Original Research Article

Pattern of brain metabolite ratios among diabetics: Magnetic resonance spectroscopy

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Abstract

Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. In early stages of type 2, the predominant abnormality reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. All the patients of age group above 30 years, based on blood sugar level (available or no) underwent single voxel H-MRS 1.5Tesla and the scans was reviewed in the department of radio-diagnosis. In this study 30.00% of the patients were aged between 61 to 70 years. The mean age was 57.93 ± 12.82 Year and median age was 57 years with 32 being minimum and 83 being maximum. In this study majority of the patients (97.50%) had raised fasting blood sugar levels (>125 mg/dL).

Key Words: Brain Metabolite Ratios, Diabetics, Magnetic Resonance Spectroscopy.

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INTRODUCTION

Diabetes mellitus (DM), a chronic metabolic disorder of impaired metabolism of carbohydrates, fats, and proteins, characterized by hyperglycemia resulting from decreased utilization of carbohydrate and gluconeogenesis from amino acids and fatty acids.[1] First diseases described with an Egyptian manuscript mentioning “too great emptying of urine”.[2,3] Indian physicians around same time identified the disease and classified it as “Madhumeha” or “Honey urine”, noting urine would attract ants. “Diabetes” or “to pass through” was first used in 230 BC by Greek Apollonius of Memphis. Galen named the disease “diarrhoea of the urine” (diarrhoeaurinosa).[4] Diabetes is classified into four broad categories viz. type 1, type 2, gestational diabetes and other specific types. The "other specific types" are a collection of few dozen individual causes.[5] Type 1 DM is characterized by loss of insulin producing beta cells of the islets of langerhans in pancreas, leading to insulin deficiency. Majority of type 1 diabetes is the immune-mediated nature, in which T-cell mediated autoimmune attack leads to the loss of beta cells and thus insulin. Traditionally, termed as juvenile diabetes because a majority of these diabetes cases were in children.[5] Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. In early stages of type 2, the predominant abnormality reduced insulin sensitivity. At this stage, hyperglycaemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. Type 2 DM is due to genetics and lifestyle factors including obesity, lack of physical activity, poor diet, stress and urbanization. A lack of exercise is believed to cause 7% of cases.[5] Gestational DM (GDM) involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2-10% of all pregnancies and may improve or disappear after delivery.[5] Various imaging modalities including MRI (Magnetic Resonance Imaging), MRS (Magnetic Resonance Spectroscopy), CT scan, PET (Positron Emission Tomography), SPECT (Single-Photon Emission Computed Tomography) and cerebral blood flow imaging

have been used to study the pathology of the brain inflicted by diabetes mellitus. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a sensitive, non-invasive technique that provides metabolic information on the status of viability of neurons and on the membrane metabolism of the brain. The brain metabolites, generally observed in H-MRS, are: N-acetylaspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (mI), glutamate (Glu) and glutamine (Gln). Several researchers have studied the metabolic changes in the brain due to various clinical disorders affecting the central nervous system, including tumours, infarction and ischemia, multiple sclerosis, Alzheimer's disease, and epilepsy. It has also been used to assess metabolic changes in the brain of patients with obstructive sleep apnea (OSA) and COPD.[6] With Echo times (TEs) as short as 30 milliseconds, an adequate MR spectra may be obtained and also with TEs as long as 135 to 270 milliseconds. Using long Echo times (TEs), the signal from most metabolites in the brain is lost except that of choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), and lactate. Conversely, short Echo times (TEs) allow for identification of many other metabolites (e.g., my inositol, glutamate, glutamine, and glycine.[7] 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, concentrations of 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.[8] Choline is a constituent of the cost will be phospholipid metabolism of cell membranes and reflects membrane turnover, and it is a precursor for acetylcholine and phosphatidylcholine. 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 cell. Glutamate is an excitatory neurotransmitter, which plays a role in mitochondrial metabolism. Gamma-amino butyric acid is an important product of glutamate. Glutamine plays a role in detoxification and regulation of neurotransmitter activities.[9] Hydrogen 1 (1H) magnetic resonance (MR) spectroscopy enables noninvasive quantification of in vivo metabolite concentrations in the brain. It has proved to be a powerful addition to the clinical assessment tools for numerous pathologic conditions, including epilepsy, multiple sclerosis, stroke, cancer, and metabolic diseases.[10]

MATERIAL AND METHODS

The study was conducted in the Department of Radio-diagnosis and the present study design was a one year hospital based cross sectional study.

Inclusion Criteria

- All the patients of age group above 30 years, based on blood sugar level(available or no) underwent single voxel H-MRS 1.5Tesla and the scans was reviewed in the department of radio-diagnosis.

Exclusion Criteria

- Patients of age below 30 yrs.
- Unstable patients on mechanical ventilator.

Informed Consent

Patients fulfilling the selection criteria were informed about the purpose and nature of the study and were enrolled after obtaining a written informed consent

RESULTS

Table 1: Distribution of study population according to the age

Age group (Years)	Distribution (n=40)	
	Number	Percentage
30 to 40	4	10.00
41 to 50	8	20.00
51 to 60	11	27.50
61 to 70	12	30.00
71 to 80	3	7.50
81 to 90	2	5.00
Total	**40**	**100.00**

In this study 30.00% of the patients were aged between 61 to 70 years. The mean age was 57.93 ± 12.82 Year and median age was 57 years with 32 being minimum and 83 being maximum.

Table 2: Distribution of study population according to the past medical history

Medical History	Distribution (n=40)	
	Number	Percentage
Hypertension	26	65.00
End organ damage	20	50.00
Cardiovascular events	18	45.00
Loss of intellectual tasks	17	42.50
Total	**40**	**100.00**

In this study most of the patients reported history of hypertension (65.00%) followed by end organ damage (50%).

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

Fasting blood sugar (mg/dL)	Distribution (n=40)	
	Number	Percentage
< 100	0	0.00
101-125	1	2.50
>125	39	97.50
Total	**40**	**100.00**

In this study majority of the patients (97.50%) had raised fasting blood sugar levels (>125 mg/dL).

Table 4: Distribution of study population according to the post prandial blood sugar

Post prandial blood sugar (mg/dL)	Distribution (n=40)	
	Number	Percentage
< 140	0	0.00
141-199	0	0.00
200 or more	40	100.00
Total	**40**	**100.00**

In the present study majority all the patients (100%) had raised post prandial blood sugar levels (>125 mg/dL).

Table 5: Metabolites

Variables		Distribution (n=40)		Median	Range	
		Mean	SD		Min	Max
NAA	ppm	1.88	0.13	1.80	1.40	2.05
	int	104.51	32.38	92.30	80.24	205.47
	RT	3.11	1.08	3.08	1.00	4.81
Cr	Ppm	4.29	7.87	3.04	3.02	52.80
	Int	59.50	16.62	58.90	1.00	102.03
	RT	0.98	0.38	1.00	0.70	3.20
NAA/Cr	**RT**	**3.34**	**1.29**	**3.53**	**0.94**	**6.57**
Cho	Ppm	4.40	7.46	3.22	3.19	50.38
	Int	62.73	17.15	61.78	0.73	101.66
	RT	1.15	0.51	1.04	0.50	3.56
NAA/Cho	**RT**	**3.08**	**1.56**	**2.98**	**0.85**	**7.44**
Cr2	Ppm	4.13	1.90	3.92	3.55	15.80
	Int	35.21	17.30	38.03	0.37	97.76
	RT	0.64	0.53	0.63	0.22	3.50
Cho/Cr	**RT**	**2.28**	**1.24**	**1.94**	**0.69**	**7.27**
INSdd	Ppm	5.88	13.78	3.56	3.50	90.85
	Int	46.62	28.64	34.04	15.84	104.56
	RT	0.70	0.43	0.70	0.18	1.50
Glx(glu+gln)	pm	2.387	0.11	2.42	2.00	2.50
	Int	127.44	230.25	86.28	24.65	154.10
	RT	7.02	10.62	5.71	1.43	71.62
GLx(GLU+Gln)	**RT**	**7.02**	**10.62**	**5.71**	**1.43**	**71.62**
Glc	Ppm	4.13	1.90	3.92	3.55	4.01
	Int	45.80	25.70	41.87	8.83	104.56
	RT	0.43	0.29	0.31	0.23	1.57

The characteristics of the study population with respect to different metabolite ratios is as shown in Table 5.

DISCUSSION

In this study 30.00% of the patients were aged between 61 to 70 years. The mean age was 57.93 ± 12.82 Year and median age was 57 years with 32 being minimum and 83 being maximum. These findings show that, diabetes mellitus was widely prevalent among elderly. The higher prevalence of diabetes among aged can be explained by the rise in the segment of geriatric population. In the present study with regard to clinical profile most common neurological symptom was hemiplegia / quadriplegia noted in 65% of the patient followed by headache (57.50%). Most of the patients reported history of hypertension (65.00%) followed by end organ damage (50%). With regard to diabetic characteristics, majority of the patients (97.50%) had raised fasting blood sugar levels (>125 mg/dL) and all the patients (100%) had raised post prandial as well as random blood sugar levels (>200 mg/dL) The mean fasting blood sugar levels were 143.25 ± 13.55 mg/dL with median levels of 140 mg/dL with range 125 mg/dL being minimum and 175 mg/dL maximum. Similar observations were noted with post prandial blood sugar levels (mean 305 ± 77.61 mg/dL; median 303 mg/dL Range 210- 520 mg/dL) and random blood sugar (mean 331 ± 81.95 mg/dL; median 318 mg/dL Range 214- 605 mg/dL). Recent evidences have shown that the brain is the target for diabetic end organ damage. There are seen metabolic disturbances impairing the integrity of the brain.[11]Accordingly, in the present study with regard to metabolites, NAA was decreased in 65% of the patients. Choline, Creatine and Myoinisitol were normal in all the patients diabetes while, Glucose was increased in 90% of the patients and Glx (Glu+Gln) was increased in 80% of the patients. Furthermore, NAA/Cr ratio normal (>1.6) in majority of the patients (92.50%), NAA/Cho Ratio was normal (>1.2) in majority of the patients (92.50%), abnormal Cho/Cr ratio (>1.5) was noted in 75.00%. These findings suggest that, patients with diabetes mellitus are likely to have decreased NAA, increased Glcand Glx (Glu+Gln) and normal Choline, Creatine and Myoinisitol while, low NAA/Cho Ratio, raised Cho/Cr ratio and GLx (GLU+Gln) ratio. Proton MR spectroscopy can be used to determine the resonance peaks of many kinds of brain metabolites and neurotransmitters but is most often used to monitor NAA, Cho, Cr, and lactic acid.1 NAA is a marker for neurons and axons, reflecting the number and functional status of neurons. Cho, mainly distributed in the glial cells is involved in cell membrane composition and myelin formation. Cr is associated with energy metabolism.[12] These findings were consistent with a study by Sorenson L *et al.*[13] who demonstrated that, Subjects with diabetes have metabolite differences in the brain compared with control subjects. Subjects with

painful neuropathy showed reduced NAA in the thalamus, which may explain the genesis of pain in some cases. However, the study by Sorenson L *et al*. was a case control study. Another study by Lin Y *et al*.[12] showed lower levels of NAA/Cr in the left lenticular nucleus and increased Cho/Cr levels in both the left and right lenticula of subjects with T2DM. Both FBG and HbA1c were negatively correlated with the NAA/Cr ratio in the left nuclei as well as the right, while the Cho/Cr ratio was positively correlated. No significant differences in NAA/Cr or Cho/Cr ratios were observed in the thalamus of patients with T2DM. Another study by Sinha S. *et al*.[6] concluded that, 1H-MRS analysis indicates that type-2 diabetes mellitus may cause subtle changes in the metabolic profile of the brain. Decreased concentrations of NAA might be indicative of decreased neuronal viability in diabetics while elevated concentrations of Gln and Glu might be related to the fluid imbalance resulting from disruption of glucose homeostasis which was consistent with the present study.

CONCLUSION

- Glucose was increased in 90% of the patients and Glx (Glu+Gln) was increased in 80% of the patients.
- NAA/Cr ratio normal (>1.6) in majority of the patients (92.50%),
- Normal NAA/Cho Ratio was (>1.2) noted in majority of the patients (92.50%),
- abnormal Cho/Cr ratio (>1.5) was noted in 75.00% of the patients
- 80.00% of the patients had abnormal GLx(GLU+Gln) ratio (>6.0).

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