EVALUATION OF RETINAL GANGLION CELL ACTIVITY BY PATTERN VISUAL EVOKED POTENTIALS IN TYPE 2 DIABETIC PATIENTS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the regulations

for the award of the degree of

M.D. (PHYSIOLOGY)

BRANCH – V

CHENGALPATTU MEDICAL COLLEGE,

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI – TAMILNADU

APRIL 2017

CERTIFICATE

This is to certify that this dissertation titled **"EVALUATION OF RETINAL GANGLION CELL ACTIVITY BY PATTERN VISUAL EVOKED POTENTIALS IN TYPE 2 DIABETIC PATIENTS''** is a bonafide record of work done by **DRA.C.VANAJARANI,** during the period of her Post graduate study from 2014 to 2017 under guidance and supervision in the Department of Physiology, Chengalpattu Medical College and Hospital, Chengalpattu – 603 001 in partial fulfillment of the requirement for **M.D. PHYSIOLOGY** degree Examination of The Tamil Nadu Dr. M.G.R Medical University to be held in April 2017.

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DECLARATION

I declare that the dissertation entitled **"EVALUATION OF RETINAL GANGLION CELL ACTIVITY BY PATTERN VISUAL EVOKED POTENTIALS IN TYPE 2 DIABETIC PATIENTS''** submitted by me for the degree of **MD** is the record work carried out by me during the period of **March 2015 to February 2016** under the guidance of Head of the Department, **Dr.A.ANITHA, MD, DCH.,** Department of Physiology, Chengalpattu Medical College, Chengalpattu. This dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the University regulations for the award of degree of M.D., Physiology (Branch V) examinations to be held in April 2017.

Place: Chengalpattu **Signature of the Candidate**

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INSTITUTIONAL ETHICAL COMMITTEE

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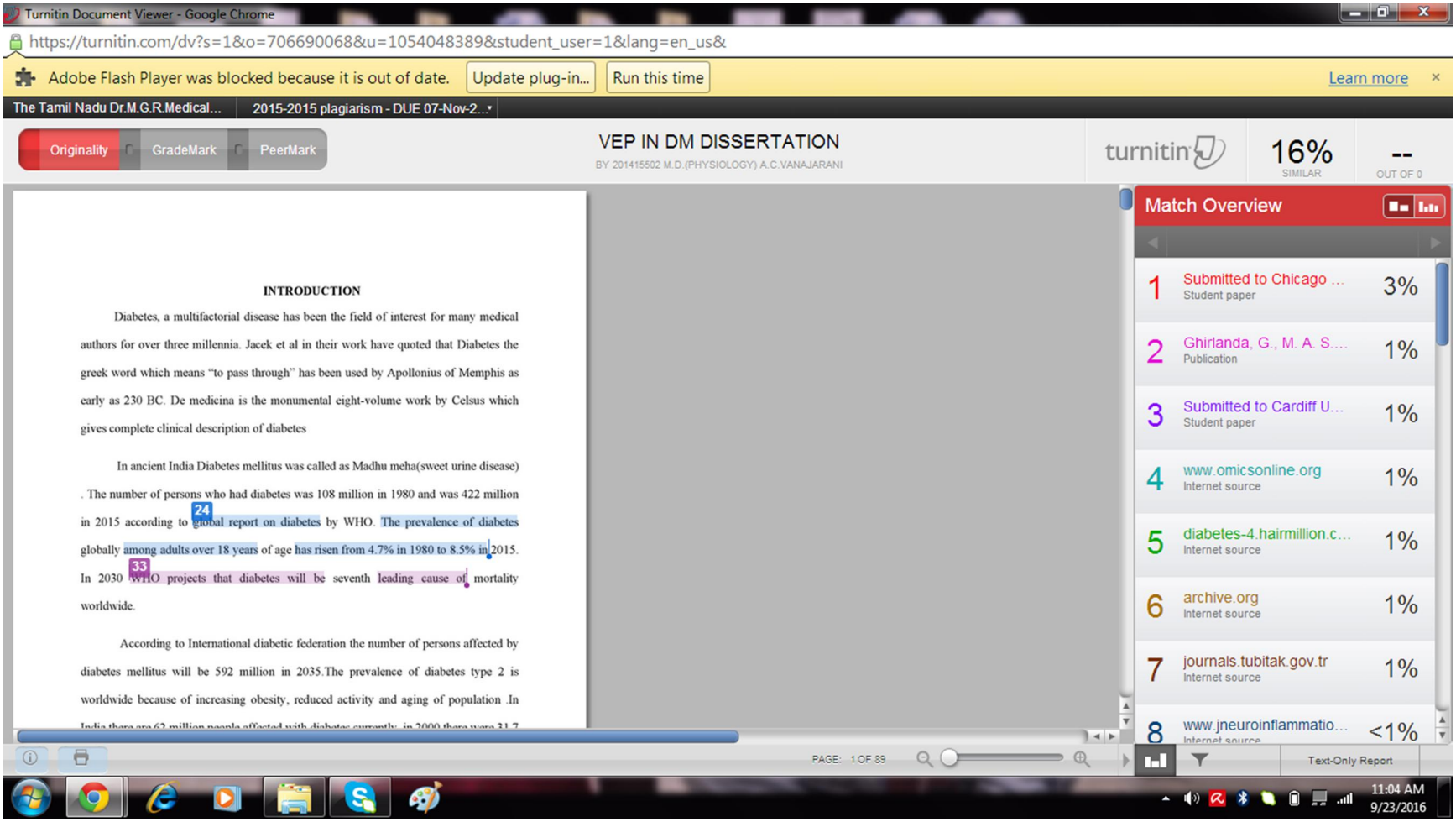
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INTRODUCTION
Diabetes, a multifactorial disease has been the field of interest for many medical authors for over three millennia. Jacek et al in their work have quoted that Diabetes the greek word which means "to pass through" has been used by Apollonius of Memphis as early as 230 BC. De medicina is the monumental eight-volume work by Celsus which gives complete clinical description of diabetes
In ancient India Diabetes mellitus was called as Madhu meha(sweet urine disease) . The number of persons who had diabetes was 108 million in 1980 and was 422 million in 2015 according to global report on diabetes by WHO. The prevalence of diabetes globally among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2015. In 2030 WHO projects that diabetes will be seventh leading cause of mortality worldwide.
According to International diabetic federation the number of persons affected by diabetes mellitus will be 592 million in 2035.The prevalence of diabetes type 2 is worldwide because of increasing obesity, reduced activity and aging of population .In
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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CVA	Cerebrovascular Accidents
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
EOG	Electrooculogram
ERG	Electroretinogram
GDM	Gestational Diabetes Mellius
HbA_1c	Glycosylated Haemoglobin
IDDM	Insulin Dependent Diabetes Mellitus
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolrance
MODY	Maturiyy Onset Diabetes Mellitus of Young
NIDDM	Non Insulin Dependent Diabetes Mellitus
NPDR	Non Proliferative Diabetic Retinopathy
PERG	Pattern Eleectroretinogram
PVEP	Pattern Visual Evoked Potential
VEP	Visual Evoked Potential

INTRODUCTION

Diabetes, a multifactorial disease has been the field of interest for many medical authors for over three millennia. Jacek et al in their work have quoted that Diabetes the greek word which means “to pass through” has been used by Apollonius of Memphis as early as 230 BC. De medicina is the monumental eight-volume work by Celsus which gives complete clinical description of diabetes.[1]

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According to International diabetic federation the number of persons affected by diabetes mellitus will be 592 million in 2035.[5]The prevalence of diabetes type 2 is worldwide because of increasing obesity, reduced activity and aging of population .[6]In India there are 62 million people affected with diabetes currently, in 2000 there were 31.7 million people affected and by 2030 79.4 million people will be affected .[7]

With longer duration of disease the glycemic control worsened in diabetic individuals.[8] Amongst the microvascular and macrovascular

complications of diabetes, the most common complication is neuropathy which is 24.6% and 16.6% is nephropathy.

HISTORY[9]

The term diabetes was coined by Apollonius of Memphis in 280 BC which means “to go through or siphon” for a disease in which patients were drained of more fluid than what they consumed. in ancient India it was known as madhu meha(sweet urine disease).[2] and in 1500BC,Hindu writings there were evidences that the urine of people with mysterious emanating disease was attracted by ants .Honey which is a Latin word was added to the word diabetes and Water tasters used to drink the urine of diabetic patients and diagnosis was often made in this manner up to 11 th century. In 16th century diabetes was recognized as a general disorder of serious nature by Paracelsus. In 1776 a brown sugar like substance in taste and appearance was found when urine of diabetic patient was evaporated. He also observed blood of these patients tasted sweet and the disease is lethal in some when the duration was less the 5 weeks and chronic condition for others. Type 1 and type 2 were distinguished for the first time. In 1797 important dietary regimen introduced to the treatment of diabetics by Rollo,a patient was treated using high fat and protein diet by him when he observed that after eating starchy food urine sugar increased Excess sugar in the urine and blood was documented by Rollo in 1798. To detect and measure sugar in urine chemical tests were developed by researchers in early 1800

The first link between diabetes and glycogen metabolism was made by Bernard who discovered that liver is the site for formation of glycogen in 1848 and in late 1850. Diabetic patients were advised to consume more amount of sugar by Priorry during treatment. In the year 1869 it was discovered that Pancreas contains cell which are of two types one of which secretes normal pancreatic juice which were later identified as Islets of Langerhans in the name of the discoverer who was a Medical student in Germany. In 1870 Brochardat a French physician noticed that in diabetic patient's urine the sugar disappeared after food rationing. Minkowski and Von Mering removed the dog pancreas and found the development of diabetes in 1889..Old child with duration of the disease 10 years had a life expectancy of 1yr in 1897 and life expectancy was 4yrs when the disease was diagnosed at age of 30 and when disease diagnosed at 50 years life expectancy was 8 yrs.

Five diabetic patients were introduced with pancreatic tissue extracts in the year 1908 and found there was reduction in the urine sugar with this treatment, but the side effects were very severe and the unknown pancreatic substance was named Insulin meaning insula (island) in Latin by De Meyer of Belgium in the year 1909.A new method was introduced by Benedict to measure urine sugar which was called as Benedicts solution in 1911 and during the period 1900-1915 the treatment for diabetes included oat cure ,the rice cure ,milk diet, for the loss of weight and fluids the treatment involved over feeding, opium and potato therapy and in 1913 Revolution in diabetic

therapy was created by book written by Allens titled studies concerning glycosuria and diabetes. During 1910-1928. Joslin considered diabetes as best of chronic disease because it was non contagious,clean,painless often and susceptible to treatment.

In 1916 a strict dietary pattern was given by Allen and in 1919 another book published regarding dietary regulation in fetus by Allen .In 1920 the thought about insulin arised in Banting after reading the book written by Mosses Barrons . In 1921a study describing isolation of pancreatic tissue successfully was published by Paulescu who was a Roman scientist and there was Discovery of Insulin and insulin was used to treat a dog without pancreas and in a meeting held at American Physiological society at Yale UniversityBanting presented it. In 1922 Leonard Thompson an 14 year old boy was tested using Collips insulin extract, which is considered the first test done on a human being and a deal was signed between Eli Lilly and university of Toronto for producing insulin on a large scale .In 1923 Nobel prize in physiology and medicine was awarded to Banting and his colleague Macleod and the commercial production of insulin was began by Eli Lillyand this substance which was produced was named insulin by the Toronto coampany.Eli Lilly called it as Isletin Insulin. In the year 1925 testing of sugar in the urine was introduced.1930-Refinement of Insulin ,long acting insulin Protamine zinc with greater flexibility was introduced.In1936-Diabetes was divided into two based on insulin sensitivity by Himsworth.In 1940 link

was made between renal , eye diseases and diabetes which are long term complications. The urine test for diabetes dip and read test was developed by Helen free in late 1940 and development of uniform insulin syringe in 1944. Insulin alone cannot prevent all diabetes related issues was written by Joslin in his book unknown diabetics in the year 1948.The marriage between people with hereditary diabetes was objected by specialists in 1950s and the amount of insulin in blood was measured by Lawrence and Bornstein in 1951. Blood glucose lowering oral agents were introduced in 1955.

In the year 1959 Type 1and Type 2 two major forms of diabetes introduced .In 1960 the level for control of diabetics increased with home testing for glucose in the urine. Blood glucose testing strips were used for the first time in1964 and there was Development of instant glucose in 1965. At the university of Manitoba in1966 pancreas transplantation was done for the first time. There was introduction of first glucose meter in 1970 and the blindness resulting from diabetes was slowed down or prevented using Laser therapy. In 1973 there was introduction of U-100 insulin and of HbA1c testing in 1976. Biosynthetic human insulin was introduced for the first time in 1983 and Accu check which was previously called as Reflolux introduced which helped in self monitoring of glucose accurately.

In 1993 there was publication of study done by diabetes control and complications and the study showed that the risk of ophthalmic complications to be the highest with 76%, followed by renal and neural complications.

Human insulin Lispro which was produced by the first recombinant DNA technology was approved by FDA in the year 1996 and during 1990-1997 there was Introduction of external insulin pumps. In the year 2003 there was formal dropping of the names IDDM for type 1 and NIDDM for type 2.[10]

DIABETES MELLITUS

It is a group of metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by complex interaction of genetics and environmental factors. Depending on etiology of DM factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization and increased glucose production.[10]

CLASSIFICATION

It is mainly based on hyperglycemia which is produced by various pathogenic processes. Previously it was based on age of onset or type of therapy. Diabetes is broadly classified into type 1 and type 2.

Current classification has two important features

- The terms insulin dependent diabetes mellitus and non insulin dependent diabetes mellitus are not used now.
- For the classification age or treatment is not taken into account

TABLE 1

Classification of Diabetes mellitus

Type of Diabetes	Normal glucose tolerance	Hyperglycemia			
		Pre diabetes	Diabetes mellitus		
		Impaired fasting glucose orimpairedglucose tolerance	Not insulin requiring	Insulin required for control	Insulin required for survival
Type 1	←	—	—	—	→
Type 2	←	—	—	→	
Other specific types	←	—	—	→	
Gestational diabetes	←	—	—	→	
Time years	←	—	—	—	→
FPG	<5.6mmol/L (100mg/dl)	5.6-6.9mmol/L (100-125mg/dl)	>7mmol/L (126mg/dl)		
2hr PG	>7.8mmol/L (140mg/dl)	7.8-11mmol/L (140-199mg/dl)	>11.1mmol/L (200mg/dl)		
HbA1c	<5.6%	5.6-6.4%	>6.5%		

TABLE 2

Etiologic Classification

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

- **Type 1**
- **Type 2**
- **Gestational Diabetes**
- **Others-**
  - Genetic mutations of β cell function-MODY
  - Genetic defecys in insulin action
  - Genetic syndromes-Downs,Klienfelters.Turners
  - Diseases of the exocrine pancreas-pancreatitis,cystic fibrosis
  - Endocrinopathies-Cushings syndrome,pheochromocytoma
  - Drug or chemical induced-glucocoticoids,thiazides, adrenergic agonists
  - Infections-congenital rubella,cytomegalovirus,coxsackie virus

TABLE 3

Criteria for the Diagnosis of Diabetes Mellitus

- **Symptoms of diabetes plus random blood glucose concentration≥ 11.1 mmol/L (200 mg/dL)[a]or**
- **Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)[b]or**
- **Hemoglobin A1c ≥ 6.5%[c] or**
- **2-h plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucosetolerance test[d]**

a-Random is defined as without regard to time since the last meal.
b-Fasting is defined as no caloric intake for at least 8 h.
c-Hemoglobin A1c test should be performed in a laboratory

Using a method approved by the National Glycohemoglobin Standardization Programme and correlated to the reference assay of the Diabetes Control and Complications Trial. Point of-care hemoglobin A1c should not be used for diagnostic purposes.

d-The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, not recommended for routine clinical use.

Note*:* In the absence of unequivocal hyperglycemia and acute metabolic decompensation,

These criteria should be confirmed by repeat testing on a different day.[11]

TABLE 4

Diagnostic Criteria for Diabetes Mellitus and Related Stages of Glycemia

	Capillary whole blood(b)*	Venous plasma
Diabetes mellitus Fasting 2hr PP	 >110mg/dl(≥6.1) >200mg/dl(≥11.1)	 >126mg/dl(≥7.0) >200mg/dl(≥11.1)
Impaired glucose tolerance Fasting 2 hr PP	 <110mg/dl(<6.1) 140-199mg/dl(7.8-11.0)	 <126mg/dl(<7.0) 140-199mg/dl(7.8-11.0)
Impaired fasting glycemia Fasting	 <140mg/dl(<7.8)d* <200mg/dl(<11.1)e*	 <140mg/dl(<7.8)d* <200mg/dl(<11.1)e*

a) The 2 hr post glucose value is those measured after 75 gm oral glucose load

b) If glucose concentration is measured on venous whole blood, the cut off levels for post load values are different

c) According to 2003 ADA recommendation

d) According to 1999 WHO recommendation

e) According to 1999 ADA recommendation[12]

Risk Factors for Type 2 Diabetes Mellitus-

- Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
- Obesity (BMI ≥25 kg/m2 or ethnically relevant definition for overweight)
- Physical inactivity

- Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Previously identified with IFG, IGT, or an hemoglobin A1c of 5.7–6.4%
- History of GDM or delivery of baby >4 kg (9 lb)
- Hypertension (blood pressure ≥140/90 mmHg)
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level>250 mg/dL (2.82 mmol/L)
- Polycystic ovary syndrome or acanthosis nigricans
- History of cardiovascular disease

Abbreviations*:* BMI, body mass index; GDM, gestational diabetes mellitus; HDL, high density Lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.[12]

PATHOGENESIS-
PANCREAS

It has β and α cells which are located in close proximity of each other in the pancreatic Islets of Langerhans

α cells constitute 25% and secrete glucagon

β cells constitute 70% and secrete insulin

D or delta cells are <5% secreting somatostatin

F cells are trace secreting pancreatic polypeptide

The human pancreas secretes 40-50 units of insulin daily. Activity of beta cells is primarily regulated by interstitial fluid glucose level. Insulin and glucagon play a key role in the Glucose homeostasis. They reflect a balance between glucose production by liver and glucose utilization in the peripheries.

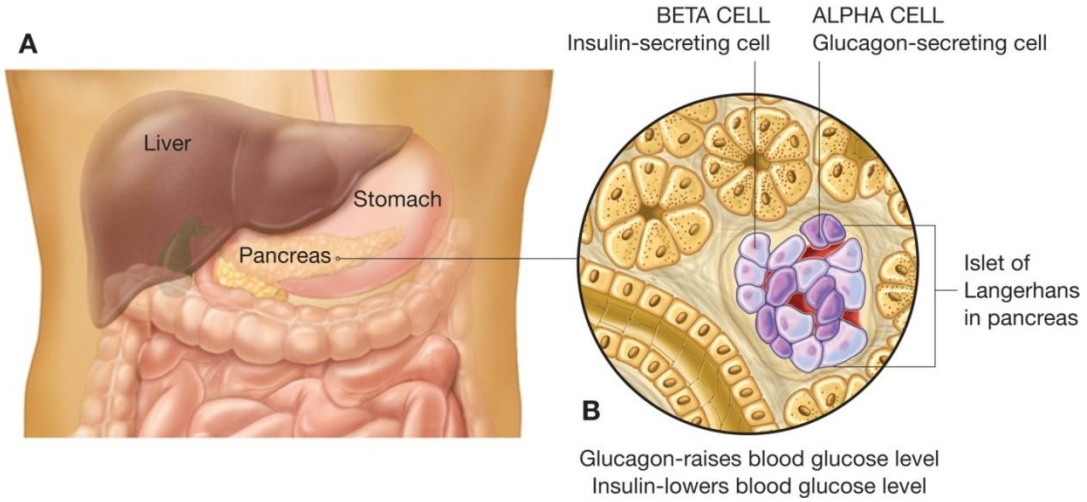


FIGURE 1: **Pancreas structure**

TYPE 1 DIABETES MELLITUS

It is due to genetic, environmental and immunological factors.

Genetic predisposition

There is a genetic predisposition in type 1 DM .Multiple genes are involved and more common in identical twins. The genes are located on HLA region of chromosome 6.Most individuals have HLA DR3, and/or DR4, DQA1*0301,DQB1*0302,DQB1*0201.

PATHOPHYSIOLOGY

There is infiltration of pancreatic Islets with lymphocytes which is called as insulitis.The inflammatory process declines after beta cell destruction and islets become atrophic. The process by death of beta cells occurs is not known but it might be due to effect of metabolites of nitric oxides, apoptosis and cytotoxic effect of CD8+ T cells The autoimmunity plays a main role in the depletion of pancreatic Islets . The components include insulin,glutamic acid decarboxylase(GAD the enzyme essential for synthesis of neurotransmitter GABA), ICA-512/IA-2 (homology with tyrosine phosphatase).[10]

At present the theories say that the autoimmune mechanism initially affects single molecule of beta cell and then spreads to other islet cells and the immune system causing destruction of beta cells creating a series of secondary auto antigens. Most of the antibodies present in the islet cells are directed against glutamic acid decarboxylase.[13]

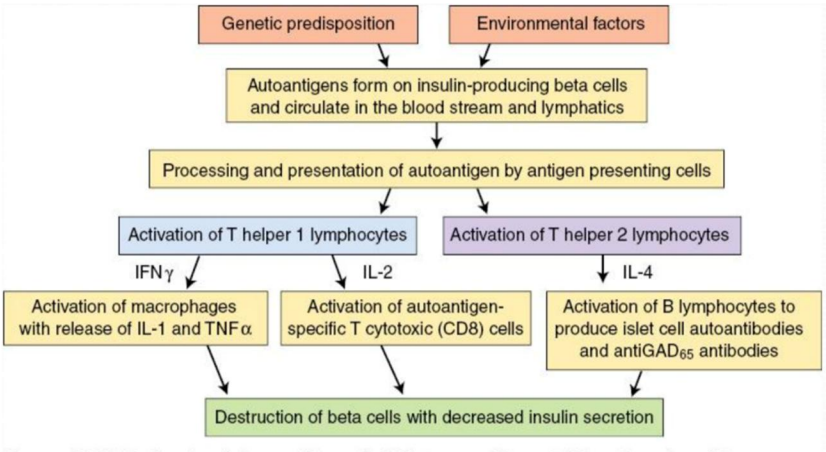


FIGURE 2 : Pathogenesis of type 1 diabetes mellitus

Environmental factors :

Autoimmune process is triggered by several environmental factors like viruses (coxsackie,rubella,enteroviruses)

Type 2 DIABETES MELLIUS:

The development of type 2 diabetes mellitus is mainly due to insulin resistance and abnormal insulin secretion

Genetic considerations :

- Strong genetic predisposition present
- Occurring in 70-90 % of identical twins
- Disease involves multiple genes and also other factors like obesity, nutritional factors and sedentary life style of the individual
- More than 70 genes have been identified
- Islet cell function, their development or insulin secretion are altered by these genes

PATHOPHYSIOLOGY-

- The characteristic features of Diabetes mellitus type 2 are
- Impaired secretion of insulin
- Insulin receptor insensitivity
- Excessive production of glucose by liver
- Obesity

- glucose tolerance remains near normal in the early stages of disorder despite resistance to insulin because the pancreatic output is increased by beta cells of pancreas in a compensatory process
- As increased secretion of insulin which occurred as compensation and insulin resistance progresses in certain individuals the islets of pancreas are not able to maintain the hyperglycemic state.
- IGT characterized by postprandial glucose elevations develops
- As the insulin secretion decreases further and an increase in glucose production by the liver leads to development of diabetes with hyperglycemia in fasting state
- Finally beta cell failure occurs and impaired insulin secretion and resistance to insulin leads to pathogenesis of diabetes mellitus type 2

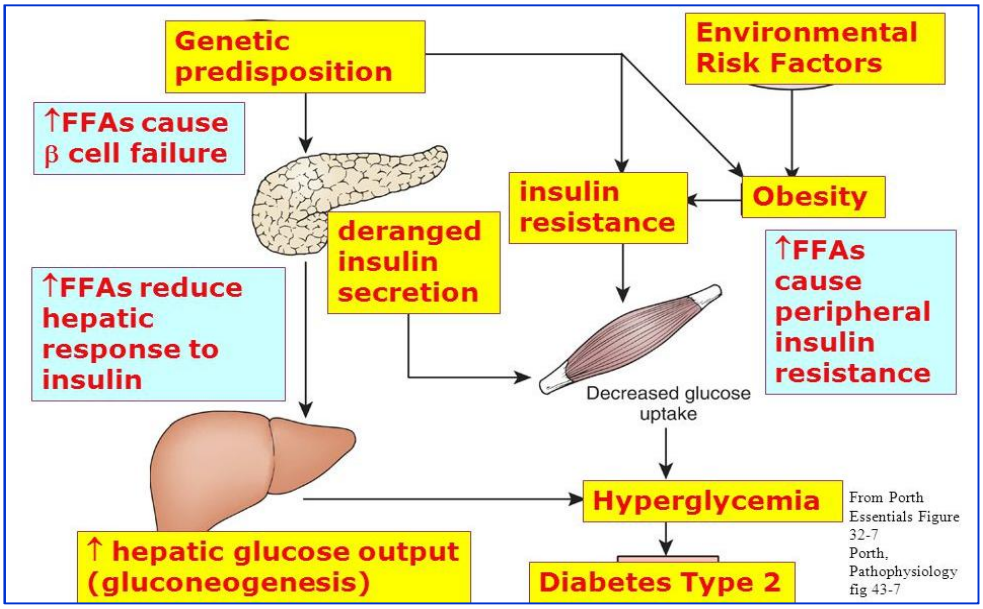


FIGURE 3: Type 2 DM pathogenesis

CLINICAL FEATURES

TYPE 1 DIABETES MELLITUS

- Weight loss
- Polyuria
- Increased thirst(polydipsia)
- Polyphagia
- Weakness and overwhelming fatigue with leg cramps
- Unnoticed and uncared for symptoms of anorexia,nausea,abdominal pain and signs of dehydration appear
- These may progress to other symptoms of ketoacidosis that is drowsiness heavy breathing, sweating and fruity odor

TYPE 2 DIABETES MELLITUS

- Polyuria
- Polydipsia
- Nocturia
- Lassitude
- Loss of weight
- Headache
- Progressive loss of vision
- Giddiness
- Paresthesia
- Respiratory and CVS complaints
- Muscle ache

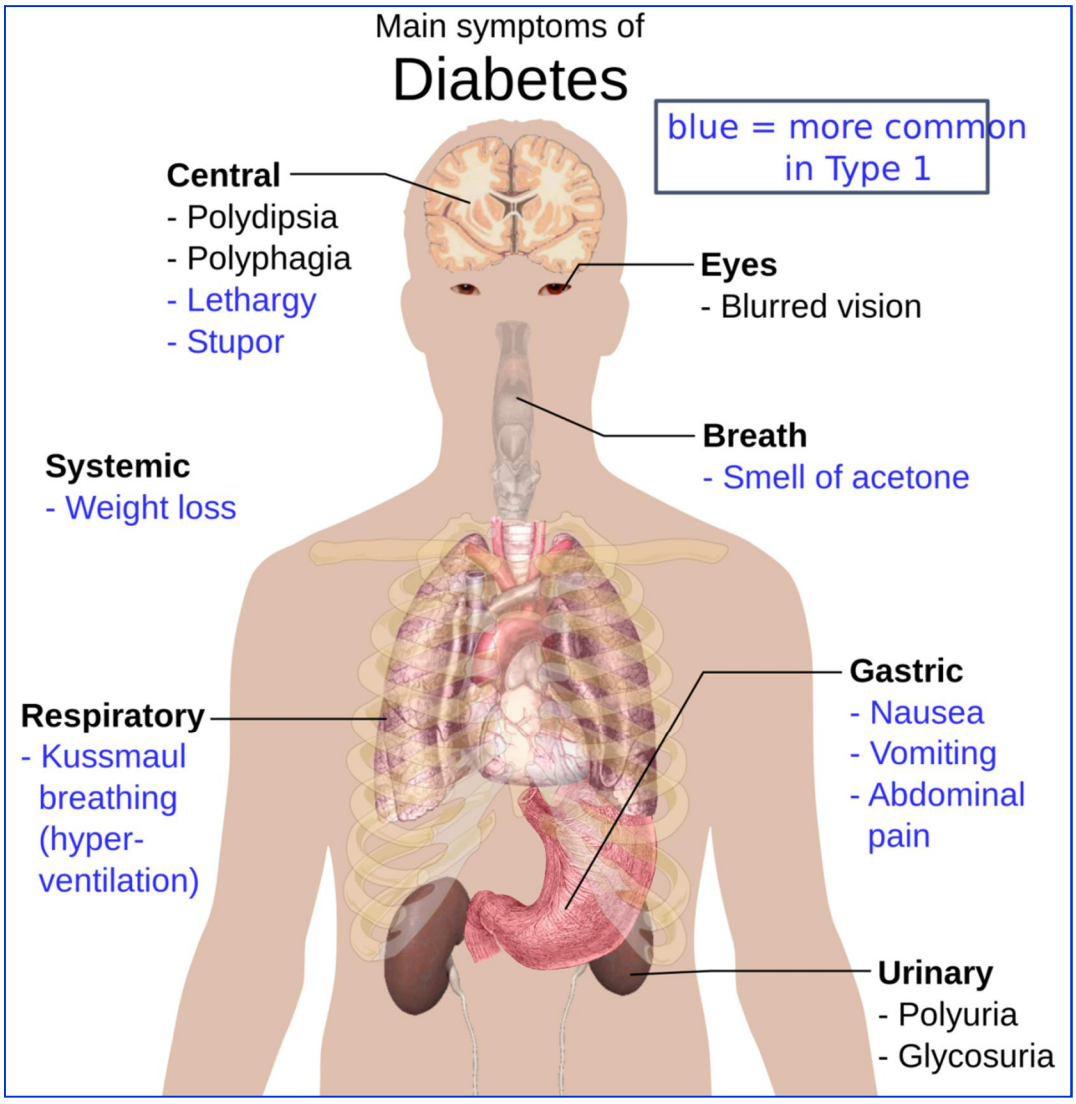


FIGURE 4: Clinical features of DM

COMPLICATIONS

The complications related to diabetes affects number of systems in the body and are responsible for most of the morbidity and mortality. Diabetes is the major cause of blindness in adults in America. Thecomplication doesnot occur until second decade of hyperglycemia. At the time of diagnosis most people with diabetes mellitus type 2 have complications.

Complication of diabetes mellitus are divided into-

- ❖ Acute
- ❖ Chronic

Acute complication

(Diabetic ketoacidosis) and hyperglycemic hyperosmolar state

Chronic complications divided into-

Microvascular and macrovascular complications

Micro vascular complications

Eye diseases:

Diabetic retinopathy (Non proliferative and Proliferative)

Macular edema

Diabetic nephropathy (Albuminuria and decreased renal function)

Diabetic neuropathy

- Sensory and motor (mono and polyneuropathy)
- Autonomic

Macro vascular complications

Coronary artery disease

Peripheral arterial diseases

Cerebrovascular diseases

Non vascular complications

Gastroparesis,Infection ,Skin ,infectious ,cataract

Glaucoma, periodontal disease, hearing loss,cherioarthropathy

Other comorbid conditions

- Mood disorders,sleep related disorders,abnormal liver function tests,osteoporotic changes,cognitive disorders,male infertility due to low testosterone levels

DIABETIC RETINOPATHY (DR)

The leading cause of blindness which is avoidable in both developing and developed countries is Diabetic retinopathy in DM. These cases are more likely to become blind than non diabetics. It is sixth common cause of visual loss in India.[14]

Diabetic retinopathy global prevalence report says that there are about 93 million DR, 17million PDR, and 21 million macular edema. WHO estimates 4% 0f 45 million cases of blindness is due to eye condition and uncorrected refractive error throughout the world is due to Diabetic retinopathy. More than 75% of patients who have DM for more than 20 years will have some form of DR.[15]

Incidence of blindness after 10 years of onset of DM was 18-40% and 4.8% in type I and II DM.[14]

Type I DM patients are free from retinopathy during the first five years of diagnosis. After two decades nearly all DM type 1 patients and more than 60% of type II DM patients have retinopathy.

In Type II DM the prevalence of DR at first at first ophthalmological examination has been reported to be 11-25%*.Another study shows the disease started years before diagnosis.[16]

RISK FACTORS

1) Duration of Diabetes

When the diagnosis of diabetes is made before the age of 30 years there is 50% incidence of diabetic retinopathy and it is 90% when the diagnosis is made after 30 years, the development of DR within 5 years of onset of diabetes before puberty is rare, but at the time of presentation 5% of patients with type 2 diabetes have DR.Duration of the disease is strong predictor for proliferative disease than for maculopathy.

2) Poor control of diabetes

The development or progression of DR can be delayed when there is tight blood glucose. There is progression of retinopathy when the blood glucose control is sudden. Type 2 diabetics are benefited better than the type 1 from better control. The risk of proliferative disease is associated with increased HbA1c.

3) Pregnancy

Rapid progression DR occurs in pregnancy. Other risk factors include severity of retinopathy in pre pregnancy state, poor control of diabetes in pregnancy; exertion of too rapid control in early stages of pregnancy .It should be controlled strictly and appears beneficial in patient with type 2 diabetics

4) Nephropathy

If present with diabetics causes worsening of DR

5) Other risk factors

Smoking, cataract surgery,hyperlipidemia and obesity and anemia

PATHOGENESIS

DR is a microangiopathy affecting small blood vessels which are damaged due to hyperglycemia

1) Cellular damage

Mechanism include accumulation of sorbitol intracellulary,oxidative stress caused by free radical excess,advanced glycated end products accumulation and activation excessive protein kinase C isoforms.Ion channel disruption is an important early feature.

2) Capillaropathy

There is death of pericytes, capillary basement membrane thickening, vascular smooth muscle cell loss and endothelial cell proliferation. It is also characterized by erythrocyte and leucocytes abnormality, increased stickiness

of platelets and increased viscosity of plasma. Capillary dysfunction is manifested by leakage and occlusion.

3) Neovascularization

It is due non perfusion of capillaries which causes retinal hypoxia which may progress to neovascularization extending preretinally, intraretinall. Intraretinal micro vascular abnormalities (IRMA) are shunts running within the retina from arterioles to venules. Imbalance between angiogenic factors and anti angiogenic factors is the cause of new vessel growth which attempts to revascularize the hypoxic retina. There are many angiogenic factors present which includes VEGF, VEGF-A, PDGF, Hepatocyte growth factor. The endogenous inhibitors of angiogenesis are endoststin, angioststin, and pigment epithelium derived factor. The activity of retinopathy is determined by net balance between VEGF and Endoststin.

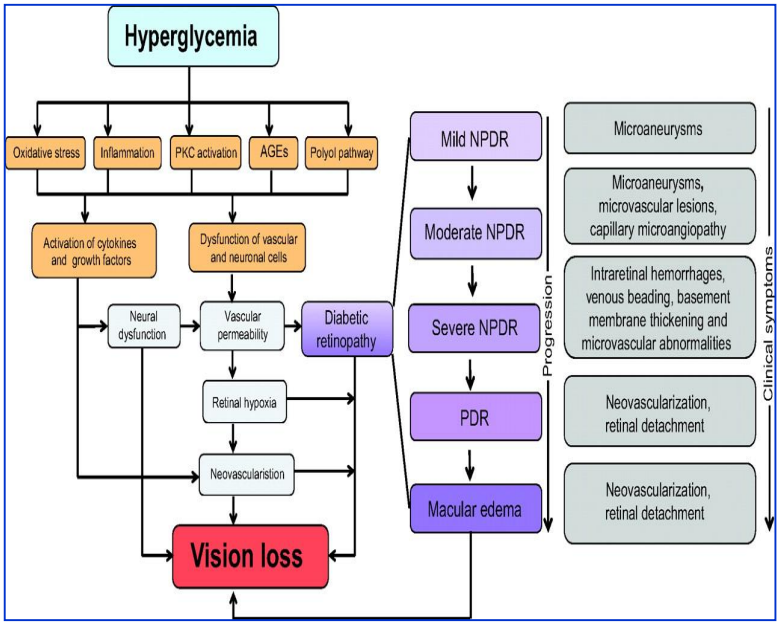


FIGURE 5: Pathogenesis of DR

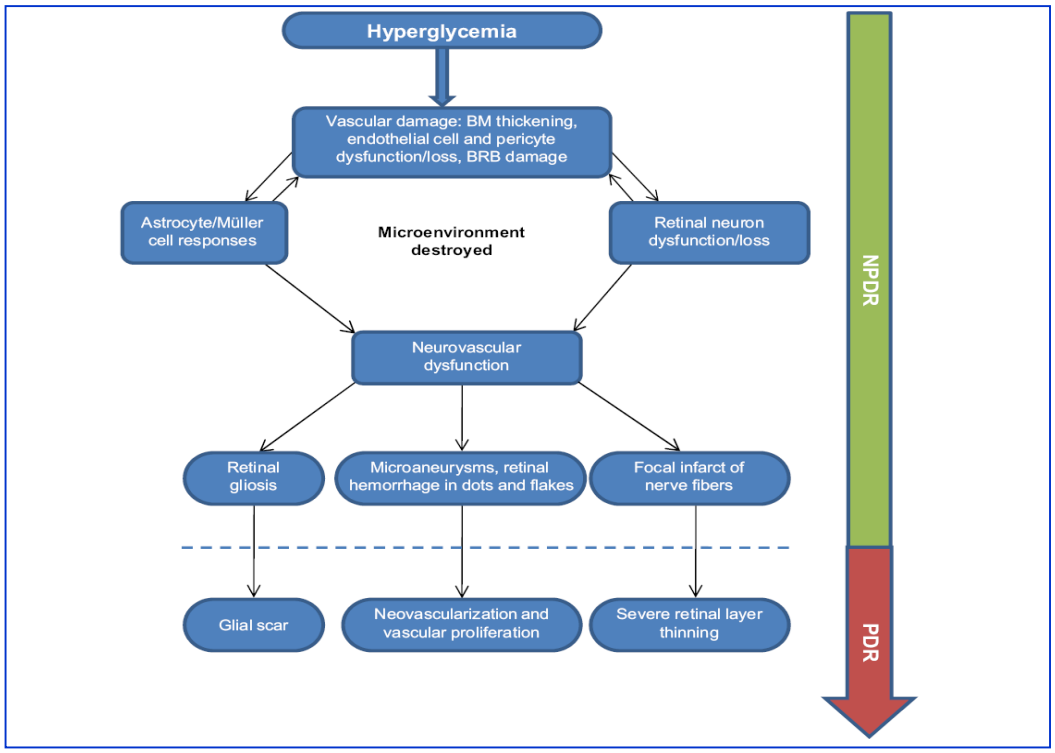


FIGURE 6 : Neurovascular hypothesis for pathogenesis of DR

CLASSIFICATION

The ETDRS classification (the modified Airlie House classification) is widely used internationally.

NONPROLIFERATIVE DIABETIC RETINOPATHY

1) No diabetic retinopathy

2) Very mild-micro aneurysms only

3) Mild-Any or all of microaneurysms,retinal haemorrhages, exudates, cotton wool spots, upto the level of moderate NPDR,No IRMA or significant beading.

4) Moderate-Severe retinal hemorrhages(about 20 medium-large per quadrant) in 1-3 quadrants or mild intraretinal micro vascular abnormalities, significant venous beading can be present in no more than I quadrant and cotton wool spots commonly present.

5) Severe-4-2-1 rule

One are more of severe hemorrhage in all 4 quadrants

Significant venous bleeding in 2 or more quadrants

Moderate IRMA in 1 or more quadrants

6) Very Severe-Two or criteria for severe

PROLIFERATIVE DIABETIC RETINOPATHY

1) Mild-moderate-It is characterized by new vessels on the disc (NVD) or New vessels elsewhere (NVE) but extent insufficient to meet the high risk criteria

2) High risk-New vessel on the disc greater than the ETDRS standard.Any NVD with vitreous or pre retinal hemorrhage

3) NVE greater than ½ disc areas with vitreous are pre retinal hemorrhage

SIGNS OF NONPROLIFERATIVE DIABETIC RETINOPATHY

1) Micro aneurysm

It is characterized by localized out pouching of the capillary wall that may be formed either by focal dilation of capillary wall where the pericytes are absent

2) Retinal hemorrhages

a) Retinal nerve fiber layer hemorrhages from larger superficial pre capillary arterioles.

b) Intraretinal hemorrhages are from venous end of capillaries and are located in compact middle layers of retina with a resistant dot/blot configuration.

c) Deeper dark round hemorrhages are hematologic retinal infarcts and located within the middle retinal layer.

3) Exudates sometimes termed as hard exudates are caused by chronic localized edema and develop at the junction of normal and edematous retina. They are composed of lipoprotein and lipid filled macrophages.

4) Cotton wool spot is made up of accumulation of neuronal debris within the nerve fiber layer due to nerve axons disruption.

5) Venous changes are dilation, looping, beading and sausage segmentation.

PROLIFERATIVE RETINOPATHY

1) New vessel at disc-neovascularization on or within one disc diameter of the optic nerve head.

2) New vessel elsewhere-Neovascularization further away from the discs.

3) New vessels on iris-NVI known as rubeosis iridis carry a high likelihood of progression to neovascular glaucoma.

4) Fluorscein angiography-Highlights neovascularization during early phase of angiogenesis.[17]

ELECTROPHYSIOLOGY IN DIABETES

Neuroretinal function changes in diabetes using electrophysiological studies have been studied since long. Conventional ERGs were not sensitive for detecting early retinal changes in diabetes[18, 19] the photopic a and b wave amplitude were used. Full field flash ERG in diabetes used, decreased oscillatory potential amplitude and increase in oscillatory potential implicit time .[20,21] Focal ERG also used .[22]Recently location specific technique used to test electrical neuroretinal function called as mfERG developed by SUTTER et al in 1992.[23]

Visual electrophysiology includes the electro oculogram(EOG),the eletroretinogram(ERG) and VEP. The positive component (P100) is by far the most consistent and highest amplitude and shows little variation in latency between or within individuals .[24]

Neurodegenerative part of Diabetic retinopathy has been given more attention in recent years.[25]More recently and frequently used in these patients is electrophysiological examination which could be used to investigate

disturbance due to neural retinal degeneration. In diabetic patients there is progressive delay in VEP which measures optic nerve .[26]

PATTERN REVERSAL VEP IN DM

In DM frequently involved system is the nervous system as its complication which occurs when duration of diabetes is increased. Abnormal function occurs in the visual pathway of diabetic patients. In DM both vascular and metabolic abnormalities are responsible for visual abnormalities affecting retina, optic nerve and visual pathway.In the retina and macula both ganglion and preganglionic components of DM patients are involved due to abnormalities in metabolism. Along post retinal visual pathway neural conduction may be delayed.

Common complication of DM is Diabetic retinopathy affecting the retinal blood vessels, which is leading cause of blindness and in most cases the patient remains symptomless which does not respond to treatment.

The blood vessels lose their intactness with fluid leaking into retina causing maculopathy which causes visual dysfunction and loss of vision. There are multifactorial causes for visual dysfunction in DM.

VEPs are highly sensitive,reliable,non invasive recording from scalp to detect conduction defects in anterior visual pathway. The neural component of retina in diabetic patient's eye undergoes minimal changes, before the micro vascular lesions develop and whichcannot be detected bynormalfundus

examination and hence such diabetic changes and can be detected by PVEP which is useful for prognosis during treatment. There is an alteration in latency in DM patients which can be detected by PVEP which detects any abnormalities in the visual pathway. Neurons for vision respond selectively to visual patterns as a result of this PVEP are more sensitive for assessing visual pathway than old flash method.

There are several studies done in diabetic patients using PVEP in western countries, but there are only few studies done in our country. VEPs are highly sensitive,reliable,non invasive recording from scalp to detect conduction defects in anterior visual pathway .

Hence the present study is an attempt done to detect retinal ganglion cell activity in patients with type 2 diabetes mellitus and compare the VEP among diabetics with retinopathy and without retinopathy, To compare the latencies among diabetics and non diabetics and to correlate VEP changes between patients with type 2 diabetes mellitus with retinopathy and those who do not have retinopathy[27, 28]

VISUAL EVOKED POTENTIAL

Dubois Raymond and Herman demonstrated normal electric potentials recorded from the surface of a muscle on contraction. Cerebral counter parts were discovered by Caton and found not only EEG, He also discovered on sensory stimulation with visual stimuli produced evoked potential changes.

The sensory areas in the cortex were marked by him and also described by experimentation the operating technique,electrodes,instrumentation in 1887.The position of electrodes which responded to sound was marked by Beck and the first photograph of an evoked potential recorded from cortex of a dog on stimulation of sciatic nerve was given by Pravdich-Neminsky.[29]

The visual stimuli response was recorded from animal piamater surface in 1930.[30] In 1934 Adrian and Mathew observed electrical activity in occipital EEG when visual stimuli was given.[31]In 1940 EEG as a clinical neurologic test was launched by Berger which is used worldwide.[30]Dawson first demonstrated a signal averaging device in1951 and signal averaging computers have been available since early 1960.[30]

Ciganek developed the first nomenclature for occipital EEG components in 1961 and in the same year Hirsch and colleagues recorded VEP on occipital lobe and they discovered amplitudes recorded along calcrine fissure were the longer.Spelhman used a checker board stimulation to describe human VEPs.[31]In 1960 PVEP methods developed and popularized and they are more sensitive to optic nerve lesions than flash VEP.[29]

In 1970 AM. Haliday at queen square in London and Lorrin A Riggs at brown university developed pattern reversal stimulation.[30].Haliday and colleagues completed the first clinical investigation using VEP by recording delayed VEPs in patient with retro bulbar neuritis.[29]Haliday back projected a checker pattern on to a translucent screen with two projectors that each

projected reversal checker board images. Riggs originally projected alternating vertical stripes using a reversing mirror system.[30]

Adrian and Mathew introduced VEP for clinical and research purposes since five decades.[31]VEP used in the diagnosis of optic neuritis used by Halliday et al. is used to assess cases of suspected multiple sclerosis.

REVIEW OF LITERATURE

Diabetes, a multifactorial disease has been the field of interest for many medical authors for over three millennia. Jacek et al in their work have quoted that Diabetes the Greek word which means “to pass through” has been used by Apollonius of Memphis as early as 230 BC. De medicina is the monumental eight-volume work by Celsus which gives complete clinical description of diabetes.Untill early part of the twentieth century, till the discovery of insulin by Banting and Best the prognosis of diabetes was no better than 3000 years ago. It is the work of Frederick Sanger which paved the way for the production of human insulin by recombinant DNA technology. Genetech in 1978 did the gene coding for human insulin. Insulin, approved by FDA is the first genetically manufactured drug .[1]

Diabetes is recognized as the global epidemic, presently one of the most important challenges in healthcare. Diabetes prevalence for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. WHO global report on Diabetes says that the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. International diabetic federation projects that 592 million people will be affected with diabetes by the year 2035.[3]

In India in 2000 there were 31.7 million people affected, which increased to 62 million people currently, and it is predicted to affect 79.4 million people with present prevalence rate by 2030**.** [7]

Diabetes prevalence is more in males than females in age group lesser than 60years, but there are more females with diabetes than males in older age group. The most important demographic changes in diabetes prevalence across the world is due to increase in the number of people >65 years of age.

In Diabetes, type 2 can be exacerbated by the present changes in the lifestyle which includesmodified food habits and work schedules obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reaven's syndrome).

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus (DM), a chronic metabolic disorder affecting many people leading to premature death in seventh decade. The disease being a component of metabolic syndrome has multifactorial risk factors including genetic predisposition, environmental and other risk factors. The morbidity and mortality associated with the disease is increasing because of its insidious onset, incidental diagnosis and complications at the time of diagnosis. The developing countries bear the brunt of the disease having about 80% of the people with the disease.

It is estimated that by the year 2030 about 439 million people will be affected with type 2 DM.incidence varies from one region to other in relation to environmental and life style risk factors. With the present scenario in the forthcoming two decades, the proportion of patients with type 2 DM will increase in the age group between 45 to 64 years.[32]

PATHOGENESIS

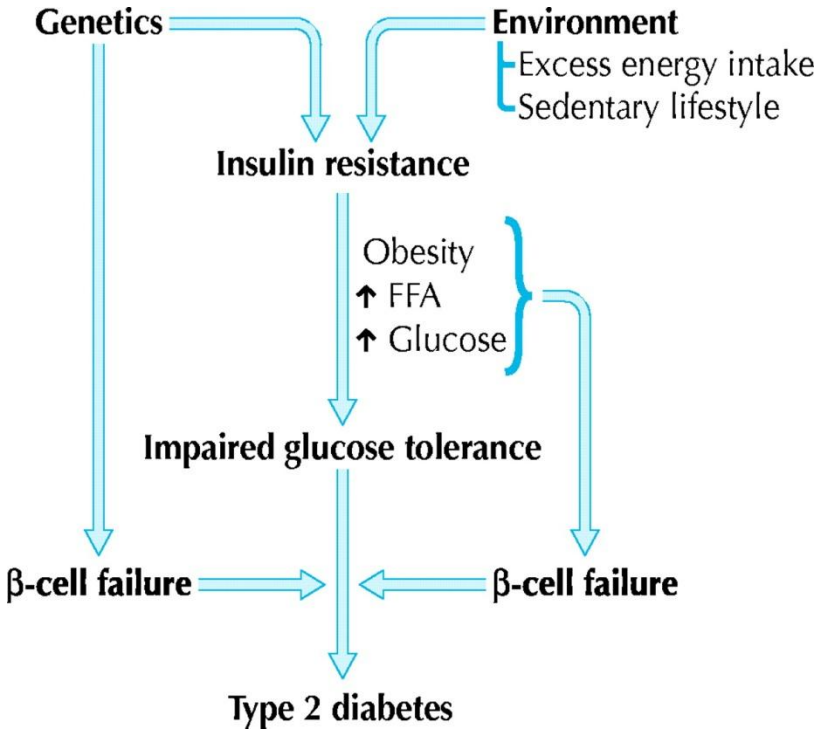


FIGURE7: DM type 2 pathogenesis

TABLE 5

Complications of diabetes mellitus

Acute complications	Chronic complications
Hypoglycemia, Hyperglycemic crises, Diabetes Ketoacidosis (DKA) Hyperglycemic hyperosmolar state (HHS)	**Micro vascular complications**-Diabetic retinopathy, Diabetic nephropathy, Diabetic neuropathy **Macrovascularcomplications**-Coronary artery disease, Peripheral arterial diseases, Cerebrovascular diseases **Non vascular complications**-Gastroparesis, Infection, Skin, infectious cataract, glaucoma, periodontal disease, hearing loss, cherioarthropathy Other co morbid conditions - Depression, obstructive sleep apnea, fatty liver disease, hip fracture, osteoporosis (in type 1 diabetes), cognitive impairment or dementia, low testosterone in men.

Zeinab Nasralah et al has stated the major cause of avoidable blindness in both developing and developed countries is DR and about 12000-24000 persons have visual loss every year because of DR as given by ADA. The leading cause of blindness in the world, DR affects about 4 million people between the age group of 20 to 74 years. Type and duration of diabetes, blood glucose, blood pressure, and possibly lipids are the risk factors for the occurrence of diabetic retinopathy.[33]

Nagi et al in their work have found that11-25% in newly diagnosed type2 DM had DR as an incidental finding and in another study by Klien et al.the prevalence of diabetic retinopathy in type2 DM patients within 5 years of diagnosis is 29% (32). J.H.Kempen et al in their study have found that prevalence of DR is directly proportional to prevalence of DM and Harris et al studied non-insulin-dependent diabetes (NIDDM) subjects in the United States and Australia Prevalence of retinopathy and duration of diabetes subsequent to clinical diagnosis were determined for all subjects. They found clinically significant morbidity at the time of diagnosis and for years before diagnosis.[34].

Pathogenesis

There are various factors in the pathogenesis of diabetic retinopathy, such as bio-chemical mechanisms, rheological changes and structural changes.Maitra A. revealed prolonged hyperglycemia [35] is the major etiologic agent in the micro vascular complications of diabetes mellitus and Enden MKV have attributed prolonged hyperglycemia leads excess sorbitol

formation .[36] Chronic hyperglycemia causes accelerated oxidative stress in cells resulting in toxic end products as shown by .[37]

Peyman GA has shown Rheological changes[38]like increased platelet adhesion and aggregation and Xia has found proteinkinase C activation [39] and vascular endothelial growth factor release as an additive factor.

S.M.Park et al has found in their study that neurodegenerative changes in the diabetic retina occurring before diabetic retinopathy could be inevitable by the altered energy (glucose) metabolism, in the sense that dynamic image-processing activity of the retinal neurons is exclusively dependent on glucose. This study investigated the morphological changes in the neural retina, including neuronal cell death, of a streptozotocin-induced model of diabetes. A slight reduction in the thickness of the inner retina was observed throughout the diabetic retinas; suggest that the visual loss associated with diabetic retinopathy could be attributed to an early phase of substantial photoreceptor loss, in addition to later microangiopathy.[40]

Timothy et al,stated that retinal ganglion cells show altered structural characteristics and also death of retinal ganglion cells. Together these studies show that retinal ganglion cells undergo apoptosis in humans with diabetes, leading to a reduction in the thickness of the nerve fiber layer.[41]

Ganglion cells, glial cells, microglia cells which are non vascular cells undergo functional and structural changes in addition to vascular changes,

which results in pathogenesis of diabetic retinopathy.Neurons are unable to proliferate so loss of these cells in toto can lead to chronic neurodegeneration.[42]

In the earlier stages of diabetic retinopathy functional changes were detected prior to development of vascular dysfunction therefore the effect of hyperglycemia may be direct on neural retina rather than secondary to the breakdown of blood retinal barrier. Neurosensory deficits occur prior to clinically identifiable vascular complications in DR.

Ying yu et al. stated the nerve fiber layer thickness in retinal superior quadrant was significantly reduced in patients with fifteen year diabetic history, which suggests a loss of axons in this area.[43]

Ghirlanda et al in their study used60 patients with diabetes mellitus with short duration of disease and 39 control subjects.Patients were divided into two groups: 50 DM patients had no retinopathy, whereas 9 DM patients had five or fewer microaneurysms on fluorescein angiography in both eyes according to the second level of the Klein classification.Study showed there is selective neurosensory deficit of inner retinal layers is produced but the photoreceptors appear unaffected. There was no significant difference between diabetic and control groups for sex and age at the time of study and between the two diabetic groups for age at onset of disease. Diabetes duration was longer and HbA1c values were higher in retinopathic patients than in the nonretinopathic group. Early functional abnormalities were found in the

postreceptoral retina of diabetic patients with no or minimal signs of retinopathy, whereas photoreceptor function was slightly affected only after the onset of ophthalmoscopically detectable retinopathy .[44]

V.Gayathri et al in their study with 40 type 2 DM patients and 20 age and sex matched controls have found that Diabetic retinopathy caused due to degeneration of neural retina is related to metabolic control that is the glycemic status. [45]

Classification of Diabetic retinopathy

(Zeinab Nasralah et al) DR is divided into two sub-classifications based on vascular pathology detected by fundus exam: [33]

- Non-proliferative diabeticretinopathy (NPDR)
- Proliferative diabetic retinopathy (PDR).

NPDR occurs in the early stage of the disease and is characterized bymicroaneurysms, macular edema and other vascular lesions.

1. No diabetic retinopathy

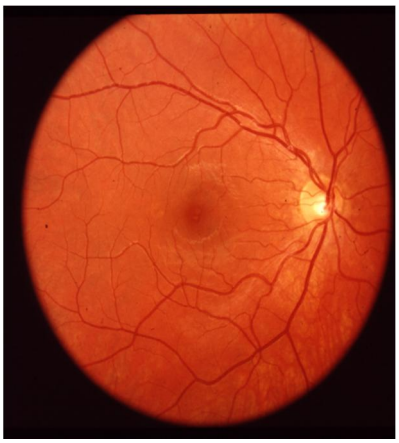


FIGURE 8: Normal fundus

2) Very mild-micro aneurysms only

3) Mild-Any or all of microaneurysms,retinal haemorrhages, exudates, cotton wool spots,upto the level of moderate NPDR,No IRMA or significant beading

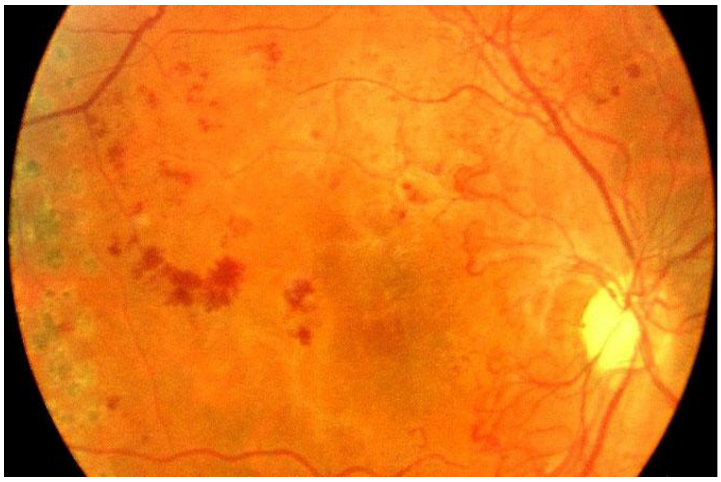


FIGURE 9:Mild NPDR

4) Moderate-Severe retinal hemorrhages(about 20 medium-large per quadrant) in 1-3 quadrants or mild intraretinal micro vascular abnormalities, significant venous beading can be present in no more than I quadrant and cotton wool spots commonly present

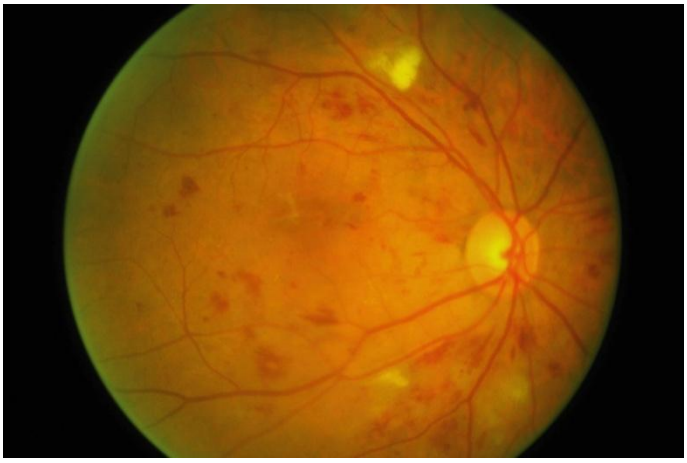


FIGURE 10: Moderate NPDR

5) Severe-4-2-1 rule

One are more of severe hemorrhage in all 4 quadrants

Significant venous bleeding in 2 or more quadrants

Moderate IRMA in 1 or more quadrants

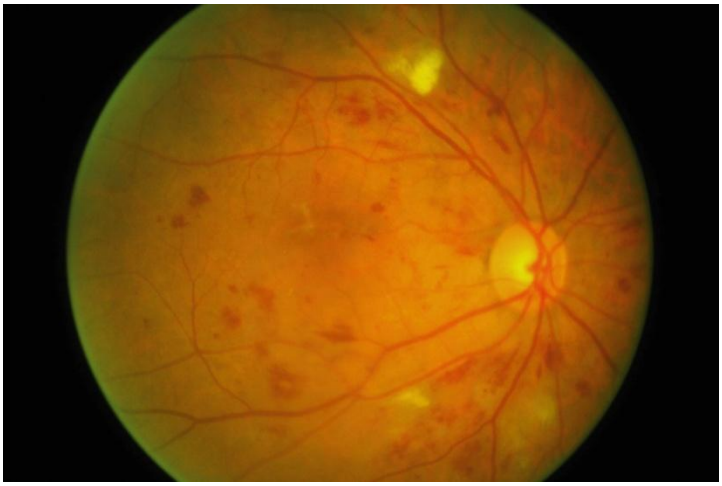


FIGURE 11 : Severe NPDR

6) Very Severe-Two or criteria for severe

Proliferative diabetic retinopathy is the advanced stage of DR and is characterized by highly permeable neovascularization, hemorrhages, and retinal detachment .[33]

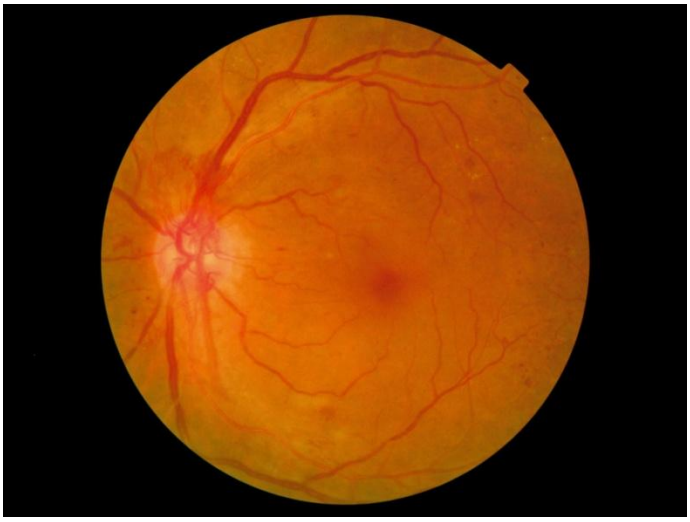


FIGURE 12: Proliferative diabetic retinopathy

VEP

The peripheral nervous system involvement in diabetes mellitus has been shown in previous studies. However, little is known about the central nervous system involvement in diabetes as stated by Algan Met al,Puvendran et al.,[46,47]in their studies. They find the potential use of Evoked potentials as a convenient and non-invasive tool for the evaluation of central nervous system. Visual evoked potentials (VEPs) could be used to evaluate disturbances in the central visual pathways. Omer azal et al have stated VEPs is very helpful in determining subclinical lesions in the optic nerve and the brain stem; therefore, it is a convenient tool in the diagnosis and follow-up of neurologic disorders .[48]

ASSESSMENT OF VEP IN DM PATIENTS

There are several studies done in diabetic patients using PVEP in western countries, but there are only few studies done in our country. VEPs are highly sensitive,reliable,non invasive recording from scalp to detect conduction defects in anterior visual pathway . Hence the present study was done to detect retinal ganglion cell activity in patients with type 2 diabetes mellitus and compare the VEP among diabetics with retinopathy and without retinopathy, to compare the latencies among diabetics and non diabetics and to correlate VEP changes between patients with type 2 diabetes mellitus with retinopathy and those who do not have retinopathy.[27]

VEP IN DM

Avachar Kiran Narayan et al in his study has taken 60 healthy subjects and 60 diagnosed DM patients of age 20-40 years stated excess glucose leads to decrease in $Na^{+}K^{+}$ ATPase activity, accumulation of sodium in axons resulting in decreased nerve conduction velocity and break down of nerve structurally.VEP Changes in diabetic patients occur much before the development of overt retinopathy and the prolongation of latencies in this study is due to damage to optic nerve probably due to polyol pathway dependent or due to microvascular damage.[49]

Zeinab Nasralah et al concluded that VEP latencies increased when the duration of Diabetes mellitus was longer. Early in the course of the disease optic nerve may be damaged or independent of retinal vascular pathology. As indicated by various studies there is development of Neuropathy in optic nerve as well as retina which were conducted in diabetic animals. The reduction in VEP latency is due to decrease in size of optic nerve in rats whereas amplitude decreased and latency increased in human subjects.[33]

D.Matanovic et alstudy included 61 patients with diabetes.In total, there were 44 male patients and 17 female patients. There were three groups according to the insulin therapy.Groups were studied at the beginning of the study and at the end of the study. Comparisons were made between metabolic control and VEP parameter at the start and after six months. With strict glycemic control. Significant improvement was shown in VEP parameters.[50]

R.Sivakumar et al carried out their Experiments was done with 50 normal and 300 NIDDM subjects. The NIDDM subjects were divided based on ophthalmoscopic examination subjects were into four groups first group included the control and the remaining three groups had diabetic retinopathy.The analysis of evoked potential responses paved way for diabetic retinopathy diagnosis and treatment prognosis.

Retinopathy causes alterations in optic nerve functions and has not been studied before. Early diagnosis of retinopathy can be done by studying VEP of optical nerve and occipital cortex.[51]

In diabetes there is a significant risk factor for the development of diabetic retinopathy and it depends on the duration of the disease .[47]there is minimal retinopathy in diabetic patients whose disease duration is more than twenty years.[52]

Deepika Chopra et al stated in diabetic patients VEP response changes occur much before the development of overt retinopathy or clinically apparent sensory neuropathy. Hence VEP which finds early abnormalities in central optic pathway in diabetics could be recommended as a screening test.[53]

Algan M et al in their study stated P_{100}latency was prolonged in diabetic patients where six of them had diabetic retinopathy. Study included fifty type 1 diabetes mellitus and nineteen type 2 patients .The control group consisted of fifty four subjects of the same age as diabetic patients.[46]

Nikhan Yasmeem et al concluded in diabetic retinopathy individuals there was P_{100} wave latency prolongation when compared to control group suggesting that the processing of information by visual cortex is slow in diabetics due to central neuropathy changes. Twenty type 2 Diabetic individuals in age group 45-60 yrs were included in the study group. Control group consisted of 10 (age & sex matched) non-diabetic individuals. Moreover the results were highly significant for the left side when compared to right side emphasizing on the dominance of right visual cortex in processing of information on repetitive visual stimulation.[54]In another study by Szabela et al in type2 DM showed P_{100} wave latency prolongation and there is also difference also seen between both eyes.[55]

Sangeeta gupta et al revealed there is significant P_{100} latency prolongation,duration of DM found to vary the P_{100} latency and blood sugar level did not have correlation with PRVEP abnormalities* Their study was conducted on 116 subjects. Out of 116 subjects, 64 subjects were diabetics who were newly diagnosed patients of diabetes mellitus and 52 subjects were age and sex-matched healthy volunteers.[56]

Avachar Kiran Narayan et al in his study which involved 60 controls and 60 subjects with DM showed statistically significant prolongation ofP_{100} latencies in both eyes.[49]

In this study by Heravian et al involved forty diabetic patients which included twenty subjects each with retinopathy and without retinopathy and

forty non diabetic patients. The results were significant in terms of P_{100}amplitude and N75 amplitude in DM patients with retinopathy and those who did not have retinopathy. There was also significant difference in P_{100}latency between controls and diabetic without retinopathy and with retinopathy, whereas in other studies done by,. N75-P_{100}decreased, but it was not statistically significant.[27]

A.Collier et al. studied 22 subjects with diabetes mellitus, out of which 11 had background retinopathy and 6 had proliferative retinopathy stated that all patients with proliferative retinopathy show delayed VEP compared to patient without retinopathy and those with back ground retinopathy. The results did not show difference between group with back ground retinopathy and without retinopathy.[57]

Omer Azal et al in their study enrolled 20 diabetic patients which included 6 type1 and 14 type2 subjects and 20 age and gender matched controls. Out of twenty diabetic patients three of them had diabetic retinopathy.In diabetic patients P_{100} latency was significantly prolonged compared to control group.[48]

Puvendran et al in their study with 16 diabetics and 35 normal subjects revealed that visual evoked response detects demyelinations of optic nerve and this is a sensitive method and demyelination results in prolongation of latency in P_{100}.[47]

Martinelli et alstated was reduction in amplitude in patients with retinopathy compared to those who did not have retinopathy. The progression of retinopathy was poorly identified henceit is not suitable test for monitoring retinopathy. The study also failed to differentiate diabetic patients without retinopathy from patients with early retinal changes and showed there was little relationship between duration of diabetes.[58]

Bhanu R et al showed most common cause of blindness in diabetics is retinopathy. In this study retinal ganglion cell damage was assessed by using VEP.200 sweeps of stimuli was given. The sign of preclinical diabetic retinopathy is ganglion cell damage in patient with DM which is due to glutamate accumulation extracellularly causing functional and anatomical changes before vascular damage.DR is due to oxidative stress which leads to formation of free radicals and also showed that VEP latency is prolonged and is due to hypoglycemia. This study was done when the first sign of diabetic retinopathy is seen; VEP detects diabetic pre retinopathy DM.[59]

In diabetic patients VEP response changes occur much before the development of overt retinopathy or clinically apparent sensory neuropathy and duration of disease correlated with these. Hence VEP which finds early abnormalities in central optic pathway in diabetics should be recommended as a screening test. Very early in the course of disease optic nerve may be or independent of retinal vascular pathology. Development of optic neuropathy and involvement of retina are indicated by various studies in diabetic animals.

Pairisi et al[60] showed alterations in VEP latency occur only after 3.3 years after the disease presentation and not at the onset of disease.[60]

Ghirlanda et al in their study showed when the disease duration is shorter (3.8± 3.5 years) selective neurosensory deficit of inner retinal layers are produced but the photoreceptors appear unaffected.[44]

Review of literature highlights the fact of definite involvement of retinal layers with or without photoreceptors involvement this fact is reflected in electrophysiological studies as prolongation of VEP latency but the contribution of duration with or without retinopathy and difference in proliferative and non proliferative retinopathy was not definitely stressed so the aim of the present study was to analyze the retinal ganglion cell involvement through VEP.

AIM

To detect retinal ganglion cell activity in diabetes mellitus patients type 2 and compare the VEP among diabetes mellitus patients with non proliferative diabetic retinopathy and diabetes mellitus patients without Non proliferative diabetic retinopathy.

OBJECTIVES

1) To detect retinal ganglion cell activity in type 2 diabetic patients by using pattern reversal VEP

2) To compare the latencies among diabetics and non diabetics

3) To correlate VEP changes between diabetic patients with diabetic retinopathy and those without retinopathy (Nonproliferative)

RECOMMENDED STANDARDS FOR PVEP[61]

1) PVEP-type of pattern consists of checker board, here checker board stimuli used

2) Pattern elements size-The size of individual checks described by visual angle subtended at the subjects eye.

3) Size of visual field
   Central 8 and peripheral 8-32 degrees

4) Presentation method-
   Pattern reversal

5) Rate of presentation-

Transient PVEP the frequency is 1 Hz and for steady state PVEP it is 4-8 Hz.

6) Stimulus luminance-

The mean luminance of central field is 50cd/m^2 and back ground luminance is 20-40cd/m^2.Difference in luminance between center and periphery of field should not exceed 20%.

7) Contrast-

It should be between 50%-80%

8) Type of stimulator-

TV, video monitor, oscilloscope,

9) Electrodes-

- Standard disk EEG electrodes used
- Fixed according to 10-20 International system
- Recording electrode Oz placed 2cm above the inion
- Reference electrode Fpz placed 12 cm above the nasion
- Ground electrode Cz placed over the vertex

10) Recording equipment-

- Amplification ranging between 20,000-100000
- Low cut filter set at1-3Hz and high cut filter at 100-300Hz
- Sweep duration-250-500ms

- 200-500 averages recorded
- Montage 2 channels-channel1 Oz-Fpz and channel 2 Oz-linked ear
- 4 reversal/sec
- Distance between subject eye and screen 70-100cm
- Field size should be greater than 80
- pattern element size 28-32", 56-64" smaller size 14-16" fovea stimulation

INDICATIONS FOR VEP

- Demyelinating diseases (Multiple sclerosis, optic neuritis, glaucoma, ischaemic optic neuropathy)
- HIV infection
- Nutritional and toxic optic neuropathy
- Hereditary and degenerative diseases
- Compressive lesions affecting anterior visual pathways
- VEP in cortical blindness
- Malingering and hysteria
- Intra operative monitoring
- Refractive errors
- Trauma of visual system
- Neurofibromatosis
- Infections of visual cortex

- Visual field defects like hemianopia
- Central scotoma

CONTRAINDICATIONS-

- Marked visual impairment
- Acute optic neuritis
- Inability to cooperate with testing procedure

CLINICAL USEFULNESS OF VEP-

- It is standardized and reproducible test of optic nerve function
- When compared to MRI it is more sensitive in detecting lesions affecting the visual pathway in front of optic chiasma
- Less costly when compared to others
- Useful in excluding certain diseases when the results are negative

RECORDING OF VEP

It normally consists of 3 waves

- The transient VEPs consists of series of waveforms of opposite polarity
- N denotes negative wave form
- P denotes positive wave form
- Commonly used waveforms are N75,P100,N145
- The peak latencies and peak to peak amplitudes of these are measured

- P_{100}peak latency, its duration and amplitude are used for VEP analysis (Chappan 1990)
- Normal values are as follows

Parameters	Shaharkhi et al (1978) Mean± SD	Misra and Kalita
P_{100} latency (ms)	102.3± 5.1	96.9± 3.6
R-L(ms)	1.3± 2.0	1.5± 0.5
Amplitude (μv)	10.1± 4.2	7.8± 1.9
Duration	63.0± 8.7	55.9± 7.7

N75 mainly results from fovea stimulation and originates in area 17

P_{100} originates in area 19

N145 reflects activity of area 18

FACTORS THAT INFLUENCE VEP[62]

1) Age-

Amplitude of P_{100} is high infants and children, after 50 years amplitude decreases

2) Sex –

P_{100} latency is longer in men due to bigger size of head.

P_{100} amplitude is greater in women due to hormonal influence

3) Drugs-

Drugs causing miosis ex pilocarpine increase P_{100} latency which is due to decreased area of retinal illumination, Mydriatics cause decrease in P_{100} latency

4) Eye dominance-

VEP recorded by stimulating the dominant eye duration and amplitude of P_{100} is reduced which is due to neuroanatomic asymmetry in human visual cortex

5) Eye movement-

The amplitude of P_{100} is decreased but latency remains unaffected

6) Visual acuity-

When the visual acuity is decreased the amplitude of P_{100} is decreased but latency remains normal.

VEP ABNORMALITIES[62]

1) Prolongation of latency

Commonest cause is demyelination of optic pathway, amplitude remains normal.

2) Amplitude reduction-

It is seen in optic neuropathy and in refractive errors, media opacities, and retinal disease.

3) Combined latency and amplitude defects-

This occurs in optic nerve compression that causes segmental demyelination and axonal loss.

4) Shape abnormalities-

a) Bifid P100 has two peaks, this is rare in normal individuals

b) W shaped VEP has two peaks which are separated by10-50 ms

DESIGN OF THE STUDY-

Case control study

Control-Healthy non diabetic individuals

Case –Type II DM patients

Group I-Control

Group II-Diabetic without retinopathy

Group III-Diabetic with non proliferative retinopathy

MATERIALS AND METHODOLOGY

80 diabetic Patients both male and female attending Diabetic OP at Chengalpet Medical College and 40 healthy individuals were selected for the study (120)

INCLUSION CRITERIA-

- Age group : 30 to 60 yrs / Both gender
- Diabetic retinopathy cases (Early Treatment Diabetic retinopathy Study)

- Normal visual acuity
- Abnormal blood glucose (ADA criteria)

EXCLUSION CRITERIA-

- Known Hypertensive /evidence of cardiovascular illness
- Past H/O CVA,demyelinating diseases(multiple sclerosis)
- Cataract
- Glaucoma
- Evidence of optic atrophy
- Known Smoker / Alcoholic /tobacco chewing/ Any medication affecting optic nerve(ATT,Chloroquine etc)
- Proliferative diabetic retinopathy

MATERIAL

Physiopac (Neuroperfect EMG-2000)

METHODOLOGY

Investigation details-

- Fasting and 2 hour postprandial blood sugar
- Ophthalmological examination-
  - Best corrected visual acuity
  - Intra ocular pressure
  - Dilatation and fundoscopy(slit lamp with +90d lens)
- Institutional ethical committee approval was got

ON THE DAY OF RECORDING

Subjects were advised

- To come with oil free hair after the last hair wash
- To avoid any miotic/mydriatic 12 hours before the procedure
- The usual glasses if any should be worn during the test

PROCEDURE

- Informed consent
- Anthropometric measurements height in cm and weight in kg measured
- Blood pressure recording done using sphygmomanometer

VEP RECORDING

During procedure-

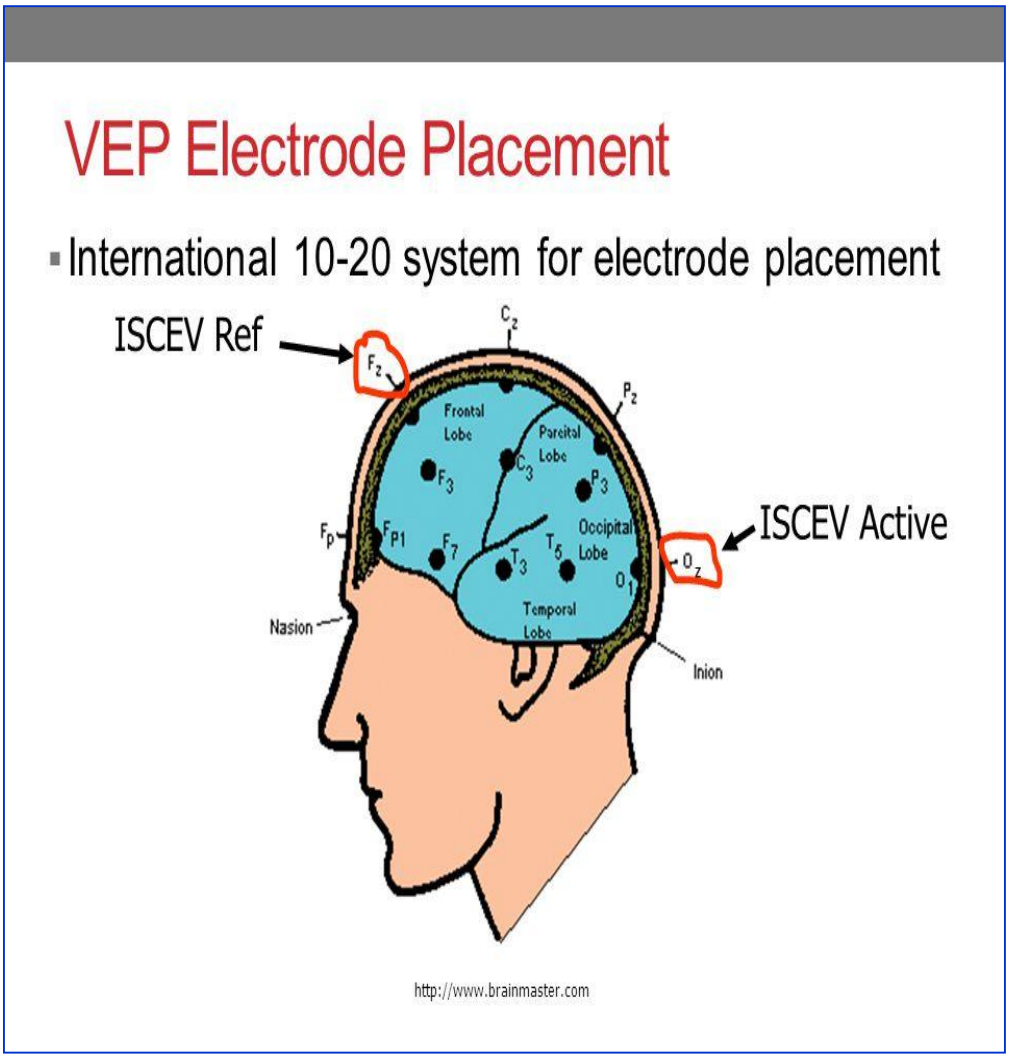
Subject was seated at a distance of 1metre from VEP monitor screen

Subject was explained about the procedure

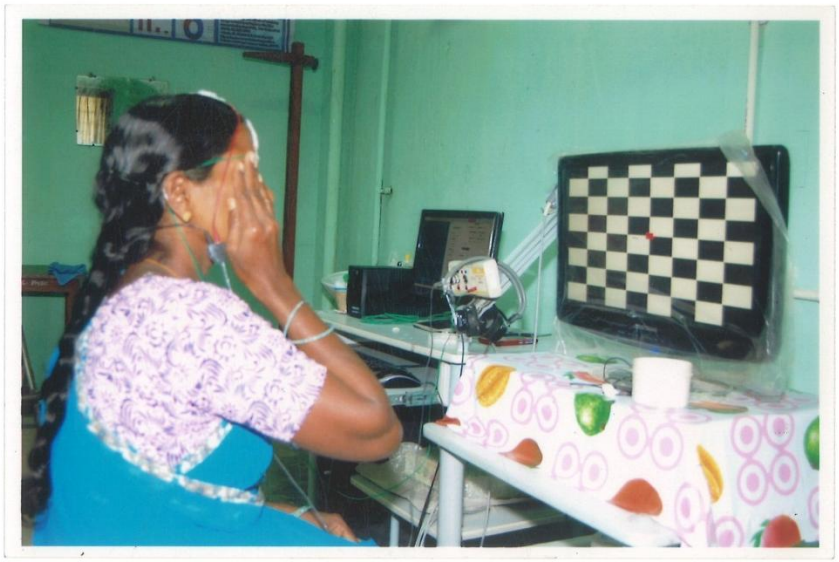
Electrodes were fixed in the following position after preparing the skin by abrading and degreasing

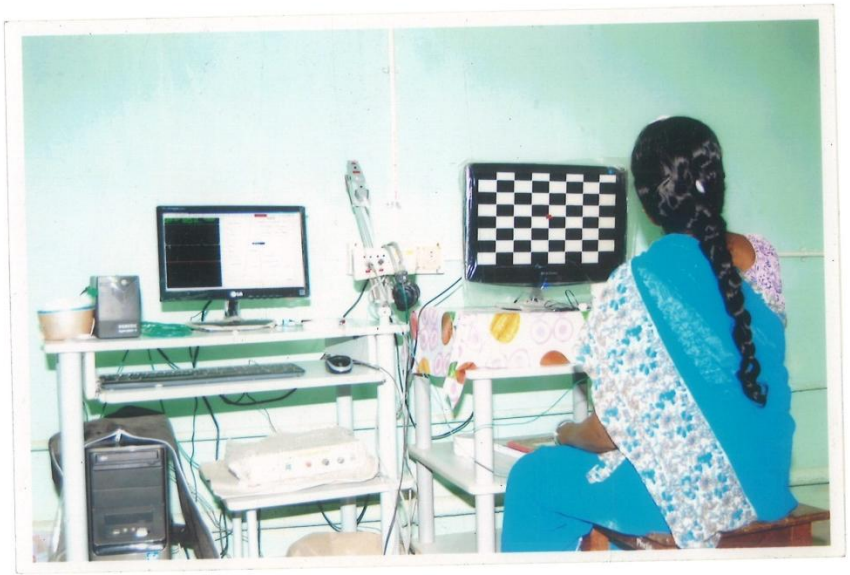
- Recording electrode –just above inion as per 10-20 international system
- ground Electrode – at forehead
- Reference Electrode – placed 12cm above nasion
- Electrodes were connected to the Physiopac.
- Pattern reversal stimulus(black and white checks)

- Subject was instructed to see the centre red square on the VEP monitor screen
- In each recording 200 sweeps averaged
- Each eye tested separately
- Other eye was patched
- Recording was done in a dark room
- VEP was recorded using Physiopac(Neuroperfect EMG-2000)



VEP RECORDING





Medicaid Systems Neuro Lab.
 # 389 Industrial Area.
Chandigarh.
Phone Number : 0172-2641203

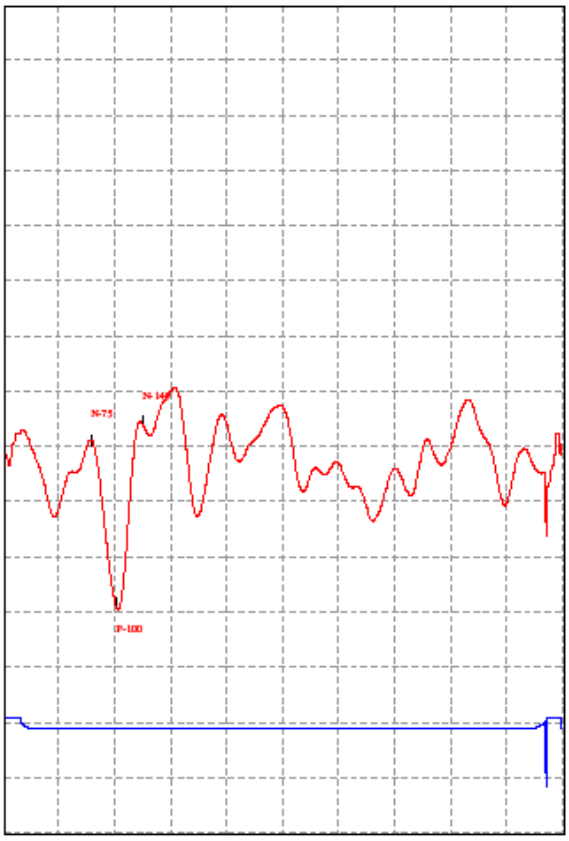
 # C10 UMA

Sensitivity	Frequency	Sweep
1 µV	2 Hz -200 Hz	50 m sec

VEP

Left Eye

3/24/2016



Rec.Site	Stim Mode	N-75	P-100	N-145	N75-P100
---	Checker	77.5 ms	100 ms	123.75 ms	3.03 µV
---	Checker	---	---	---	---

RESULTS

Data analysis of data was done using SPSS software 20 utilizing Spearman's correlation coefficient, ANOVA, and Tukey test. Level of Significance was kept at $P<0.05$

TABLE 6

Parameter	**Group I n=40 mean ± SD**	**Group II n=40 mean ± SD**	**Group III n=40 mean ± SD**
Age	42.44 ± 6.74	46.95 ± 7.44	48.60 ±8.24
Height	156.68 ± 3.08	156.75 ± 3.08	156.68 ± 3.49
Weight	60.65 ± 4.954	65.30±12.75	64.22±7.12
FBS	89.25±12.68	133.38±37.33	164.45±45.39
PPBS	137.52±27.18	201.65±84.51	284.28±95.93
SBP	115.95±8.08	115.00±9.60	116.50±11.44
DBP	75±5.54	72.50±4.83	73.75±5.401
Duration	NA	4.85±2.61	6.55±3.25

The above table shows base line data of control and study group.

TABLE 7

Shows the base line data of study and control group with p value

Parameter	Group I N=40 Mean ±S.D	Group II N=40 Mean ±S.D	Group III N=40 Mean ±S.D
FBS	89.25±12.68	133.38±37.33**	164.45±45.39**
PPBS	137.52±27.18	201.65±84.51**	284.28±95.93**
SBP	115.95±8.08	115.00±9.60	116.50±11.44
DBP	75±5.54	72.50±4.83	73.75±5.401
Duration		4.85±2.61**	6.55±3.25**

* $p \leq 0.01$ is highly significant

**$p \leq 0.001$ very highly significant

Fasting blood sugar,postprandial blood sugar and duration mean values are very highly significant between control and study group.

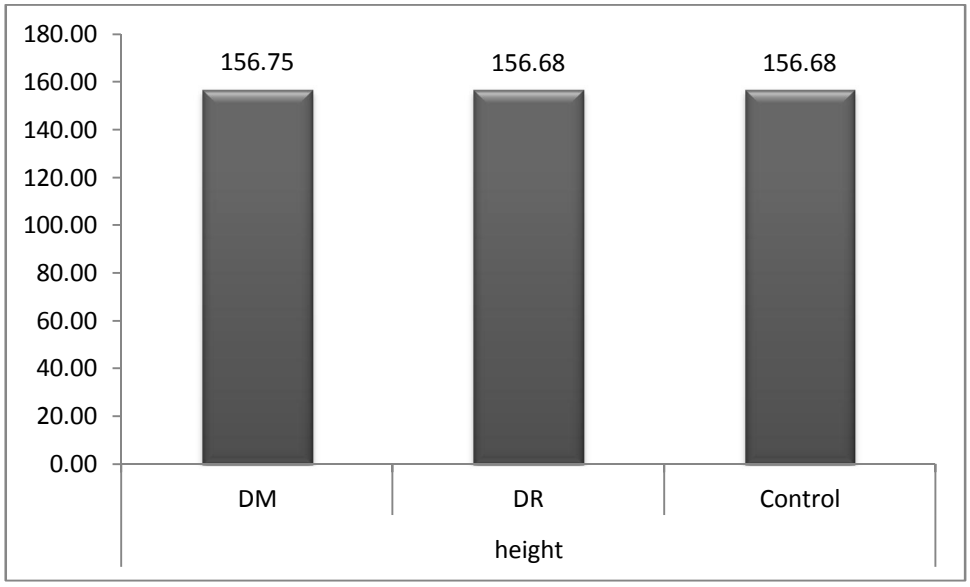


FIGURE 14: Height distribution

Mean values of height between three groups

In control it is 156.68cm, DM-156.75cm, and DR-156.68 cm

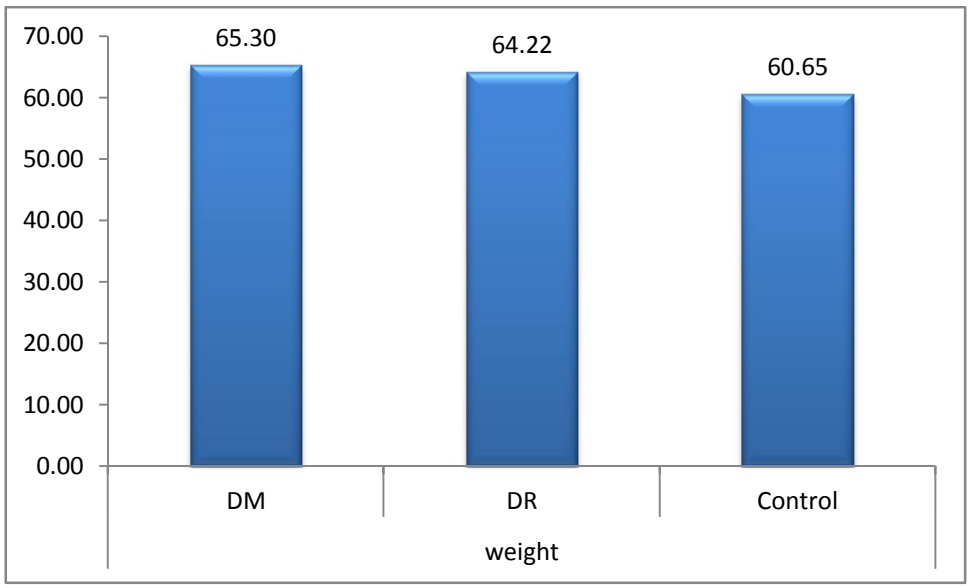


FIGURE 15: Weight distribution

Mean values of weight between three groups

In control-60.65kg, DM-65.30kg, DR-64.22kg

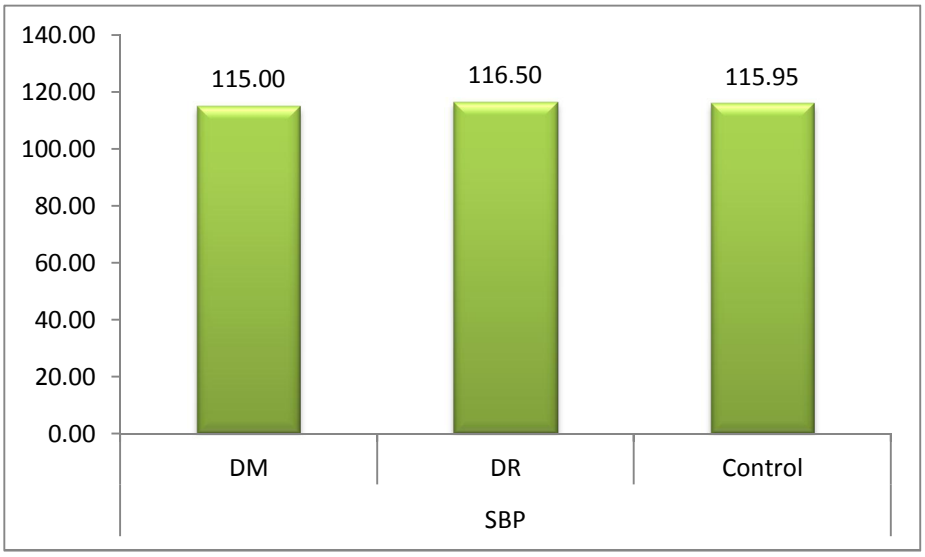


FIGURE 16: Systolic BP distribution between study group and control group

Figure shows mean SBP values in three groups

Control-115.95mmHg, DM-115.00mmHg, DR-116.50mmHg

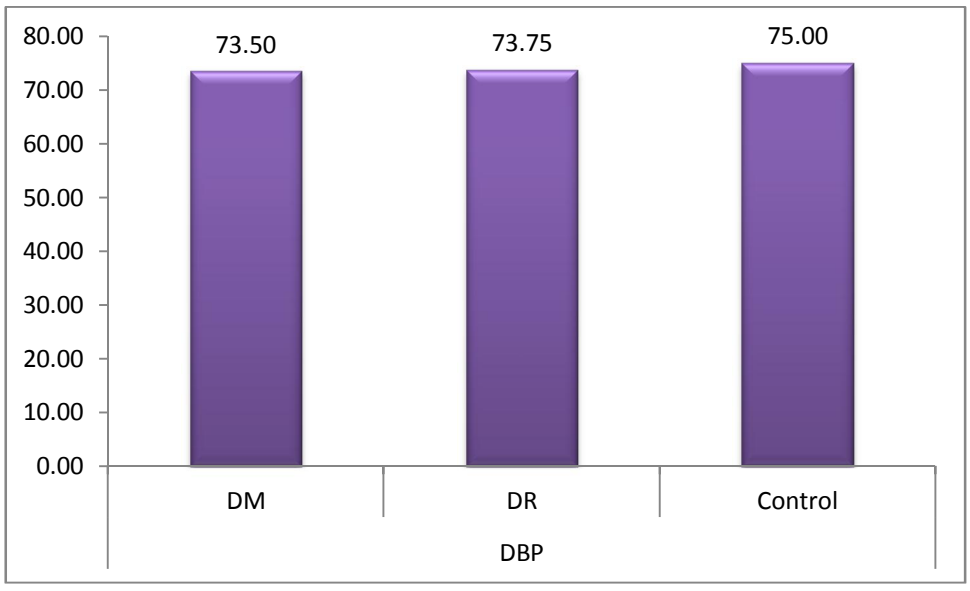


FIGURE 17: Diastolic BP distribution

Figure shows mean values of diastolic BP between study groups

Control-75.00mmHg, DM-73.50mmHg, DR-73.75mmHg

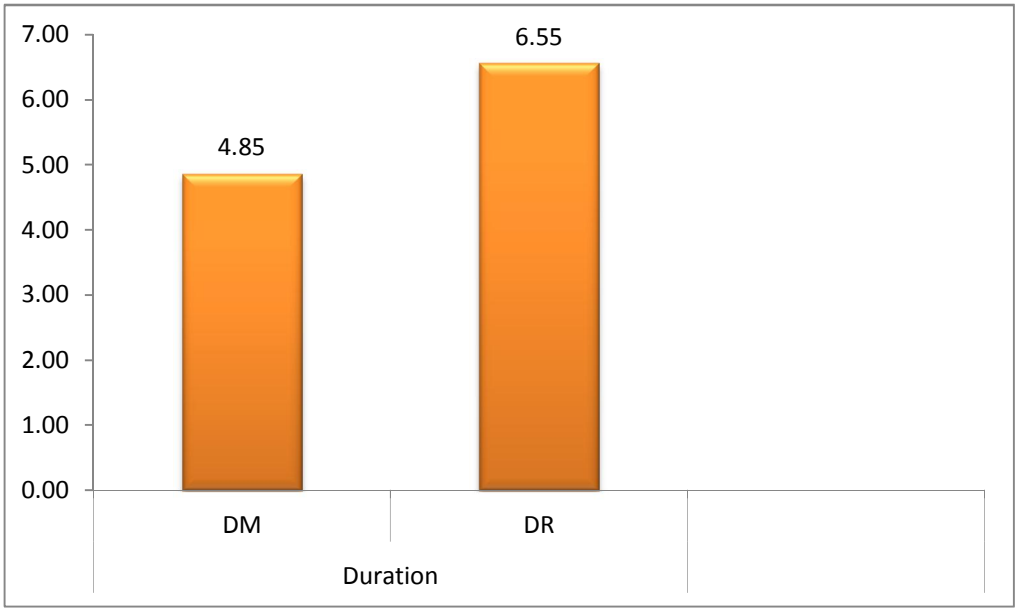


FIGURE 18: Duration of Diabetes distribution

Mean duration of the disease in patients without retinopathy is 4.85years and mean duration of the disease in patients with retinopathy is 6.55 years

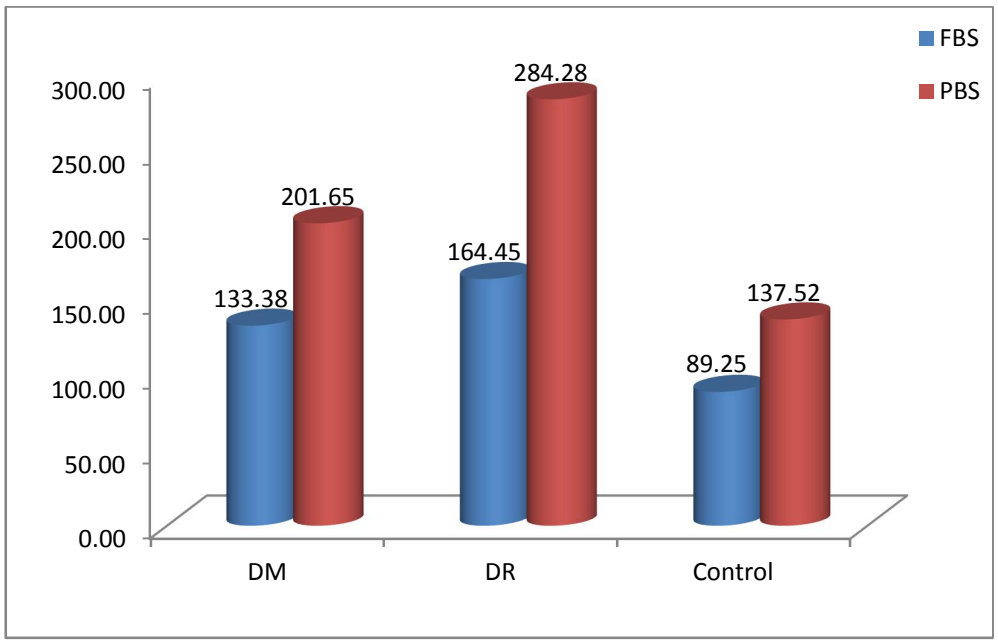


FIGURE 19: FBS and PBS distribution

FBS and PBS mean values are more in DM and DR compared to control Control-89.25mg% and 137.52mg%, DM-133.38mg% and 201.65mg% DR-164.5MG% and 284.28mg%

TABLE 8

Mean latency values of VEP (right eye)

Parameter	Group I Number40	Group II Number40	Group III Number40
	Mean±SD	Mean±SD	Mean±SD
P_{100} right latency	96.79±5.93	104.98±5.09**	109.26±6.67**
N75 right latency	72.48±8.21	75.43±10.83	76.11±10.20
N145 right latency	137.76±17.35	140.42±13 .00*	143.16±13.27

* p≤0.01 is highly significant

**p≤0.001 very highly significant

P_{100} latency prolongation is very highly significant in right eyes of DM and DR group compared to control group.

TABLE 9

Mean latency values of VEP (left eye)

Parameter	Group I Number 40	Group II Number 40	Group III Number 40
	Mean±SD	Mean±SD	Mean±SD
P_{100} left latency	98.28±5.31	103.09±17.48**	108.46±5.83**
N75 left latency	72.86±8.54	74.59±11.70	77.24±9.52
N145 left latency	139.52±17.56	140.76±22.21	143.16±12.32

* p≤0.01 is highly significant

**p≤0.001 very highly significant

P_{100} latency prolongation is very highly significant in left eyes of DM and DR group compared to control group

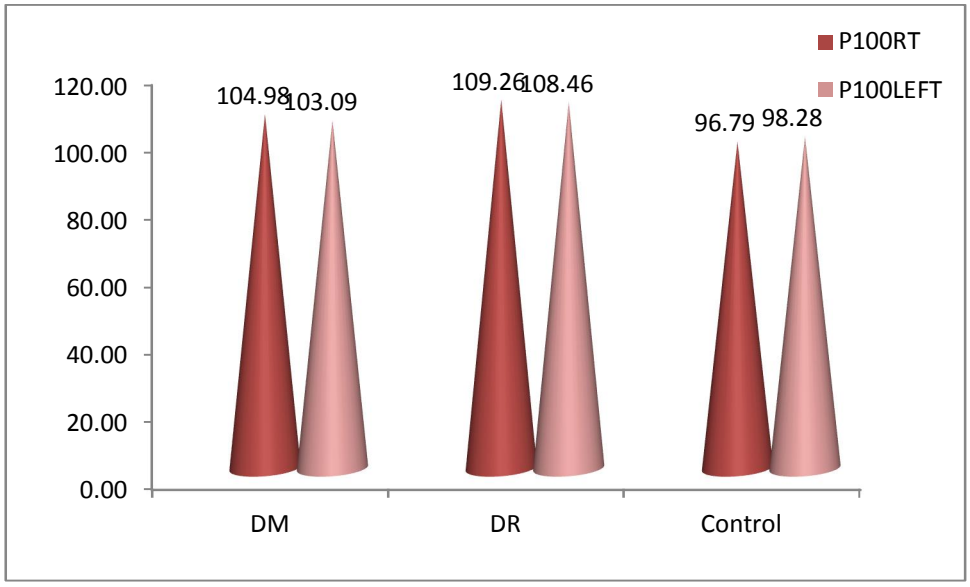


FIGURE 20: P_{100} Latency distribution

Figure shows mean P_{100}latency value between study and control group

P_{100} latency prolonged in DM and DR compared to control

TABLE 10

Mean amplitudes values of VEP(right eye)

Parameter	Group I Number40 Mean±SD	Group II Number40 Mean±SD	Group III Number40 Mean±SD	p value
P_{100}Right amplitude	2.15±1.49	2.32±1.24	2.49±1.30	0.53
N75 right amplitude	0.89±0.52	6.93±0.43	0.92±0.54	0.937
N75PP_{100}right amplitude	2.97±1.62	3.12±1.46	7.87±2.762	0.301

There is no significant difference in mean amplitudes between the control and study group.

TABLE 11

Mean amplitude values of VEP (left eye)

Parameter	Group I Number40	Group II Number40	Group III Number40	p value
	Mean±SD	Mean±SD	Mean±SD	
P100 left amplitude	2.65±1.45	2.36±1.09	2.93±1.46	0.215
N75 left amplitude	1.13±0.68	0.87±0.42	1.01±0.56	0.136
N75P100 left amplitude	3.72±2.13	3.25±1.22	3.69±1.77	0.406

There is no significant difference in mean amplitudes between study and control group.

TABLE 12

Gender variations in control and study group

SEX	DM		DR		Control	
	P_{100}RT	P_{100}LEFT	P_{100}RT	P_{100}LEFT	P_{100}RT	P_{100}LEFT
Male	106.69	101.24	111.85	109.99	95.15	95.67
Female	103.58	104.60	106.39	106.78	97.50	99.39

TABLE 13

Gender variation seen in DM patients with and without retinopathy

Group		Sex	N	Mean	SD
DM	$P_{100}RT$	MALE	18	106.69±*	5.92
		FEMALE	22	103.58±	3.90
	$P_{100}LT$	MALE	18	101.24±	25.85
		FEMALE	22	104.60±	4.65
DR	$P_{100}RT$	MALE	21	111.85±*	6.81
		FEMALE	19	106.39±	5.35
	$P_{100}LT$	MALE	21	109.99±	6.14
		FEMALE	19	106.78±	5.13

* $p \leq 0.01$ is highly significant

**$p \leq 0.001$ very highly significant

Mean values are highly significant in both DM and DR group in males.

TABLE 14

Correlation of duration of disease between DM patients with and without retinopathy

		Group			Total	
		Group I	**Group II**	**Group III**		
Duration	<5	27	20	0	47	Chi sq = 3.91 P = 0.1
	>5	13	20	0	33	
Total		40	40	0	80	

			Duration	**P_{100}RT**	**P_{100}LEFT**	**Group**
Spearman's rho	Duration	Correlation Coefficient	1.000	.105	-.027	.254*
		Sig. (2-tailed)	.	.354	.810	.023
		N	80	80	80	80
	P100RT	Correlation Coefficient	.105	1.000	.729**	-.522**
		Sig. (2-tailed)	.354	.	.000	.000
		N	80	120	120	120
	P100LEFT	Correlation Coefficient	-.027	.729**	1.000	-.509**
		Sig. (2-tailed)	.810	.000	.	.000
		N	80	120	120	120
	Group	Correlation Coefficient	.254*	-.522**	-.509**	1.000
		Sig. (2-tailed)	.023	.000	.000	.
		N	80	120	120	120

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

P_{100} significantly correlates with duration of DM

DISCUSSION

Type 2 DM is one of the most serious challenges to health care, because of the Increase in the prevalence of sedentary life styles and obesity. Peripheral nervous system abnormalities are well documented but central nervous system changes have received less attention especially their correlation with visual function.

The disturbances in central nervous system can be evaluated using VEP which is a simple sensitive and non invasive method.VEP wave P_{100}originates in the striate and peristriate occipital cortex due to primary visual cortex activation and also discharge of thalamocortical fibers.

The P_{100}waveform of VEP is generated in striate and peristriate occipital cortex not only due to activation of primary cortex but also due to thalamocortical discharge. In diabetic patients anterior visual pathways get involved before the development of retinopathy and due to damage to the optic nerve. VEP response abnormalities in diabetic patients occur before the development of overt retinopathy due to preclinical micro vascular or neurodegenerative changes within or upstream retina. There is increased tendency of ischemia which could lead to microangiopathy which is present even at the time of diagnosis in type 2 DM.

In this studyVEP was done on(120)80 type 2 DM patients who were age, gender matched and BMI matched with 40 healthy controls and

analyzed using Neuroperfect EMG.The commonly used waveforms are N75,P_{100} and NI45, of which P_{100}peak latency is the most reliable form of latency and hence P_{100} duration and amplitude are used for VEP analysis(Chappan) is used there is significant prolongation of P_{100} latency in the study group which included type 2 diabetic individuals.

VEP amplitude can be modified by attention, cranial shape, distribution of sulci of brain and size of brain. P_{100} amplitude changes occur in individuals at particular age, at 10-15 years there is decrease in amplitude then it is stabilized and remains constant up to 40 years, there after shows gradual decline to almost half of adult value at age of 25 years.

Age must be considered an important factor when conducting VEP studies as it has been shown in previous studies that P_{100} peak time increases with age and has been attributed to age related changes in retina and rostral part of visual system.In the present study the age groups of the subjects were between 30-60 years and the controls were age matched in view of the fact that age related changes could influence the latencies in VEP.The increase in P_{100} latency in the study subjects could be due to diabetes mellitus. Similarly,A.A.Alidani[63]in his study in diabetic individuals showed that the mean values of P_{100}latency were increased in diabetics, but it was not significant statistically between different age group whereas the difference in meanP_{100} latency was significant statistically between diabetic patient and control with same age group.

The number of male and females who participated in the present study were 69 and 51 .The mean values of P_{100} in control group is 95.15 in right and 95.67 in left eyes of males and 97.50 and 99.39 in right and left eyes of females. The mean values of P_{100}wave latency in DM group is 106 in right eye and 101.24 in left eye in males and 103.58 and 104.60 in right and left eyes of DM group in females. In this study $P_{100}$was prolonged in males (right eye) in diabetic group and also in males (right eye) in DR group and it is statistically significant. In females though P_{100} values in left eye in DM group is increased, it is not statistically significant. Sangeetha gupta et al.[55]in their study on influence of gender on VEP showed that gender influence was found as increased P_{100}latency in males in his study as in the present study. Similarly,Ruby Sharma et al showed N70, P_{100},N155 waves were longer in males than females . On the contrary, Phuralitpam et al [65]in their study had no statistically significant difference in P_{100} latency between males and females. Gender difference could be attributed to anatomical or endocrinal differences amongst both the sexes.

In the present study the mean values of P_{100} latency is statistically significant between study and control group. The mean values of control group in right eye is 96.79 and 98.28 in left eye and study group mean values of P_{100} in right eye is 104.98 and in left eye is103.09 in type 2 DM group and in DR group mean values in right eye is 109.26 and in left eye is 108.46.Delay of P_{100} latency in patients with type 2 diabetes mellitus with retinopathy and

without retinopathy when compared with controls in the present study is similar to the studies done by Heravian et al.[27],. Deepika chopra et al [53], P.G.Ramam et al [28], Gayathri et al [45] and Omer azal.[48]

Regan et al in their study has shown that there is a great interindividual variations in amplitude of VEP compared to latency and Farisa et al in their study showed that there was no significant difference in P_{100}amplitude between control and diabetics. Kothari et al showed that P100 is higher in females and there is negative correlation between P100 amplitude and height.

In the present study there is significant difference in fasting blood sugar values and postprandial sugar levels between diabetes and controls which could have influenced the P_{100} latencies in diabetics. The mean values of FBS in control is 89.25mg% and PBS is137.52 mg% ,FBS in DM group is 133.38 mg% and PBS is201.65 mg% and in DR group the FBS is164.45 mg% and PBS is284.28 mg%. P_{100}wave latency increased as the blood glucose level increased. The present study is consistent with Gayathri et al.[45], PG RAMAN et al[28],A.A.Alidani et al[63]. HERAVIAN ET AL.[28]in their study on diabetics with and without retinopathy showed that the relation between P_{100} and blood glucose level was not significant and Vincenzo et al.in their study found that VEP latency did not correlate with blood glucose on the contrary to the present study.

P_{100}prolongation in relation to increasing blood glucose can be due to exposure to the toxic glycemic metabolites for longer period. Marilyn et al. in

his study showed that there were three mechanisms for tissue function alteration in DM as a result of increased blood glucose level which are polyol pathway, myoinositol depletion, non enzymatic protein glycosylation. The pathophysiology of CNS involvement is not clear and it may be due to ischaemia, decreased protein synthesis, depleted myoinositol,high sorbitol. Neuropoietic cytokines IL1 and IL6 leukemia inhibitory factor,ciliary neurotropic factor TNFα,TGFβ exhibit pleiotropic effects on homeostasis of glial and on neurons in central, peripheral and ANS. These are produced locally by macrophage, lymphocyte, mast cells and fibroblast could cause the microvascular and macrovascular complications. This could be attributed to the microvascular changes in the retina and optic nerve.

In the present study P_{100} latency is compared to duration of type 2 DM.The mean values of duration of type 2 DM group is 4.85 years and for DR group is6.55 years.In this study the $P_{100}$was prolonged as the duration increased and is statistically significant between the DM and DR group.This finding in the study is consistent with other studies of Gayathri etal[45], Martinelli etal.[58], Deepika chopra et al.[53],Bhanu etal.[59],Kumar et al.. (2014),Shrivatsava etal.[66](2014), (2012),Chopra etal. (2011),Dolu etal. (2013) and Azal etal.[48](1998) found that the correlation between duration of DM P_{100}latency was significant whereas Ghirlanda etal.[44]showed that even with short duration of disease also P_{100}latency was increased.Mohammed AA Idani[63]Ismail,Heravian et al.[27],Ziegler etal. (1999) Algan et al.[46](1989) in their

study did not find any significant relation between latency P_{100}wave and diabetes mellitus duration.

The prolongation P_{100}which is more as the duration increases could be due to the prolonged neurophysiologic variations caused by ischemic neuronal and retinal structural damage caused by microvascular abnormalities.

In the present study VEP parameters were compared between diabetes mellitus patients with retinopathy and diabetic patients who did not have retinopathy. There was no significant difference in mean values of P_{100}DR and DM group as age matched subjects were chosen for the study.The prolongation of P_{100}latency could be attributed to diabetes. Klein et al.[52], have shown that with increasing age in type 1 DM the prevalence and severity of DR increases but not in type 2 DM.

In this study there was prolongation of P_{100} latency in DR which was more in male.

In the present study there was very highly significant prolongation of P_{100} latency in DR group compared to DM .This is consistent with study done by Farisa khatoon et al[64],Algan et al.[46] in their study have reported that P_{100}ave latency was prolonged in DM patients in which six of them had DR.

The reasons for prolongation may be due to damage to ganglion cells in inner most retinal layer and related to impairment of neural conduction at post retinal level due to accumulation of extracellular glutamate leading to

functional and anatomical changes giving rise to vascular damage. Bhanu et al[58]in their study have found that besides microvascular abnormalities oxidative stress and consequence of glucose metabolism play great role in pathological progress of DR,that may be due to increase in free radicals and reduced activity of antioxidant mechanism which is considered as a sign of preclinical DR.

In the present study mean values of FBS and PBS was more in DR compared to DM group.New England journalstudy showed that the relationship between glycemic control and development and progression of DR are indirectly related.The risks of microvascular complications occur due to chronic hyperglycemia.

In this study the mean values of duration in diabetes was more in DR compared to DM.Karlica et al in their study showed vascular damage in DR is due to non enzymatic glycosylation products.Ying yu et al[43]found that VEGF plays an important part in angiogenesis and its concentration is also increased in patients with DR.

VEP a non invasive technique used to examine the activity of visual system, the effect of nerve conduction change can be assessed by noting the peak time delay of the VEPS.The P_{100} latency prolongation represents the size of the demyelinated optic nerve fibers therefore VEPprovides an insight to the underlying demyelination of optic nerve in type 2 DM before structural and functional visual changes leading to clinical presentation highly sensitive instrument to measure demyelination of the optic nerve.

LIMITATIONS AND FUTURE SCOPE

1) Sample size can be increased

2) This study is related to blood sugar and duration both play an important role in evaluation of microvascular changes hence Glycosylated Haemoglobin should have been taken into account

3) Hence in future glycated haemoglobin should be correlated

4) In females hormonal influence is present and hence it should also be taken into account

CONCLUSION

DM is a chronic life style disease with far reaching implications for millions of people who suffer from it as well as being a condition which can lead to both acute and chronic complications and even death. With looming possibility that the already excessively high global number of people living with DM may increase to 592 million by the year 2035, diabetic clinics need to include an examination of physiology of optic nerve in DM patients.DM patients need to be examined from foot to eye to prevent complications and improve their condition

The results of the present study done on 80 type 2 DM patients with and without retinopathy showed statistical significant relevance in P_{100} latency without obvious clinical symptoms. These findings are highlighting the possibility of CNS involvement sub clinically.. They ascribe these findings to the possibility that due to the blood brain barrier, transport for glucose decreases in CNS and the levels of glycation products are lower in CNS to its level in peripheral nerves.

The study revealed that the P_{100} latency is indeed associated with FBS and duration of diabetics. In addition the use of PVEP in DM is a useful non invasive procedure to detect retinal dysfunction at the ganglion cell levels and can thus be considered as preclinical diabetic retinopathy screening and avert the morbidity.

SUMMARY

- The present study was done with120 subjects both male and female of age group 30-60 years to evaluate the retinal ganglion cell activity in type 2 diabetics using pattern reversal VEP
- VEP recording was done using physiopac(Neuroperfect EMG 2000)after institutional ethical committee clearance and informed consent
- P_{100} latency indicating demyelination of optic pathway was prolonged in the study group with prolongation more in DM when compared to control group
- P_{100} latency was more prolonged in diabetic patients who had retinopathy when compared to those without retinopathy showing the relationship between their glycemic status and duration of disease
- Demyelination of optic nerve pathway detected by $\mathbf{P_{100}}$ latency of VEP is a reliable and sensitive indicator to detect the subclinical involvement of CNS dysfunction in type 2 DM. Retinal ganglion cell activity due to microvascular lesions related to hyperglycemic status and duration of diabetes are easily evident for an early intervention to prevent further morbidity and mortality.

BIBLIOGRAPHY

1. Jacek Zajac, Anil Shrestha, Parini Patel et al,The Main Events in the History of Diabets.

2. Diapedia by Driebit Amsterdam,The living textbook of diabetes.

3. Global report on diabetes WHO, Geneva 2016.

4. Mathew CP, Loncar P, Plosmed, Projections of global mortality and burden of disease from 2002 to 2030,2006,3(11)4):e442.

5. International Diabetes Federation Diabetes atlas 7th edition 2015.

6. L. Guariguataa,D.R.Whiting,I.Hambleton et al. IDF Diabetes Atlas, Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice 103 (2014) 137 – 149.

7. Seema Abhijeet kaveeshwar,Jon Cornwall, The current state of diabetes mellitus in India.Australasian Medical Journal 2014; 7, 1, 45-48.

8. Mohan V,Shah,Saboo B, Current glycemic status and diabetes related complications among type 2 diabetes patients in India: data from the A1chieve study. JAPI (Suppl) 201361:12–15.

9. Defeat diabetes foundation www.defeatdiabetes.

10. Harrisons principles of internal medicine .19 th edition; McGraw Hill education.

11. American Diabetes association; Diabetes care 37(suppl 1):S14, 2014.

12. Joslin Diabetes Mellitus 14th edition,Lippincott,Williams and Wilkins.

13. Raju SM, Raju B, (2010), Illustrated Medical Biochemistry 2nd edition, Jaypee brothers medical publishers limited, New Delhi, India.

14. Ramandeep singh MS,Kim Ramasamy,PNB etal,Diabetic retinopathy an update. Indian J ophthal.2008 May-June; 56(3): 179-188.

15. Report of WHO consultation Geneva, Switzerland, 9-11, Nov 2005.

16. UK prospective diabetes study 6, complications in newly diagnosed type 2 diabetic patients and their associations with different clinical and biochemical risk factors. Diabetes Res, 1990; 13(1):1-11.

17. Jack J Kanski, 7th edition, clinical ophthalmology and systematic approach with Ken NIschal Andrew Pearson.

18. Juen S, Kieselbach GF. 1990 Electrophysiological changes in juvenile diabetes. Without retinopathy. Arch Ophthalmol; 108:372-375.

19. Holopigian K, Seiple W, Lorenzo M,etal, 1992 A comparison of photopic and scotopic electroretinographic changes in early diabetic retinopathy. Invest Ophthalmol Vis Sci; 33:2773-2780.

20. Bresnick GH, Condit RS, Palta M,et al , 1985 Association of hue discrimination loss and diabetic retinopathy. Arch Ophthalmol; 103:1317-1324.

21. Tzekov R, Arden GB. 1999 The electroretinogram in diabetic retinopathy. Surv Ophthalmol; 44:53-60.

22. Deschenes MC, Coupland SG, Ross SA,et al 1997 Early macular dysfunction detected by focal electroretinographic recording in non insulin dependent diabetics. Without retinopathy. Doc Ophthalmol; 94:223-237.

23. Sutter EE, Tran D 1992 the field topography of ERG components in man. The photopic luminance response. Vision Res. Mar; 32(3):433-46.

24. Electrophysiology in visually impaired children by Maria Michelle.

25. David A. Antonetti, Alistair J et al, Seeing Beyond Glucose-Induced Microvascular Disease. Diabetes 2006; 55 (9):2401–2411.

26. Anastari M, Lauricella et al,VEP in Insulin dependent diabetics. Acta Diabetol,1985;22(4):343-4.

27. Javed Heravian, Ehyaei A, Shoeibi N et al, Pattern visual evoked potential in patients with type 2 Diabetes Mellitus.J Ophthalmic Vis Res 2012;7(3):225-230.

28. PG.Ramam,Sodani A, George B,A study of visual evoked potential changes in Diabetes Mellitus.Int J Diab Dev Countries(1997),vol 17.

29. Ruchi Kothari,Pradeep Bokariya, Comprehensive Review of Methodologies Employed for Visual Evoked Potentials.Scientifica volume 2016.

30. Visual evoked potentials by Donnel J Creel-Web vision.

31. Google.

32. Abdulfatai B. Olokoba, Olusegun A et al, Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Medical Journal (2012) Vol. 27, No. 4: 269-273.

33. Zeinab Nasralah,William Robinson,Gregory R Jackson et al,Measuring visual function in Diabetic Retinopathy ,progress in basic and clinical research.J Clin Exp Ophthalmol 2013,4:6.

34. Nagi , Pettitt DJ, Bennett PH, et al,Diabetic Retinopathy assessed by fundus photography in PIMA Indians with impaired glucose tolerance and NIDDM.Diabret Med 1997;14(6):449-56.

35. Maitra A. In The Endocrine system: Robbins and Cotran pathologic basis of diseases, Eighth edition, published by Elsevier, 2010, 1131-1146.

36. Enden MKV, Nyengaard JR. Elevated Glucose levels increase Retinal Glycolysis and Sorbital pathway metabolism. Invest Ophthalmol Vis Sci 1995; 36:1675-1685.

37. Murata T, Nakagawa K. The relation between expression of Vascular Endothelial Growth Factor and Breakdown of the Blood Retinal Barrier in Diabetic Rat Retinas. A Journal of Technical Methods and Patholog. 1996; 74(4):819-825.

38. Peyman GA, Golberg MF. In Principles and practice of Ophthalmology 2.

39. Xia P, Inoguchi T. Characterisation of the Mechanism for the Chronic Activation of Diacylglycerol-Protein Kinase C Pathway in Diabetes and Hypergalactosemia. Diabetes 1994; 43:1122-1129.

40. S.M.Park,J.W.Park,S.J.Park ,Apoptotic death of photoreceptors in the streptozotocin induced diabetic rat retina.Diabetologia, 2003 vol 46(9) :1260-1268.

41. Timothy SK,Alistair JB, Retinal ganglion cells in diabetes ,J Physiol (2008) 586.18 pp 4401–4408.

42. A.J.Barber,T.W.Gardner,S.F Abcouver,The significance of vascular and neural apoptosis to the pathology of Diabetic Retinopathy. Investigative ophthalmology and qvisual science.2011 vol 52; 502:1156-1163.

43. Ying Yu,Hui Chen,Shao BO Su ,Neuroinflammatory response in diabetic retinopathy,Journal of neuroinflammation.(2015) 12:141.

44. Ghirlanda, Di-Leo MAS, Marietti G et al,Detection of inner retinal dysfunction by steady state focal electroretinogram pattern and thicker in early IDDM.Diabetes 1991;9:1122-1127.

45. V. Gayathri, Vijayalakshmi B, Chandrasekhar M, et al, Electro-physiological assessment of neuropathy in visual pathway of diabetes mellitus. Journal of Diabetology ,Feb 2012;1:4

46. Algan M, Ziegler O, Gehin P, Got I,et al, Visual evoked potentials in diabetic patients. Diabetes Care, 1989 March, 12(3) 227-229.

47. K.Puvendran K, Devathansan G,Wong OK ,Visual evoked response in diabetes. Journal of Neurology, Neurosurgery and Psychiatry 1983; 46:643-647.

48. Omer Azal,Abdullah Ozkardes,M.Emin Onde et al,Visual evokd potentials in Diabetic patients.Tr.J.of Medical S ciences. 28 (1998) 139-142.

49. Avachar Kiran Narayan,Sonawane Nikhil Pandurang, Mundewadi Shafiue Ahmed et al, Visual evoked potential changes in diabetes mellitus. International Journal of Biomedical and Advance Research 2015; 6(07): 537-540.

50. D.Matanovic,S Papovic,B. Parapid et al, Influence of the metabolic control on latency values of visual evoked potentials (VEP) in patients with diabetes mellitus type 1.Archieves Italiennes de Biolgie,150:251-258, 2012.

51. R.Sivakumar, G.Ravindran, M.Muthaya et al, Diabetic retinopathy analysis. Journal of Biomedicine and Biotechnology. 2005:1 (2005) 20-27.

52. Klein R, Klein BE. Wisconsin Epidemiologic Study on Diabetic Retinopathy III. Prevalence and risk factors of diabetic retinopathy when age at diagnosis >30 years. Arch Ophthalmol 1984; 102(4):527-532.

53. Deepika chopra,Gupta M,Manchanda KC et al, A of visual evoked potential in type 2 DM.A journal of clinical and diagnostic research. 2011 June (vol 5(3):519-522.

54. Nikhat Yasmeen, Mohammed Muslaiuddin Khalid, Abdul Raoof Omer Siddique et al, Comparative study of visual evoked potentials in diabetic vs non-diabetic individuals. IJBR (2014) 05 (10)

55. Szabela DA,Loba J,Palenga-Pydyn D et al,The picture of VEP in type 2 DM. Klin Oczna 2005;107(7-9):498-501.

56. Sangeeta Gupta , Gaurav Gupta, V.K. Deshpande, Visual evoked potential changes in patients with diabetes mellitus without retinopathy. Int J Res Med Sci. 2015 Dec; 3(12):3591-3598.

57. A Collier,J D Mitchell, Visual evoked potential and contrast sensitivity function in diabetic retinopathy.British Medical Journal 27 July 1985, vol 291.

58. Martinelli V ,Filippi M,Meschi F et al, VEP and Pattern electro retinogram in insulin dependent diabetes mellitus. Clin Vision Sci 1991; 6: 437- 443.

59. Bhanu R ,Vinutha Shankar M.S,Karthiyanee Kutty et al ,Visual evoked potential in non insulin dependent diabetes mellitus without retinopathy:A pilot study. Current Neurobiology 2012;3 (1):55-59.

60. Parisi V,Uccoli,G .Monticome et al,Visual evoked potentials after photostress in newly diagnosed insulin dependent diabetes mellitus

patients. Graefe's Archive for Clinical and Experimental Ophthalmology 1995; 233: 601-604.

61. U. K. Mishra and J. Kalita, “Visual evoked potential,” in Clinical Neurophysiology: Nerve Conduction, Electromyography,and Evoked Potentials, U. K. Misra and J. Kalita, Eds., pp. 309–327, Reed Elsevier India, New Delhi, India, 2nd edition, 2016.

62. G.K.Pal Text book of practical physiology 3rd edition.

63. A.A.Alidani ,Sarkis k.Strak,Khalid A.AI-maraj et al,The study of VEP in patients with diabetes mellitus.The medical journal of Basrah University, 2009; vol 2 :27

64. Farisa Khatoon, Farah Bahmed, Nazeema Khatoon,visual evoked potential as an early marker of diabetic retinopathy, Indian Journal of Clinical Anatomy and Physiology,April-June 2016;200-204.

65. Jayshree Phurailatpam,Arun Kumar Sharma,Ramji Singh et al,Effect of age on reversal VEP in Indian population.Intrenational Journal of clinical and experimental Physiology Apr-Jun 2014 vol 1 (2)

66. Sanjeev kumar shrivastava, virendra verma, p.s. tonpay, milind shiralkar, et al visual evoked potentials in type-1 diabetes without retinopathy: co-relations with duration of diabetes. Journal of Evolution of Medical and Dental Sciences/ Volume 3/ Issue 05/February 03, 2014.

PROFORMA

Name :

Age :

Sex :

Height :

Weight :

Occupation :

Socioeconomic status :

Present complaints with duration:

H/O Diabetes Mellitus and duration

H/O eye complaints

Past history:

- H/O hypertension/ H/O cardiovascular disease
- H/O CVA
- H/O Cataract
- H/O Glaucoma
- Vitreous opacities
- H/O Eye trauma

Treatment history:

- Details of Diabetic treatment and duration
- Any side effects for the drug
- H/O treatment of any eye problem

Personal history:

- H/O smoking
- H/O alcoholism
- H/O Tobacco chewing
- H/O ATT,Antimalarials

Family history:

- H/O similar illness in family members

Clinical examination:

- Vital signs
- General examination
- Examination of respiratory system/CVS
- Examination of CNS
- Ophthalmological examination-best corrected visual acuity

  Intra ocular pressure

  Dilatation and fundoscopy-(slit lamp with +90D lens)

Investigations

- Fasting and postprandial blood sugar
- Visual evoked potential (VEP)

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு : நீரிழிவு நோய் விழித்திரை பாதிப்பு உள்ளவர்களிடம் விஷீவல் இவோக்ட் பொட்டன்ஷியல் பரிசோதனை மூலம் விழித்திரை செயல்பாடு மதிப்பீடு செய்தல்

ஆய்வு செய்யப்படும் இடம் :

பங்கு பெறுபவரின் பெயர் :

பங்கு பெறுபவரின் வயது : பங்கு பெறுபவரின் எண்:

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விபரங்கள் எனக்கு விளக்கப்பட்டுளளது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கின்றேன். எந்த காரணத்தினாலோ எந்த சட்டச்சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவை இல்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் சாட்சியாளரின் கையொப்பம்

இடம்: இடம்:

தேதி: தேதி:

PATIENT CONSENT FORM

STUDY DETAIL :

"**EVALUATION OF RETINAL GANGLION CELL ACTIVITY BY PATTERN VISUAL EVOKED POTENTIAL IN TYPE II DIABETIC PATIENTS"**

STUDY CENTRE:

Department Of Physiology Chengalpattu Medical College, Chengalpattu.

PATIENT NAME: AGE: SEX:

IDENTIFICATION NUMBER:

I confirm that have understood the purpose of procedure for the above study.

I have the opportunity to ask question and all my questions and doubts have been answered to my satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw anytime without giving any reasons, without my legal rights being affected.

I understand that my investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arrives from the study.

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team.

I hereby give consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic test.

Signature of investigator Signature/Thumb impression of participant

Date:

Place: Participant's Address:

MASTER CHART

NAME		Age	sex	place		height	weight	BMI	SBP	DBP	F SUGAR	PP SUGAR	Duration	Treatment	P100 RT	P100LEFT	N 75 RT	N75 LEFT	P100RT A	P100LT A	N75RT A	N75LT A	N145 RT	N145 LT	N75P100R	N75P100L
DIABETES MELLITUS																										
Lalitha		59	F	Amanapakam		156	65	20.7	120	80	140	190	3	d	98.75	107.5	85	86.25	0.93	0.94	0.18	1.24	123.75	157.5	1.11	2.14
Kupammal		56	F	Sithatur		155	65	23.7	110	70	107	127	6	d	100	101.25	86.25	78.75	4.9	0	0.79	0	130	130	5.69	0
Devanesan		46	M	Thirukatchur		155	65	27.1	110	70	144	191	5	d	100	100	72.5	46.25	1.86	2.5	0.91	1	126	145	2.77	3.55
Ashok		55	M	Chengalpet		156	64	26.3	110	70	154	180	5	d	105	107.5	76.25	73.75	3.3	1.65	1.03	1.07	141.25	140	4.33	2.72
Velu		48	M	Pvkalathur		154	60	25.3	100	70	160	200	6	d	106.25	102.5	60	73.75	0.93	1.99	1	0.89	146.25	145	1.93	2.88
Queenmary		37	F	Thirukatckur		152	120	51.9	130	80	110	150	1	d	102.5	102.5	78.75	71.25	1.62	1.61	1.35	1.39	128.75	136.25	2.97	3
Sheela		39	F	tambaram		153	100	42.7	120	80	120	180	3	d	100	101.25	77.5	73.75	1.24	2.69	0.74	0.77	118.75	143.75	1.98	3.46
Usha		40	F	chengalpet		154	80	33.7	110	70	110	150	3	d	103.75	102.5	76.25	72.5	1.62	1.08	0.62	0.84	118.75	117.5	1.18	1.92
Selvi		44	F	Chengalpet		156	70	29.1	120	80	100	140	2	d	107.5	106.25	80.5	81.25	2.79	2.26	0.74	0.24	145	142.5	3.53	2.46
Vimala		59	F	mamandur		157	65	26.4	110	70	107	127	3	d	108.75	110	83.75	80	3.16	3.16	0.84	0.29	150	143.75	4	3.45
Punitha		40	F	mamandur		155	60	25	100	70	100	130	5	d	110	108.75	77.5	81.25	2.53	2.49	0.56	1.15	145	141.25	3.09	3.64
Balaraman		38	M	annathur		165	60	22	120	80	165	275	1	d	112.5	105	82.5	87.5	2.38	3.48	0.84	0.94	155	155	3.22	4.42
Guru		43	M	cheyur		162	58	22.1	110	70	150	200	3	d	108.75	113.75	85	80	1.95	2.89	0.3	0.42	157.5	151.25	2.25	3.31
Hari		42	M	uthiramerur		160	60	23.4	100	70	150	180	3	d	102	115	85	67.5	3.08	2.49	1.23	0.96	115	163.75	2.1	3.08
Thanikachalam		60	M	pinayur		160	70	27.3	110	70	136	246	10	d/i	102.5	106.5	62.5	58.75	2.04	2.3	0.84	0.53	151.25	137.5	2.86	2.83
Hari		43	M	chrompet		165	65	23.9	120	80	130	240	10	d/i	113.75	102.5	61.25	67.5	1.96	2.21	0.14	0.87	143.75	148.75	2.1	3.08
Siva		34	M	mangalam		160	80	31.2	110	70	120	200	8	d	101.25	110	70	73.75	1.87	0	0.45	0	113.75	165	2.32	0
Suganthi		38	F	thimavaram		156	50	20.5	120	80	259	410	6	d/i	98.75	96.25	83.75	60	2.86	1.77	1.01	0.2	141.25	142.25	3.87	1.97
Saranya		46	F	chengalpet		155	48	20	110	70	200	410	5	i	105	98.75	77.5	65	2.56	3.76	0.9	0.52	142	137.5	3.46	4.28

NAME	Age	sex	place	height	weight	BMI	SBP	DBP	F SUGAR	PP SUGAR	Duration	Treatment	P100 RT	P100LEFT	N 75 RT	N75 LEFT	P100RT A	P100LT A	N75RT A	N75LT A	N145 RT	N145 LT	N75P100R	N75P100L
Kanagamani	48	F	thandalam	150	60	26.7	130	70	240	411	6	d/i	105	103.75	62.5	45	2.7	3.38	0.65	1.39	158.75	143.75	3.35	4.21
Amsaveni	49	F	thandalam	155	64	26.6	110	70	200	410	5	d/i	102.5	102.5	51.25	68.75	3.39	3.13	1.72	0.83	142.5	147.5	5.1	3.86
Thenmozhi	39	F	kalathur	156	55	22.6	120	80	180	310	5	d/i	97.5	105	53.75	75	1.52	2.71	1.61	0.62	155	145	3.13	3.33
Chandrasekar	60	M	mmnagar	155	50	20.8	110	70	120	180	10	d	116.25	112.5	96.35	98.75	2.74	3.24	0.8	0.73	153.75	153.75	3.54	3.97
Nanda	43	M	mamandur	158	60	24.59	120	80	100	180	10	d	117.5	116.25	98.75	96.25	2.6	2.93	0.98	1.11	157.5	152.5	3.58	4.04
Nandini	56	F	Athimanam	156	60	24.7	120	80	130	300	5	d	102.5	103.75	82.5	75	0.75	1.82	0.32	0.96	163.75	123.75	1.07	2.8
Vaidialingam	57	M	Lendrathur	158	60	24	130	80	109	104	10	d/i	103.75	96.25	73.75	65	2.5	2.71	0.77	1.42	143.75	143.75	3.27	4.13
Mathialagan	44	M	chengalpet	160	69	27	120	80	100	110	8	d/i	96.25	105	65	76.25	2.74	3.35	1.54	1.06	143.75	140	4.28	4.4
Govindan	44	M	jaminendrathur	157	65	26.4	110	70	120	140	6	d	102.5	0.25	60.25	57.5	3.53	2.15	1.7	0.96	143.75	136.25	5.23	3.1
Hemalatha	58	F	Spkoil	155	60	25	110	70	100	160	5	d	107.5	103.75	76.25	77.5	2.99	2.68	1.73	1.42	142.5	143.75	4.27	4.11
Kumari	50	F	pazhaveli	156	59	24.2	120	80	120	180	5	d	102.5	113.75	66.25	85	1.8	1.57	1.41	0.96	140	142.5	3.3	2.53
Shanthi	45	F	paranur	160	65	25.4	110	70	110	150	6	d	111.25	113.75	78.75	85	2.24	2.73	0.78	1.85	122.5	145	3.02	4.58
Kala	59	F	pvkalathur	156	59	25	100	70	120	160	3	d	101.25	97.5	65	66.25	2.47	2.93	1.57	1	147.5	145	4.04	4.46
Kothandam	60	M	nerkundram	156	59	24.2	140	70	120	160	3	D	111	103	92.5	95	0.16	0.96	1.23	1.24	140	136.25	0.4	2.2
Venmathi	35	F	paunchur	155	55	22.9	110	70	124	245	2	d	102.5	101.25	73.75	75	1.42	2.42	1.01	1.38	145	138.75	2.43	3.8
Malliga	45	F	kavithandalam	156	60	24.7	130	80	110	130	3	d	108.75	105	76.25	70	1.97	1.78	0.68	1.04	138.75	153.75	2.65	2.82
Selvi	39	F	kalathur	154	65	27.4	130	70	100	140	5	d	101.25	107.5	68.75	76.25	0.78	1.66	1.6	0.09	136.25	140	1.84	2.75
Das	54	M	mamandur	158	65	26	120	70	120	160	3	d	103.75	101.25	70	67.5	7.41	6.06	1.14	0.64	115	150	8.55	6.7
Faerida	54	F	madurantakam	155	68	28.3	110	70	110	150	2	d	101.25	108.75	81.25	85	1	1.95	0.34	0.98	143.75	148.75	1.34	2.93
Manarsamy	54	M	padalam	160	79	30.9	100	70	120	180	3	d	111.25	113.75	85	78.75	3.04	3.85	0.54	1.21	150	15.75	3.58	5.06
DM Madanagopal	60	M	Chengalpet	158	70	28	110	70	120	180	1	i	106.25	111.25	77.5	86.25	1.54	1.19	0.64	0.69	140	141.25	2.18	1.88

NAME		Age	sex	place		height	weight	BMI	SBP	DBP	F SUGAR	PP SUGAR	Duration	Treatment	P100 RT	P100LEFT	N 75 RT	N75 LEFT	P100RT A	P100LT A	N75RT A	N75LT A	N145 RT	N145 LT	N75P100R	N75P100L
DIABETIC RETINOPATHY																										
DEVAKI		36	F	VALLIPURAM		156	55	22.6	110	70	191	252	3	d	98.75	118.75	67.5	76.25	1.61	0.33	2.21	1	146.25	136.25	3.82	1.33
SHAKUNTHALA		43	F	PV KALATHUR		155	60	25	120	80	200	260	3	d	101.25	112.5	65	87.5	2.21	2.14	0.92	0.38	163.75	142.5	3.13	2.52
Deviprasad	D	47	m	Thandalam		160	80	31.2	110	70	195	200	5	d	115	112.5	87.5	91.25	2.46	3.29	0.81	0.1	163.75	141.25	3.27	3.39
Marimuthu		42	M	Maduranthagam		145	45	21.4	100	70	213	459	3	i	105	102.5	76.25	78.75	3.83	4.14	1.17	0.98	146.25	142.5	5	5.12
Sampatham		60	F	Chengalpattu		150	60	26.7	110	70	200	400	3	i	105	101.25	76.25	77.5	3.2	3.04	0.73	0.74	140	145	3.93	3.78
Prabakar		45	M	Thirukazhukundram		157	65	26.4	100	70	215	410	5	i	112.5	110	86.25	77.5	2.09	2.82	0.92	0.83	145	143.75	3.01	3.65
Tamilselvan		45	M	Chengalpattu		160	60	25.6	120	80	201	398	15	D	107.5	110	66.25	48.75	1.57	2.94	0.5	0.24	150	143.75	2.07	3.18
Kanniappan		55	M	Mangalam		163	65	24.5	110	70	210	380	10	d	108.75	101.25	56.25	80	1.9	1.41	0.63	0.58	148.75	141.25	2.53	1.99
Palani		58	M	Pulipakkam		157	60	24.3	120	80	199	400	10	d	102.5	111.25	75	66.25	1.55	0.97	0.47	1.04	157.5	137.5	2.02	2.01
Ganeshwari		47	F	Maduranthagam		155	69	28.7	110	70	160	280	10	d	105	105	56	78.75	2.39	1.94	0.9	0.39	145	147.5	3.29	2.33
Charles		56	M	Puzhuthivakam		158	70	28	110	70	224	414	3	d	105	102.5	67.5	68.25	5.37	6.8	0.63	1.09	141.25	145	6	7.89
Krishnana		59	M	MM Nagar		155	69	28.7	100	70	200	400	13	d	106.25	103.75	70	72.5	5.29	4.62	0.1	0.59	137.5	135	5.39	5.21
Latha		40	F	Peramanur		166	60	21.8	110	70	190	390	10	d	105	103.75	76.25	73.75	0.88	3.95	0.29	1.48	140	137.5	5.43	1.17
Girija		43	F	Pulipakkam		155	65	27.1	100	70	150	300	8	d	102.5	103.75	76.25	73.75	3.25	3	0.47	1.03	133.75	135	3.72	4.03
Fathima		48	F	Perungalathur		157	59	23.9	110	70	120	200	10	d	105	106.25	72.5	72.5	0	3.88	0	2.58	133.75	130	0	6.46
Perumal		43	M	Olakkur		155	60	25	110	70	100	140	5	d	122.5	106.25	61.25	77.5	1.77	2.15	1.77	1.73	155	143.75	2.75	3.81
Nambi		46	M	Paranur		156	65	26.7	130	80	80	130	6	d	118.75	107.5	73.75	65	1.84	2.29	1.06	1.03	162.5	150	2.9	3.32
isakiammal		50	F	athimanam		155	60	25	110	70	75	130	5	d	120.25	116.25	75	78.75	2.03	2.39	1.76	1.25	181.25	166.25	3.79	3.64
Jayabarathi		40	F	Meyur		156	60	24.7	100	70	154	280	3	d	101.25	108.75	80	81.25	1.42	2.12	0.15	1.7	120	120	1.57	3.82
kumar		48	m	uthiramerur		158	60	24	140	70	120	160	3	D	125	120	102	102.5	0.55	0.61	1.23	0.97	145	146	178	1.58
Kaliyamoorthi		45	M	Thakalapetai		157	60	24.3	110	70	233	440	10	I/D	107.5	110	72.5	80	3.17	4.64	0.92	1.58	133.75	118.75	4.09	6.22
Elango		48	M	Manapakkam		155	70	29.1	130	70	250	400	8	I/D	107.5	110	72.5	78.75	3.16	2.53	0.74	1.02	137.5	143.75	3.9	3.55

NAME	Age	sex	place	height	weight	BMI	SBP	DBP	F SUGAR	PP SUGAR	Duration	Treatment	P100 RT	P100LEFT	N 75 RT	N75 LEFT	P100RT A	P100LT A	N75RT A	N75LT A	N145 RT	N145 LT	N75P100R	N75P100L
Rukku	43	F	Andapet	157	65	29.1	110	70	220	390	10	I/D	111.25	108.75	76.25	81.25	2.74	4.53	0.73	1.01	137.5	141.25	3.47	5.54
Raja	48	M	Thakalapetai	160	80	31.2	120	70	230	310	8	I/D	111.25	110	80	78.75	3.95	3.13	0.87	1.42	136.25	143.75	4.82	4.55
Ramani	40	F	Rajakulipettai	154	58	24.5	130	80	106	163	3	d	116.25	107.5	92.5	92.5	0.03	0.02	0.18	0.13	137.5	143.75	0.21	0.15
Muralishree	56	F	Paranur	156	55	22.6	130	90	120	280	8	d	105	101.25	57.5	72.5	2.4	2.67	0.71	0.31	138.75	137.5	3.11	2.98
Nirmala	34	F	Vallam	155	80	33.3	140	80	142	246	5	d	111.25	107.5	80	78.75	4	5.6	1.96	1.95	130	132.5	5.96	7.55
Sindhu	45	F	Padalam	150	60	26.7	120	80	150	300	3	d	108.75	110	78.75	77.5	3.17	4.41	2.03	1.53	160	160	5.2	5.94
Dhanasekar	43	M	Maruvathur	160	70	27.3	110	70	130	280	10	d	112.5	111.25	82.5	80	4.06	3.76	0.54	0.8	163.75	160	4.6	4.56
Raja	57	M	Meyur	157	65	26.4	130	80	150	300	10	d	110	107.5	80	78.75	4.29	4.98	1.49	1.3	160	161.25	5.78	0.8
Revathi	35	F	Vallam	155	60	25	110	70	154	300	5	d	107.5	107.5	68.75	67.5	3.04	3.41	0.96	1.65	160	168.75	4	5.09
Ranjani	38	F	Deewanur	158	70	28	130	80	120	220	10	d	103.75	103.75	71.25	71.25	2.31	3.65	0.88	2.07	172.5	168.75	3.19	5.72
Lakshmanan	48	M	Thatchur	157	75	30.4	120	80	150	230	8	d	105	103.75	75	70	2.6	2.07	1.26	0.71	171.25	171.75	3.86	2.78
Murugan	54	M	mampakam	160	65	25.4	110	70	120	160	6	d	118.75	116.25	81.25	77.5	3.07	2.54	1.31	1.25	143.75	137.5	4.38	3.29
Kamala	49	F	Padur	158	65	26	120	80	150	200	6	d	107.5	106.25	77.5	72.5	2.78	3.92	0.44	0.08	143.75	137.5	3.2	4
Jagan	54	M	Cheyyur	160	65	25.4	110	70	150	298	5	d	106.25	108.75	72.5	80	3.91	3.38	0.53	0.4	141.25	138.75	4.44	3.78
Malliga	34	F	P.V.Kalathur	155	60	25	130	80	186	265	3	I	101.25	98.75	82.5	58.75	2.37	2.7	0.43	0.93	143.75	137.5	2.8	3.63
Gowri	39	F	Tambaram	160	70	27.3	110	70	190	260	5	I	105	101.25	87.5	80	2.6	2.96	1.62	0.58	128.75	128.75	4.22	3.54
Balaji	57	M	madurantakam	158	70	28	120	80	110	186	3	d	123.75	121	96.25	90	0.51	0.61	1.07	0.83	150	128.75	1.58	1.47
Kathiravan	60	M	Deewanur	156	59	24.2	140	70	120	160	3	D	117.5	123.75	92.5	95	0.16	0.96	1.23	1.24	140	136.25	0.4	2.2

NAME	Age	sex	place	height	weight	BMI	SBP	DBP	F SUGAR	PP SUGAR	Duration	Treatment	P100 RT	P100LEFT	N 75 RT	N75 LEFT	P100RT A	P100LT A	N75RT A	N75LT A	N145 RT	N145 LT	N75P100R	N75P100L
CONTROL																								
Sherif	39	M	Chennai	155	58	24.1	110	70	100	140			100.5	100.5	81.5	84	4.8	2.99	1.52	0.82	121.5	127	6.32	3.81
Vanitha	34	F	Annanagar	158	58	23.2	110	70	80	130			101.75	101.25	81.25	78.75	1.62	6.71	0.5	2.06	176.25	163.75	2.12	8.77
Vasantha	43	F	Tambaram	155	50	20.8	120	80	90	140			97.5	100	82.5	80	1.19	0.65	0.63	0.4	120	128.75	1.82	0.69
Saritha	32	F	Natham	156	60	24.7	110	70	100	140			100.25	101.76	82.5	82.5	6.06	7.02	1.08	1.23	157.5	158.75	7.14	8.25
Muneeswari	34	F	Ratinakinaru	155	60	25.57	110	70	90	130			100.75	103.75	81.25	78.75	0	5.76	0	2.02	172.5	172.5	0	8.18
JAYA	40	f	Kaavur	159	60	23.7	130	90	80	130			100	100	68.75	66.25	2.26	2.55	0.31	1.23	128.75	128.75	2.57	3.78
Uma	37	F	Meyur	157	65	26.4	110	70	75	120			98.75	100	68.75	77.5	1.52	2.17	0.66	0.86	117.5	123.75	2.18	3.03
Poonguzhali	30	F	Chengalpattu	154	65	27.4	110	70	90	140			100	101.25	73.75	67.5	3.75	5.98	1.61	2.5	142.5	141.25	5.36	8.45
Vijaya	31	f	Oragadam	156	60	24.7	120	80	80	130			100	100	68.75	71.25	3.32	3.77	1.5	1.75	140	146	4.82	5.52
Rani	49	F	Kalathur	156	65	26.7	110	70	90	130			98.75	100	78.75	68.75	3.16	3.5	0.68	1.75	142.5	137.5	3.84	5.31
Muniammal	48	F	Aandipakkam	158	60	24	130	80	96	135			97.5	95	72.5	72.5	1.27	2.22	1.21	1.8	142.5	133.75	2.67	4.08
Indra	45	F	Neikuppi	155	65	27.1	110	70	100	140			100	97.5	68.75	72.5	0.9	1.17	1.68	1.68	130	141.25	2.58	2.85
Kalaiarasi	50	F	Chengalpattu	160	65	25.4	110	70	80	130			100	98.75	70	71.25	0.86	1.65	1.14	2.05	133.75	143.75	2	3.7
Kanniappan	40	M	Vallipuram	158	70	28	120	80	90	140			81.25	76.25	57.5	52.5	0.36	0.71	1.87	1.96	105	103.75	2.23	2.67
Gopal	47	M	Neikuppi	157	65	26.4	120	80	90	130			77.5	77.5	56.25	55	0.54	0.45	1.9	2.07	110	102.5	2.44	2.52
Kanniammal	40	F	Chengalpattu	155	56	23.3	120	80	90	130			98.75	100	75	73.75	1.45	2.13	0.82	1.71	137.5	132.5	2.27	3.84
Dhanalakshmi	40	F	Mamandur	154	60	25.3	110	70	80	140			98.75	100	76.25	85	1.94	0.64	0.65	0.6	146.5	147.5	2.59	0.7
Thangam	49	F	Mamandur	155	65	27.1	110	70	90	120			98.75	100	80	62.5	0.95	1.91	0.15	0.76	142.5	151.25	1.1	2.67
Kala	39	F	Kalathur	156	58	23.8	130	80	90	140			96.25	100	81.25	88.25	0.69	1.12	0.35	0.69	141.25	132.5	1.84	1.81
Shakunthala	40	F	Indranagar	156	55	22.6	120	80	100	130			100	100	70	71.25	2.68	3.75	0.83	0.89	151.25	140	3.51	4.64
Rukumani	42	F	Alancheri	155	54	22.5	110	70	80	140			76.25	100	77.5	82.5	0.02	0.95	0.39	0.16	97.5	131.25	0.41	1.11

NAME	Age	sex	place	height	weight	BMI	SBP	DBP	F SUGAR	PP SUGAR	Duration	Treatment	P100 RT	P100LEFT	N 75 RT	N75 LEFT	P100RT A	P100LT A	N75RT A	N75LT A	N145 RT	N145 LT	N75P100R	N75P100L
Sarasu	40	F	Natham	154	59	24.9	120	80	90	150			92.5	100	62.5	83.25	0.57	1.93	0.7	0.01	116.25	132.5	1.27	1.94
Uthamalingam	49	M	Paranur	160	75	29.3	110	70	100	130			96.25	100	58.75	76.25	1.28	0.58	0.9	0.92	138.75	122.5	2.18	1
Kamalam	45	F	Manapakkam	155	56	23.3	110	80	80	130			92.5	98.75	78.75	61.25	2.34	3.08	0.44	0.77	130	122.5	2.78	3.85
Karthick	56	M	Chengalpattu	156	60	24.7	130	80	90	130			98.75	98.75	68.75	70	2.82	2.52	0.94	0.97	148.75	145	3.76	3.49
Damayanthi	36	F	Madhuranthagam	156	50	20.5	110	70	95	140			98.75	96.25	68.75	71.25	2.41	2.74	0.83	0.98	160	163.75	3.24	3.72
Murali	47	M	Meyur	157	60	24.3	130	80	80	130			96.25	98.75	67.5	68.75	2.79	2.31	1.44	1.57	147.5	156.25	4.23	3.88
Vanajarani	40	F	tindivanam	155	63	26.2	110	70	80	130			100	100	72.5	67.5	2.56	2.64	0.95	0.64	131.25	130	3.51	3.28
Kanaga	36	F	Madhuranthagam	156	60	24.7	120	80	90	120			98.75	100	77.5	76.25	2.56	2.64	0.95	0.64	132.5	131.25	3.51	3.28
Karigalan	58	M	vandavasi	160	65	25.4	110	70	85	120			100	100	81.25	87.5	0.5	1.86	0.5	0.47	132.5	136.25	1.65	2.33
Kaniappan	45	M	Chengalpattu	156	60	24.7	110	70	80	139			92.5	100	77.5	63.75	2.27	1.93	0.09	0.55	122.5	128.75	2.96	2.48
Rani	39	F	thirukazhukundram	155	55	22.9	120	80	90	140			100	100	50	78.75	2.23	1.87	0.57	0.65	132.5	130	2.8	2.52
Rajeshwari	36	F	karunkuzhi	157	59	23.9	110	70	86	132			96.25	100	83.75	85	3.32	1.65	0.92	0.04	125	128.75	4.24	1.69
Ramesh	38	M	chengalpet	158	60	24	130	80	75	135			100	100	80	75	2.14	1.64	0.05	0	156.25	190	2.79	0.64
Karkuzhali	47	F	Mmnagar	156	60	24.7	110	70	85	130			98.75	95	77.5	68.75	1.86	2.63	1.37	1.1	158.75	151.25	3.23	3.73
Raghuvaran	40	M	uthiramerur	160	60	23.4	130	80	80	135			100	100	77.5	76.5	0.63	1.59	1.99	2.56	171.25	177.25	2.62	4.15
Andal	43	F	Kknagar	158	60	24	118	80	95	140			95.75	95	65	66.25	5.51	5.72	1.32	1.35	133.75	131.25	6.86	7.04
Raji	46	F	padalam	155	58	24.1	120	80	95	135			92.75	98.75	67.5	66.25	4.54	4.54	1.23	1.29	137.5	138.75	0.06	5.83
Senthil	50	M	chengalpet	158	62	24.8	110	70	80	130			95	95	65	68.75	4.66	4.71	0.4	1.05	137.5	135	5.06	5.16
Sethu	56	M	Guduvancheri	165	70	25.7	100	70	153	300			103.75	101.25	66.25	61.25	1.53	1.66	0.54	0.59	141.25	143.75	2.07	2.25