International Journal of Diabetes Research 2016, 5(3): 54-61
DOI: 10.5923/j.diabetes.20160503.03

A Preliminary Study on whether HbA_{1c} Levels can Predict Visual Dependence for Spatial Orientation in Asymptomatic Type 2 Diabetic Patients

Rima Abdul Razzak[1,*], Jeffery Bagust [2], Sharon Docherty[3], Wiam Hussein[4], Zuheir Hassan[1], Ghada Al-Kafaji[5], Abdullah M. Alotaibi[6]

[1]Dept. of Physiology, Arabian Gulf University, Manama, Kingdom of Bahrain
[2]Anglo-European College of Chiropractic (AECC), Bournemouth, United Kingdom
[3]Faculty of Health and Social Sciences, Bournemouth University, Bournemouth, United Kingdom
[4]Dr Wiam Diabetes and Endocrine Clinic, Bahrain
[5]Al-Jawhara Center for Molecular Medicine and Genetic Disorders, Arabian Gulf University/Al-Jawhara, Kingdom of Bahrain
[6]College of Medicicne and Medical Sciences, Arabian Gulf University, Manama, Kingdom of Bahrain

Abstract **Introduction:** Diabetes-induced vestibular dysfunction has been commonly reported, and asymptomatic patients with type 2 diabetes display higher degrees of perceptual visual dependence for spatial orientation than healthy controls. This study aims to assess whether HbA_{1c} can predict such visual dependence in the diabetic patients. **Methods and Materials:** Diabetic patients were divided into 2 groups: 22 subjects with "good" ($HbA_{1c} < 7\%$) and 25 with "poor" ($HbA_{1c} \geq 7\%$) glycemic control. Otolithic vestibular function was tested using the computerized rod-and-frame test (CRFT) and results for the two diabetic groups were compared to 29 healthy controls. **Results:** When the frame was tilted, the diabetic group with "good" glycemic control had largest positioning errors, with a significant difference only in comparison to the control group. The "good" glycemic group exhibited larger degree of asymmetry under titled frame condition. Although HbA_{1c} was not associated with vestibular asymmetry in any diabetic group, it was significantly associated with visual dependence in the "good" glycemic group. During frame tilts, 10 diabetic patients had positioning errors above the reference range of 3.3°, 8 of which belonged to the "good" glycemic diabetic group. **Conclusions:** Diabetes disease processes may affect vestibular symmetry during visuo-vestibular conflicts, even in asymptomatic diabetics within the recommended glycemic range. The weak correlations between HbA_{1c} and CRFT parameters may indicate that HbA_{1c} cannot fully predict visual dependence or asymmetry on the CRFT in patients with diabetes, and different glycemic disorders may affect vestibular dependent spatial orientation in diabetic patients.

Keywords Glycemic control, Visual dependence, Computerized rod and frame test (CRFT)

1. Introduction

Disease processes of diabetes compromising one side more than the other may result in vestibular dysfunction asymmetry creating a tonic discharge imbalance within the vestibular system. Normally any asymmetry of responses is reduced by recalibration of vestibular inputs by regulatory long term central compensatory mechanisms [1, 2]. Recent studies [3-5] have confirmed vestibular dysfunction and more specifically subclinical changes in vestibular function in patients with Type 2 diabetes mellitus as a newly defined diabetes-related complication. These changes have been attributed to microvascular changes and microangiopathy that can lead to generalized vestibulotoxicity due to ischemia of vestibular structures [6-8]. Parkash and Sumati (2013) reported that even at the earlier stages of diabetes (less than 4 years), 31% of patients had subclinical vestibular dysfunction as measured by electronystamography (ENG) testing [4].

Subjective visual vertical (SVV) testing assesses spatial orientation via vertical perception through evaluating a subject's ability to position a line to vertical position without a vertical reference. The ability to normally deviate within ± 2° from gravitational vertical by most people [9-11] relies on the integration of visual and vestibular, mainly otolithic, inputs centrally in the brain [12]. Visual dependence, or the effect of visual cues on perception of vertical, is tested by introducing a frame around the rod. Under normal conditions of testing, a tilted surrounding frame distracts the subjects and acts as an inaccurate visual cue for vertical perception, evoking a rod and frame effect (RFE) in the direction of the

* Corresponding author:
reemala@agu.edu.bh (Rima Abdul Razzak)
Published online at http://journal.sapub.org/diabetes

tilted frame in healthy individuals.

A previous study [13] using the same subject population as the current study, assessed the spatial cognitive dysfunction (disorientation) that may occur with vestibular disorders in Type 2 diabetic patients without peripheral neuropathy by using the computerized rod and frame test (CRFT) to measure perception of vertical. Findings indicated greater magnitude and asymmetry of visual dependence in diabetic patients during visuo-vestibular conflict compared to healthy age-matched controls.

Given that diabetics have different levels of glycemic control, it is expected that patients with poor glycemic control will have greater microvascular complications of Type 2 diabetes, since a 1% rise in glycosylated haemoglobin (HbA_{1c}) levels is associated with a 37% increase in microvascular disease [14]. This may be extended to the vestibular complications associated with Type 2 diabetes, and one would expect greater odds or levels of vestibular dysfunction in diabetics with higher HbA_{1c} levels. In fact, this was validated by Agrawal's study [15] which reported diabetics with serum HbA_{1c} levels of 7.0% or greater to have a higher prevalence of vestibular dysfunction with higher HbA_{1c} levels significantly increasing the odds of vestibular dysfunction by 60% in age-adjusted analyses. Thus glycemic control level may predict the degree of subclinical vestibular dysfunction. Our theory is that diabetics with poorer glycemic control may have a greater level of vestibular dysfunction, and their level of dependence on visual input may be enhanced, increasing verticality perception errors during visuo-vestibular conflicts. Using identical patient data as the previous study by Abdul Razzak et al [13], the current study aims to investigate the level of visual dependence healthy controls and in patients with Type 2 diabetes with different levels of glycemic control. Whether HbA_{1c} level can predict vestibular asymmetry effects in diabetic patients will also be explored.

2. Methods and Materials

Subjects

29 asymptomatic healthy participants (20M and 9F; mean age = 56.64 ± 5.45 years), and 47 patients (34M and 13F; mean age = 57.0 ± 6.10 years) diagnosed with type 2 diabetes mellitus at the Gulf Diabetes Specialist Center in Bahrain volunteered for this study. The diabetic patients were then divided into two groups according to HbA_{1c} level; 22 patients with "good" glycemic control (HBA_{1c} < 7% (53 mmol/mol)) and 25 patients with "poor" glycemic control ($HbA_{1c} \geq 7\%$). Random blood sugar levels were measured on the day of the test to rule out hypoglycemia.

Exclusion criteria for all participants included dizziness or vertigo during the day of testing or in the past year. Screening for dizziness and vertigo was done by questioning participants whether they had experienced any recurring episodes of dizziness or vertigo in the past year, since vertigo is the historical hallmark of a vestibulopathy. Whether participants experienced symptoms such as tinnitus, aural fullness or hearing loss was also explored. None of the participants had experienced any of the above symptoms in the past year.

Table 1. Clinical, subclinical features and anthropometric measures in control subjects and diabetic patients

	Control Subjects	Diabetic Patients
Age (years)	56.64 ± 5.45 (49.0 – 69.0)	57.0 ± 6.10 (46.0 – 69.0)
Height (m)		
Male	1.76 ± 0.05 (1.65 – 1.84)	1.72 ± 0.06 (1.58 – 1.81)**
Female	1.61 ± 0.05 (1.52 – 1.67)	1.55 ± 0.06 (1.46 – 1.66)**
BMI (Kg/m^2) -Total	27.4 ± 4.1 (22.2 – 36.4)	30.0 ± 5.3* (21.2– 54.3)
Male	27.81 ± 4.01 (22.20 – 36.36)	29.09 ± 3.67 (31.20 – 37.91)
Female	26.33 ± 4.35 (22.58 – 35.07)	33.00 ± 7.64 (26.42 – 54.28)*
Duration of diabetes (years)	--	10.1 ± 8.0 (0.3 – 35.0)
Glycemic measures	FBG: 98.7 ± 8.5 mg/dl	HbA_{1c}: 7.1 ±1.0 % (5.3 – 10.4)
Hypoglycemic Drugs	--	47 Yes
Hypertension (Controlled)	3 Yes, 26 No	38 Yes, 10 No
Dizziness in past year	None	None

Values represent mean ± SD and (Range of data)
* *P*-value < 0.05; ** *P*-value < 0.01 for differences between control and diabetic mean values with Student t-test
Controls (Male: n = 20, Female: n = 9); Diabetics (Male: n = 34, Female: n = 13)
FBG: Fasting blood glucose; HbA_{1c}: Glycated hemoglobin

Inclusion criteria for the diabetic patients are the absence of diabetic retinopathy and peripheral neuropathy to rule out any complications in the visual or proprioceptive system that may be confounding factors to our current findings. Neurological examinations in the diabetic patients were performed by medical/health professionals at the medical center. All the diabetic patients have been routinely to the eye clinic at the Gulf Diabetes Specialist Center where ophthalmologists carried out a comprehensive eye exam; a complete report was then included in the patients' records. In this study, all cases had their eye exam done within the past year and showed no evidence of retinopathy.

All patients in this study were tested for peripheral neuropathy in the clinic before joining the study as part of the inclusion criteria. Patients with a diagnosis or history of any form of diabetic neuropathy or on any form of treatment were excluded from the study. However, all cases had foot examination by the endocrinologist. The feet were inspected for any skin breaks, red or callused areas, decreased or absent pedal pulses, and delayed capillary refilling, bony deformities, and protective sensation. Protective sensation was assessed by the 5.07 Semmes-Weinstein (10-g) nylon mono filament test (SWME). The monofilament was applied to a non-callused area on the dorsum of the first toe, and the SWME threshold was defined as the total number of times the application of the 10-g monofilament was not perceived by the subject.

Also the vibration testing was done by the 128-Hz tuning fork applied to the bony prominence situated at the dorsum of the first toe. The patient was asked to report the perception of both the start of the vibration sensation and the cessation of vibration, and the vibration testing threshold was defined as the total number of times the application of the vibrating tuning fork was not felt. Ankle reflexes were obtained at both ankles. With the patient sitting or lying, the examiner gently dorsiflexed the foot and struck the Achilles tendon briskly with the reflex hammer. The reflex was scored as 0 (absent with reinforcement), 1 (present, decreased), 2 (normal), or 3 (increased). Superficial pain sensation was conducted with a sterile small, disposable, hand-held device used to deliver blunt or sharp stimuli (Neurotip) at many sites over the plantar aspect of each foot with the stimulus applied once per site. Patients were asked to identify a felt sensation as sharp or dull. Findings were scored as sharp, dull, or absent for each site. No diabetic patient showed any evidence of peripheral neuropathy.

Informed voluntary consent to participate in the study was obtained from the subjects before any data collection. The research ethics committee at the Arabian Gulf University (AGU) and the Gulf Diabetes Specialist Center in Bahrain approved the research protocol, which also complied with the ethical standards of the Helsinki declaration.

Computerized rod and frame test (CRFT)

The CRFT was used to assess verticality perception and visual dependence for spatial orientation for all subjects. The detailed description of the materials and procedures of the test are presented in a previous article [16].

Subjects were presented with a square white frame on a plain black background. The test comprised 18 presentations, the first two being for instruction and not included in the analysis. The first presentation in each test always contained the upright (untilted) frame, and the second presentation employed a tilted frame and was used to confirm that the subject understood the task. For the remaining 16 presentations, SVV was measured in four visual contexts: no visual reference (SVV); the frame untilted and aligned with the true gravitational vertical (0°, $Frame^{0}$); the frame tilted clockwise (+18°, $Frame^{+18}$), or tilted counter-clockwise (-18°, $Frame^{-18}$) with respect to the vertical. The parameters analysed in this study were the mean values for the absolute SVV error for each individual in the absence and presence of a frame (either erect or tilted clockwise or counter-clockwise).

Another parameter investigated was the asymmetry of the errors induced by the tilted frame around the untilted frame error. The asymmetry of the errors induced by the tilted frame around the untilted frame error was investigated by deriving an asymmetry index (δ°) from the signed data. For each individual this was calculated by summing the differences between the mean signed errors in the tilted frame conditions ($Frame^{+18}$, $Frame^{-18}$) and the mean signed error in the $Frame^{0}$ condition.

$$\textit{Visual dependence asymmetry index } (\delta^{\circ}) = (Frame^{+18} - Frame^{0}) + (Frame^{-18} - Frame^{0})$$

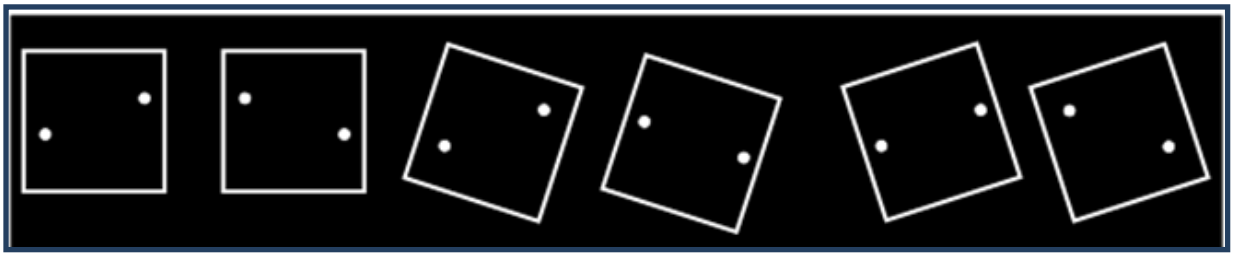

Figure 1. Presentations of "rod" and frame during testing. Order of presentation randomly assigned by computer

A symmetrical response to the frame tilt is indicated by a value of δ close to 0. Larger values indicate increased asymmetry, with the sign showing the direction of the skew. The direction of the skew is important for each individual, but when assessing group data there is a risk of positive and negative values cancelling, and so the absolute value of δ was used in the analysis of the results.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS 15) software. All data passed normality by the Kolmogorov and Smirnov test. Parametric statistics were used since all data followed a normal distribution. Analysis of variance was used to compare mean errors between groups or between frame contexts; post-hoc analysis was performed when $p < 0.05$. For all tests, the significance level was fixed at 0.05. Data from asymptomatic subjects served as control values. When included in the analysis, the reference range for error distributions in this control group was calculated as mean +2SD of these data.

3. Results

Participants

There were no significant differences between the three groups with regards to age or body mass index (BMI). Comparison of the two diabetic groups found no significant difference in the duration of the disease however there was a significantly higher mean HbA_{1c} level in the group with "poor" glycemic control (Table 1). The controls had a normal mean fasting glucose level (measured on the day of the test) of 98.6 ± 8.5 mg/dl (Range: 81.0 mg/dl – 105.0 mg/dl).

Perception of Visual Vertical

SVV/ Visual Dependence Errors and Glycemic Control

In the absence of cues given by a surrounding frame, all control subjects and most diabetic subjects from both subgroups fell within a range considered normal for SVV (< 2°). The difference between the mean values was less than 0.5 degrees in each case (less than one mouse click, Table 1). When the groups were presented with a visual frame tilted by 18 degrees in either a clockwise or counter clockwise direction their positioning errors increased significantly in comparison to the frameless presentations ($P < 0.001$ in all cases). For all groups, a combined Frame ^{18} value ($Comb^{18°}$) was averaged from the absolute values of $Frame^{+18}$ and $Frame^{-18}$ since they did not differ significantly ($P > 0.05$ for all cases).

The distribution of errors for all groups is presented in Fig. 2A. The difference between mean $Comb^{18°}$ errors of controls and "good" glycemic control diabetics approached 1 degree (2 mouse clicks) with analysis showing a significant difference ($P = 0.01$). The difference between the healthy controls and "poor" glycemic control group was less than 0.5° (1 mouse click). There was no significant difference between the means of the two diabetic subgroups ($P > 0.05$).

There were also differences in the numbers of subjects falling above the reference range for $Comb^{18°}$ errors calculated from control data (mean + 2SD = 3.3°). None of the control subjects exceeded this value however only 2 diabetics with "poor" glycemic control (7.7%) and 8 diabetics with "good" glycemic control (33.3%) exceeded it ("poor" and "good" glycemic control: Fisher's test; $P = 0.03$). The mean $Comb^{18°}$ error for these 8 subjects with "good" glycemic control falling into this category was 4.57 ± 0.98°.

Visual Dependence Asymmetry and Glycemic Control

The differences in the asymmetry index between the three groups were significant (One-way ANOVA: $P < 0.0001$). Healthy controls had a significantly smaller mean asymmetry index in comparison to each of the diabetic groups (Table 1). The asymmetry index in the "good" glycemic control group was significantly larger than the "poor" group. There was a significant positive correlation ($r = 0.55$, $P = 0.007$) between the asymmetry index and $Comb^{18}$ errors in the "good" glycemic group but this was not the case for either the healthy subjects ($r = 0.31$, $P = 0.10$) nor the "poor" glycemic control group ($r = 0.30$, $P = 0.15$).

HbA_{1c} Association with Some Parameters

In the "good" glycemic group, $\%HbA_{1c}$ was not associated with the duration of diagnosis of the disease ($r = 0.33$, $P = 0.12$). As for the verticality parameters, $\%\ HbA_{1c}$ did not correlate with the asymmetry index ($r = 0.36$; $P = 0.10$) but was significantly associated with the level of visual dependence represented by the $Comb^{18}$ errors ($r = 0.45$; $P = 0.04$; $n = 22$). For the "poor" glycemic control, $\%\ HbA_{1c}$ correlated positively with the duration of the disease ($r = 0.51$, $P = 0.01$), indicating decreased glycemic control with longer duration of diabetes exposure (Figure 3). Similar to the other diabetic group, $\%\ HbA_{1c}$ did not correlate with the asymmetry index ($r = 0.22$; $P = 0.29$) but was significantly associated SVV errors without a frame ($r = 0.41$; $P = 0.04$).

Table 2. Comparison of demographics, subclinical features and subjective visual vertical data parameters between healthy control subjects and diabetic patients with "good" and "poor" glycemic control

	Control (n =29)	"Good" Glycemic Control (n = 22)	"Poor" Glycemic Control (n=25)	Difference across groups (*P*-value)	Post-hoc analysis (*P*-value)		
					Control vs "Good" Glycemic Control	Control vs "Poor" Glycemic Control	"Good" vs "Poor" Glycemic Control
Age	56.6 ± 5.5 (49.0 – 69.0)	58.0 ± 6.22 (47.5 – 68.0)	56.2 ± 6.0 (46.0 – 69.0)	0.56	--	--	--
BMI (kg/m^2)	27.4 ± 4.1 (22.2 – 36.4)	30.6 ± 5.9 (24.5 – 54.3)	29.6 ± 4.6 (21.2 – 43.2)	0.48	--	--	--
Years with diabetes	--	8.9 ± 10.1 (0.3 – 35.0)	11.2 ± 5.6 (1.0 – 23.0)	N/A	--	--	0.34
HbA_{1c} (%)	--	6.3 ± 0.4 (5.3 – 6.9)	7.9 ± 0.8 (7.0 – 10.4)	N/A	--	--	< 0.0001
Abs SVV (°)	0.90 ± 0.44 (0.13 – 1.88)	1.13 ± 0.54 (0.38 – 2.37)	1.05 ± 0.62 (0.38 – 2.38)	0.30	--	--	--
Comb [18](°)	1.69 ± 0.79 (0.38 – 3.19)	2.73 ± 1.64 (0.94 – 6.31)	2.13 ± 1.11 (0.56 – 5.50)	0.01	0.01	0.10	0.16
Asymmetry Index (°)	0.90 ± 0.92 (0.00 – 3.13)	2.70 ± 1.51 (0.13 – 5.75)	1.68 ± 1.12 (0.38 – 5.25)	< 0.0001	< 0.0001	0.008	0.01

Values given are mean ± SD and (Range of data). Student t-test was used for comparison between the two diabetic groups and one-way ANOVA for comparison of controls and both diabetic groups. SVV indicates unsigned positional errors (in degrees) for vertical when no frame is present. "Comb[18°]" refers to the mean of unsigned errors generated when the tilted frame was present (data for both tilted frame conditions have been combined). N/A: not applicable; bold indicates $P < 0.05$

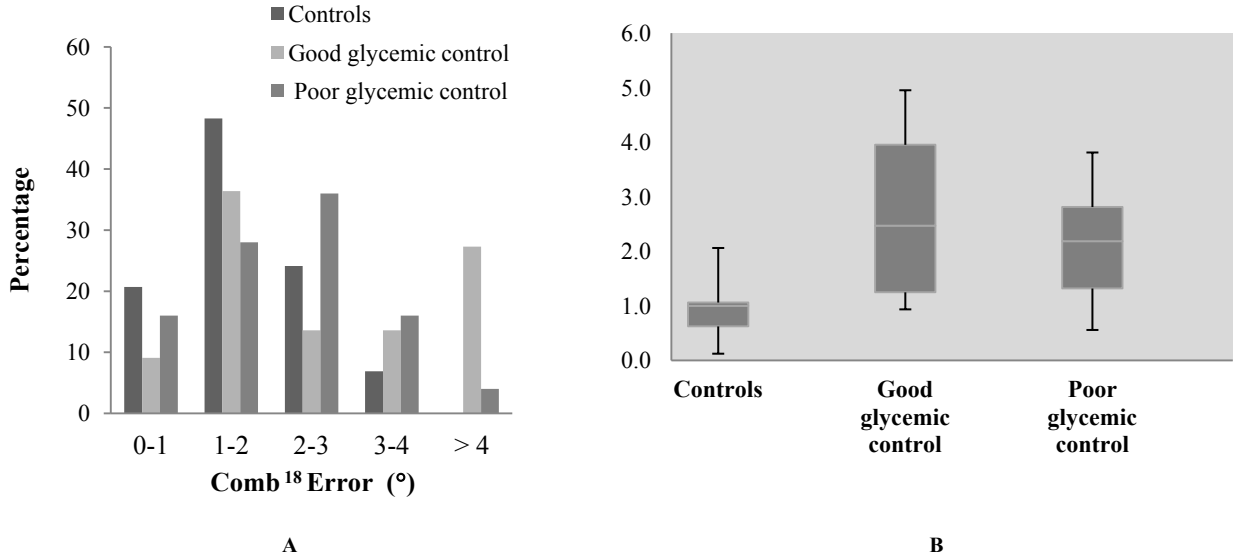

Figure 2. **A.** Distribution of the positioning errors to vertical. **B.** Box and Whisker plots of the data with median and inter-quartile range of unsigned deviation errors for both controls and both diabetic groups with a tilted surrounding frame (Comb [18°]). Diabetics: "Good" glycemic control ($HbA_{1c} < 7\%$); "Poor" glycemic control ($HbA_{1c} \geq 7\%$)

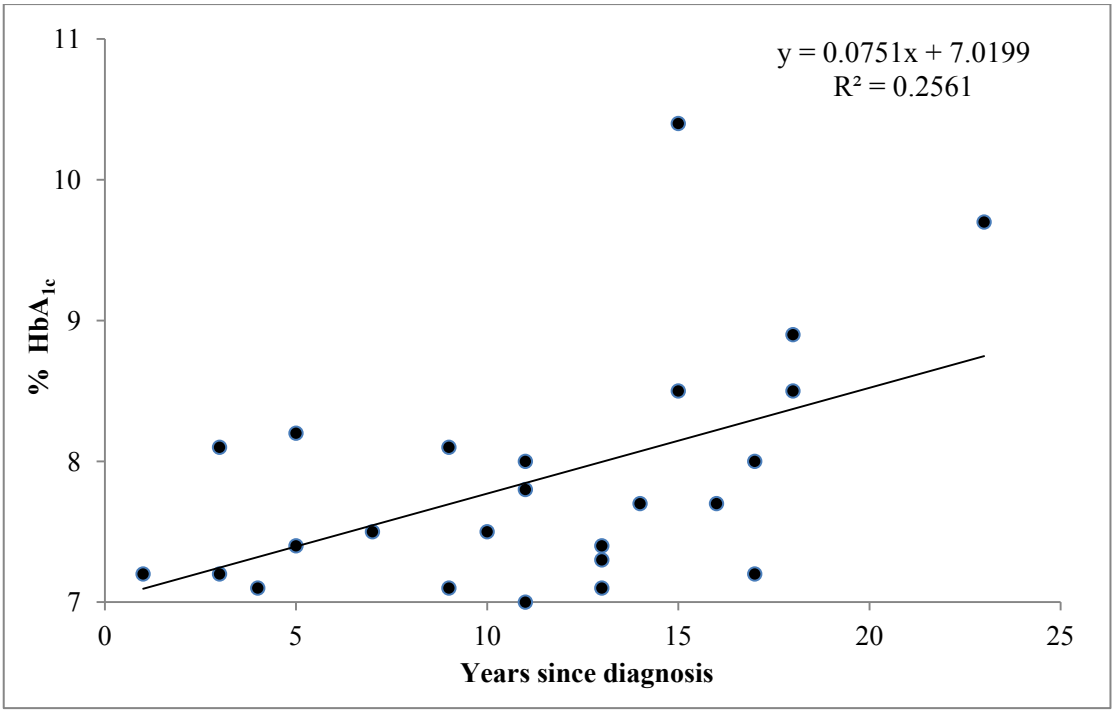

Figure 3. Relationship between duration of diabetes and plasma glucose levels as measured by % glycated haemoglobin (HbA_{1c}) in "poor" glycemic group

4. Discussion

Our previous results suggested that vestibular otolithic function may be affected in diabetic patients as evidenced by differences from healthy controls in magnitude and asymmetry of visual dependence for spatial orientation on the CRFT [13]. In the current study, we investigated whether glycemic control (measured by HbA_{1c} levels) might predict visual dependence for spatial orientation in patients with Type 2 diabetes, relying on two parameter of verticality perception: the absolute (unsigned) deviation error and the asymmetry index. The cut-off HbA_{1c} value of 7% was used to assign patients to the two groups of diabetics with differing glycemic control; one could argue that including two diabetic groups comprised of patients with widely separate HbA_{1c} levels, such as 7% or less and 9% or greater may have been more discriminative, however the rationale for using a cut-off of HbA_{1c} of 7% is because it is the recommended target of diabetes management and sustained glycemic control by many Diabetes Associations worldwide [17, 18].

Results point to increased level of visual dependence even in asymptomatic diabetics with glycemic control within the recommended target of HbA_{1c} < 7.0% (53 mmol/mol). The greater deviation errors when a conflicting visual surrounding was introduced provided evidence of greater visual dependence in each of the diabetic groups compared to the healthy controls. The greater asymmetry index in each of the diabetic groups than healthy controls may reflect alteration of vestibular input by the disease processes of diabetes. This is probable as most diseases of the inner ear or vestibular nerve are destructive in nature, decreasing input from the ears, and the disease processes of diabetes are not expected to affect vestibular function bilaterally to the same extent.

Even though there was no significant difference in deviation errors (Comb $^{18°}$) between the diabetic groups, patients with "poor" glycemic control were paradoxically less asymmetrically visually dependent than the "good" glycemic diabetics on the CRFT. Such results may indicate that in the diabetic patients with "poor" glycemic control, the central compensatory mechanisms of *vestibular* tone imbalance may have already been primed in response to the deleterious effects of sustained chronic hyperglycemia on both vestibular organs. It is interesting that in the "poor" glycemic group, HbA_{1c} levels correlated positively with the duration of the disease, indicating worse glycemic control and sustained hyperglycemia with the progression of the disease. Such sustained chronic hyperglycemia is known to negatively affect the vascular endothelium and is correlated with many diabetes mellitus-related microvascular complications [19], some of which may be vestibular microangiopathy.

Overall, diabetics within the recommended target of HbA_{1c} < 7.0% (53 mmol/mol) processed verticality as inefficiently as diabetics above the recommended range of HbA_{1c} during visuo-vestibular conflicts. However, all of the patients exhibiting combined errors above the reference range had HbA_{1c} levels between 6 and 8.1%. Therefore it is possible that those in the "good" glycemic control group (or those with low "poor" values), have vestibular damage due to glucose fluctuations resulting from interprandial glucose decrements followed by postprandial hyperglycemia, which is highly prevalent throughout the day in Type 2 diabetic

patients with HbA_{1c} levels well below 7.0% [20]. These acute glucose fluctuations would have more deleterious effects than sustained hyperglycemia in the development of diabetic complications as both upward (postprandial glucose increments) and downward (interprandial glucose decrements) changes activate oxidative stress [21-26].

With asymmetrical vestibular damage, the resultant aberrant bilateral otolithic inputs to the vestibular nuclei of patients with diabetes may not be as effective as those of healthy controls in counteracting the effects of the conflicting visual illusion produced by the tilted frame on SVV perception. This would lead to greater difficulty with visuo-vestibular integration centrally in the brain. The discrepancy between the two diabetic groups in vestibular asymmetry, along with the association between visual dependence and vestibular asymmetry in diabetics with "good" glycemic control, suggests different compensatory mechanisms to recalibrate vestibular input for asymmetry reduction in the groups. Additionally, the relatively weak but significant association in both groups between HbA_{1c} and SVV (frameless or within a tilted frame) indicates that HbA_{1c} levels cannot fully predict diabetic complications in the vestibule. As a result, other glycemic factors either affecting vestibular symmetry or central compensatory mechanisms may be involved.

5. Limitations and Conclusions

A major limitation of this study is that the dysfunction of SVV and increased visual dependence may not be necessarily caused solely by vestibular imbalance since SVV is a higher brain function. Without doubt, brain areas involved in SVV do utilize vestibular and visual inputs, but it is also possible that the diabetic patients may well have had vascular complications in the brain areas involved in SVV integration. Additionally, vestibular tests that may indicate any subclinical vestibular symptoms such as nystagmus which represents the physical exam hallmark of vertigo and vestibulopathy were not performed on the diabetic patients.

Another limitation is ignoring to consider participants' blood pressure status, an important clinical factor that is evidently different between the control and diabetic group, with 81% of the diabetic patients having controlled hypertension, and only 10% in the control group. However, results of a previous study on cochlear function in hypertensive subjects suggested that patients with systemic arterial hypertension may have cochlear dysfunction associated hypertension but without clear evidence of vestibular dysfunction [27].

Despite of these limitations, our study has demonstrated that the visual dependence asymmetry index is a more sensitive indicator than absolute errors of differences between the two diabetic groups, since CRFT failed to distinguish the level of visual dependence (absolute errors) between the patient groups with diabetes. Because positioning errors above the reference range were found in diabetics who had a mean HbA_{1c} of 6.75%, it seems that even diabetics with glycemic control within the recommended range or slightly above may be vulnerable during visuo-vestibular conflict situations due to vestibular asymmetry. This asymmetry of responses may cause difficulty in maintaining upright orientation in diabetic patients, because any unneeded adjustment in posture by subjects who may misinterpret any tilted or swaying references as tilting or swaying of their own bodies may cause loss of their balance [28].

ACKNOWLEDGMENTS

This study was funded as a research grant by the Research Committee at the Arabian Gulf University (AGU) at Al-Manama, Bahrain.

REFERENCES

[1] Curthoys I S, Halmagyi G M. Vestibular compensation: a review of the oculomotor, neural, and clinical consequences of unilateral vestibular loss. J Vestib Res 1995, 5 (2): 67–107.

[2] Brandt T, Strupp M, Arbusow V. *Dieringer N.* Plasticity of the vestibular system: central compensation and sensory substitution for vestibular deficits. Adv Neurol *1997,* 73: 297–309.

[3] Li J, Zhang T, Shen J, Gong J, Wang H, Zhang J, Pang Y. The changes in vestibular function in patients with diabetes mellitus and its clinical significance. J Clin Otorhinol, Head and Neck Surgery 2008, 22(1): 10 – 13.

[4] Parkash M, Sumathi K. Evaluation of subclinical vestibular dysfunction in type II diabetes mellitus-correlating with HbA_{1c}. Int J Pharma Bio Sci 2013, 4(4): 137 – 140.

[5] Kamali B, Hajabolhassan, F, Fatahi, J, Esfahani, EN, Sarrafzadeh, J, Faghihzadeh, S. Effects of diabetes mellitus type I with or without neuropathy on vestibular evoked myogenic potentials. Acta Medica Iranica 2013, 5(12): 107 – 112.

[6] Zelenka J et al. Disorders in blood supply of the inner ear as early symptom of diabetic angiopathy. J Laryngol Otol 1965, 79: 314 – 319.

[7] Makishima K, Tanaka et al. Pathological changes of the inner ear and central auditory pathways in diabetics. Ann Otol Rhinol Laryngol 1971, 80: 218 – 228.

[8] Nathan DM. The pathophysiology of diabetic complications: how much does the glucose hypothesis explain? Ann Intern Med 1996, 124: 86 – 89.

[9] Boehmer A. The subjective visual vertical as a clinical parameter for acute and chronic vestibular (otolith) disorders. Acta Oto-Laryngol 1999, 119: 126 – 127.

[10] Murray KJ, Hill KD, Phillips B, Waterston J. The influence of otolith dysfunction on the clinical presentation of people with a peripheral vestibular disorder. American Physical Therapy Association 2: 143 sical., 2007.

[11] Akin FW, Murnane OD. Subjective visual vertical test. Semin Hear 2009, 30(4): 281 – 286.

[12] Vingerhoets RAA, De Vrijer M, Van Gisbergen JAM, Medendorp WP. Fusion of visual and vestibular tilt cues in the perception of visual vertical. J Neurophysiol 2009, 101: 1321 – 1333.

[13] Abdul Razzak R, Bagust J, Docherty S, Hussein W, AlOtaibi A. Augmented asymmetrical visual field dependence in asymptomatic diabetics: evidence of subclinical asymmetrical bilateral vestibular dysfunction. J Diabetes Complicat 2015, 29: 68 – 72.

[14] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000, 321(7258): 405– 412.

[15] Agrawal Y, Carey JP, Della Santina CC, Schubert MC, Minor L BY. Diabetes, vestibular dysfunction, and falls: analyses from the national health and nutrition examination survey. Otol Neurotol 2010, 31: 1445 – 1450.

[16] Docherty S, Bagust J. From line to dots: an improved computerized rod and frame system for testing subjective visual vertical and horizontal. BMC Res Notes 2010, 3(9): (www.biomedcentral.com/1756-0500/3/9).

[17] International Diabetes Federation (Clinical Guidelines Task Force) 2012. Global guidelines for type 2 diabetes: glucose control levels- recommendations. 43 – 47.

[18] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R. Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach position statement of the American diabetes association (ada) and the European association for the study of diabetes (EASD). Diabetes Care 2012, 35(6): 1364 – 1379.

[19] Campos C. Chronic hyperglycemia and Glucose toxicity: pathology and clinical sequelae. Postgrad Med 2012, 124(6): 90 – 97.

[20] Van Dijk J-W, Manders RJF, Hartgens F, Stehouwer CD, Praet SFE, van Loon LJC. Postprandial hyperglycemia is highly prevalent throughout the day in type 2 diabetes patients. Diabetes Res Clin Pr 2011, 93: 31 – 37.

[21] Monnier L, Colette C. Owens DR. Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? J Diabetes Sci Technol 2008, 2(6): 1094 – 1100.

[22] Ceriello A, Kilpatrick ES. Glycemic variability: both sides of the story. Diabetes Care 2013, 36: S272 – S275.

[23] Risso A, Mercuri F, Quagliaro L, Damante G, Ceriello A. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. Am J Physiol Endocrinol Metab 2001, 281(5): E924 - E930.

[24] Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. Diabetes 2003, 52(11): 2795-2804.

[25] Quagliaro L, Piconi L, Assaloni R, Da Ros R, Maier A, Zuodar G, Ceriello A. Intermittent high glucose enhances ICAM-1, VCAM-1 and E-selectin expression in human umbilical vein endothelial cells in culture: the distinct role of protein kinase C and mitochondrial superoxide production. Atherosclerosis 2005, 183(2): 259-267.

[26] Piconi L, Quagliaro L, Assaloni R, Da Ros R, Maier A, Zuodar G, Ceriello A. Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. Diabetes Metab Res Rev 2006, 22(3): 198 - 203.

[27] Esparza CM, Jáuregui-Renaud K, Morelos CM, Muhl GE, Mendez MN, Carillo NS, Bello NS, Cardenas M. Systemic high blood pressure and inner ear dysfunction: a preliminary study. Clin Otolaryngol 2007, 32(3): 173 - 178.

[28] Isableu B, Ohlmann T, Cremieux J, Amblard B. Selection of spatial frame of reference and postural control variability. Exp. Brain Res 1998, 114: 584 – 589.