matthew Dobson confirmed that the sweet taste comes from an excess of a kind of sugar in the urine and blood.

The French physician, Priorry, during the late 1850s, used to advise diabetic patients to eat extra large quantities of sugar as a treatment modality. In 1869, Paul Langerhans, a German medical student, announced in a dissertation that the pancreas contains two systems of cells; one set that secretes the normal pancreatic juice. The function of the other was unknown. Several years later, these cells were identified as the "islets of Langerhans."

During the time period from 1910-1920, the physicians Frederick Madison Allen and Elliot P. Joslin, emerged as the two leading diabetes specialists in the United States. Joslin believed diabetes to be "the best of the chronic diseases" because it was "clean, seldom unsightly, not contagious, often painless and susceptible to treatment." In 1913, after three years of extensive studies on diabetes, Frederick Allen published "*Studies Concerning Glycosuria and Diabetes*"; a book that was significant for the revolution in diabetes therapy which was developed from it. Allen in 1919 also published "*Total Dietary Regulation in the Treatment of Diabetes*".

In this article he cited the exhaustive case records of 76 out of the 100 diabetes patients he had observed. He became the director of diabetes research at the Rockefeller Institute in the same year.

Sir Harold Percival (Harry) Himsworth was the first person to clearly make the distinction between what is now known as type 1 diabetes and type 2 diabetes, and this was published in January 1936.

During 1940's, the link was found between diabetes and its long-term complications involving the organs like the kidneys and eyes. This was followed by the development of the long acting insulin NPH in the 1940s. It was also during this period that the American Diabetes Association was founded by 28 physicians. Identification of the first of the sulfonylureas occurred in 1942. In 1944, standard insulin syringe was developed, helping to make diabetes management more uniform.

In 1946, Dr. Best co-founded a diabetes association under the name of Diabetic Association of Ontario. Later, in 1953, it was formally established as the Canadian Diabetes Association. In the same year, Nova Scotia and Alberta establish provincial diabetes organizations. In 1956, L'Association Diabète Quebec was established.

In 1950's insulin zinc proportions were developed by Hallas – Moller and coworkers as lente (slow acting) insulin. In 1955, oral drugs are introduced to help lower blood glucose levels. The initial phenformin was withdrawn worldwide (in the U.S. in 1977) due to its potential for sometimes fatal lactic acidosis and metformin was first marketed in France in 1979, but not until 1994 in the US.

Sir Frederick Sanger identified the amino acid sequence of insulin in beef, pork and sheep in 1956 for which he received a Nobel Prize, amino acid sequence of insulin in humans was identified only in the 1960's.

In 1959, two major types of diabetes were recognized; type 1 (insulin-dependent) diabetes and type 2 (non-insulin-dependent) diabetes.

During the 1960's, apart from identifying the amino acid sequence in humans, the purity of insulin was improved. The method of testing for urinary sugar levels at home increased the level of control of diabetes in people during the same period. The first pancreas transplant was performed at the University of Manitoba in the year 1966.

The radioimmunoassay for insulin, was discovered by Rosalyn Yalow and Solomon Berson for which Yalow received the 1977 Nobel Prize in Physiology or Medicine. In 1980, U.S. biotech company Genentech developed biosynthetic human insulin was isolated from genetically altered bacteria, which produce large quantities of insulin.

The purified insulin was distributed to pharmacies for use by diabetes patients. Initially, this development was not regarded by the medical profession as a clinically meaningful development. The first insulin pen delivery system was introduced in 1986.

In 1988, Dr. Gerald Reaven identified the constellation of symptoms now called metabolic syndrome.

In 1989, the Banting Museum and Education Centre in London, Ontario was inaugurated; Her Majesty Queen Elizabeth & the Queen Mother lighted the Flame of Hope.

Identification of the first thiazolidinedione as an effective insulin sensitizer was during the 1990s.

In 1993, Diabetes Control and Complications Trial (DCCT) report was published, DCCT results clearly demonstrated that intensive therapy (i.e., more frequent doses and self-adjustment according to individual activity and eating patterns) delayed the onset and progression of long-term complications in individuals with type 1 diabetes.

In 1995, DES launched its first education awareness campaign. In the same year, the Canadian Diabetes Association launched its web site. It turned out to be an award-winning source of diabetes-related information for people all over the world. In the year 1996, the 75th Anniversary of the discovery of insulin was celebrated around the world. As part of the celebration, the Canadian Diabetes Association presented a symposium entitled "75 Years of Progress in Diabetes Care, Management and Treatment." By this time, the advent of insulin analogues which had vastly improved absorption, distribution, metabolism, and excretion characteristics were found to be clinically meaningful.

During 1998, the United Kingdom Prospective Diabetes Study (UKPDS) was published. UKPDS results clearly identified the importance of good glucose control and good blood pressure control in the delay and/or prevention of complications in type 2 diabetes. The clinical practice guidelines for the management of diabetes in Canada were released by the Canadian Diabetes Association during the same year. Guidelines for the Nutritional Management of Diabetes were released in the year 1999.

In 2001, the Diabetes Prevention Program was launched in USA. In 2003, the names Insulin Dependent Diabetes Mellitus (IDDM) for Type 1 & Non-Insulin Dependent Diabetes Mellitus (NIDDM) for Type 2 Diabetes were formally dropped. Clinical Guidelines by American Diabetes Association were issued in the same year.

The Human Genome Project was also started in 2003. The first genome-wide association studies for diabetes were initiated in 2007.

During 2008, the Canadian Diabetes Association released their updated clinical practice guidelines on management of Diabetes. The American Diabetes Association released their updated clinical Practice Guidelines on management of Diabetes also in the same year and it was again updated in the year 2012.

## EPIDEMIOLOGY

Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes worldwide, accounting for 90% of cases globally. An epidemic of T2DM is under way in both developed and developing countries, although the brunt of the disorder is felt disproportionately in non-European populations as evidenced by studies in Latin American populations, Native American and Canadian communities, Pacific and Indian Ocean island populations, and in India and Australian Aboriginal communities.

Globally, the number of people with diabetes is expected to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025. Alarming increases in the prevalence of diabetes have occurred in various Chinese populations. Type 2 diabetes has become one of the world's most important public health problems.<sup>16</sup>

The reported prevalence of DAN is widely variable depending on the number studies have been carried out in the community, clinic, or tertiary referral center, Type and number of tests performed and the presence or absence of signs and symptoms of autonomic neuropathy. Other factors include the lack of a standard accepted definition of DAN, different diagnostic methods, variable study selection criteria, and referral bias<sup>17</sup>.

Another group observed nearly an identical prevalence rate 16.6% for Insulin-Dependent diabetes.<sup>18</sup>

Verrotti et al. found that 47 of 110 diabetic children and adolescents showed one or more abnormal tests for cardiovascular autonomic dysfunction, these results, indicate that prevalence rates will vary depending on, d criteria used to define autonomic dysfunction<sup>19</sup>.

**TABLE NO 2 EPIDEMIOLOGIC DETERMINANTS AND RISK FACTORS  
OF TYPE 2 DIABETES<sup>16</sup>**

<b>GENETIC FACTORS</b>  Genetic markers  Family history  “Thrifty gene(s)”
<b>DEMOGRAPHIC CHARACTERISTICS</b>  Sex  Age  Ethnicity
<b>BEHAVIORAL AND LIFESTYLE-RELATED RISK FACTORS</b>  Obesity (including distribution of obesity and duration)  Physical inactivity  Diet  Stress  Westernization, urbanization, modernization

Sex, age, and ethnic background are important factors in determining risk of developing T2DM. Disorder is more common in women, and the increased prevalence in certain racial and ethnic groups has already been alluded to, Age is a critical factor<sup>16</sup>.

Type 2 diabetes has been viewed in the past as a disorder of aging, with an increasing prevalence with age, remains true today, however, a disturbing trend has become apparent in which the prevalence of obesity and T2DM in children is rising dramatically, in the past, it was believed that the overwhelming majority of children with diabetes had type 1 diabetes (T1DM), and only 1% to 2% of diabetic children were considered to have type 2 or other rare forms of diabetes<sup>16</sup>.

#### **RISK FACTORS FOR TYPE 2 DIABETES MELLITUS<sup>16</sup>**

1. Habitual Physical Activity
2. Over weight BMI>25.
3. Race/ethnicity (e.g., African American, Latin American, Native American, Asian American, Pacific Islander).
4. Previously identified IFG or IGT.
5. Hypertension ( $\geq 140/90$  mm Hg in adults)
6. HDL cholesterol  $\leq 35$  mg/dL (0.90 mmol/L) and/or a triglyceride level  $\geq 250$  mg/dL (2.82mmol/L)
7. History of GDM or delivery of a baby weighing  $>9$  lb (4.1 kg).
8. PCOD

**TABLE NO 3. CRITERIA FOR THE DIAGNOSIS OF TYPE 2 DIABETES MELLITUS<sup>16</sup>**

<b>TEST</b>	<b>NORMOGLYCE MIA (mg/dl)</b>	<b>IFG(mg/ dl)</b>	<b>IGT(mg/ dl)</b>	<b>DIABET ES</b>
<b>FPG</b>	<100	100-125		>126
<b>2hr PG</b>	<140		140-199	>200
<b>PLASMA CONCENTRATI ON</b>				>200mg/d l

### **SCREENING FOR TYPE 2 DIABETES MELLITUS<sup>16</sup>**

Undiagnosed T2DM is common, with an estimated lag of 5 to 7 years between the onset of diabetes and diagnosis. It is estimated that in up to 30% of affected people the disease are undiagnosed. Subjects with IGT and undiagnosed T2DM are at significantly increased risk for coronary heart disease, stroke, and peripheral vascular disease.

Thus, this delay in the diagnosis of T2DM causes an increase in microvascular and macrovascular disease. In addition, affected individuals have a greater likelihood of having dyslipidemia, hypertension, and obesity.

Screening with a fasting plasma glucose level is recommended every 3 years for individuals over the age of 45, as well as for younger individuals who are overweight (body mass index  $\geq 25 \text{ kg/m}^2$ ) and have one or more additional risk factors<sup>16</sup>.

## **GLYCOSYLATED HAEMOGLOBIN**

### **HISTORY**

Glycated hemoglobin is also known as glycohemoglobin, glycosylated hemoglobin or as hemoglobin A1c, HbA1c, A1C, or Hb1c. About 40 years ago Glycated haemoglobin (HbA1c) was initially identified as an "unusual" haemoglobin in diabetic patients.

HbA1c was first separated from other forms of hemoglobin by Huisman and Meyering in the year 1958, It was characterized as a glycoprotein by Bookchin and Gallop in 1968, Samuel Rahbar et al. in 1969 first described its relationship with diabetes. The use of hemoglobin A1c for monitoring the degree of control of glucose metabolism in diabetic patients was proposed in 1976 by Anthony Cerami, Ronald Koenig and coworkers<sup>22</sup>.

### **STRUCTURE AND BIOSYNTHESIS<sup>23</sup>:**

Biosynthesis of HbA1c involves post – translational, non-enzymatic slow glycosylation of Hb A within the RBC, occurring continuously throughout its 120 days life span in the circulation.

The terminology of glycated haemoglobin is confusing but needs to be understood since the various methods in use measure different components of the whole. A brief consideration of the chemical reactions involved in the formation of glycated haemoglobin will help to explain both the basis for using this measurement, and the rather confusing terminology that surrounds the subject.

1. Initially uncharged amino groups of haemoglobin react non-enzymically and reversibly with the open-chain form of glucose to produce a Schiff's base.

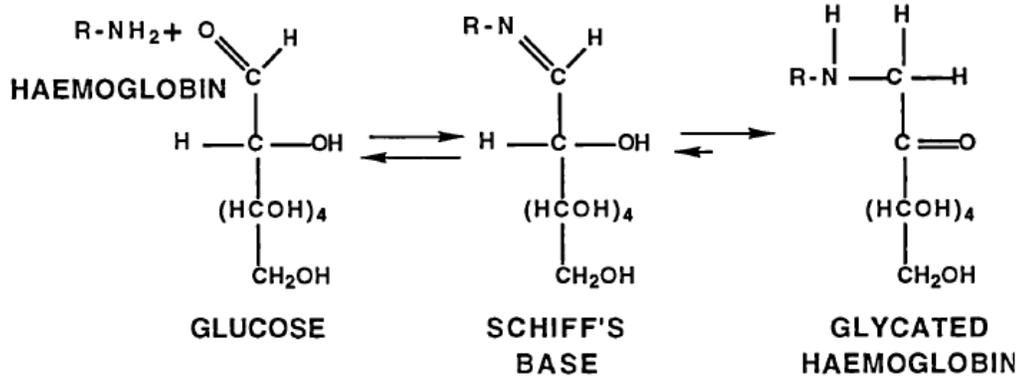
2. This may subsequently undergo an Amadori rearrangement reaction to form the more stable Amadori product, which is referred to as glycated haemoglobin<sup>23</sup>.

Most factors which might affect these nonenzymic reactions in the blood are fairly constant, including pH and the concentration of haemoglobin, the main factor that changes is the concentration of blood glucose, proportion of glycated haemoglobin formed is a reflection of the 'average' concentration of blood glucose over the previous 48 weeks.

The most abundant form of glycated haemoglobin is called HbA<sub>1c</sub>, formed when glucose reacts with the N-terminal valine residue of the β globin chains, this product is more negatively charged than the main type of adult haemoglobin, HbA<sub>1c</sub>, and was discovered because it eluted earlier from a cation exchange column. There are two other minor peaks, HbA<sub>1a</sub> and HbA<sub>1b</sub>, which can be separated on large columns. These three fractions run together and more quickly on many ion exchange and electrophoretic methods, in which case they are called the fast fraction or HbA<sub>1c</sub> = HbA<sub>1c</sub> (1a + 2b + 3c).

Glucose also reacts with the N-terminal valine of the α globin chain and several ε amino groups of lysine residues on both the α and β globin chains. Although these forms are not separated from HbA<sub>0</sub> by those methods that depend on separation by charge, they are specifically retained by the aminophenyl boronate ligands used in affinity chromatography columns.

**Schematic representation of the adduction of the glucose to the amino terminal  
of the beta chain of Hemoglobin to form HbA1c. Figure 1**



**CLINICAL SIGNIFICANCE OF HBA1C<sup>22</sup>:**

The HbA1c level is directly proportional to average blood glucose concentration over the previous 4 weeks to 3 months or the average lifespan of the erythrocyte, it is important to remember that HbA1c only reflects glucose concentrations over 4 to 8 weeks provided there is a normal hemoglobin concentration and normal red blood cell survival, Total glycated hemoglobin (Total GHb) refers to all the glycated hemoglobins, including glycated hemoglobin variants.

Prior Expert Committees have not recommended use of the HbA1c for diagnosis of diabetes, in part due to lack of standardization of the assay. However, HbA1c assays are now highly standardized so that their results can be uniformly applied both temporally and across populations. In their recent report 25, an International Expert Committee, after an extensive review of both established and emerging epidemiological evidence, recommended the use of the HbA1c test to diagnose diabetes, with a threshold of 6.5%, and ADA affirms this decision.

The diagnostic HbA1c cut-off point of 6.5% is associated with an inflection point for retinopathy prevalence, as are the diagnostic thresholds for FPG and 2-h PG<sup>24</sup>.

The diagnostic test should be performed using a method that is certified by the NGSP and standardized or traceable to the DCCT reference assay. Point-of-care HbA1c assays are not sufficiently accurate at this time to use for diagnostic purposes.

There is an inherent logic to using a more chronic versus an acute marker of dysglycemia, particularly since the HbA1c is already widely familiar to clinicians as a marker of glycemic control. Moreover, the HbA1c has several advantages to the FPG, including greater convenience, since fasting is not required, evidence to suggest greater preanalytical stability, and less day-to-day perturbations during periods of stress and illness<sup>24</sup>.

These advantages, however, must be balanced by greater cost, the limited availability of HbA1c testing in certain regions of the developing world, and the incomplete correlation between HbA1c and average glucose in certain individuals. In addition, the HbA1c can be misleading in patients with certain forms of anemia and hemoglobinopathies, which may also have unique ethnic or geographic distributions<sup>24</sup>.

For patients with a hemoglobinopathy but normal red cell turnover, such as sickle cell trait, an HbA1c assay without interference from abnormal hemoglobins should be used. For conditions with abnormal red cell turnover, such as anemias from hemolysis and iron deficiency, the diagnosis of diabetes must employ glucose criteria exclusively<sup>24</sup>.

The established glucose criteria for the diagnosis of diabetes remain valid. It is likely that in such cases the health care professional would also measure an HbA1c test as part of the initial assessment of the severity of the diabetes and that it would (in most cases) be above the diagnostic cut-off point for diabetes. However, in rapidly evolving diabetes, such as the development of type 1 diabetes in some children, HbA1c may not be significantly elevated despite frank diabetes. Just as there is less than 100% concordance between the FPG and 2-h PG tests, there is not full concordance between HbA1c and either glucose-based test<sup>24</sup>.

**DIAGNOSIS OF DIABETES<sup>24</sup>:**

- HbA1C assay is an accurate, precise measure of chronic glycemic levels and correlates well with the risk of diabetes complications.
- HbA1C assay has several advantages over laboratory measures of glucose.
- Diabetes should be diagnosed when HbA1C is 6.5%, should be confirmed with a repeat HbA1C test. Confirmation is not required in symptomatic subjects with plasma glucose levels > 200 mg/dl.
- Hb A1C testing is not possible, previously recommended diagnostic methods are acceptable.
- Hb A1C testing is indicated in children in whom diabetes is suspected but the classic symptoms and acasual plasma glucose >200 mg/dl are not found.

**For the identification of those at high risk for diabetes<sup>24</sup>:**

- The risk for diabetes based on levels of glycemia is a continuum there is no lower glycemic threshold at which risk clearly begins.
- Categorical clinical states pre-diabetes, IFG, and IGT fail to capture the continuum of risk and will be phased out of use as Hb A1C measurements replace glucose measurements.
- Diagnosis of diabetes, the HbA1C assay has several advantages over laboratory measures of glucose in identifying individuals at high risk for developing diabetes.
- HbA1C levels below the threshold for diabetes but 6.0% should receive demonstrably effective preventive interventions.
- HbA1C level at which population-based prevention services begin should be based on the nature of the intervention, the resources available, and the size of the affected population.

## CARDIAC AUTONOMIC NEUROPATHY

### HISTORY:

Sympathetic and parasympathetic innervations in the heart play a major role in the regulation of cardiac function. The existence of sensory nerve endings in the heart was first suggested in 1894 although Wollard, in 1926, concluded that a large portion of cardiac sensory endings were of vagal origin.

Wollard observed that an experimental bilateral stellectomy did not markedly modify what he considered to be the normal aspect of the sensory supply to the heart. Subsequently, Holmes observed survival of the 'terminal nervous network' after vagotomy, thus hypothesizing that sympathetic afferent fibres were likely to be implicated.

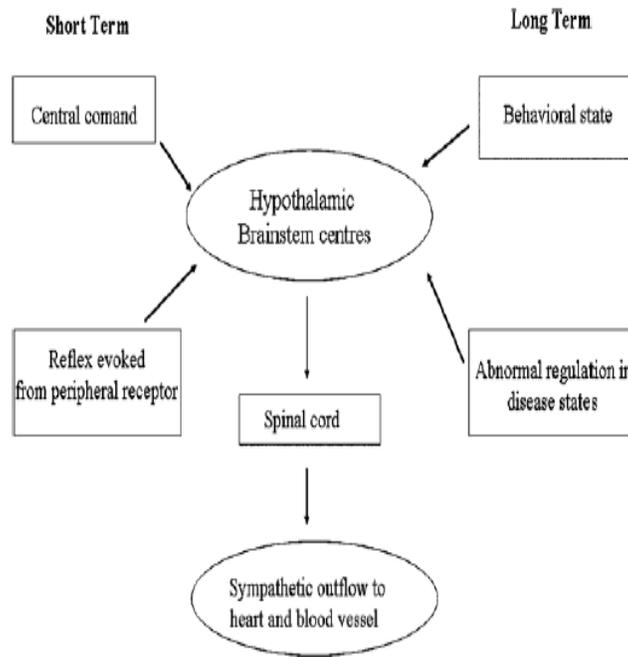
In 1963, Khabarova observed that "afferent fibers of spinal type innervate the same regions and layers of the heart as the vagal fibers, and their afferent fibers and endings frequently lie side by side with afferent fibers and endings of the vagus nerve".

This opinion has the merit of agreeing with the electrophysiological findings which, so far, have suggested that vagal and sympathetic sensory nerve endings are intermingled in all regions of the heart<sup>27</sup>.

## **ANATOMY**

Great progress has been made over the past two decades in identifying the central pathways and neurotransmitters that regulate the cardiovascular system, particularly those that subserve the short-term reflex control of sympathetic activity, importance of the hypothalamus and other forebrain regions in cardiac regulation has been recognized for many years, but relatively little is known about the functional organization of forebrain mechanisms that regulate the cardiovascular system, both in the short- and long-term. Much more attention is now being paid to define these forebrain mechanisms, these Central mechanisms can be up- or down-regulated in response to long-term physiological, para physiological stimuli, such as exercise training<sup>28</sup>, changes in environmental temperature<sup>29</sup>, heart failure<sup>30</sup>, hypertension, and diabetes.<sup>31</sup>

**Figure 2: Representing short and long term mechanisms that influence sympathetic outflow to heart and blood vessels:**



## **STUDY OF AUTONOMIC NEUROPATHY**

Quantitative tests of autonomic function have historically lagged behind measures of motor and sensory nerve function deficits, lack of interest in the development of such measures was partly due to the erroneous view that autonomic neuropathy was only a small contributor to Neuropathy<sup>27</sup>

In the early 1970s, Ewing et al. proposed five simple non-invasive cardiovascular reflex tests that have been applied successfully in many studies in 1985<sup>32</sup>

In fact, many studies using these tests have provided information on the prevalence of DAN its natural history, clinical prognosis and relationship with other chronic diabetic complications, clinical reflex tests, the tests used most widely, and best known in their physiological bases are heart rate variation on deep breathing and lying-to-standing, the Valsalva manoeuvre and BP response to standing<sup>27</sup>

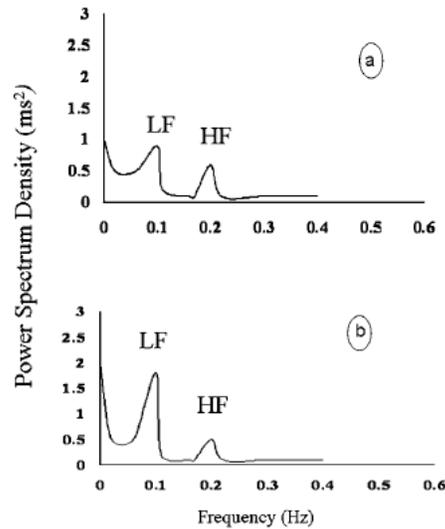
In addition to traditional cardiovascular reflex tests, other methods have been developed, such as plasma NE and NE spillover, spectral analysis of HRV, which assesses indirectly cardiac autonomic dysfunction, PET, which is the first technique able to provide a direct characterization of the pattern and extent of cardiac sympathetic dysfunction<sup>33</sup>, and MIBG ([<sup>123</sup>I]-meta-iodobenzylguanidine) scintigraphy, which is a recent non-invasive method for the in vivo evaluation of sympathetic activity through measurement of postganglionic presynaptic noradrenergic uptake.<sup>34</sup>

In spite of PET and MIBG to directly characterize cardiac autonomic dysfunction, spectral analysis appears to remain the primary technique in evaluating cardiac autonomic dysfunction due to its low cost, ease of use and good intra-individual reproducibility, advantage of spectral analysis is the possibility of assessing not only the amount of overall variability, but also the frequency-specific oscillations and the relative impact on variability of sympathetic and vagal modulation in the heart.<sup>34</sup>

Two major oscillatory components are usually detectable in spectral analysis.

1. synchronous with respiration, is described as HF (high frequency; 0.18–0.40 Hz and varying with respiration) and is generally considered a marker of vagal activity, whereas the other, corresponding to the slow waves of arterial pressure, is described as LF (low frequency; 0.03–0.15 Hz)<sup>34,35</sup> Show in the fig:3

Figure 3: Spectral Analysis of RR Interval In Healthy Subjects And In Type II DM:



Manoeuvres enhancing the sympathetic drive or pathological condition associated with sympathetic hyperactivity lead to a marked relative increase in the LF component, disagreement in its relationship with sympathetic tone is due to the observation that both LF and HF are reduced after atropine Infusion.

Nevertheless, the hypothesis that LF can be influenced by the vagus is valid only if LF is evaluated in absolute and not in relative terms, thus it is more appropriate to consider the relationship between LF and HF (LF/HFratio) in terms of sympatho-vagal balance, rather than consider them separately as independent indices of sympathetic and vagal activity<sup>27</sup>.

Previous studies have demonstrated that an unbalanced sympathetic/parasympathetic tone, with a prevalence of sympathetic activity, is associated with higher cardiovascular mortality in Type II diabetic patients. Such unbalanced sympathetic/parasympathetic tone can be responsible for many cases of sudden death in diabetic patients, despite the absence of documented pre-existing heart disease.<sup>37-40</sup>

## **PATHOGENESIS OF CARDIAC AUTONOMIC NEUROPATHY<sup>41</sup>.**

Hypotheses concerning the multiple etiologies of diabetic neuropathy include

1. Metabolic insult to nerve fibers.
2. Neurovascular insufficiency.
3. Autoimmune damage.
4. Neurohormonal growth factor deficiency<sup>41</sup>.

### **FACTORS HAVE BEEN IMPLICATED IN THIS PATHOGENIC PROCESS.**

Hyperglycemic activation of the polyol pathway leading to accumulation of sorbitol and potential changes in the NAD:NADH ratio may cause direct neuronal damage and/or decreased nerve blood flow.

Activation of protein kinase C induces vasoconstriction and reduces neuronal blood flow. Increased oxidative stress, with increased free radical production, causes vascular endothelium damage and reduces nitric oxide bioavailability; alternately, excess nitric oxide production may result in formation of peroxynitrite and damage endothelium and neurons-Nitrosative stress<sup>42,43</sup>

Immune mechanisms may also in a subpopulation of neuropathy implicated.<sup>44,45</sup>

Reduction in neurotrophic growth factors and deficiency of essential fatty acids.<sup>46,47</sup> formation of advanced glycosylation end products, localized in endoneurial blood vessels<sup>48</sup> also result in reduced endoneurial blood flow and nerve hypoxia with altered nerve function.

The result of this multifactorial process may be activation of polyADP ribosylation depletion of ATP, resulting in cell necrosis and activation of genes involved in neuronal damage<sup>49,50</sup>.

## **CLINICAL MANIFESTATION<sup>41</sup>:**

The metabolic disorders of diabetes lead to diffuse and widespread damage of peripheral nerves and small vessels.

Clinical manifestations of autonomic dysfunction and other microvascular complication frequently occur concurrently but in inconsistent patterns . The ubiquitous distribution of the ANS renders virtually all organs susceptible to autonomic dysfunction. Therefore, a patient diagnosed with diabetes should be suspected of having at least subclinical disturbances of the ANS. Overt signs and symptoms of autonomic disease fall into one or more of the following categories.

### **CARDIOVASCULAR:**

- Exercise intolerance.
- Orthostatic hypotension
- Silent myocardial ischemia
- CAN and mortality
- Association of CAN with major cardiovascular events
- CAN and sudden death.
- Cerebrovascular disease and CAN.
- Progression of CAN.

### **GASTROINTESTINAL:**

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

**GENITOURINARY:**

- Neurogenic bladder (diabetic cystopathy)
- Erectile dysfunction
- Retrograde ejaculation
- Female sexual dysfunction (e.g., loss of vaginal lubrication)

**METABOLIC:**

- Hypoglycemia unawareness
- Hypoglycemia-associated autonomic failure

**SUDOMOTOR**

- Anhidrosis
- Heat intolerance
- Gustatory sweating
- Dry skin

**PUPILLARY**

- Pupillomotor function impairment
- Argyll-Robertson pupil.

## **EVALUATION OF CARDIOVASCULAR SYMPTOMS:**

### **1. Exercise Intolerance.**

A reduced response in heart rate and blood pressure during exercise, decreased cardiac output in response to exercise in individuals with CAN was demonstrated by Roy et al.<sup>51</sup> Severity of CAN has also been shown to correlate inversely with an increase in heart rate at any time during exercise and with the maximal increase in heart rate. Decreased ejection fraction, systolic dysfunction, and diastolic filling limit exercise tolerance<sup>51</sup>.

Given the potential for impaired exercise tolerance, diabetic patients who are likely to have CAN should be subjected to cardiac stress testing before undertaking an exercise program<sup>52</sup>.

### **2. Orthostatic Hypotension:**

Orthostatic hypotension is defined as a fall in blood pressure, i.e., 20 mmHg for systolic or 10 mmHg for diastolic blood pressure, in response to postural change, from supine to standing<sup>53</sup>.

OH in diabetics is usually due to damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature<sup>54</sup>, decrease in cutaneous, splanchnic, and total vascular resistance occurs in the pathogenesis of this disorder. Physiologically, in response to postural change there is an increase in plasma nor epinephrine, there may be a reduction in response relative to the fall in blood pressure in patients with OH<sup>55</sup>.

Diminished cardiac acceleration and cardiac output, particularly in association with exercise, may also be important in the presentation of this disorder<sup>56</sup>, frequent fluctuations in the degree of OH reflect, postprandial blood pooling, hypotensive role

of insulin, Changing patterns of fluid retention due to renal failure and congestive heart failure<sup>57-59</sup>

### **SYMPTOMS**

1. Typically present with lightheadedness and presyncopal symptoms.
2. Dizziness, weakness, fatigue, visual blurring, and neck pain also may be due to OH patients, however, remain asymptomatic despite significant falls in blood pressure<sup>60</sup>.

### **Treatment Goals Of Oh Due To CAN:**

Consist of therapies to increase the standing blood pressure, balanced against preventing hypertension in the supine position.

Provide education to patients so that they avoid situations that result in the creation of symptoms and syncopal attacks<sup>61</sup>.

### **Silent Myocardial Ischemia<sup>41</sup>:**

The cause of silent myocardial ischemia in diabetic patients is controversial. It is clear, however, that a reduced appreciation for ischemic pain can impair timely recognition of myocardial ischemia or infarction and there by delay appropriate therapy.

## **CARDIOVASCULAR AUTONOMIC NEUROPATHY AND DIABETES**

DAN is among the least recognized and understood complication of diabetes, despite its significant negative impact on survival and quality of life in people with diabetes<sup>62,63</sup>.

Metabolic disorders of diabetes lead to diffuse and widespread damage of peripheral nerves and small vessels, One of the most overlooked complications of diabetes is CAN<sup>64</sup>.

CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and it causes abnormalities in heart rate control and vascular dynamics<sup>65</sup>. Reduced heart rate variation is the earliest indicator of CAN<sup>66</sup>

Recently, in the National Cholesterol Education Program (NCEP), diabetes has been considered a factor for cardiovascular risk development<sup>67</sup>,it is recommended that greater precautionary measures, similar to those for established CVD, should be taken in patients with diabetes.<sup>68-70</sup>

Several studies have provided evidence for an increased mortality risk among diabetic individuals with CAN compared with individuals without CAN<sup>71,73</sup>.

Ewing et al.reported a 2.5 year mortality rate of 27.5% that increased to 53% after 5 years in diabetic patients with an abnormal autonomic function test compared with a mortality rate of only 15% over the 5 year period among diabetic patients with normal autonomic function test results.<sup>72</sup>

A study by O'Brien et al. reported 5 year mortality rates of 27% in patients having asymptomatic autonomic neuropathy compared with an 8% mortality rate in diabetic subjects with normal autonomic function tests.<sup>72</sup>

Rathmann et al. reported the results of a study designed to assess the risk of mortality due to CAN among patients with CAN but without a clinical manifestation of severe complications (proteinuria, proliferative retinopathy, coronary heart disease or stroke) 8 years after their first clinical examination<sup>73</sup>.

Autonomic dysfunction was found to be an independent risk factor with a poor prognosis, despite the increased association with mortality, the causative relationship between CAN and the increased risk of mortality has not been established conclusively.

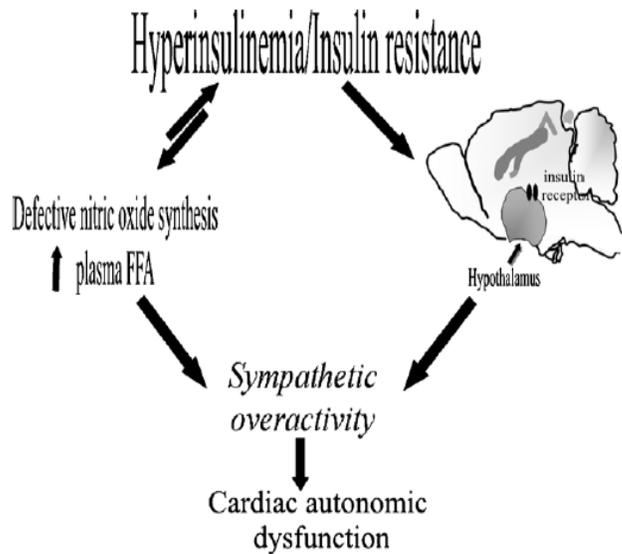
Several mechanisms have been suggested as being responsible for autonomic dysfunction and, among these, hyperinsulinaemia/insulin resistance seems to play a crucial role, there is strong evidence that acute physiological and pharmacological (euglycaemic clamp) increments in plasma insulin concentration stimulate sympathetic activity, as determined by measurements of venous plasma catecholamines concentration<sup>74</sup>, plasma NE spillover<sup>75</sup> or direct microneurographic recordings of sympathetic nerve action potentials targeted at the skeletal muscle vasculature<sup>76</sup>.

In particular, short-term infusion of insulin and chronic hyperinsulinaemia induce a re-setting in cardiac autonomic control, mainly secondary to an increase in sympathetic activity these findings strengthen the hypothesis that hyperinsulinaemia/insulin resistance is implicated directly in the pathogenesis of cardiovascular mortality associated with Type II diabetes mellitus through sustained overactivation of the cardiac sympathetic nervous system<sup>33-35</sup>.

Over the past decade, evidence has been accumulated indicating a double mechanism of action of insulin: central, neural action and a peripheral action, insulin crosses the blood–brain barrier<sup>36,38</sup>, and insulin receptors have been found in several distinct regions of the central nervous system such as the median hypothalamus<sup>37</sup>. Peripheral effects of insulin, at the cardiac sympathetic level, are mediated by NEFAs (non-esterified fatty acids) and the NO (nitric oxide)/ L-arginine pathway.

Insulin-resistant states are characterized by alteration in both of these functions. Recent evidence indicates that these two regulatory systems interact closely and that a defect in NO synthesis and an increase in plasma NEFAs may have an important role with regard to sympathetic action.<sup>27</sup>

**FIGURE 4: Effects Of Hyperinsulinemia In Relation To Cardiac Autonomic Dysfunction:**



NO release accounts for the vasodilator action of insulin<sup>83</sup>. In vitro, insulin activates L-arginine transport and stimulates NO release in cultured vascular endothelial cells<sup>84</sup>.

In vivo, insulin-induced vasodilatation is abolished by a stereospecific inhibitor of NO synthase, L-NMMA (NG-monomethyl-L-arginine), and by an inhibition of the synthesis of tetrahydrobiopterin, a cofactor necessary for NO synthesis<sup>85,86</sup>.

Insulin may stimulate NO release either by a direct local effect on the vascular endothelium or by stimulating sympathetic nitrergic fibers. Comparison of vasodilatation during local intraarterial and systemic intravenous insulin infusion has provided conflicting results<sup>83</sup>.

Insulin stimulates NO release and blood flow in the denervated limb in patients who have undergone regional sympathectomy, indicating that it stimulates blood flow by a direct action at the vasculature<sup>87</sup>. Consistent with this hypothesis, insulin causes hypotension in patients with autonomic failure<sup>88</sup>.

In innervate limbs, however, stimulation of sympathetic vasodilator outflow by insulin appears to be necessary to induce vasodilatation, because the prevention of insulin-induced sympathetic activation by dexamethasone abolished the insulin-induced vasodilatation<sup>89</sup>.

The sympathetic nervous system modulates insulin-induced vasodilatation, as indicated by the much more rapid vasodilatation in the denervated compared with the innervated limb in patients with regional sympathectomy<sup>90</sup>.

Possibility of balance existing between the central neural sympatho-excitatory (via stimulation of neural peptide release) and sympatho-inhibitory (by stimulating NO release) action of insulin, as NO inhibits central neural sympathetic vasoconstrictor outflow<sup>91,92</sup>, it is possible to conclude that insulin causes vasodilatation by stimulating release of NO through a direct local effect on the vasculature and by stimulating neural vasodilator outflow.

Sympathetic vasoconstrictor tone restricts insulin induced vasodilatation, and the mechanisms causing this sympathetic overactivity are not known.

Hyperinsulinaemia is a candidate mechanism, but it is not invariably associated with sympathetic overactivity, as demonstrated by the normal sympathetic nerve activity in patients with insulinoma<sup>93,94</sup>, and alternative mechanisms need be considered.

NO inhibits central neural vasoconstrictor outflow in animals<sup>95,96</sup> and humans, it is therefore possible that the defect in NO synthesis found in many insulin-resistance<sup>states97</sup> contribute to sympathetic overactivity.

This defect in NO synthesis could be acquired or inherited, With regard to an inherited defect, recent studies indicate that polymorphisms in endothelial NO synthase are risk factors for CVD associated with insulin resistance<sup>98</sup>.

Thus it is possible to hypothesize that a defect in NO synthesis could contribute to both impaired insulin induced vasodilatation and sympathetic overactivity characteristic of an insulin-resistance state.

Study demonstrate that cardiac sympathetic overactivity occurs in Type II diabetic patients by raising plasma NEFA concentrations. In contrast, the same group of patients submitted to intensive insulin treatment to improve metabolic control had a secondary decline in plasma NEFA levels and a decrease in cardiac sympathetic nervous system activity<sup>101</sup>, more recently, we have demonstrated that increased post-prandial plasma NEFA concentrations are associated with an enhanced degree of oxidative stress and an increased LF/HF ratio, an index of cardiac sympathovagal balance<sup>102</sup>.

Such data seem to be particularly relevant in explaining the relationship between plasma NEFAs, oxidative stress and sudden death in Type II diabetic patients. In fact, it has been shown that increased plasma NEFA concentrations are a pro-oxidant factor<sup>102</sup>

## **ASSOCIATION OF CAN WITH MAJOR CARDIOVASCULAR EVENTS:<sup>41</sup>**

Relationship between baseline CAN and the subsequent incidence of a fatal or nonfatal cardiovascular event, defined:

1. Myocardial Infarction.
2. Heart failure.
3. Resuscitation from ventricular tachycardia or fibrillation.
4. Angina, the need for coronary revascularization.

**Katz et al.** showed that a simple bedside test that measured 1-min HRV during deep breathing was a good predictor of all-cause mortality for 185 patients (17.8% with DM) after MI<sup>107</sup>.

These investigators also suggested that cardiovascular autonomic function testing provided a predictive value that could be used to identify a subgroup of patients after an MI who are at high risk for cardiovascular death<sup>108</sup>.

## **PROGRESSION OF CAN<sup>41</sup>:**

Results of the cardiovascular autonomic function tests that are mediated mainly by the parasympathetic nervous system (e.g., heart rate response to deep breathing) are typically abnormal before those, responses that are mediated by the sympathetic nerves, increased frequency of abnormalities detected via tests of the parasympathetic system may merely be a reflection of the test (e.g., sensitivity) and not of fiber damage. Thus, it may be better to describe the natural history of autonomic dysfunction as developing from early to more severe involvement rather than to anticipate a sequence of parasympathetic and sympathetic damage.

Although much remains to be learned about the natural history of CAN, following observations provide some insight to progression of autonomic dysfunction:

1. It can be detected at the time of diagnosis.
2. Neither age nor type of diabetes are limiting factors in its emergence, being found in young individuals with newly diagnosed type 1 diabetes and older individuals newly diagnosed with type 2 diabetes.
3. Poor glycemic control plays a central role in development and progression, Intensive therapy can slow the progression and delay the appearance of abnormal autonomic function tests.
4. Subclinical autonomic neuropathy can be detected early using autonomic function tests.
5. Autonomic features that are associated with sympathetic nervous system dysfunction (e.g., orthostatic hypotension) are relatively late complications of diabetes.
6. CAN and diabetic nephropathy that contributes to high mortality rates.
7. Some individuals with symptoms associated with autonomic neuropathy die suddenly and unexpectedly .
8. Clinical signs and symptoms of autonomic dysfunction do not always progress.this underscores the need for performance of quantitative autonomic function tests to identify individuals at risk for premature death.
9. The relationship between autonomic damage and duration of diabetes is not clear although numerous studies support an association.
10. Prevalence and mortality rates may be higher among individuals with type 2 Diabetes, potentially due in part to longer duration of glycemic abnormalities before diagnosis.

## **MATERIALS AND METHODS**

### **1. SOURCE OF DATA:**

- The material for the present study was collected from Outpatient and inpatient department of medicine in BLDEU'S Shri B.M.Patil's medical college hospital and research centre, Bijapur .
- Period of study is from SEPTEMBER 2011 to JULY 2013.

### **2. METHOD OF COLLECTION OF DATA:**

- By detail history
- By detail clinical examination.
- By relevant investigations like Measurement of Blood Pressure by Mercury Sphygmomanometer, modified mouth piece for cardiovascular reflexes .
- Quantitative estimation of Microalbuminuria by ELISA.
- HBA1C by High performance Liquid Chromatographic methods.
- Ophthalmoscopy for Retinopathy changes.

## INCLUSION CRITERIA:

Patients diagnosed and established with Type 2 Diabetes mellitus.

### 3. EXCLUSION CRITERIA:

1. Presence of Uncontrolled Hypertension
2. Heart failure.
3. Fever.
4. Urinary Tract Infection.
5. Cirrhosis of Liver.
6. Other CNS causes:
  - Guillain Barre syndrome.
  - Myasthenia Gravis.
  - Myopathies.
  - Polymyositis.
  - Botulism.

### 5. SAMPLE SIZE:

Prevalence of Diabetic Autonomic Neuropathy is 50% in Type 2 Diabetes Mellitus, and allowable error at 20%, and 5 %, and calculated sample size is 156 using the below statistical formula:  $n = \frac{(1.96)^2 \times P}{L^2}$

### 6. STATISTICAL ANALYSIS:

Data will be analysed using Chi-square Test.

Descriptive Statistics and Analysis ANNOVA TEST is used.

Data will be presented diagrammatically and by Mean±SD

## **INVESTIGATIONS**

1. Blood- Hb, Total count ,Differential count , ESR .
2. Urine – Protein , Sugar , Microscopy for Microalbuminuria..
3. Lipid Profile
4. Blood sugar on admission,FBS on 2<sup>nd</sup> Day
5. PPBS
6. Serum Creatinine
7. ECG
8. Modified mouth Piece for Cardiovascular Reflexes.
9. Ophthalmoscopy

## RESULTS

The Prevalence study on Cardiac autonomic Neuropathy in Type II Diabetes comprised of 96 subjects and Research Study was done based on the Response elicited from the patient up on performing various Cardiovascular Autonomic tests with and in comparison with HbA1c, and other respective Parameters.

In this study CAN was found in 75% of the patients, in response to various autonomic test, 65% found in significance to Parasympathetic activity, and 35% significance to sympathetic activity based on the statistical analysis.

Statistical evaluation revealed that Heart Rate response to Valsalva was most sensitive in determining parasympathetic CAN, abnormal in 58 (60%) patients, borderline in 30 (31%) patients, and normal in 8 (8.3%) patients.

This was followed by HR response to deep breathing, abnormal in 24 (25%) patients and normal in 72 patients, HR response to standing showed abnormal 48 (50%), borderline 13 (13.5%) and normal in 35 (36.4%).

BP response to sustained Handgrip abnormal 41 (43%), borderline 51 (53%), normal 4 (4.1%), and BP response to orthostatic test abnormal 40 (42%), borderline 26 (27%), and normal 30 (31.2%).

In correlation to HbA1c showed abnormality in 88 (91.7%) patients and normal in 8 (8.3%) patients.

Microalbuminuria was detected in 45 patients (46.9%), and Diabetic retinopathy 15 (15.6%).

## **1. TESTS REFLECTING PARASYMPATHETIC ACTIVITY:**

### **A.Heart rate response to valsalva manoeuvre**

HR response to Valsalva maneuver was evaluated and grouped in to Normal,Borderline,Abnormal pts with Mean, SD,CV ratio show in **table no 4,5** Mean VR among abnormal patient is 0.8152,and the confidence interval for is (0.7623-0.8681),among bordeline patient is 1.1763, and the confidence interval for borderline patient is (1.1484-1.2041),normal patient is 1.4230, and the confidence interval in normal patient is 0.9685-1.1019),and the Data representation is shown in Graph no 3,VR was significantly decreased in Abnormal compared to Border line Patients compared to Normal Patients correlated with P-value <0.0001.

### **B.Heart rate response to deep breathing:**

Heart rate response to Deep Breathing was evaluated and grouped in to Normal, Abnormal pts with Mean, SD,CV ratio show in table no 6,7.Mean Deep Breathing among abnormal patient is 5.1667 , and the confidence interval is (4.6287-5.7046),and normal patient is 12.0287 , and the confidence interval in normal patient is (11.256-12.7299).

The Data representation of Mean of Deep breathing difference in the different groups is shown in Graph no4,shows progressive decline in HR response to Deep Breathing in comparing with Normal and Abnormal in Patients with type 2 DM,with P value < 0.0001.

### **C.Heart rate response to standing (PTI):**

Heart rate response to Standing was evaluated in to Normal, Abnormal pts with Mean, SD,CV ratio show in **table no 8,9**.Mean PTI among abnormal patient is 0.7781 , and the confidence interval is (0.7372- 0.8191),among borderline patient is 1.0454 , and the confidence interval is (1.0117-1.0791). among normal patient is

0.14519 and CI is (1.2170-1.31761),and comparison of Data presentation was show in Graph no 5.

PTI was significantly decreased in Abnormal compared to Border line Patients compared to Normal Patients correlated with P-value <0.0001.

## **2. TESTS REFLECTING SYMPATHETIC ACTIVITY:**

### **Blood Pressure response to standing (Orthostatic test):**

Blood Pressure response to standing was evaluated and grouped in to Normal, Abnormal pts with Mean, SD,CV ratio show in table no10,11,12.Mean orthostatic test among abnormal patient is 6.0000 , and the confidence interval is (5.2581- 6.7481), among borderline patient is 12.8077 , and the confidence interval in borderline patient is (12.3838-13.2316),among normal patient is 2.13708 and CI is (1.65802-1.31761),and comparison of Data presentation was show in Graph no 6,can thus be concluded that the decrease in systolic Blood pressure on standing, a measure of cardiac sympathetic function is Increased in Abnormal compared to Border line Patients compared to Normal Patients correlated with P-value <0.0001.

### **A. Blood Pressure response to sustained handgrip**

Blood Pressue response to sustained Hand Grip was grouped in to Normal, Abnormal pts with Mean, SD,CV ratio show in table no13,14.Mean BP among abnormal patient is 1.2058, and the confidence interval is (1.1423- 1.2692),mean BP among borderline patient is 0.8594, and the confidence interval in borderline patient is (0.8101-0.9087),among normal patient is 0.5900and CI is (0.3947-0.7853),and comparison of Data presentation was show in Graph no7,BP response to sustained hand grip was significantly decreased in Abnormal compared to Border line Patients compared to Normal Patients correlated with P-value <0.0001.

### **STATISTICAL RESULTS OF THE DATA:**

The data was arranged into appropriate tables for discussion under different headings. One sample test was applied to find the mean of test result in each group. Multiple comparisons by Chi-Square test and Descriptive Statistics using ANOVA were done to compare the cardiovascular indices between the study groups.

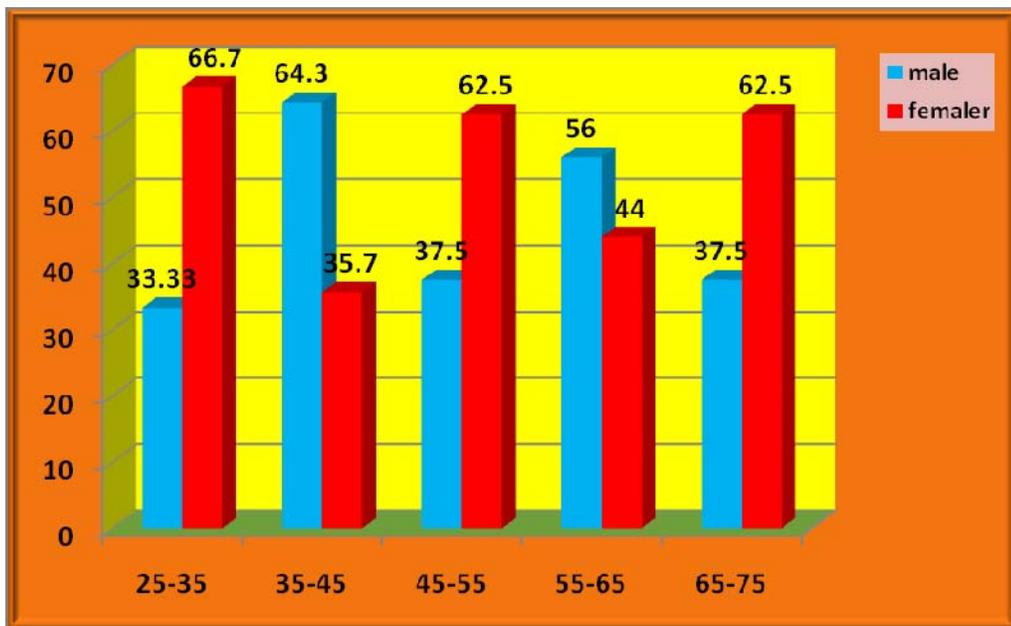
The mean difference were highly significant at  $P < 0.001$ , statistically significant at  $P < 0.05$  and non significant at  $P > 0.05$  level. Conclusions were drawn based on outcome of statistical treatment.

### **AGE DISTRIBUTION:**

Study comprised of 96 subjects comprising both male and female with age group between 35-70, and comprised 48 male patients and 48 female patients, which would be represented in the following Graphical Presentation.

Maximum number of patients in the age group 45-55(33.3%), followed by age group 55-65(26%) and younger patients 25-35(3%) constituted insignificant portion of the study.

**Graph 1: Distribution male and female of patients according to age**



**Graph No 2: Frequency and percentage distribution of patients according to sex**



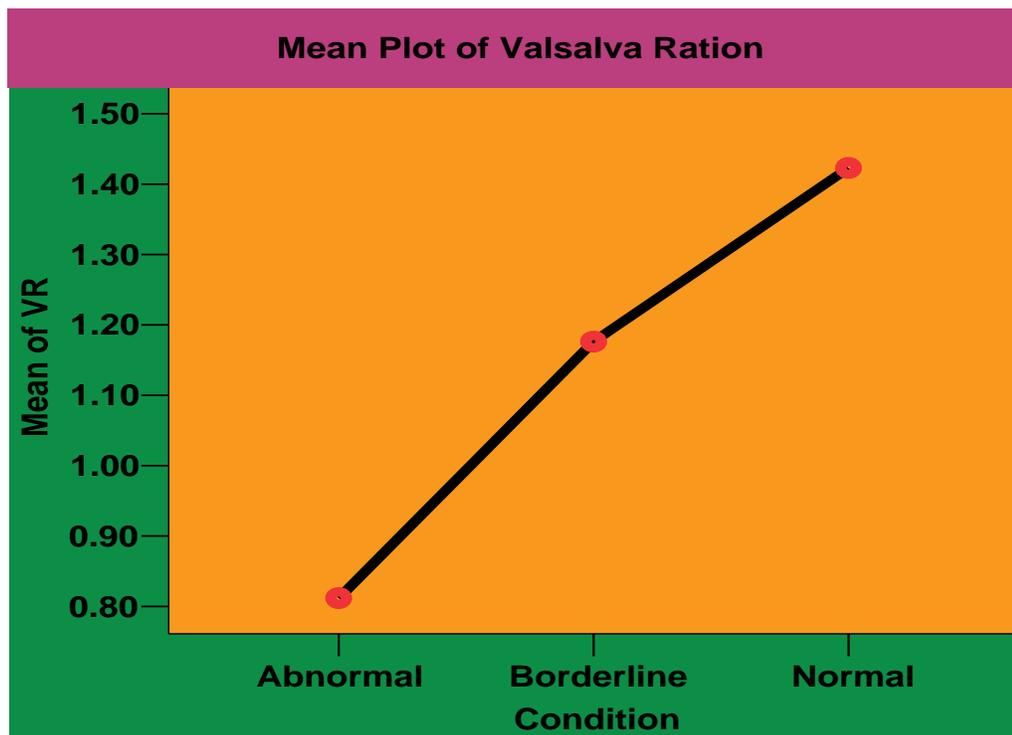
**Table no 4 : Homogeneity of valsalva ratio among the patients with Type 2**

**Diabetes Mellitus.**

Variation	Sum of Squares	D.F	Mean square	F-ratio	P-value
Between groups	7.479	2	3.739	123.038	<0.0001
Within group	2.804	93	0.030		
Total	10.23	95			

**Graph no 3: Mean plot of Valsalva ratio among patients with Type 2 Diabetes**

**Mellitus:**



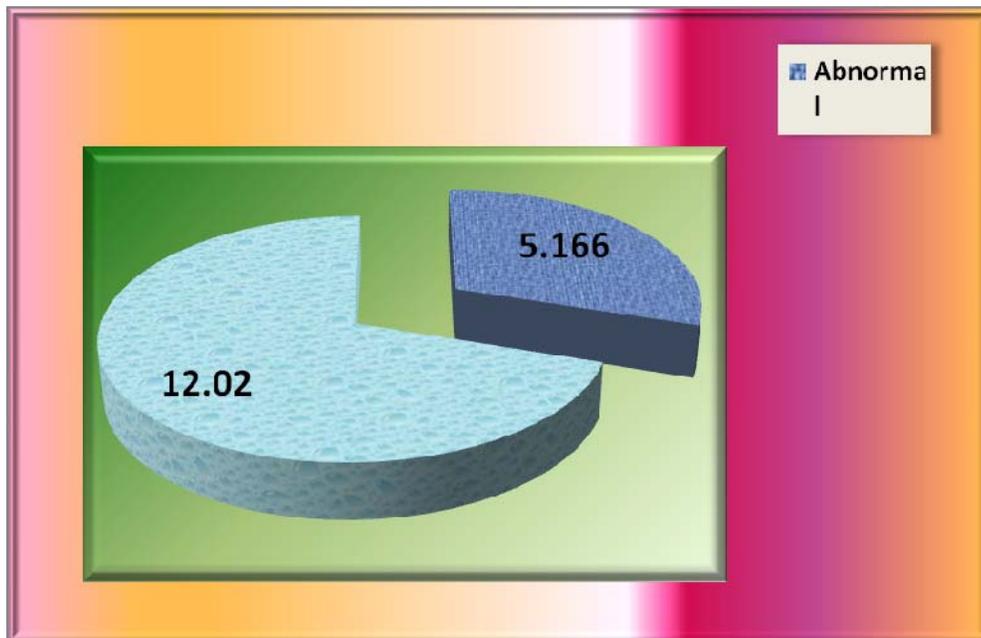
**Table No 5: Descriptive statistics of Valsalva ratio with Mean, SD,95%CI.**

<b>Hr variation to valsalva</b>	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Abnormal	58	0.8152	0.20124	0.02642	0.7623	0.8681	0.30	1.11
Borderline	8	1.1763	0.03335	0.01179	1.1484	1.2041	1.13	1.20
Normal	30	1.4230	0.12967	0.02367	1.3746	1.4714	1.30	1.70
Total	96	1.0352	0.32899	0.03358	.9685	1.1019	0.30	1.70

**Table no 6: Homogeneity of Deep breathing in relation to HR variation among the patients with Type 2 Diabetes mellitus**

<b>HR Variation to Deep Beathing</b>	<b>Sum of Squares</b>	<b>D.F</b>	<b>Mean square</b>	<b>F-ratio</b>	<b>P-value</b>
<b>Between groups</b>	847.347	2	847.347	118.655	<0.0001
<b>Within group</b>	671.278	94	7.141		
<b>Total</b>	1518.625	95			

**Graph no 4 : Response of Heart Rate variation to Deep Breathing in Patients with Type 2 Diabetes Mellitus:**



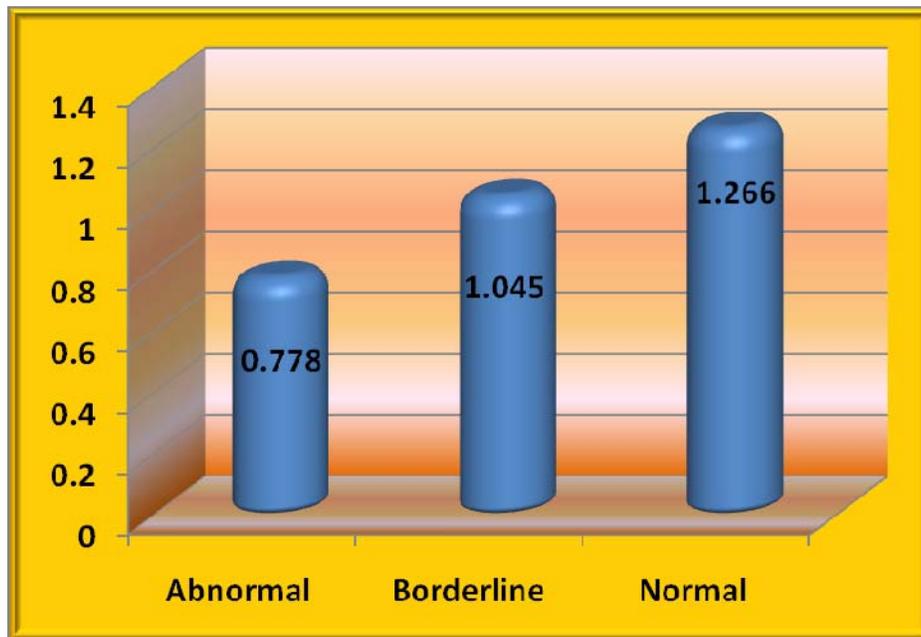
**Table No 7 : Descriptive statistics with regard to Mean,SD,95%CI,with Patient Response to HR variation during deep breathing**

HR Variation to Deep Breathing	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Abnormal	24	5.1667	1.27404	.26006	4.6287	5.7046	2.00	7.00
Normal	72	12.0278	2.98811	.35215	11.3256	12.7299	8.00	18.00
Total	96	10.3125	3.99819	.40806	9.5024	11.1226	2.00	18.00

**Table No 8: Homogeneity of Patient Response to HR variation from Supine to Standing Posture.**

Variation	Sum of Squares	D.F	Mean square	F-ratio	P-value
Between groups	4.877	2	2.438	134.215	<0.0001
Within group	1.690	93	0.018		
Total	6.566	95			

**Graph no 5: Distribution of patients in to Normal,Borderline,Abnormal in Realtion of HR Variation from Supine to Standing.**



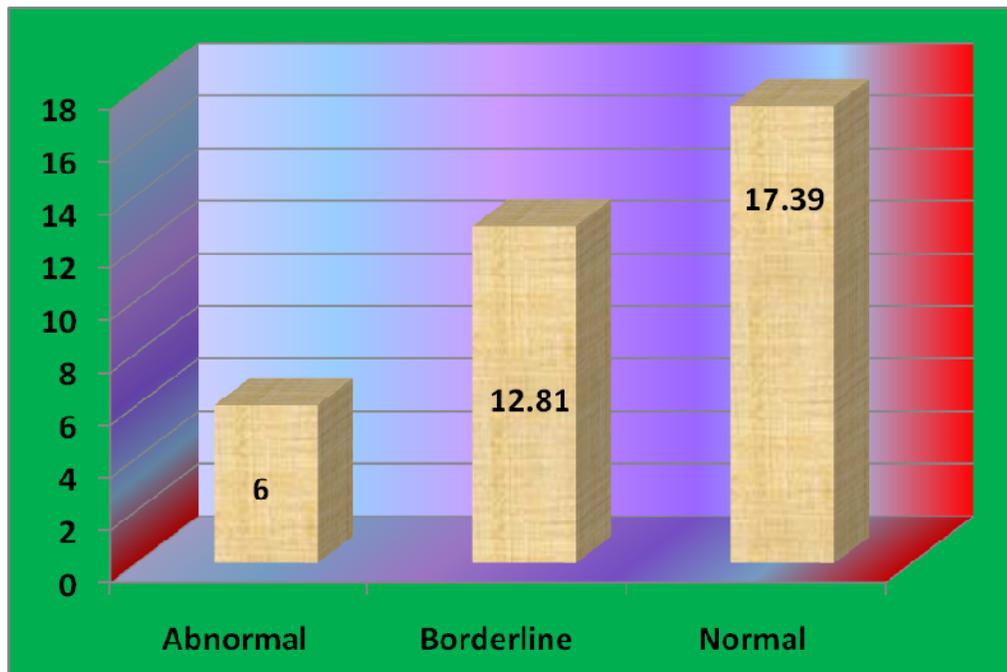
**Table No 9: Descriptive statistics in relation to Mean, SD,CI, HR Variation from supine to standing:**

HR variation from supine to Standing	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Abnormal	48	0.7781	.14108	.02036	.7372	.8191	.44	1.00
Borderline	13	1.0454	.05577	.01547	1.0117	1.0791	1.01	1.20
Normal	35	1.2669	.14519	.02454	1.2170	1.3167	1.08	1.60
Total	96	.9925	.26291	.02683	.9392	1.0458	.44	1.60

**Table No 10 : Homogeneity of respons of CV of BP from supine to standing:**

Variation	Sum of Squares	D.F	Mean square	F-ratio	P-value
Between groups	2287.423	2	1143.711	282.573	0.0001
Within group	376.417	93	4.047		
Total	2663.840	95			

**Graph no 6 : Mean graph BP variation from Supine to Standing Posture**



**Table No 11: Descriptive statistics with regard to Mean, SD, CI and BP response among the patients from Supine to Standing Posture**

BP response to standing	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Abnormal	40	6.0000	2.35053	.36709	5.2581	6.7419	1.50	10.00
Borderline	26	12.8077	1.04954	.20583	12.3838	13.2316	11.50	14.00
Normal	30	17.3931	2.13708	.39685	16.5802	18.2060	16.00	22.00
Total	96	11.2854	5.29532	.54045	10.2125	12.3583	1.50	22.00

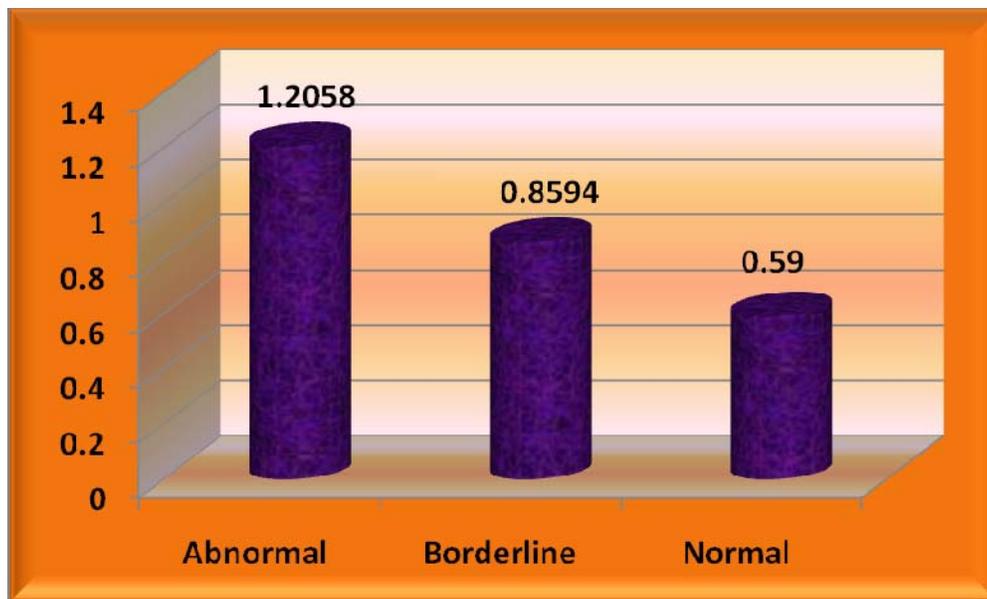
**Table 12 : Mean, SD and CV of Fall in SBP in three study groups with P<0.0001:**

GROUPS	MEAN	SD	CI	CV%
NORMAL	7.0000	4.20454	95%	60.0
BORDER LINE	10.4000	7.67882	95%	73.0
ABNORMAL	18.4667	8.92394	95%	48.3

**Table No 13 : Homogeneity of the patients BP Response to Sustained Hand Grip:**

BP Response to Hand Grip:	Sum of Squares	D.F	Mean square	F-ratio	P-value
Between groups	3.388	2	1.694	49.565	0.0001
Within group	3.178	93	0.034		
Total	6.566	95			

**Graph no 7: Mean BP response to Sustained Hand Grip:**



**Table No 14: Descriptive statistics using ANOVA with regard to Mean,SD,CI in**

**Relation to BP response to sustained Hand Grip:**

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Abnormal	41	1.2058	0.19830	.03135	1.1423	1.2692	0.72	1.60
Borderline	51	0.8594	0.17711	.02456	.8101	.9087	0.44	1.30
Normal	4	0.5900	0.12275	.06137	.3947	.7853	0.50	.76
Total	96	0.9925	0.26291	.02683	.9392	1.0458	0.44	1.60

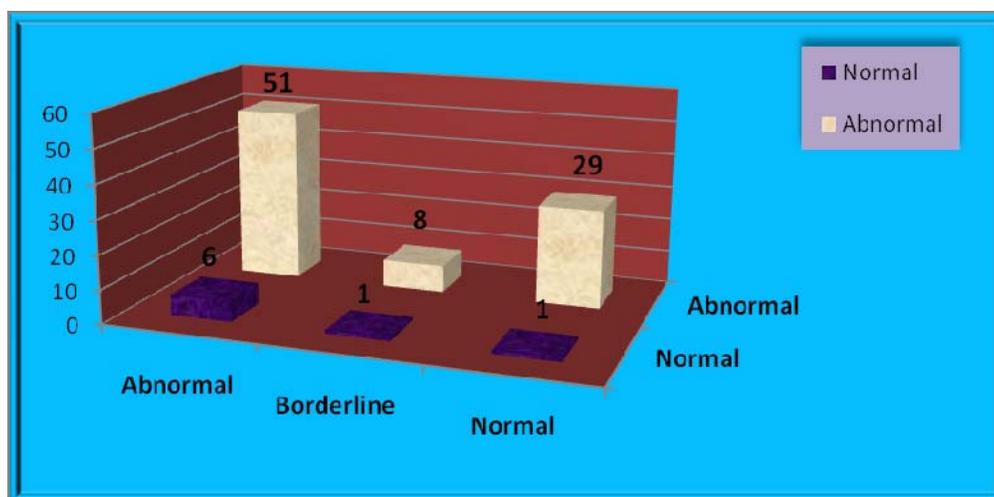
**Table no 15 : Distribution of patients in relation to HbA1c:**

HBA1C	Frequency	Percent
Normal	8	8.3
Abnormal	88	91.7
Total	96	100.0

**Table No16 : Correlation of HBA1C Value with Valsa ratio:**

VALSARATIO	HBA1C				Total	P-VALUE
	Normal		Abnormal			
N	Frequenc y	Percentag e	Frequenc y	Percentag e		
Abnormal	06	10.5	51	89.5	57	<0.001
Borderline	01	12.5	08	87.5	09	
Normal	01	33.3	29	66.7	30	
Total	08		88			

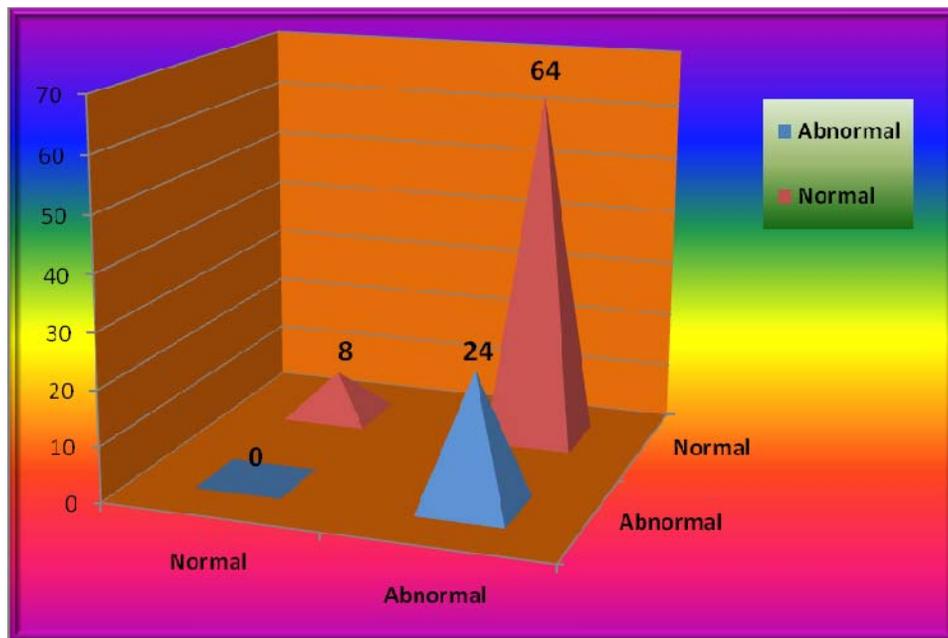
**Graph no 8 : Correlation Of Hba1c Value With Valsa Ratio**



**Table no17 : Correlation of HBA1C in Relation to deep breathing:**

	HBA1C				Total	P-VALUE
	Normal		Abnormal			
DEEPBREATHING	Frequency	Percentage	Frequency	Percentage		
Abnormal	00	00	24	100		0.008
Normal	08	11.1	64	88.9		
Total	08		88			

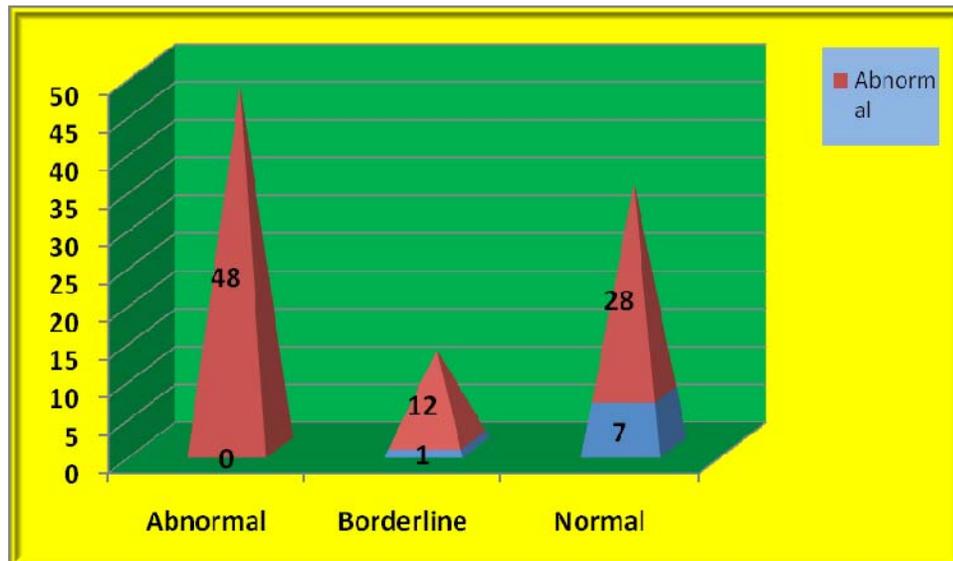
**GRAPH NO 9 : Hr Response To Deepbreathing In Correlation With Hba1c.**



**Table no18: Correlation Of Hba1c In Relation To Hr Response Fom Supine To Standing**

	HBA1C				Total	P-VALUE
	Normal		Abnormal			
HRSTANDIN G	Frequenc y	Percentag e	Frequenc y	Percentag e		
Abnormal	00	00	48	100	48	0.005
Borderline	01	7.7	12	92.3	13	
Normal	07	20	28	80	35	
<b>Total</b>	<b>08</b>		<b>88</b>		<b>96</b>	

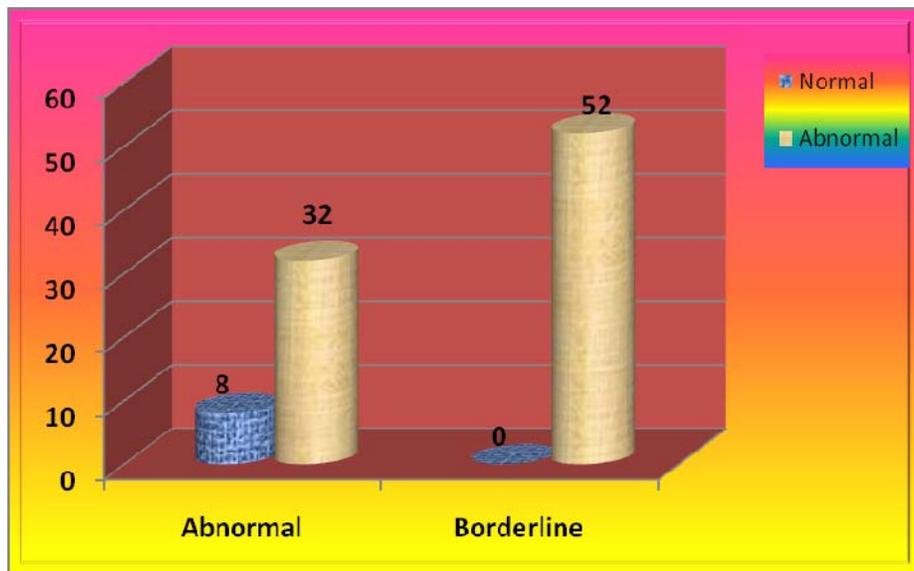
**GRAPH NO 10: HR RESPONSE IN CORRELATION WITH HBA1C IN RESPONSE TO STANDING**



**Table no 19 : Correlation of HBA1C with BP response from Supine to Standing Position**

SBPDBP	HBA1C				Total	P-VALUE
	Normal		Abnormal			
	Frequency	Percentage	Frequency	Percentage		
Abnormal	08	20	32	80	40	0.002
Borderline	00	00	52	100	52	
Normal	00	00	04	100	04	
<b>Total</b>	<b>08</b>		<b>88</b>		<b>96</b>	

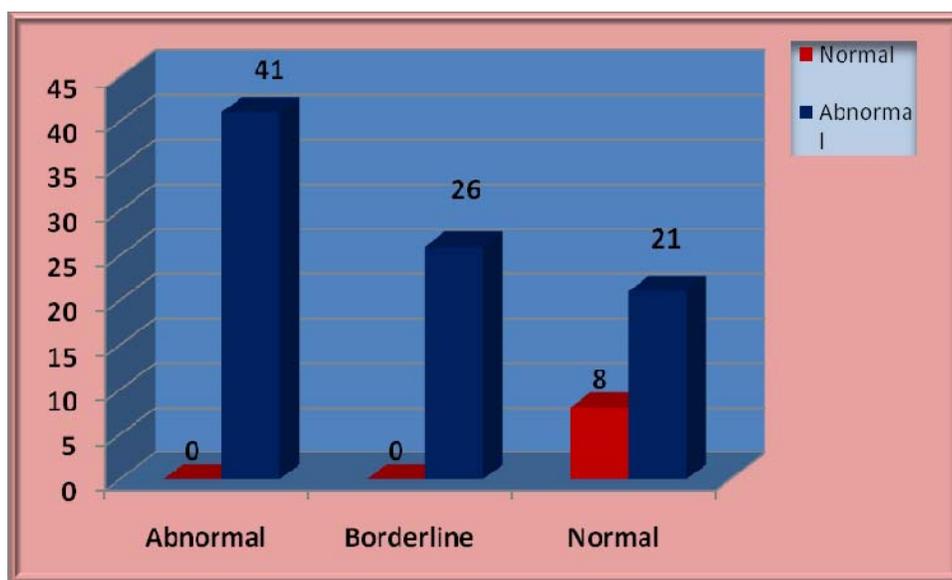
**Graph no11: BP Response to Standing in correlation to HBA1C:**



**Table no 20 :Correlation of HBA1C WITH SUSTAINED HAND GRIP**

HANDGRIP	HBA1C				Total	P-VALUE
	Normal		Abnormal			
	Frequency	Percentage	Frequency	Percentage		
Abnormal	0	0	41	100	41	< 0.001
Borderline	0	0	26	100	26	
Normal	8	27.6	21	72.4	29	
Total	8		88		96	

**Graph no 12: Correlation of HBA1C WITH SUSTAINED HAND GRIP:**



## DISCUSSION

Cardiovascular autonomic neuropathy is the most common and earliest complication of hyperglycemia in relation to type 2 diabetes mellitus. Various studies have shown that the degree of cardiac autonomic dysfunction depends on long term glycemic control, duration of diabetes, age and genetic constitution of the individual. Quantitative autonomic function tests are widely used to assess autonomic function. The Deep breathing test, Valsalva maneuver, Postural Variation, Orthostatic test and Isometric handgrip tests have been used as simple, reliable and reproducible as well as non-invasive methods of studying the cardiac autonomic function. Cardiac autonomic dysfunction indicates diffuse damage throughout the Autonomic Nervous system.

Against this background the study was conducted to assess the **PREVELANCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DM**. **PREVELANCE** is defined by the proportion of a population found to have a condition, and it is arrived at by comparing the number of people found to have the condition with the total number of people studied during that period of time.

Patients diagnosed with Type 2 DM, and depending up on their chronicity of the disease and Response of the Patient HR,BP variation is assessed by performing various autonomic tests and their correlation to HBA1C,and based on this results,discussion and conclusions were drawn.

Heart rate response to Valsalva maneuver was evaluated in 96 subjects grouped in to Normal,Borderline,Abnormal pts with Mean, SD,CV ratio show in table no 4,5 , Mean VR among abnormal patient is 0.8152 , and the confidence interval is (0.7623 0.8681),among bordeline patient is 1.1763, and the confidence interval for borderline patient is (1.1484-1.2041), normal patient is 1.4230 , and the confidence interval for normal patient is 0.9685-1.1019),and the Data representation is shown in

Graph no 3,VR was significantly decreased in Abnormal compared to Border line Patients compared to Normal Patients correlated with P-value <0.0001.

,The finding of the present study is in conformity with earlier studies.

Hague R et al studied 5 tests of autonomic function in in a group of 25 diabetics. Valsalva ratio proved to be the most valuable single indicator of generalized autonomic dysfunction and suggested that Valsalva procedure is most valuable and simple out patient test for autonomic neuropathy.<sup>106</sup>

Kruter RH, Eizirik DL, Gross JL. Studied VR in 48 diabetic and 48 normal individual matched by age and sex. Diabetic patients with some evidence of diabetic neuropathy showed VR values lower than their control groups ( $1.58 \pm 0.07$  vs  $1.81 \pm 0.7$ ),the study concluded that the VR is an effective indicator of autonomic neuropathy.<sup>107</sup>

Smith SA performed VR in 59 diabetic patients and found that 35 had normal, 6 had borderline and 18 had abnormal results. compared to other autonomic function tests VR correlated maximally with sinus arrhythmia tests, repeat measurements of ratios in healthy and diabetic subjects yielded coefficient of variation of 15.4% and 10.5% respectively.<sup>10</sup>

Heart rate response to Deep Breathing was evaluated in 96 subjects grouped in to Normal, Abnormal pts with Mean, SD,CV ratio show in table no 6,7 , Mean Deep Breathing among abnormal patient is 5.1667 , and the confidence interval is (4.6287-5.7046), among normal patient is 12.0287 , and the confidence interval in normal patient is (11.256-12.7299).

Data representation of Mean of Deep breathing difference in the different groups is shown in Graph 4,shows progressive decline in HR response to Deep

Breathing in comparing with Normal and Abnormal in Patients with type 2 DM, with P value < 0.0001.

The finding of the present study is in conformity with earlier studies. Oikawa N et al, studied Heart rate (HR) variations during deep breathing in 162 healthy subjects and 168 diabetics by use of an instantaneous-HR -change continuous recorder, indices of HR variations, mean of HR during deep breathing and the standard deviation (SD) of the HR were determined, 95% confidence limits were calculated for the normal range and the values below normal range were defined as abnormal, and the incidence of abnormal response were 38%, Deep breathing difference was found to be the most sensitive index for the autonomic neuropathy<sup>109</sup>.

Mackay JD et al, studied Heart rate (HR) variations using HR monitoring in the diagnosis of diabetic autonomic neuropathy, and 287 diabetics aged between 20 and 49 years were studied for HRV on deep breathing proved to be the more sensitive diagnostic index of autonomic neuropathy and was abnormal or borderline in 62 of 64 patients with established autonomic symptoms.<sup>110</sup>.

Ewing DJ, Campbell IW, and Clarke BF studied Heart rate changes in diabetes mellitus. During lying, sitting, and standing in 61 diabetics with varying degrees of cardiovascular reflex abnormalities. Patients with parasympathetic abnormalities alone had the highest heart rates, while those with both parasympathetic and sympathetic involvement had slightly less rapid heart rates, which were still faster than those in diabetics with normal cardiovascular reflexes. 38 other diabetics in whom autonomic function tests had been done at least three times had a similar pattern of resting heart rate, 25 pts had unchanged tests, those with parasympathetic involvement alone had the highest heart rates, other 13 subjects whose autonomic function changed from normal to abnormal showed a sequential increase in heart rate as cardiac

parasympathetic damage developed, followed by a fall in heart rate, but not back to normal, as sympathetic damage developed as well, increased resting heart rates in diabetics may be due in some patients to cardiac parasympathetic damage alone and in others, to combined parasympathetic and cardiac sympathetic damage, sequential heart rate changes support the view that the vagus nerve is affected before the cardiac sympathetic nerves<sup>71</sup>.

Heart rate response to Standing (PTI) was evaluated in 96 subjects grouped into Normal, Abnormal pts with Mean, SD, CV ratio show in table no 8,9, Mean among abnormal patient is 0.7781, and the confidence interval is (0.7372- 0.8191), among borderline patient is 1.0454, and the confidence interval in borderline patient is (1.0117-1.0791). mean among normal patient is 0.14519 and CI is (1.2170-1.31761), and comparison of Data presentation was show in Graph no:5, PTI was significantly decreased in Abnormal compared to Border line Patients compared to Normal Patients correlated with P-value <0.0001.

It can thus be concluded that the heart rate response to standing, a measure of cardiac parasympathetic function is reduced in diabetics compared to controls. The finding of the present study is in conformity with earlier studies discussed below.

Oikawa N et al, studied Heart rate (HR) variations from lying to standing posture in 162 healthy subjects and 168 diabetics by use of an instantaneous-HR – change continuous recorder. As indices of HR variations, SD of HR, the mean difference between maximal and minimal HR during deep breathing (delta I-E) and the HR increase on standing (delta HR) were determined, the incidence of abnormal response were 19% in the SD of HR (Resting supine), and 22% in the SD of HR (standing). The 90% confidence limits were calculated for the normal range and the values below normal range were defined as abnormal.<sup>109</sup>

In healthy subjects, the values for each test declined with age and the log-transformed data fitted the linear regression. In diabetics, the incidence of abnormal response was 19% in the SD<sup>109</sup>.

Beylot M, Haro M, Orgiazzi J, Noel G, studied HRV in 117 diabetic and 46 control subjects and found abnormal HRV from lying to standing in 8%. Borderline HRV in 20% of the patients.<sup>108</sup>

Flynn AC, Jelinek HF, Smith M, Studied HRV from lying to standing on 48diabetic and 48 non diabetic subjects. They observed a significant difference ( P = 0.03) between ECG recordings of diabetics and control group.<sup>111</sup>

Blood pressure response to standing was evaluated in 96 subjects grouped in to Normal, Abnormal pts with Mean, SD,CV ratio show in table no10,11,12, Mean among abnormal patient is 6.0000 , and the confidence interval is (5.2581- 6.7481), among borderline patient is 12.8077 , and the confidence interval in borderline patient is (12.3838-13.2316), among normal patient is 2.13708 and CI is (16.5802- 1.31761),and comparison of Data presentation was show in Graph no:6,it can thus be concluded that the decrease in systolic Blood pressure on standing, a measure of cardiac sympathetic function is Increased in Abnormal compared to Border line Patients compared to Normal Patients correlated with P-value <0.0001.

Finding of the present study is in conformity with earlier studies discussed below

Barakai and Madacsy L Studied cardiac autonomic dysfunction in 110 Patients with diabetes mellitus and 130 non diabetic controls, and found an abnormal and significant BP variation( P<0.05) from lying to standing, compared with controls<sup>112</sup>.

Ewing DJ, Martyn CN, Young RJ and Clarke BF Assessed autonomic function in 774 diabetic subjects, using all 5 simple, non invasive cardiovascular autonomic function tests for 10 years. And observed abnormal blood pressure variation from lying to standing in 20% of the subjects<sup>32</sup>.

Dyrberg T, Benn J, Christiansen JS, Hilsted J and Nerup J Conducted five simple bed side cardiac autonomic function tests in 75 diabetic subjects, and observed a significant blood pressure variation (  $P < 0.01$ ) from lying to standing<sup>113</sup>

Blood Pressure response to Sustained Hand Grip was evaluated in 96 subjects grouped in to Normal, Abnormal pts with Mean, SD,CV ratio show in table no13,14 , Mean among abnormal patient is 1.2058, and the confidence interval is (1.1423-1.2692), among borderline patient is 0.8594, and the confidence interval in borderline patient is (0.8101-0.9087),among normal patient is 0.5900and CI is (0.3947-0.7853),and comparison of Data presentation was show in Graph no 7,BP response to sustained hand grip was significantly decreased in Abnormal compared to Border line Patients compared to Normal Patients correlated with P-value  $< 0.0001$ .

Finding of the present study is in conformity with earlier studies discussed below.

Popovic et al studied effect of sustained hand grip on BP variation in 90 subjects further divided in to groups of 30 each as Diabetic type I,Diabetic type II and non diabetic control. They observed an abnormal BP variation in type II Diabetics than compared to other groups.<sup>114</sup>.

Ewing DJ, Martyn CN, Young RJ and Clarke BF Assessed autonomic function in 774 diabetic subjects, using all 5 simple, non invasive cardiovascular autonomic function tests for 10 years. And observed abnormal blood pressure response to sustained hand grip in 20% of the subjects.<sup>32</sup>

Dyrberg T, Benn J, Christiansen JS, Hilsted J and Nerup J Conducted five simple bed side cardiac autonomic function tests in 75 diabetic subjects, and observed a significant blood pressure response (  $P < 0.01$ ) to sustained hand grip<sup>72</sup>.

MEAN,SD,CV of HbA1c were taken and related the difference between Normal and Abnormal values, and compared to the patients response to various autonomic test in relation to both sympathetic and parasympathetic tests, with criteria considering HbA1c  $< 7$  being normal and  $> 8$  being abnormal, based on this the comparative study was undertaken, on the analysis of distribution of HbA1c in 96 subjects found that 88 pts had Abnormal values, and the difference shown in table no 15.

HbA1c in correlation to Valsalva Ratio found 57 pts to be abnormal, border line 9,30 patients normal and this result is shown in table no 16, and Data representation is shown in Graph no8 ,and found to be significant with P value  $< 0.001$ .

HbA1c in correlation to Deep Breathing was found 24 in abnormal,64 in normal, and border line 8 pts, and this result is shown in table 17 ,and Data representation shown in Graph no9 ,and found to be significant with P value  $< 0.008$ .

HbA1c in correlation to HR variation on standing and was 48 pts to be abnormal,13 pts to be in borderline,35 pts in normal. and this result is shown in table 18 ,and Data representation shown in Graph no 10 ,and found to be significant P value  $< 0.005$ .

HbA1c in correlation to BP on Standing 40 abnormal,52 border line and 4 normal. and this result is shown in table 19, and the Data representation is shown in Graph no 11, and increase in SBP on standing found to highly significant with P Value  $< 0.002$ .

HbA1c in correlation to DBP on sustained hand grip showed 41 pts Abnormal,26 Borderline,29 Normal,and the result is shown in table 20 ,and the Data representation is shown in Graph no 12,and decrease in DBP found to be significant with P value <0.001.

This study based on the analysis suggests that there is correlation of HbA1c in prevalence of cardiac autonomic neuropathy.and indicates a poor glycemic control.

## CONCLUSION

**From the present study, the following conclusions may be derived:**

In this study CAN is found in 75% of the patients, in significance to Parasympathetic activity found in 65% of patients and Sympathetic activity in 35 % of patients, and conclusions of this study showed that Prevalence of CAN in relation to study groups differed significantly from control, suggesting that cardiovascular autonomic function declines in type 2 diabetes patients.

Parasympathetic function tests are more sensitive detection of CAN than Sympathetic Cardiac autonomic function tests.

Valsalva ratio is most sensitive Parasympathetic cardiac autonomic function followed by HR response to deep breathing, followed by HR response to standing.

Blood Pressure to sustained hand grip is more sensitive to detect cardiac sympathetic activity than Blood Pressure to standing.

The cardiovascular autonomic dysfunction was significantly higher in uncontrolled diabetics with HbA1c >8, and response of the patient to individual Parasympathetic and sympathetic test and correlation with HbA1c showed significant relation and results that cardiac autonomic dysfunction is accelerated in patients with poor glycemic control.

Evaluation of cardiovascular reflexes in type 2 DM subjects with paucity of related symptoms constitutes an important feasible and reproducible bedside clinical technique and is well correlated it should be included as a routine in work-up of patients of type-2 diabetes as it often uncovers autonomic neuropathy even in asymptomatic state.

It is of crucial importance to pinpoint some high risk cases with probability of sudden cardiac death. It is also a pointer to embark upon a search for other complications of diabetes often associated with it.

The longer-term aim of management should,be the prevention or reversal of autonomic damage, particularly in its early stages.

Our results obtained is related to the, study which was done in Eastern Indian,with exceptions the sample size was higher than the original study and relation of HbA1c is correlation with CAN is significant compared to the Study Done in Eastern India.

Results obtained in this study are correlating with other studies.

## SUMMARY

The present study was designed to assess the cardiovascular autonomic function in type2 diabetics by cardiovascular reflex tests. They include heart rate response to deep breathing, valsalva maneuver and standing to evaluate the parasympathetic function and blood pressure response to standing and sustained handgrip to evaluate the sympathetic function.

Autonomic function was found to be altered significantly in diabetics. Both parasympathetic and sympathetic cardiovascular responses were altered. However I glycemic control of HbA1c > 8 showed significant cardiac autonomic dysfunction compared to the well with glycemic HbA1c < 7. This suggests that Prevelance of CAN in relation Of hyperglycemic glycemic levels adversely affect cardiovascular autonomic function through various metabolic and vascular mechanisms.

Therefore assessment of Autonomic Cardiac reflexes affords a satisfactory method for evaluation of CAN.

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**ANNEXURE I**  
**CONSENT FORM**

**TITLE OF RESEARCH: “Prevalence of Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus**

**GUIDE : DR. R.M.HONNUTAGI**

**P.G. STUDENT : DR.C.UDAY BHANU**

**PURPOSE OF RESEARCH:**

I have been informed that the purpose of this research is to study the Prevalence of cardiac Autonomic in Type 2 Diabetes Mellitus

**PROCEDURE:**

I understand that a detailed medical history of mine will be taken & that I shall have to undergo a complete physical examination and be subjected to investigations.

**RISKS AND DISCOMFORTS:**

I understand that there is no risk involved and I may experience mild discomfort during the above-mentioned procedures.

**BENEFITS:**

I understand that my participation in this study will help in determining the Prevalence of cardiac Autonomic in Type 2 Diabetes Mellitus.

**CONFIDENTIALITY:**

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulations of hospital. If the data is used for publications, the identity of the patient will not be revealed.

**REQUEST FOR MORE INFORMATION:**

I understand that I may be asked for more information if required, for inclusion into study at any time.

**REFUSAL OR WITHDRAWAL OF PARTICIPATION:**

I understand that my participation is voluntary and I may refuse to participate or withdraw from the study at any time.

**INJURY STATEMENT:**

I understand that, in the unlikely event of injury to me anytime during the study, I shall get medical treatment for the same but no further compensations.

**CONSENT STATEMENT**

I, \_\_\_\_\_ unreservedly and in my full sense give my complete consent to take part in this study. The risk and benefits as mentioned above have been read by me/explained to me in my vernacular language.

**Signature of Patient**

**ANNEXURE II**

**BLDE'S SHRI B.M.PATIL MEDICAL COLLEGE HOSPITAL AND**

**RESEARCH CENTRE, BIJAPUR**

**SCHEME OF CASE TAKING**

Name:

CASE NO:

Age:

IP NO:

Sex:

DOA:

Religion:

DOD:

Occupation:

Residence:

Presenting complaints with duration:

1. Dizziness
2. Palpitations
3. Abnormal Sweating
4. chestpain.
5. Urinary Symptoms

**Past History:**

History of hypertension

History of diabetes mellitus

Past history of IHD

**Personal History:**

Diet

Appetite

Sleep

Bladder and bowel habits:

Smoking/Tobacco chewing/Snuff Inhalation

Duration

Number of cigarettes/beedis pack year smoked

Amount of tobacco chewed/snuff inhaled

Alcohol

**Family History:**

History of suggestive of Ischemic Heart Disease/hypertension/ diabetes mellitus

**Treatment History:**

**General Physical Examination**

Built:Thin/Normal/Obese

Weight(kg)

Height(cm)

Pallor:

Icterus:

Clubbing:

Cyanosis

Generalized Lymphadenopathy:

## **SYSTEMIC EXAMINATION.**

1. Cardiovascular System:
2. Respiratory System:
3. Per Abdomen:
4. Central Nervous System

## INVESTIGATIONS

### Haematology:

Haemoglobin	gm %
Total WBC counts	Cells/mm <sup>3</sup>
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour

### Biochemistry

Serum creatinine	
Random blood sugar	
Fbs day 4	
Hba1c	

### Urine examination:

Albumin	
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**ECG RECORDING:**

1. TESTS PERFORMING PARASYMPATHETIC ACTIVITY:
2. TESTS PERFORMING SYMPATHETIC ACTIVITY:

ANNEXURE III  
ETHICAL CLEARANCE



B.L.D.E. UNIVERSITY'S  
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103  
INSTITUTIONAL ETHICAL COMMITTEE



**INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE**

The Ethical Committee of this college met on 26-10-2011 at 10-30 am to scrutinize the Synopsis/Research projects of postgraduate/undergraduate student/Faculty members of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis/Research project has been accorded Ethical Clearance.

Title "A Cross sectional Study on prevalence of Cardiac autonomic neuropathy in type 2 diabetes mellitus."

Name of P.G./U.G. student/Faculty member Dr. C. Chay Bhanu  
Dept of medicine

Name of Guide/Co-investigator Dr. D.M. Honnatagi prof medicine

  
DR.M.S.BIRADAR,  
CHAIRMAN  
INSTITUTIONAL ETHICAL COMMITTEE  
BLDEU'S, SHRI.B.M.PATIL  
MEDICAL COLLEGE, BIJAPUR.  
Chairman  
Ethical Committee  
BLDEA'S Shri. B.M. Patil  
Medical College  
Bijapur-586103

- Following documents were placed before E.C. for Scrutinization
- 1) Copy of Synopsis/Research project.
  - 2) Copy of informed consent form
  - 3) Any other relevant documents.

## KEY TO MASTER CHART

BMI	-	Body MASS Index
BP	-	Blood Pressure
DBP	-	Diastolic Blood Pressure
DBD	-	Deep Breathing Difference
RV	-	Rate Variability
HbA1c	-	Hemoglobin A1c
SBP	-	Systolic Blood Pressure
WT	-	Weight

## MASTER CHART

SL. NO	NAME	AGE	SEX	HEIGHT cm	WT - KG	BMI	RBS DAY 1	FBS-D4	HBA 1C %	URINE ALBUMIN	TEST FOR CARDIAC SYMPATHETIC ACTIVITY			BP BEFORE HAND GRIP (MM.HG)			MEAN	BP TO SUSTAINED HAND		DBD	TESTS FOR CARDIAC PARASYMPATHETIC ACTIVITY			FUNDOSCOPIC EXAMINATION
											SUPINE BP	STANDING BP	DIFFERENCE SBP-DBP	DB P 1	DB P 2	DB P 3		DBP(MM.HG)	VALSALVA RATIO		HR TO DEEPBREATHING	HR TO STANDING	CONCLUSION	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
1	PARATEWWA	55	F	152	45	19.4	175	128	11	TRACE	120/80	104/78	16 mm.hg	80	80	80	80	84	4	1.04	8/MIN	0.88	NON PROLIFERATIVE DIABETIC RETINOPATHY	
2	BABUGOWDA PATIL	65	M	160	85	26.5	227	127	7.2	TRACE	160/80	140/90	20 mm	80	80	80	80	92	12	1	6/MIN	0.77	NORMAL FUNDUS	
3	BHIMAPPA	70	M	188	94	26.5	270	85	8	TRACE	160/100	140/90	20mm.hg	90	90	90	90	104	14	0.92	8/MIN	0.72	PROLIFERATIVE DIABETIC RETINOPATHY	
4	NOORJHAN	50	F	160	80	25	201	143	8	ABSENT	140/80	130/80	10mm.hg	82	84	84	82.6	98	16.4	1.3	15/MIN	1.1	NORMAL FUNDUS	
5	GANGADHAR	51	M	160	70	21.8	172	152	12	ABSENT	120/70	110/70	10mm.hg	74	74	74	74	80	6	1.02	7/MIN	0.82	NORMAL FUNDUS	
6	MAHADEVI	62	F	154	43	18.1	149	102	8	ABSENT	120/80	110/80	10mm.hg	80	80	80	80	98	18	1.04	16/MIN	0.92	NOMAL FUNDUS	
7	DURGANATH	50	M	160	70	21.8	293	240	13	TRACE	150/90	130/80	20mm.hg	90	92	92	91.5	92	2	1.02	6/MIN	0.8	PROLIFERATIVE DIABETIC RETINOPATHY	
8	KAREPPA	45	M	160	50	15.6	245	160	8.3	ABSENT	130/80	120/80	10mm.hg	80	80	80	80	102	22	1.31	12/MIN	1.2	NORMAL FUNDUS	
9	HANAMANTAYA	55	M	160	40	12.5	115	90	8	ABSENT	120/80	116/76	4mm.hg	76	78	78	77.5	94	16	1.2	14/MIN	1.2	NOMAL FUNDUS	
10	MUTTAPPA	55	M	162	44	16.7	188	169	9	ABSENT	130/80	114/70	16mm.hg	82	80	80	80.5	94	14	1.3	12/MIN	1.3	NOMAL FUNDUS	
11	INDUMATHI	40	M	162	60	22.8	272	135	5.2	ABSENT	120/80	110/80	10mm.hg	84	82	80	82	98	16	1.3	13/MIN	1.4	NORMAL FUNDUS	
12	BASAPPA	40	M	162	45	17.1	230	172	8.7	ABSENT	130/80	110/80	20mm.hg	80	80	82	80.5	88	7.5	0.9	8/MIN	0.9	MILD PROLIFERATIVE CHANGES	
13	ROSHANBI ABDUL	50	M	140	55	28.1	232	190	8.2	ABSENT	130/80	110/70	20mm.hg	76	76	76	76	82	6	0.88	8/MIN	0.9	NOMAL FUNDUS	
14	KAMALLAWWA	50	F	154	65	27.4	145	102	7.2	ABSENT	120/80	110/70	10mm.hg	70	70	70	70	86	16	1.2	12/MIN	1.2	NORMAL FUNDUS	
15	VALLABHAI RATHOD	45	F	160	90	28.1	265	166	8	TRACE	160/90	140/90	20mm.hg	92	90	90	90.5	94	4	0.7	6/MIN	0.62	PROLIFERATIVE DIABETIC RETINOPATHY	
16	RUDRAPPA	40	M	16	65	20.	16	11	7.	ABSENT	120/80	110/80	10mm.hg	80	80	80	80	92	12	1.3	12/MIN	1.2	NORMAL FUNDUS	





60	SAROJINI	70	F	17 0	70	24	26 0	14 0	9. 4	TRACE	144/90	130/78	14mm.hg	70	70	70	70	80	10	0.8	6/MIN	0.65	MILD PROLIFERATIVE CHANGES
61	KESU	40	M	16 2	60	22	36 2	21 0	10	TRACE	138/78	120/72	18mm.hg	72	72	72	72	74	2	0.44	4/MIN	0.6	MILD PROLIFERATIVE CHANGES
62	ISHWARAMMA	50	F	15 0	45	19	21 6	11 0	7. 6	ABSENT	120/80	110/74	10mm.hg	74	72	72	72. 5	88	16	1.4	14/MIN	1.6	NORMAL FUNDUS
63	NINGAPPA	50	M	16 0	70	27	35 2	28 0	9. 8	TRACE	158/92	138/84	20mm.hg	84	80	80	81. 5	92	11. 5	1.04	9/MIN	0.8	MILD PROLIFERATIVE CHANGES
64	RANNAPPA	40	M	16 2	65	24	24 0	13 0	7. 1	ABSENT	130/80	120/70	10mm.hg	70	70	70	70	86	16	1.41	18/MIN	1.2	NORMAL FUNDUS
65	MAINABAI	50	F	15 8	55	22	27 6	14 0	8. 9	TRACE	140/80	114/74	26mm.hg	72	72	72	72	84	12	1.11	12/min	1.01	NORMAL FUNDUS
66	GANGAMMA	60	F	16 0	58	23	24 0	13 2	8. 4	TRACE	130/84	110/70	20mm.hg	70	70	70	70	82	12	1.2	14/MIN	1.02	NORMAL FUNDUS
67	YEMMENAPPA	65	M	17 2	65	22	18 0	90	7	ABSENT	120/70	114/68	6mm.hg	70	70	70	70	86	16	1.44	18/MIN	1.4	NORMAL FUNDUS
68	MALIKARJUN	40	M	17 0	72	24	16 0	10 0	6. 2	ABSENT	120/80	116/78	4mm.hg	78	78	78	78	94	16	1.34	16/MIN	1.3	NORMAL FUNDUS
69	SHANTHIBI	55	F	16 2	61	23	37 9	18 6	11	TRACE	130/70	106/68	24mm.hg	68	68	68	68	72	4	0.5	6/MIN	0.8	PROLIFERATIVE DIABETIC RETINOPATHY
70	ABDUL	48	M	15 8	45	19	10 4	90	6	ABSENT	110/70	104/66	6mm.hg	68	68	68	68	88	20	1.54	16/MIN	1.3	NORMAL FUNDUS
71	HUSANBEE	40	F	15 5	55	19	19 6	13 0	8. 1	ABSENT	120/80	110/80	10mm.hg	80	80	80	80	92	12	1.01	10/MIN	1.01	NORMAL FUNDUS
72	MAHADEVI	50	F	16 0	61	23. 1	16 0	90	7. 9	ABSENT	130/80	110/70	20mm.hg	70	74	74	72. 4	82	10	1	12/MIN	1.02	NORMAL FUNDUS
73	MUTTUSAB	60	M	15 6	55	23. 4	21 0	15 6	9. 7	TRACE	134/84	114/78	20mm.hg	76	78	78	77. 5	88	11. 5	0.75	6/min	0.9	MILD PROLIFERATIVE CHANGES
74	MAHANUDA	60	M	16 9	65	22. 9	14 3	13 0	9. 7	TRACE	144/82	120/74	24mm.hg	78	78	78	78	84	6	0.8	4/MIN	0.72	MILD PROLIFERATIVE CHANGES
75	SOMAPPA	65	M	16 2	60	22. 7	20 8	14 0	8. 9	TRACE	130/70	110/60	20mm.hg	68	68	68	70	82	12	1.15	14/MIN	1.02	NORMAL FUNDUS
76	ASHOK	40	M	15 9	60	28. 4	22 0	20 1	10	TRACE	120/70	100/60	20mm.hg	64	64	64	64	80	16	0.65	4/MIN	0.52	PROLIFERATIVE DIABETIC RETINOPATHY
77	SHARANA BAI	40	F	15 2	51	23. 2	15 0	10 2	8. 1	ABSENT	120/80	108/68	12mm.hg	70	70	70	70	82	12	1.13	13/MIN	1.02	NORMAL FUNDUS
78	SIDDHU	40	M	16 2	65	25	35 0	22 5	10	PRESEN T	144/84	114/70	30mm.hg	86	84	84	82	88	6	0.4	4/MIN	0.6	PROLIFERATIVE DIABETIC RETINOPATHY
79	SURYAKANTH	47	F	15 0	47	21	18 0	90	7. 2	ABSENT	120/70	110/70	10mm.hg	70	70	70	70	90	20	1.51	18/MIN	1.08	NORMAL FUNDUS
80	TUKARAM	45	M	15 6	57	22. 4	20 0	14 0	8. 3	TRACE	130/90	110/70	20mm.hg	74	74	74	74	80	6	0.7	8/MIN	0.75	MILD PROLIFERATIVE CHANGES

81	SHANTHABAI	50	F	16 1	62	23. 9	28 0	18 7	10	PRESEN T	110/80	80/60	30mm.hg	64	64	62	62. 5	66	3.5	0.4	3/MIN	0.5	PROLIFERATIVE DIABETIC RETINOPATHY
82	BABURAY	41	M	16 0	60	23. 4	24 4	18 5	8. 4	PRESEN T	148/88	128/78	20mm.hg	78	80	80	78. 5	90	12	0.8	12/MIN	1	MILD PROLIFERATIVE CHANGES
83	KESAPPA	54	F	15 9	61	24. 1	16 6	12 6	9. 3	TRACE	138/78	122/74	16mm.hg	76	76	76	76	84	8	1.02	13/MIN	1	MILD PROLIFERATIVE CHANGES
84	GUNDARAO	56	M	15 3	55	23. 4	21 7	10 0	9. 4	ABSENT	148/74	128/70	20mm.hg	72	72	72	72	84	12	1.01	14/MIN	1.02	MILD PROLIFERATIVE CHANGES
85	CHANNAMMA	60	F	15 0	45	21	17 6	14 0	8	ABSENT	130/80	118/78	12mm.hg	80	80	80	80	94	14	1.02	12/MIN	1	NORMAL FUNDUS
86	KALAVATHI	48	F	16 0	72	27	19 6	11 0	8	TRACE	132/80	118/78	14mm.hg	78	78	78	78	90	12	1.01	12/MIN	1.03	NORMAL FUNDUS
87	PADMAVATHI	61	F	15 4	62	26	16 7	12 0	9. 4	ABSENT	130/80	110/76	20mm.hg	76	76	76	76	86	10	1.03	13/MIN	1.01	NORMAL FUNDUS
88	RATHNABAI	55	F	15 4	75	31	18 3	13 0	9. 3	ABSENT	150/90	130/80	20mm.hg	82	82	82	82	88	6	0.55	4/MIN	0.75	MILD PROLIFERATIVE CHANGES
89	ATHMARAM	45	M	16 0	60	23	14 0	90	8	ABSENT	120/80	114/80	6mm.hg	80	80	80	80	96	16	1.41	14/MIN	1.08	NORMAL FUNDUS
90	PARUBAI	40	F	15 2	45	19	16 0	11 0	7	ABSENT	110/70	104/68	6mm.hg	70	70	70	70	90	20	1.51	18/min	1.1	NORMAL FUNDUS
91	SHAMBULINGA	60	M	16 4	75	27	19 6	14 9	8. 8	TRACE	140/80	120/78	20mm.hg	80	80	80	80	92	12	1.13	12/min	1.03	NORMAL FUNDUS
92	ALLABAKSH	50	M	16 8	65	23	16 0	11 0	6. 8	ABSENT	120/80	116/80	4mm.hg	80	80	80	80	96	16	1.51	18/MIN	1.2	NORMAL FUNDUS
93	IRRAMMA	55	F	15 2	60	25	15 0	12 0	9. 7	ABSENT	130/70	120/70	20mm.hg	70	70	70	70	84	14	1.01	12/MIN	1	NORMAL FUNDUS
94	SAHESH	40	M	16 0	60	23. 4	16 0	11 0	7	ABSENT	120/70	110/70	10mm.hg	70	70	70	70	90	20	1.61	18/MIN	1.08	NORMAL FUNDUS
95	KASTHURIBAI	48	F	15 2	51	22	25 0	22 0	9. 7	PRESEN T	150/90	120/80	30mm.hg	80	80	80	80	82	2	0.3	2/MIN	0.5	PROLIFERATIVE DIABETIC RETINOPATHY
96	SHIVAPPA	45	M	15 6	56	23	43 5	16 0	10	ABSENT	110/70	94/70	16mm.hg	70	70	70	70	80	10	1.02	12/min	1.1	MILD PROLIFERATIVE CHANGES