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To Investigate Role of Glycosylated Hemoglobin (Hba1c) as a Biomarker for Prediction of Dementia and Cognitive Dysfunction in Type 2 Diabetic Patients

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Abstract

Introduction: Diabetes Mellitus is one the major disease burden globally. One of the significant complications of the uncontrolled Diabetics is Cognitive dysfunction and Dementia. In this study we laid focus on the Evaluation of HbA1C as a Biomarker to predict Dementia and Cognitive Dysfunction in Type 2 Diabetic Mellitus.

Aim of the study: A pilot study to investigate HbA1C as a Biomarker for prediction of Dementia and Cognitive Dysfunction in Type 2 Diabetic Mellitus in a Hospital Setting.

Methods and results: A prevalence study in which 60 subjects (n=30 Type 2 Diabetics; n=30 non Diabetic) were enrolled. In this study HbA1C values were correlated with that of individual memory and cognition batteries* score. The range of the HbA1C values was 7.1 to 13.3. The mean values of HbA1C in the Diabetic group (n=30) was found to be 9.19.The corresponding values of Pearson's Correlation "r" in the diabetic group of the w.r.t. various Cognitive batteries were: General Practitioner Assessment of Cognition (GPCOG)=-0.53; Attendant Informant Tool (AI)=-0.43; Memory Impairment Screen (MIS)=-0.37; Negative values of the Pearson's Correlation "r" indicates that lower the respective battery score, poorer is the cognitive function. In the Diabetic group GPCOG, AI and MIS were found to be significantly correlated with HBA1C. Similarly, in the non- Diabetic group (n=30), no significant Dementia and Cognitive Impairment was recorded when same group of Cognitive Batteries were administered.

Conclusion: It is quite evident from the results that HbA1C as biomarker has a great potential to predict Dementia and Cognitive decline in uncontrolled Diabetes. However, the study needs to be conducted on a larger scale along with comparative analysis with tools like Functional MRI and other standard biomarkers.

Keywords: Diabetes; Dementia; Alzheimers

Abbreviations: AI: Attendant Information Tool; CDT: Clock Drawing Test; GPCOG: General Practitioner Assessment of Cognition; HbA1C: Glycosylated Hemoglobin; KFT: Kidney Function Test; MIS: Memory Impairment Screen; MINI COG: Mini Cognition; MCI: Mild Cognitive Impairment; NS: Not Significant; OHA: Oral Hypoglycemic Agent; PPBS: Post Prandial Blood Sugar; RBS: Random Blood Sugar; T2DM: Type 2 Diabetes Mellitus

Introduction

Diabetes mellitus (DM) is globally one of the key disease burdens. It impacts 250 million people worldwide, with approximately 6 million new diagnosed patients every year. The prevalence of Diabetes varies for various age groups. In the people above 80years of age the prevalence is 15% as compared to 12% in population above 65-70 years [1-3].

Research suggests that poorly controlled Diabetes can impact the Cognitive functionality of the patients in a negative way [4-13]. Further, based on the literature the Alzheimer's type Dementia is found to be linked with the uncontrolled type 2 Diabetes Mellitus [7-13].

In a population based cohort study, impaired insulin metabolism and insulin resistance was found to be linked with increased risk of developing Alzheimer's disease [8].

Association between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) common pathology is evident by virtue of various epidemiological researches and other scientific research. Researchers have proposed Type -3 Diabetes to Alzheimer's disease based on the shared pathophysiology between the two [9].

Structural imaging of brain in Diabetic subjects reveal that cerebral anatomy is distorted which can lead to cognitive impairment. Out of these, subcortical and cortical atrophy being the important structural changes found in Diabetic subjects [4].

Interestingly, the cognitive impairment was found to be significant in those Diabetic subjects who had fairly controlled hypertension, thus indicating the poor Diabetes control as an independent risk factor for predicting Dementia and Cognitive dysfunction in Diabetes Mellitus [10].

In a study conducted by Cosway et al. [11], it was found that duration of Diabetes is significantly linked to impaired functions especially with respect to the verbal memory. In a two year follow up study on patients with early Alzheimer's disease, Burns et al. found that that insulin resistance was linked with the cognitive dysfunction [12]. Saczynski et al. [13] assessed the cognitive impairment in Diabetic subjects and

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concluded that patients with Diabetes have greater tendency to develop challenges pertaining to Cognitive functioning.

Cognitive decline is more significant in the obese type 2 Diabetic patients versus the normal weight ones. A recent study clearly indicates that Diabetic subjects with poor control have poor cognitive assessment scores. In a population based Case Control study conducted on 371 patients, association between Diabetes and Early Stage Diabetes was found in male subjects.

In an Animal model study it was found that the Diabetes was associated with multiple complications including cognitive decline in the Rat brain.

In a recent review, it was found that early management of the pre diabetes may help to prevent the multiple complications of Diabetes including Cognitive decline.

In one of recent study conducted in 2017, it was found that patients suffering from Type 2 diabetes with already diagnosed mild cognitive impairment were at a greater risk to develop Dementia.

In a study conducted by Merhan et al. it was found that cognitive decline in the type 2 diabetes may be due to the oxidative stress and lower levels of antioxidant markers.

In the current study we investigated the association of Dementia and Cognitive Dysfunction and uncontrolled type 2 Diabetes using HbA1C as a biomarker.

HbA1C (Glycosylated Hemoglobin) as a biomarker to diagnosis and prognosis of the disease has been reviewed by an International Expert Committee which was set up with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation. Following advantages were observed by the International Expert Committee with respect to routine blood sugar testing versus HbA1C.

- HbA1C provides better index of overall glycemic exposure.

- HbA1C predicts better risk for long-term complications

- Comparatively less biologic variability.

- No empty stomach blood samples required.

- Frequency of testing every 3 months.

- Results do not vary with acute illness (e.g. stress).

HbA1C has been used widely in India as a biomarker for Diabetic diagnosis and an indicator of diabetes control in Clinical practice. With the benefits of testing requirement every 3 months, accurate results and cost effectiveness HbA1C has become more acceptable as compared to

routine investigations like Random Blood Sugar, Post Prandial Blood Sugar, Glucose Tolerance test (Figure 1).

Historically, different approaches have been used to diagnose Dementia and Cognitive decline. Cognitive assessment batteries like General Practitioner Assessment of Cognition (GPCOG), Attendant Informant Tool (AI), Memory Impairment Screen (MIS); MINI COG have been used both for Clinical practice and research. All these tools require training and in routine are not carried out by the general physicians. These tests are more common in Neurology, Psychiatry and Neuropsychology clinics. Other radiological techniques like Magnetic Resonance Imaging, Positron Emission Brain Scans are quite expensive and time consuming for initial Dementia screening.

In this study, we show that that higher values of HbA1C can be a good indicator of poor Cognitive batteries score and therefore Dementia and Cognitive decline in Type 2 Diabetic Patients. In the Indian scenario, Diabetic subjects visiting to the Physicians do get their HbA1C tested every 3 months based on their Physician's advice. Correlation of individual Cognitive batteries scores with poor Diabetes control can be a promising and cost effective screening for Dementia (Figure 2).

Current study did reveal that there is a correlation between the Cognitive decline and the poor Diabetes control. HbA1C seems to be a great biomarker to predict Dementia and Cognitive decline in Type 2 Diabetes. Higher values of HbA1C can be linked to the Dementia and Cognitive assessment by the experts using more specific screening tools. The study needs to be conducted on a larger scale along with comparative analysis, correlation of HbA1C values with the Functional MRI assessments and other biomarkers.

Research Methodology

Patients and methods

Patients: Thirty (n=30); Type 2 Diabetics were enrolled in the study from the Out-Patient Department and hospitalized patients from Sarvodaya Hospital and Research Center, Faridabad, Delhi, NCR, India. Control group comprised of thirty (n=30) Non-Diabetic subjects as confirmed by Random Blood Sugar testing and hospital/out patient records. Ethical clearance from the University Ethics Committee and written permission from the Hospital was sought before the initiation of the study.

Age group of both Diabetic and control group was between 35-80 years of age. Patients with Type 2 Diabetes were required to have minimum 5 years of Type 2 Diabetes history as defined by "American Diabetic Association Criteria" [14]. HbA1C (Glycosylated Hemoglobin) greater than 7 in the Diabetic group. Participants should be well versed
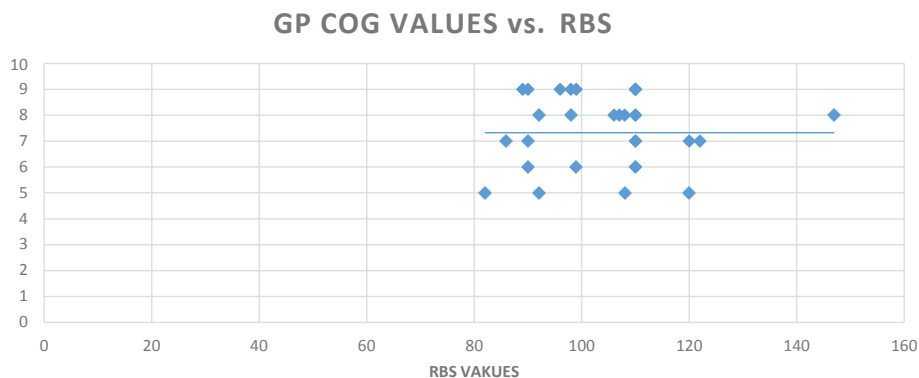

Figure 1: Scatter plot of HbA1C values versus the GPCOG score (diabetic group n=30).
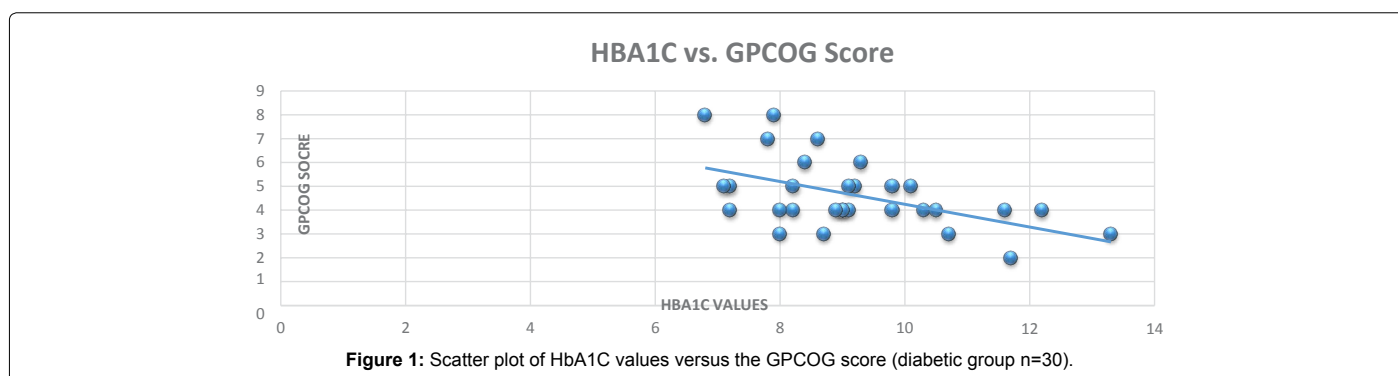
Figure 2: Scatter plot of RBS values versus the GPCOG score (control group n=30).
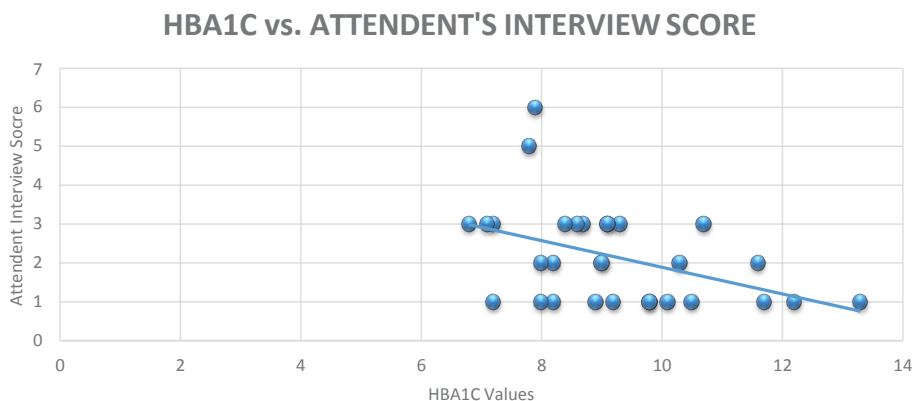

Figure 3: Scatter plot of HbA1C values versus the attendant's interview score (diabetic group n=30).

with written and spoken either Hindi or English language.

Subjects willing to participate and signing off informed consent form in the study were only enrolled in the research project.

Stringent exclusion criteria were adopted to prevent bias. Subjects of age less than 35 years, pregnant women and Children were excluded from the study. Patients with a history of other "chronic systemic diseases, neurological conditions, psychiatric disorders, alcohol and drug abuse were not included in the study.

Methods: In both the groups, demographic details of the participants were recorded as patient information form. The patient information form included age, sex socio economic status, education, marital status, occupation, duration of diabetes and diabetes complications like retinopathy, neuropathy nephropathy, whether on OHA (Oral Hypoglycemic Agents), insulin or both, family history of diabetes and history of other diseases. Pregnancy status of the women subjects was confirmed by history. The participants with diabetes were questioned about preceding episodes of hypoglycemia. All the subjects were clinically examined to rule out any acute ailment which can interfere the study proceedings.

Once the initial screening was over, the participants were explained about the probable benefits about the study participation. Candidates willing to participate in the study were then shared English/Hindi version of the Informed Consent Forms as applicable. The study context was clearly explained to the subjects and before participation informed consent forms were duly signed off by all the participants.

Cognition measurement tools

Cognitive batteries used in the current study were adopted from "The Alzheimer's Association" [15] (http://www.alz.org) with a written permission from the association.

The Cognitive tools are helpful for early detection and diagnosis of dementia and have been developed by a group of clinical dementia experts. The current research was single point prevalence study as Cognitive tools were administered only one time (Figure 3).

Three validated patient assessment tools: the General Practitioner Assessment of Cognition (GPCOG) including Attendant Information tool was also used to seek details from the patient's attendant/family members, the Memory Impairment Screen (MIS) and the Mini-Cog TM. Cognitive batteries were also translated to Hindi language along with the existing English language to enrol the patients at a faster pace.

The general practitioner assessment of cognition (GPCOG) [16]

The General Practitioner Assessment of Cognition (GPCOG) test comprised of two assessments. First step is patient assessment followed by the attendant information tool. The patient examination battery comprised of a name and address for subsequent recall test, time orientation and Clock drawing test for Visio-Spatial parameter assessment. Total score of the battery was 9 (nine). If patient scores 9, no significant cognitive impairment and further testing not necessary. In case score is 5-8, more information required for which Step 2,

attendant informant assessment was performed. Scores between 0-4, cognitive impairment was indicated and subjects were advised to get further investigations done to rule out cause of Cognitive decline and possible Dementia (Table 1).

In the attendant information test, 6 questions (which will add to total score of 6) were asked from the patient's relative comparing the current status with 5-10 years old scenario. To get a total score, the number of items answered 'no', 'don't know' or 'N/A') were added. If patient scored 0-3, cognitive impairment is indicated and the subject was advised accordingly [16] (Table 2).

Memory impairment screen (MIS) [17]

In the MIS battery administration, patient was shown a sheet of paper with the 4 items to be recalled in 24-point or greater uppercase letters (on other side) and was asked to read the items aloud. Patient was told that each item belongs to a different category. A category cue was given to the patient and asked to indicate which of the words belongs in the stated category (e.g. "Which one is the game?"). Allow up to 5 attempts. Failure to complete this task indicated possible cognitive impairment. In case subject identified all 4 words, the sheet of paper was removed and patient was told to remember the words in a few minutes. Meanwhile the patient was engaged in distractor activity for 2 to 3 min, such as counting to 20 and back, counting back from 100 by 7, spelling WORLD backwards. After the distracting activity patient was asked to recall the 4 words with and

without cues respectively. FREE RECALL was allotted 2 points per word and CUED RECALL-1 point per word (Table 3).

The maximum score for the MIS is 8.

- 5-8 No cognitive impairment
- ≤ 4 Possible cognitive impairment

Mini COG™

Patient was provided 1 version of 6 versions of three (3) unrelated clinically validated words and was asked to remember the assigned three words. Then the subject was asked to repeat the words to ensure the learning was correct [18-21].

In the second step patient was asked to draw the face of a clock and advised to draw hands to read 10 minutes after 11:00 (or 20 min after 8:00). After this step was over, patient was asked to recall the three words from Step 1.

Scoring

In case of 3 recalled words, test was Negative for cognitive impairment. In case of 1-2 recalled words+normal CDT (Clock drawing test) test was Negative for cognitive impairment. For 1-2 recalled words+abnormal CDT and for 0 recalled words, positive for cognitive impairment (Table 4).

GPCOG Score Range	No. of Patients	Battery Scoring Instructions	Cognitive Decline Status
Category 1			
Patient scores 9	0	· If patient scores 9, no significant cognitive impairment and further testing not necessary.	NA
Category 2 (Score)			
Patient scores 5-8	13	· 5-8, more information required. Proceed with Step 2, informant section.	· Administered the Informant/Attendant Interview.
Category 3 (Score)			
Patient scores 0-4	17	· If patient scores 0-4, cognitive impairment is indicated	· Cognitive Impairment is indicated. · 56.56% of the Patients were found to have Cognitive Decline when administered GPCOG test.

Table 1: GPCOG score range vs. cognitive impairment in the diabetic group (n=30).

GPCOG Score Range	No. of Patients	Battery Scoring Instructions	Cognitive Decline Status
Category (Score)			
Patient scores 0-3	28	· If patient scores 0-3, cognitive impairment is indicated	· Cognitive Impairment is indicated.

Table 2: Attendant score range vs. cognitive impairment in the diabetic group (n=30).

GPCOG Score Range	No. of Patients	Battery Scoring Instructions	Cognitive Decline Status
Category 1			
Patient scores 5-8	1	· If patient scores 5-8, no significant cognitive impairment.	No cognitive impairment.
Category 2 (Score)			
Patient scores 0-4	29	· If patient scores 0-4, cognitive impairment is indicated	· Cognitive Impairment is indicated.

Table 3: MIS (memory impairment screen) vs. cognitive impairment in the diabetic group (n=30).

MINI COG Score Range	No. of Patients	Battery Scoring Instructions	Cognitive Decline Status
Category 1			
3 recalled words	2	3 recalled words - Negative for cognitive impairment	Negative for cognitive impairment
Category 2 (Score) normal CDT (Clock Drawing Test)			
1-2 recalled words +	4	1-2 recalled words + normal CDT- Negative for cognitive impairment	Negative for cognitive impairment
Category 3 (Score)			
1-2 recalled words + abnormal CDT	23	1-2 recalled words + abnormal CDT- Positive for cognitive impairment	Positive for cognitive impairment
Category 4 (Score)			
0 recalled words	1	0 recalled words - Positive for cognitive impairment	Positive for cognitive impairment

Table 4: MINI COG test and cognitive impairment in the diabetic group (n=30).

Statistical analysis

To assess associations between the Diabetes related Cognitive impairment, Pearson's correlation coefficient (r) was calculated for various variables in the Diabetic patients and non-Diabetic subjects using IBM SPSS Statistics trial version (Figure 4).

Key focus was laid down on the parameters like duration of Diabetes, no of hypoglycemic episodes in the Diabetic group, HbA1C (Glycosylated Hemoglobin) values, age of subjects versus the individual battery score. Pearson's correlation was calculated with the corresponding 2 tailed significance level. Similarly, the various parameters were correlated with the individual battery scores in the non-Diabetic group.

Results

In this prevalence study 60 subjects were enrolled. Out of these thirty (n=30) were type 2 Diabetic patients and rest were (n=30) non diabetics. The study was conducted in a hospital setting including both indoor and outdoor patients. In this study HbA1C values were compared with that of individual GPCOG, Attendant Interview, MIS and MINI COGTM. Mean and standard deviation of HbA1C were calculated and comparison was done with the corresponding Pearson's Correlation values.

The mean values of HbA1C in the Diabetic group (n=30) was found to be 9.19 with a standard deviation of 1.58. The corresponding values of Pearson's Correlation "r" in the diabetic group of the various Cognitive batteries were: GPCOG=-0.53, Attendent Interview=-0.43, MIS=-0.37, Negative values of the Pearson's Correlation "r" indicates the negative correlation of HbA1C values with Cognitive batteries score. Lower the respective battery score, poorer is the cognitive function. Significant correlation was also found between HbA1C and duration of Diabetes, age and number of hypoglycemic episodes in the Diabetic group (Table 5a).

In the subjects who were administered the MINI Cog TM battery similar results were obtained indicating the HbA1C can be used as a Novel Biomarker to predict Dementia in Diabetic subjects. Out of the 30 subjects in the Diabetic group, 24 were found to be positive for the cognitive impairment (Figure 5).

In the Diabetic group, GPCOG score, Attendant Information Score and MIS Score were found to be Non-Significantly correlated 2 tailed (NS) with respect to the Weight in Kg, Kidney function test values

Figure 4: Scatter plot of RBS Values versus the attendant's interview score (control group n=30).
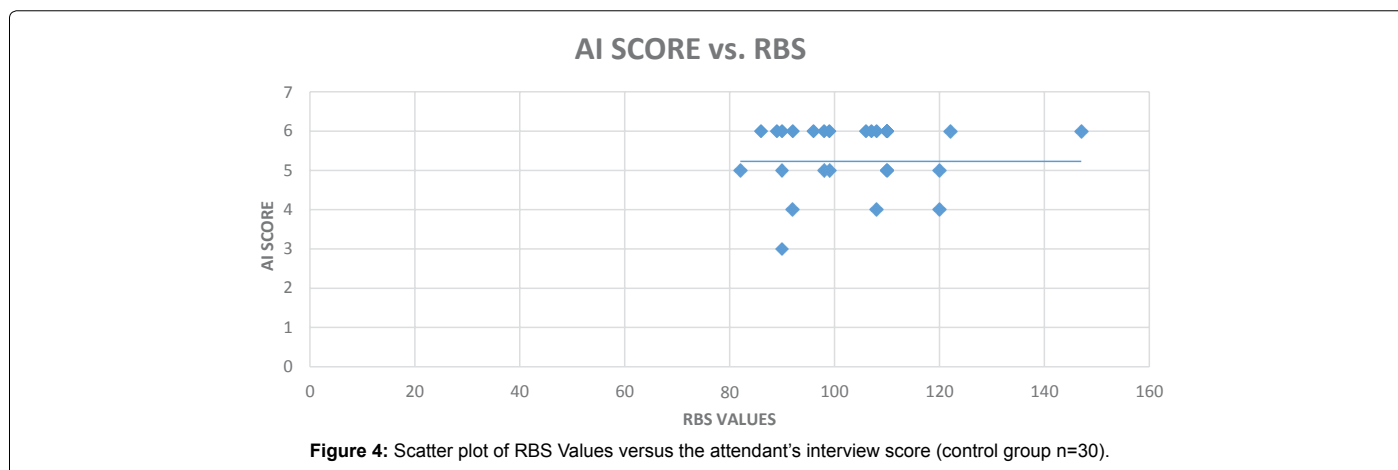
		HbA1C Levels	Duration of Diabetes (Years)	Ages (Years)	H/O No. of Hypoglycemic Episodes
GPCOG SCORE	Pearson's Correlation	-0.520	-0.426	-0.563	-0.547
	Significance (2-tailed)	0.003 (S)	0.019 (S)	0.001 (S)	0.002 (S)
Attendant Information Score	Pearson's Correlation	-0.429	-0.572	-0.565	-0.360
	Significance (2- tailed)	0.018 (S)	0.001 (S)	0.001 (S)	0.051 (S)
MIS Score	Pearson's Correlation	-0.375	-0.518	-0.582	-0.453
	Significance (2- tailed)	0.041 (S)	0.003 (S)	0.001 (S)	0.012 (S)

GPCOG score, Attendant Information Score and MIS Score were found to be Significant (S) 2 tailed with respect to the HbA1C levels (Diabetes control), Duration of Diabetes Mellitus in Years, Age in years and Number of Hypoglycemic Episodes

Table 5a: Different variables, their correlation and corresponding level of significance in the diabetic group (n=30).

		Weight in Kg	Kidney Function Test (Values)	OHA Treatment Duration in years	OHA+Insulin Treatment in Years
GPCOG SCORE	Pearson's Correlation	-0.228	-0.251	0.03	-0.262
	Significance (2-tailed)	0.225 (NS)	0.180 (NS)	0.986 (NS)	0.162 (NS)
Attendant Information	Pearson's Correlation	-0.084	-0.340	-0.230	-0.380
	Significance (2-tailed)	0.657 (NS)	0.066 (NS)	0.904 (NS)	0.390 (NS)
MIS Score	Pearson's Correlation	-0.001	-0.354	0.001	-0.342
	Significance (2- tailed)	0.996 (NS)	0.06 (NS)	1.000 (NS)	0.065 (NS)

GPCOG score, Attendant Information Score and MIS Score were found to be Non-Significantly correlated 2 tailed (NS) with respect to the Weight in Kg, Kidney function test values (KFT), Duration of OHA (Oral Hypoglycemic Agents) treatment in years and Duration of OHA+Insulin Therapy in years

Table 5b: Different variables, their correlation and corresponding level of significance in the diabetic group (n=30).

(KFT). Duration of OHA (Oral Hypoglycemic Agents) treatment in years and Duration of OHA+Insulin Therapy in years (Table 5b).

Similarly, in the non-Diabetic group (n=30), no significant Dementia/Cognitive Impairment was found when same group of Cognitive Batteries were administered.

In the non-Diabetic group, GPCOG (Significance 2-tailed=0.864), AI score (Significance 2-tailed=0.520) and the MIS scores (Significance 2-tailed=0.685) were found to be non-significantly correlated with the RBS values (Table 6).

Discussion

Various studies have been provided evidence between the association of Diabetes Mellitus and Cognitive Impairment across the globe under different geographical conditions [21-35]. Studies suggest that out of multiple domains of the Cognitive Impairment, only limited are adversely impacted [21-35]. Type 2 Diabetes Mellitus is associated with faster brain aging [36,37].

		RBS Values
GPCOG Score	**Pearson's Correlation**	0.033
	Significance (2-tailed)	0.864 (NS)
Attendant Information	Pearson's Correlation	0.122
	Significance (2-tailed)	0.520 (NS)
MIS Score	Pearson's Correlation	0.077
	Significance (2-tailed)	0.685 (NS)

Table 6: RBS (random blood sugar) values, their correlation and corresponding level of significance in the non-diabetic group (n=30).
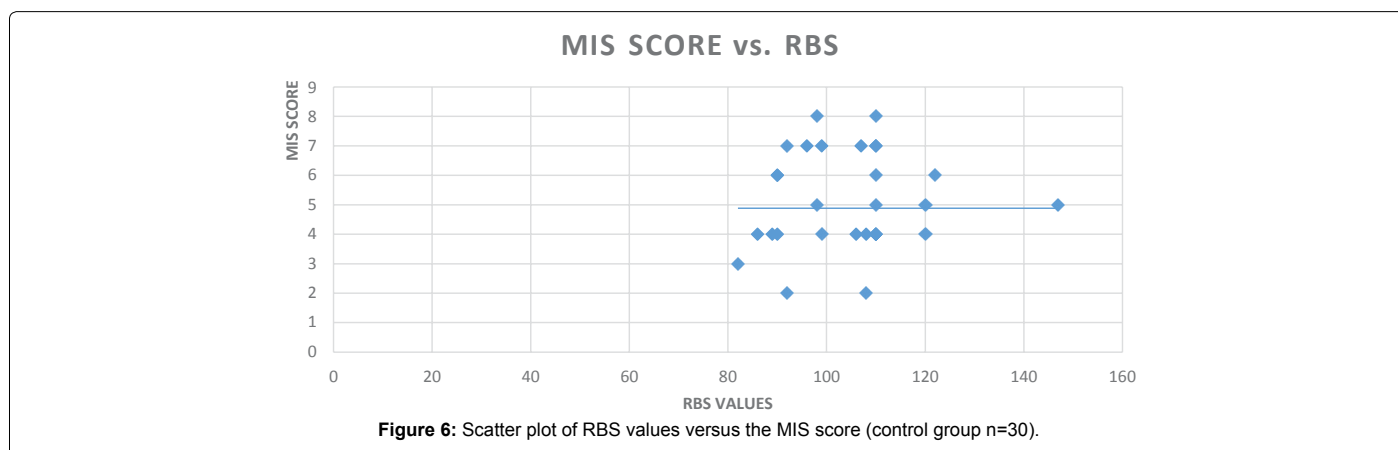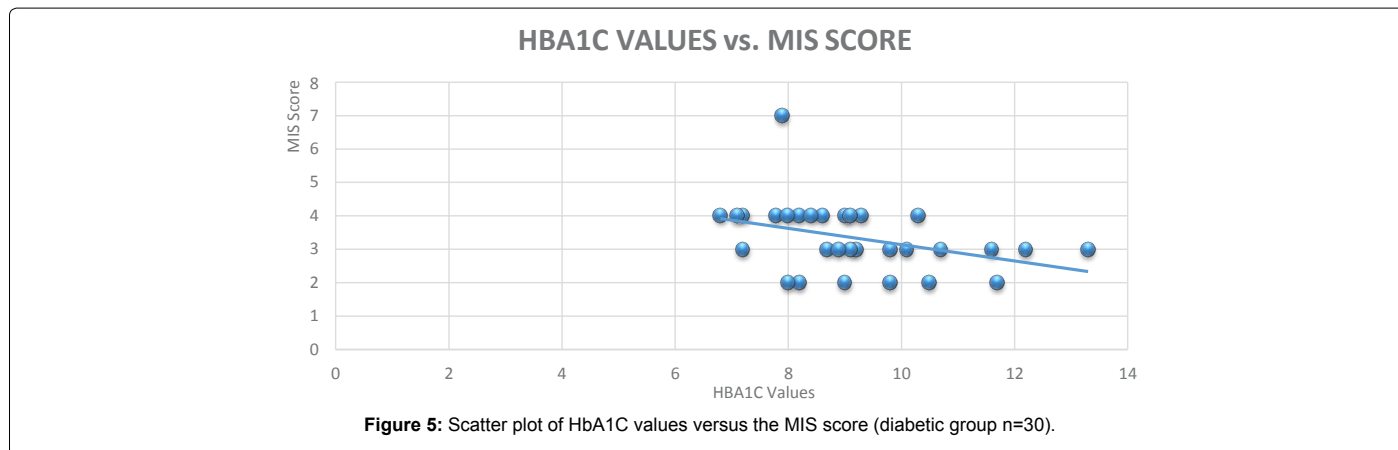
Diabetes mellitus (DM) is globally one of the key disease burdens. It impacts 250 million people worldwide, with approximately 6 million new diagnosed patients every year. The prevalence of Diabetes varies for various age groups. In the people above 80years of age the prevalence is 15% as compared to 12% in population above 65-70 years.

Limited observational studies have been conducted in the North India in which Cognitive Impairment and Diabetes Mellitus have been investigated to bear a correlation. The current pilot study was conducted in the Delhi National Capital Region of North India to Determine Prevalence of Dementia and Cognitive Dysfunction in Type 2 Diabetic Subjects versus Non-Diabetic Control Group. The results are indicative of correlation between the Diabetes Mellitus and Cognitive decline. Clearly duration of Diabetes, poorly controlled Diabetes and number of hypoglycemic episodes were found to be strongly correlated with the Cognitive decline [38-40].

The current study highlights the usage of already existing Biomarkers like HbA1C in predicting/diagnosing the newer indication. HbA1C has been used to define the control of Diabetes Mellitus and we proposed the same for the predicting the Cognitive and Memory decline in this pilot study. In this study the HbA1C levels were found to be significantly correlated with the scores of different batteries: GPCOG (Significance 2-tailed=0.003), AI score (Significance 2-tailed=0.018) and the MIS scores (Significance 2-tailed=0.041) in the Diabetic group. Significant correlation was also found between HbA1C and duration of Diabetes, age and number of hypoglycemic episodes in the Diabetic group (Figure 6).

Figure 5: Scatter plot of HbA1C values versus the MIS score (diabetic group n=30).

Figure 6: Scatter plot of RBS values versus the MIS score (control group n=30).

In the subjects who were administered the MINI Cog TM battery similar results were obtained indicating the HbA1C can be used as a Novel Biomarker to predict Dementia in Diabetic subjects. Out of the 30 subjects in the Diabetic group, 24 were found to be positive for the cognitive impairment. In the non-Diabetic group, GPCOG (Significance 2-tailed=0.864), AI score (Significance 2-tailed=0.520) and the MIS scores (Significance 2-tailed=0.685) were found to be non-significantly correlated with the RBS values.

HbA1C has been used widely in India as a biomarker for Diabetic diagnosis and an indicator of diabetes control in Clinical practice. With the benefits of testing requirement every 3 months, accurate results and cost effectiveness HbA1C has become more acceptable as compared to routine investigations like Random Blood Sugar, Post Prandial Blood Sugar, Glucose Tolerance test [40-47].

In the current study it was found that other parameters like duration of Diabetes, age of the subjects and number of hypoglycemia episodes, were also significantly correlated with the poor cognitive function and memory loss. This adds to the study limitation and asks for much larger study within the diabetic group to further evaluation of the Clinical application of HbA1C biomarker to predict Dementia and Cognitive decline.

On the basis of the significant results of this study HbA1C as a biomarker seem to have great clinical application to predict Dementia and Cognitive decline in Diabetic subjects. This can provide a platform for further investigating the poor Diabetes control and its correlation with the Cognitive decline and Dementia.

Conclusion and Perspective

The current pilot study evaluates the role of HbA1C as a biomarker to predict Dementia and Cognitive decline in Diabetic subjects. In the current study HbA1C was found to be significantly correlated with the multiple batteries used for Cognition and Memory screening. Saying that other parameters like duration of Diabetes, age of the subjects and history of hypoglycemia episodes were also significantly correlated with respect to cognitive decline.

Going forward, larger group studies are required focusing on the comparison between uncontrolled Diabetes with and without hypoglycemic episodes [48].

Further, Imaging techniques also like structural and functional MRI also possess a significant potential in the context of screening and diagnosis of various memory impairment disorders. Functional MRI evaluates the blood flow response and compares that with the brain activity. It was found that age did not impact the hemodynamic blood flow making Functional MRI an important radiological tool to diagnose disease related Dementia [49].

A team of Radiologists and Scientists from Harvard Medical School and universities reviewed multiple Neuroimaging markers for the diagnosis of Dementia of Alzheimer's type. Team found that fMRI task-related abnormal increase in hippocampal in the preclinical and early stage of MCI (Mild Cognitive Decline) followed by decreased activity as the disease progress [50].

Functional MRI can be one of the key diagnostic tool to further strengthen the current study findings. We also stress upon the study to be conducted on a much larger population to get more significant results.

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