Cognitive dysfunction in diabetes is associated with glycemic control in an urban Indian population: A prevalence study

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ABSTRACT
We evaluated the correlation between HbA1C and Cognitive derangement of type 2 Diabetics in the current prevalence study. We further investigated the role of poor Diabetes control versus hypoglycemia episodes as independent predictors of cognitive derangement in 240 type 2 Diabetics. In pilot phase, comparison between Diabetics (n=30) and non-Diabetic subjects (n=30) for Cognitive derangement using cognitive batteries: GPCOG, AI tool and MIS was done. PET CT brain findings of one of Diabetic subjects were also observed. Further study was conducted on 240 diabetic subjects using batteries validated in the pilot phase. Pilot study provided statistically significant results of correlation between HbA1C levels versus GPCOG Score, Pearson’s Correlation r1 = -0.448*, for AI Score Pearson’s Correlation r2 = -0.196* and for MIS score Pearson’s Correlation r3 = -0.472*. The prevalence ratio for both groups was calculated as 5.8125, which implies Diabetics had > 5 fold risk of deranged cognition as compared to the non-Diabetic group. Using independent T-test, mean GPCOG score in the Hypoglycemia group (n=162) and without hypoglycemia group (n=78) were found to be 3.02 and 4.63 respectively. Similarly, based on the independent T-test, the mean AI score in the Hypoglycemia group (n=162) and without hypoglycemia group (n=78) were found to be 2.068 and 2.564, respectively. PET CT brain findings were suggestive of reduced FDG uptake indicating Alzheimer’s type of cognitive derangement. HbA1C can be linked to poor cognitive derangement in case of poor diabetes control. Hence HbA1C can be a useful biomarker to predict cognitive derangement in type 2 Diabetics. *Significance level <0.01, Negative correlations are indicative of lower the values of battery scores higher would be cognitive derangement.

INTRODUCTION
Diabetes mellitus (DM) is increasingly affecting millions of people worldwide and is the key disease burden. Evidence suggests that poorly controlled diabetes can adversely impact the cognitive functionality of the patients. Impaired insulin metabolism and insulin resistance was found to be linked with increased risk of developing Alzheimer’s type of Dementia. A number of studies have been conducted focusing on Diabetes association with cognitive decline. (Schrijvers et al., 2010) provided evidence of the association between insulin resistance and alzheimer’s disease within first 3 years of diabetes. Certain researchers have cited alzheimer’s disease...
as type 3 diabetes indicating a linkage between diabetes and cognitive decline. (Akter et al., 2011). Another group has proposed that diabetes disease risk reduction can possibly helpful in decreasing possible dementia (Palta et al., 2018). One of the study indicated a mild association of diabetes and alzheimer’s type of dementia in males (Kadohara et al., 2017). Some of the animal studies have an indiated association between diabetes and dementia ar molecular levels (Chomova et al., 2017).

Eberhardt and Topka (2017) proposed that if pre-diabetes is managed well, that can lead to the prevention of the cognitive decline in these patients along with other neuropathological derangements. A study conducted by (Ciudin et al., 2017) provided evidence between diabetes and mild cognitive impairment. At a molecular level, oxidative stress is responsible for alzheimer’s pathology and also diabetic pathology. Hence there is a possibility of an association between the two (Ragy and Kamal, 2017).

However, studies associating cognitive derangement with poor Diabetes control as indicated by HbA1C and further evaluating the role of hypoglycemia in Cognitive derangement are limited. In the current study, we used validated batteries to investigate the role of HbA1C as a biomarker to predict cognitive derangement in type 2 Diabetics. (Gupta et al., 2018). PET CT brain findings of one of the patients from the pilot study group was also observed before initiation of the main study on 240 subjects.

We hypothesized that poor Diabetes control and hypoglycemia episodes in type 2 Diabetics are separate predictors of cognitive derangement. Further, we aimed to compare poor Diabetes control patients with or without hypoglycemia episodes with respect to the cognitive derangement.

The current study addresses a very important aspect i.e., poor diabetes control and related cognitive derangement in a developing country like India, which is termed as a Diabetic hub of the globe. Study findings are very important and can be easily extrapolated to a global scenario as well as Diabetes being life-style disorder is spreading at a much faster pace round the globe.

MATERIALS AND METHODS

Participants

Human subjects (n=300) with a history of Diabetes and non-diabetic subjects were enrolled in this study.

This was a 2-phase cross-sectional prevalence study in which data pertaining to exposure and disease outcome was collected in parallel from different groups at a single given point of time. Patients were enrolled from either outpatient department or hospitalized patients from Sarvodaya Hospital and Research Center, Faridabad, Delhi NCR, India. Ethical clearance was sought from the University Ethics Committee of Amity University Uttar Pradesh, Noida, India and written permission from the Hospital were taken before initiation of the study. All the subjects have provided written, informed consent to participate in the study.

Demographic details of the participants were recorded as patient information form. The patient information form included age, sex socio-economic derangement, education, marital derangement, 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 derangement of the women subjects was confirmed by history. (Refer to Table 1 for demographic details)Candidates willing to participate in the study were then shared the 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.

Procedure

Once the initial screening was over, the participants were explained about the probable benefits about the study participation. Age group of both diabetic and control groups was between 35-80 years of age. Patients with type-2 diabetes were required to have a minimum of five years of type-2 diabetes history as defined by the "American Diabetic Association Criteria.” HbA1C (glycosylated hemoglobin) greater than 7 in the diabetic group was also an inclusion criterion.

Inclusion and Exclusion criteria

Inclusion criteria: Age group between 35 –80 years, patients of Type 2 Diabetes as defined by "American Diabetic Association Criteria ", minimum of 5 years of Diabetic History, HBA1C greater than 7, must be verse with written and spoken English/Hindi, should be willing to participate & signing off informed consent form in the study.

Exclusion criteria: Patients of age less than 35 years, patients with a history of other “Chronic Systemic Diseases”, pregnant women and Children, patients with alcohol and drug abuse, patients with a history of any Neurological, Psychiatric disorders.

Sample size was calculated based on the preva-
Figure 1: Describes the study conducted in two phases: pilot & main phase

In the current study, we investigated the association of 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 (Nathan et al., 2009).

Following advantages were observed by the International Expert Committee with respect to routine blood sugar testing versus HbA1C.

1. HbA1C provides a better index of overall glycemic exposure.
2. HbA1C predicts better risk for long-term complications
3. Comparatively less biologic variability.
4. No empty stomach blood samples required
5. Frequency of testing every 3 months.
6. 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 requirements 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.

**Cognitive assessment**

Cognitive batteries used in the study were adopted from “The Alzheimer’s Association” (http://www.alz.org) with written permission from the association. Three validated patient assessment tools, the General Practitioner Assessment of Cognition (GPCOG), Attendant Information (AI) and Memory Impairment Screen (MIS), were used to seek details from patients and their family members.

In pilot phase comparison between Diabetics (n=30) and non-Diabetic subjects (n=30) for Cognitive derangement using cognitive batteries: General Practitioner Assessment of Cognition (GPCOG), Attendant Informant Tool (AI) and Memory Impairment Screen (MIS) was done. In the second phase, we further investigated the role of poor Diabetes control versus hypoglycemia episodes as predictors of Cognitive derangement in 240 type 2 Diabetics. Follow up study comprised of two arms; arm 1 (n=78) type-2 diabetic patients without a history of hypoglycemia and in arm 2 (n=162) type-2 diabetic patients with a history of hypoglycemia. Further PET CT brain findings of one of the Diabetic subjects were observed.

**Brain FDG PET scan acquisition protocol**

We observed findings of a high-resolution CT scan was performed using a dedicated PET scanner with 32slice/sec Multidetector Computerized Tomography (MDCT). Serial axial sections were obtained from the skull base to vertex. The patient’s blood glucose level at the time of injection was 116 mg %.

**Statistical analysis**

To assess associations between diabetes and cognitive impairment, Pearson’s correlation coefficient (r) was calculated for various variables in the diabetic patients using IBM SPSS Statistics 25 software. A key focus was laid down on the parameters like number of hypoglycemia episodes in the diabetic group, HbA1C (glycosylated hemoglobin) values versus the individual battery scores. Pearson’s correlation was calculated with the corresponding 2-tailed significance level. The prevalence ratio was calculated for the Diabetic and non-Diabetic group. Further, both cohorts were compared with respect to the cognition batteries scores using the student’s t-test.

**RESULTS AND DISCUSSION**

**Cognitive derangement was found to be significantly correlated with HbA1C levels in Diabetics**

Based on the independent student’s t-test, the mean GPCOG score in the hypoglycemia group (n=162)

**in the pilot study**

Pilot study provided statistically significant results of correlation between poor Diabetes control as measured by HbA1C and Cognitive derangement in cases (n=30). HbA1C levels versus GPCOG Score, Pearson’s Correlation r1= -0.448 (Significance level <0.01) for AI Score Pearson’s Correlation r2= -0.196(Significance level <0.01) and for MIS score Pearson’s Correlation r3= -0.472(Significance level <0.01) In the non-Diabetic group n= 30, RBS levels when compared with GPCOG (r=0.864), AI (r=0.122) and MIS (r=0.077) scores statistically insignificant correlation values were recorded.

We also calculated the Prevalence ratio for both the groups as 5.8125, which implies patients with Diabetes had more than 5 fold risk of development of poor cognition when compared with the non-Diabetic group.

**Follow up study on 240 Diabetic subjects further validated the association between HbA1C levels and Cognitive derangement in type 2 Diabetes Mellitus.**

We found that both the arms taken together (n=240), Pearson’s correlation coefficient (r) between individual HbA1C versus different cognitive batteries were; HBA1C versus General Practitioner Assessment of Cognition (GPCOG) score (r1= -0.448), HBA1C versus Attendant Informant Tool (AI) score (r2= -0.196) and HBA1C versus Memory Impairment Screen (MIS) score (r3= -0.472) at significance value of <0.01 Table ??

Moreover, Pearson’s correlation coefficient (r) in group without hypoglycemia arm (n=78) was found to be statistically significant as well. The correlation coefficient were calculated between HBA1C versus GPCOG score (r1= -0.510), HBA1C versus AI score (r2= -0.507) and HBA1C versus MIS score (r3= -0.628) at significance value of < 0.01 Table ??

Similarly, Pearson’s correlation coefficient between individual HbA1C values and different cognitive batteries was also calculated in group with hypoglycemia arm (n=162), and these values were HBA1C versus GPCOG score (r1= -0.226), HBA1C versus AI score (r2= -0.290), HBA1C versus MIS score (r3= -0.278) at significance value of < 0.01. Negative values of Pearson’s correlation indicate that lower the respective battery score, the poorer is the cognitive function Table ??

**Diabetics with Hypoglycemia episodes had more severe Cognitive derangement as compared with Diabetics with no Hypoglycemia episode.**

Based on the independent student’s t-test, the mean GPCOG score in the hypoglycemia group (n=162)
Table 1: Different variables along with the respective range

<table>
<thead>
<tr>
<th>Variables</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>35-75</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>45-92</td>
</tr>
<tr>
<td>Duration of diabetes (Years)</td>
<td>6-17</td>
</tr>
<tr>
<td>No. of hypoglycemic episodes</td>
<td>0-9</td>
</tr>
<tr>
<td>HBA1C values</td>
<td>7-17</td>
</tr>
</tbody>
</table>

Table 2: HbA1C values and their correlation with different cognitive batteries scores in various categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Cognitive Batteries</th>
<th>HbA1C</th>
<th>Pearson's correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C values and their correlation with different cognitive batteries scores (n=240 including hypoglycemia episodes patients)</td>
<td>GPCOG Score</td>
<td>HbA1C</td>
<td>-0.448*</td>
</tr>
<tr>
<td></td>
<td>Attendant Information Score</td>
<td>HbA1C</td>
<td>-0.196*</td>
</tr>
<tr>
<td></td>
<td>MIS Score</td>
<td>HbA1C</td>
<td>-0.472*</td>
</tr>
<tr>
<td>HbA1C values and their correlation corresponding cognitive batteries scores in patients without history of hypoglycemia (n = 78)</td>
<td>GPCOG SCORE</td>
<td>HbA1C</td>
<td>-0.510*</td>
</tr>
<tr>
<td></td>
<td>Attendant Information Score</td>
<td>HbA1C</td>
<td>-0.507*</td>
</tr>
<tr>
<td></td>
<td>MIS Score</td>
<td>HbA1C</td>
<td>-0.628*</td>
</tr>
<tr>
<td>HbA1C values and their correlation corresponding cognitive batteries scores in patients with history of hypoglycemia (n = 162)</td>
<td>GPCOG SCORE</td>
<td>HbA1C</td>
<td>-0.226*</td>
</tr>
<tr>
<td></td>
<td>Attendant Information Score</td>
<td>HbA1C</td>
<td>-0.290*</td>
</tr>
<tr>
<td></td>
<td>MIS Score</td>
<td>HbA1C</td>
<td>-0.278*</td>
</tr>
</tbody>
</table>

* Significance (2- tailed) <0.01; Negative correlations are indicative of lower the values of battery scores higher would be cognitive derangement

Table 3: Independent Students’ t-test results in diabetics with and without hypoglycemia arms

<table>
<thead>
<tr>
<th>Independent t-test*</th>
<th>Mean GPCOG Score</th>
<th>Mean Attendant Information Score</th>
<th>Mean MIS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>With hypoglycemia Group (n=162)</td>
<td>3.02</td>
<td>2.068</td>
<td>1.963</td>
</tr>
<tr>
<td>Without hypoglycemia Group (n=78)</td>
<td>4.63</td>
<td>2.564</td>
<td>3.013</td>
</tr>
</tbody>
</table>

*At level of significance < 0.01 (2 tailed) and 95% confidence interval

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Figure 2: (a-c and a’-c’)-Scatter plots depicting Pearson’s correlation between cognitive batteries in Diabetic (n=30) and non-Diabetic (n=30) in the pilot study. (a)-GPCOG vs RBS values (a’)-GPCOG vs HBA1C values (b)-MIS vs RBS values (b’)-MIS vs HBA1C values (c)-AI score vs RBS values (c’)-AI score vs HBA1C values

and without hypoglycemia group (n=78) was found to be 3.02 and 4.63, respectively. Similarly, based on the independent student’s t-test, the mean AI score in the hypoglycemia group (n=162) and without hypoglycemia group (n=78) was found to be 2.068 and 2.564, respectively. Moreover, the MIS score in the hypoglycemia group (n=162) and without hypoglycemia group (n=78) was calculated to be 1.963 and 3.013, respectively. Overall, poor Diabetes control and hypoglycemia episodes are separate contributors to Dementia and Cognitive derangement; however, later can lead to more severe cognitive derangement in type 2 DiabeticsTable 3.

PET CT brain findings in Diabetic Subject with severe Cognitive derangement

PET CT brain provided evidence of age-related cerebral cortical atrophy with a mild widening of sulci. The ventricular system appears not dilated. Mild diffusely decreased radio-active glucose uptake is seen along the bilateral cerebral and cerebellar cortex with relative sparring of the sensory-motor cortex. Reduced radioactive glucose uptake noted in bilateral mesial temporal and parietal regions (Figure 3 and Figure 4)

India has been termed as the Diabetic capital of the world. Worldwide diabetes population in on the rise (Zimmet et al., 2001). There is a parallel increase in Dementia cases in India. ARDSI 2010 report highlights that by 2030 there will close to 7 million Dementia cases in India. (ARDSI, 2010). Global studies have emphasized on Diabetes association; however, very limited research has been undertaken in the Indian scenario. World Health Organization report indicated there will be around 366 million by the year 2030 (WHO report, 2000).

Earlier studies have indicated that diabetes pathology can aggravate the cognitive decline Awad et al. (2004). Animal models of dementia have proposed that there is an association between diabetes and dementia (Biessels et al., 1996). Human studies indicated the association between diabetes and dementia and have proposed further studies
Figure 3: Brain PET slices of a 74-year-old diabetic woman revealed significant FDG hypometabolism involving bilateral parietal cortices and extending right mesial temporal regions (white arrowheads). Features appear consistent with AD.

in this domain (Biessels et al., 2008). A metaanalysis done by (Brands et al., 2005) provided evidence of mild to moderate association between diabetes and dementia. Another study conducted by (Cole et al., 2007), the proposed molecular correlation between dementia and diabetes pathology. Nerve damage has been associated as diabetes complications, which can be associated with dementia as well (Brownlee, 2001). Diabetes, dementia and age association was studied by (Croxon and Jagger, 1995) and it was observed that there is an increased risk of dementia in those elderly patients who have already developed diabetes. Dementia and poor Diabetes control have been reported to co-exist in Diabetic patients (Elias et al., 1997) hence an opportunity to explore the correlation between the two.

The current study is first of its kind comparing uncontrolled Diabetes using HbA1C as a biomarker, hypoglycemia episodes with Cognitive derangement using validated batteries. Observations made in this study are highly significant and provide direction towards Cognitive care requirements in Diabetic patients. No similar study has been conducted thus far in the northern part of India. The study was conducted in two phases: A pilot (n= 60 subjects ) was helpful in establishing the validity of the batteries used and providing contrast in the Diabetics and non-Diabetic population.HBA1C was used as a biomarker to predict Diabetes control which is the gold standard of average glucose assessment (Nathan et al., 2009).

In the pilot phase, diabetic group(n=30) 29 Patients were found to have Cognitive derangement when administered GPCOG test,28 out of 30 patients reported cognitive derangement based on MIS scores. In the non-diabetic group, the battery scores
were found to be statistically insignificant, indicating no cognitive derangement (Figure 2 a-c).

Further Prevalence ratio for both groups was calculated as 5.8125, which implies Diabetics had greater than 5 fold risk of development of Dementia and Cognitive derangement when compared with a non-Diabetic group. This was a significant finding of the pilot study.

In the follow-up study, 240 diabetic patients were enrolled and the results establishing a correlation between Cognitive derangement with poor control Diabetes as measured by HbA1C and Hypoglycemia episodes were found to be statistically significant (Refer to Table ??).

Earlier imaging studies have indicated cortical atrophy in cases of Dementia (Ewers et al., 2011) though there are limited functional brain imaging studies which investigated Dementia and Diabetes association. (Grinband et al., 2017). We observed the PET CT brain of one of the Diabetic subjects with marked cognitive derangement and the results were indicative of Alzheimer’s type pathology. Axial $^{18}$F-FDG brain PET slices of a 74-year-old woman with progressive dementia revealed significant FDG hypometabolism involving bilateral parietal cortices and extending to the mesial temporal regions, more predominantly affecting the right side. Mild hypometabolism involving bilateral anterior cingulated cortices is also seen with preserved glucose metabolism in the sensori-motor cortex, bilateral basal ganglia, thalami and cerebellum. These features appear consistent with AD. (Figure 3). 3-dimensional stereotactic surface projection images (generated using comparison with a normal standardized brain database, NeuroQ$^{TM}$ software package, GE healthcare) showing relative glucose metabolism (top panel) and extent of...
hypometabolism (lower panel) in standard projections (Right lateral, left lateral, right medial, left medial, anterior, posterior, superior and inferior). These images also confirm the moderate glucose hypometabolism along bilateral parieto-temporal cortices (white arrowheads). (Figure 4)

Diabetic patients with Hypoglycemia episodes were found to have much greater Cognitive derangement as compared to those who had no history of hypoglycemia. The finding is aligned with earlier research providing evidence pertaining to HbA1C levels and poor cognition.

Going forward, a strong association between Insulin resistance and Cognitive derangement needs to be laid down as it has been emphasized in earlier studies as well (Cosway et al., 2001).

The current study provides strong evidence pertaining to the role of HbA1C as a biomarker to predict cognitive derangement in type 2 Diabetes. This study also evaluates the association of hypoglycemia episodes with cognitive derangement and provides evidence that hypoglycemia episodes can be a separate predictor of the same. We further validated the batteries in a pilot study before the initiation of the main research observation. PET CT brain of one the subject also provided evidence of Alzheimer’s type dementia based on the regions involved in the brain and provides a new investigational approach in dementia diagnosis. PET CT brain is an important intervention in India to rule out cancer and dementia protocols usage has been very limited (Alavi et al., 2010).

Being an observational study adds to one of the key limitations of the study. Being a single point correctional observation also adds to the limitations. Randomized controlled clinical trials involving diagnostic tools like functional MRI and PET CT brain (Sharma et al., 2012) are asking for future studies to arrive to a final consensus among neuro-scientists and neurologists on the same.

CONCLUSIONS

The current study is first of its kind comparing uncontrolled Diabetes, hypoglycemia episodes with Cognitive decline using assigned batteries. Observations made in this study are highly significant and provide direction towards Cognitive care requirements in Diabetic patients. No similar study has been conducted thus far in the northern part of India. The study was conducted in phases: A pilot (n= 60 subjects ) was helpful in establishing the validity of the batteries used and providing contrast in the Diabetics and non- Diabetic population. In the main study, 240 diabetic patients were enrolled and the results were highly significant, thus establishing a correlation between Cognitive decline/Dementia with poor control Diabetes and Hypoglycemia episodes. We also observed a PET CT brain of one of the Diabetic subjects with marked cognitive decline and the results were indicative of Alzheimer’s type pathology. Diabetic patients with Hypoglycemia episodes were found to have much greater Cognitive decline as compared to those who had no history of hypoglycemia.

Though there is awareness of Dementia and Cognitive decline in elderly population; however, Diabetes-related Dementia is neither well understood, nor the diagnosis is easy. The current study provides an evidence that Dementia and Cognitive decline can be secondary to Diabetes Mellitus and hence utmost priority needs to be given to incorporate Cognitive decline as a complication of Diabetes in Indian National and Global Health Policy. Bringing Dementia and Cognitive decline into the Diabetes Management guidelines will definitely help the aging Diabetic population.

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Author Contributors
Aman Gupta was responsible for the Study concept, design, preparation of the manuscript, data collection and interpretation. Abhishek Kumar Singh was associated with Cognitive battery validation, data interpretation and manuscript revision.

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

REFERENCES
