Dear Reviewer,

The proposed comments are showed in *italic* format and highlighted and the corrections are showed after that.

Regards,

1) Editor comment;

In page 3 [2] line 7-8: "children with diagnosed T1D within the first few years of their life and" should be omitted.It is unnecessary explanation.

In addition, hypoglycemic attacks in children ~~with diagnosed T1D within the first few years of their life~~ and elderly should be avoided.

2) Editor comment;

In page 3, "Adves rse effects of diabetes on cognitive system and memory disorders" is highly pretentious; therefore it absolutely should be need to support references or should be omitted.

Adverse effects of diabetes on cognitive system and memory disorders have been noticed by researchers for a long time [2- 4].

3) Editor comment;

Since Topic in this manuscript is "Diabetes mellitus and cognitive impairments", "Overview of memory and cognition" section which is general information about memory, should be shortened.

Overview of memory and cognition

Cognition is defined as "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses" [5].

Memory is the retention, recording, and process of retrieving knowledge. All knowledge gained from experience such as known facts, remembered events, gained and applied skills would be considered as a memory [6]. Memory can be categorized into declarative and non-declarative memory. Declarative memory mostly corresponds to the learning and recalling new facts, events, and materials. ~~This form of memory would use to remember facts and events intentionally and consciously. On the other hand,~~ Non-declarative memory refers to the many forms of memory that are reflectively or incidentally~~. For instance, remembering how to swim or ride a bicycle belong in this category [6].~~

The "brain working memory" is defined as the ability to keep the record of many bits of information at the same time and the recall of this information immediately if needed for subsequent thoughts [7]. When working memory is damaged, a wide range of cognition impairments occur and the patient will not be able to appropriately use his/her own information for thinking in different situations [6].

The majority of advanced cortical functions arise from association cortex. Different signals from multiple parts of the cortex and from subcortical regions predominantly from the thalamus arrive at the same time to these areas. The main association areas are (1) the parieto-occipitotemporal association area, (2) the prefrontal association area, and (3) the limbic association area. Parieto-occipitotemporal association area analyses the spatial coordinates of the body and also has the main role for language comprehension, reading and naming objects [7]. ~~Prefrontal association area is in close relation with the motor cortex and is necessary for programming advanced motor movements and also for "working memory" [7]. The center of language motor programming is placed in the Broca's area in the frontal cortex that is in close connection with Wernicke's center. Wernicke's area that is placed in the posterior part of the superior temporal lobe translates the complex meaning of various patterns of somatic, visual, and auditory signals and is vital for intelligence. The limbic cortex is~~

~~responsible for initiating activation of the other parts of the brain and learning process by emotional and motivational drives [7].~~

Our knowledge about mechanisms of thinking and memory is little .It seems that each thought arises from simultaneous activation of many parts of the different area in the brain such as cerebral cortex, limbic system, thalamus and reticular formation of the brainstem. The memory is the result of some events in synaptic transmission by changing its basic sensitivity ~~that is a consequence of neural activity. "Memory traces" are the name of pathways that would create or facilitate due to these events. The process of thinking can activate these traces and recreate memories [7].~~

Constant neural activity that arises from traveling nerve signals to a temporary memory trace can create a "short term memory". A temporary chemical or physical synaptic change that belongs for a few minutes up to several weeks makes an “intermediate long term memory”. Structural alterations in synapses occur when a “long term memory" is created and can be used weeks to years later [7].

The hippocampus and to a lesser degree the thalamus are responsible for deciding which thoughts are important enough to be saved as a memory [7].

It is possible to acquire information about the patient’s cognitive, memory, behavioral, linguistic, and executive functioning through Neuropsychological tests. These data can be used in the diagnosis of cognitive disorders and for localization of the abnormality in the brain as well as to assessment of therapeutic effects of any treatment modality on the cognitive dysfunction. Neurocognitive domains and some examples for their assessment are categorized in the table 1.

Neuropsychological evaluation (NPE) measures the cognitive abilities in the patient quantitatively and its results must be interpreted in the setting of the patient's age, education, gender and cultural background. In addition, reliability, validity, sensitivity and specificity of these tests are important items that should be considered.

4) Editor comment;

In page 8, "neurogenes " is corrected as "neurogenesis"

They have pointed out the effects of diabetes on hippocampus neurogenesis and depression and the resulting cognitive [30].

5) Editor comment;

"Scientists consider a key role for oxidative stress in diabetic patients' development of AD" expression should be edited.

Scientists consider a key role for oxidative stress in the development of AD in patients with diabetes mellitus.

6) Editor comment;

"Thus, insulin resistance is the fundamental feature that links T2D to the future development of AD" is also pretentious expression, "Thus, insulin resistance seems to be the fundamental..." could be better.

Thus, insulin resistance seems to be the fundamental feature that links T2D to the future development of AD.

Editor comment;

The authors described the relationship between diabetes mellitus and cognitive impairments. It is timely and interesting review. It would be better to add a description of the brain changes on MRI between diabetes and AD.

Brain imaging in diabetes

Brain imaging can be an important tool to clarify the underlying pathogenesis for cognitive impairments in diabetic patients. Some researchers have been reported both focal and global cerebral changes [37].

Slight brain structural abnormalities have been reported in T1D [25,38]. A study showed that the gray matter density of patients with T1D was less than the control group and this finding correlated with severe hypoglycemic attacks and higher HbA1c levels. This assessment was performed with voxel-based morphometry—a well-known quantitative MRI technique [25,38].

The direction of water diffusion in tissues is measured by using diffusion tensor imaging (DTI) that is an index for the integrity of white matter [25]. DT1 shows microstructural abnormalities particularly in the optic radiations and posterior corona radiata in T1D patients. These findings correlate with longstanding diabetes and high concentrations of HbA1c [39]. These abnormalities may be the underlying pathogenesis in the mental slowing that is the main cognitive problem in T1D [40]. DT1 Technique will be a good research tool for future studies in this setting.

There is a relationship between T2D and lacunar infarcts/cerebral Atrophy. This association between T2D and white matter lesions (WML) is less clear [37].

It was reported that Hippocampal atrophy is a consistent neuroimaging finding in patients with T2D [41], but a relatively recent study that evaluated the data from one cohort study and two case control studies, concluded that these patients did not have any specific vulnerability to hyppocampal atrophy. Nevertheless; they have greater global brain atrophy compared to controls [42].