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Review Article

Radiology Section

Proton Magnetic Spectroscopy in Diabetic Brain: A Comprehensive Review

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ABSTRACT

Diabetes Mellitus (DM) is on the rise making it a major concern for global health. DM can be classified into type 1 or type 2, and both can lead to changes in brain metabolites. These can result in serious complications like cognitive decline, particularly if not managed properly by diabetic patients. Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique that allows us to study the brain metabolite levels. The present review utilises available Magnetic Resonance Imaging (MRI) data to understand how brain metabolites are affected in both type 1 and type 2 diabetes (T2DM). Research shows that in individuals with diabetes, there are changes in important brain chemicals such as Creatine (Cr), N-Acetyl Aspartate (NAA), Myo-Inositol (MI), Choline (Cho), glutamate, and glutamine. A consistent finding across multiple studies showed a reduction in NAA levels, which is a key indicator of brain neuron health. This suggests that diabetes negatively impacts the function of neurons in the brain. Changes were seen in other metabolites indicating potential disruptions in energy regulation and membrane function. This review concludes that alterations in brain metabolites as measured using MRS, could serve as a non-invasive biomarker for tracking the progression of DM and its related complications.

Keywords: Bio-metabolites, Hypoglycaemia, Magnetic resonance imaging, N-acetyl aspartate, Retinopathy

INTRODUCTION

Once considered a minor significance to world health, DM is now a significant threat. Major contributing factors to the increase in diabetes rate have been escalating changes in the human environment, behaviour, and lifestyle along with globalisation [1]. Diabetes can be mainly classified as Type 1 and Type 2 Diabetes. Type 1 Diabetes (T1DM) is an autoimmune disorder characterised by destroying pancreatic β-cell islets causing absolute insulin deficiency. Diabetes Type 1 can occur in three different stages. The first stage is pre-symptomatic, evidenced by the presence of β cells autoimmunity, and has normoglycaemia along with more islets autoantibodies. Stage 2 is characterised by dysglycaemia with β cell autoimmunity and is pre-symptomatic. Symptoms of disease arise from insulin deficiency in children; this marks the beginning of stage 3 [2]. Collaborative research across multiple centers and technological advancements have enhanced the understanding of Type 1 treatment. There should be confrontment in lifestyles and behaviour to regimen diabetes care; issues such as illness management, unawareness about hypoglycaemia, and caregiver can be observed commonly, but this can be managed with proper attention and knowledge [3].

Resistance to insulin and abnormality in its secretion are the main reasons for T2DM. It accounts for 90% of the cases globally and can result in metabolic hypertension, visceral obesity, hypercoagulability, and microalbuminuria [4]. Diabetes is a global endemic. In 2019 about 463 million diabetic patients were registered, from which 4.2 million death were reported. This value is estimated to increase by 25% in 2030 and to 51% by 2045 [5].

Effect of T1DM on the Brain

Alteration in glucose stability is the primary cause of T1DM. Adverse outcomes have been noticed in children's brains diagnosed with T1DM. There is a significant increase in cognitive impairment in the later adult stage seen in those diagnosed with the disease around the mean age of 8 [6]. A greater incidence of hyperintensities of white matter and loss of functional connectivity has been revealed by MRI studies [7,8]. Thus, it affects both the structure and practical aspects of the brain. Psychologically there are mood swings and disturbances in eating activities. Alteration in metabolic rate has also been noticed. Diabetic ketoacidosis and chronic hyperglycaemia are more injurious than severe hypoglycaemia [9].

Effects of T2DM on the Brain

T2DM can cause brain damage. Reduction in cognitive function concerning attention and memory has been noticed in a poorly controlled diabetic patient. There are specific abnormalities in the central nervous system. Glucose transport at the blood-brain barrier is primarily carried out by the glucose transporter GLUT1 [10]. Some research suggests that brain glucose uptake and metabolism may be influenced by overall levels of blood glucose (glycaemia) [11-13]. Under conditions of chronic hypoglycaemia, some, though not all, researchers have observed an increase in glucose transporters at the blood-brain barrier [12,13]. Conversely, chronic hyperglycaemia in rodents has been linked to a reduction in glucose transporters at the blood-brain barrier [11]. These studies suggest that changes in glucose transport, possibly mediated by GLUT1, maybe one way the brain adjusts to shifts in overall glucose metabolism. MRS is used to evaluate such changes. It identifies the slight changes in glucose concentrations inside the brain as a cause of altered glucose transporter [14].

T2DM affects brain atrophy during midlife; white matter hyperintense lesions with more chances of lacunar infracts have been noted. Cognitive function was seen to be involved in older patients with loss of verbal memory and verbal fluency [15].

IMPACT OF DIABETIC MELLITUS ON SPECIFIC BRAIN AREAS

Frontal Lobe

Blood flow to cerebral regions is decreased in patients with T2DM in the frontal cortex [16]. Patients who are not able to tolerate glucose have elevation in their Cho/Cr level [17]. Myoinositol/Cr ratio is raised in T2 DM category. In DM and DM with depression group, there was an increase in MI/Cr level in frontal white matter [18].

Parietal Lobe
There is an elevation of mL/Cr in parietal white matter [19]. Cho/Cr level is elevated in the parietal case of glucose intolerance, and it is reduced in T2DM patients. In the right parieto-occipital region, there was a reduction in NAA level and an elevation in glucose level [20].

Thalamus
Metabolites are not changed considerably in the thalamus of patients with diabetes [20,21], but there is an elevation of Glx/GABA level in the right thalamus of the neuropathy group [22].

Occipital Lobe
Depletion of glucose level is noted [14]. Cho/Cr and MI/Cr level are raised within the gray matter of the occipital lobe [19]. There is an elevation of Cho/Cr within the gray matter of the left occipital lobe in both T2DM and hypothyroidism T2DM category [20]. NAA is reduced, and elevation of dextrose levels is seen in T2DM patients in their right parieto-occipital area [23].

Subcortical Nuclei
There is a reduction in NAA/Cr level within lenticular nucleus of left-side and elevation of Cho/Cr level within lenticular nuclei involving both sides [21]. Glutamine and glutamate levels are reduced within the left compared to right subcortical area. Also, it is seen that mL/Cr levels are increased in both subcortical nuclei [18].

Spectroscopy
Biochemical changes in the brain, especially tumours, can be measured using MRS. A chemical comparison between abnormal tumour tissue and normal brain tissue is made. The frequency of metabolites parts per million (ppm) such as Cho, amino acid, myoinositol, lipid, lactate, alanine, Cr, and NAA is measured, and graph is plotted with varying peak height. Metabolite ppm is compared with normal brain tissue to determine tissue type [24].

Spectroscopy of Brain
MRS was first used to evaluate brain metabolite in 1980 [25]. It was first used to study the 31 P nucleus, which was used to access energy metabolites such as phosphocreatine and Adenosine Triphosphate (ATP) [26]. Inorganic metabolites such as phosphate and phosphoeters were also accessed. In 1990s data point configuration and water signal nulling techniques made proton spectroscopy extremely common as it has greater sensitivity and convenience [27]. 1.5 Tesla /3 Tesla, were used to obtain signals from Cho, Cr, NAA with longer Time to Echo (TE) in normal brains. At the same time, other compounds, such as alanine and lactate, are observed in pathological conditions in which their concentrations are increased [28]. Glutamate, glutamine, lipids, and myoinositol are detectable at short echo times. Spectroscopy study of the brain is mainly used to evaluate brain tumours [29].

N-Acetyl Aspartate (NAA)
It resonates at 2.01 ppm and produce largest normal brain spectrum, along with unresolved contribution from NAA glutamate (NAAG) [30]. CNS has the most abundant amino acids in the form of NAA. It is responsible for the production of the acetyl group, which in turn synthesises lipids, regulates protein synthesis, and helps NAAG product breakdown [31]. It is often referred to as a neuronal marker as it has restrictions on neurons, axons, and dendrites [32]. Other studies suggest that NAA is also found in non-neuronal cells (isolated oligodendrocytes or mast cells) [33-35]. NAA is recognised as a marker of oligodendrocyte metabolism in multiple sclerosis and is recorded by MRS [36]. It covers the metabolic pathways involving NAA in oligodendrocytes and how disruptions in these pathways can lead to Canavan disease [37]. Study provides insights into the metabolic pathways involving NAA in mast cells and suggests potential roles in immune response modulation [38].

Creatine (Cr)
The Cr signal consists of Cr and phosphocreatine, both are involved in energy metabolism via Cr kinase reaction, which generates ATP. It resonates at 3.03 ppm. The Methylene group of Cr resonates at 3.91 ppm [35]. In a typical brain, Cr shows large white to grey matter regional variations with the former having less as well as high content in the cerebellum compared to the region involving supratentorium [39].

Choline (Cho)
Cho signal consists of trimethylamine groups of glycerophosphocholine, phosphocholine, and little free Cho. It resonates at 3.20 ppm [40]. These are responsible for membrane synthesis and degradation; their level is elevated in a pathological state where increased membrane turnover can be seen. Demyelination can also increase due to inflammation or degradation of myelin phospholipids [36].

Lactate
The resonance peak is obtained at 1.31 ppm. It is detected only in disease conditions like hypoxia and mitochondrial disease [26,28,41].

Myoinositol
Larger signals with short echo times are seen with MI at 3.5-3.6 ppm. It is a part of the inositol triphosphate intracellular second messenger system. Its level is increased in Alzheimer's dementia and demyelinating diseases [42].

Glutamate and Glutamine
Its dominant neurotransmitter, the complete overlap of glutamate and glutamine, can be appreciated at 1.5 T. As the field increases, they can be better resolved and separated individually with proper spectral analysis. Glutamate elevation is observed in patients with plaques involving multiple sclerosis, and in Reyes syndrome there is elevation of Glutamine [43].

SPATIAL LOCALISATION METHODS

Single-Voxel Technique
Signal selection: Slice-selective 90° pulses select signals from intersection regions. Peripheral signals outside the Field Of View (FOV) are removed using field crusher gradients by altering phases of excitation and receiving pulses.

Voxel size: Typically, 4-8 cm^3 voxels are used [44,45].

STEAM (STimulated Echo Acquisition Mode) vs. PRESS (Point RESolved Spectroscopy)
Steam: Uses three 90° pulses to produce a stimulated echo. Advantages include higher bandwidth, lower power requirements, better slice profiles, and shorter echo times, especially beneficial at field strengths above 3T.

Press: Involves one 90° and two 180° refocused pulses to produce a spin echo, resulting in signals that are double those of STEAM. Long TE PRESS has superior Signal-to-Noise Ratio (SNR) and is better for metabolites with longer T2 (Cr, NAA, lactate, and Cho), while short TE is better for those with shorter T2 [46].

Laser technique: Used when inhomogeneous surface coils or non-uniform RF fields prevent achieving the desired flip angle. This localisation technique utilises half-adiabatic passage 90° pulses and three pairs of hyperbolic secant refocusing pulses. These help to achieve homogeneous excitation and also minimise chemical shift displacement errors during imaging [47].

Multivoxel Technique
MRSI: Uses the PRESS sequence for signal excitation in two phase-encoding directions to ensure a homogeneous B0 field in the desired region. It offers spatial resolution with limited phase encoding steps and avoids scalp lipid excitation.

Advantages and disadvantages: It minimises artifacts due to field inhomogeneity, residual water, and lipids for large spatial coverage using larger TE (140-280 ms). However, it can produce inhomogeneous signals around the edges of the PRESS voxel due to inadequate 180° slices [48].

ADVANCED MRSI TECHNIQUES

Advanced MRI Techniques

I. Magnetic Resonance Spectroscopy (MRS) Turbo Spin Echo Imaging

Technique: Uses gradient encoding in the phase direction to acquire multiple signal echoes, reducing scan time by a factor of 3-4 per TR.

Disadvantages: Reduction in signal in late echoes due to T2 relaxation, making it less effective for compounds with shorter T2 relaxation times.

Application: Primarily used to study brain tumours [49].

II. Echo Planar Imaging Spectroscopy and Spiral Spectroscopy Imaging

Echo Planar Imaging (EPI): Collects spectral and spatial information using fluctuating gradient readout. Reduces scan time by minimising phase encoding steps but requires high-performance gradients. Potential ghost artifacts are compensated by combining data from spatial transformation with readout lines of opposite directions.

Spiral spectroscopy imaging: Uses gradient waveforms in two dimensions to fill k-space in a spiral trajectory from center to periphery. Multiple gradient waveforms per TR achieve an optimal FOV and spatial resolution. Raw data is resampled in a linear k-space and processed with a Fourier transformation algorithm [50].

III. Parallel Encoded MRSI

Technique: Utilises multiple receiver phase array coils with varying sensitivity profiles to reduce scan time and encode spectral signals.

Unwrapping: Each coil's sensitivity profile helps unwrap aliased spectroscopy images produced in SENSE. SMASH and GRAPPA techniques estimate missing data points in k-space [51,52].

Spectroscopy technique for suppression of water and lipid: To visualise brain metabolites within brain; water, and lipids needs to be suppressed as there is a high concentration of lipids in the scalp, and 80 M of water is present inside the brain. CHESS technique is used to suppress water inside the brain spectra. Best suppression can be acheived using the CHESS technique with sufficient delay and varied flip angle application. WET and Vapor techniques are used to produce pulses. Lipid suppression is performed using three techniques; spatial outer volume suppression, frequency selective saturation pulses, and inversion recovery pulse sequence [53].

Spectral editing technique: Spectral editing techniques are used to obtain information from metabolites that are obscured in conventional brain MRS, such as GABA while suppressing signals from unwanted compounds. MEGA-PRESS sequence is used. It uses coupled spin systems. This coupling system between two functional groups modifies the signal in one group by application of the desired rf pulse. The second scan is acquired using non selective rf pulse and TE of approximately 68 milliseconds, which results in inverted peaks; then subtraction of the first scan from the second is done to obtain resonance [54].

Spectral data interpretation and quantification: There is a direct relationship between metabolic concentration and area of spectral peak. Various factors such as baseline distortions, non-ideal lineshapes, resonance overlap, time of relaxation, sequences used, and hardware of scanner make this measurement complicated. This can be overcome by simple integrations linear combination model, which is used for automatic phase correction and baseline correction [55].

This review delves into the application of proton magnetic spectroscopy in understanding the diabetic brain mainly focusing on the alteration of metabolites and their potential as biomarkers for diabetic mellitus, providing a comprehensive overview of its utility in diagnosing and monitoring diabetes-related brain changes.

DISCUSSION

Diabetic Patients with Retinopathy

Diabetic Retinopathy (DR) is a microvascular complication. In this case, there will be loss of vision due to sequelae of maculopathy (macular oedema and ischemia) and neovascularisation of the retina (vitreous haemorrhage and retinal detachment) and iris (neovascular glaucoma) [56]. Retinopathy can be used as an indicator of cerebrovascular dysfunction due to homology between retinal and cerebral microvasculature. Tong J et al., conducted a study using H-MRS to evaluate changes in brain metabolite in DM type 2 patients having DR. The study included T2 DM DR patients, Non-DR T2DM patients (DM group), and patients in the control group. A 3.0 TMRI/MRS imager was used to perform single voxel 1H-MRS (TR: 2000 ms, TE:30 ms) in the left white matter of the frontal region, left-sided lenticular nucleus, and optic radiation of the left-side. The study showed that the NAA/Cr ratios of the DR group were 11.7% and 6.5%, lower than those of the DM group in the frontal white matter and optic radiation, respectively. MI/Cr ratios were raised by 22% in the lenticular nucleus of the DM group than those in the normal group, while in DR group MI/Cr ratios were decreased by 24.6% than those in the DM group. In white matter of the frontal region, NAA/Cho ratios were found to be 15.5% lower compared to the NC group. The study indicated a negative association of NAA/Cr ratios with the severity of DR in optic radiation and white matter of the frontal region. Reduction in NAA and MI suggested glial and neuronal loss, respectively. This study concluded that patients with DR suffered cerebral neuron and glial cell damage [57].

Ozsoy E conducted another study to estimate changes in different metabolites inside diabetes patients involving the visual cortex by application of magnetic spectroscopy imaging between two group having proliferative and non-proliferative DR. The analysis was performed with three groups as mentioned Group-1: normal subjects, Group 2: diabetes patients without retinopathy (NPDR), and Group-3: diabetic patients with non-proliferative diabetic retinopathy (PDR). Depending on the HbA1c levels, diabetic patients were divided into two groups. In all cases left visual cortex, amounts of creatinine, NAA, Cho were evaluated using MRS. Estimation of NAA/Cr, Cho/Cr, and NAA/Cho ratios were done. No significant differences were seen between the groups. This study concluded that the decrease in NAA/Cr and NAA/Cho ratios in the visual cortex with progression in DR was insignificant, and elevation in HBA1c levels with depletion in NAA concentration in the visual cortex indicated neuronal loss. Thus, according to this study, visual cortex metabolic changes are linked with acute events [58].

Hypertension

Hypertension is seen in 60% of T2DM patients. Hence, these patients might have pronounced brain metabolite alterations [59]. A study was conducted by Cao Z et al., on patients having Diabetic Hypertension (DHT) and control volunteers to see the alteration in brain metabolites. The study concluded that Cho/Cr and NAA/Cr ratios were reduced dramatically in the cortical frontal region [60]. Another study done by Kario K et al., summarised reduction in NAA/Cr ratio in the white matter of parietal region in contrast to control volunteers . Above study showed region-specific disorders of the brain metabolite could be caused by DHT, and Cho/Cr and NAA/Cr ratios can be used as biomarkers for indication of damage [61].

Diabetic Peripheral Neuropathy

Diabetic Peripheral Neuropathy (DPN) is clinically manifested as paraesthesia, ulcers, osteomyelitis, and loss of sensibility. Its

mechanism is, however, unclear till date [62]. Sorensen L et al., studied three subgroups: T2 DM patients without pain, T2DM patients with neuropathic pain, and healthy controls to evaluate the level of brain metabolite in patients with diabetic neuropathy. The study revealed that Cr and NAA levels in the thalamic and dorsolateral prefrontal cortex region in the DM patient group were reduced compared to healthy volunteer controls. In the thalamic region, the NAA level was lower in DPN patients compared to DM patients without pain [63]. Another study by Selvarajah D et al., showed decreased NAA/Cho ratio and NAA/cr ratio for patients with DPN versus DM patients and healthy volunteer controls in the thalamic region. Further, NAA/cr level were correlated positively with sural 12 amplitudes and velocities of nerve conduction [64]. Therefore, DM can affect both brain as well as peripheral nerve metabolism.

Effect of T1DM on Brain Metabolites

Sarac K et al., studied changes in metabolites with uncontrolled T1DM in children's brain using spectroscopy. A single voxel was used. A note of medications, hypoglycaemia episodes, disease duration, and haemoglobin A1C level was made. Regions such as the left basal ganglion, left posterior parietal white matter, and pons were studied using voxels. (Cho/Cr) and (NAA/Cr) and ratios were measured. HbA1C average level was found to be (8.2-19.4), which meant the number of episodes of ketoacidosis was (0-9), and the daily insulin injections average number was (2-4). A total of 132 spectra were sampled. MRS showed that in the pons, there were lower levels of Cho/Cr and NAA/Cr ratio, and in the left white matter side of the posterior parietal region there was lower NAA/Cr in diabetic children as compared to control. Observation showed no correlation between several hypoglycaemia and metabolite ratios. A decrease in NAA in the pons region indicates a neuronal loss or impaired function, and a reduction in Cho relates to dynamic changes in membrane lipids [65].

Another study was performed by Mangia S et al., on patients with well-controlled T1 DM and non-diabetic controls acquired during a hyperglycaemic clamp (HbA1C glycosylated haemoglobin):75±2%. The result showed a reduction in the grey matter of the lobe of the occipital by 6% ($p<0.05$) in glutamate and NAA. Other brain metabolites showed no significant changes [66].

A study by Heikkilä O et al., showed a similar reduction in NAA of 6% in regions such as white matter, frontal cortex, and thalamic region of patients and controlled. An increase of 20% in NAA and MI was observed in the white matter of the frontal lobe, and an elevation of 8 % was seen in the frontal cortex. The study showed that peripheral glucose was an important determinant of brain energy expenditure [67].

T2DM changes in Brain Metabolites

A study was conducted by Sinha S et al., to investigate the brain metabolite concentrations of NAA, Cho, MI, glutamate, glutamine, Cr, and glucose in T2DM patients and control subjects. They used single-voxel proton MRS to examine the right frontal, right parietal-temporal, and right parietal-occipital regions of the brain. It was seen that when compared with the control, Glutamine and Glutamate were increased in the frontal region on the right-side. A lower NAA level was noted in the occipital region, the right parietal, and the frontal region of the right-side. Glucose level was increased in all areas of the brain. No significant changes were seen in Cho, MI, and Cr [23].

Another study was conducted by Lin Y et al., to show metabolite levels in the thalamic region, and lenticular nuclei Cho, NAA, and Cr levels were studied. Subjects with DM type 2 and control were studied using a single voxel MRS. It was seen that left lenticular nuclei had decreased NAA/Cr ratio, and there was an increased Cho/Cr ratio in bilateral lenticular nuclei. The negative correlation of HbA1C and fasting blood glucose was seen with NAA/Cr ratio, and a positive correlation of the Cho/Cr ratio with the same variables was noted. No significant changes were observed in the thalamus [21].

Sahin I et al., found an alteration in brain metabolites in patients with impaired glucose tolerance. The study was performed on patients with T2 DM, control, and impaired glucose intolerance patients. Placement of voxel was done in the thalamus, parietal white matter, and frontal cortex. Compared to the control, patients with impaired tolerance to glucose had elevated Cho/Cr ratio in their cortical frontal region. In the parietal case, there was lower Cho/Cr in T2 DM than in the control. In the diabetic group, the parietal white matter Cho/Cr ratio was decreased, and the frontal cortical MI/Cr ratio increased compared to the control. Well-controlled diabetic patients have a higher Cho/Cr ratio than patients with poorly controlled T2 DM [17].

Based on collective findings, T2DM can cause changes in the metabolic status of the brain. A decreased concentration of NAA indicates reduced viability of neurons, while elevated Glutamine and Glutamate indicate fluid imbalance [57]. Marker for neurons and axons is shown by NAA, showing functional status as well as the number of neurons. Cr is associated with energy metabolism, and cell membrane and myelin formation are done by Cho. Several studies have shown diabetes's effect on the cortex of the brain and its impact on specific nuclei of the brain have been shown in few studies [17,21,23]. Most studies suggest diabetes affects the function and several neurons of the central region, which is shown by the decrease in NAA level [65-67]. Poor glycaemic control in diabetic patients is associated with brain damage by A1C level 2 and dysfunction of neurons [21,67].

CONCLUSION(S)

The present review focused on the effect of DM and other associated conditions on different metabolites of the brain. Significant alterations in metabolite levels of the brain, such as MI/Cr, NAA/Cr, Glu, Glutamine, and Cho, are noted in patients with DM when compared to control volunteers, suggestive of neurotransmission, metabolism of energy, and impairment of lipid membrane metabolism. Lactate levels are seen elevated in ischemic conditions and cerebral infarction, which indicate an increase in anaerobic glycosis. Decrease in NAA level indicates affected neuronal integrity. There is a decrease in cognition function with increased myoinositol. Brain metabolites can be used as non invasive biomarkers for DM related complications and advancement. Furthermore, they can be used to monitor the effectiveness of the treatment.

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