IMPACT OF TYPE 2 DIABETES MELLITUS ON COGNITIVE FUNCTION

Dissertation submitted to

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

CHENNAI – 600032

In partial fulfillment of the requirement for the degree of

Doctor of Medicine in Physiology (Branch V)

M.D. (PHYSIOLOGY)

APRIL 2016

DEPARTMENT OF PHYSIOLOGY

COIMBATORE MEDICAL COLLEGE

COIMBATORE – 14

CERTIFICATE

This dissertation entitled **"IMPACT OF TYPE 2 DIABETES MELLITUS ON COGNITIVE FUNCTION"** is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfillment of regulations for the award of M.D. Degree in Physiology in the examinations to be held during April 2016.

This dissertation is a record of fresh work done by the candidate **Dr.S.KANCHANA BOBBY,** during the course of the study (2013-2016). This work was carried out by the candidate herself under my supervision.

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DECLARATION

I, **Dr.S.KANCHANA BOBBY** solemnly declare that the dissertation entitled **"IMPACT OF TYPE 2 DIABETES MELLITUS ON COGNITIVE FUNCTION"** was done by me at Coimbatore Medical College, during the period from July 2014 to June 2015 under the guidance and supervision of **Dr.N.Neelambikai.M.D.,** Professor, Department of Physiology, Coimbatore Medical College, Coimbatore.

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch - V) in Physiology. I have not submitted this dissertation on any previous occasion to any University for the award of any degree.

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Dissertation Topic : IMPACT OF TYPE 2 DIABETES MELLITUS ON COGNITIVE FUNCTION.

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Coimbatore

15.7.2014

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ACKNOWLEDGEMENT

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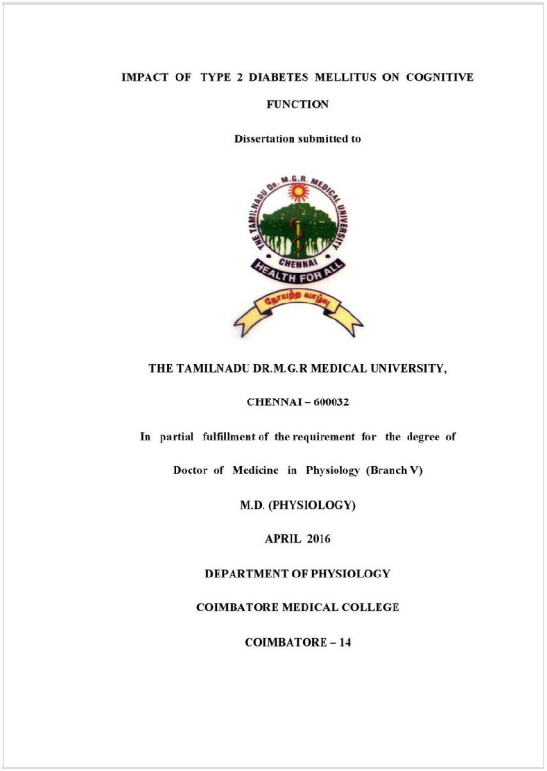

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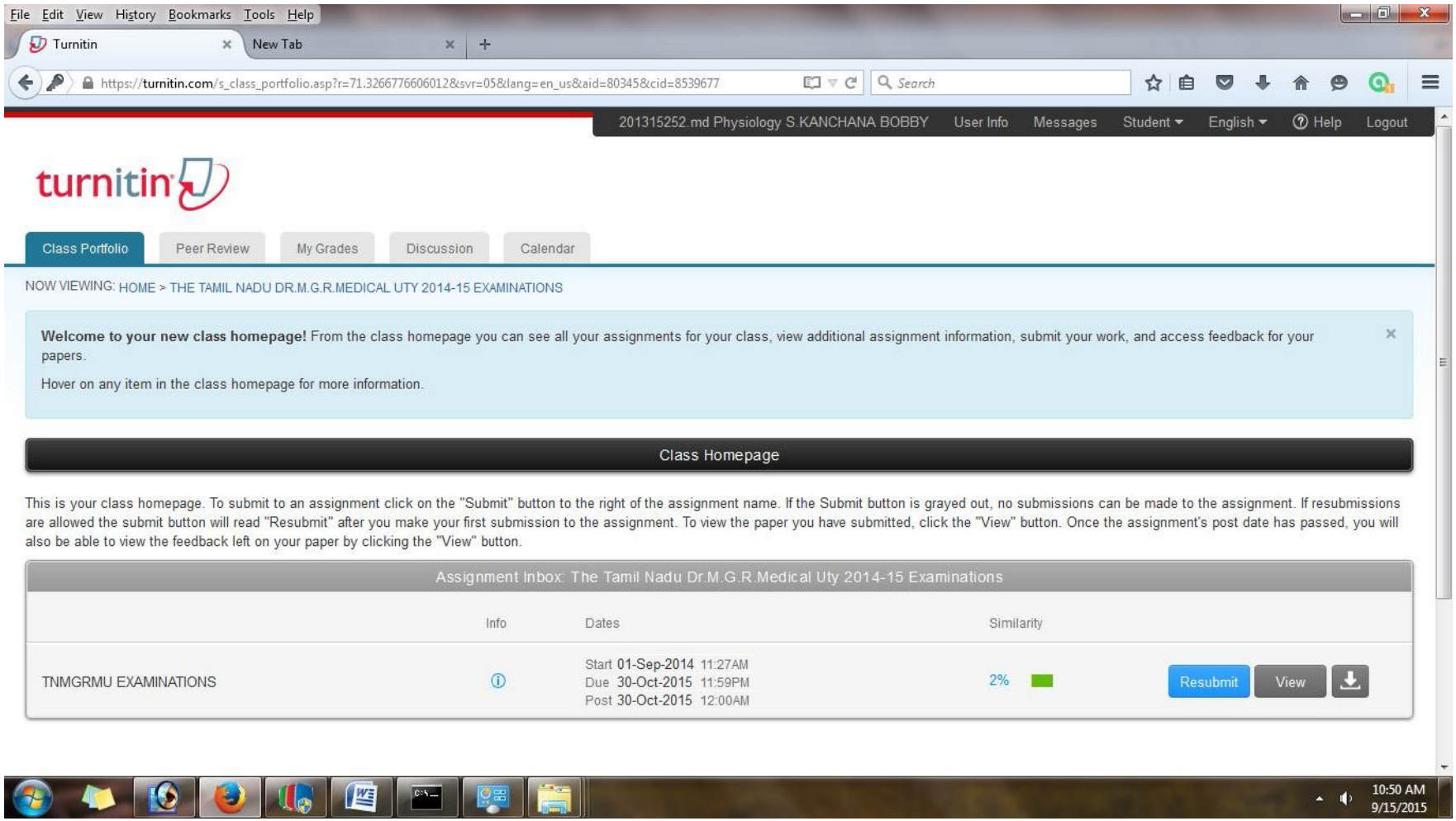
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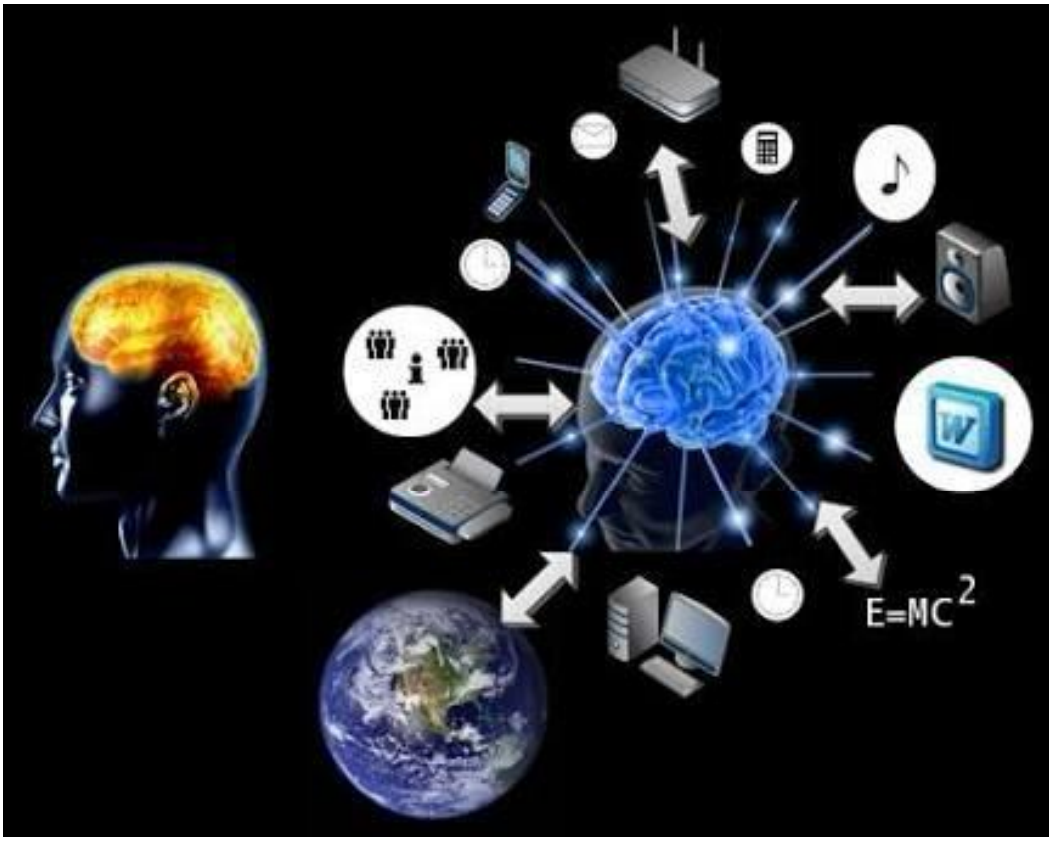


CONTENTS

ABBREVIATIONS USED IN THE STUDY

- MMSE MINI MENTAL STATUS EXAMINATION
- DM DIABETES MELLITUS
- FBS FASTING BLOOD SUGAR
- PPBS POSTPRANDIAL BLOOD SUGAR
- HbA1C HEMOGLOBIN A 1C
- ATP ADENOSINE TRI PHOSPHATE
- AGEs ADVANCED GLYCATION END PRODUCTS
- BMI BODY MASS INDEX
- GLUT GLUCOSE TRANSPORTER
- LDL LOW DENSITY LIPOPROTEINS
- VLDL VERY LOW DENSITY LIPOPROTEINS
- ADA AMERICAN DIABETES ASSOCIATION
- IRS INSULIN RECEPTOR SUBSTRATE
- MRI MAGNETIC RESONANCE IMAGING
- NEFA NON-ESTERIFIED FATTY ACIDS
- CNS CENTRAL NERVOUS SYSTEM
- AD ALZHEIMER'S DISEASE

INTRODUCTION

INTRODUCTION

One of the most challenging problems of the 21st century with regard to health is diabetes mellitus.[1] It is a heterogenous group of metabolic disorders with chronic hyperglycemia and glucose intolerance[2] and also it has been considered as "a distinct kind of accelerated aging" since it surges an individual's liability to degenerative disease.[3]

According to recent analysis by International Diabetes Federation, about 382 million people suffer from diabetes, which is projected to reach about 592 million in 2035. The majority of this 382 million people fall under the age group of 40 to 59 years. India is the second leading country with 65.1 million people suffering from diabetes in 2013, which is expected to go up by 109 million by 2035.[1]

Type2 DM is the most common diabetes, wherein insulin resistance is the key factor with relative insulin deficiency[2] and accounts for about 85% to 95% of all diabetes. It has been on the increase in most of the countries due to abrupt social and cultural changes, enhancing urbanization, changes in the dietary pattern, aging of the population, physical inactivity and unhealthy behaviour.[1]

Though it is generally seen in adults, there is an increase in adolescents and children too. Type2 DM has been viewed as a serious global health crisis.[1] The people having type2 DM are often diagnosed only when complications have already established.[1]

The lethal effect of DM in renal, cardiac, retinal, and peripheral nervous system are well known and widely accepted[4]. The consistently high blood glucose levels is a significant cause for the complications of diabetes, particularly neurological manifestations.[1] More recently, the question of impairment of cognition in type2 DM has been the subject of much speculation.[5]

Cognitive functions denotes "acquisition, processing, integration, storage plus recovery of information". It comprises attention, perceptions, memory, and executive function - higher order planning and decision-making.[6]

The relationship linking neuroendocrine impairment with decline of cognition have been documented. Abnormalities of thyroid hormone, adrenal cortex (Cushing's, Addison's) as well as other endocrinological dysfunctions usually produce notable impairment of cognition, frequently without any motor and sensory symptoms.[6]

Cognitive dysfunction is a less known and less addressed complication of diabetes mellitus.[7] Diabetes is related with a slow progressive end organ damage in brain. Diabetic subjects have 1.5 times more chances to get cognitive decline[7] since it accelerates the process of brain aging which is manifested by atrophy of the tissues due to hypoperfusion resulting in functional as well as cognition impairment. The risk effect is more when diabetes occurs in mid life than in later life.[8] Even the moderate consequence of type2 DM on cognition has significant public health issue.[9]

Numerous cross-sectional and large population based studies have evaluated the association of impairment of cognition in type2 DM and various defects in cognition – "reduction in the speed of psychomotor activites, verbal memory, processing of speed, working memory, executive task, complex motor functions, quick recall" and many others have been reported.[4]

Cukierman-Yaffe T et al., assessed in 3000 subjects the association of cognitive status with hyperglycemia (ACCORD-MIND) and found that higher HbA1c status was related with decline in cognition in type 2 DM subjects.[7]

Evaluation of the neurocognitive functions by using different test batteries to assess the various domains of cognition is the gold standard till today.[10] Among the neurocognitive tests, MMSE - the Mini-Mental Status Examination which was introduced in the year 1975 is most commonly used.[11]

The MMSE is a questionnaire which tests several aspects of cognitive domains – "orientation, registration, verbal recall, calculation, visual construction, attention and language".[12]

Though type2 DM is considered as a risk factor for cognitive decline, it is not regularly assessed in routine clinical care. Cognitive decline may lead to bad diabetic control and poor adherence to treatment modalities, including diet plans.[12]

As treatment of type2 DM includes self-management behaviours along with the highly entangled parameters such as blood sugar monitoring, diet charting, medication, diabetes subjects with impairment of cognition have difficulty in managing their problem. They may have trouble in identifying acute problems like hypoglycemia.[13]

Effective performance of cognitive functions is essential for the basic survival and meaningful living and also for the development of competent and independent individuals.[3]

Hence, this study has been designed to assess cognition in type2 DM and non-diabetics using MMSE and also to evaluate the influence of age, sex, diabetic duration and glycosylated hemoglobin percentage on cognitive functions.

AIMS & OBJECTIVES

AIM AND OBJECTIVES

AIM:

- To assess cognitive status using MMSE in type2 DM subjects and controls.

OBJECTIVES:

- To compare mean MMSE scores between type2 DM subjects and controls.
- To evaluate correlation between mean MMSE score and Glycosylated Haemoglobin in type2 DM subjects.
- To find out association between mean MMSE score and type2 DM duration.
- To find out relation of age and sex with mean MMSE score in type2 DM subjects.
- To compare mean scores of various cognitive domains in MMSE in type2 DM subjects and controls.

REVIEW OF LITERATURE

EBER'S PAPYRUS

REVIEW OF LITERATURE

DIABETES MELLITUS: DM is a group of metabolic disorders with chronic hyperglycaemia and disturbances in fat, carbohydrate, protein metabolism because of the absolute or relative insufficiency of insulin secretion and/or action. Long term hyperglycemia is linked with specific microvascular and increased risk of macrovascular complications.[14]

HISTORY OF DIABETES:[15,16]

As early as 1500 BC, the reference to diabetes existed as evidenced by an Egyptian manuscript Eber's Papyrus, as "Too great emptying of the urine". During the same period, physicians of India observed that the ants were attracted to the urine from some people and termed the condition as "madhumeha" or "honey urine."

In 250 BC, Apollonius of Memphis coined the word "diabetes" which means "to pass through". Sushruta and Charaka first recognized Type1 and type2 DM on observing the development of diabetes in thin younger individuals and later onset of diabetes in obese individuals (5th century).

OSCAR MINKOWSKI

JOSEPH VON MERING

The first complete documented clinical explanation about diabetes was "Cicero medicorum" by Aulus Cornelius Celsus (30 BC–50 AD). Aretaeus of Cappadocia, (2nd century AD) first distinguished diabetes insipidus and diabetes mellitus. But the term "mellitus" or "from honey" was added much later by Thomas Willis to differentiate diabetes insipidus (1674).

Joseph Von Mering and Oskar Minkowski (1889) discovered that diabetes was associated with pancreas based on their findings that removal of pancreas in dogs produced symptoms of diabetes. Gustave Edouard Laguesse (1893) observed pancreatic islets depicted by Paul Langerhans (1869) may be a source of substance concerned with control of blood sugar.

The Belgian physician Jean de Mayer (1909) and Sir Edward Albert Sharpey-Schafer (1910) named the substance "insulin" from the latin word "insula" meaning island. This discovery paved way for a number of researches concentrating and isolating the substance - insulin. Banting and Best (1922) isolated the hormone successfully. Professor Macleod and JB Collip along with their co-workers effectively purified the insulin. This gave way for a successful treatment.

BEST AND BANTING

Leonard Thompson, 14year old boy was first treated in 1922. For their brilliant job on the discovery of insulin, Banting and Macleod were given "NOBEL PRIZE" in 1923. As an honor to Banting, "World Diabetes Day" is held on his birthday, November 14. The molecular weight of insulin was determined by Svedberg (1934). In the middle of 1950s, Frederick Sanger described the molecular structure of insulin and got "NOBEL PRIZE" for his work in 1958.

CLASSIFICATION OF DM[17]

- **Type1 DM**
- **Type2 DM**
- **Gestational diabetes mellitus**
- **Other forms**

A. Beta-cell function genetic defects: MODY 3, MODY 1, MODY 2, other MODY types, Permanent neonatal diabetes, Mitochondrial DNA, Transient neonatal diabetes.

B. Genetic defects of insulin action: Insulin resistance of Type A, Leprechaunism, Rabson-Mendenhall syndrome, lipoatrophic diabetes

C. Exocrine pancreas disorders: Pancreatitis, Neoplasia, Cystic fibrosis, Fibrocalculous pancreatopathy.

D. Endocrinopathies: Acromegaly, Cushing's syndrome, Glucagonoma.

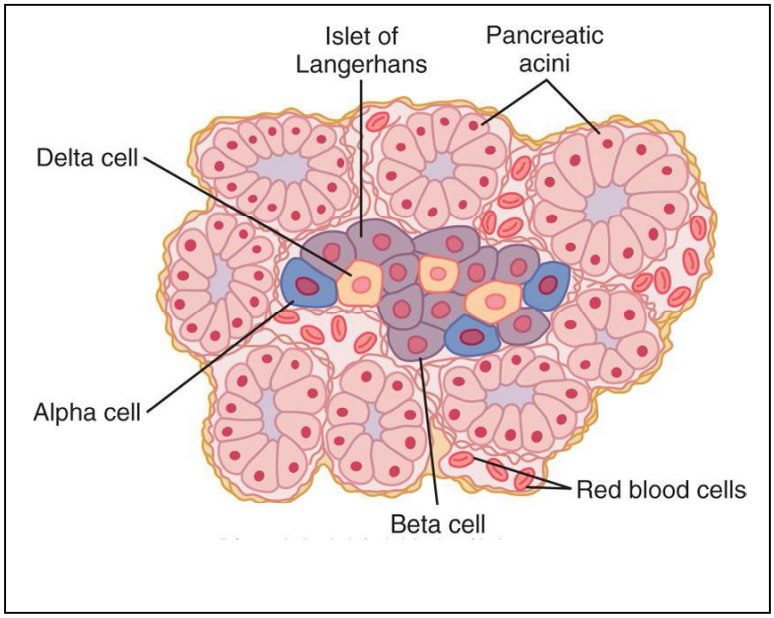
E. Drug or chemical induced: Vacor, Pentamidine, Nicotinic acid, Glucocorticoids, Thyroid hormone, . Diazoxide.

F. Infections: Congenital rubella, Cytomegalovirus

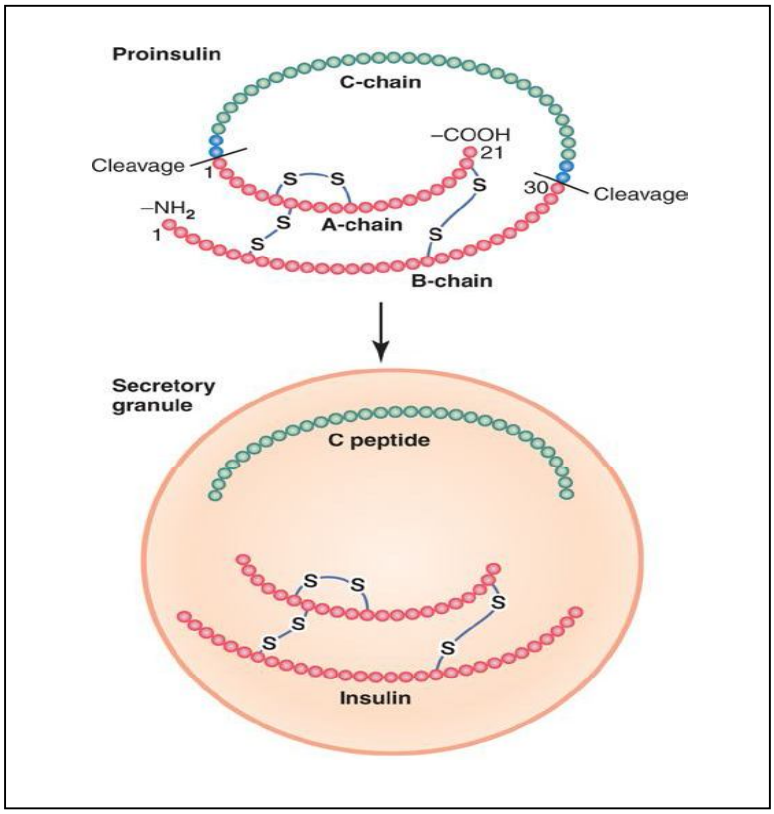
G. Immune-mediated diabetes of uncommon forms: Stiff-man syndrome, Anti-insulin receptor antibodies

H. Other genetic syndromes sometimes related with DM: Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia.

ISLET OF LANGERHANS



STRUCTURE OF INSULIN AND PROINSULIN



DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS (AMERICAN DIABETES ASSOCIATION):[18]

- Symptoms of DM with RBS >200 mg/dl (or)
- FBS concentration >126 mg/dl (or)
- 2 hours postprandial blood sugar concentration (PPBS)>200mg/dl during oral glucose tolerance test

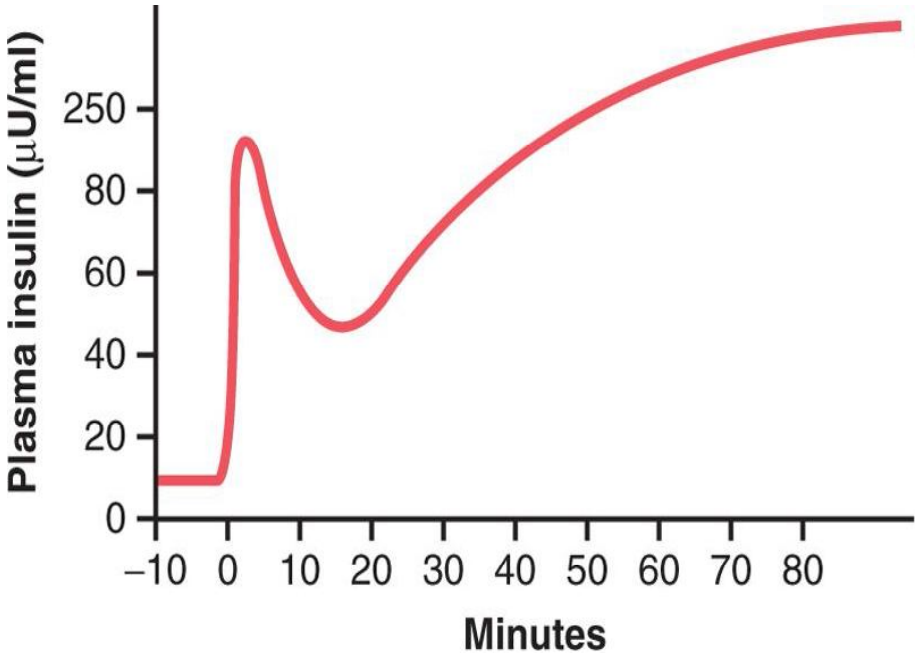
Most consistent method for diagnosis is a measurement of FPG concentration.

CRITERIA FOR DIAGNOSIS OF DIABETES AND PRE DIABETES[19]

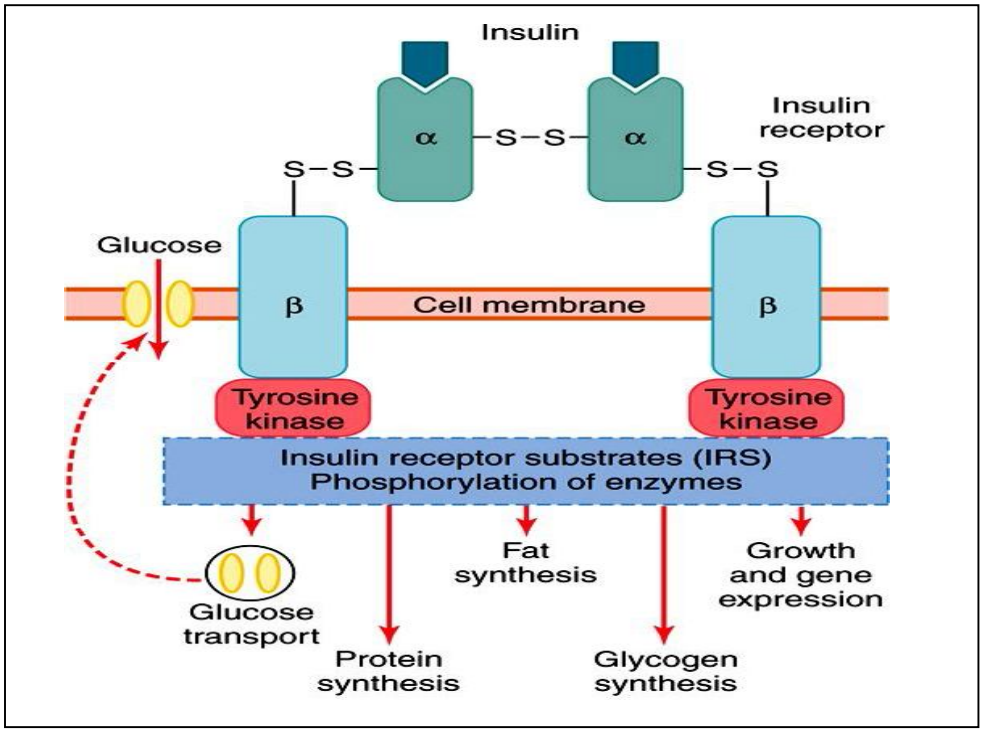
Test	**Normo-glycemia**	**IFG**	**IGT**	**High risk**	**Diabetes**
FBS(mg/dl)	<100	100-125			≥126
PPBS(mg/dl)	<140		140-199		≥200
HbA1c(%)				5.7-6.4	≥6.5

INSULIN: Insulin, the major hormonal regulator of glucose metabolism is synthesized and secreted from beta cells in pancreatic islets. This is a polypeptide hormone of the gene family of IGF-I, IGF-II and Relaxin, with a molecular weight of about 5808 Da.[14,20]

PHASES OF INSULIN SECRETION



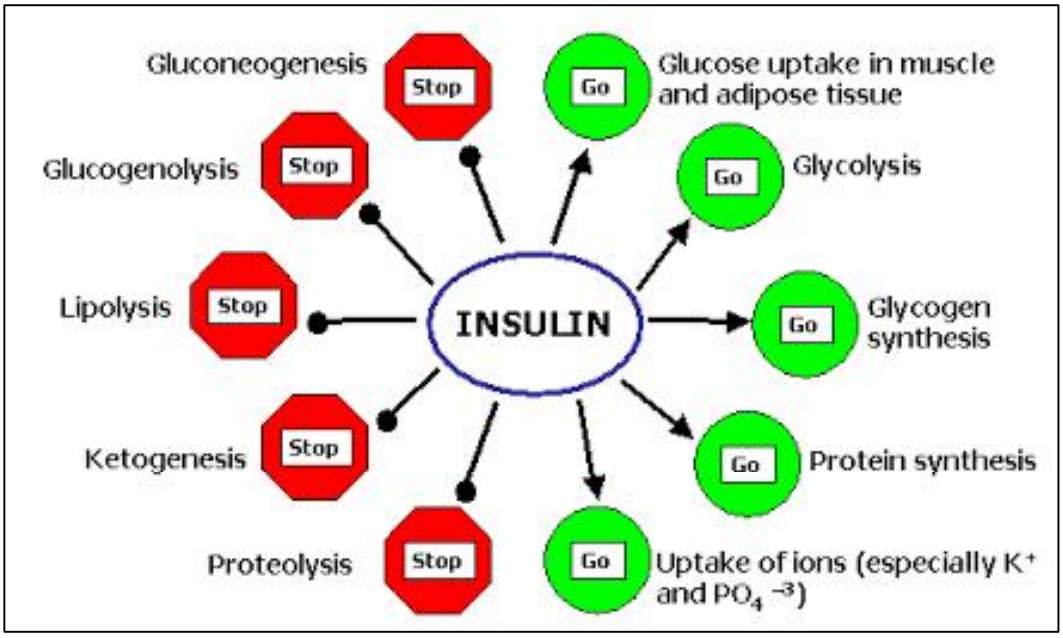
MECHANISM OF ACTION OF INSULIN



The human insulin gene is present in region p13 of the short arm of chromosome 11. Its biosynthesis takes place in two intermediate stages. First, the formation of preproinsulin and next is the consequent conversion to proinsulin and insulin.[14,21,22] Insulin is released by the process of exocytosis (emiocytosis). The release occurs in a biphasic manner. There is rapid oscillations for every 8-15 minutes with overlapping of slower oscillations every 80-150 minutes. In humans, the basal secretion rate is about 0.5-1 U/hr or 40 U/day because of rapid secretion after each meal.[14,21,22] Carbohydrate nutrients, non-carbohydrate nutrients, neural factors, hormonal factors, play a vital role in regulating insulin secretion.[19,23]

MECHANISM OF ACTION: Insulin receptor is located on the cell membrane of target tissues and insulin brings about its action by binding with it. Insulin moves across the capillary wall and binds with α subunit of insulin receptor present in the target tissues. β subunit gets autophosphorylated by the activation of the tyrosine kinase enzyme. Lastly the effects which takes place are, the expression of genes within the nucleus, protein synthesis, phosphofructokinase, glucokinase, activation and deactivation of enzymes involved in fatty acid and glucose metabolism and translocation of GLUT to the cell membrane.[21]

PHYSIOLOGICAL ACTIONS OF INSULIN



PHYSIOLOGICAL ACTIONS OF INSULIN[21,22,24]

On carbohydrate metabolism: From the orally ingested glucose, in a normal healthy person, 50% of glucose gives energy to tissues by glycolysis, 40% of glucose converted and stored as fat and 10% of glucose stored as glycogen. Insulin mainly exerts its action by acting on target organs like skeletal muscle, adipose tissue and liver. The ultimate effect of insulin on carbohydrate metabolism is to reduce the blood glucose level. It is regarded as the only effective "ANTIDIABETOGENIC HORMONE" in the body. Insulin decreases level of blood glucose by increasing taking up of glucose in the target tissues by translocating GLUT transporters to the cell membrane. Glucose uptake in skeletal muscle, smooth muscle, cardiac muscle and adipose tissues, WBCs, mammary glands are all insulin dependent whereas in nervous tissues, RBCs, retina, blood vessels and intestinal mucosa it is insulin independent. In liver, the mechanism of glucose uptake is by increasing the utilization of glucose.

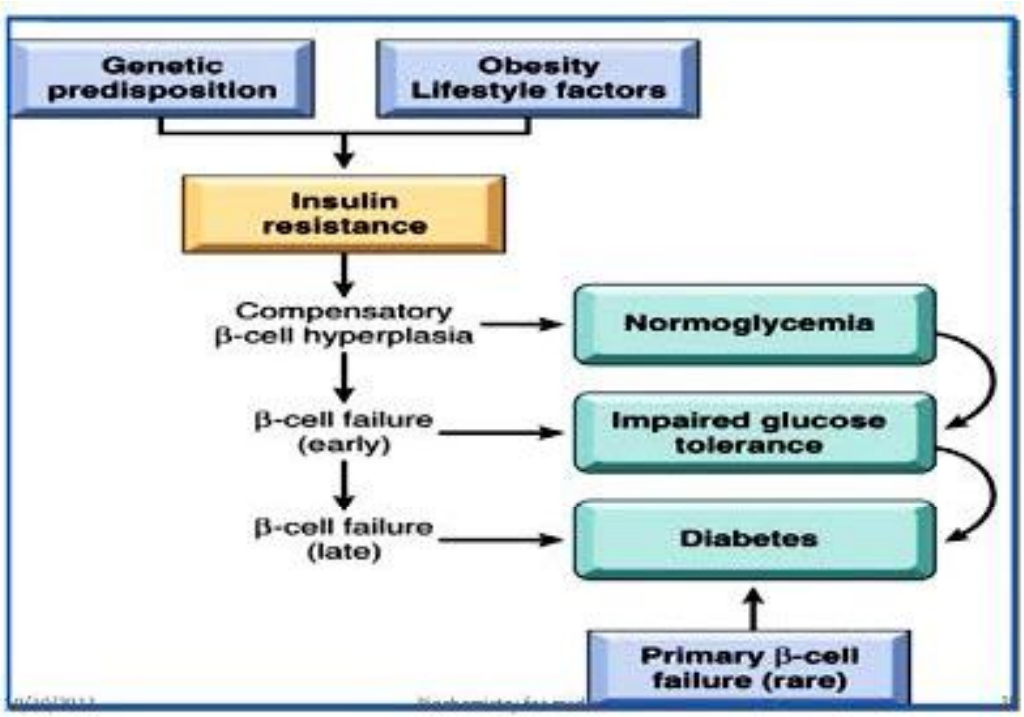
On fat metabolism: Insulin aids the storage of fat and lessens the fatty acid mobilisation and oxidation by following mechanisms. Lipolysis is inhibited by insulin by impeding the enzyme, hormone sensitive lipase.

By stopping lipolysis and further discharge of free fatty acids into the circulation, insulin decreases the formation of ketoacids in the liver. Because of this, insulin is considered as major "ANTIKETOGENIC HORMONE" in the body. Lipogenesis is induced by insulin by activating the enzyme lipoprotein lipase, which is present in the vascular endothelium. Insulin enables the synthesis of fatty acids from glucose by stimulating the enzyme acetylcoA carboxylase. Cholesterol synthesis from acetylcoA is facilitated by insulin by stimulating the enzyme HMGcoA reductase.

On protein metabolism: Insulin helps in the synthesis of proteins in the muscle and liver. It stimulates the entry of aminoacids into the muscle tissues. Protein synthesis is enhanced in ribosomes by stimulating the gene transcription and translation of mRNA. By decreasing the lysosomal enzyme activity, insulin causes inhibition of proteolysis. Insulin keeps the amino acids for protein synthesis in the liver by reducing the gluconeogenesis.

GLUCAGON: Glucagon secreted by α cells in pancreatic islets - "PRIMARY COUNTER REGULATORY HORMONE" accountable for increasing the glucose level in blood. This is brought about by increasing the gluconeogenesis and glycogenolysis in the liver. It also decreases glycolysis and lipogenesis from glucose in the liver.[21]

PATHOPHYSIOLOGY OF TYPE 2 DM



PATHOPHYSIOLOGY OF TYPE2 DM:[14]

Pathophysiology of type2 diabetes is a complex one and it is linked to the involvement of environmental factors and genetic factors.

Genetic relation of type2 diabetes: Type2 diabetes has a strong genetic association. Diabetes risk is about 40% if both parents are having type2 DM and chance to develop DM is about 70-90% in identical twins. It is a polygenic form of disease. There is involvement of more than 20 genes. Few examples of genetic polymorphism are mutations present in the genes encoding the proteins like PPAR-γ, K+ATP channel, zinc transporter, insulin receptor substrate protein and calcium dependent cysteine protease (calpain10).[18]

The three classical abnormalities of type2 DM are,

Insulin Resistance, impaired secretion of insulin from the β cells and enhanced formation of glucose by the liver

Insulin resistance:[16] It is the reduced sensitivity of target tissues like skeletal muscle as well as adipose tissue to insulin which is the main abnormality in type2 diabetes mellitus.[18]

Historical aspects of insulin resistance: Gerald 'M' reaven was the one who described first about metabolic syndrome and he explained that obesity and physical inactivity is responsible for nearly 25% of insulin resistance and another 50% is by genetic factors. Himsworth was the first person who said that hyperglycemia in some diabetic patients is because of decreased insulin sensitivity in the target tissues.

Genetic Factors comprise mutation of genes encoding, Insulin receptor substrate 1 & 2, Phosphatidyl inositol 3 kinase, GLUT transporter proteins, Liver glucokinase promoter gene.

Environmental Factors: The environmental factors are obesity, decreased physical activity and nutrition.

Obesity: Central obesity is the most potent risk factor of diabetes. Apart from the increase in quantity of adipose tissue, the adipose tissue dysfunction also is accountable for insulin resistance. Central adipocyte has more lipolytic action than adipocytes of peripheral tissues. So more amount of non esterified fatty acids is released into the circulation. These NEFA gets collected in liver and skeletal muscle and decrease insulin sensitivity by initiating phosphorylation of serine residues instead of tyrosine residue of insulin receptor substrate proteins.

Central adiposity causes more release of adipokines like resistin, retinol binding protein-4 and reduced release of adiponectin and leptin into the circulation. Resistin is responsible for the insulin resistance. Usually leptin and adiponectin upsurges the insulin sensitivity by triggering the AMP activated protein kinase enzyme action. This protein kinase enzyme in turn stimulates fatty acid oxidation in the liver and skeletal muscle. Ultimately increased resistin and decreased adiponectin collectively decrease the insulin sensitivity in target tissues.

Reduced physical activity: Exercise increases the uptake of glucose in the target organs and reduces the blood glucose level in diabetics. Urbanisation has ended in reduced physical activity which is an another factor for more prevalence of diabetes in urban people than rural.

Nutritional factors: Nutritional factors include high carbohydrate diets such as refined flour, raw rice, pasta, aerated soft drinks, sweet and sugar. Intake of high saturated fat diets like coconut oil, omega 6 fatty acid rich foods like corn, vanaspathi and decreased intake of fruits and vegetables can also lead to type 2 diabetes. Deficiency of chromium, zinc, selenium in the diet and also vitamin D deficiency may end in diabetes.

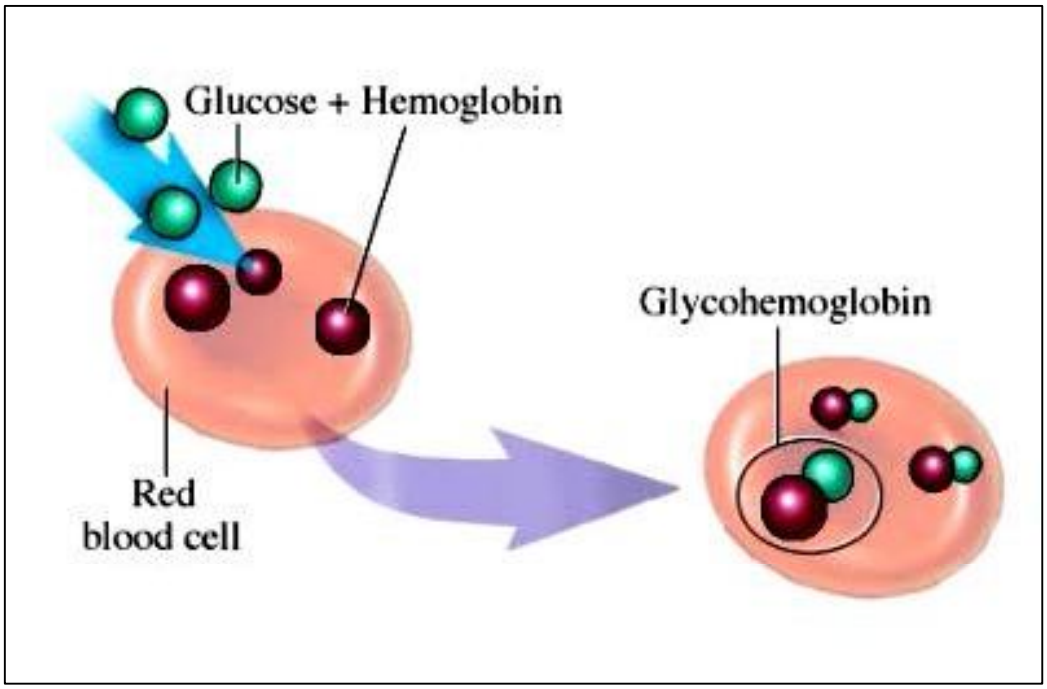
Insulin resistance related metabolic abnormalities : The target organs like adipose tissues and skeletal muscles have decreased glucose utilisation. This is due to reduced insulin sensitivity. Also, there is increased gluconeogenesis in the liver which finally ends in hyperglycemia. This increased hepatic gluconeogenesis is held responsible for the increase in fasting plasma glucose concentration wherein decreased peripheral utilisation of glucose is accountable for postprandial hyperglycemia in diabetes mellitus. The storage of glycogen is also affected. In adipose tissue, increase in lipolysis leads to discharge of more free fatty acids into circulation, which ends in increased concentration of VLDL proteins and triglycerides in the blood.

IMPAIRMENT OF INSULIN SECRETION:[16] Impairment in insulin secretion is due to progressive β cell dysfunction with decline in β cell mass. It occurs in four phases and has been described as,

Phase I: In the first phase, there is a rise in the mass of β cell to overcome the resistance to insulin, which ends in hyperinsulinemia.

Phase II: (prediabetic stage). This is the early stage of β cell impairment. Here the β cell response to glucose is affected. But its reaction to other stimulants is normal.

GLYCOSYLATED HEMOGLOBIN



Phase III: In this phase the response of β cells to glucose stimulus as well as to other secretogogues is grossly decreased.

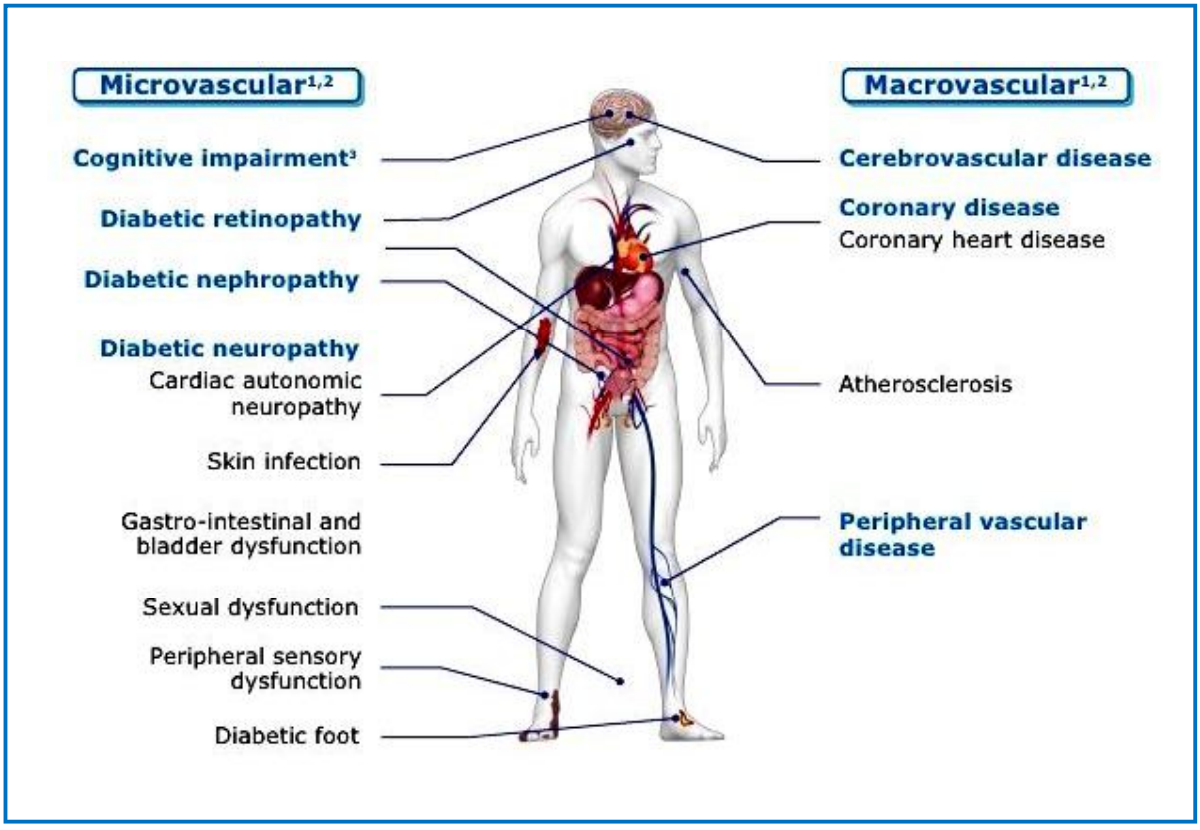
Phase IV: β cell proliferation is absent in this phase. This is due to chronic hyperglycemia which ends in 40-50% reduction in the β cell mass.

GLYCOSYLATED HEMOGLOBIN:[16]

HbA1c is regarded as the best tool in analyzing long term glycemic control in DM. Glycosylation brought about by the binding of glucose with β chain of HbA at its amino terminal valine. This will modify the pattern of movement in cation exchange chromatography. The major glycosylated haemoglobin is the HbA1c . The normal value is 4 - 6%.

Importance of glycemic control: Diabetes mellitus management has mainly focused on the prevention of chronic complications and to control the progression of the disease. UKPDS study documented the connection between good control of DM and prevention of complications in type2 DM. American diabetes association suggested HbA1c <7% as an aim for better control in diabetic subjects.

COMPLICATIONS OF TYPE 2 DIABETES



COMPLICATIONS OF TYPE2 DM[14,18]

Acute complications:

Diabetic ketoacidosis, Hyperglycaemic hyperosmolar state.

Chronic complications:

Microvascular diseases:

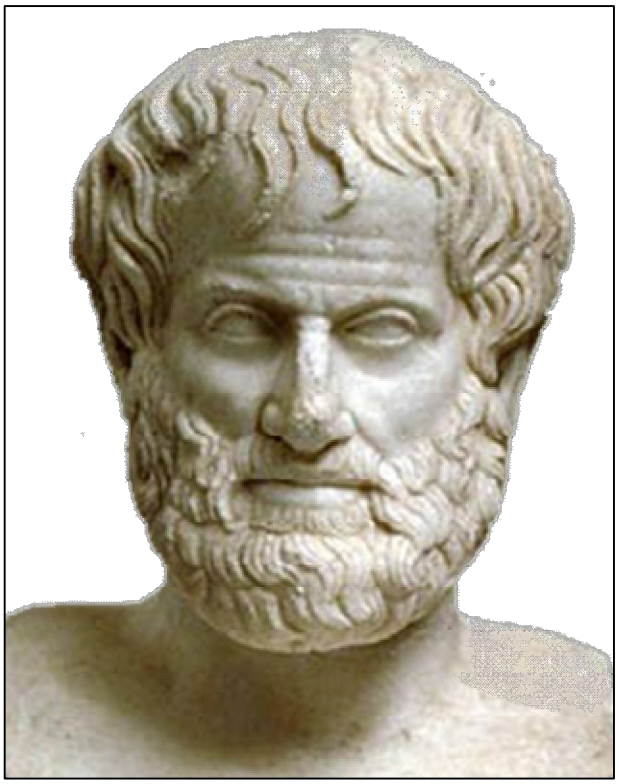
Retinopathy, Neuropathy, Nephropathy

Macrovascular diseases:

Coronary artery disease, Peripheral arterial disease, Cerebrovascular disease.

These complications of Diabetes mellitus on the renal, retinal, peripheral nervous system and cardiovascular system are extensively acknowledged. Diabetes associated complications in the central nervous system are now being widely documented and investigated.[13] Apart from cerebrovascular disease, less addressed and less known complication is the impairment of cognitive function.[5] Cognitive dysfunction is now considered as an emerging complication of type 2 diabetes mellitus.[2]

ARISTOTLE



JEAN PIAGET

COGNITION:

"A man is immortal due to cognition

Knowledge is the root of his immortality"

The word cognition originates from the latin word "cognoscere" which has the meaning as "to become acquainted with or to get to know" and the term refers to the mental processes and abilities that comprises transformation, reduction, elaboration, storage, recovery and usage of the stored information. These processes are concerned in perceiving, remembering, problem solving and thinking. Cognitive processes often use the present knowledge and produce new knowledge.[25]

History of cognition[26]

The word "cognition" came into existence during 15th century when it had the meaning as "awareness and thinking".

Aristotle perhaps the first cognitive scientist who concentrated on areas of cognition related to perception, memory and mental imagery described that processing of cognition starts with sensation of the outside world by the special senses. Each special sense registers sensory information of one kind.

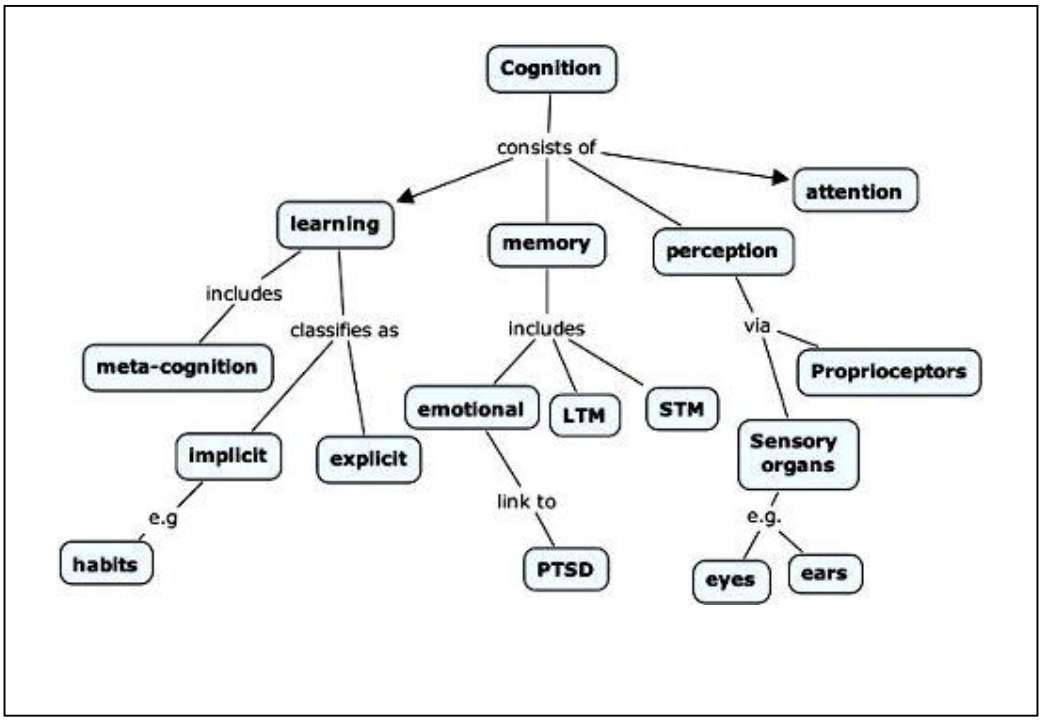
Wilhelm Wundt (1832–1920) greatly stressed the idea of observing the inner state of mind of an individual which he called as introspection.

Herman Ebbinghaus (1850–1909) analyzed the function as well as capability of human memory and established his own research wherein he created more than 2,000 syllables of non- existent words. He also observed his individual skill to study the words created by him and postulated numerous variables which might have affected his capacity to recall the non-words in addition to learning.

Mary Whiton Calkins (1863–1930) experimented her work on the memory capacity of humans. The recency effect - the ability for the people to precisely recall final items given through a series of stimuli can be accredited to her studies.

William James (1842–1910) dissatisfied with previous works of Wundt's and Ebbinghaus, focused on the learning skills of humans in everyday life . James ' significant contribution to cognition was his classic textbook "Principles of Psychology" which featured several elements of cognition like attention, perception, memory, reasoning.

COGNITIVE FUNCTIONS



Jean Piaget one of the influential Psychologist is well known for his work on the cognitive development in children. He concentrated in the unique abilty of the humans to do “abstract symbolic reasoning”. He proposed the Piagets theory explaining the developmental stages of children namely the sensorimotor, pre-operational, concrete operational, formal operational stage.

COGNITIVE FUNCTIONS:[27,28]

Basic cognitive functions	Higher cognitive functions
Attention	Speech and language
Memory	Visuospatial capacities
Perception	Executive functions
Processing speed	

Attention: Fundamental and a compound process of cognition which includes several subprocesses focused on diverse features of attention. These sub-processes are selective attention, divided attention and sustained attention.

Selective attention denotes the ability of an individual to concentrate on certain stimuli whereas removing those not related to work at hand such as while doing tasks of visual search, subjects will be asked to search for a target letter in visual display which is surrounded by other letters.

Divided attention and attention switching is the ability to perform or switch between two works simultaneously. For example, people are requested to do semantic judgements of words given visually wherein at the same time monitor for an auditorily given digit.

Sustained attention denotes the focusing and attention in a work which is relevant over a long period of time. For instance, observing the gas gauge or cookies in the oven.

Memory: It is 2 types – Declarative memory and Non-declarative memory.

Declarative memory is the person's capability to declare the evidence of memory ability. This again includes episodic memory, semantic memory, prospective memory and working memory.

Episodic memory is the capacity to recollect the information of previous events, episodes and experiences. For example, recollecting the details of current conversations.

Semantic memory is the ability to recall the known facts or the names of familiar people.

Prospective memory is the capability to do the planned actions at the suitable moment in future.

Working memory is the short term maintenance and manipulation of information. For instance, maintaining a mental arithmetic.

Non-declarative memory is the undeclared knowledge or the lack of awareness. It includes procedural memory and implicit memory. Procedural memory is the motor memory and implicit memory is the performance affected by the past with consciousness.

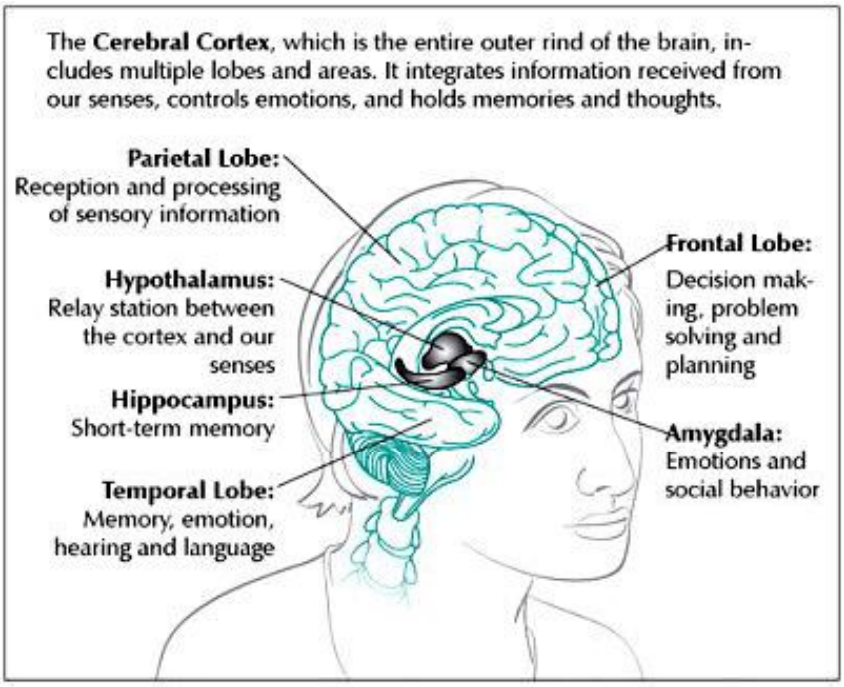
Perception: It is described as the use of earlier knowledge to collect and understand the stimuli which is registered by senses (touch, smell, hearing). It energetically systematizes and infers the sensory information so as to make it meaningful. Visual perception is the commonly studied sensory function.

Processing speed: This includes psychomotor speed which is the physical or the motor response to a stimulus and the information processing which is the dealing of an information to make decisions as quick as possible.

Speech and language: This is the ability to transform the sounds into words and form verbal output. It includes the capacity to write and read.

Visuospatial abilities: It is the skill to analyze and process the incoming visual stimulus and also to recognize the spatial association between objects, to imagine the scenarios and images.

STRUCTURES INVOLVED IN COGNITION



Executive functions: These are the capacities which allow goal-oriented performance such as capability to plan and carry out an aim. These include:

Flexibility – rapidly changing over to the appropriate mental mode

Theory of mind – deep knowledge about other individuals plans, dislikes and likes

Reasoning – higher order approach and theoretical formulation, information strategy and conceptual thinking

Inhibition – interfering or opposing resolution or withholding an unsuitable response

STRUCTURES INVOLVED IN COGNITION:[22]

Frontal lobe: Frontal lobe relates and incorporates all the elements of behaviour at highest level. The frontal lobe lies in front of central sulcus and above the posterior ramus of lateral sulcus. It forms about one-third of cortical surface. On functional basis, it is subdivided into two main areas such as precentral cortex and prefrontal cortex.

Precentral cortex: It refers to the posterior part of frontal lobe and contains primary motor area (area 4), premotor area (area 6, 8, 44, 45) and supplementary motor area. Area 4 is concerned with the initiation of voluntary movements and speech. Area 6 is involved in the co-ordination of the voluntary movements and also believed to be the cortical center for extra-pyramidal system.

Area 8 or frontal eyefield helps in the conjugate movement of eyeballs. Area 44 and 45 is a special region in the premotor cortex situated in the inferior frontal gyrus. This area, especially in the dominant hemisphere is responsible for the movements of the tongue, lips and larynx which are involved in speech.

Prefrontal cortex (PFC): Prefrontal cortex is the anterior part of frontal lobe lying anterior to area 8 and area 44. The major areas here are 9 to 14, 23, 24, 29, 32 and 44 to 47. It has numaerous afferent and efferent connections. The afferents come from dorsomedial nucleus of thalamus, anterior nuclei of thalamus, hypothalamus, corpus striatum, amygdala and midbrain.

Efferent projections go to thalamus, tegmentum, pontine nuclei, caudate nucleus and mamillary bodies. It forms the center for the higher functions like emotions, learning, memory, social behaviour and planned actions and is regarded as the seat of intelligence since short-term memories are registered here. It is also involved in the control of intellectual activities. PFC plays an important role in working memory, with right PFC in visuospatial tasks and left in verbal tasks.

Parietal lobes: This lobe extends from the central sulcus and merges with the occipital lobe behind and temporal lobe below. It has three functional areas - primary sensory area (3,1,2), secondary sensory area and sensory association area (5,7,40). Primary sensory area is concerned with the perception and integration of cutaneous and kinaesthetic sensations and also the discriminative features of sensations such as spatial recognition. Secondary sensory area is also involved in the perception of sensation. Sensory association area helps in differentiating the relative intensity of different stimuli.

Temporal lobes: This lobe lies below the posterior ramus of lateral sulcus. Major areas here are primary auditory area (41,42,) and auditory association area (22,21,20). Primary area deals with the perception of auditory information such as loudness, pitch, source and direction of sound. Wernicke's area (22) is concerned with the interpretation of the auditory information and comprehension of spoken language. Area 21 and 20 also do the same.

Occipital lobe: This lobe lies behind the parieto-occipital sulcus. It contains visual cortex having three areas namely primary visual cortex(area 17), visual association area (area 18) and occipital eye field (area 19). These areas are involved in the processing of the visual sequence such as perception and recognition of the printed words. Discrimination of the colour and movement within the visual fields happens here.

Basal Ganglia: These are scattered masses of grey matter submerged in the subcortical region of the cerebral hemisphere which includes caudate nucleus, putamen, globus pallidus, subthalamic nucleus and substantia nigra. It forms wide interconnections with cerebral cortex and thalamus as well as gets prominent dopaminergic input from midbrain. It is mainly concerned with the integration and regulation of motor activities such as cognitive control of motor activity, timing of the intensity of movements, subconscious execution of movements, control of reflex muscular activity, control of muscle tone and arousal mechanism. Fibers between cerebral cortex and caudate nucleus plays a vital role in cognitive process because of the interrelations of caudate nucleus with orbitofrontal and dorsolateral frontal lobe.

Cerebellum: There are relevant findings supporting that cerebellum has a role in executive task. It is classically needed when a task involves co-ordination and manipulation, or to inhibit habitual responses. Transsynaptic and neuroimaging studies show promising proof that in cerebellar cortex, the posterior and lateral parts connect to dorsolateral prefrontal cortex via the dentate nucleus and the thalamus to bring about executive task. Thus, cerebro – cerebellar complex through this anatomical basis manipulate cognitive activities.

Hippocampus and Amygdala: Hippocampus is formed due to the projection of hippocampal sulcus into the floor of inferior horn of lateral ventricle. It has many indirect connections to cerebral cortex and provides signals for memory consolidation and also behavioural responses. Amygdala is a large aggregate of cells located above the inferior horn of lateral ventricle. The basolateral nuclei of amydala plays an important role in behavioural activities.

COGNITIVE IMPAIRMENT:

Cognitive impairment is the decline in cognitive functions. It occurs gradually in stages starting from normalcy to late dementia. The stages are no cognitive impairment, mild cognitive impairment, cognitive impairment-no dementia, dementia.[29]

Mild cognitive impairment (MCI):[30] MCI is the intermediary phase linking normal as well as pathological aging with cognitive dysfunction. Two common subtypes of MCI are being recognized. One is amnestic MCI and other is non-amnestic form.

Autopsy findings from studies done in MCI:[31]

- Unusual mass of beta-amyloid protein in addition to microscopic protein cluster distinctive of Alzheimer's disease (AD)

- ❖ Lewy bodies related to parkinson's disease and dementia
- ❖ Decreased blood flow throughout the blood vessels of the brain.

Imaging studies of brain in MCI:[31]

- ❖ Shrinkage of hippocampus – part vital for memory
- ❖ Plaques all over the brain
- ❖ Expansion of the ventricles
- ❖ Decreased glucose usage in major brain areas.

Factors for MCI:[31]

The main factors contributing to MCI are,

- ❖ Aging phenomenon
- ❖ Comprising a particular gene called APO-e4
- ❖ Other medical and lifestyle factors,

  Diabetes, Smoking, Depression, Hypertension, Dyslipidemia, Lack of physical exercise, Thyroid disease, Chronic psychological stress, Cerebrovascular disease, Cobalamine deficiency, Cerebral infection

Aging: Aging is a complex and gradual sequence in which tissues, cells and organs and whole organism degenerates in a progressive and irretrievable way which in turn affects the quality of life.

This process largely impacts the brain and causes degeneration of mitochondrial and neuronal membranes, which ultimately leads to the loss of the integrity of cells in addition malfunctioning neuron. The age-associated decrease in the synthesis and signalling of neurotransmitters, along with the decrease in synaptic density and plasticity damages about 50% of myelinated axons length which all ends in less efficient brain with aging.[32]

APO-e4: The relation of APO-e4 with AD is significant. It can help to diagnose AD in symptomatic individuals but have only little role in asymptomatic people.[32]

Insulin resistance: Even small alterations in the metabolism of glucose can have major impact on brain due to the more metabolic demand for brain's energy. It has been associated with decreased levels of growth factors of neurons and reduced volume of brain. Impaired signaling of insulin and resistance to insulin seems to have vital role in AD.[32]

Inflammation: Under normal healthy conditions, blood-brain barrier stops inflammatory agent infiltration and permits only selected nutrients and small molecules into the central nervous system. But when there is chronic systemic inflammation due to obesity, smoking,

disturbed patterns of sleep and bad dietary habits, it compromises the structural integrity of blood-brain barrier. Because of this, the irritants to move into the brain and induces the formation of inflammatory cytokines which includes IL-18, IL-6, IL-1 beta. These cytokines lead to impaired neurogenesis and also destroy the already existing neurons.[32]

Oxidative stress: The brain because of its reduced antioxidant content and increased oxygen consumption is more prone to free radical damage. Mitochondria has major function in the brain metabolism since it provides ATP through oxidative phosphorylation in order to carry out the processes which are energy dependent. Amyloid beta enhances the production of reactive oxygen species.[32]

Hormonal imbalance: Steroid hormone receptors are distributed all over the brain and these receptors are involved in the control of vast genes of cognition. Physiological changes in thyroid gland seems to cause decline of cognitive functions during normal aging. Subclinical thyroid dysfunction is considered as a contributing factor for declining cognitive functions during aging.[32]

Association between these factors and cognitive impairment are being frequently recognized. Among all these, type 2 DM has great influence on the society since it has been regarded as a global pandemic and a serious public health issue. So the query of cognitive impairment in type 2 diabetes is of much importance to meet the day-to-day challenges of the disease and also to understand the medication, treatment, nutrition and to the life as a whole.

COGNITIVE DYSFUNCTION AND TYPE2 DM:

DM causes slow but progressive end organ impairment of brain.[33] Type2 DM is linked to reduced activity on numerous domains of cognitive function such as sluggishness of psychomotor speed, frontal lobe activity, verbal memory, quick recall, delayed recall, fluency, visual preservation plus attention. It is also related to structural, functional and metabolic abnormalities in brain.[34]

Structural changes in brain: Type2 Diabetes mellitus not only causes macroscopic changes but also microscopic changes in the brain.[34] Numerous neuroimaging studies have shown cortical and sub-cortical atrophy and white matter hyperintensities.[13]

Global Brain Atrophy and enlargement of ventricles: Total brain volume reduction as well as cortical/subcortical reduction has been consistently observed in type2 DM as per neuroimaging studies. Enlargement of ventricles is also recognized as an important marker for cerebral atrophy and is seen in type2 DM.[34] It is observed that retinopathy, HbA1c level and duration of diabetes were related with cortical atrophy and glucose toxicity, vascular damage and hyperinsulinemia aggravate the atrophy of the brain.[13]

Regional Atrophy of brain: The most constantly stated regional atrophy of type2 DM is the medial temporal lobe atrophy particularly in the hippocampus. Type2 DM was related to hippocampal and amygdala atrophy as per MRI findings.[35] It is also revealed that obese adolescents with type2 diabetes had reduced volume of brain particularly in frontal lobe. The structural integrity of grey matter and white matter is diffusely decreased.[36]

Type2 diabetic subjects have shown significant grey matter deficits in the prefrontal regions including orbitofrontal and anterior cingulated gyrus. So structural alterations in the PFC has a vital role in cognitive impairment.[34]

White matter hyperintensities (WMH):[37,38] Magnetic Resonance Imaging in type2 diabetic patients have shown leukoaraiosis. White matter changes are related to decreased performance in neurocognitive tests such as attention, information processing in addition to memory. WMH severity is associated with impairment of cognitive functions.

Functional changes in the brain: Structural changes in the brain often alter the functional connectivity within the brain in type2 DM.[13] Hippocampus showed reduced functional connectivity with fusiform gyrus, temporal gyrus, frontal gyrus, anterior cingulate gyrus, posterior cingulate gyrus, medial frontal gyrus and percuneus and inferior parietal lobe.[39] Reduced functional connectivity in brain is seen in type2 DM subjects with microvascular complications on a resting state fMRI.[13] Diabetic retinopathy is considered as an important microvascular complication and also an independent risk factor to cognitive decline of type2 DM. Now it has been described that these microvascular complications might cause progression of functional abnormalities of brain and the cognitive decline seen in type2 DM.[40]

Metabolic changes in the brain: Non-invasive inspection of the brain metabolites is made possible by magnetic resonance spectroscopy (MRS).

MRS is very useful to find out the metabolic changes in type 2 diabetes. There exists some relation between N-acetyl aspartate (NAA) and neuronal damage. Both animal and human studies suggested a reduction in NAA/creatine ratio in diabetes.[34] Depressed acetylcholine formation, reduced serotonin turnover, decreased activity of dopamine and increased nor-epinephrine have been noted in diabetes mellitus.[41]

EFFECT OF COMORBIDITIES OF TYPE2 DIABETES ON COGNITIVE FUNCTION:

Obesity and cognition: Obesity has now become a worldwide epidemic producing intense effects on health. It has been linked to increased heart disease, hypertension, diabetes and stroke. Recent research establishes specific relationship of adiposity to cognitive function.[42]

The pathophysiology of obesity on cognition are not explained well. Studies have shown that,

- Obesity and high intake of fat results in systemic inflammation and increased free fatty acids in the circulation. Obesity related systemic inflammation in turn produces inflammation in brain, mainly in hypothalamus, which is partly accountable for the poor cognitive results.[42]

- Circulating free fatty acids, immune cells, cytokines, on reaching brain causes central inflammation especially in the hypothalamus together with proliferation and activation of microglia.[42]
- The inflammation within the hypothalamus probably is the cause for the synaptic remodelling as well as degeneration of neurons resulting in changes of the internal connections of the hypothalamus and projections to other areas of the brain which are crucial for cognition such as hippocampus, amygdala and reward-processing centers.[42]
- Remodelling of the hypothalamus also produces deregulation of hypothalamo-pituitary-adrenal axis and the consequent formation of increased glucocorticoids. This further causes enhanced formation of glutamate, calcium and reactive oxygen molecules and decrease in neuronal spine density and apotosis of neurons in hippocampus. Also there is direct inflammation of hippocampus and amygdala. Collectively all the above mechanisms produces changes in the connection and signalling of cell, neuro degeneration and atrophy of brain resulting in cognitive impairment.[42]

The treatment of obesity and inflammation in brain such as restriction of calories, physical exercise and bariatric surgery have shown promising evidence in improving cognition. Attention, memory and executive function improved significantly in subjects who underwent bariatric surgery. In an animal experimental model, loss in weight associated with restriction of calories or bypass surgery in gastric region enhanced learning as well as memory.[42]

Hypertension and cognition: Hypertension being a well-known cause for cerebrovascular disorder has subtle influence on brain which is shown by cognitive dysfunction. Hypertension is related with poor presentation on visuospatial skills, learning, attention, executive functions, memory, psychomotor abilities and perceptual skill tests.[6]

Shilpa Gaidhane, assessed the cognitive function in 62 hypertensives , 21 normotensives and 41 prehypertensives. Cognition was evaluated by MMSE. The mean MMSE score as well as the orientation, calculation, attention, immediate recall and language (except registration) was significantly less in hypertensives when compared to normotensives and prehypertensives.[43]

The study done by Li Tuo et al., to find the effects of duration of hypertension on cognitive function inferred that hypertension in long term duration will increase the risk of cognitive dysfunction.[44] Strassburger et al., described that there was a substantial enlargement of the ventricular cerebri, reduction of the left cerebral hemisphere volume, and more risk of cognitive dysfunction in hypertensive patients.[45]

Christiane Reitz et al., observed that mild cognitive dysfunction is associated with hypertension.[46] The effects of blood pressure on cognitive decline in a study of healthy older people by JM Starr et al., concluded that people with high systolic blood pressure are at cognitive decline risk.[47]

The possible mechanisms for cognition impairment in hypertension are,

- Hypertension causes vascular modifications such as arterial stiffness, endothelial dysfunction, atherosclerosis and oxidative stress, which in turn affects cerebral blood flow and cerebral metabolism and thus exacerbate the ischaemia and microcirculatory disturbances which finally end in ischaemic and hypoxic demyelinations.[44]

- Long term hypertension may also cause degeneration, damage and death of oligodendrocytes; disorganization and swelling of astrocytes and microglial activation. Cognitive dysfunctions correlates with the existence of focal ischaemic lesions.[44]
- Arteriosclerosis and lipohyalinosis of small cerebral artery disease causing longstanding white matter ischaemia are the vital factor for the prognosis in stroke development.[48]

Dyslipidemia and cognition: Lipid disorders are allied with greater risk for cardiovascular disease as well as cognitive dysfunction. Dyslipidemia by enhancing atherosclerosis and by increasing the amyloid deposition accelerate the cognitive decline.[6]

Komulainen et al., did a 12-year follow up study with 101 women of 40-60 years. He found that women having low baseline high density lipoprotein cholesterol had more risk of poor memory.[49] Penelope et al., examined the association between total cholesterol and cognition performance in the Framingham Heart Study. They found that lower levels of total cholesterol were related to decrease in the cognitive performance.[50]

Kivipelto et al., found that elevated serum cholesterol in midlife is a vital contributing factor to cognitive impairment.[51] Ingrid Berk-Planken, observed that verbal memory improvement was correlated with improvement of the diabetic dyslipidemia in type2 DM.[52]

STUDIES RELATED TO TYPE2 DM AND COGNITION:

The association of diabetes and cognitive impairment with respect to duration, diabetic control, disease onset age and other complications of diabetes mellitus and the consequence of short term glucose control over cognitive function was observed by Priyam Mukherjee et al., and they found that cognitive decline was present in diabetes and diabetic control leads to improvement of cognitive function.[53]

Penelope et al., did a large prospective cohort study to analyze whether non-insulin dependent diabetes mellitus and blood pressure contributes for the worse cognitive functions and concluded that diabetes and blood pressure are linked with poor cognitive outcome in relation to history as well as duration.[54] Rajesh V, Kannadasan T and Anand Vijayakumar P R, evaluated the relation of age, gender and social habits to cognition in DM patients. They did a randomised prospective study on 500 diabetic patients and found that older patients with diabetes had a declining cognitive function and also women with diabetes had greater decline.[55]

Hiroyuki Umegaki et al., focussed on 63 diabetic patients to find out the risk factors related with decline in cognitive functions. These participants were administered MMSE on baseline, third year and after 6-years follow up and concluded that higher HbA1c levels was correlated with cognitive impairment.[56]

Astrid C.J. Nooyens, assessed the relation between type2 DM and impairment of cognition. Cognitive status was analyzed two times in five year period. The study showed that type2 DM subjects had a greater decline in cognitive performance. At the end of follow-up, impairment of cognition was 2.6 times higher in type2 DM subjects.[57]

The involvement of central nervous system as a likely complication of diabetes was examined by Jayant Dey et al., in 28 younger type2 diabetes (age<55 years) with duration 5-18 years and 28 non diabetic control subjects who were demographically similar. Neuropsychometric tests were performed using MMSE, neurobehavioral cognitive status examination, and P300 latencies. There was no correlation of diabetic duration and HbA1c levels on cognitive function. They concluded that CNS involvement presenting like impairment of cognition must be included as probable complication of chronic type2 DM.[58]

R.K.Solanki, conducted a study to find the relation between diabetes mellitus with cognitive functioning and depressive features in 50 diabetic subjects and 30 control subjects. He found that 48% of elderly diabetic patients had cognitive dysfunction and he concluded that poor metabolic control was associated negatively with cognitive index significantly and also hyperglycemia was negatively and significantly correlated with attention, immediate memory, verbal memory, visuospatial memory and psychomotor functioning. Genesis of diabetic decline is complex and it may be related to longstanding poorly controlled diabetes.[59]

Christopher M. Ryan, did a cross-sectional study and examined the extent to which type2 diabetes affects memory, learning, problem solving and psychomotor speed in 50 middle aged adults in the age group of 34-65 years with type2 DM and 50 controls who were demographically similar. A detailed neuropsycological assessment was done. He found that type2 DM subjects in middle age exhibited sluggishness of psychomotor activity, which was related to bad glycemic control, on the other hand memory, learning and problem solving skills were intact. Psychomotor sluggishness might be due the process of neuropathy of CNS provoked by long standing hyperglycemia.[60]

Marzieh Nazaribadie et al., in his study assessed the attention, memory and visuospatial ability dysfunctions in 32 type2 DM subjects, 28 pre –diabetic subjects and 30 healthy individuals in Endocrine and Metabolism center for a period of three months. They got significant differences in cognitive functions in the study group and they further added that monitoring of neuropsycological status besides glycemic control is important in these patients.[8]

Giancarlo Logroscino, evaluated the relationship of type2 DM on cognition at baseline and after two years follow up in 18,999 women. The study showed that women having type2 DM have more chances of impairment of cogntion.[61] L Kataria, H Pandya, S Shah, R Gerg, investigated the cognitive functions in type2 diabetes subjects. They found that attention, recall, calculation, language, orientation and registration were the affected domains in the study group. The relationship of the duration of the diabetes with cognitive impairment was highly significant.[4]

Carol E. Greenwood, Stacey Hebblethwaite, Randall J. Kaplan and David J.A. Jenkins, focussed in their study to find out whether acute consumption of carbohydrates adds to or aggravates memory dysfunction. They found that fasting HbA1c levels was negatively

related with immediate and delayed paragraph recall performance and higher fasting levels of blood glucose was associated with poor recall of word lists. They concluded that bad glycemic control is linked with poor performance on declarative memory tests and acute intake of more glycemic index foods contributes further to impairment of memory.[62]

A cross sectional study was done by Renata C Alencar et al., to establish the cognitive levels of diabetic patients as well as the factors contributing for the impairment of cognition. They concluded that cognition screening must be done for type2 DM subjects and there is relation between duration and cognition impairment. They also suggested that early implementation of the MMSE can detect the cognitive changes.[12]

The study done by Shuba N, Karan, assessed the cognitive levels of type2 DM and healthy controls by MMSE and 3MS. In addition, the association of age, sex, diabetes duration, glycosylated haemoglobin percentage on cognition in was also examined. They found that diabetics showed lower levels of cognitive performance and also suggested that earlier application of MMSE may find a milder cognitive dysfunction.[63]

The relationship of DM duration and control of blood glucose with mild dysfunction of cognition was investigated by Rosebud O. Roberts et al., and they found an association between of cognitive dysfunction with the age of onset, duration and control of DM.[64] Carla Ruis, MSc et al., analyzed the cognitive function of recent onset type2 DM. Study showed that moderate decrements in cognitive function are present even in the earlier phase of type2 DM and it was also said that a history of macrovascular disease and smoking contribute to early decrements.[65]

Farah Madarshahian, Mohsen Hassanabadi and Mohsen Koshniat Nikoo compared cognitive levels as well as self care of the foot in overweight type2 DM subjects. One group was engaged in regular exercise and the other group did not exercise. The study showed that regular physical activity promoted the cognitive status as well as the self care of the foot in diabetes.[66]

The ability of processing information and cognitive dysfunction was studied by R. Cosway et al., and the results of the study revealed that there was no signtificant difference on any domains of cognition but the duration was associated with poor verbal memory performance.[67]

Rostam Seyfaddini, did a historical cohort study to distinguish the relation of DM and cognitive dysfunction. Mini Mental Status Examination and Wisconsin Card Sort Test were used to estimate cognitive functions. The findings of the study strongly support the association between diabetes mellitus and cognitive decline and cognitive dysfunctions were 8 times more in diabetic group than control group.[68]

Study done by Mirena Valkova et al., confirmed the hypothesis that global cognitive dysfunction is related with diabetic polyneuropathy.[69] Barbera Van Harten et al., estimated the relation of cognitive performance and MRI measures and diabetes associated factors like HbA1c, DM duration and treatment, increased blood pressure and cholesterol as well as polyneuropathy. Study showed that type2 diabetics had impairment of cognition and there was significant association of diabetic duration and HbA1c with the decline in cognition.[70]

Prevalence of type2 DM in urban older adults and the association of diabetes with cognitive impairment was studied by S.C. Tiwari et al., They did this in 900 subjects aged 55 years and above. Among them, 145 subjects had diabetes mellitus and remaining were without

diabetes. It was found that diabetes mellitus was prevalent in 13.7% and 16.9% of urban older adults in those aged 55-59 years. They concluded that subjects with diabetes mellitus have 1.3 times more risk of developing cognitive impairment.[71]

Mohammed Abdul Hannan Hazari et al., assessed the pattern of cognitive impairment in association to the diabetic duration using P300 ERP, three stimuli oddball paradigm. They found that cognitive dysfunction is not related linearly to diabetic duration and the cognitive decline using P300 ERPs was more prominent when the duration of diabetes was more than 5 years.[72]

Chukwuemeka O Eze et al., determined the prevalence of cognitive impairment in a cross-sectional, descriptive, hospital based study for a period of three months. Cognitive function was assessed by MMSE. About 40% (180) of the type 2 diabetic subjects had cognitive impairment and also advanced age, low education, presence of diabetic complications was identified as risk factors for cognitive dysfunction.[73]

The relation of cognition and glycemic status was explored by Jane S. Saczynski et al., in AGES-Reykjavik study. They also analysed the association of HbA1c level, diabetic duration, and medication use on

cognitive performance. They found that type2 DM subjects had poor cognitive performance than normoglycemics and the subjects with undiagnosed diabetes had more decline in cognitive performance.[74]

Musleh Uddin Kalar et al., examined the cognitive status of type2 DM in 200 subjects diagnosed after 30 years of age using MMSE. The difference in cognitive impairment between four parameters of cognition was statistically significant. They observed lower cognition in type2 diabetes.[75]

Oguz Tekin et al., evaluated the impairment in cognitive functions in type2 DM subjects and also examined the association of the duration of the disease, long-term complications and glycemic control on cognitive functions. The study showed that type2 DM destroys cognitive function. Duration of disease, high HbA1c levels, retinopathy, and hypertension are important risk factors additionally. So they concluded that cognition assessment should be become as a routine process in managing type2 diabetes mellitus.[76]

Linda B. Hassing et al., studied the comorbid effects of type2 DM and hypertension on cognitive dysfunction. Cognitive status was assessed using MMSE and they concluded that comorbid effects of diabetes and hypertension accelerated cognitive decline.[77]

David G. Bruce, determined the longitudinal interpreters of cognitive impairment in diabetics. Cognitive decline predictors are age, schooling, relative amount of albumin-creatinine in urine. They found that microalbuminuria was considered as a risk factor for decline in cognitive function.[78]

Hence, this study has been intended to evaluate cognitive levels of type2 diabetics and also to analyze association of age, sex, duration of type2 DM and glycosylated haemoglobin levels with cognitive functions so that diabetic patients can lead an independent and competent life.

MATERIALS & METHODS

MATERIALS AND METHODOLOGY

STUDY DESIGN: Cross-sectional study.

STUDY PLACE: The study was carried out in the department of Physiology, in association with department of Diabetology and Biochemistry, Coimbatore Medical College & Hospital, Coimbatore.

STUDY PERIOD: The study was conducted from July 2014 to June 2015.

STUDY SUBJECTS:

Inclusion criteria: 100 type 2 DM subjects of both sexes between 40-60 years age group and a total of 100 apparently healthy individuals taken as control group who were age, sex, BMI (body mass index) & education matched.

Exclusion criteria:

1. Patients with history of,

- Type1 DM
- Hypertension
- Dyslipidemia
- Smoking
- Obesity

- h/o taking CNS medications
- h/o active treatment for cancer in the previous 2 years
- h/o Cerebrovascular disease / Cardiovascular disease
- known case of dementia / psychiatric disease
- clinically hypothyroid / hyperthyroid
- h/o difficulty in doing daily activites
- h/o sleep deprivation

2. Illiterates
3. Deafness
4. Blindness
5. Known alcoholics

MATERIALS USED FOR THE STUDY:

1. **Proforma** : To obtain the detailed history and to record the vital parameters
2. **Portable weighing machine**: To record the body weight in kilograms
3. **Stadiometer**: To measure the standing height in centimeters
4. **Standardized Mercury Sphygmomanometer**: To record the Blood pressure
5. **Quantimate Turbidimetry Analyser**: To measure plasma glycosylated haemoglobin (HbA1c)
6. **Auto Analyser**: To measure the Random blood sugar

7. **Mini Mental Status Examination Questionnaire**: To evaluate the cognitive level of the study participants.

METHODOLOGY:

After obtaining clearance from the institutional ethical committee, the subjects were selected and grouped. The procedure was described in detail to the subjects and informed consent was obtained.

The Study Protocol Consists Of,

History taking and Clinical Examination: Detailed history was taken from the subjects to rule out signs and symptoms of hypertension, cardiovascular diseases and psychiatric diseases. A thorough clinical examination was done.

Measurement of Anthropometric Indices:

Weight of subject: The Subjects were instructed to wear light clothing and to stand erect with their arms relaxed at their side, with both feet close together. By using a portable standard weighing machine, weight in kilograms was recorded. Weight measured to nearest 0.5 kg.

Height of subject: By using a stadiometer, height of subject in centimetres was measured by asking the subject to stand erect and the vertical height was measured. Height measured to nearest 0.5cm.

BMI: BMI determined through Quetelet's Index.

BMI = Weight (Kg) / Height (m^2).

TURBIDIMETRY

HbA1C KIT

Measurement Of Blood Pressure:

First, the subjects were asked to sit and relax for 15 minutes in a quiet room with comfortable room temperature. Then blood pressure was recorded in all subjects by using a standard sphygmomanometer having a cuff size of 25 x 12.5cms.

Blood Investigation:

Median cubital vein was selected for venous blood collection. After cleaning with spirit and cotton swab, a disposable sterile needle fitted with 5 ml syringe was introduced into the vein and 4ml of blood was collected and poured into separate containers having different anticoagulants.

METHODS OF MEASUREMENT:

Turbidimetric Immunoassay:

- **For measuring HbA1c**

Reagents used:

R1 - latex particles

R2 - mouse antiHbA1c antibody solution

R3 - Goat antimouse human IgG antibody solution

Quantia hemolysing reagent solution.

ASSESSMENT OF COGNITIVE STATUS BY MMSE

BLOOD INVESTIGATION

Principle: Immunoassay method is based on agglutination reaction. After adding hemolysing solution, test sample is allowed to react with latex Reagent (R1). The amount of binding depends on relative concentration of HbA1c in the blood. Then the mixure is allowed to react with mouse antiHbA1c antibody reagent (R2), wherein R2 bind to latex bound HbA1c molecules. Goat antimouse human IgG antibody (R3) binds with HbA1c-R2 complex by agglutination reaction and it should be measured at 630nm. Change in turbidity of sample depends on concentration of HbA1c in the sample.[79]

GLUCOSE OXIDASE – PEROXIDASE METHOD:

- **For measuring Random blood sugar**

Principle:

Glucose present in the test sample was oxidised forming gluconic acid as well as hydrogen peroxide through glucose oxidase enzyme. Then enzyme peroxidise promotes the reaction between 4-aminoantipyrine and phenol to yield quinoneimine dye complex. Absorbance was read and which was correspond to the glucose concentration in the test sample.[80]

5. Cognition Assessment:

Cognitive status of the study subjects determined using Mini Mental Status Examination questionnaire.

Folstein, McHugh, Fanjiang suggested the following cut-off scores for the classification of cognitive impairment. The MMSE scores of ≥27 revealed a normal cognition, those of 21-26 revealed a mild cognitive impairment, those of 11-20 revealed a moderate cognitive impairment and those of ≤10 revealed a severe cognitive impairment. These cut-off scores were used to grade the level of cognition.[63]

The criteria which was created by Crum et al., was used for comparing the subjects MMSE scores with a reference group based on their educational levels and ages. Subjects in this study were within 40-60 years of age and had college level education. The normal cut-off for the subjects with college level education in this age group was 29 points. A score less than this was taken as impaired cognition. The MMSE scores were corrected according to this.[11]

STATISTICAL ANALYSIS

STATISTICAL ANALYSIS

The data obtained from all the chosen subjects were noted in Master Chart. Analysis was done in computer using **Epidemiological Information Package (EPI 2010)** devised by Centre for Disease Control, Atlanta.

Using this, range, frequencies, percentages, mean, standard deviation, chi-square and 'p' values were estimated. Student's 't' test was employed to find significant difference between quantitative variables (age, height, weight, BMI, MMSE scores) and Fisher's chi-square test for qualitative variables (sex). 'p' value < 0.05 denoted significant association. Correlation coefficient was calculated using Excel software. A value greater than $\pm$ 0.5 is taken to indicate the existence of correlation between the variables.

RESULTS

RESULTS

GROUPING OF SUBJECTS:

Group I - **100** type2 DM subjects

Group I A - **48** type2 DM subjects having HbA1c $\leq 7\%$

Group I A1 - DM with duration below 5 years

Group I A2 - DM with duration above 5 years

Group I B - **52** type2 DM subjects having HbA1c > 7%

Group I B1 - DM with duration below 5 years

Group I B2 - DM with duration above 5 years

Group II - **100** age, sex & BMI matched healthy individuals as controls.

Table 1: Age Distribution

Age Group	Group I		Group II	
	n	%	n	%
41 – 45 yrs	32	32	35	35
46 – 50 yrs	38	38	36	36
51 – 55 yrs	30	30	29	29
>55 yrs	-	-	-	-
Total	100	100	100	100
Age (years)				
Range	41 – 55 yrs		41 – 55 yrs	
Mean	48.1		47.7 yrs	
SD	4.0		4.0	
'p'	0.5129 Not significant			

Age wise distribution is same in both the study and the control group. The mean age in group I and group II was 48.1 years and 47.7 years respectively.

Figure 1: Age Distribution In Group I And Group II

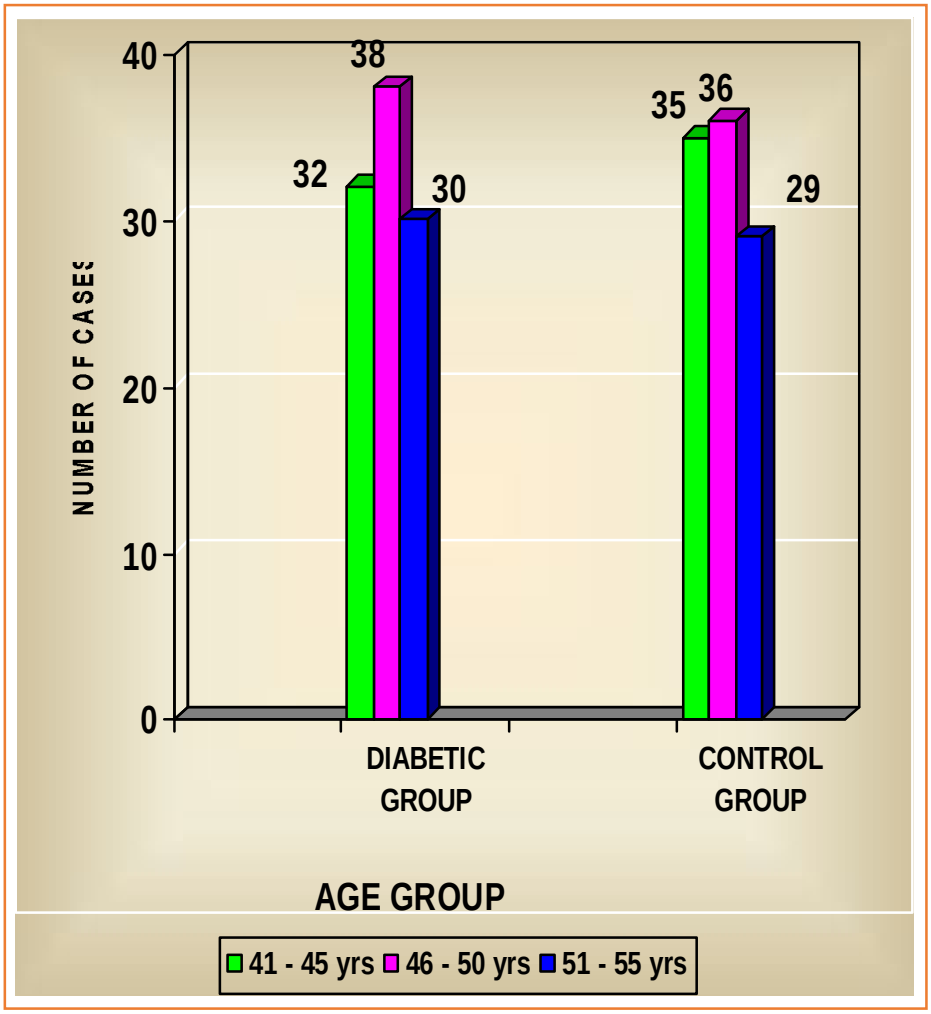


Table 2: Gender Distribution

Sex	Group I		Group II	
	n	%	n	%
Male	54	54	51	51
Female	46	46	49	49
Total	100	100	100	100
'p'	0.777 Not Significant			

Gender wise distribution is same in both the study and the control group.

Figure 2:

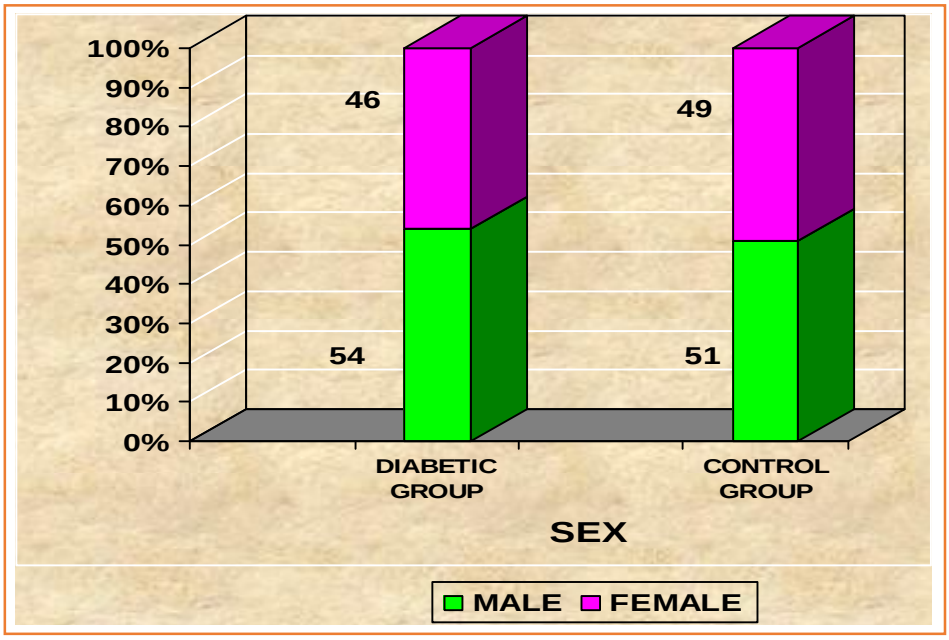


Table 3: Comparision of Height, Weight and BMI Between Group I and Group II

	Group I		Group II		'p'
	Mean	SD	Mean	SD	
Weight (kgs)	62.6	5.9	61.7	5.9	0.2681 Not Significant
Height (cms)	159.8	7.5	157.1	7.0	0.0868 Not significant
BMI	24.64	1.38	25.13	1.9	0.1675 Not Significant

There is no statistical difference in Height, Weight and BMI between group I and group II.

Figure 3:

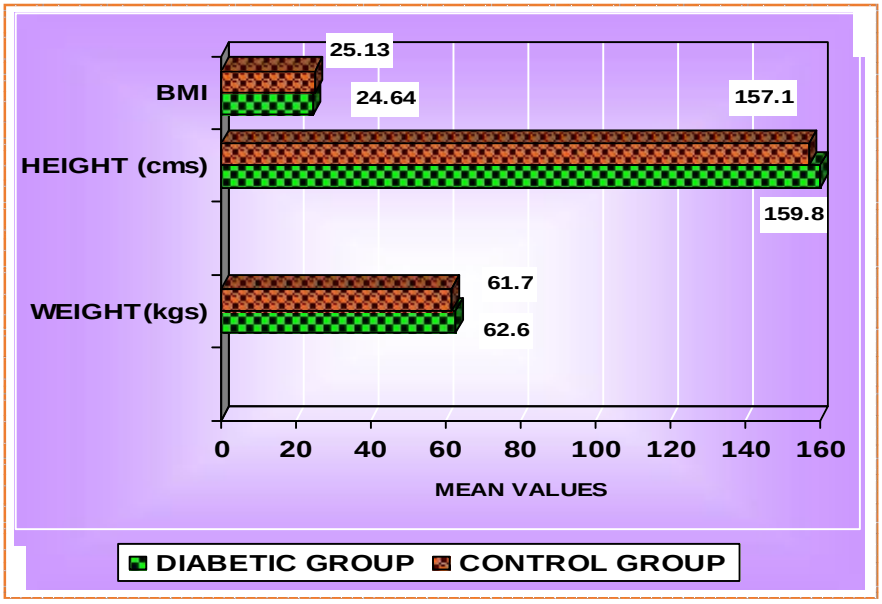


Table 4: Distribution of Type 2 diabetic subjects according to HbA1c levels.

HbA1c	Type 2 Diabetes Group	
	n	%
Good glycemic control (≤7)	48	48
Poor glycemic control (>7)	52	52
Total	100	100
HbA1c		
Mean	8.36	
SD	2.33	

There is equal distribution of cases in type 2 DM subjects having good glycemic control and poor glycemic control.

Figure 4:

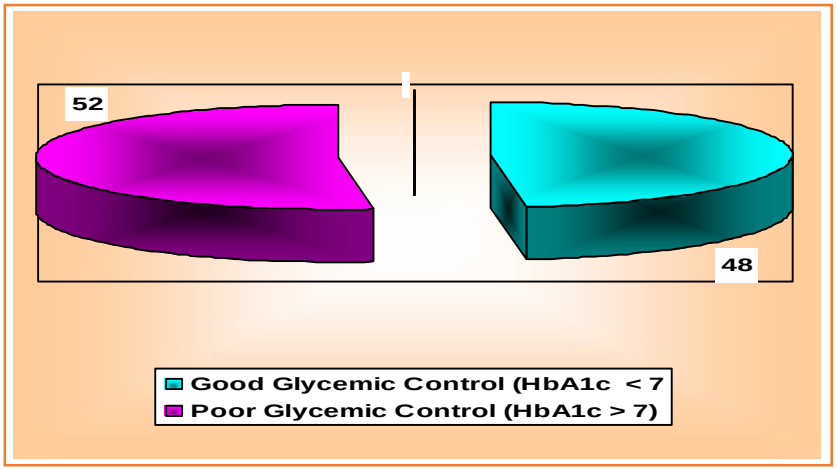


Table 5: Distribution of Type 2 DM subjects according to diabetic duration.

Duration of diabetes	type 2 Diabetes group	
	n	%
≤ 5 years	54	54
➢ 5 years	46	46
Total	100	100

There is equal distribution of type 2 diabetic subjects with diabetic duration below 5 years and more than 5 years.

Figure 5:

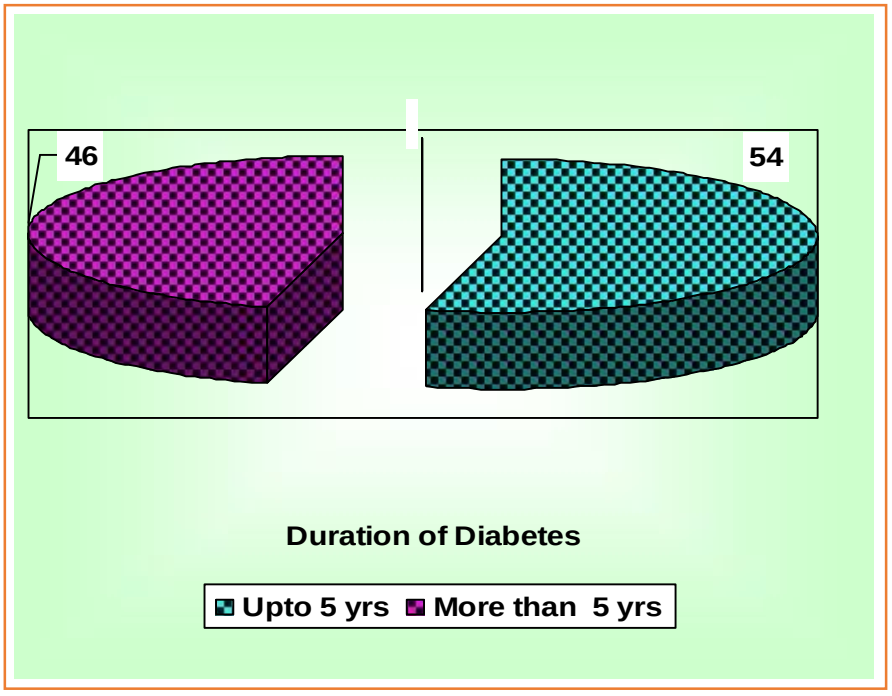


Table 6: Distribution of subjects according to MMSE grades.

Grade of MMSE	Group I		Group II	
Normal Cognition (≥ 27)	-	-	100	100
Mild cognitive impairment (21 – 26)	93	93	-	-
Moderate cognitive impairment (11-20)	7	7	-	-
Serve cognitive impairment (≤ 10)	-	-	-	-
Total	**100**	**100**	**100**	**100**

About 93% of them had mild cognitive impairment and 7% of them had moderate cognitive impairment in group I.

Figure 6:

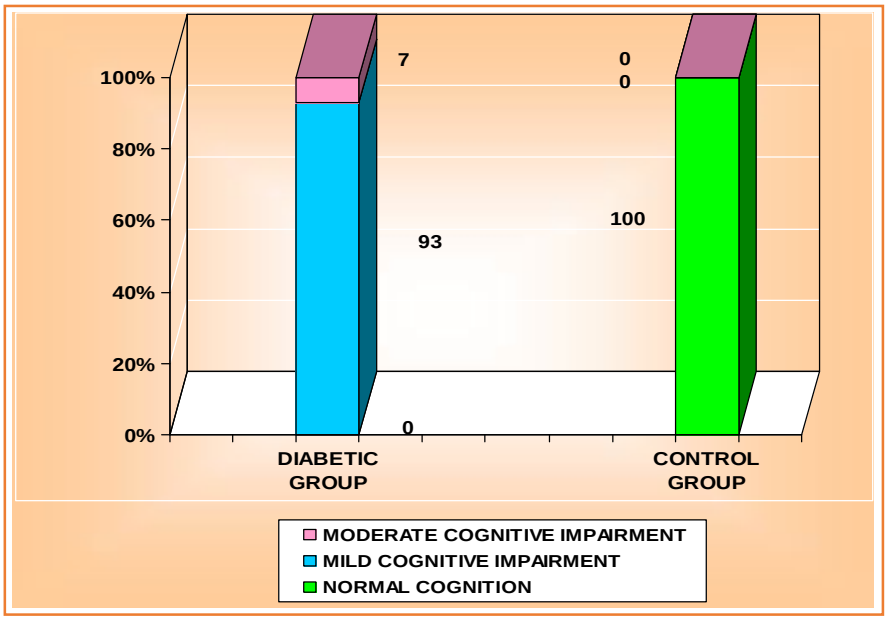


Table 7: Comparison of the mean MMSE score with HbA1c levels in Group IA And Group IB.

HbA1c %	MMSE Score	
	Mean	**SD**
Good Glycemic Control (HbA1c ≤ 7) - IA	24.2	0.9
Poor Glycemic Control (HbA1c > 7) - IB	21.96	1.07
'p'	**< 0.0001 Significant**	

Significant difference in mean MMSE score was present in type 2 subjects with good control (IA) and poor control (IB) of diabetes.

Figure 7:

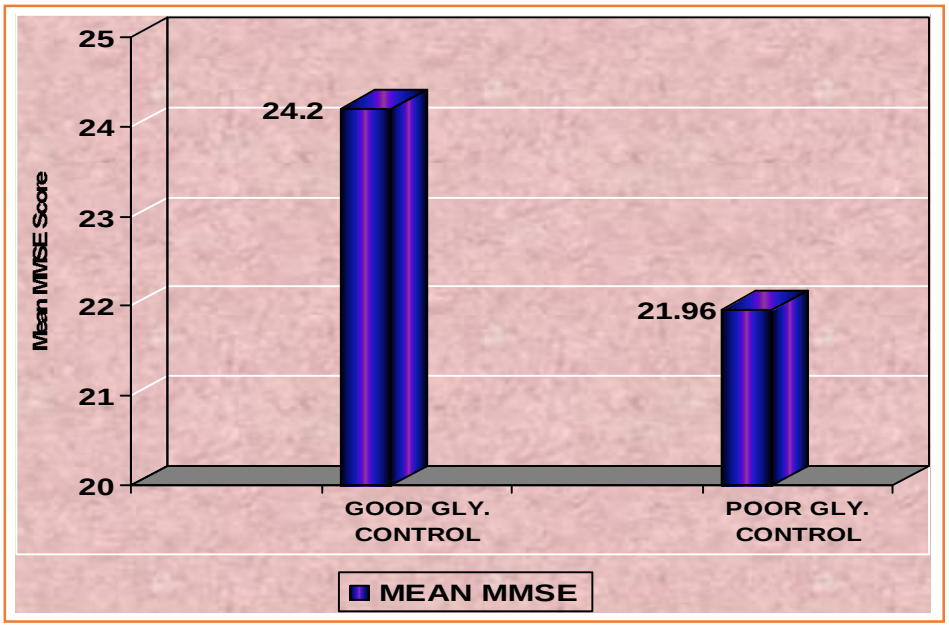


Table 8: Comparison of the mean MMSE scores with the duration of diabetes.

Duration of diabetes	MMSE score	
	Mean	SD
≤ 5 yrs	23.46	1.55
➢ 5 yrs	22.54	1.28
'p'	**0.0018 Significant**	

Statistically significant difference in mean MMSE score was present between type2 diabetic subjects with duration less than 5 years and duration more than 5 years.

Figure 8:

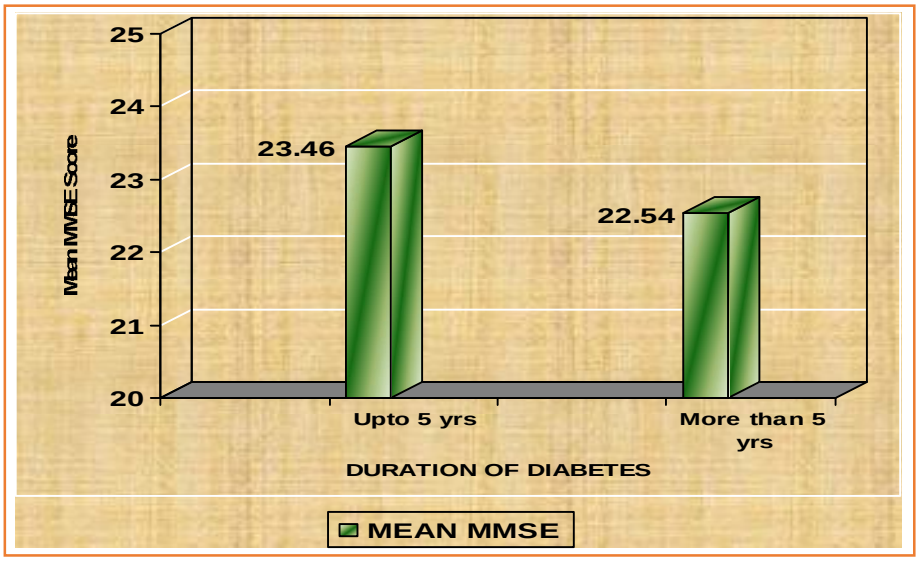


Table 9: Comparison of the Age and mean MMSE Score In Type 2 Diabetic Subjects

Age Group	MMSE score	
	Mean	SD
41 – 45 yrs	23.25	1.59
46 – 50 yrs	22.95	1.49
51 – 55 yrs	22.93	1.44
'p'	**0.6334 Not Significant**	

Comparison of the mean MMSE score in different age groups of type 2 diabetic subjects was not statistically significant.

Figure 9:

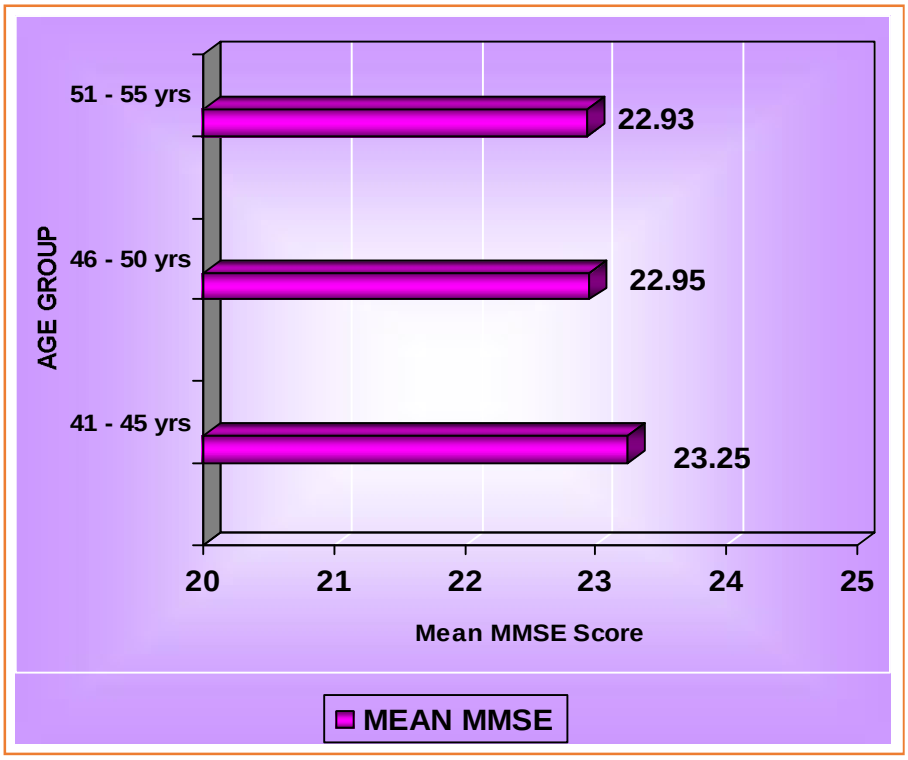


Table 10: Comparison of Sex and the mean MMSE Score in Type 2 Diabetic Subjects.

Sex	MMSE score	
	Mean	SD
Male	23.04	1.38
Female	23.04	1.6
'p'	**0.983 Not Significant**	

Comparison of mean MMSE score between males and females in type 2 diabetic subjects was not statistically significant.

Figure 10:

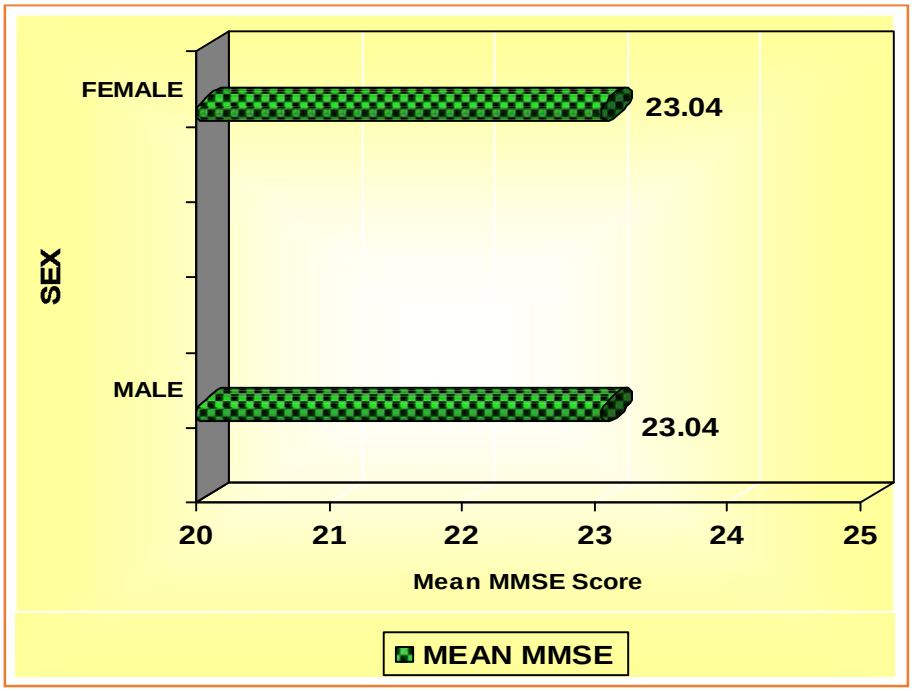


Table 11: Comparison of the Various Cognitive Domains of MMSE.

Cognitive Domains	GROUP I		GROUP II		'p'
	Mean	SD	Mean	SD	
Orientation (10)	7.71	0.77	9.7	0.46	**<0.0001 Significant**
Registration (3)	2.41	0.49	2.9	0.3	**<0.0001 significant**
Attention & Calculation (5)	3.62	0.53	4.72	0.45	**<0.0001 significant**
Recall (3)	2.2	0.47	2.9	0.3	**<0.0001 significant**
Language & visual construction (9)	7.03	0.82	8.72	0.47	**<0.0001 significant**
Total points (30)	23.04	1.5	29.01	0.82	**<0.0001 significant**

Comparison of the mean scores of various cognitive domains in group I and group II was significant.

Figure 11: Comparison of the Various Cognitive Domains of MMSE.

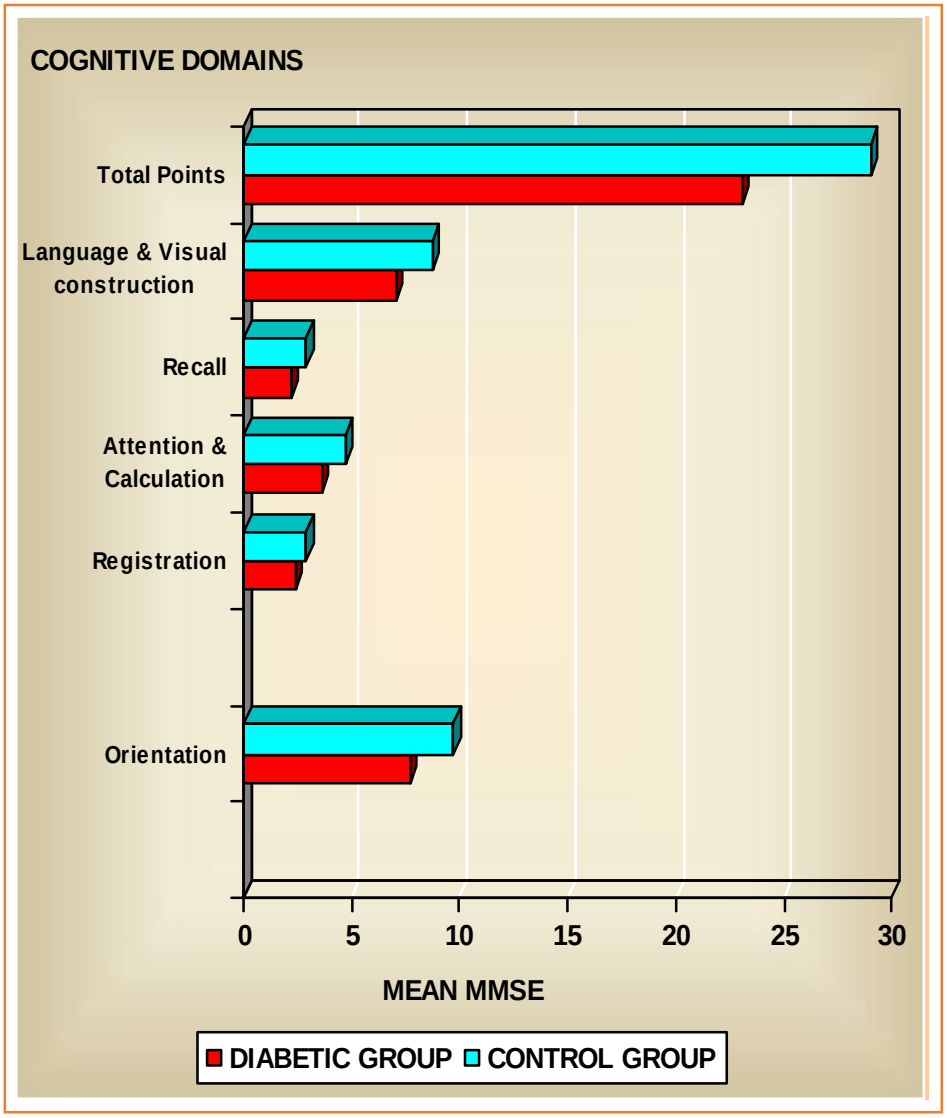


Table 12: Comparison of the mean MMSE scores within the groups.

Category	MMSE		'p'
	Mean	**S.D.**	
Group I (Type 2 DM cases)	23.04	1.5	**< 0.0001 Significant**
Group II (Controls)	29.01	0.51	
Group IA1 (DM with HbA1c ≤ 7 and <5 yrs duration)	24.81	0.69	**< 0.0001 Significant**
Group IA2 (DM with HbA1c ≤ 7 and > 5 yrs duration)	23.5	0.51	
Group IB1 (DM with HbA1c > 7 and ≤5 yrs duration)	22.21	0.96	0.0641 Not significant
Group IB2 (DM with HbA1c > 7 and > 5 yrs duration)	21.67	1.13	
Group IA1 +IB1(DM with ≤ 5 yrs duration)	23.46	1.55	**0.0018 Significant**
Group IA2 +IB2(DM with > 5 yrs duration)	22.54	1.28	
Group IA (DM with good glycemic control (HbA1c ≤ 7)	24.21	0.9	**< 0.0001 Significant**
Group II (Controls)	29.01	0.82	
Group IB (DM with poor glycemic control(HbA1c > 7)	21.96	1.07	**< 0.0001 Significant**
Group II (Controls)	29.01	0.82	
Group IA DM with (HbA1c ≤ 7)	24.21	0.9	**< 0.0001 Significant**
Group IB DM with (HbA1c > 7)	21.96	1.07	

Figure 12: Comparison of the mean MMSE scores within the groups.

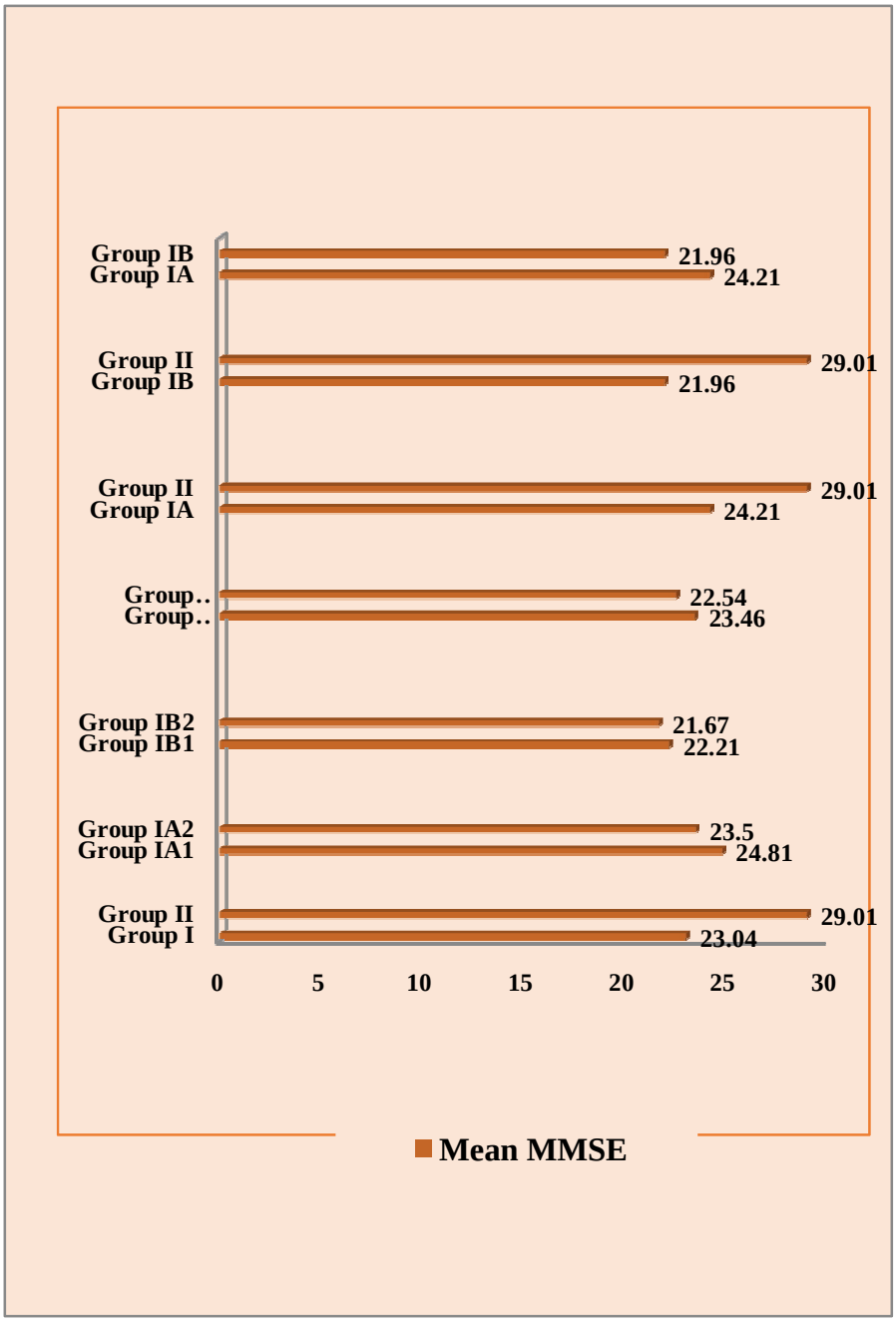
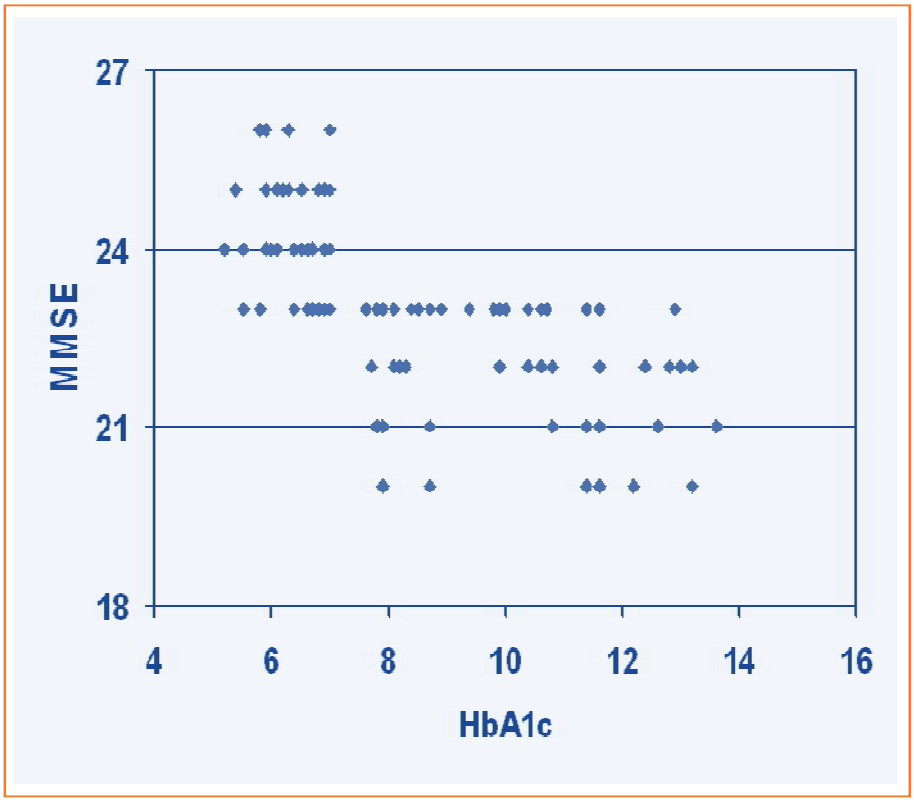


Figure 13:

Correlation Coefficient between MMSE score and HbA1c.



Significant negative correlation between MMSE score and HbA1c levels (r = - 0.6988).

DISCUSSION

DISCUSSION

Diabetes is regarded as an epidemic disease with 382 million diabetics throughout the world.[1] It is a chronic disease which ends in long term complications. Cognitive dysfunction is also considered as an important chronic complication.[58] Even though advancement is being made, cognitive dysfunction is still a neglected field in diabetes. A conserved cognitive status is vital for the awareness of the disease and its compliance.[4]

In the present study, 100 type2 diabetic subjects were taken as the study group and 100 age, sex, BMI and education matched healthy individuals were taken as the control group. The cognitive status of the type2 DM subjects and healthy controls without diabetes was evaluated through MMSE. About 93% had mild cognitive impairment and 7% had moderate cognitive impairment in the study group and 77% had normal cognition and 23% had mild cognitive impairment in the control group after making correction for age and educational qualification. There was a significant decrease in MMSE score among the diabetics ($p<0.0001$).The mean MMSE score was 23.04 ± 1.5 in study subjects whereas in control subjects it was 29.01 ± 0.51.

These findings in the current study show the presence of cognitive dysfunction in type2 diabetes subjects. This is similar to various studies which also specified an impairment in cognitive functions in type2 diabetics.

Shuba N & Karan assessed the cognitive status of type2 diabetics through MMSE and compared the mean MMSE scores with non-diabetics. They found that type2 DM is related to cognitive dysfunction.[63] Another study done by Rostam Seyfaddini, strongly supported the relation of type2 DM and cognitive dysfunction and they described that impairment in cognition was 8 times more in diabetic group compared to control group.[68] Musleh Uddin Kalar et al., also observed the same.[75] Oguz Tekin et al., described that type2 diabetes destroys cognitive function.[76]

Jayant Dey et al., in his study found that cognitive dysfunction should be considered as a possible long term definite complication of type2 diabetes.[58] L Kataria, H Pandya, S Shah, H Shah, R Gerg identified high frequency of cognitive decline in several domains of cognitive function in type2 DM subjects.[4] Priyam Mukherjee et al., also described that impairment in cognition is related with type2 DM.[53]

Jane S Saczynski et al., found in his study that cognitive dysfunction is seen in both diagnosed as well as undiagnosed type2 DM.[74] Francine Grodstein, Robert S. Wilson, Jennifer Chen, JoAnn E. Manson, in their study evaluated the association of type2 DM and cognition among women and observed that type2 DM is linked to decreased scores on various aspects of cognitive domains.[81]

The presence of impaired beta cell with or without resistance to insulin ends in persistent hyperglycemia in type2 DM which has intense impact on almost all organs including brain and thus cognition.[82] Numerous mechanisms might elucidate the association between type2 DM and cognition. They include, hyperglycemia, insulin and insulin resistance.[10]

Even though glucose is the major energy source for the brain, long term hyperglycemia has deleterious effects on the brain. Human brain which constitutes about 2% body weight uses about 25% blood glucose. Apart from providing energy, it also gives vital substances for neurons which includes glutamate and acetylcholine. Thus hyperglycemia is considered as one of the factors which leads to impairment of cognition.[41]

Both chronic and acute hyperglycemia can lead to cognitive decline in DM. Elevated blood glucose levels can induce end organ injury by the formation of reactive oxygen molecules, particularly superoxide which alters functions via a number of ways such as polyol pathway stimulation, enhanced production of AGEs, protein kinase C induction through diacylglycerol as well as more glucose shunt via hexosamine pathway. Similar mechanisms operating within brain induce impairment of cognitive function seen in type2 DM subjects.[10]

The effect of hyperglycemia causing damage to the nervous tissues, can be through polyol pathway which is evident by increase in sorbitol concentration in cranial nerves, cerebral cortex, sciatic nerve, and retina in streptozotocin treated rats.[10,5]

Increased expression of AGEs receptors in neurons, glial cells and also destruction of myelin and white matter suggesting a probable role of AGEs receptors in the impairment of cerebral functions was shown in diabetic mice experiments.[10,5] Significant increase in protein kinase C-α in brain in untreated diabetic rat indicate the role of diacylglycerol and enhanced glucose shunting to decline of cognition.[10]

Neurogenesis in the hippocampus plays a vital role in memory and learning. Animal experiments have shown that a hyperglycemic environment stimulates the proliferation of adult neural progenitors, wherein it is detrimental to their survival. Cognitive dysfunction and brain atrophy in type2 DM seems to be due to impaired neurogenesis.[83]

Long term hyperglycemia increases the chance of cerebral micro vascular as well as macro vascular disorders. These vascular disorders have long been suggested to cause cognitive abnormalities.[10] It has been considered to be a critical contributing factor to the structural and functional changes seen in brain of diabetic patients.[13] Retinopathy is a well known micro vascular complication of type2 diabetes. Cerebral and retinal arterioles have similar morphologic and physiologic properties, so retinal micro vascular injury is considered to be a marker of cerebral micro vascular disease.[40]

DM is also linked with hypercoagulability. This is due to the increased concentration of procoagulant factors and anti-fibrinolytic factors and also nitric oxide metabolism alteration. These factors ultimately end in thrombotic vascular events. Diabetic subjects have a two to six fold more chances of thrombotic stroke.[41]

Basement membrane thickening of capillaries, a characteristic feature in diabetic microangiopathy, is found within the brain of type2 DM subjects.[84] The combination of hyperglycemia and ischaemia may be more damaging to the brain. Lactate and glutamate accumulation are the two possible mechanisms of the relation between hyperglycemia and ischaemia. Hyperglycemia gives increased substrate for lactate formation which worsens the acidosis within cells and the glutamate accumulation causes extensive neuronal damage.[85]

Damage to neurons and vascular endothelium also occurs due to the high osmotic stress caused by hyperglycemia which in turn disrupts the blood brain barrier leading to the leakage of vascular substances which further enhances neuronal damage.[86]

Cognitive dysfunction is not only related to hyperglycemia, but also with insulin action. Insulin is regarded as the vital hormone in neuron nourishment. It moves into the brain through the blood brain barrier and binds with the receptors for insulin in the brain. These receptors are present in wide areas of the brain, particularly in higher concentrations in hypothalamus, cerebral cortex and cerebellum, hippocampus and prefrontal regions concerned with cognition.[87]

Insulin impacts the release as well as reuptake of neurotransmitters such as acetylcholine and nor-epinephrine which seems to improve memory as well as learning. Insulin also triggers signal transduction which leads to changes of gene expression involved in long-term memory consolidation. Impaired secretion of insulin end in deregulation of glucose in brain particularly in areas of memory and learning.[88] Insulin may also be related to hypercortisolemia which is connected to the decline of cognition.[89]

Insulin resistance and increased insulin levels also can influence cognition. There is enhanced formation of AGEs in these conditions which might cause aggravation of the oxidative stress in the CNS which in turn can impair cognition.[90] Impairment of long term potentiation, a basic process in consolidation of memory can also be due to insulin resistance.[41] Signalling of insulin may have a part to play in synaptic plasticity by modifying the activities of glutamate and GABA receptors. In resistance of insulin, there might be alteration in the signaling of insulin receptor in brain which can lead to cerebral insulin resistance and consequent down regulation of the pathway regulated by insulin crucial to cognition.[91]

In the current study, correlation of various parameters such as age, sex, diabetic duration and glycosylated hemoglobin with mean MMSE score was also done. It was found that diabetic duration and glycosylated hemoglobin levels considerably correlated with cognitive decline wherein age and sex were not significantly related.

Mean MMSE score and Age:

Most of the studies done on type 2 diabetes subjects showing impaired cognitive function have incorporated older subjects (above the age of 60 years).[58] It has been postulated that age-related cognitive dysfunction is mostly observed after the age of 65 years and its prevalence seems to be 10-20%.[92]

Thus cognitive decline can be expected after 60 years of age as a part of normal aging even without type2 diabetes mellitus.[92] This has numerous explanations. First, increasing age is an independent risk factor to cognitive dysfunction. Aging characteristically causes deposition of senile plaques which produces neuronal death by apoptosis. This furthur induces the atrophy of cerebral cortex and the consequent impairment of cognition. Second, aging is also associated with other factors of cognitive dysfunction such as stroke, dyslipidemia, hypertension and cardiac diseases.[73]

Most of the type2 DM subjects are between 40-59 years.[92] Taking aware of this fact, patients between the age of 40-60 years were used in this study to reduce the impact of aging on cognitive function.

In the present study, the mean MMSE score of 41-45 years age group was 23.25±1.59 whereas in 46-50 years age group was 22.95±1.49 and for those between 51-55 years was 22.93±1.44. Cognitive decline is seen in all the three age groups, but the comparison of the mean MMSE scores between the groups was not significant. This suggests that type2 diabetes might be a vital contributing factor to the progression of cognitive decline compared to aging.

Rosebud O. Roberts et al., suggested that diabetes onset before 65 years independently linked to mild cognitive impairment.[64] Satyajeet Roy et al., assessed the cognitive function in type2 DM subjects of 60years otherwise even younger and found that cognitive decline affects one-fifth of the subjects in this age group and is related to glycemic control as well as the duration of type2 diabetes.[92]

Astrid C.J.Nooyens et al., in their study revealed that middle age type2 DM had more cognition impairment than those subjects without diabetes of same age group.[57] L. Kataria et al., did their study in type2 diabetics having mean age of 54.16±11.41 years. They reported that cognitive decrement is seen in all the age groups in their study but it was not statistically significant.[4]

Rajesh V, Kannadasan T, Anand Vijayakumar analyzed the cognitive status in type2 DM subjects between different age groups. They found significant variation in mean MMSE scores between age groups but patient above 60 years exhibited more decline.[55] S.C. Tiwari et al., in their study reported that type2 DM is a risk factor for impairment in cognitive functions irrespective of the cut-off age of either 60 years or 55 years.[71]

Christopher M Ryan, Michelle O Geckle described that middle aged type2 diabetic subjects (mean age 50.8 years) with poor metabolic control exhibited psychomotor slowing.[60] Anna Janocha et al., evaluated the cognitive skills particularly sensorimotor function in type2 DM having recognized depression in 37 to 52 years age group. They described that poor control of diabetes, depression as well as mean diabetes duration might cause mutual interactions ending in premature cognitive dysfunction.[93]

Jie Ding et al., explained that cerebral micro vascular disease may accelerate the age-linked decline of cognitive functions observed in diabetic people.[40]

Mean MMSE score and Gender:

The mean MMSE scores in males and females in type2 diabetic subjects showed no significant difference in this study. Both the sexes had similar scores which depicted a decline in cognition. Similar to that, study done by Priyam Mukherjee et al., concluded that cognitive dysfunction is related with diabetes and no significant relationship of sex of patients with cognitive decline.[53] Ruis et al., also confirmed the same.[65] Study done by Shuba N, Karan, showed no significant difference on comparing the mean 3MS scores between males and females. Both males and females had moderate cognitive impairment.[63]

In contrast to the above findings, study done by Jie Ding et al., found a significant relation of diabetic retinopathy with various cognitive measures only in men. They described that sex-specific association of diabetic retinopathy on cognitive function may be influenced by the lower prevalence of diabetic complications in women compared to men. When adjustment was made for macrovascular disease there was no relation of sex on cognitive function.[40]

Rajesh V, Kannadasn T, Anand Vijayakumar P.R reported in their study that diabetic women are more prone to cognitive decline than men in the same age group due to the fact diabetes-associated macrovascular disease as well as premature failure of oestrogen protection (because of early menopause) are seen more in women.[55]

Mean MMSE score and HbA1c levels:

The mean MMSE scores of type2 DM subjects with glycosylated hemoglobin levels was analyzed and it was found that participants with higher HbA1c levels performed poorly in cognitive test suggesting that glycemic control has an influence on cognitive function. Correlation coefficient between MMSE score and HbA1c was negative in this study, from which it is inferred that increase in HbA1c levels is associated with decrease in MMSE scores.

HbA1c is formed by the irreversible combination of glucose with hemoglobin. It is not confounded by other reducing sugars, so it is more valid and also a good indicator of long term blood glucose level.[29] The American Diabetes association recommends that maintaining an HbA1c level of less than 7% helps to prevent micro vascular complications.[94] Higher HbA1c levels has been related with poor cognitive performance in numerous studies.

Satyajeet Roy et al., observed the association of HbA1c levels and cognitive status in type 2 diabetic subjects in 26-60 years age group. They described that about 11.6% of them with good glycemic control and about 30.2% of them with poor glycemic control had cognitive decline. Overall, there was negative correlation between the cognitive score and poor glycemic control which shows that as the HbA1c levels increases, the cognitive impairment also enhances.[92] Oguz Tekin et al., reported that high HbA1c levels is an added risk factor for the decline of cognition in type2 DM.[76]

Study by Priyam Mukherjee et al., revealed that higher HbA1c levels was associated with cognitive dysfunction.[53] Tali Cukierman-Yaffe et al., also observed the same.[7] The relation between glycemic control and executive function was examined by Ha.T.Nguyen et al., and they found that poor glycemic control is associated with impairment of executive functioning domain of cognitive function.[95]

Richard H Tuligenga et al., established in their study that poor glycemic control is linked with faster cognitive decline.[96] Orchard TJ, Forrest KY, Becker DJ, explained that cumulative glycemic exposure (severity & duration of hyperglycemia) is important for microvascular complications and the chances of cognitive dysfunction.[97]

A prospective study done by Hiroyuki Umegaki et al., described that, increased HbA1c status is connected to poor cognitive outcome.[56] Study done by Jose. A. Luchsinger et al., showed that improved HbA1c was related with less global cognitive decline.[98] Anna Janocha et al., reported that unfavourable increase in HbA1c levels translated into cognitive impairment.[83] Maggi et al., found that higher HbA1c percentage was associated with delayed verbal memory decline.[99]

Rajeshkanna NR, Valli S, Thuvaragah P, examined the relation between decrease in cognition and glycemic control among type2 DM individuals. They found a considerable decline in cognitive functions in those with higher HbA1c percentage in addition a significant negative relationship of MMSE scores with HbA1c level.[29]

Higher HbA1c percentage shows inadequate effect or insulin action because of insufficient activity or secretion of insulin. Numerous insulin receptors are present all over the brain. Some help in glucose transport and some play a role in cognition. It has been said that decline of cognition might be due decreased insulin action on brain.[7]

Mean MMSE score and type2 DM duration :

In the present study, it was also seen that reduction in mean MMSE score in type2 DM subjects having duration above 5 years was significant when compared to those with duration less than 5 years. It shows that longer duration has an effect over cognitive function. Numerous studies support the same.

In a study conducted by Divya Yogi-Morren et al., it was shown that subjects with long duration of DM performed poorly on tests on working memory, basic attention, and executive function.[100] Rosebud O. Roberts et al., investigated the connection of the duration of type2 DM with cognitive dysfunction and concluded that longer duration is related with poor cognitive outcome.[64] Study done by Renata C Alencar confirmed the same.[12]

A prospective cohort study done by Penelope K. Elias et al., described that duration of DM is a significant risk factor for poor cognitive performance.[54] Richard H Tuligenga et al., in his Whitehall II cohort study interpreted that accelerated cognitive decline in type 2 DM subjects is dependent on duration of the disease.[96]

Peggy J.J. Spauwen et al., in his Maastricht Aging study explained that baseline type 2 diabetics had greater cognitive decline than controls without diabetes and when they were followed for 12 years there was a significant dysfunction in cognition.[101] Anna Janocha et al., reported that increase in the diabetes duration ends in impairment of cognitive function.[93]

Francine Grodstein, Robert S. Wilson, Jennifer Chen, JoAnn E. Manson, explored in their study that longer duration of type2 DM might be related with poor scores on neurocognitive tests.[81] L.Kataria, H Pandya, S Shah, H Shah, R Gerg revealed the same in their study.[4] Mohammad Saadatina et al., in their study found that poor cognitive function was related with longer diabetic duration.[102]

Satyajeet Roy et al., established a negative correlation between cognition as well as diabetic duration and also observed a incremental pattern of cognitive decline in those with more than 10 years duration.[92] Mohammed Abdul Hannan Hazari, Barra Ram Reddy, Nazia Uzma, Bhaskarpillai Santhosh Kumar, analyzed the cognitive dysfunction pattern with regard to diabetic duration and concluded that decline in cognitive functions was more in type2 DM with duration above 5 years.[72]

Study done by Rajeshkanna NR, Valli S, Thuvaragah P showed a positive correlation of HbA1c level with duration of diabetes suggesting that cognitive dysfunction is more with higher level of HbA1c in the long run.[29]

Ai Takeuchi et al., found that duration of diabetes was significantly related with the backward digit span test tested for attention and working memory. They described that duration of the disease seems to reflect the collective influence of the disease, with the decline of the backward digit span indicating diabetic-induced impairment of cognition.[103]

Longer duration of type2 DM is related to cerebral macro vascular disease, infarctions in brain, white matter hyper intensities, which seems to impair cognitive function. Constant exposure to increased blood glucose for a longer period might hasten the cognitive decline.[7] Thus duration of diabetes as well as the diabetic control level as measured by HbA1c might be vital in the pathogenesis of cognitive dysfunction in type2 DM.

SUMMARY

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- Mean MMSE score was compared between type2 DM and controls.

- Mean MMSE score significantly decreased in diabetic subjects than controls.

- Mean MMSE score was decreased in diabetic patients more than 5 years duration.

- Mean MMSE score significantly decreased in type2 DM subjects who had HbA1c > 7% .

- Mean MMSE score was negatively correlated with HbA1c level.

CONCLUSION

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The current study implies that cognitive dysfunction was significantly related to type2 DM and also there was a strong relation of the cognitive decline with diabetic duration and control.

Numerous vascular, metabolic and psychosocial factors has vital role to play in the progression of cognitive dysfunction in diabetic subjects. Irrespective of the mechanism, type2 DM has a cyclical relation with the decline of cognition which seems to be complicated along with the progression of the disease. This association yet again promotes the severity of the disease due to poor compliance to therapy, irregular routine follow up and health education.

Glycemic control is a vital aspect in the management of type2 DM. Effective control needs proper diet, regular exercise, monitoring blood glucose by self and management of medications. A person's cognitive skill to bring about the above mentioned needs is thus crucial for self management of diabetes.

With type2 DM emerging as global pandemic, it is important that screening of diabetic complications should also include the assessment of cognitive status. Early recognition and management of the cognitive dysfunction will help in improving quality of life as well as independent living in type2 DM subjects.

LIMITATIONS

1. Cross-sectional nature of this study does not allow us to measure decline in cognitive function over time.
2. Given the cross-sectional design, duration of diabetes could not be measured objectively, other than by self-report. Self-report of duration of diabetes is not a reliable measure because it only provides information on the time of diagnosis of diabetes, not when these disease processes first began. That is, an individual may be diabetic for a period of time before this condition is diagnosed.
3. A cohort study with larger sample size will help to examine the change in cognitive function in association with diabetes.
4. MMSE is considered as a screening test. Other methods to confirm the diagnosis was not used. Also the subjects were examined only once, thus numerous assessments are needed for accurate confirmation of decrements.

FUTURE SCOPE OF THE STUDY

As an extension of this study, cognitive tests can be repeated after a certain period and the impairment can be found. Other tests for cognition can be included. Longitudinal study designs can be employed to find out more accurately the association of type2 DM and cognitive function as well as identify the contributing factors for the cognitive impairment.

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ANNEXURES

ஒப்புதல் படிவம்

பெயர்_____வயது____, முகவரி_____
_____ஆகிய நான் உடலியங்கியல் துறை, கோவை மருத்துவ கல்லூரி பட்டமேற்படிப்ப, மாணவி ஆகிய மரு.கு. காஞ்சனா பாபி அவர்கள் "**அறியும் ஆற்றல் மீது இரண்டாம் வகை சர்க்கரை நோயின் தாக்கம்**" என்ற தலைப்பில் செய்யும் ஆய்வில் கலந்துக் கொண்டு ஒத்துழைக்க சம்மதிக்கிறேன்.

இந்த ஆய்வின் செய்முறை மற்றும் இது தொடர்பான அனைத்து விளக்கங்களையும் கேட்டுக்கொண்டு எனது சந்தேகங்களையும் தெளிவு படுத்திக்கொண்டேன் என்பதையும் தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழுமனதாக சுயசிந்தனையுடன் கலந்துகொள்வதுடன் எந்த நேரத்திலும் இந்த ஆய்விலிருந்து விலகிட எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இந்த ஆய்வில் எனது விவரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை/ விருப்பம் இல்லை என்பதை தெரிவித்துக்கொள்கிறேன்.

பெயர் :

இடம் :

தேதி :

கையொப்பம் :

CONSENT FORM

Dr.S.Kanchana Bobby, Post Graduate student in the Department of Physiology, Coimbatore Medical College is studying “Impact of Type 2 diabetes mellitus on cognitive function”. Details of the study was explained to me clearly.

I hereby give my consent to participate in this study. The data obtained herein may be used for research and publication.

Name :

Place :

Signature :

PROFORMA

1. NAME:

2. AGE IN COMPLETED YEARS:

3. SEX:

4. EDUCATION:

5. MARITAL STATUS:

6. OCCUPATION:

7. PHYSICAL STATUS: HEIGHT : WEIGHT: BMI:

8. HISTORY OF DISEASES:

9. HISTORY OF ANY DRUG INTAKE :

10. PERSONAL HABITS : SMOKING /ALCOHOL

11. LEVEL OF PHYSICAL ACTIVITY:

12. BLOOD PRESSURE:

13. EXAMINATION OF CARDIOVASCULAR SYSTEM:

14. EXAMINATION OF RESPIRATORY SYSTEM:

15. EXAMINATION OF ABDOMEN:

16. EXAMINATION OF CENTRAL NERVOUS SYSTEM:

15. LAB INVESTIGATIONS:

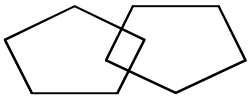
a. Random blood sugar – for controls.

b. HbA1c – for cases.

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

MASTER CHART

TYPE 2 DIABETICS WITH GOOD GLYCEMIC CONTROL

S.No	AGE	SEX	WT	HT	BMI	HbA1c	MMSE SCORE						DURATION
							ORI	REG	A & C	RECALL	L & V	TOTAL SCORE	
1	42	M	53	146	25.2	6.5	9	2	4	2	8	25	<5
2	45	F	60	155	25	7	8	3	4	3	7	25	<5
3	52	M	62	155	25.8	6.3	8	3	4	3	8	26	<5
4	50	M	59	156	24.2	6.8	9	2	4	2	8	25	<5
5	46	F	65	161	25	7	8	2	4	3	8	25	<5
6	41	F	52	156	21.3	6.9	7	3	4	2	8	24	<5
7	44	M	52	146	24.3	5.9	9	2	4	2	8	25	<5
8	55	F	52	150	23	6.2	9	3	4	2	7	25	<5
9	43	F	68	162	25.9	6	8	2	3	2	8	24	<5
10	47	M	63	156	25.8	7	9	3	4	3	7	26	<5
11	51	M	69	163	25.9	6.4	7	2	5	2	7	24	<5
12	49	M	58	156	23.8	5.2	8	2	4	2	8	24	<5
13	54	M	62	156	25.4	5.9	8	2	4	2	8	24	<5
14	42	F	63	153	26.9	5.9	9	3	4	2	8	26	<5
15	44	F	69	162	26.2	5.4	9	2	4	2	8	25	<5
16	44	F	63	153	26.9	6.8	9	2	4	3	7	25	<5
17	52	M	65	162	24.4	6.7	7	3	4	3	7	24	<5
18	54	F	58	153	25.4	6.9	8	3	4	1	8	24	<5
19	44	M	58	155	24.1	7	8	2	4	2	9	25	<5
20	48	F	68	170	23.5	6.5	9	2	4	2	7	24	<5
21	51	M	70	165	25.7	6.3	8	2	5	2	8	25	<5
22	54	M	68	165	24.9	6.1	8	2	4	2	8	24	<5
23	47	M	57	158	22.8	5.8	8	3	4	3	8	26	<5
24	43	F	62	155	25.8	7	8	3	3	3	8	25	<5
25	45	F	68	164	25.3	6.9	9	2	3	3	8	25	<5
26	49	M	57	159	22.6	6.1	8	2	3	3	7	25	<5
27	52	F	62	158	24.8	6.4	7	2	3	2	8	23	>5
28	43	F	55	149	24.7	6.5	9	2	4	2	7	24	>5
29	46	M	61	156	25.1	5.9	8	2	3	3	8	24	>5
30	49	F	68	170	23.5	5.5	8	2	3	2	9	24	>5
31	50	M	70	164	26.1	6.6	8	2	3	3	7	23	>5
32	50	F	68	162	25.9	6.8	8	2	4	2	7	23	>5

TYPE 2 DIABETICS WITH GOOD GLYCEMIC CONTROL

S.No	AGE	SEX	WT	HT	BMI	HbA1c	MMSE SCORE						DURATION
							ORI	REG	A & C	RECALL	L & V	TOTAL SCORE	
33	52	M	56	163	21.1	6.9	7	3	4	2	8	24	>5
34	43	M	67	160	26.1	7	8	3	4	2	7	24	>5
35	47	M	67	162	25.5	6.8	8	2	3	2	8	23	>5
36	49	M	70	174	23.1	5.5	8	2	4	2	7	23	>5
37	50	M	68	172	23	5.9	8	2	4	2	8	24	>5
38	53	F	58	153	24.7	5.8	8	2	4	2	7	23	>5
39	55	F	68	160	26.5	6.8	8	2	3	3	7	23	>5
40	44	M	65	168	23	7	8	2	4	2	7	23	>5
41	46	F	64	158	25.7	6.9	7	3	4	3	7	24	>5
42	42	F	62	159	24.6	6.9	8	3	3	2	7	23	>5
43	51	M	69	167	24.8	6.7	8	3	3	2	7	23	>5
44	54	M	58	149	26.1	7	9	3	4	1	7	24	>5
45	50	M	66	168	23.4	5.9	7	3	4	2	8	24	>5
46	43	F	60	156	24.6	5.5	8	2	4	2	7	23	>5
47	47	M	67	164	25	6.5	8	3	4	2	7	24	>5
48	49	M	68	176	22	6.6	7	3	4	2	8	24	>5

ORI - Orientation, REG - Registration, A&C - Attention & Calculation, L&V - Language & Visual Construction

TYPE 2 DIABETICS WITH POOR GLYCEMIC CONTROL

S.No	AGE	SEX	WT	HT	BMI	HbA1c	MMSE SCORE						DURATION
							ORI	REG	A & C	RECALL	L & V	TOTAL SCORE	
49	51	M	64	157	26	7.6	8	2	4	2	7	23	<5
50	54	F	69	166	25	8.2	7	2	4	2	7	22	<5
51	50	F	76	172	25.7	10.6	8	2	4	2	7	23	<5
52	42	M	64	158	25.7	7.8	8	2	3	2	7	23	<5
53	46	F	59	152	25.5	12.6	7	3	3	2	6	21	<5
54	49	M	68	172	23	10.7	8	2	4	2	7	23	<5
55	52	M	64	165	23.7	8.1	8	2	3	2	7	22	<5
56	54	F	54	148	24.6	7.8	8	3	3	3	6	23	<5
57	50	F	56	152	24.3	9.9	7	3	4	3	5	22	<5
58	43	M	56	149	25.4	10.8	7	3	3	3	5	21	<5
59	44	F	64	158	25.7	10	8	2	4	2	7	23	<5
60	42	F	63	157	25.6	8.5	8	2	4	2	7	23	<5
61	41	M	62	158	24.8	7.7	8	2	3	2	7	22	<5
62	55	F	56	152	24.2	13	7	2	4	2	7	22	<5
63	51	F	54	146	25.7	11.4	8	2	4	2	7	23	<5
64	50	M	53	145	25.2	11.6	7	2	4	2	7	22	<5
65	47	F	56	149	25.4	13.2	7	2	3	2	7	22	<5
66	42	M	74	168	26.4	12.9	7	2	4	2	8	23	<5
67	45	M	68	166	25.1	10.6	9	2	4	2	6	23	<5
68	45	F	67	172	23.1	10.4	9	2	3	2	7	23	<5
69	51	M	62	156	25.8	7.9	8	2	4	2	7	23	<5
70	53	F	55	152	23.9	8.4	7	3	3	2	8	23	<5
71	50	F	61	154	26.5	13.6	7	3	3	2	6	21	<5
72	44	M	52	160	20.8	13.2	6	3	3	2	6	20	<5
73	46	M	57	155	23.7	11.6	7	2	4	2	6	21	<5
74	49	F	61	167	22.5	12.8	6	3	3	3	7	22	<5
75	52	F	59	154	25.6	8.7	7	2	3	2	6	20	<5
76	54	M	71	168	25.3	8.7	8	2	4	2	7	23	<5
77	43	F	75	172	25.8	11.6	6	3	3	2	6	20	>5
78	47	F	67	165	24.8	10.6	6	3	4	3	6	22	>5
79	47	M	60	158	25	9.9	7	3	4	3	6	23	>5

TYPE 2 DIABETICS WITH POOR GLYCEMIC CONTROL

S.No	AGE	SEX	WT	HT	BMI	HbA1c	MMSE SCORE						DURATION
							ORI	REG	A & C	RECALL	L & V	TOTAL SCORE	
80	49	F	66	164	25.3	8.7	7	2	4	2	6	21	>5
81	50	F	72	168	25.7	8.9	7	2	4	3	7	23	>5
82	50	M	66	172	22.7	7.8	7	2	3	3	6	21	>5
83	44	M	62	157	25.8	8.3	7	3	3	2	7	22	>5
84	42	F	67	163	25.7	8.1	8	3	4	2	6	23	>5
85	48	M	54	152	23.4	11.6	8	2	3	2	8	23	>5
86	44	F	61	165	22.5	10.8	8	2	4	2	6	22	>5
87	51	F	64	173	22	10.4	8	2	3	2	7	22	>5
88	42	M	66	172	22.7	13.2	7	2	3	2	6	20	>5
89	43	F	69	164	26.5	7.9	8	3	3	2	7	23	>5
90	45	M	63	159	25	7.7	8	3	3	2	6	22	>5
91	49	M	56	155	23.3	9.8	8	3	4	2	6	23	>5
92	52	F	58	152	25.2	9.4	8	3	4	2	6	23	>5
93	54	M	74	168	26.4	10.6	7	3	4	2	6	22	>5
94	50	F	57	152	24.7	11.4	7	3	3	2	6	21	>5
75	50	M	53	156	22	12.4	7	2	3	3	7	22	>5
96	46	M	52	147	24.7	7.9	7	3	3	2	6	21	>5
97	49	M	64	159	25.6	7.9	6	3	3	2	6	20	>5
98	51	M	61	166	22.5	10.8	7	3	3	2	6	21	>5
99	51	M	71	168	25.3	11.4	7	2	3	1	7	20	>5
100	55	M	63	169	22.5	12.2	7	2	3	2	6	20	>5

ORI - Orientation, REG - Registration, A&C - Attention & Calculation, L&V - Language & Visual Construction

CONTROL GROUP

S.No	AGE	SEX	WT	HT	BMI	HbA1c	MMSE SCORE					
							ORI	REG	A & C	RECALL	L & V	TOTAL SCORE
1	51	M	58	146	27.2	96	10	3	5	3	9	30
2	43	F	65	163	24.4	120	10	3	4	3	9	29
3	46	M	58	151	25.4	115	10	3	5	3	9	30
4	43	M	73	168	25.8	106	9	3	5	3	9	29
5	42	F	54	158	21.6	102	10	3	5	3	8	29
6	48	F	62	157	25	116	10	3	5	2	9	29
7	53	F	59	162	22.4	118	10	3	5	3	9	30
8	55	M	66	160	25.7	94	10	3	5	3	8	29
9	50	F	58	155	24.1	86	10	3	5	3	9	30
10	47	F	68	162	25.9	110	10	3	5	3	9	30
11	43	M	63	161	24.3	100	10	3	5	3	9	30
12	53	F	68	170	23.5	98	10	3	5	3	9	30
13	44	F	68	158	27.2	126	9	3	5	3	9	29
14	46	M	63	165	23	132	10	3	4	3	9	29
15	41	M	60	158	24	145	10	3	4	3	9	29
16	52	M	65	155	27	112	10	3	5	3	8	29
17	50	F	63	157	25.5	124	10	3	5	3	9	30
18	53	F	60	151	26.3	140	10	3	5	3	8	29
19	49	M	68	165	24.9	98	10	3	5	3	9	30
20	48	M	60	153	25.6	117	10	3	5	3	9	30
21	44	F	57	158	22.8	114	10	3	5	3	9	30
22	43	F	63	156	25.8	136	10	3	5	3	9	30
23	41	M	65	167	23.3	145	9	3	5	3	9	29
24	51	F	68	162	25.9	116	10	3	5	3	8	29
25	54	F	59	153	25.2	124	9	3	4	3	9	28
26	55	M	54	150	24	116	10	2	5	3	9	29
27	44	M	68	162	25.9	118	10	3	4	2	9	28
28	46	F	63	161	24.3	136	10	3	4	3	9	29
29	47	M	68	170	23.5	122	10	3	5	2	9	30

CONTROL GROUP

S.No	AGE	SEX	WT	HT	BMI	HbA1c	MMSE SCORE					
							ORI	REG	A & C	RECALL	L & V	TOTAL SCORE
30	49	M	68	158	27.2	106	10	3	4	3	8	28
31	51	F	62	158	27.5	102	10	3	5	3	9	30
32	54	M	70	164	28	116	9	3	5	3	8	28
33	50	M	65	162	25	118	10	3	4	3	9	29
34	49	M	55	150	24	94	9	3	5	3	9	29
34	44	F	48	152	21.3	86	9	3	4	3	8	27
36	43	F	55	148	24	110	9	3	5	3	8	28
37	47	M	57	150	25.3	100	10	3	4	3	9	29
38	51	M	65	168	23	98	9	3	5	2	9	28
39	53	F	64	162	25	126	10	3	5	3	9	30
40	50	F	60	156	26.6	132	9	2	5	2	9	28
41	49	M	59	160	23	145	10	3	5	3	9	30
42	47	M	58	156	24	112	10	3	5	3	9	30
43	43	F	57	150	25.3	124	10	3	5	3	8	29
44	45	F	69	163	26.9	140	10	3	5	3	9	30
45	48	M	55	155	24.4	106	9	2	4	3	9	28
46	51	F	60	168	21.4	102	9	3	4	3	9	28
47	50	M	72	163	28	116	10	3	5	3	8	29
48	48	F	65	158	26	118	10	3	5	3	9	30
49	44	M	56	150	24.8	94	10	3	4	3	9	29
50	45	F	48	150	21.3	86	9	3	5	3	9	29
51	44	F	63	156	26.2	110	10	3	5	3	8	29
52	43	M	59	152	26.2	100	9	2	5	3	8	27
53	53	F	67	155	27.9	98	9	3	5	2	9	28
54	51	F	58	155	25.7	126	9	3	4	3	9	28
55	50	M	55	152	23.9	132	10	2	4	3	9	29
56	55	M	62	156	25.8	145	10	3	5	2	9	30
57	52	M	69	162	27.6	112	10	3	5	3	9	30
58	44	F	65	160	25.3	112	10	3	5	3	9	30

CONTROL GROUP

S.No	AGE	SEX	WT	HT	BMI	HbA1c	MMSE SCORE					
							ORI	REG	A & C	RECALL	L & V	TOTAL SCORE
59	51	F	70	163	27.3	124	10	3	5	3	9	30
60	46	M	65	158	25.39	140	10	3	5	3	8	29
61	49	F	63	153	28	98	10	2	5	3	9	29
62	53	F	68	156	29.56	117	9	3	5	3	9	29
63	44	M	52	146	24.7	114	9	3	5	3	9	29
64	42	F	65	157	25	136	9	3	5	3	9	29
65	47	F	58	151	25.7	145	9	3	5	3	9	29
66	49	M	70	168	25	116	9	3	4	3	8	27
67	51	M	54	158	21	124	9	3	5	3	8	28
68	44	M	62	157	24.2	116	9	3	5	3	9	29
69	47	M	57	162	22.6	118	10	2	5	3	9	29
70	51	F	55	152	24.4	136	10	3	5	3	8	29
71	51	F	58	148	25.7	122	9	3	5	3	9	29
72	55	M	60	155	25	124	10	2	5	3	8	28
73	48	F	52	156	21.6	102	9	3	5	3	8	28
74	46	M	55	146	25	96	10	3	5	2	9	29
75	45	M	72	170	24.8	120	9	2	5	3	9	29
76	45	F	65	160	25.3	115	10	3	5	3	9	30
77	55	F	59	156	24.5	106	10	3	5	3	7	28
78	50	F	70	158	29.1	102	10	3	4	3	9	29
79	46	M	73	162	32.4	116	10	3	5	3	9	30
80	47	F	55	148	24.4	118	10	3	4	3	9	29
81	49	M	62	155	25.8	94	10	3	5	3	8	29
82	42	M	56	145	25.4	86	10	3	4	3	8	27
83	51	F	53	146	24	110	9	3	5	3	9	29
84	42	F	55	152	24.4	114	10	3	5	3	9	30
85	44	M	58	148	26.3	96	9	3	5	3	9	29
86	46	F	60	155	25	112	10	3	5	3	9	30
87	47	F	52	156	21.6	116	10	3	4	3	8	28

CONTROL GROUP

S.No	AGE	SEX	WT	HT	BMI	HbA1c	MMSE SCORE					
							ORI	REG	A & C	RECALL	L & V	TOTAL SCORE
88	51	M	55	146	25	106	10	3	5	3	8	29
89	49	F	72	170	24.8	98	10	3	4	3	9	29
90	44	F	65	160	25.3	118	10	3	4	3	8	28
91	45	M	59	156	24.5	102	10	3	4	3	9	29
92	55	M	70	158	29	96	10	2	4	2	9	28
93	44	F	73	162	28.5	112	9	3	5	3	9	29
94	43	M	55	148	25	90	10	3	4	3	9	29
95	42	F	62	155	25.8	110	9	3	4	3	8	27
96	41	M	56	145	24.4	120	10	3	5	2	9	30
97	42	M	65	162	24.8	132	10	3	4	3	9	29
98	53	M	64	166	23.2	136	10	3	5	3	9	30
99	44	M	63	161	24.3	128	10	3	4	3	9	29
100	47	M	68	163	25.6	138	10	3	5	3	8	29

ORI - Orientation, REG - Registration, A&C - Attention & Calculation, L&V - Language & Visual Construction