Diagnostic Accuracy of Serum 1,5-anhydroglucitol as a Surrogate Measure of Glycemic Variability Among Adult Filipinos with Type 2 Diabetes Mellitus: A Retrospective Cross-sectional Study

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Abstract

Background: Among the various glycemic indices in current use, glycemic variability has the greatest contribution in the development of microvascular and macrovascular complications in Type 2 Diabetes mellitus (T2DM). Most metrics that are currently used to measure glycemic variability are derived from continuous glucose monitoring (CGM) data. However, CGM is burdensome to the patient due to its relatively high cost as well as the need for multiple visits with the health care provider. With the use of serum 1,5-anhydroglucitol (1,5-AG) as a biomarker of glucose fluctuations, physicians and patients alike could have an easier surrogate measure of glycemic variability thus aiding in achieving target glucose control. This study aims to determine the diagnostic accuracy of 1,5-AG as compared to the glycemic variability metrics derived from CGM as a surrogate measure of glycemic variability among adult Filipinos with T2DM.

Methods: Retrospective analysis of data of adult patients aged 20 years old and above diagnosed with T2DM referred for CGM at the Diabetes, Endocrine, Metabolic, and Nutrition Center of Cardinal Santos Medical Center from January 2017 to October 2021 who underwent serum 1,5-AG level determination within 2 weeks of CGM were collected. Diagnostic accuracy was obtained by computing the sensitivity, specificity, positive (PPV) and negative predictive values (NPV), and Youden index. Pearson correlation coefficient was used to determine the correlation of 1,5-AG and the different metrics. Analysis of variance (ANOVA) was used to check for statistical significance with 99% confidence interval and a $p < 0.05$ considered as statistically significant.

Results: This study involving 37 subjects showed a good diagnostic accuracy of serum 1,5-AG levels with the different measures of glycemic variability derived from CGM namely mean amplitude of glycemic excursion (MAGE), continuous overlapping net glycemic action at 1-hour intervals (CONGA-1), and mean of daily differences (MODD) with significant correlation among patients with HbA1c ≤ 7%. Subjects were on CGM for approximately 6 ± 1 day with statistically significant difference between the good and poor glucose control group ($p<0.05$). Determination of diagnostic accuracy between 1,5-AG and MAGE showed good accuracy (Sensitivity = 95.3%, Specificity = 100%, PPV = 100%, NPV = 75.43%, Diagnostic accuracy 96%, and a Youden Index of 92.3) with a statistically significant correlation among subjects with HbA1c level ≤ 7% ($p=0.021$). There is likewise good diagnostic accuracy between CONGA-1 and 1,5-AG level (Sensitivity = 99%, Specificity = 75.29%, PPV = 89.1%, NPV = 97%, Accuracy = 89.50% and Youden index of 58.41) with a statistically significant correlation among subjects with HbA1c ≤ 7% ($p=0.038$). Comparison with interday glycemic variability showed fair diagnostic accuracy between MODD and 1,5-AG (Sensitivity = 79.17%, Specificity = 78%, PPV = 97%, NPV = 32%, Accuracy = 76.89%, and Youden index of 49.07) and a statistically significant correlation among subjects with HbA1c ≤ 7% ($p=0.009$).

Conclusion: There is good diagnostic accuracy of serum 1,5-AG levels with the different measures of glycemic variability derived from CGM namely MAGE, CONGA-1, and MODD with significant correlation among patients with HbA1c ≤ 7%. Among diabetics with HbA1c ≤7%, 1,5-AG could be used as a surrogate measure of glycemic variability and excursions.

Keywords: serum 1,5-anhydroglucitol, continuous glucose monitoring, type 2 diabetes mellitus

Introduction

T2DM is increasing in both prevalence and incidence worldwide.[1] According to the International Diabetes Federation, the global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The prevalence in the country last 2020 is estimated at 6.3% affecting approximately 3,993,300

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million Filipinos. The burden of T2DM is very much present, hence, glycemic control must be reached and targeted.[2] Most diabetes management guidelines focus on treating the glycemic triad namely, HbA1c, Fasting Plasma Glucose (FPG), and Post-prandial Glucose (PPG). Currently, monitoring of glycemic control is based on self-monitoring of blood glucose (SMBG) and determination of HbA1c levels.[3,4] However, Hirsch has enumerated several cases wherein despite achieving target HbA1c level, there are still patients who develop cardiovascular and cerebrovascular complications.[5] Thus, there is a need to recognize other factors that may contribute to the development of these complications.[6] With the increased recognition of the deleterious effects of glycemic variability, glycemic management has shifted to a new model of glycemic control targeting the *glycemic pentad* with the addition of glycemic variability and hypoglycemia.[7]

HbA1c level does not reflect glucose levels on a daily basis and it does not reflect occurrence and frequency of intra- and inter-day glycemic variability which are involved in the initiation of cardiovascular complications.[8] Chronic hyperglycemia is the primary risk factor for the development of complications in T2DM; however, it is believed that frequent or large glucose fluctuations may independently contribute to diabetes-related complications. Postprandial spikes in blood glucose, as well as hypoglycemic events, has been associated with increased cardiovascular events in T2DM. Glycemic variability (GV) includes both of these events; hence, minimizing GV can prevent future cardiovascular events.[8]

CGM provides continuous feedback on estimated glucose values and glucose trends. It measures interstitial glucose levels at 5-minute intervals and is regarded as the gold standard for measurement of short-term glycemic variability.[9] Serum 1,5-anhydroglucitol is a relatively new marker of hyperglycemia.[4] According to Selvin, et.al., low serum 1,5-AG can serve as a marker of short-term hyperglycemia and concentrations are thought to reflect hyperglycemic episodes over a period of approximately 1–2 weeks.[10]

This paper is a continuation of an unpublished research done by Cheng, B. et al., at Cardinal Santos Medical Center entitled "Diagnostic accuracy of serum 1,5-anhydroglucitol as a surrogate measure of glycemic variability among adult Filipinos with Type 2 Diabetes mellitus: A retrospective cross-sectional study" which showed good accuracy between 1,5 AG and the measures of *intraday* glycemic variability, namely, MAGE and CONGA-1; as well as a fair accuracy between 1,5 AG and the measure of *interday* glycemic variability, MODD.

The said study recommended using a larger sample size to increase the confidence interval, to better control confounding factors, and assess the correlation between the two tests.[11] Our study hopes to increase the confidence interval to 99% by adding six additional subjects to the previously done study. The increased confidence interval will decrease the margin of error and increase the sensitivity and specificity of the study further solidifying the validity of the study.

CGM provides continuous real-time measurement of glucose levels and enables one to achieve glycemic targets and mitigate glycemic excursions. It is a small device that is inserted into the subcutaneous area and measures interstitial glucose levels continuously, recording values every 5 minutes. CGM is the ideal mode of measuring glycemic variations in patients as it is able to measure real time interstitial glucose every 5 minutes as transmitted by the sensor. However, the process of putting the sensor and keeping it for 5-7 days as well as its high cost are a hindrance to its use in the local setting. An alternative method, the serum 1,5 AG is being studied as an equally effective replacement.

1,5-AG is a marker that responds rapidly and significantly to changes in glycemia, is metabolically stable, is able to demonstrate low biological variability, and is easily measured.[12] 1,5-AG was first discovered in the plant family *Polygala senega* in 1888. According to research, 1,5AG comes mostly from foods with a mean intake of ~4.4 mg/day. It was also found that the closed pyran ring structure confers metabolic stability. The rate of intake is matched by the daily excretion rate and a bodily pool of ~500–1,000 mg of 1,5AG is constantly maintained.[13] It is freely filtered by the glomeruli and a small amount is reabsorbed in the renal tubule by the sodium glucose active co-transporter SGLT4 where absorption is competitively inhibited by glucose.[4] When the plasma glucose levels exceed the renal threshold for glucosuria (approximately 180mg/dL), 1,5-AG is excreted in the urine. Low serum 1,5-AG level signifies short-term postprandial hyperglycemia and hyperglycemic excursions.[14] Lastly, it has a half-life of 1-2 weeks, hence concentrations of 1,5-AG are thought to reflect the average maximum blood glucose level during the past 1-2 weeks.

General Objectives. This paper aims to determine the diagnostic accuracy of serum 1,5-AG as compared with the different glycemic variability metrics derived from CGM as a surrogate measure of glycemic variability among adult Filipinos with T2DM at the Diabetes Center of Cardinal Santos Medical Center from January 2017 to October 2021.

Specific Objectives. This paper specifically aims to: 1) describe the clinical profile of diabetic patients who underwent CGM at the Diabetes Center of Cardinal Santos Medical Center from January 2017 to October 2021 taking note of their age, gender, co-morbidities, duration of diabetes treatment, number and types of hypoglycemic agents in current use, fasting blood glucose levels, HbA1c levels, and 1,5-AG levels, 2) describe the metrics derived from CGM in terms of intra-day glycemic variability namely: CONGA-1 and MAGE, and inter-day glycemic variability using MODD, of each subject, 3) determine the diagnostic accuracy of serum 1,5-AG with the glycemic variability indices derived from CGM (CONGA-1, MAGE, and MODD) using Sensitivity, Specificity, PPV, NPV, and Youden index, and

4) determine the correlation of serum 1, 5-AG with the glycemic variability indices derived from CGM (CONGA-1, MAGE, and MODD) via Pearson correlation.

Significance of the study. This study will determine the diagnostic accuracy of serum 1,5-AG as a surrogate measure of glycemic variability among adult Filipinos with T2DM. Diabetes monitoring has now shifted to the percentage of glucose results that is within range, with minimal hypoglycemia and hyperglycemia as compared to monitoring of HbA1c which only gives the approximate glucose level within the last 3 months. Serum 1,5-AG, which reflects the glycemic variability on a daily basis, can help physicians tailor more appropriate medications to achieve target serum glucose level taking into account episodes of hypoglycemia and hyperglycemia. In addition, as compared to CGM, it is more cost effective and convenient for the patient. Serum 1,5-AG only entails one time extraction and will give a rough estimate of a patient's glucose within the last 1-2 weeks.

Scope and Limitations. This is a retrospective cross-sectional study and the researchers would only be reviewing the charts of adult Filipinos diagnosed with T2DM who underwent CGM at the Diabetes center of Cardinal Santos Medical Center from January 2017 to October 2021.The outcome determined in this study include the diagnostic accuracy of serum 1,5-AG level with the glycemic variability indices derived from CGM data.

Definition of Terms

- Type 2 Diabetes mellitus (T2DM) – American Diabetes Association criteria: Fasting plasma glucose level of 126mg/dL or higher; Hemoglobin A1c level of 6.5% or higher; and a 2-hour 75g oral glucose tolerance test plasma glucose level of 200mg/dL or higher
- Continuous Glucose Monitor (CGM) – An FDA-approved device that provides continuous real-time measurement of glucose levels throughout the day and night. A glucose sensor is inserted under the skin to measure glucose levels in tissue fluid. It measures interstitial glucose level at 5-minute interval and is regarded as the reference standard method for assessment of short-term glycemic variability.[4]
- Glycemic variability – Fluctuations of blood glucose level between high (peak) and low (nadir) levels. It may refer to intra-day or day-to-day variation.[5] It refers to the extent on which a glucose reading varies from the mean glucose, the degree of up and down fluctuations of a glucose reading (amplitude), as well as the frequency and duration of the variations.[15]
- Mean amplitude of glycemic excursion (MAGE) – Average of all glycemic excursions (except excursion having value <1 SD from mean glucose) in a 24h time period; measures within-day glycemic variability; most commonly used metric of glycemic variability
- Continuous overlapping net glycemic action at 1-hour intervals (CONGA-1) is the standard deviation of the summated differences between each glucose level and the corresponding glucose level measured 1h earlier; measures within a day glycemic variability
- Mean of daily differences (MODD) is the mean of the absolute difference between glucose values of 2 days. Reflects inter-day glycemic variability.
- Sensitivity is the probability that a test result will be positive when the disease is present (true positive rate).
- Specificity is the probability that a test result will be negative when the disease is not present (true negative rate)
- Positive Predictive value (PPV) is the probability that the disease is present when the test is positive
- Negative Predictive value (NPV) is the probability that the disease is not present when the test is negative

Methodology

Research Design. This is a retrospective cross-sectional study of adult Filipino patients diagnosed with T2DM according to the American Diabetes Association criteria who underwent CGM and serum 1,5-AG determination within 2 weeks of CGM at the diabetes center of Cardinal Santos Medical Center from January 2017 to October 2021.

Inclusion Criteria. All adult patients aged 20 years old and above diagnosed with T2DM according to the American Diabetes Association criteria referred for CGM at the Diabetes, Endocrine, Metabolic, and Nutrition Center of Cardinal Santos Medical Center from January 2017 to October 2021 who underwent serum 1,5-AG

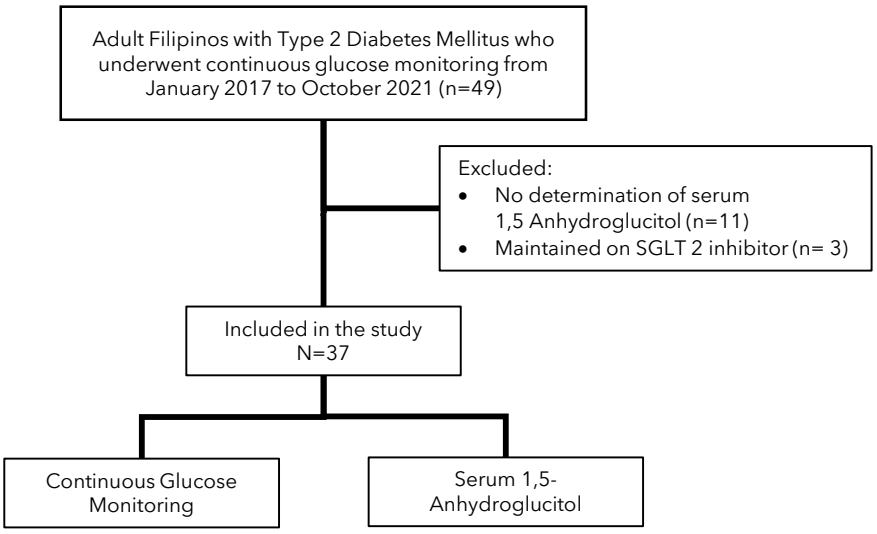

Figure 1. Study Procedure

level determination within two weeks of CGM.

Exclusion Criteria. Patients were excluded if they (1) have conditions that could falsely elevate blood glucose levels like acute infection or clinically stressful conditions at the time of the study; (2) have active malignancy or end-stage cardiac, pulmonary, hepatic and renal diseases; or (3) are taking medications that could alter glomerular function (i.e., Angiotensin converting enzyme inhibitor and Sodium Glucose co-transporter 2 inhibitor). Patients were also excluded if they were not able to undergo serum 1, 5-AG determination within 2 weeks of CGM.

Sample Size. Using *OpenEpi®*, sample size was computed using 99% confidence interval. A population size of 40 was used based on the number of patients who underwent CGM from January 2017 to October 2021. A hypothesized frequency of 92.6% was used based on the sensitivity of 1,5-AG from the study of Wang.[10] This is in comparison with the previously done study by Cheng, et al which only included 31 subjects with a confidence interval of 92%.

Data Collection. Data of T2DM patients who underwent CGM at the Diabetes, Endocrine, Metabolic, and Nutrition Center of Cardinal Santos Medical Center from January 2017 to October 2021 who also underwent serum 1,5-AG determination within 2 weeks of CGM were collected (*Figure 1*). Data extracted included age, gender, co morbidities, duration of diabetes treatment, number and types of hypoglycemic agents in current use, fasting blood glucose levels, HbA1c levels, and 1,5-AG levels. For this study, the researchers utilized glycemic variability metrics derived from CGM namely, MAGE and CONGA-1 to measure intraday glucose variability and the MODD as measure of interday glycemic variability as patterned after the study of Kim et al.[2] Other data extracted from the CGM include mean glucose level and glucose management index (estimated HbA1c). Serum 1, 5-AG levels were obtained by reviewing patient charts from each respective consultant's clinic who agreed to share the data. Data obtained were tabulated and processed using *Microsoft Excel* spreadsheet. Data were expressed as mean ± standard deviation and as absolute number and percentage. MAGE, MODD, and CONGA-1were calculated using the *Glycemic Variability Analyzer Program* script and processed using the *MATLAB R2019a* software. Subjects were further divided into three groups based on HbA1c level: (1) Good glucose control (HbA1c ≤7%), (2) Acceptable glucose control (HbA1c 7.1-8%),

Table I. Baseline Characteristics of subjects who underwent CGM at the Diabetes center of Cardinal Santos Medical Center from January 2017 to October 2021

	Total (n=37)	HbA1c ≤7% (n=15)	HbA1c 7.1-8% (n=11)	HbA1c >8% (n=11)	p-value
Age (year)	63 ± 11.04	62± 12.67	65±9.3	62 ± 12.78	p=0.93
Gender					p=1.00
Male	23 (62.16%)	10 (66.67%)	6 (54.55%)	7 (63.64%)	
Female	14 (37.83%)	5 (33.33%)	5 (45.45%)	4 (36.36%)	
Duration of diabetes (year)	14 ± 10.38	10..7± 9.97	22± 13.94	11.3± 9	p=0.32
Treatment					p=1.00
Insulin	25 (67.57%)	8 (72.72%)	8 (72.72%)	9 (81.81%)	
Long acting alone	6 (24%)	1 (12.5%)	1 (12.5%)	4 (44.44%)	
Intermediate	17 (68%)	6 (75%)	6 (75%)	5 (55.56%)	
Long acting + Rapid acting	2 (8%)	1 (12.5%)	1 (12.5%)	0 (0%)	
Oral hypoglycemic agents	32 (86.49%)	13 (86.67%)	6 (54.54%)	10 (90.90%)	
Insulin alone	5 (13.51%)	2 (13.33%)	2 (18.18%)	1 (9.09%)	
Oral hypoglycemic agents alone	12 (32.43%)	7 (46.67%)	9 (81.81%)	2 (18.18%)	
Insulin + Oral hypoglycemic agents	20 (54.05%)	6 (53.33%)	6 (54.54%)	8 (72.72%)	
Comorbidities					p=1.00
Kidney Transplant	4 (10.8%)	4 (26.00%)	0 (0%)	0(0%)	
Ischemic Heart Disease	6 (16.21%)	2 (13.33%)	2 (18.18%)	2 (18.18%)	
HbA1c (%)	7.57± 1.5	6.3± 0.99	7.9 ± 1.3	10.1 ± 0.6	p<0.0001
FBS (mg/dL)	143.8± 39.2	103.45± 26.6	136.13±34.65	170.69 ± 45.2	p=0.006
1.5-anhydroglucitol (µg/mL)	7.233± 4.10	7.99 ±4.10	10.21± 6.00	3.99± 1.60	p=0.0109

Table II. Data and Glycemic Variability Indices derived from CGM

	Total (n=37)	HbA1c ≤7% (n=17)	HbA1c 7.1-8% (n=10)	HbA1c >8% (n=10)	p-value
Average Glucose (mg/dL)	154.53 ±37.76	120.26±23.67	164.57± 45.34	184.11 ± 43.23	p=0.021
MAGE (mg/dL)	113.67 ±21.87	92.69± 25.56	119.87± 21.45	116.46 ± 30.87	p=0.25
CONGA-1 (mg/dL)	32.25± 9.24	18.84± 4.24	26.52± 12.76	20.87 ± 5.76	p=0.15
MODD (mg/dL)	42.54± 17.46	33.57 ± 13.76	46.87± 15.76	46.86 ± 15.22	p=0.145

and (3) Poor glucose control (HbA1c >8%). This was based on the study done by Sun, where they showed that 1,5-AG was better correlated with the glycemic variability metrics from CGM among subjects with HbA1c level <8%.[2]

Statistical Analysis. *Microsoft Excel* spreadsheet was used to tabulate data gathered from the CGM including mean glucose level, glucose management index (estimated HbA1c), CONGA-1, MAGE, and MODD. Analysis of variance (ANOVA) was used to test for any statistical significance between the three groups followed by *Tukey post hoc analysis* if there were any statistically significant differences (99% CI and a $p < 0.05$). *OpenEpi*® was used to analyze the diagnostic accuracy by computing the sensitivity, specificity, PPV and NPV. Youden index was also used to compute for the diagnostic accuracy. Glycemic variability metrics were used as reference standard and 1,5-AG as the index test.

Ethical Considerations. The clinical protocol was reviewed and approved by the Research Ethics Review Committee (RERC) of Cardinal Santos Medical Center. The researchers ensured that all information gathered were kept strictly confidential and used solely for the purpose of the study.

Table III. 2 x 2 table comparing the Mean Amplitude of Glucose Excursion (MAGE) and 1,5-Anhydroglucitol level

1,5-Anhydroglucitol	MAGE		Total
	Positive (>82mg/dL)	Negative (<82mg/dL)	
Positive (<10ug/dL)	27	1	28
Negative (>10ug/dL)	3	6	9
Total	30	7	37

Table IV. 2 x 2 table comparing the Continuous Overall Net Glycemic Action over 1-hour interval (CONGA-1) and 1,5 anhydroglucitol

1,5-Anhydroglucitol	CONGA-1		Total
	Positive (>18mg/dL)	Negative (<18mg/dL)	
Positive (<10ug/dL))	19	6	25
Negative (>10ug/dL))	2	10	12
Total	21	16	37

Table V. 2 x 2 Table comparing the Mean of Daily Difference (MODD) and 1,5 anhydroglucitol

1,5-Anhydroglucitol	MODD		Total
	Positive (>18mg/dL)	Negative (<18mg/dL)	
Positive (<10ug/dL))	23	2	25
Negative (>10ug/dL))	8	4	12
Total	31	6	37

Results

In this study, review of the patient charts showed 49 subjects referred for CGM at the Diabetes Center of Cardinal Santos Medical Center from January 2017 to October 2021 (*Table I*). Eleven subjects did not have serum 1,5-AG tests and were excluded from the study. Three subjects were on SGLT inhibitor and were also excluded. A total of 37 subjects were thus eventually included in this study. Among these, 15 (40.54%) had good glucose control (HbA1c ≤ 7%), 11 (29.73%) had acceptable glucose control (HbA1c 7.1 - 8%), and 11 (29.73%) had poor glucose control (HbA1c > 8%). Subjects had a mean age of 62 ± 10 years with no statistically significant difference among the three groups ($p=0.90$). Majority of subjects were males (62.16%) diagnosed with T2DM for approximately 14 ± 10.5 years. Most of the subjects (40.74%) are maintained on a combination of Insulin and oral hypoglycemic agents with majority (70%) using an intermediate-acting insulin and an average of two oral hypoglycemic agents. Subjects with good glycemic control are mostly maintained on oral hypoglycemic agents alone (52.94%) while subjects on the acceptable and poor glycemic control are on a combination of insulin and oral hypoglycemic agents (70%).

HbA1c levels are significantly different statistically among the three groups ($p<0.0001$) with *Tukey post hoc analysis* showing significant difference in all groups ($p<0.01$). Fasting blood glucose levels are also significantly different statistically between the good and poor glycemic control groups only ($p<0.01$). Determination of serum 1,5-AG level showed that most subjects have glycemic variability (7.568 ± 3.81, with a normal value > 10ug/mL) including subjects with good glucose control based on HbA1c level with statistically significant difference between those with acceptable and poor glucose control ($p<0.01$).

Subjects were on CGM for approximately 6 ± 1 days with 1778 ± 403 glucose values (*Table II*). Average glucose level detected was 167.10 ± 39.04 mg/dL with statistically significant difference between the good and poor glucose control group ($p<0.05$).

Intra-day glycemic variability can be seen in all groups based on a high MAGE value (113.67 ± 21.87, with a normal value of < 82mg/dL) and high CONGA-1 value (32.25 ± 9.24, with a normal value of ≤ 18mg/dL) with no statistically significant difference in the three groups ($p=0.25$, $p=0.15$ and $p=0.145$, respectively) (*Table II*). Inter-day glycemic variability is present as well in all the groups as shown by the high MODD value (42.54 ± 17.46 with a normal value of ≤18mg/dL) but with no statistically significant difference among the three groups ($p=0.145$).

Comparison between 1,5-AG and MAGE showed good diagnostic accuracy (Sensitivity=95.3%, Specificity=100%, PPV=100%, NPV=75.43%, Diagnostic accuracy=96%, and a Youden Index of 92.3) (*Table III*) with a statistically significant correlation among subjects with HbA1c level ≤ 7% ($p=0.021$) (*Figure 2*).

There is likewise good diagnostic accuracy between CONGA-1 and 1,5-AG level (Sensitivity=99%, Specificity=75.29%, PPV=89.1%, NPV=97%, Accuracy=89.50%, and Youden index of 58.41) (*Table IV*) with a statistically significant correlation among subjects with HbA1c ≤ 7% (*p=0.038*) (*Figure 3*).

Comparison with interday glycemic variability showed fair diagnostic accuracy between MODD and 1,5-AG (Sensitivity=79.17%, Specificity=78%, PPV=97%, NPV=32%, Accuracy=76.89%, and Youden index of 49.07) (*Table V*) and a statistically significant correlation among subjects with HbA1c ≤ 7%(*p=0.009*) (*Figure 4*).

Discussion

Diabetes complications such as retinopathy, nephropathy and cardiovascular disease are consequence of uncontrolled hyperglycemia. Glucose variability has been suggested by a number of studies as an independent risk factor for complications of diabetes.[15] Glycemic variability (GV) is defined by the measurement of fluctuations of glucose or other related parameters of glucose homoeostasis over a given interval of time.[16] Recent studies have shown that GV, hypoglycemia and hyperglycemia are all closely related to oxidative stress. Transient hyperglycemia was also studied as a possible cause of epigenetic changes, such as cellular metabolic memory increasing insulin resistance, pancreatic β-cell dysfunction and apoptosis.[17]

Several studies also supported correlation of increased risk of both cardiovascular and microvascular complications with long-term GV, in terms of fasting glucose and/or HbA1c variability.[17] Among patients with T2DM and ACS, GV was assessed using Standard Deviation (SD) during initial hospitalization. A GV cutoff value of > 2.70 mmol/L (48.6mg/dL) was the strongest independent predictive factor for midterm major adverse cardiac events.[18] There is no consensus on the best method of determining glycemic variability. Long term GV was done based on serial determination of Hba1C, FPG and PPG measurements with calculation of SD and

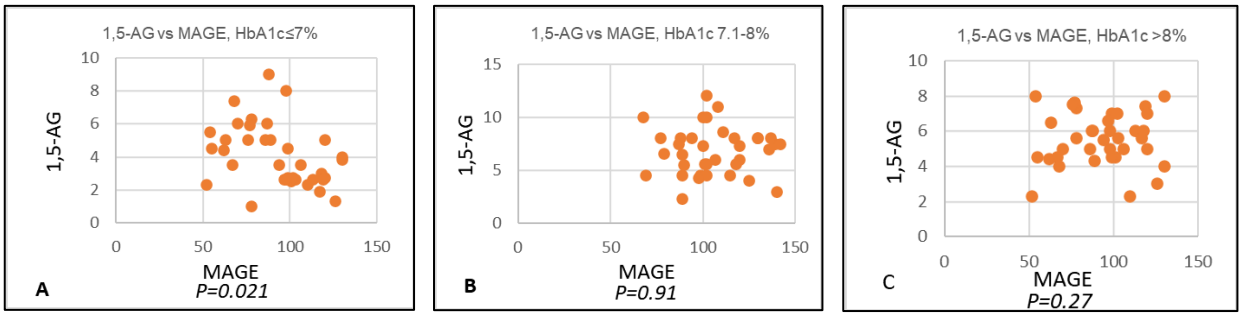

Figure 2. Pearson Correlation between 1,5-AG and MAGE

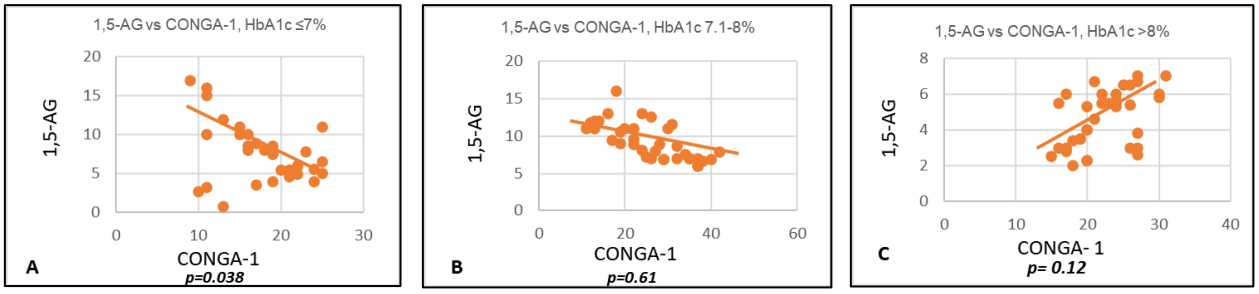

Figure 3. Pearson Correlation between 1,5-AG and CONGA-1

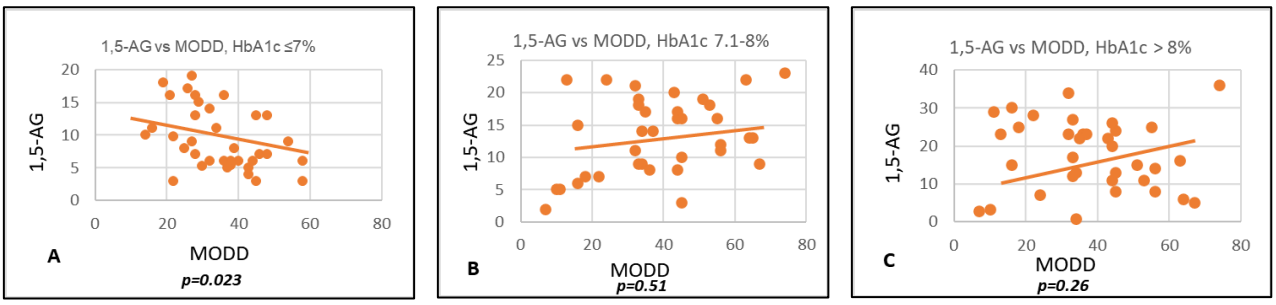

Figure 4. Pearson Correlation between 1,5-AG and MODD

coefficient of variation. Short term GV has been monitored through self-monitoring of blood glucose introduced in the late 1980s and in 1999 professional CGM was introduced.[6] Compared to SMBG, CGM provides a more comprehensive record during the day and night periods, with its interstitial glucose measurements at 5 min intervals.[15] HbA1C levels reflect blood glucose levels over that past 2-3 months, while fructosamine can be used to evaluate glycemic control over 10-14 days.[12] 1,5-AG levels in blood respond within 24h as a result of glucose's competitive inhibition of 1,5-AG reabsorption in the kidney tubule. Previous studies showed that 1,5-AG could be a marker of previous (1–2 weeks) exposure to hyperglycemia above the glucose renal threshold, reflecting post-prandial hyperglycemic peaks.[20]

Serum 1,5-AG reflects glycemic excursions, often in the postprandial state, more robustly than HbA1C or frucostasamine.[19] Hence 1,5-AG may be a useful complementary marker to HbA1c to assess glycemic control in moderately controlled patients with diabetes. In another study, namely the Atherosclerosis Risk in Communities (ARIC) study, it was shown that compared to persons with 1,5-AG ≥ 6 µg/mL without any history of diabetes, patients with a1,5-AG value of < 6.0 µg/mL had an increased risk of coronary heart disease, stroke, heart failure and death.[10]

In this study, there is a good diagnostic accuracy of 1,5-AG with both MAGE and CONGA-1. MAGE, which reflects the mean, is more useful to the clinician as it reflects average blood glucose as compared to CONGA-1 which reflects the standard deviation of the glucose levels. There was fair accuracy of MODD, which reflects inter-day glycemic variability, compared to serum 1,5-AG level. All the three metrics showed a statistically significant correlation with 1,5-AG among subjects with HbA1c ≤ 7% with no significant difference among subjects with HbA1c > 7%. There is depletion of the body pool of 1,5-AG among diabetics with elevated HbA1c due to accelerated urinary excretion thus, it may be insensitive in reflecting changes of glucose level in poorly controlled diabetic patients.[6]

Conclusion and Recommendations

Accurate measurement of glucose is vital for management of T2DM. Serum 1,5-AG assay is readily available for intermediate-term monitoring allowing patients to seek medical intervention in a timely manner. Hyperglycemic excursions increase diabetic complications as it increases glycation and activates oxidative stress hence these excursions must be detected in order to implement appropriate treatment. This study showed a good diagnostic accuracy of serum 1,5-AG levels with the different measures of glycemic variability derived from CGM namely MAGE, CONGA-1, and MODD with statistically significant correlation in patients with HbA1c level ≤ 7%. We then suggest that in patients with HbA1c ≤ 7%, serum 1,5-AG could be used as a surrogate measure of glycemic variability and excursions. As compared to CGM, 1,5-AG determination only requires a single blood extraction without the inconvenience of a device being hooked to the patient.

This cross-sectional study was conducted retrospectively thus selection bias cannot be avoided. We recommend a prospective study with a larger sample size to better control confounding factors and assess the correlation between 1,5-AG determination and CGM. Another study involving non-diabetic individuals would also be helpful to fully characterize the glycemic fluctuations among adult Filipinos.

Financial Disclosure: There are is no monetary disclosure.

Conflict of Interest: There is no conflict of interest in the publication of this manuscript.

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