Effect of short-term memory and working memory in diabetes with comorbidities condition

Anand Vijayakumar P.R.*, Seema A., Kokul Rajan P.

Department of Pharmacology (A DST FIST sponsored department), JSS College of Pharmacy (JSS Academy of Higher Education & Research), Rocklands, Udhagamandalam-643001, Tamil Nadu, India

Article History:
Received on: 09 Apr 2020
Revised on: 07 May 2020
Accepted on: 22 Jul 2020

Keywords:
Cognition,
Dementia,
Hippocampal damage,
Memory,
Type 2 diabetes

ABSTRACT
Cognitive function refers to the ability of humans to function normally which includes physical as well as mental interpretation like ability to focus, concentrate, learn, plan, determine, execute, manipulate and problem solving. Etiologic of cognitive dysfunction includes AD, depression, anxiety and vascular dementia, hippocampal sclerosis etc., Diabetes associated with cognitive decline are related to short fall of learning and memory. Cognitive impairment/dysfunction in diabetic patients has been divided into three stages, stage one, stage two and stage three. Stage one, occur in all groups of different ages and it is characterized by mild and subtle changes in cognition. Deficit in short-term memory and working memory leads to major problems like Alzheimer disease and dementia. The pathophysiology of cognitive decline associated involves microvascular injury, hyperglycaemia, insulin resistance and oxidative stress. Diabetes associated with comorbidities condition leads to decrease in short-term memory and working memory. From this review we observed short term memory retains small amount of data in cognizance which are readily available state for short period of time whereas working memory manipulates the information through visual and auditory storage and it is important in understanding and improving the memory. Conclusion of this review is that, there is a decrease in short-term memory and working memory in type 2 diabetes patient condition. But there is no evidence of which type comorbidity condition affects more in short-term memory and working memory. So, further research study to be carried out.

*Corresponding Author
Name: Anand Vijayakumar P.R.
Phone: 9443181573
Email: ootyanand2004@gmail.com

ISSN: 0975-7538
DOI: https://doi.org/10.26452/ijrps.v11i4.3158

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execute, express, retain the information, manipulate and solving the problems (Sharma and Antonova, 2003).

**Theories of cognition aging and work**

Cognitive impairment/dysfunction in diabetic patients has been divide into three stages, stage one, stage two and stage three. Stage one, occur in all groups of different ages and it is characterized by mild and subtle changes in cognition. Periodic assessment of one’s ability to perform crucial self-management task should be carried out. Stage two is a mild to moderate cognitive impairment stage. It is most commonly occurred in patients above the age of 60. In these patients the impairment is in one or two domains that impaired the daily living activity. Stage three or stage of Dementia which is commonly characterized by forgetfulness and decline in executive functions like reasoning, planning and problem solving (Hopkins et al., 2016).

The different factors that are known to act as essential part in cognitive dysfunction in some diabetic patients are hyperglycaemia, hypoglycaemia, macrovascular disease, insulin resistance, absence of C-Peptide and absence of Apoε4 Allelle (Kodl and Seaquist, 2008).

Aspects of cognition consists of the term such as sensation, thinking, retention, recall, perception, imagery, problem-solving and many more (Neisser, 2014).

Cognitive functioning impairment was known to be associated with syndromes like type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The ability and capacity to grasp and hold the stimuli for a short period of time and make use of it directly, process and manipulate it is called “Working Memory”. Reasoning, learning and understanding are the cognitive tasks where working memory plays a pivotal and crucial role (Sharma and Antonova, 2003). Working memory was reported to be associated with the activation of dorsolateral prefrontal cortex (DLPF) (Stufflebeam and Rosen, 2007).

Working memory has limited capacity for processing the information of same data or other which are preserved and at the same time coordination of resources was suggested to be the key role of working memory (Bharadwaj et al., 2015), (Swanson et al., 2009).

There are three subcomponents in working memory. They are: a) It is assumed to be attention controlling system and important in skills and which is most susceptible to effect AD which is referred a central executive system; b) the second, processes and manipulates visual perception and action which is referred as visuospatial sketch pad; and c) the last it stores and rehearse speech based info and is required for both native and second language vocabulary (Swanson et al., 2009).

Short-term memory (STM) that involve remembering novel information across brief intervals was observed to associate with medial temporal lobe (MTL) damage (Kumaran, 2008).

Unlike LTM, STM does not require the synthesis of proteins (Goelet et al., 1986).

**Microvascular dysfunction and hyperglycaemia**

There is a tight link between microvascular and metabolic physiology. Many organs are affected by microvascular dysfunction in diabetes condition. Diabetes associated comorbidities such as depression and cognitive impairment. Microvascular damage can cause cerebral microbleeds, lacunar infarcts and white matter hyperintensities (WMHs), which are together called as cerebral small-vessel disease. It can also cause abnormal cerebral microvascular structure and function. Reduced cognitive performance, clinical cognitive impairment (dementia), leads to brain dysfunction. According to the data obtained from the cross sectional and prospective systematic reviews, it was found that risk towards dementia and depression is greater in patients with cerebral small vessel disease. (Rensma et al., 2018).

In individuals with or without T2D, microalbuminuria is also considered as one of the factors for cognitive impairment (Martens et al., 2017), and depression (Martens et al., 2016). Diabetic patients are susceptible to cerebral MVP and its clinical consequences, as it is related to large artery stiffening.

**Pathophysiology**

Central nervous system problem due to type1 and type2 diabetes, which have sensitive brain buildings and reactive to fluctuations in glucose homeostasis. Diabetic encephalopathy occurs due to interaction between direct and indirect metabolic significance of insulin deficit, enduring hyperglycaemia and additional components such as hereditary and eco-friendly causes (Stranahan, 2015).

Diabetes associated with cognitive decline are related to shortfalls of learning and memory. This may result in risk of AD, dementia and affecting disorder (Biessels et al., 1994), (Talbot et al., 2012).

Diabetes related cognitive deterioration linked with structural modifications in the brain. This modification along with brain atrophy and electrophysiologically deficits, terminate in declined memory and mental act. The hippocampus region of brain involved in memory construction and associative learning.
It is mostly pretentious by this pathological condition because of its sensitivity variations in glucose and insulin homeostasis. The comparative degree of cognitive dysfunction and cognitive aberrations are established changes in both type of diabetes (Hershey et al., 2004).

Mental, problem solving, learning, motor speed and memory impairments are associated with Type 1 diabetic patients. Declarative memory deficits are reported in children (Brands et al., 2005), changes in intellectual performance and information processing speed, psychomotor functioning due to mild central brain atrophy in younger adult. (Ferguson et al., 2005), (Kodi and Seaquist, 2008). Tasks involved in moderate impairment of verbal memory results in increase memory deficits and decreased executive function. This results in reduction of psychomotor speed in patients with type 2 diabetes present (Ryan et al., 2006), (Tomlinson and Gardiner, 2008).

Diabetic complications which is generally considered due to hyperglycaemia, activating few metabolic and molecular modification. This leads to progressive neuronal dysfunction (Cherbuin et al., 2012). Glucose is the main metabolic nutrient source, which is poorly controlled in diabetes cases (prolonged hyperglycaemia). Glucose transport is bothered and often lead to dysregulation of osmolality and metabolism of the brain. Atrophy of the hippocampus and amygdala (Cherbuin et al., 2012) (Gorelick et al., 2011) are caused due to high glucose levels which suggest that a well control of blood glucose levels progresses cognitive performance in type 2 diabetic patients (Tomlinson and Gardiner, 2008).

**In Hyperglycaemia**

Blood brain barrier and its transport function are pretentious by increase in vascular permeability, lowering of perfusion rates, thickening of capillary walls and abnormal proliferation of endothelial cells which occurred in hyperglycaemic condition which consequently affect the transport function and integrity of blood brain barrier (Sochocka et al., 2017).

The transport of choline is hinder by Vascular damage of BBB leading to brain deprivation of choline transmitter and it affects the brain homeostasis. Cognitive damage produced by tau(γ)-phosphorylation and disruption of brain homeostasis is promoted via vascular damage thereby decrease the clearance of amyloid-β(1-β) protein. Oxidative stress and inflammation production via chemicals induced CNS damage. Any damage in BBB elevate the penetration of free radicals and pro-inflammatory and further penetrate the CNS (Francis et al., 1999) (Talbot et al., 2012).

**Insulin sensitivity**

Two mechanisms are involved in the impairment of insulin-signalling pathway I) Inhibition of molecules (AMPK, JNK, GSK3β, mPLK, IKKβ) from other pathways. II) Inhibition of the upstream components by the downstream component’s pathway (mTOR/S6K, MAPK, PKC), identical to negative feedback mechanism. Serine phosphorylation of IRS is involved in the latter, blocking further signal propagation and further suggested that phosphorylation IRS by serine to be a biomarker of T2DM. Insulin resistance and activated insulin is an inducer of IRS kinases (e.g., S6K1, PKC). Insulin receptors which are expressed by all organs, including the brain (Boucher et al., 2014) (Zhao et al., 1999) is conserved for insulin-signalling pathway and in the brain particularly hippocampus region insulin receptors are expressed which are accountable for recall and cognition (Droge, 2002).

**Oxidative stress**

Two mechanisms are involved in ROS modulation of insulin-signalling pathway I) To insulin response, ROS is produced where advanced organism have progressed the use of ROS and NO as signalling molecules for supplementary physiological function which includes signal transduction from membrane, monitoring of oxygen tension and regulation of vascular tone. II) ROS negatively controls the insulin pathway leads to decrease insulin secretion and subsequently insulin sensitivity (Butterfield et al., 2014). Increased free radicals promotes loss of synapse, neuronal function disruption, apoptosis and cell damage results in cognitive impairment (Redish and Touretzky, 1997).

**Effect of STM and WM**

**Working Memory**

A part of Hippocampal region is a working memory (WM) which delivers brief storage and manipulation of the data which is required for cognitive task such as language understanding, Knowledge and perceptive. It is derived from the concept of unitary short-term memory system. There are three subcomponents of working memory, they are central executive, The visuospatial sketchpad and the phonological loop.

1. Central executive duplicates system concerned with the attentional regulator of behaviour with succeeding progresses almost certainly reliant on parallel growths in the study of attention and switch of action.
2. Visual perception and actions are processed by visuospatial sketchpad

3. The speech perception and production systems used for active memory which is represented by phonological loop. Thus, phonological loop is likely to overlay substantially with speech perception and production.

**Short Term Memory (STM)**

Active or primary memory are referred to be STM, the data are presently alert of or intellectual about. When sensory memory is considered it provides the information found in short term memory. If STM are not prepared or maintained, they last for few secs and the limit of STM it can hold seven plus or minus two items. STM stores data for approximately 20 to 30 seconds and few information lasts up to a minute, but most data deteriorate quickly. Old information is evacuated by new information when it enters the short-term memory. There is a variation in quantity of information which is stored in short term memory.

**Comparison STM and WM**

This takes place by withholding of memories which needs shifting of information from short term stores to long term memory, where capacity and duration are limited in short term memory. There are limited unlike methods that the content can be transferred to long term memory given below.

**Adaptation of short-term memory to long term memory**

Practice helps to convert the information into long term memory. Chunking is one of method by breaking smaller segment data into long term memory data. But mechanism is mysterious. STM can be improved by doing exercise has shown in the recent research work.

**Comorbidities condition**

**Hyperglycaemic condition**

Decreased cognitive function due to chronic raised glucose concentration which lead to poor learning and memory power. Cognitive function in elder adults is improved by pharmacological improvement of glycaemic control (Gradman et al., 1993). In animal studies there is an evidence that streptozotocin induced hyperglycaemia leads to decreased Ach synthesis and release in rats’ brain (Welsh and Wecker, 1991) leads to loss of cortical neurons, results in impaired memory (Baura et al., 1993).

**Hyperinsulinemia**

A numeral of mechanisms can be hypothesized by which cognitive functioning can be modified by insulin. Since the insulin transportation occur via BBB, insulin concentration in the serum is closely related to insulin present in the cerebrospinal fluid (Shibata et al., 1986). Hypothalamus and hippocampal region are rich in insulin receptors. Reduction in cholinergic transmission is also mediated by insulin receptors (Palovcik et al., 1984) (Perlmuter et al., 1990).

**Dyslipidaemia condition**

Dyslipidaemia is linked with the insulin resistance syndrome. Only few studies have recommended for cognitive impairment by increased triglyceride level and they are inversely linked with verbal fluency test (Meneses et al., 1996) in diabetic patients. In ageing patient with T2D showed decline reaction time in hypertriglyceridemia condition.

**Hypertension condition**

Increased blood pressure is linked with type 2 diabetes and insulin sensitivity syndrome. It is focused on many researches on deviation in cognitive function. Rats with hypertensive related with age, there is a drop-in learning. Mechanism that can be hypothesized is that hypertension is linked with brain white matter lesions, cerebrovascular disease and lacunar brain infarct. Hypertension associated with white matter lesion cause cognitive impairment during assessment of magnetic resonance imaging (Breteler et al., 1994). We observed short term memory retains small amount of data in cognizance which are readily available state for short period of time whereas working memory manipulates the information through visual and auditory storage, and it is important in understanding and improving the memory. There is a substantial evidence to support that the T2D is associated with cognitive impairment. Thus, long term diabetes and its comorbidities leads to dysfunction of working memory and short-term memory which further may lead to chronic disorder like Alzheimer, dementia and brain dysfunction. Since the specific mechanism for hippocampal region is unclear and further studies should be carried out.

**CONCLUSIONS**

Short term and working memory were found to decrease in the presence of diabetic condition, which was further deteriorated in the presence of comorbid conditions like hypertension, hyperinsulinemia, hyperlipidaemia and depression. There is no evidence to know which type of comorbidity effects severely this condition. So, further research should be carried out to find which type of comor-
bidity will affect short-term and working memory severely in diabetic condition.

**Conflict of Interest**
The authors declare that they have no conflict of interest for this study.

**Funding Support**
The authors declare that they have no funding support for this study.

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