Cerebral metabolic changes in diabetes type 2 studied using in-vivo proton MRS

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Introduction: Type-2 diabetes mellitus (DM) is a major public health problem worldwide [1]. Recent studies showed that the brain is a target for diabetic end-organ damage, though the pathophysiology of diabetic encephalopathy is still not well understood. Both vascular and metabolic disturbance have been suggested to impair the integrity of the brain in diabetes [2]. A recent review on reports CT, MRI and MR spectroscopy (MRS) documented possible brain abnormalities among obese adolescents with type 2 diabetes patients; which may result from combination of subtle vascular changes, glucose and lipid metabolic abnormalities and subtle differences in adiposity in the absence of clinically significant vascular disease [3].The objective of the present study is to investigate the effect of diabetes on metabolic profile of brain in patients with diabetes and controls using in-vivo MRS in three brain regions namely, right frontal, right parieto-temporal and right parieto-occipital.

Patients and Methods: Ten patients with type-2 diabetes and seven healthy volunteers were recruited from the outpatient clinic of Department of Medicine. Institute ethics committee approved the study and informed written consent was obtained. Complete history, physical examinations and laboratory tests were performed in all subjects to exclude diseases other than diabetes. The patients were using oral hypoglycemic agents for DM. Diabetes mellitus was diagnosed according to the WHO criteria. Glycosylated hemoglobin (HbA_{1C}) assay was done using HPLC.^{1}H-MRS study was carried out in all 17 subjects (10 in diabetes group and 7 in controls group).Volume-localized ^{1}H MR spectroscopy was carried at 1.5 Telsa (SONATA, Siemens Health Care, Germany) by using a CP coil. Multislice T1-weighted images in the coronal and sagittal planes of the whole brain were acquired using a standard spin-echo pulse sequence (TE= 15 ms; TR= 520 ms; 3-5 mm slice thickness; 256 x 256 matrix). While T2-weighted axial images were acquired using: TE= 90 ms; TR= 250 ms; 3-5 mm slice thickness; 256 x 256 matrix. These images were used to select the region of interest for performing the volume-localized ^{1}H MR spectroscopy using PRESS pulse sequence with the following parameters: TR = 2000 ms; TE = 30 ms; NS = 128. Spectra were acquired from right frontal, right parietotemporal and right occipital white matter. Concentration of metabolites was determined using LC Model. Student't test was performed to compare the concentration metabolites between controls and patients with DM and a p value of <0.05 was considered as significant.

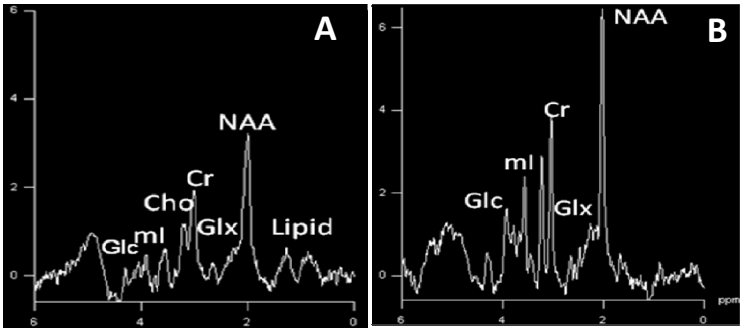

Figure 1: Proton MR spectrum from right parieto occipital region of a patient (A) and a control (B)

Results & Discussion: Fig. 1 shows the representative ^{1}H MR spectrum from the right frontal region of a patient with DM and a control subject. The concentration of N acetyl aspartate (NAA) and glutamate (Glu), glutamine (Gln) and glucose (Glc) were significantly different in diabetes group compared to controls (see Table 1).Our result indicated that NAA was significantly decreased in right frontal and right parieto-occipital area in diabetes patients. Glucose was increased in all brain regions studied compared to healthy control. NAA is an amino acid acts as major osmolytes, and is a marker of neuronal viability [4]. It is a non-specific marker and is thought to be involved in Coenzyme A interactions and lipogenesis within the brain. The primary role of NAA is neuronal-glial cell specific signalling for the maintenance of normal central nervous function [5]. Reduced NAA reflects axonal or neuronal dysfunction or loss in neuronal density such as seen in stroke, hypoxia, neoplasm, epilepsy, multiple sclerosis, and dementia [6]. In our study, decreased NAA levels observed in diabetes patients reflects neuronal loss may be due to chronic hyperglycemia or ischemia supporting report of an earlier study [6]. Further, glucose was found to be significantly higher in all areas of brain studied in diabetes group. Glucose may be increased during osmotic disturbances related to hyperglycemia in diabetes patients in agreement with literature [7]. Further, glutamine levels were higher in frontal and parieto-occipital area except in parieto-temporal area. Glutamines are putative osmolytes and their presence may be a marker of fluid imbalance resulting from regular disruption of glucose homeostasis. Hypoglycemia may stimulate glutamine release, leading to elevated glutamine levels supported by other authors, but in children with type 1 diabetes mellitus [8]. Our findings represent a cascade of changes in brain metabolites where hypoxic damage to glial cells that lead to neuronal dysfunction particularly in frontal white matter and parieto-occipital lobe depicting cognitive executive functional abnormalities in diabetes patients. In conclusion, ^{1}HMRS demonstrated that Type 2 diabetes mellitus may cause cerebral metabolic changes which are indicative of slowly progressive neuronal dysfunction through an ischemic/hypoxic mechanism due to chronic hyperglycemia.

Table 1: Concentration of metabolites (mL/L) in patients with type-2 diabetes and controls.

Metabolite Concentration	Right Frontal		Right Parieto-temporal		Right Parieto-occipital	
	Patient (n=10)	Control (n=7)	Patient (n=9)	Control (n=6)	Patient (n=9)	Control (n=4)
NAA	4.53±0.69	5.23±0.74*	5.53±0.42	5.83±0.76	5.44±0.52	6.08±0.25*
Cr+PCr	3.23±0.26	3.43±0.50	3.84±0.31	3.61±0.42	3.72±0.26	3.86±0.22
GPC+PC	0.94±0.16	0.86±0.14	1.03±0.30	1.09±0.13	0.97±0.13	0.90±0.19
tNAA	5.01±0.54	5.29±0.76	6.20±0.28	6.53±0.54	6.06±0.32	6.42±0.38*
Glu+Gln	7.98±2.57	5.32±1.43*	6.74±1.30	6.72±1.94	7.49±1.64	6.44±1.68
Glc	1.57±0.98	0.43±0.21*	2.33±0.86	0.69±0.88*	1.78±0.67	0.79±0.45*
mI	2.93±0.60	2.65±0.43	3.06±0.62	2.66±0.36	3.03±0.38	2.81±0.25

* denotes P < 0.05.

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