ORIGINAL ARTICLE

Glycated Hemoglobin: A Predictor of Cognitive Deficits in Type 1 Diabetes Patients

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ABSTRACT

Objective: To determine the association of Glycated Hemoglobin with frontal lobe cognitive dysfunction in type 1 diabetes patients.

Study Design: Case control study.

Place and Duration of Study: Bahawal Victoria Hospital, Bahawalpur, Pakistan from June 2016 until August 2017.

Materials and Methods: Fifty diabetic patients and fifty healthy adults were tested for fasting HbA_{1c} levels. Following, they were administered Frontal assessment battery. Participants were given separate instructions for assessment of each frontal lobe function and they completed Frontal assessment battery in a single testing session. Data was analyzed for group differences on each frontal lobe function through ANOVA. Bivariate correlations were computed to assess the relationship between frontal lobe functions and $HbA_{1c.}$ Regression analysis was used to assess HbA_{1c} as a predictor of frontal lobe cognitive functioning.

Results: Diabetic patients showed impaired performance on frontal lobe cognitive functions in contrast with healthy individuals. HbA_{1c} and frontal lobe cognitive functions were negatively correlated. Deficient glycemic control was associated with frontal lobe cognitive deficits. HbA_{1c} was found as a significant predictor of frontal lobe cognitive functioning.

Conclusion: Higher level of HbA_{1c} is a predictor of frontal lobe cognitive functioning deficits in patients with Type 1 diabetes.

Key Words: *Cognition, Fasting Glucose, Glycemic Control, Glycemic Index, Type 1 Diabetes.*

Introduction

Diabetes Mellitus (DM) increases risk of cognitive decline.[1] Type 1 DM involves mental flexibility, visual perception and attention whereas Type 2 DM may cause memory deficits or reduced executive function.[2] Neurocognitive changes in Type 1 DM involve volume loss and atrophy of cerebral cortex.[3,4] Frontal lobes are involved in multiple cognitive processes i.e., executive functions, memory, attention, language etc. and constitute two-thirds of the human brain.[5] Temporal lobes have a role in memory and thinking processes and pathophysiology in this brain region leads to cognitive and neurodegenerative disorders.[6] Deficit in gray matter volume is also associated with higher glycated haemoglobin (HbA_{1c}) levels.[7,8] DM pathophysiology includes lesions of the subcortical white matter, cortical infarcts, density of neuritic plaques, hyperphosphorylated tau (i.e., group of neuronal microtubule-associated proteins) within axons, oxidative stress, and inflammation of nerve pathways.[9,11] Deregulation of major excitatory receptors of the central nervous system (i.e., glutamatergic receptors which control synaptic activity during learning and memory) accelerates cognitive deficits.[12,13] Cognitive impairments, brain aging and neurodegeneration are associated with molecular changes in protein kinases, second-messenger system and glutamate-receptors.[14,15] It was also found that DM prolongs peripheral as well as central conduction time (onset, peak latencies and velocity) in spinal cord structures. These changes are connected with demyelination along fibers needed to conduct nerve impulses through periphery and brain cortex.[16,17] Segmental demyelination, axonal degeneration and nerve loss involve peripheral nerves whereas velocities of sensory- motor nerve conduction are involved in deficits of the distal limbs.[18,19]

Previous research has shown that chronic hyperglycemia is associated with cognitive decline in

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Funding Source: NIL; Conflict of Interest: NIL
Received: August 06, 2018; Revised: May 04, 2019
Accepted: May 09, 2019

non-demented elderly patients.[20] Increased glycated hemoglobin is associated with significant reduction in cognitive functioning in patients with diabetes.[21] This association has been observed in patients with metabolic syndromes and coronary heart disease. [22] High peaks of glucose over several years can even cause dementia.[23] To date, frontal lobe dysfunctions in relation with glycemic control have not been examined in Pakistani subjects. Given the brain structural and functional changes, it was hypothesized that diabetic patients would show weaker frontal lobe related functioning than healthy adults. Glycemic control as assessed through HbA_{1c} would be associated with frontal lobe functioning and could therefore predict frontal lobe dysfunctions. HbA_{1c} is an index of circulating glucose levels over 2-3 months. The objective of this study was to assess the association of glycated Hemoglobin with frontal lobe cognitive dysfunction in type 1 diabetic patients.

Materials and Methods

This study had a case control design and was conducted at the endocrinology and diabetes department of Bahawal Victoria hospital Bahawalpur, Pakistan from June 2016 to August 2017. The study was ethically approved by The Islamia University of Bahawalpur and followed principles of Helsinki declaration. Purposive sampling was used. Fifty patients diagnosed with type 1 DM were included with criteria as (i) age range 35-55 years (ii) diagnosed with type 1 DM (iii) having no medication other than antidiabetics, whereas exclusion was done with reports of psychological disorder, neurological disorder, history of head trauma, cancer and diseases of the central nervous system. Fifty healthy demographically matched individuals took part in the study. Healthy individuals were included with age range 35-55 years and with no present use of any medication. The exclusion criterions were: (i) history /present complaints of diabetes. (ii) history/present illness of substance use, psychiatric disorder, neurological disorder, history of head trauma, cancer and diseases of the central nervous system.

All participants gave written informed consent. Participants had a fasting blood glucose test. Subsequently, they were administered Frontal Assessment Battery- F-A-B[24] to examine frontal lobe functions. It is brief and easy to administer and has good psychometric properties. The total score consists of a cumulative score of six individual neuropsychological tasks (score range 0-18). In the "Similarities" (conceptualization) task, patient is required to indicate superordinate concept of objects from the same semantic category (score range 0-3 high score shows intact performance). Lexical verbal fluency (mental flexibility) examines semantic retrieval. Patient is required to say as many words as possible starting with S except nouns and surnames in 60 seconds (score range 0-3, more than nine correct responses=3). In motor series, patient executes a series of motor acts (score range=0-3; at least 6 consecutive series alone=3). Conflicting instructions assess self control by hitting the table one time fewer than the administrator hits. After the practice trial, patient has to follow an alternating numbered order (score 0-3, high score shows no error). Prehension behavior examines the activated behaviors. The administrator hints palms without uttering a word when subject placed their hands on knees. Subject is instructed not to take the administrator's hands. Doing so will be scored as three. Total score is cumulative of subscales of F-A-B which is 0 to 18; high score is intact cognition. SPSS (version 20) was used to analyze data. Descriptive statistics (mean, standard deviation and t-test) were used to analyze demographic and clinical characteristics of sample as shown in Table I. Interaction of group with subscales of F-A-B with factors as 6 F-A-B (within subject) x 2 Group (diabetic patients vs. healthy control subjects: between subject) was assessed using ANOVA. Bivariate correlations were computed to assess the relationship between Total FAB score, subscale scores and HbA_{1c}. Regression analysis was conducted to assess HbA_{1c} as predictor of FAB scores.

Results

Results showed that the main effect of F-A-B $F(1, 98) = 1.78$, $p = .11$, $\eta p2 = .01$ was non-significant whereas the main effect of Group was significant $F(1, 98) = 1844.64$, $p = .001$, $\eta p2 = .95$. The interaction between FAB and Group was significant $F(1, 98) = 3.11$, $p = .01$, $\eta p2 = .03$. Group differences on subscales are reported in Table II. Correlation between HbA_{1c} and FAB scores on lexical verbal fluency (-.45, $p = .001$), motor series (-.33, $p = .01$), Go-Nogo (-.35, $p = .01$),

prehension behavior (-.36, *p*=.01), and total FAB scores (-.81, *p*=.001) were significant whereas correlations between glycemic control (blood glucose) and similarities (-.27, *p*=.055), and conflicting instructions (-.16, *p* = .26) were not significant. Regression analysis showed that HbA1c significantly predicted FAB total scores *F* (1, 49) = 95.99, *p*=.001, R^2 = .66, β= -.81, *t* = -9.79, *p*=.001. Odd ratio was 1.00, p<0.001, 95%. Risk for cognitive deterioration was significantly different *t* (49) = 42.73, *p* =.001, *M* = 47.55, SD = 7.86 between patients (50.34%) and healthy individuals (2.78%).

Table I: Characteristics of Patients with Diabetes and Healthy Individuals

	Diabetic Patients	Healthy Individuals		
	n	n		
	50	50		
Gender (Male/Female)	25/25	25/25		
	M ±SD	M ±SD	*T*	*p*
Age (Years)	46.36 ±5.18	46.28 ±5.43	*t* (49)=0.18	.85
Education (Years)	14.06 ±1.49	14.28 ±1.45	*t* (49)=0.67	.50
Duration of diabetes (Years)	2.00 ±1.47	NA	-	-
HbA1c (%)	7.40 ±0.60	5.2±0.2	-	-
Glucose (mmol/l)	8.00±0. 70	5.1±0.1		

Note. Hba1c= Glycated Hemoglobin (%)

Table II: Group Differences on Subscale Scores of Frontal Assessment Battery (N= 100)

			Diabetic Patients			Healthy controls
	M ±SD	SE	Lower-upper bound	*M* ±SD	SE	Lower-upper bound
Similarities	1.58 ±.49	.05	1.49-1.69	2.90 ±.30	.05	2.78-3.01
Lexical verbal fluency	1.48 ±.50	.06	1.36-1.59	2.88 ±.32	.06	2.76-2.99
Motor series	1.60 ±.49	.05	1.48-1.71	2.92 ±.27	.05	2.80-3.03
Conflicting instructions	1.50 ±.50	.05	1.38-1.61	2.91 ±.26	.05	2.80-3.03
Go-Nogo	1.52 ±.50	.05	1.40-1.63	2.90 ±.27	.05	2.80-3.03
Prehension behavior	1.26 ±.44	.04	1.16-1.35	2.96 ±.19	.04	2.86-3.05

Note: Lower-Upper Bound Is Reported On 95% Confidence Interval

Discussion

This study was designed to examine frontal lobe functions and glycemic control in Type 1 DM. Further objective was to determine whether any relationship between these two variables exists in Type 1 DM. It was hypothesized that patients with Type 1 DM would show frontal lobe cognitive deficits and deficient glycemic control. In addition, impaired glycemic control was related with frontal lobe cognitive deficits. Neuropsychological measures of frontal-lobe-related functions were used to assess frontal lobe functions and glycemic control was assessed through $HbA_{1c.}$ There were few important findings: (i) Functioning of the frontal lobe was weaker in diabetics (ii) F-A-B subscales and glycemic control correlated (iii) glycemic control significantly predicted frontal lobe dysfunctions. Previous studies have illustrated that neurodegeneration in Alzheimer's disease and Diabetes is similar[6-8], for instance lesions of the subcortical white matter, cortical infarcts, density of neuritic plaques, Aβ plaques and NFTs-hyperphosphorylated tau within axons, oxidative stress, inflammation of pathways, deregulation of excitatory receptors in central nervous system, and long-term potentiation in hippocampus.[9-11] Furthermore, these changes extend to molecular changes in protein kinases, second-messenger systems, glutamate-receptors[14,15], delay in nerve conduction times, [16,17] segmental demyelination and deficits of the distal limbs.[18,19] Results of this study are consistent with literature suggesting global cognitive deficits in type 1 diabetic patients[2] and neurocognitive changes in Type 1 DM such as reduced cerebral volumes and atrophy of frontal and temporal lobes[3,4]. Frontal lobes encompass two-thirds of the brain and are responsible for multiple cognitive processes[6] whereas temporal lobes are involved in memory and thinking processes. Degeneration in these brain areas are related with cognitive deficits.[5] The finding of the present study that glycemic control is associated with frontal lobe dysfunctions can be seen in the context of deficient gray matter volume and greater glycated hemoglobin as an index of reduced cognition in patients with DM.[7,8,20,21]

Conclusion

Higher level of HbA_{1c} is a predictor of frontal lobe cognitive functioning deficits in patients with Type 1 diabetes.

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