Original Research Article

Assessment of changes in brain metabolites in patients with type-2 diabetes mellitus using proton magnetic resonance spectroscopy – One year hospital based cross sectional study

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Abstract

Diabetes mellitus is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world and a major growing threat to global public health. Diabetes Mellitus has evolved into a global epidemic and India has the second largest population with diabetes. Patients with type 2 diabetes mellitus accompanied with baseline blood chemistry reports or history referred for a H-MRS during the study period at Department of Radio Diagnosis. Once a patient fulfilled the inclusion criteria for this study he / she was administered the predesigned / pretested proforma Demographic characteristics of the study population such as age, sex were obtained through an interview. In the present study, NAA was decreased in 65% of the patients. Choline, Creatine and Myoinisitol were normal in all the patients diabetes (i.e. it is normal) while, Glucose was increased in 90% of the patients and Glx (Glu+Gln) was increased in 80% of the patients.

Key Words: Brain Metabolites, Type-2 Diabetes Mellitus, Proton Magnetic Resonance Spectroscopy.

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INTRODUCTION

Diabetes mellitus (DM), a metabolic disease is characterized by hyperglycemia which results from defects in either insulin secretion or insulin action or both.[1] Patients with little or no endogenous insulin secretory capacity called as Type 1 (previously Insulin Dependent Diabetes Mellitus [IDDM]) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response are known as Type 2 (Previously known as Non Insulin Dependent Diabetes Mellitus [NIDDM]).[1,2] Diabetes mellitus is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world and a major growing threat to global public health.[1] Diabetes Mellitus has evolved into a global epidemic and India has the second largest population with diabetes. Diabetes and its complications caused 40.9 million deaths in 2014 and every seven second a person dies from diabetes or its complication. Based on the recent statistics of International Diabetes Association it is estimated that worldwide 387 million people have diabetes and by 2035 this will rise to 592 million. The prevalence in India is over 65 million and these figures are expected to increase to over 100 million by 2030.[3,4] The rise of prevalence has been more alarming in developing countries than in developed countries (69% versus 20%). Unfortunately, more than 50% of the diabetic patients in India remain unaware of their diabetic status, which increases the risk of development of

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diabetic complications in them.[5]It has also been found that 66% of the Indian diabetics are not diagnosed, as compared to 50% in Europe and 33% in the USA. India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country.[6] The rising prevalence of type 2 DM is closely associated with westernization, industrialization and socioeconomic development.[5] The chronic hyperglycemia of diabetes results in long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. Hence, early identification of the risk factors associated with diabetes and appropriate interventions aimed at preventing the onset of diabetes and its complications are urgently required. Previous studies have reported that, diabetics had a 20–70% more decline in cognitive performance, and a 60% higher risk of dementia.[7] 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.[8] There are different methods to assess the cognitive dysfunction namely, Neurocognitive testing,[9] evoked potentials, EEG, MRI, fMRI, SPECT, PET.[9] 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.[10] 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.[11]Myo-inositol levels are believed to represent glial proliferation or an increase in glial cell size both of which may occur in inflammation.[12] 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] Overall, the brain is a target for diabetic end-organ damage, though the pathophysiology of diabetic encephalopathy is still not well understood. Many metabolic changes are seen in T2DM patients. Each of these metabolites appears at specific parts per million frequency and reflect specific cellular and biochemical process.[12] The present study was undertaken to get an insight into the pathophysiology of cerebral damages caused due to diabetes by assessing the changes in brain metabolites in patients with T2DM using proton magnetic resonance spectroscopy so as to provide important information in treatment of T2DM patients and improve the health care quality by early diagnosis of brain changes occurring in T2DM patients.

MATERIAL AND METHODS

This study was carried out at Department of Radio Diagnosis, a teaching hospital attached Medical College. Patients with type 2 diabetes mellitus accompanied with baseline blood chemistry reports or history referred for a H-MRS during the study period at Department of Radio Diagnosis. Once a patient fulfilled the inclusion criteria for this study he / she was administered the predesigned / pretested proforma Demographic characteristics of the study population such as age, sex were obtained through an interview. The patients were then briefed about the procedure i.e. about the noise of the gradient coils and need to control the body movements for successful image acquisition. The patient was asked to lie in supine position.

Imaging

Magnetic resonance imaging

- MRI brain of all patients was carried out using 1.5 Tesla Symphony Maestro class-MRI with the help of a dedicated brain coil.

The tests were performed using following parameters.

- FOV – 230 mm
- Slice thickness – 4 mm
- Matrix size – 256 x 256
- The following sequences were obtained: spin-echo T1-weighted (axial/saggital), spin-echo T2-weighted (axial/coronal/FLAIR), MR spectroscopy of brain.

1H Magnetic resonance spectroscopy: Global shimming and local shimming were carried out prior to spectroscopic measurements to adjust for static and dynamic magnetic field in homogeneities. The global shimming was optimized at 15-17 Hz, and FWHM between 5-7 Hz. Areas of edema, adjoining calvarium, ventricles and paranasal sinuses were avoided to prevent signal contamination. Optimal shimming and water suppression were achieved in most cases. 1H MR spectroscopy was carried out using multivoxel (MV) techniques at short TE (30 ms), long TE (270 ms) and intermediate TE(135ms) wherever appropriate, with an acquisition time of approximately 5-10 minutes each using STEAM (stimulated echo acquisition method) sequence. The voxel size was selected depending upon the area of interest and multi voxel MRS is being used. Based on the literature,prior experience with normal subjects and software standardization values of Cho/Cr > 1.5, NAA/Cr < 1.6 and NAA/Cho < 1.2 were taken as abnormal.

Outcome variables: The MR spectroscopic results were evaluated for the distribution of spectra across the area of interest and for signal ratios in different metabolites. The metabolites and ratios assessed were:

1. NAA/Cr
2. Cho/Cr
3. NAA/Cho

RESULTS

Table 1: Distribution of study population according to the sex

Sex	Distribution (n=40)	
	Number	Percentage
Male	22	55.00
Female	18	45.00
Total	**40**	**100.00**

In the present study 55% of the patients were males and 45% were females. The male female ratio was 1.22:1

Table 2: Distribution of study population according to the Neurological symptoms

Neurological symptoms	Distribution (n=40)	
	Number	Percentage
Headache	23	57.50
Hemiplegia / Quadriplegia	26	65.00
Blurring of vision	20	50.00
Memory loss	18	45.00
Depression	15	37.50
Total	**40**	**100.00**

In the present study most common neurological symptom was hemiplegia / quadriplegia noted in 65% of the patient followed by headache (57.50%).

Table 3: Distribution of study population according to the random blood sugar levels

Random blood sugar (mg/dL)	Distribution (n=40)	
	Number	Percentage
< 200	0	0.00
200 or more	40	100.00
Total	**40**	**100.00**

In the present study all the patients (100%) had elevated random blood sugar levels.

Table 4: Distribution of study population to the findings on Spin echo T1 weighted axial / saggital

Findings	Distribution (n=40)	
	Number	Percentage
Hypo	16	40.00
N	10	25.00
SIN	5	12.50
AT	3	7.50
ES	2	5.00
AT, SIN	1	2.50
MAS	1	2.50
PAN	1	2.50
Blank	1	2.50
Total	**40**	**100.00**

In the present study on Spin echo T1 weighted axial / saggital imaging most of the patients with hypointense (40.00%) areas.

Table 5: Distribution of study population to the findings on Spin echo T2 weighted axial / coronal/FLAIR

Findings	Distribution (n=40)	
	Number	Percentage
Hyperintense	16	40.00
Normal	10	25.00
SIN	4	10.00
AT	4	10.00
ES	2	5.00
MAS	1	2.50
PAN	1	2.50
SIN, Hyper	2	5.00
Total	**40**	**100.00**

In the present study on Spin echo T2 weighted axial / coronal imaging most of the patients with hyperintense (40.00%) areas.

Table 6: Distribution of study population according to the Metabolites

Metabolites	Findings	Distribution (n=40)	
		Number	Percentage
NAA	Normal (2.0)	14	35.00
	Low (<2.0)	26	65.00
	Raised	0	0.00
	Total	**40**	**100.00**
Choline	Normal (3.20)	40	100.00
	Raised (<3.20)	0	0.00
	Low (>3.20)	0	0.00
	Total	**40**	**100.00**
Creatine (Cr)	Normal (3.0)	40	100.00
	Low (< 3.0)	0	0.00
	Raised (>3.0)	0	0.00
	Total	**40**	**100.00**
Myoinositol	Normal (3.5)	40	100.00
	Low (<3.5)	0	0.00
	Raised (>3.5)	0	0.00
	Total	**40**	**100.00**
Glucose	Normal (3.4-3.8)	4	10.00
	Raised (> 3.40)	36	90.00
	Low (< 3.40)	0	0.00
	Total	**40**	**100.00**
Glx (Glu+Gln)	Normal (2.20 – 2.40)	8	20.00
	Raised (>2.40)	32	80.00
	Low (<2.20)	0	0.00
	Total	**40**	**100.00**

In the present study, NAA was decreased in 65% of the patients. Choline, Creatine and Myoinisitol were normal

in all the patients diabetes (i.e. it is normal) while, Glucose was increased in 90% of the patients and Glx(Glu+Gln) was increased in 80% of the patients.

DISCUSSION

Diabetes is a major health problem affecting approximately 18 million Americans. It is a growing crisis that has devastating complications including heart disease, peripheral neuropathy, renal disease, and retinopathy.[13] Type 2 diabetes mellitus is an extremely prevalent metabolic disease, which is associated with a variety of acute and chronic complications. The brain is a target for diabetic end-organ damage, though the path physiology of diabetic encephalopathy is still not well understood. Many metabolic changes are seen in Diabetes Mellitus -2 patients. Previous works have shown that DM causes metabolic changes in the brain, especially in the cerebral cortex and white matter. Most studies[9,12] suggest that diabetes affects either the number or the function of central neurons, which is mirrored by a reduction in NAA levels and a lower NAA/Cr ratio. However, studies investigating the effects of diabetes on Cho metabolism have produced inconsistent results. [9,12] Each of these metabolites appears at specific parts per million frequency and reflect specific cellular and biochemical process. Concentration of which will be measured in parts per million. Among the metabolites N-acetyl aspartate is a neuronal marker and decreases in DiabetesMellitus-2.Creatine provides a measure of energy stores and Choline is a measure of increased cellular turnover which may or may not show changes in the brain. Glutamate and Glutamine levels are increased in type 2 diabetes mellitus.[9] Proton resonance imaging provides a measure of brain chemistry in a time span of 10 to 15 minutes and can be added to conventional imaging protocols, because it is very safe and there are no known health risks associated with the magnetic field or the radio waves used by the machine. T1 and T2 weighted images will be taken prior to proton magnetic resonance imaging to mark the area of interest so that spectrum can be put while performing Proton Magnetic resonance imaging. This study was aimed to investigate the effect of diabetes on the metabolic profile of brain of patients having diabetes using invivo magnetic resonance spectroscopy to get an insight into the pathophysiology of cerebral damages caused due to diabetes.

It is reported that, the prevalence of diabetes is higher in men than women. Same was true in the present study as most of the diabetics were males (55%) and 45% were females. The male female ratio was 1.22:1. In this study, with regard to imaging characteristics, the most common location was Frontal, parietal and temporal region (57.50%). On Spin echo T1 weighted axial / saggital imaging most of the patients had hypointense (40.00%) areas. On Spin echo T2 weighted axial/coronal/FLAIR imaging most of the patients had hyperintense (40.00%) areas. Glutamate and N-acetylaspartyl-glutamate are localized with N-acetyl aspartate in neurons. Breakdown of N-acetyl-aspartylglutamate releases both N-acetyl aspartate and glutamate and subsequent breakdown of N-acetyl aspartate leads to aspartate. These compounds are excitatory amino acids and are increased with ischemia. It is possible that, in the near future, concentrationsof N-acetyl-aspartyl-glutamate and glutamate may serve to monitor treatments designed to protect brain tissues by blocking excitatory amino acids. In certain other conditions also N-acetyl aspartate is of importance. Example in Canavan disease (it is the only disease in which N-acetyl aspartate is increased).In normal spectra, N-acetyl aspartate is the largest Peak.[14] Choline is a constituent of the phospholipid metabolism of cell membranes and reflects membrane turnover, and it is a precursor for acetylcholine and phosphatidylcholine5. The latter compound is used to build cell membranes, whereas the former is a critical neurotransmitter involved in memory, cognition, and mood. Therefore, increased Choline probably reflects increased membrane synthesis and/or an increased number of cells. Overall based on the results of this study it is it is clear that patients with type 2 diabetes mellitus are likely to have alteration in brain metabolite profile. However, besides the results presented herein, this study has some limitations which need to be addressed such as small sample size and study design we presume that case control study design may have provided the exact risk of alteration of brain metabolites in patients with type 2 diabetes mellitus. In addition, estimation of HbA1c a reliable marker of glycaemic control was not taken into account. Hence, the conclusions of the present study need to be validated further with large sample size and glycaemic control.

CONCLUSION

Based on the results of this study it may be concluded that, patients with type 2 diabetes mellitus are likely to have alteration in brain metabolite profile. Furthermore, patients with type 2 diabetes mellitus may have decreased NAA, increased Glc and Glx (Glu+Gln) and normal Choline, Creatine and Myoinisitol while, normal NAA/Cho Ratio, raised Cho/Cr ratio and GLx(GLU+Gln) ratio. Proton magnetic resonance spectroscopy is helpful in the evaluation of type 2 brain metabolites in patients with type 2 diabetes mellitus.

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