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EFFECT OF TYPE 2 DIABETES MELLITUS ON BRAIN METABOLITES BY USING PROTON MAGNETIC RESONANCE SPECTROSCOPY-A SYSTEMATIC REVIEW

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Abstract

Cerebral metabolism will be affected in T2DM either by chronic hyperglycemia or by chronic hypoxia. Proton magnetic resonance spectroscopy (^{1}H-MRS) of the brain provides detailed information about the structure, dynamics, reaction state and chemical environment of molecules. It also measures the levels of brain metabolites such as myo-inositol (mI), N acetyl aspartate (NAA), creatine (Cr), choline (Cho), glutamate (Glu), glutamine (Gln) and gamma amino butyric acid (GABA). Several studies suggest that people with type 2 diabetes mellitus (T2DM) are at an increased risk of cognitive impairment in comparison with the general population. The altered metabolites may cause cognitive dysfunction in T2DM. This review article concludes that in T2DM, metabolite levels were altered in different regions of brain.

Keywords

Brain metabolites; Cognition; Type 2 diabetes mellitus; Proton Magnetic Resonance Spectroscopy of brain

INTRODUCTION

The global prevalence of diabetes, and especially T2DM, is increasing at an alarming rate. According to the recent update by the International Diabetes Federation (IDF) more than 382 million adults aged 20–79 years had diabetes in 2013 and it is expected to increase to 592 million by 2035[1]. Diabetes is a major health problem affecting multiple organs in the body. This may lead to long-term complications in peripheral and central nervous system[2,3,4]. Diabetics had a 20–70% more decline in cognitive performance, and a 60% higher risk of dementia[5]. Cells and their extracellular matrix share a dynamic and reciprocal relationship, modulations of matrix components by glycation leads to altered cell behavior in cell spreading, phosphorylation of key intracellular signaling molecules and expression of extracellular matrix proteins and all these cellular alterations may contribute for cognitive and metabolite changes in diabetics[6]. There are different methods to assess the cognitive

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dysfunction namely, Neurocognitive testing[7], evoked potentials, EEG, MRI, fMRI, SPECT, PET[8]. Magnetic resonance spectroscopy is an analytical method used in chemistry that enables the identification and quantification of metabolites in samples. It differs from conventional MR imaging in that spectra provides physiologic and chemical information instead of anatomy[9]. ^{1}H-MRS is often used to measure the levels of N-acetyl-aspartate (NAA), total choline (Cho), total creatine (Cr) and myo-inositol (mI). NAA is a measure of neuronal density and a marker of normal functioning of neurons. Cho is associated with membrane turnover (gliosis or necrosis) and Cr is associated with energy metabolism which is considered to be relatively constant[10]. Myo-inositol levels are believed to represent glial proliferation or an increase in glial cell size both of which may occur in inflammation[11]. ^{1}H-MRS studies have been performed in a small number of patients with T2DM, reporting increased mI/Cr but inconsistent findings with respect to NAA/Cr and Cho/Cr[12–17]. This systematic review was conducted on various available articles on T2DM with ^{1}H-MRS of brain.

MATERIALS & METHODS

Articles were searched from Medline, Scopus.com, Google.com, Google Scholar and Pubmed.com by using the following medical terms: type 2 diabetes mellitus, proton magnetic resonance spectroscopy of brain, cognitive dysfunction, cerebral metabolites, frontal lobe and hippocampus. The abstracts were screened and potentially relevant articles were retrieved. These articles were included if they met the following criteria:

- Original article written in English.
- Article must be on type 2 diabetes mellitus with ^{1}H-MRS of brain.
- Article on cognition in type 2 diabetes mellitus with ^{1}H-MRS of brain.

Type 2 diabetes mellitus affects different regions of brain to different degrees

In meta-analysis by Van Harten (2006), neuro imaging studies confirm that structural changes occur in diabetes. White matter lesions, lacunar infarcts and cortical atrophy were seen in diabetes mellitus subjects[18] and these changes may result in cognitive impairment.

Frontal lobe

Decreased cerebral blood flow in frontal lobe has been described in T2DM (O'Rourke 2007). Cross-sectional studies on T2DM reported an association between white matter lesions and frontal lobe dysfunction[19,20]. Cognition is inversely proportional to mI levels in dorsolateral frontal white matter of non-diabetic controls, in diabetics with depression there was no correlation between mI levels and cognition where as in diabetics without depression the relation between cognition and mI levels was not concrete[21]. In the frontal cortex increased Cho/Cr levels were seen in impaired glucose tolerance group and increased mI/Cr levels in T2DM group, NAA/Cr and Cho/Cr levels of T2DM were decreased but HbA_{1c} level was inversely proportional to NAA/Cr and Cho/Cr[17]. Increased mI/Cr in frontal white matter was seen both in DM and DM with depression groups but mI levels were increased more in frontal white matter of DM group than in DM with depression group[12]. Cho/Cr was

increased in frontal white matter of hypothyroidism group but not in DM or DM with hypothyroidism groups[16].

Occipital lobe

Brain glucose levels in occipital lobe were decreased insignificantly and there was no correlation between plasma glucose and brain glucose levels[22]. Cho/Cr and mI/Cr were increased in occipital gray matter of diabetics[23]. Cho/Cr in left occipital gray matter was increased both in T2DM group and T2DM with the hypothyroidism group as well[16]. Decreased NAA and increased glucose levels in right parieto-occipital areas of T2DM subjects[24].

Parietal lobe

In parietal white matter of diabetics mI/Cr levels were increased[23]. Cho/Cr levels were increased in parietal white matter of impaired glucose tolerance group but decreased in T2DM group where as HbA_{1c} levels were inversely proportional to Cho/Cr in parietal white matter but no significant metabolite changes were observed in left parietal white matter[16]. Decreased NAA levels in right parieto-occipital region and increased glucose levels in right parieto-temporal and also in right parieto-occipital region[15].

Thalamus

No significant metabolite changes were observed in thalamus of diabetics[16,25,27] but Glx/GABA levels were higher in right thalamus of diabetic neuropathy group[26].

Subcortical nuclei

Decreased NAA/Cr in the left lenticular nucleus and increased Cho/Cr were observed in left and right lenticular nuclei of T2DM. NAA was inversely proportional to fasting blood glucose and HbA_{1c} levels, where as Cho/Cr was directly proportional to fasting blood glucose and HbA_{1c} in both left and right lenticular nuclei[25]. Glutamate and glutamine levels were decreased more in left subcortical nucleus than the right subcortical nucleus and also increased mI/Cr in both left and right subcortical nuclei[12].

Hippocampus

Hippocampus is a vital structure for learning and memory, increased density of insulin receptors have been found in this region of the brain (Havrankova et al., 1978 & Unger 1991). During chronic stress structural and functional changes have been observed in the rat hippocampus[28]. Glc and Ins levels were significantly increased in ZDF rats when compared with non-diabetic rats, similar changes were observed in patients with diabetes mellitus[23,29]. Serum CRP (c-reactive protein) and RAGE (Receptor for Advanced Glycated Endproducts) were increased along with increased mI levels of left hippocampus in subjects aged above 55 years[27]. There were distinct group wise differences in MRI and ^{1}H-MRS findings between amnestic MCI (Mild Cognitive Impairment) and non-amnestic MCI subtypes. Patients with amnestic MCI tend to have smaller hippocampal volumes and elevated mI/Cr compared with patients with non-amnestic MCI and cognitively normal controls. On the other hand non-amnestic MCI patients have normal hippocampal volumes and normal mI/Cr

but a greater proportion of these patients have cortical infarctions compared with the amnestic MCI patients[30]. Prominent temporal white matter microvascular structural abnormalities were found among T2DM subjects[31].

Specific areas

There was no correlation between cognition and brain metabolites even though cognitive decline was observed in T2DM subjects[32]. NAA/Cr decreased more in the infracted area of DMCI (Diabetes Mellitus Cerebral Infarction) than in NDCI (Non Diabetics Cerebral Infarction) and also in non-infarcted contralateral areas, Lact/Cr increased more in infracted area of DMCI than in NDCI[33]. Increased Glx and decreased GABA levels in right posterior insular areas of diabetic neuropathic patients[26].

CONCLUSION

Most of these studies concluded that there were definite alterations of brain metabolites in T2DM. Few of them revealed that there was a definite cognitive decline in T2DM. NAA levels were mostly decreased, which means neuronal integrity has been effected. Lactate levels were increased in cerebral infarctions and in ischemic conditions which is an indication of increased anaerobic glycolysis. Myo-inositol levels were increased along with decreased cognition. Brain glucose levels even though increased in some studies, but not significantly, which means there was impaired glucose uptake in T2DM. Excitatory neurotransmitters (Glu,Gln) were increased and inhibitory neurotransmitters (GABA) were decreased in T2DM subjects suggestive of abnormal pain regulation. Some studies absolutely contradicting by others in terms of brain metabolite concentrations and this could be because of the following reasons:

- Different studies were done at different parts of the globe.
- Metabolite concentrations vary from one region of brain to the other.
- Different capacities of the MRI machines (1.5 – 7 Tesla) with different shimming and filtering powers were used.
- If the studies were done immediately after a cognitive task or kept the brain idle before the test if so for how long.

Limitations of our review

- There were less number of ^{1}H-MRS studies on T2DM with cognitive dysfunction and brain metabolites.
- Due to its cross-sectional designs it does not permit us to draw elaborative conclusions.
- Meta-analysis of data could not be done because all these studies were not on same region of brain.

Future prospects

- ^{1}H-MRS with other advanced magnetic resonance techniques such as fMRI, Diffusion/Diffusion Tensor Imaging and Perfusion-weighted imaging will prove to be useful in both clinical and research settings.
- Longitudinal studies with large sample size may provide more accurate values.
- More longitudinal studies in different lobes of the brain are required for better analysis.
- To see the relation between brain metabolites and cognition in T2DM.

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Biography

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