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Glycemic Variability among Older Adults with Type 2 Diabetes

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Abstract

Objective: The aim of this study was to evaluate Glycemic Variability (GV) among older adults with type 2 diabetes in a tertiary center (Putrajaya Hospital) using the Continuous Glucose Monitoring System (CGMS) and to compare the GV between patients with optimal versus suboptimal glycemic control.

Research designs and methods: A total of 138 patients (69 with HbA1c<7% (53 mmol/mol) and another 69 with HbA1c ≥ 7% (53 mmol/mol) with type 2 diabetes age 65 and above were included in this study. All subjects underwent baseline clinical evaluation followed by monitoring using CGMS for six days. Data from CGMS was extracted to calculate GV using the Easy GV software available at www.easygv.co.uk.

Results: The patients with HbA1c ≥ 7% (53 mmol/l) had significantly longer duration of diabetes, higher use of insulin, more micro-vascular complications, higher systolic blood pressure, higher fasting blood glucose, total cholesterol and triglyceride levels. The Mean Amplitude Glycemic Excursions (MAGE), Continuous Overlapping Net Glycemic Action (CONGA, Standard Deviation (SD), M-value, Average Daily Risk Ratio (ADDR), Lability Index (LI) , High Blood Glucose Index (HBGI), Mean of Daily Difference (MODD), Glycemic Risk Assessment in Diabetes Equation (GRADE) and Mean Absolute Glucose (MAG) were significantly higher in the group with HbA1c ≥ 7% (53 mmol/mol). The Low Blood Glucose Index (LBGI) [2.14(IQR 3.4) versus 2.11(2.6)] which represents risks of hypoglycemia was the only parameter which was not significantly different between both groups.

Conclusions: We present the glycemic variability parameters for older adults with type 2 diabetes. Among this population, the risk of hypoglycemia is similar between those with optimal HbA1c versus their counterparts. This underscores the importance of looking out for hypoglycemia in every older individual with type 2 diabetes.

Keywords: Type 2 diabetes; Glycemic variability; Older adults; Hypoglycemia; Continuous glucose monitoring system (CGMS); HbA1c; Microvascular complications; Macrovascular complications

Introduction

Diabetes in the older adults (defined as those aged 65 years and above) is an emerging epidemic associated with higher mortality, reduced functional status and increased risk of institutionalization [1]. In the local setting, the latest National Health and Morbidity Survey (NHMS 2015) reported that 17.5% of Malaysian adults aged 18 and above have diabetes. In the older population, above the age of 65, the prevalence was between 37 – 39% [2]. Therefore a special focus on care of older persons with diabetes is pertinent to reduce the multitude of diabetic related complications and to improve the quality of life among the patients.

Both sustained hyperglycemia and acute glucose fluctuations contribute to the dysglycemia in diabetes and lead to diabetes complications through two main mechanisms; excessive protein glycation and oxidative stress [3]. Landmark studies have confirmed that post prandial hyperglycemia is an independent risk factor for macrovascular complications [4]. However, glycemic variability (GV) that includes both upward and downward acute glucose changes has been found to cause deleterious effects on endothelial function and oxidative stress which lead to development and progression of cardiovascular complications in diabetes as well. It was found that in type 2 diabetes, the urinary excretion of 8-iso-PGF2α, which is a reliable marker of the activation of oxidative stress was highly, positively correlated with GV [5].

HbA1c which reflects average blood glucose over 2-3 months, is the commonest tool used to reflect glycemic control. However it cannot be used to assess postprandial hyperglycemia and fasting hyperglycemia separately and is unable to reflect short term glycemic changes or variability. Various other factors such as renal function, anemia and certain hemoglobinopathies also affect the validity of HbA1c results. Even patients who have HbA1c levels below 7% (53 mmol/mol) have been found to have GV and postprandial hyperglycemia [6].

Because of the limitations of HbA1c, other tools are required to measure GV. However GV is a complex phenomenon with intra and inter-day components as well as minor and major fluctuations; thus several approaches have been developed to quantify it. By using data from the continuous glucose monitoring system (CGMS), various objective parameters can be assessed. This include the standard deviation (SD), M-Value, Mean Amplitude of Glucose Excursion (MAGE), average daily risk ratio (ADRR), Lability Index (LI), Low Blood Glucose Index (LBGI), High Blood Glucose Index (HBGI) continuous overlapping net glycemic action (CONGA), mean of daily differences (MODD), Glycemic Risk Assessment in Diabetes Equation (GRADE) and Mean absolute Glucose (MAG).

The GV among older adults with type 2 diabetes in a multiracial population like ours is not known. The aim of this study was to

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evaluate GV among older adults with type 2 diabetes attending the Diabetes Clinic in a tertiary center (Putrajaya Hospital) using the CGMS and to compare the GV between patients with optimal HbA1c of <7% (53 mmol/mol) versus suboptimal glycemic control with HbA1c ≥ 7% (53 mmol/mol).

Research Designs and Methods

This was a single center cross sectional study performed over a 6-month period between August 2014 till February 2015. Consecutive patients attending the diabetes clinic in Putrajaya Hospital who fulfilled the inclusion criteria were offered to participate in the study [7]. The inclusion criteria were patients with type 2 diabetes (based on WHO criteria for diagnosis of diabetes) aged 65 years and above with a duration of diabetes of at least 5 years and treated with at least one glucose lowering medication (either oral hypoglycemic agents or insulin).

The exclusion criteria were subjects with secondary diabetes, type 1 diabetes, those who are taking medications that may impair glucose metabolism (example steroids) and subjects with recent addition or omission of glucose lowering medications in the past 3 months. Sample size was calculated using Dupont et al. [8,9] sample size calculations formulae.

The study population was divided into two groups of patients with type 2 diabetes age 65 years and above. The first group consisted of 69 patients with HbA1c<7% (53mmol/mol) and the second group another 69 patients with HbA1c ≥ 7% (53mmol/mol). All subjects underwent baseline clinical evaluations followed by monitoring using CGMS for six days. During evaluation by CGMS, each patient kept an activity log. During Visit 1, informed consent was obtained. Baseline history and clinical assessment were carried out. Information collected included age, duration of diabetes, family history of diabetes, presence of co-morbidities, glucose lowering medications, anti-hypertensives and lipid lowering medications used as well as complications of diabetes. Anthropometric measurements included weight, height, waist and hip circumference. Weight and height were taken using a standardized SECA measuring station and column scale. Waist circumference was measured midway between the highest point of the iliac crest and the bottom of the ribcage. Hip circumference was measured around the widest portion of the buttock. Body Mass Index (BMI) in kg/m^2 and Waist Hip Ratio (WHR) were calculated. Blood pressure was taken by an automated blood pressure machine (Omron). Two measurements were taken and the mean blood pressure reading was then recorded. Baseline biochemical assessment included fasting venous glucose, fasting lipid profile, HbA1c, serum creatinine, e-GFR (Glomerular Filtration Rate) and urine protein. These blood investigations were performed on Visit 1 or within a month prior to Visit 1.

CGMS (Medtronic Minimed) monitoring was performed over 6 days, using the Enlite sensor from Medtronic. Subjects were encouraged to continue their regular daily activities, diet and medications. Minimal care of CGMS site was required and this was explained to patients. Each subject was provided with a standardized glucometer (Free Style Freedom Lite) and instructed to keep an activity log which included pre-meals and pre-bed capillary blood glucose measurements, relevant activities which included meal time and contents, physical activities, timing of glucose lowering medications and hypoglycemic events if any. Following completion of 6 days, CGMS was removed and data downloaded and analyzed. GV parameters were calculated using Easy GV software which is available at www.easygv.co.uk.

Statistical analysis was performed with SPSS (version 21) statistics software. The statistical tests used were Chi-square and Fischer's exact tests for the categorical data. Meanwhile for numerical data, independent t-test was used for parametric data and Mann-Whitney test for non-parametric data. Spearman's correlation was used to evaluate the associations between HbA1c and MAGE. A multivariate regression analysis was used to determine confounding factors for MAGE. P<0.05 was considered to be statistically significant.

Results

The patients with HbA1c ≥ 7% (53 mmol/mol) had longer duration of diabetes (Median=14, IQR 10 years) compared to those who had HbA1c<7% (53 mmol/mol) (Median=10, IQR 10years). The group with HbA1c ≥ 7% (53 mmol/mol) comprised more insulin users, higher microvascular complications and higher systolic blood pressure. Baseline investigations showed that the patients in this group had higher fasting blood glucose, total cholesterol and triglyceride levels. Both groups had similar number of blood glucose measurements from the CGM. Those with HbA1c<7% (53 mmol/mol) had a median of 2020 (IQR 67) readings while those with HbA1c ≥ 7% (53 mmol/mol) had 2026 (IQR 62) readings (p<0.226). Both groups also had correlation numbers for CGM of >0.79 which is regarded as the level above which is considered clinically acceptable and optimal correlation. The correlation number (generated from CGM data) is derived from the comparison between the blood glucose readings from the CGM compared to finger prick blood glucose readings. The baseline characteristics of all the subjects are summarized in Table 1.

The patients with HbA1c ≥ 7% (53 mmol/mol) had significantly higher GV in all parameters except one. The MAGE, CONGA, SD, M-value, ADDR, LI, HBGI, MODD, GRADE and MAG were significantly higher in the group with HbA1c ≥ 7% (53 mmol/mol). The LBGI was the only parameter which was not significantly different between both groups. The differences in the GV parameters were shown in Table 2.

A Spearman's correlation coefficient was computed to assess the relationship between HbA1c and MAGE. There was a positive but significant correlation between HbA1c and MAGE with r=0.37, p of <0.001 (Table 3 and Figure 1). We also found that our patients with microvascular complications had significantly higher MAGE (5.17 mmol/l ± 1.678) compared to those who did not (4.55 mmol/l (± 1.876); p value 0.049. MAGE between those with and without macrovascular complications were however not significantly different.

Discussion

The two groups of older adults with Type 2 diabetes studied were similar in terms of age, gender and represented the ethnic diversity in Malaysia. The group with HbA1c ≥ 7% (53 mmol/mol), had longer duration of disease. Co-morbidities such as hypertension and dyslipidemia and the associated medications for their treatment were not different between the groups. Oral glucose lowering medications used were not significantly different between the groups but insulin use was higher in the group with HbA1c ≥ 7% (53 mmol/mol). (68.1% versus 40.6%, p=0.001). Total cholesterol, triglyceride and systolic blood pressure were also noted to be significantly higher in the group with ≥ 7% (53 mmol/mol). In essence, the group with poorer glycemic control also seemed to have higher cardiovascular risks.

Unexpectedly, although the group with HbA1c ≥ 7% (53 mmol/mol) had higher composite of microvascular complications (75.4%) compared to 54.6% in the group with HbA1c<7% (53 mmol/mol)

	HbA1c<7% (53 mmol/mol)	HbA1c ≥ 7% (53 mmol/mol)	P value
N	69	69	
Age*	69 (IQR 6)	68 (IQR 6)	0.05
Gender			
Female	29 (42%)	28 (40.6%)	0.865
Male	40 (58%)	41 (59.4%)	
Duration (years) *	10 (IQR 10)	14 (IQR 10)	0.001
Family history	51 (73.9%)	44 (63.8%)	0.198
Race			
Malay	35	39	0.57
Chinese	19	14	
Indian	14	13	
Others	1	3	
Glucose Lowering Medications			
Oral Hypoglycemic Agents	58 (84.1%)	55 (79.7%)	0.507
Sulfonylurea	28 (40.6%)	28 (40.6%)	1.00
Metformin	52 (75.4%)	51 (73.9%)	0.845
DPP4 inhibitors	12 (17.4%)	11 (15.9%)	0.819
Insulin	28 (40.6%)	47 (68.1%)	0.001
Human insulin	25 (36.2%)	41 (59.4%)	0.006
Insulin Analog	5 (7.2%)	12 (17.4%)	0.007
Co-morbidities			
Hypertension	60 (87%)	65 (94.2%)	0.145
Dyslipidemia	66 (95.7%)	67 (97.1%)	1.00
Others	21 (30.4%)	12 (17.4%)	0.072
Medications			
Anti hypertensives	59 (85.5%)	65 (94.2%)	0.091
ACE inhibitor	46 (66.7%)	53 (76.8%)	0.186
Beta blocker	22 (31.9%)	31 (44.9%)	0.115
Calcium Channel Blocker	33 (47.8%)	41 (59.4%)	0.172
Diuretics	13 (18.8%)	21 (30.4%)	0.114
Alpha blockers	7 (10.1%)	6 (8.7%)	0.771
Lipid lowering agents	65 (94.2%)	67 (97.1%)	0.681
Statin	64 (92.8%)	65 (94.2%)	1.00
Fibrates	1 (1.4%)	5 (7.2%)	0.208
Ezetimibe	2 (2.9%)	1 (1.4%)	1.00
Complications			
Microvascular	37 (53.6%)	52 (75.4%)	0.008
Retinopathy	20 (29%)	27 (39.1%)	0.209
Neuropathy	18 (26.1%)	36 (52.2%)	0.002
Nephropathy	22 (31.9%)	27 (39.1%)	0.374
Macrovascular	24 (34.8%)	27 (39.1%)	0.597
Ischemic Heart Disease	22 (31.9%)	24 (34.8%)	0.718
Cerebrovascular Accident	5 (7.2%)	6 (8.7%)	0.753
Examination			
Systolic BP (mmHg)	141 (± 19.1)	149 ((± 22.5)	0.033
Diastolic BP (mmHg)	76 ((± 10.2)	76 ((± 12.8)	0.769
Body Mass Index*	26.8 (IQR 4.61)	27.2 (IQR 6.20)	0.751
Waist Hip Ratio*	0.92(IQR 0.100)	0.95 (IQR 0.008)	0.061
Investigations			
Fasting Blood Sugar* (mmol/l)	5.9 (IQR 1.60)	7.60(IQR 3.30)	<0.001
HbA1c* (%) [mmol/mol]	6.6 [49] (IQR 0.65)	8.5 [69] (IQR 1.80)	<0.001
Creatinine* (µmol)	95 (IQR 54.5)	102 (IQR 53.5)	0.717
eGFR*	66 (IQR 27.25)	63.0 (IQR 24.64)	0.498
Total Cholesterol(mmol/l)	4.22 (± 0.911)	4.23 (± 1.149)	0.001
LDL (mmol/l)	2.39 (± 0.804)	2.38 (± 0.889)	0.805
HDL(mmol/l)	1.28 (± 0.364)	1.18 (± 0.239)	0.058
Tg*(mmol/l)	1.2 (IQR 0.70)	1.5 IQR (1.1)	0.018
CGM related values			
Number of readings*	2020 (IQR 67)	2026(IQR 62)	0.226
Correlation number*	0.90 (IQR 0.10)	0.93 (IQR 0.09)	0.191

Note: *data expressed in median (IQR)
Abbreviations: LDL: Low Density Lipid; HDL: High Density Lipid, Tg: Triglyceride; CGM: Continuous Glucose Monitoring

Table 1: Baseline characteristics.

Parameters	HbA1c<7% (53 mmol/mol)	HbA1c ≥ 7% (53 mmol/mol)	P value
CONGA*	6.49 (IQR 1.29)	8.10 (IQR 2.23)	<0.001
SD	2.18 (± 0.910)	3.01(± 0.854)	<0.001
M-VALUE*	4.13 (IQR 6.04)	10.51 (IQR 10.30)	<0.001
MAGE	4.45 (± 1.801)	5.45 (± 1.600)	0.001
ADDR	15.30 (± 8.587)	27.69(± 12.068)	<0.001
LI *	2.19 (IQR 1.651)	3.17 (IQR 2.235)	0.001
LBGI*	**2.11 (IQR 2.61)**	**2.14 (IQR 3.43)**	**0.743**
HBGI*	3.85 (IQR 4.89)	9.28 (IQR 6.49)	<0.001
MODD	2.29 (± 0.974)	3.11 (± 0.942)	<0.001
GRADE*	2.89 (IQR 3.32)	7.52 (IQR 6.25)	<0.001
MAG *	1.40 (IQR 0.66)	1.65 (IQR 0.69)	<0.001

Note: *data expressed in median (IQR)
Abbreviations: CONGA: Continuous Overlapping Net Glycemic Action; SD: Standard Deviation; MAGE: Mean Amplitude of Glucose Excursion; ADDR: Average daily risk ratio; LI: Lability Index; LBGI: Low Blood Glucose Index; HBGI: High Blood Glucose Index; MODD: Mean of Daily Differences; GRADE: Glycemic Risk Assessment in Diabetes Equation; MAG: Mean absolute Glucose

Table 2: Comparison of GV parameters between 2 groups.

Variable	Mean (± SD)	r	P value
HbA1c	7.7 (61mmol/mol) (± 1.67)	0.37	P<0.001
MAGE	5.0 (± 1.77)		

Abbreviation: MAGE: Mean Amplitude of Glucose Excursion

Table 3: Spearman's correlation coefficients (*r*) of HbA1c and MAGE (n=138).

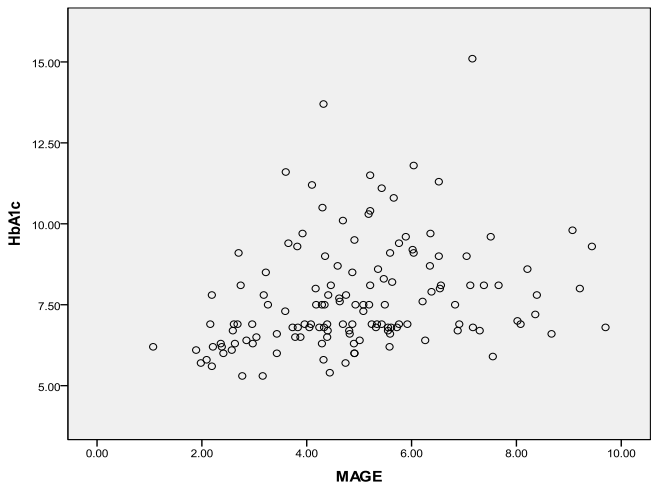

Figure 1: Correlation between HbA1c and MAGE.

Authors	Characteristics of subjects	HbA1c/ blood glucose	MAGE reported
This study	Malaysian Type 2 diabetes age 65 years and above	HbA1c<7% (n=69)	4.45 mmol/l (± 1.80)
		HbA1 ≥ 7% (n=69)	5.45 mmol/l (± 1.60)
Hill et al. [7]	Normal non diabetic Asians	FBS <6.7 mmol/l (n=7)	1.3 (0.7)
Jian Zhou et al. [15]	Normal non diabetic Chinese patients	Normal OGTT (n=434)	1.73 mmol/l (1.08)
Fang et al. [10]	Elderly (>60 years old) Chinese male patients with Type 2 diabetes	HbA1c<7% (n=153)	3.48 mmol/l ± 1.46
		HbA1 ≥ 7% (n=138)	4.33 mmol/l ± 1.67
Xu et al. [14]	Type 2 diabetic patients with well controlled diabetes without diabetic neuropathy (Chinese population)	Mean HbA1c 6.4% ± 0.4 (n=45)	4.5 mmol/l ± 0.9
	Type 2 diabetic patients with well controlled diabetes with diabetic neuropathy (Chinese population)	Mean HbA1c 6.5% ± 0.4 (n= 45)	5.8 mmol/l ± 1.6
Gong et al. [13]	Chinese patients admitted for acute myocardial infarct, irrespective of diabetes status	Hba1c ≥ 6.5% with mean of 7.68 ± 1.13	4.10 mmol/l ± 1.34
Engler et al. [11]	German patients with Type 2 diabetes	HbA1c<7% (n=63)	2.6 mmol/l ±1.1
		HbA1c ≥ 7% (n=45)	4.8 mmol/l ± 2.1
Gribovschi et al. [16]	Romanian patients with type 2 diabetes	Mean HbA1c 8.42 % (± 1.99)	3.41 mmol/l (± 1.98)

Table 4: Comparison of MAGE with other studies.

Factors	P value	Confidence interval 95%
Sulphonylurea use	<0.001	0.869, 1.831
Human insulin use	<0.001	0.695, 1.969
Analog insulin use	0.005	0.399, 2.163

Table 5: Multivariate regression analysis for confounding factors of MAGE.

(p 0.008), there were no differences between the groups in terms of macrovascular complications. One possible explanation is that cardiac ischaemia may be silent and undetected in elderly patients with diabetes and the information obtained regarding macrovascular complications was based on history with no formal assessment done.

The MAGE, which is one of the commonest parameters used to quantify glycemic variability, estimates the major fluctuations in glucose profiles. It is obtained by measuring the arithmetic mean of the differences between consecutive peaks and nadirs provided that the differences are greater than one SD of the mean glucose value [4]. MAGE is generally regarded as the "gold standard" parameter to describe glycemic variability. The MAGE in our group of patients with HbA1c ≥ 7% (53 mmol/mol) was 5.45 mmol/l (± 1.600); significantly higher than the 4.45 mmol/l (± 1.801) in the group with HbA1c<7% (53 mmol/mol). In comparison with MAGE reported in other studies (Table 4), except for one study [7,10-15], our patients seem to have more glycemic variability; even those with good glycemic control from HbA1c point of view. Feng et al. [13] reported a similar MAGE (among Chinese population) with ours. This reflects the fact that many other factors such as types of food and therapies affect glycemic variability. Further analysis showed that among our patients, there is a significant correlation between HbA1c and MAGE; a focus in glycemic variability seems important, especially in those with higher HbA1c. A further multivariate regression analysis of factors that may affect MAGE such as duration of diabetes, fasting blood sugar, HbA1c, uses of metformin, sulphonylurea, DPP4 inhibitor, human insulin, analog and beta blocker as well as eGFR, presence of micro and macrovascular complications was performed and we found that the most significant factors confounding MAGE are the use of sulphonylurea, human insulin and analog (Table 5). This suggests that in patients who have high MAGE, the use of these agents may need to be reviewed.

The LBGI and the HBGI split the overall glucose variation into two independent sections related to excursions into hypo- and hyperglycemia, and at the same time equalize the amplitude of these excursions with respect to the risk they carry [16-19]. The LBGI and HBGI formulae are implemented by converting glucose values into risk scores [7]. Larger values of LBGI and HBGI indicate higher risk for hypo and hyperglycemia respectively. In repeated studies it has been established that four risk categories of the LBGI can be identified: minimal risk for hypoglycaemia: LBGI ≤ 1.1, low risk: 1.1 < LBGI ≤ 2.5, moderate risk: 2.5 < LBGI ≤ 5; and high risk: LBGI > 5 [16]. Interestingly, in our study, both groups of patients did not differ in terms of LBGI but the HBGI was three times higher in the group with HbA1c ≥ 7% (53 mmol/mol). This highlights the importance of focusing in hypoglycemia in all elderly patients regardless of HbA1c.

SD is calculated from patient's blood glucose readings and shows how much variation or dispersion from the average blood glucose level (mean). It is appropriate for assessing intraday glycemic variability. The CONGA is similar to the SD. The determination is based on the assessment of the differences between glucose values measured at regular time intervals, then on the calculation of SD of these differences. It assesses the intraday GV [4]. The M-value is a logarithmic transformation of the deviation of glycaemia from an arbitrarily assigned "ideal" glucose value. It is calculated on each glucose value using a formula then divided by total values to derive at a mean. It attempts to provide, in a single numerical value, an expression of both the mean glucose value and the effect of glucose swings [4]. Most parameters such as SD are more sensitive to hyperglycemic surges than to hypoglycemic changes. This is due to the asymmetry of

blood glucose scale; which can be corrected numerically. The ADRR which is calculated by transforming each glucose value using a formula and then attributing a risk value to the transformed point is a measure of glucose variability which was designed to be equally sensitive to hypoglycemia and hyperglycemia levels of glucose [17]. A lability value is calculated by processing three glucose readings and then moves on to the next three values and so on. The LI is the mean of these values [7]. LI measures how labile or brittle a patient's diabetes is. The MODD formula is calculated as the average of the difference between values on different days but at the same time [4]. It provides an assessment of interday GV. The GRADE score of glucose profiles summarizes the degree of risk associated with a glucose profile. The GRADE formula converts glucose values to a risk score, calculates the median and provides the risk attributable to hypoglycemia and hyperglycemia [7]. Normal GRADE value has been reported as <5 [18]. MAG calculates the sum of the differences between successive glucose values divided by the total time measured in hours.

Despite the seemingly complex explanation/formula of each GV parameter, our study showed a very simple conclusion which is - all the parameters calculated consistently showed higher GV among our group of patients with HbA1c ≥ 7% (53 mmol/mol) except for LBGI. However the fact that even those with HbA1c <7% (53 mmol/mol) showed some degree of GV indicates that glycemic control should be evaluated beyond HbA1c alone. CGMS is emerging as a valuable tool to aid in glycemic management. Its pictorial presentation allows clinicians to identify glycemic excursions and individualize therapy. However, the GV parameters calculated in our studies allow a more objective assessment of GV and can be used to monitor progress. The MAGE in our opinion is the most useful parameter. It is more widely used and therefore comparisons with values from other studies offer a better light to GV among our population of patients. The concept of care manager who plays the link between patients and healthcare providers has been shown to contribute positive impact towards patients' knowledge and self-management skills [19]. Sharing and explaining the GV parameters obtained with patients via their care managers could empower them further and lead to greater self sufficiency.

Limitations of this study are lack of data on smoking history and the possible underestimation of macrovascular complications as history of these complications are obtained from patients and clinical notes entered by physician with no formal assessment like angiography. The strength of this study is that it is the first done locally to assess glycemic variability among older diabetics.

Conclusion

We present the glycemic variability parameters for older adults with type 2 diabetes. Among this population, the risk of hypoglycemia is similar between those with optimal HbA1c versus their counterparts.

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