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RESEARCH ARTICLE

ELECTROENCEPHALOGRAPHIC CHANGES IN TYPE 2 DIABETES MELLITUS DURING HYPERVENTILATION AND POST-HYPERVENTILATION

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Abstract

Diabetes mellitus is the most common metabolic disorder that results in various complications including the brain abnormalities. Hyperventilation (HV) is a classic activation procedure during routine electroencephalography (EEG) recording that increases the yield of electrical activity generated in the cerebral cortex.

Objectives: To investigate the electroencephalographic (EEG) changes in type 2 diabetes mellitus (T2DM) patients during hyperventilation (HV) and post-HV.

Methods: The 16-channel EEG recording of 35 male patients with T2DM on oral hypoglycemic medication and 35 age- and sex-matched healthy subjects (controls) were done during and after hyperventilation for 3 minutes each. The quantitative EEG analysis was done using Fast Fourier Transformation (FFT). The EEG power spectra were subjected to log-transformation and compared using student's t-test.

Results: The T2DM patients had diffuse increase in low-frequency slow waves at delta range ($p < 0.05$) and high-frequency fast waves at beta range ($p < 0.05$) as compared to the controls in EEG during HV. There was a prolonged existence of delta activity at few brain regions ($p < 0.05$) and beta activity in some brain regions ($p < 0.05$) in the EEG after cessation of HV during post-HV.

Conclusion: The increased yield of EEG activity at delta and beta ranges in T2DM patients during HV and the prolonged existence of these responses after cessation of HV are suggestive of central nervous system (CNS) abnormalities in T2DM patients.

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Introduction:-

Diabetes mellitus (DM) remains most common metabolic disorder, with an estimated 415 million adults affected by diabetes worldwide (1). A complex interaction of direct and indirect metabolic consequences of insulin deficiency and additional genetic and environmental factors result in chronic complications affecting nephrons, blood vessels, retina, and neurons (2).

Several studies have reported the manifestations of cerebral disorders in type 2 diabetes mellitus (T2DM) at neurochemical, electrophysiological, structural, and neurobehavioral levels (3, 8, 9). The alterations in cerebral

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blood supply, metabolic derangements, recurrent episodes of hypoglycemia, and poor metabolic control also affect the brain (3). A bidirectional relationship exists between diabetes mellitus (DM) and major depressive disorder (MDD) (4). Delirium, substance use disorders, depression, anxiety, and psychotic illnesses like schizophrenia, and eating disorders are some of the psychiatric disorders particularly relevant with regard to DM (5).

Electroencephalography (EEG) is a tool for recording spontaneous electrical activity generated in the cerebral cortex using multiple electrodes placed on the scalp. EEG signal is a reflection of electrical currents flowing in the extracellular space generated by the algebraic summation of excitatory and inhibitory postsynaptic potentials occurring on many cortical neurons. The scalp electrodes pick up the summated excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP) conducted through the skull. One estimate suggests that 6 square centimeters (cm^2) of cortical surface area must be synchronously activated for a potential to be recorded at the scalp (6, 7). Quantitative EEG (QEEG) is a more advanced form of EEG, which converts electrical signals from the brain to digital form. This reveals the EEG patterns undetectable by the naked eye (7).

Hyperventilation (HV) is a classic activation procedure during routine EEG recording that increases the yield of EEG. The subjects are usually asked to hyperventilate for 3 minutes, at the rate of 20 breaths per minute. It usually activates the three-per-second spike and wave discharge of primary generalized epilepsy (6, 7).

Patients with T2DM have increased EEG activity in low-frequency slow waves and high-frequency fast waves indicative of diffuse central neuropathy (8). Baskaran et al reported similar neurophysiological abnormalities in both DM and MDD, including elevated EEG activity in low-frequency slow waves (9). The recurrent episodes of hypoglycemia enhance the varying brain electrical responses to HV in different subjects. A buildup of diffuse slow activity occurs 30 to 60 seconds after the conclusion of HV. These changes occur due to a fall in partial pressure of carbon dioxide (PCO_2) in arterial blood, which leads to cerebral vasoconstriction and thus to reduced cerebral blood flow. The prolonged existence of any response in EEG after cessation of HV is abnormal (10). Some studies have reported central neuropathy in DM as evidenced by EEG changes (3, 8). To the best of our knowledge, very few studies have recorded EEG changes in DM during HV. In our study, we provoked the brain activity in T2DM patients by voluntary HV to reveal the effects of HV on brain activities of T2DM patients during EEG recording.

Material and Methods:-

This was a comparative cross-sectional study conducted on 35 male patients with T2DM and 35 age- and sex-matched controls. The subjects were selected using a convenience sampling technique based on the inclusion and exclusion criteria. The T2DM patients were newly diagnosed or follow-up cases on oral hypoglycemic medication including sulphonylureas and metformin. The controls had no symptoms of any diseases, normal on clinical examination, normal fasting blood sugar (FBS), age- and sex-matched, were not on any medication, and without any clinical evidence of infectious, systemic, metabolic, and neuropsychiatric illnesses.

The participants were familiarized with the laboratory setting and the study design. All the participants were informed of the potential risks and recording procedures, and informed written consent was obtained. They were interviewed using standard questionnaires for their medical history. Their detailed medical history, clinical examinations, and health status were documented using standard case history sheets. The recent reports on FBS, post-prandial blood sugar (PPBS), and glycated hemoglobin ($\text{HbA}_{1\text{C}}$) of the T2DM patients were noted. The FBS of controls was assessed and documented. The weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), and heart rate (HR) of both the T2DM patients and controls were measured using standard tools and methods. Their body mass index (BMI) was calculated using the standard formula, i.e., $\text{BMI} = \text{weight in kilogram (kg)} / \text{height in square meter (m}^2\text{)}$. The digital EEG machine (Nihon Kohden- Neurofax: optiplex GXMT5120) was used for 16-channel EEG recording.

EEG Recording:-

Each subject was advised to come with clean scalp and hair, with proper last night's sleep (minimum 6 hours) and after 2 hours of light breakfast. In addition, the subjects were suggested not to drink tea/coffee 24 hours before the test. The temperature of the lab was maintained at $26 \pm 2^\circ\text{C}$. All the equipment was checked prior to the recording procedure. They were advised to be relaxed and their comfort was maintained before and during the recording procedures. All the recordings were done between 10-11:30 a.m. to minimize the variation due to time.

Each subject is allowed to take rest for 10 minutes in the supine position on the dental chair after adjusting the head and back of the chair according to subject's comfort. The International 10-20 common average reference system was used for scalp electrode placement. The EEG recording was undertaken in a quiet, relaxed environment, with the

subject lying comfortably in supine position. The 16-channel EEG was recorded first for 6 minutes at rest during eyes-open and eyes-close conditions for 3 minutes each. Then the subject was asked to hyperventilate for 3 minutes, at the rate of 20 breaths per minute. The EEG recorded during HV and post-HV for 3 minutes each was considered for QEEG analysis.

EEG Data Acquisition and Analysis:-

EEG waveforms were reduced and analyzed by using *Focus software version (1.1)*. Initially, the records were visually inspected on the computer screen to check for artifacts due to eye blinks, and detectable eye and body movements. After visual inspection, three artifact-free-5-second epochs were selected from just before the end of 1st, 2nd and 3rd minutes of EEG recording during HV, and post-HV. Thereafter, Fast Fourier Transformation (FFT) method was applied to these data for decomposition of EEG waveforms into sine wave components in terms of respective frequencies.

These components were used to estimate the spectral power in square microvolt (μV^2) for frequency in the ranges of delta (0.5-4.0 Hz), theta (4.0-7.0 Hz), alpha1 (7.0-10.0 Hz), alpha2 (10.0-13.0 Hz), and beta (13.0-32.0 Hz) bands. The spectral power for each band, thus obtained from different regions of the brain was exported to Microsoft Excel worksheet for further analysis. The powers from three epochs were averaged for each subject. The data obtained from the T2DM patients and controls were compared.

Statistical Analysis:-

The data obtained were exported to Statistical Package for the Social Sciences (SPSS *version 18*) and were tested for normal distribution. The data of age, weight, height, BMI, SBP, DBP, HR, RR, and FBS were normally distributed and expressed in terms of mean \pm standard deviation (SD). The data of EEG power spectra were subjected to statistical analysis after log transformation as they were non-normally distributed. The EEG power spectra were expressed as mean \pm standard deviation. The Unpaired t-test was applied to compare the variables between the T2DM patients and controls. A *p value* of < 0.05 was considered statistically significant.

Results:-

The age, weight, height, BMI, SBP, DBP, HR, and RR were comparable among the T2DM patients and controls. The FBS of the T2DM patients were significantly more ($p < 0.05$) than that of the controls (Table 1). The T2DM patients had PPBS of 259.69 ± 82.10 mg/dl and HbA1C of 7.15 ± 1.10 %.

Table 1:- Anthropometric, cardio-respiratory and FBS variables in T2DM and healthy controls.

Parameters	Mean \pm SD		<i>p value</i>
	T2DM patients (n=35)	Controls (n=35)	
Age (year)	52.87 \pm 2.6	53.43 \pm 2.75	0.387
Weight (Kg)	63.09 \pm 5.82	64.17 \pm 6.88	0.477
Height (cm)	163.69 \pm 8.32	166.21 \pm 8.02	0.200
BMI (Kg/m ²)	23.54 \pm 1.92	23.09 \pm 1.33	0.250
SBP (mm Hg)	120.05 \pm 5.38	119.98 \pm 5.58	0.957
DBP (mm Hg)	74.7 \pm 4.92	73.95 \pm 4.77	0.515
HR (beats per min)	79.94 \pm 5.87	79.91 \pm 6.64	0.987
RR (per min)	13.70 \pm 1.78	13.86 \pm 1.79	0.699
FBS	167.21 \pm 54.17	92.14 \pm 10.78	0.001

Kg, Kilogram; Kg/m², kilogram per square meter; cm, centimeter; mg/dl, milligram per deciliter; mm Hg, millimeter of mercury; min, minute.

During hyperventilation, the T2DM patients had significantly more delta and beta activity ($p < 0.05$) across all the scalp electrode sites (Table 2). During post-hyperventilation, the delta activity was significantly more ($p < 0.05$) in the T2DM patients at midline frontal (Fz), right parietal (P4), right occipital (O2), left anterior frontal (Fp1), left temporal (T5), and left occipital (O1) regions (Table 3). The T2DM patients had significantly more beta activity ($p < 0.05$) at midline (Fz, Cz, Pz), bilateral frontal (Fp1, Fp2, F3, F4, F7, F8), left temporal (T3, T5), bilateral central (C3, C4), and left parietal (P3) regions (Table 3).

Table 2:- EEG power spectra in T2DM patients and healthy controls during hyperventilation.

Electrode Site	Group	Delta (μV^2)		Theta (μV^2)		Alpha1 (μV^2)		Alpha2 (μV^2)		Beta (μV^2)	
		Mean \pm SD	p value	Mean \pm SD	p value	Mean \pm SD	p value	Mean \pm SD	p value	Mean \pm SD	p value
Fz	T2DM	1.87 \pm 0.23	0.000	1.51 \pm 0.26	0.893	1.50 \pm 0.48	0.184	1.54 \pm 0.40	0.088	1.50 \pm 0.22	0.001
	Control	1.64 \pm 0.28		1.50 \pm 0.36		1.65 \pm 0.44		1.34 \pm 0.57		0.96 \pm 0.62	
Cz	T2DM	1.91 \pm 0.21	0.000	1.60 \pm 0.31	0.822	1.50 \pm 0.44	0.060	1.64 \pm 0.41	0.114	1.53 \pm 0.17	0.001
	T2DM	1.66 \pm 0.26		1.62 \pm 0.31		1.69 \pm 0.43		1.43 \pm 0.65		1.13 \pm 0.61	
Pz	T2DM	1.86 \pm 0.22	0.000	1.44 \pm 0.22	0.372	1.54 \pm 0.56	0.098	1.53 \pm 0.50	0.253	1.53 \pm 0.20	0.003
	Control	1.58 \pm 0.28		1.50 \pm 0.32		1.74 \pm 0.45		1.69 \pm 0.66		1.12 \pm 0.73	
Fp2	T2DM	1.90 \pm 0.31	0.002	1.05 \pm 0.33	0.077	1.49 \pm 0.63	0.931	1.21 \pm 0.32	0.373	1.31 \pm 0.17	0.004
	Control	1.67 \pm 0.29		1.19 \pm 0.34		1.48 \pm 0.49		1.11 \pm 0.56		0.95 \pm 0.70	
F8	T2DM	1.48 \pm 0.33	0.001	0.84 \pm 0.46	0.115	1.65 \pm 1.93	0.093	0.96 \pm 0.38	0.157	1.11 \pm 0.38	0.009
	Control	1.20 \pm 0.37		0.68 \pm 0.36		1.06 \pm 0.53		0.80 \pm 0.57		0.72 \pm 0.79	
T4	T2DM	1.26 \pm 0.23	0.002	0.93 \pm 0.33	0.188	1.30 \pm 0.63	0.145	1.14 \pm 0.49	0.087	1.32 \pm 0.50	0.002
	Control	1.05 \pm 0.32		0.84 \pm 0.20		1.11 \pm 0.43		0.93 \pm 0.51		0.83 \pm 0.74	
T6	T2DM	1.39 \pm 0.29	0.001	0.87 \pm 0.41	0.124	1.47 \pm 0.63	0.773	1.30 \pm 0.45	0.181	1.31 \pm 0.37	0.001
	Control	1.07 \pm 0.48		1.01 \pm 0.31		1.52 \pm 0.65		1.13 \pm 0.63		0.88 \pm 0.64	
F4	T2DM	1.74 \pm 0.26	0.000	1.21 \pm 0.25	0.333	1.51 \pm 0.55	0.872	1.35 \pm 0.37	0.100	1.57 \pm 0.49	0.001
	Control	1.46 \pm 0.35		1.16 \pm 0.19		1.49 \pm 0.50		1.14 \pm 0.65		0.96 \pm 0.66	
C4	T2DM	1.72 \pm 0.22	0.000	1.67 \pm 0.68	0.401	1.46 \pm 0.48	0.269	1.48 \pm 0.40	0.104	1.39 \pm 0.40	0.001
	Control	1.45 \pm 0.30		1.55 \pm 0.50		1.59 \pm 0.46		1.30 \pm 0.51		0.95 \pm 0.53	
P4	T2DM	1.79 \pm 0.32	0.000	1.41 \pm 0.36	0.947	1.69 \pm 0.49	0.738	1.59 \pm 0.44	0.074	1.29 \pm 0.40	0.003
	Control	1.43 \pm 0.33		1.41 \pm 0.41		1.65 \pm 0.51		1.41 \pm 0.43		0.96 \pm 0.51	
O2	T2DM	1.78 \pm 0.26	0.000	1.05 \pm 0.44	0.066	1.71 \pm 0.52	0.420	1.49 \pm 0.44	0.672	1.60 \pm 0.51	0.005
	Control	1.45 \pm 0.28		1.21 \pm 0.26		1.81 \pm 0.56		1.55 \pm 0.74		1.16 \pm 0.74	
Fp1	T2DM	1.91 \pm 0.30	0.004	1.42 \pm 0.35	0.143	1.30 \pm 0.54	0.134	1.20 \pm 0.31	0.587	1.50 \pm 0.40	0.003
	Control	1.71 \pm 0.27		1.31 \pm 0.29		1.47 \pm 0.43		1.28 \pm 0.72		1.07 \pm 0.70	
F7	T2DM	1.45 \pm 0.28	0.001	0.80 \pm 0.27	0.072	1.07 \pm 0.49	0.497	0.93 \pm 0.36	0.794	1.33 \pm 1.20	0.004
	Control	1.21 \pm 0.30		0.71 \pm 0.16		1.00 \pm 0.41		0.89 \pm 0.74		0.65 \pm 0.59	
T3	T2DM	1.23 \pm 0.24	0.016	0.82 \pm 0.42	0.061	1.03 \pm 0.42	0.995	1.18 \pm 0.48	0.335	1.38 \pm 0.69	0.001
	Control	1.07 \pm 0.30		1.02 \pm 0.43		1.03 \pm 0.37		1.03 \pm 0.79		0.81 \pm 0.64	
T5	T2DM	1.39 \pm 0.25	0.001	1.06 \pm 0.42	0.507	1.54 \pm 0.75	0.469	1.31 \pm 0.44	0.528	1.23 \pm 0.61	0.002
	Control	1.07 \pm 0.46		1.13 \pm 0.48		1.42 \pm 0.65		1.41 \pm 0.83		0.78 \pm 0.58	
F3	T2DM	1.72 \pm 0.25	0.001	1.26 \pm 0.24	0.952	1.46 \pm 0.82	0.759	1.33 \pm 0.36	0.412	1.51 \pm 0.52	0.002
	Control	1.50 \pm 0.28		1.26 \pm 0.24		1.41 \pm 0.43		1.48 \pm 1.05		0.98 \pm 0.81	
C3	T2DM	1.67 \pm 0.21	0.000	1.26 \pm 0.29	0.269	1.49 \pm 0.49	0.650	1.31 \pm 0.71	0.524	1.61 \pm 0.61	0.005
	Control	1.43 \pm 0.30		1.34 \pm 0.33		1.54 \pm 0.49		1.43 \pm 0.91		1.08 \pm 0.89	
P3	T2DM	1.67 \pm 0.19	0.001	1.24 \pm 0.35	0.381	1.49 \pm 0.44	0.232	1.37 \pm 0.74	0.206	1.45 \pm 0.50	0.001
	Control	1.39 \pm 0.41		1.32 \pm 0.36		1.63 \pm 0.56		1.64 \pm 1.00		0.99 \pm 0.60	
O1	T2DM	1.74 \pm 0.29	0.000	1.18 \pm 0.29	0.195	1.51 \pm 0.50	0.143	1.36 \pm 0.86	0.205	1.32 \pm 0.26	0.001
	Control	1.41 \pm 0.26		1.29 \pm 0.42		1.70 \pm 0.57		1.43 \pm 0.65		1.13 \pm 0.61	

μV^2 , square microvolt; SD, Standard Deviation; p <0.05 considered statistically significant

Table 3:- EEG power spectra in T2DM patients and healthy controls during post-hyperventilation.

Electrode Site	Group	Delta (μV^2)		Theta (μV^2)		Alpha1 (μV^2)		Alpha2 (μV^2)		Beta (μV^2)	
		Mean \pm SD	p value	Mean \pm SD	p value	Mean \pm SD	p value	Mean \pm SD	p value	Mean \pm SD	p value
Fz	T2DM	1.79 \pm 0.23	0.041	1.39 \pm 0.29	0.683	1.50 \pm 0.49	0.617	1.26 \pm 0.38	0.096	1.54 \pm 0.45	0.000
	Control	1.64 \pm 0.34		1.36 \pm 0.28		1.56 \pm 0.50		1.10 \pm 0.41		0.95 \pm 0.46	
Cz	T2DM	1.80 \pm 0.34	0.163	1.43 \pm 0.32	0.893	1.62 \pm 0.45	0.527	1.36 \pm 0.41	0.508	1.64 \pm 0.43	0.000
	Control	1.68 \pm 0.37		1.44 \pm 0.28		1.69 \pm 0.49		1.30 \pm 0.39		1.09 \pm 0.50	
Pz	T2DM	1.79 \pm 0.30	0.092	1.29 \pm 0.40	0.602	1.76 \pm 0.52	0.339	1.50 \pm 0.48	0.489	1.51 \pm 0.24	0.003
	Control	1.66 \pm 0.33		1.33 \pm 0.25		1.64 \pm 0.56		1.43 \pm 0.44		1.17 \pm 0.60	
Fp2	T2DM	1.78 \pm 0.26	0.074	1.02 \pm 0.45	0.120	1.30 \pm 0.48	0.498	1.06 \pm 0.37	0.118	1.31 \pm 0.27	0.000
	Control	1.64 \pm 0.38		1.15 \pm 0.24		1.39 \pm 0.55		0.92 \pm 0.39		0.83 \pm 0.41	
F8	T2DM	1.31 \pm 0.43	0.967	0.42 \pm 0.63	0.054	0.82 \pm 0.56	0.690	0.63 \pm 0.37	0.105	0.91 \pm 0.27	0.000
	Control	1.31 \pm 0.59		0.68 \pm 0.29		0.87 \pm 0.57		0.49 \pm 0.37		0.51 \pm 0.51	
T4	T2DM	1.27 \pm 0.24	0.584	0.61 \pm 0.43	0.096	0.89 \pm 0.51	0.448	0.81 \pm 0.39	0.436	0.94 \pm 0.27	0.135
	Control	1.22 \pm 0.44		0.76 \pm 0.29		0.98 \pm 0.55		0.74 \pm 0.37		0.79 \pm 0.53	
T6	T2DM	1.34 \pm 0.22	0.135	0.88 \pm 0.33	0.881	1.16 \pm 0.63	0.227	1.03 \pm 0.48	0.614	1.07 \pm 0.23	0.101
	Control	1.19 \pm 0.52		0.87 \pm 0.35		1.36 \pm 0.71		0.97 \pm 0.46		0.87 \pm 0.66	
F4	T2DM	1.64 \pm 0.24	0.494	1.12 \pm 0.33	0.854	1.33 \pm 0.50	0.969	1.09 \pm 0.37	0.085	1.49 \pm 0.59	0.000
	Control	1.58 \pm 0.45		1.13 \pm 0.28		1.33 \pm 0.55		0.93 \pm 0.38		0.82 \pm 0.45	
C4	T2DM	1.62 \pm 0.34	0.749	1.17 \pm 0.37	0.352	1.47 \pm 0.46	0.861	1.28 \pm 0.43	0.413	1.51 \pm 0.41	0.000
	Control	1.60 \pm 0.36		1.24 \pm 0.28		1.49 \pm 0.53		1.20 \pm 0.38		0.98 \pm 0.44	
P4	T2DM	1.91 \pm 0.49	0.001	1.19 \pm 0.27	0.997	1.58 \pm 0.48	0.440	1.39 \pm 0.48	0.369	1.39 \pm 0.24	0.169
	Control	1.54 \pm 0.44		1.19 \pm 0.28		1.48 \pm 0.62		1.30 \pm 0.42		1.20 \pm 0.74	
O2	T2DM	1.66 \pm 0.24	0.030	1.25 \pm 0.29	0.428	1.48 \pm 0.50	0.156	1.41 \pm 0.50	0.572	1.23 \pm 0.35	0.867
	Control	1.50 \pm 0.38		1.20 \pm 0.30		1.67 \pm 0.61		1.35 \pm 0.50		1.21 \pm 0.81	
Fp1	T2DM	1.92 \pm 0.23	0.002	1.11 \pm 0.37	0.368	1.35 \pm 0.48	0.568	1.09 \pm 0.37	0.059	1.40 \pm 0.39	0.000
	Control	1.68 \pm 0.37		1.18 \pm 0.23		1.43 \pm 0.60		0.91 \pm 0.39		0.73 \pm 0.47	
F7	T2DM	1.35 \pm 0.28	0.083	0.76 \pm 0.38	0.400	0.85 \pm 0.53	0.678	0.60 \pm 0.37	0.128	1.13 \pm 0.77	0.000
	Control	1.22 \pm 0.35		0.70 \pm 0.26		0.90 \pm 0.54		0.47 \pm 0.34		0.44 \pm 0.59	
T3	T2DM	1.17 \pm 0.35	0.796	0.83 \pm 0.41	0.155	0.98 \pm 0.43	0.700	0.80 \pm 0.42	0.529	1.13 \pm 0.36	0.000
	Control	1.15 \pm 0.34		0.71 \pm 0.29		0.93 \pm 0.56		0.74 \pm 0.38		0.57 \pm 0.52	
T5	T2DM	1.29 \pm 0.19	0.019	0.98 \pm 0.65	0.145	1.22 \pm 0.56	0.501	1.00 \pm 0.48	0.724	1.14 \pm 0.31	0.001
	Control	1.15 \pm 0.30		0.80 \pm 0.35		1.33 \pm 0.76		0.96 \pm 0.54		0.83 \pm 0.45	
F3	T2DM	1.62 \pm 0.28	0.209	1.13 \pm 0.29	0.536	1.31 \pm 0.46	0.637	1.06 \pm 0.39	0.053	1.74 \pm 1.30	0.000
	Control	1.53 \pm 0.34		1.09 \pm 0.26		1.26 \pm 0.57		0.87 \pm 0.42		0.72 \pm 0.51	
C3	T2DM	1.62 \pm 0.24	0.177	1.21 \pm 0.33	0.442	1.56 \pm 0.52	0.175	1.24 \pm 0.45	0.565	1.68 \pm 0.91	0.000
	Control	1.53 \pm 0.34		1.15 \pm 0.27		1.38 \pm 0.59		1.18 \pm 0.47		0.85 \pm 0.49	
P3	T2DM	1.58 \pm 0.24	0.111	1.22 \pm 0.34	0.177	1.73 \pm 0.73	0.104	1.39 \pm 0.48	0.373	1.46 \pm 0.44	0.000
	Control	1.48 \pm 0.31		1.12 \pm 0.27		1.46 \pm 0.66		1.28 \pm 0.51		0.96 \pm 0.48	
O1	T2DM	1.63 \pm 0.20	0.016	1.23 \pm 0.40	0.055	1.58 \pm 0.49	0.936	1.39 \pm 0.47	0.331	1.27 \pm 0.20	0.197
	Control	1.68 \pm 0.37		1.44 \pm 0.28		1.69 \pm 0.49		1.30 \pm 0.39		1.09 \pm 0.50	

μV^2 , square microvolt; SD, Standard Deviation; p < 0.05 considered statistically significant

Discussion:-

Our study revealed a diffuse increase in low-frequency slow waves and high-frequency fast waves in EEG in T2DM patients on provoking their brain activity by voluntary HV. In addition, there was prolonged existence of low-frequency slow waves at few brain regions and high-frequency fast waves in some brain regions in the EEG after cessation of HV during post-HV.

The studies have shown that the EEG power spectra of delta and beta activity are more in T2DM patients at most of the brain regions (8, 9) and hyperventilation helps to increase the yield of EEG. Diffuse EEG changes characteristically occur in metabolic encephalopathies unless there is a pre-existing or concomitant structural lesion. Diffuse slowing of the EEG has been described in hyperglycemia or hypoglycemia, Addison's disease, hypopituitarism, pulmonary failure, and hyperparathyroidism. These slow waves initially may be episodic or paroxysmal and are enhanced by hyperventilation (10).

The uncontrolled diabetes mellitus can facilitate the occurrence of watershed ischemia and the EEG is slow and severely disorganized with diffusely disordered background activity (11). A meta-analysis of 24 studies showed an association of depression with hyperglycemia in T2DM (12). The elevated depressive symptoms have been associated with a higher risk of development of T2DM (13). Diabetes may place patients at risk for depression through a biological mechanism linking the metabolic changes of DM to changes in the CNS (14). There exists a common point of pathophysiology between MDD and DM (15). The prevalence of anxiety and depression symptoms in patients with diabetes was more than double the general population estimates (16). The elevated slow-wave activity as those observed in DM has been demonstrated in MDD patients (9). Kwon et al (17) found increased low-frequency EEG activity, including theta and delta power over the right hemisphere in depressed patients compared with age-matched healthy controls.

Hyperglycemia is associated with various neurological manifestations, including encephalopathy (18). The features of encephalopathy in hyperglycemia vary depending on the degrees of hyperglycemia and hyperosmolarity. The hyperglycemic encephalopathy has variable EEG findings that range from normal, at serum glucose <400 mg/dl, to the initial appearance of mixed slow and fast activity with some intermingled spiking. However, diffuse and often-continuous medium to high voltage theta-delta activity predominates with increasing serum glucose concentrations (20).

In the study done by Khan et al. (21) in 889 DM patients, they identified 57.9% and 43.5% positive for anxiety and depression respectively. Anxiety disorders are also highly prevalent in DM patients (22). The rate of clinical anxiety with co-morbid affective disorder is higher than expected in DM patients, although the reason is not clear (23). Lustman et al. (24) had also observed high rates of generalized anxiety disorders in DM patients. Beta waves (faster than 13/sec) are usually seen, especially on the frontal and central areas, in tense and anxious patients (25). Cohn (26) noted frontal beta activity (18-22/sec) in patients suffering from anxiety states.

Several activation methods, including hyperventilation, have been used in clinical EEG recording to enhance preexisting abnormalities and/or induce abnormal findings in otherwise normal EEGs (27). In our study, the hyperventilation might have enhanced the EEG manifestations of preexisting CNS abnormalities in T2DM patients. Apart from hyperglycemia, our results might have been affected by contemporary depression and anxiety or hyperglycemic encephalopathy in our diabetic patients. However, we did not assess the depression and anxiety or hepatic encephalopathy by using any other tools or neuroimaging techniques in our subjects.

Conclusion:-

The T2DM patients revealed a diffuse increase in low-frequency slow waves and high-frequency fast waves at delta and beta ranges respectively on EEG recording during hyperventilation, a classic activation method. In addition, there was prolonged existence of the responses in EEG at various sites after cessation of HV. Our findings support the belief that T2DM patients manifest CNS abnormalities as evidenced by the increased EEG activity in low-frequency slow waves and high-frequency fast waves. However, further collaborative studies including neurophysiological tests, Folstein (Mini-Mental State Examination) test, and neuroimaging techniques are needed to evident a link of DM with neuropsychiatric/cerebral disorders.

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