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The GH-Method

Comparison of Glucose Fluctuation Ratio and Glycoalbumin to Glycated Hemoglobin Ratio for a Type 2 Diabetes Patient's Clinical Data Over Six Long Periods and Two Short Periods Based on GH-Method: Math-Physical Medicine (No. 445)

Gerald C. Hsu*

eclaireMD Foundation, USA

Abstract

For research on risk assessment of having cardiovascular disease (CVD) or dementia using the glycemic variability (GV), the author chose the glycemic fluctuations (GF) (maximum glucose minus minimum glucose) as one of the key research factors for diabetic complications. Many published medical research articles have indicated the direct connection between GF or glycoalbumin (GA) and the impact on CVD, dementia, liver cirrhosis, and even diabetic retinopathy. From energy theory, it is quite easy to understand these concepts and the associated physical phenomena since energy associated with these violent vibrated glucose waves i.e., energy with high GF, causes more damage to various human internal organs. In one of the published medical papers that he read, it was mentioned that the ratio of GA and glycated hemoglobin (HbA1C) known as the GA/A1C ratio can be used as a new biomarker to measure the magnitude of GF. However, as a 26-year patient with type 2 diabetes (T2D), no physician has ever mentioned this term to him; therefore, he researched GA and discovered that it is not a common biomarker for US diabetes patients. He believes that the concept of GA to HbA1C ratio may be difficult to understand by most physicians. In addition, the GA test is not commonly available in the US, then what is the practical value of the GA/A1C ratio? During his research, he uncovered that most papers regarding this subject were written by Japanese medical research doctors. One of the articles stated that the GA examination is quite common and easily available in Japan. At this point, he decided to continue searching for a replacement term, such as GF, which is easier to comprehend along with an appropriate equation using GF divided by eAG, where eAG is the average daily glucose. Next, he uses a small portion of GF/eAG to replace the biomarker of GA/HbA1C. Finally, he created an equation of glucose fluctuation degree where (GF/eAG * portion percentage) also known as the Hsu equation. He then verifies this Hsu equation's result against the combined GA/A1C ratios based on three published formulas by two Japanese doctors, Dr. Isoda and Dr. Inoue, to get the range of predictability and prediction accuracy. He also compares the Hsu equation result against the result of GA divided by the lab-tested A1C. The conclusive findings from this study are: (1) Equation 1 (Hsu equation = 3.3% of GF/eAG) has derived a result of 2.5 which is in the middle between the results of 2.4 from Equation 2 = (GA by formula / A1C by formula) and 2.7 from Equation 3 = (GA by formula / lab-tested A1C). This observation proves that his simple equation of (3.3% of GF/eAG) directly comes from the CGM data which offers an accurate ending result in terms of glucose vibration magnitude. (2) Regardless of the data source for HbA1C, the GA value's computational formula is not simple to understand and easily available. However, they provide an upper bound and a lower bound of the results from using the Hsu equation. From a practical viewpoint, diabetes patients have to go to a hospital, clinic, or medical laboratory in order to get their HbA1C and GA results. For patients wearing a continuous glucose monitor sensor (CGMS) device, the data can be automatically collected and analyzed. However, data collection and exhibition are one aspect (easier), while data process and data analysis are completely different matters (more difficult). That is why the author applied existing Bluetooth technology to automatically transmit his glucose data from a CGMS (at a time interval of every 5-minutes and every 15-minutes) device to the developed computer software on a smartphone and then process through his application equations to obtain various results. Furthermore, the concept of GF (glucose fluctuation magnitude between maximum and minimum) can actually offer an easier comprehension for both physicians and patients.

Keywords: Glucose; Glycoalbumin; Glycated hemoglobin; Type 2 diabetes

Abbreviations: CVD: cardiovascular disease; GV: glycemic variability; GA: glycoalbumin; HbA1C: glycated hemoglobin; eAG: estimated average glucose; CGMS: continuous glucose monitor sensor; MPM: math-physical medicine

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*Corresponding author: Gerald C. Hsu, eclaireMD Foundation, USA

1. INTRODUCTION

For research on risk assessment of having cardiovascular disease (CVD) or dementia using the glycemic variability (GV), the author chose the glycemic fluctuations (GF) (maximum glucose minus minimum glucose) as one of the key research factors for diabetic complications. Many published medical research articles have indicated the direct connection between GF or glycoalbumin (GA) and the impact on CVD, dementia, liver cirrhosis, and even diabetic retinopathy. From energy theory, it is quite easy to understand these concepts and the associated physical phenomena since energy associated with these violent vibrated glucose waves i.e., energy with high GF, causes more damage to various human internal organs.

In one of the published medical papers that he read, it was mentioned that the ratio of GA and glycated hemoglobin (HbA1C) known as the GA/A1C ratio can be used as a new biomarker to measure the magnitude of GF. However, as a 26-year patient with type 2 diabetes (T2D), no physician has ever mentioned this term to him; therefore, he researched GA and discovered that it is not a common biomarker for US diabetes patients. He believes that the concept of GA to HbA1C ratio may be difficult to understand by most physicians. In addition, the GA test is not commonly available in the US, then what is the practical value of the GA/A1C ratio? During his research, he uncovered that most papers regarding this subject were written by Japanese medical research doctors. One of the articles stated that the GA examination is quite common and easily available in Japan. At this point, he decided to continue searching for a replacement term, such as GF, which is easier to comprehend along with an appropriate equation using GF divided by eAG, where eAG is the average daily glucose. Next, he uses a small portion of GF/eAG to replace the biomarker of GA/HbA1C. Finally, he created an equation of glucose fluctuation degree where (GF/eAG * portion percentage) also known as the Hsu equation. He then verifies this Hsu equation's result against the combined GA/A1C ratios based on three published formulas by two Japanese doctors, Dr. Isoda and Dr. Inoue, to get the range of predictability and prediction accuracy. He also compares the Hsu equation result against the result of GA divided by the lab-tested A1C.

2. METHODS

2.1 MPM background

To learn more about his developed GH-method: math-physical medicine (MPM) methodology, readers can read the following three papers selected from the published 400+ medical papers.

The first paper, No. 386 describes his MPM methodology in a general conceptual format[1]. The second paper, No. 387 outlines the history of his personalized diabetes research, various application tools, and the differences between the biochemical medicine (BCM) approach vs. the MPM approach[2]. The third paper, No. 397 depicts a general flow diagram containing ~10 key MPM research methods and different tools[3].

2.2 Other GV research work

There are many available articles regarding the subject of GV; however, the author decides to include the following combined excerpt from two particular published articles[3-5]. These references cite a total of 114 published papers. In this way, readers do not have to search for key information from a long list of their cited reference articles. These papers focus on the comparison of many published GV articles and concentrate on the algorithm, method, and firmware design of a web-based app software for calculating GV values[3,4].

Here is the combined excerpt:

"Several pathophysiological mechanisms were reported, unifying the two primary mechanisms: excessive protein glycation end products and activation of oxidative stress, which causes vascular complications. Intermittent high blood glucose exposure, rather than constant exposure to high blood glucose, has been shown to have deleterious effects in experimental studies. In in-vitro experimental settings and in animal studies, glycemic fluctuations display a more deleterious effect on the parameters of CV risk, such as endothelial dysfunction. There is a significant association between GV and the increased incidence of hypoglycemia.

Hypoglycemic events may trigger inflammation by inducing the release of inflammatory cytokines. Hypoglycemia also induces increased platelet and neutrophil activation. The sympathoadrenal response during hypoglycemia increases adrenaline secretion and may induce arrhythmias and increase the cardiac workload. Underlying endothelial dysfunction leading to decreased vasodilation may contribute to CV risk. Published studies have demonstrated that GV, particularly when associated with severe hypoglycemia, could be harmful not only to people with diabetes but also to non-diabetic patients in critical care settings. Overall, the pathophysiological evidence appears to be highly suggestive of GV being an important key determinant of vascular damage. Growing evidence indicates that significant GV, particularly when accompanied by hypoglycemia, can have a harmful effect not only on the onset and progression of diabetes complications but also in clinical conditions other than diabetes treated in intensive care units (ICUs). In addition to HbA1c, GV may have a predictive value for the development of T1DM complications. In insulin-treated T2DM, the relevance of GV varies according to the heterogeneity of the disease, the presence of residual insulin secretion and insulin resistance. HbA1c is a poor predictor of hypoglycemic episodes because it only considers 8% of the likelihood of severe hypoglycemia; on the contrary, GV can account for an estimated 40% to 50% of future hypoglycemic episodes. HbA1c is a poor predictor of hypoglycemic risk, whereas GV is a strong predictor of hypoglycemic episodes. GV was an independent predictor of chronic diabetic complications, in addition to HbA1c. We should note that PPG and GV are not identical, even if they are closely related. The attention dedicated to GV is derived from the above evidence concerning its effects on oxidative stress and, from the latter, on chronic diabetes complications. Control of GV has been the focus of a number of interventional studies aimed at reducing this fluctuation. Diet and weight reduction are the first therapeutic instrument that can be used for reducing GV.

Despite the various formulas offered, simple and standard clinical tools for defining GV have yet to evolve and different indexes of GV should be used, depending on the metabolic profile of the studied population. Moreover, the absence of a uniformly accepted standard of how to estimate postprandial hyperglycemia and GV adds another challenge to this debate.

The majority of these studies have used time-averaged glucose values measured as glycosylated hemoglobin (HbA1c), an indicator of the degree of glycemic control, which is why HbA1c has become the reference parameter for therapies aimed at reducing the risk of complications from diabetes. Chronic hyperglycemia is almost universally assessed by HbA1c which has been shown to correlate closely with mean glucose levels over time, as determined by continuous glucose monitoring (CGM). However, the relative contribution of postprandial glycemic excursions and fasting to overall hyperglycemia has been the subject of considerable debate. Monnier et al. suggested that the relative contributions of fasting and postprandial glucose differ according to the level of overall glycemic control. Fasting glucose concentrations present the most important contribution to hemoglobin glycosylation, whereas at lower levels of HbA1c, the relative contribution of postprandial hyperglycemia becomes predominant. Collectively, GV is likely to be incompletely expressed by HbA1c, particularly in patients with good metabolic control.

GV is a physiological phenomenon that assumes an even more important dimension in the presence of diabetes because it not only contributes to increasing the mean blood glucose values but it also favors the development of chronic diabetes complications. It appears that GV is poised to become a future target parameter for optimum glycemic control over and above standard glycemic parameters, such as blood glucose and HbA1c. Avoiding both hyperglycemia and hypoglycemia by careful use of SMBG and the availability of new agents to correct hyperglycemia without inducing hypoglycemia is expected to reduce the burden of premature mortality and disabling CV events associated with diabetes mellitus. However, defining GV remains a challenge primarily due to the difficulty of measuring it and the lack of consensus regarding the most optimal approach for patient management.

The risk of developing diabetes-related complications is related not only to long-term

glycemic variability, but may also be related to short-term glucose variability from peaks to nadirs. Oscillating glucose concentration may exert more deleterious effects than sustained chronic hyperglycemia on endothelial function and oxidative stress, two key players in the development and progression of cardiovascular diseases in diabetes. Percentages of hyperglycemia (levels between 126 and 180 mg/dl) and hypoglycemia (levels below 70.2 mg/dl) episodes should be used in the GV related research. Mean amplitude of glycemic excursions (MAGE), together with mean and SD, is the most popular parameter for assessing glycemic variability and is calculated based on the arithmetic mean of differences between consecutive peaks and nadirs of differences greater than one SD of mean glycemia. It is designed to assess major glucose swings and exclude minor ones.

The features discouraging use of glycemic variability as a parameter in clinical practice and trials are the difficulty of interpreting numerous parameters describing this phenomenon and a limited number of computational opportunities allowing rapid calculation of glycemic variability parameters in CGM data.

The UK Prospective Diabetes Study (UKPDS) showed that after an initial improvement, glycemic control continues to deteriorate despite the use of oral agents to enhance insulin secretion and to reduce insulin resistance. This deterioration can be attributed to the progressive decline of ß-cell function. Even in subjects with well-controlled type 2 diabetes, 70% of the variability of A1C can be explained by abnormalities in postprandial glucose. Chronic sustained hyperglycemia has been shown to exert deleterious effects on the ß-cells and the vascular endothelium. Monnier et al. and Brownlee and Hirsch have recently emphasized that another component of dysglycemia, i.e., glycemic variability, is even more important than chronic sustained hyperglycemia in generating oxidative stress and contributing to the development of secondary diabetes complications. In vivo studies have convincingly demonstrated that hyperglycemic spikes induce increased production of free radicals and various mediators of inflammation, leading to dysfunction of both the vascular endothelium and the pancreatic ß-cell."

2.3 Glucose fluctuations (GF)

The concept and practice of GV have existed since the clinical usage of CGM devices to monitor severe diabetes patients and insulin treatments in hospitals. Many medical papers have been published on GV; however, there is no universally accepted formula or equation for generally accepted applications[4-6].

Defining GV remains a challenge primarily due to the difficulty of data collection with its associated data cleaning, processing, comprehension, and interpretation of the results by physicians and patients along with no consensus regarding the optimal approach for its clinical management. For example, the GV derivation involves the usage of standard deviation (SD) from statistics. Although SD is widely used, it has limitations because the assumption of measured glucose data is normally distributed (similar to a Gaussian distribution), which is typically not the case for bio-waves and medical data. Besides, many research articles use glucose data collected within a few days from hospitalized patients rather than use glucose data collected over a long period, such as years, from outpatients[7-10]. The reason is that until recently, after 2016-2017, the self-monitored blood glucose (SMBG) devices became available to diabetes out-patients to collect their own glucose data at home, instead of in the hospitals or clinic centers. However, the tasks of glucose data transfer from a CGM device to a computer and then the necessary follow-on tasks of data processing, data management, and data analysis still remain a challenge, particularly for out-patients. Due to the lack of professional training and academic knowledge in this domain, most patients and clinical physicians have encountered difficulties with these tasks. Data without careful cleaning and proper preparation would create a situation of garbage inputs resulting in garbage outputs which fits the common expression in the computer science industry of "garbage in and garbage out"[11,12].

Based on the above-mentioned theoretical and technical viewpoints, the author decided to conduct his study on just applying the basic concept of GV (i.e., glucose fluctuation between peak and nadir), and without touching certain terms or derived formulas described in some of those publications.

However, he further combines the primary characteristics of wave theory, e.g., frequency, amplitude, wavelength, and the concept of energy theory to include the estimated energy associated with the GF[13,14].

He finally decided to replace the term glycemic variability (GV) with a new term glucose fluctuation (GF) where GF equals the value of maximum glucose minus minimum glucose. Not only does the new form of GF provide a straightforward and simpler interpretation with an easy to comprehend and be applied by both physicians and patients, more importantly, it can also fully represent the true meaning of GV. The word variability can involve many ideas and various things to people[15,16].

GV can be applied on many clinical cases of greater mortality in intensive care, increased rate and risk of diabetes complications, and postprandial beta-cell dysfunction (insulin health).

2.4 Glycoalbumin/HbA1C ratio study

(1) The following is an excerpt from "Improved Monitoring of the Hyperglycemic State in Type 1 Diabetes Patients by Use of the Glycoalbumin/HbA1c Ratio" by Takatoshi Imai, et al.[17]

"Generally, the level of glycoalbumin (GA) is approximately 3 times higher than that of HbA1c. However, in type 1 diabetic patients, we often find an even higher GA/HbA1c ratio of nearly 3.5. A higher GA/HbA1c ratio may reflect a postprandial hyperglycemic state and simultaneous monitoring of GA and HbA1c may improve the management of diabetic patients.

Glycoalbumin (GA) is a glycated product of albumin, which is used as an alternative marker of glycemic control. Albumin is known to be glycated 10 times faster than hemoglobin and its half-life is 17 days. While HbA1c reflects the average glycemic state of the last 2 to 3 months, GA is considered to cover the past few weeks. Therefore, GA may be more useful than HbA1c in evaluating short-term changes in glycemic control. It is possible to measure HbA1c and GA levels in routine clinical practice in Japan (i.e. not only for diabetes patients), and it is recognized that, in general, the level of GA is about 3 times higher than that of HbA1c. However, we often find a higher GA/HbA1c ratio (nearly 3.5) in patients with type 1 diabetes. This observation is of interest because a higher than usual GA/HbA1c ratio may reflect recent fluctuations in glucose levels and indicate recently increased postprandial glucose levels. Therefore, HbA1c level alone may not be sufficient to evaluate glycemic control and the risk of diabetic complications. Of course, diabetic retinopathy is affected by various factors. But, the results suggest that patients with a higher GA/HbA1c ratio had more severe diabetic retinopathy. According to a previous report that postprandial hyperglycemia is a better predictor of diabetic retinopathy than HbA1c, GA/HbA1c ratio may reflect the postprandial glycemic state and may be a useful target for the prevention of diabetic complications, rather than HbA1c alone.

(2) The following is an excerpt from "Re-evaluation of glycated hemoglobin and glycated albumin with continuous glucose monitoring system as markers of glycemia in patients with liver cirrhosis" by Hiroshi Isoda, et al.[18]

"Liver cirrhosis (LC) is frequently accompanied by glucose intolerance. The average, maximum and minimum BG in these individuals were 142±38.7, 209.3±65.7 and 85.1±25.4 mg/dl, respectively. HbA1c was significantly correlated with average BG ($r=0.447$, $P=0.015$) and maximum BG ($r=0.523$, $P=0.004$). In addition, GA was significantly correlated with average BG ($r=0.687$, $P<0.001$) and maximum BG ($r=0.648$, $P<0.001$). Neither HbA1c nor GA was significantly correlated with minimum BG. Correlation analysis yielded formulas by which HbA1c and GA were predictive of average BG in individuals with LC: Average BG=19.2 × HbA1c (%) + 36.5 and average BG=6.6 × GA (%) + 13.0, respectively. In conclusion, HbA1c and GA showed significant correlations with average and maximum BG, as determined by CGMS. The derived formulas allow for estimates of average BG based on HbA1c and GA, and may contribute to the control of glycemia in patients with LC.

Indeed, 80% of patients with LC also exhibit abnormal glucose tolerance and 25% have been diagnosed with diabetes. Indeed, guidelines formulated by an international

expert committee composed of members of the European Association for the Study of Diabetes and the International Diabetes Federation and the American Diabetes Association have set a target HbA1c as 7%, as higher levels are associated with increased risks of cardiovascular disease and diabetic nephropathy, neuropathy and retinopathy.

Glycated albumin (GA) is another indicator of glucose metabolism. Due to fact that the half-life of albumin (ALB) (17 days) is shorter compared with that of hemoglobin (30 days), GA is a better marker of short-term BG levels. GA is regarded as a more suitable marker of average glucose level in patients with greater fluctuations of glucose, including patients with acute and transient increases in postprandial BG level and night time hypoglycemia.

These results derived from studies in which patients performed 7–8 self-monitoring blood glucose (SMBG) tests per day, with average glucose levels determined from individual, discontinuous glucose concentrations. Therefore, it remains unclear whether HbA1c and GA are inappropriate indicators of average glucose levels in patients with LC.

Continuous glucose monitoring systems (CGMS) continuously measure glucose concentrations from glucose-oxidase reactions in the interstitial space and sensors placed in subcutaneous tissue. Glucose concentrations in the interstitial space are converted to BG levels based on four daily calibrations with SMBG. Sensors in CGMS measure glucose concentration every 10 sec and record average values every 5 min, resulting in more accurate average BG levels over 24 h. Significant positive correlations between HbA1c and average glucose levels, as determined by CGMS, have been observed in patients with diabetes. To date, however, correlations between HbA1c, GA and CGMS-determined average glucose levels remain to be evaluated in patients with LC.

CGMS

Patients were equipped with a CGMS device (Medtronic miniMed, Northridge, CA, USA) and monitored for 72 h. Each CGMS device was calibrated with SMBG four times per day. After the 72 h monitoring period, all recorded data were downloaded onto a personal computer. Glucose profiles and glucose excursion parameters were evaluated with MiniMedSolutions software version 3.0 (MiniMed, Symar, CA, USA). Parameters analyzed included average, maximum and minimum BG concentrations, and the standard deviation of glucose concentration.

Predictive average BG with HbA1c and GA

Predictive average BG was calculated from HbA1c using the conversion formulas for patients with type 2 diabetes and the conversion formula between HbA1c and GA: Average BG (mg/dl)=28.7 × HbA1c (%) - 46.7 and average BG (mg/dl)=6.2 × GA (%) + 38.8. After converting HbA1c to GA using the conversion formula, the correlation between GA and average BG was confirmed.

($P<0.05$ was considered to indicate a statistically significant difference.)

Their mean HbA1c and GA was 5.54±1.12% and 19.6±4.98%, respectively. HbA1c was >6.5% in 5 patients and GA was >20 mg/dl in 11 patients. CGMS was successfully performed in all patients, and the average, maximum and minimum BGs were obtained for 72 h. The average BG was >126 mg/dl in 19 patients and the maximum BG was >200 mg/dl in 13 patients. The mean minimum BG was 85.1±25.4 mg/dl, with 9 patients having a minimum BG <70 mg/dl and were considered hypoglycemic.

Diagnostic ability of HbA1c and fasting plasma glucose (FPG) for hyperglycemia

HbA1c level and FPG level are commonly used for a diagnosis of diabetes. In order to investigate the diagnostic ability of HbA1c and FPG in the patients with LC, the present study analyzed the frequency of the patients who potentially fulfilled the diagnostic criteria of diabetes (HbA1c ≥6.5% and/or FPG ≥126 mg/dl), according to the average BG measured by CGMS. As expected, only 9.1% of the patients with average BG ≥140 mg/dl, 11.1% of the patients with average BG ≥150 mg/dl and 0% of the patients with average BG ≥ 200 mg/dl met the diagnostic criteria of diabetes (HbA1c ≥6.5% and FPG ≥126 mg/dl). As expected, HbA1c and GA correlated significantly with average BG, as determined by CGMS, with GA showing a more significant correlation with average BG compared with other glycemic parameters.

Despite these significant correlations of GA and HbA1c with average BG measured on CGMS, there were differences between the

latter and average BG calculated from formulas based on HbA1c and GA. Specifically, the formula based on HbA1c tended to underestimate and the formula based on GA tended to overestimate average BG relative to that determined by CGMS. These formulas, however, were derived from patients with type 2 diabetes. Based on the CGMS data, the present study determined more accurate formulas for calculating average BG from HbA1c [average BG=19.2 × HbA1c (%)+36.5] and GA [average BG=6.6 × GA (%)+13.0] concentrations."

(3) The following is an excerpt from "A newer conversion equation for the correlation between HbA1c and glycated albumin" by Kaori Inoue, et al.[19]

"Glycated hemoglobin (HbA1c) and glycated albumin (GA) are frequently used as glycemic control markers. These markers are influenced by either altered hemoglobin metabolism or albumin metabolism. We proposed a novel equation for accurately estimating the extrapolated HbA1c (eHbA1c) value based on the GA value.

Data sets for a total of 2461 occasions were obtained from 731 patients (including non-diabetes patients) whose HbA1c and GA values were simultaneously measured. Finally, we selected 284 data sets. We then analyzed these data sets, performed a scatter plot to examine the correlation between HbA1c and GA, and established an equation describing the resulting correlation.

Based on all the data points, the resulting equation was HbA1c = 0.216 × GA + 2.978 [R^2 = 0.5882, P < 0.001].

To evaluate glycemic control, glycated proteins are often used as glycemic control markers, rather than measuring the actual glucose levels using methods such as self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM). Among the various glycated proteins, glycated hemoglobin (HbA1c) and glycated albumin (GA) are frequently used as glycemic control markers. HbA1c is used as the gold standard index of glycemic control in clinical practice for diabetes treatment. It has been reported that these markers are closely associated with the diabetic complications. Since the lifespan of erythrocytes is approximately 120 days, HbA1c reflects the plasma glucose levels over the past few months. The metabolic turnover of albumin is faster than hemoglobin, with a lifespan of approximately 17 to 23 days. Accordingly, GA is used as an index of short-term glycemic control. For example, the GA ∶ HbA1c ratio has been suggested to be a better marker of glycemic variability than HbA1c in type 1 diabetes, especially in fulminant type 1 diabetes. Importantly, a few past studies have suggested that HbA1c is closely associated with the fasting plasma glucose level, while GA is more closely associated with the postprandial plasma glucose level, compared with the HbA1c level.

Although these glycemic control markers are well correlated with blood glucose levels, HbA1c is influenced by alterations in hemoglobin metabolism and GA is influenced by alterations in albumin metabolism.

In the present study, we intended to establish a linear regression equation describing the GA value without altered albumin metabolism versus the HbA1c value without altered hemoglobin metabolism to calculate an extrapolated HbA1c (eHbA1c) value for the accurate evaluation of glycemic control. Such an equation would enable quick decisions to be made in clinical practice regarding diabetes treatment based on a given GA value, instead of measuring HbA1c, in patients whose blood control was not stable, changeable within the short-term, or with altered hemoglobin metabolism. Many studies have reported the correlation between HbA1c and GA, but few studies have discussed this correlation in detail. Thus, we investigated the correlation between HbA1c and GA by collecting only data that had not been affected by the turnover of either HbA1c or GA and proposed a novel equation for accurately estimating eHbA1c based on the GA value.

The 284 individuals whose data were analyzed consisted of 201 men (62.5 ± 0.9 years) and 83 women (65.8 ± 1.6 years). The mean HbA1c was 7.5% ± 0.1% (men) and 7.4% ± 0.2% (women), and the mean GA was 20.9% ± 0.3% (men) and 20.9% ± 0.7% (women)."

2.5 Summary of equations regarding HbA1C, GA, and eAG

From Isoda (liver paper):
eAG = 19.2 * A1C + 36.5
eAG = 6.6 * GA + 13.0

From Inonue (conversion equation paper):
A1C = 0.216 * GA + 2.978

From Isoda and Inoue (liver paper cited Inoue):
eAG = 6.2 * GA + 38.8

From ADA:
eAG (mg/dL) = (A1C * 35.6) - 77.3
eAG (mmol/L) = (A1C * 1.98) - 4.29

3. RESULTS

3.1 Diabetes data of the patient

The author is a 74-year-old male with a 26-year history of T2D. He has not taken any diabetes medication or insulin injections since 12/8/2015. This 6-month period of 184 days was selected to reduce the result graphs generation burden. Furthermore, the 184 days covered approximately 2 full life cycles of HbA1C and about 11 half-life cycles of GA.

All of his glucose data were collected via a CMGS at 15-minute time intervals. The 15-minute model provides ~96 glucose data per day. The reason he chose 15-minute interval data instead of 5-minute interval data is due to the small difference of 0.15% between the two models within the same time period from 2/14/2020 to 4/27/2021 (15-minute eGA of 115.68 mg/dL vs. 5-minute eGA of 115.85 mg/dL). However, the data processing time for the 5-minute model would take 3x longer than the 15-minute model.

3.2 Graphic diagrams of results

Figure 1 shows the continuous glucose monitor sensor (CGMS) collected eAG and GF data for this patient. It also displays four formulas for calculating HbA1C values and three formulas for calculating GA values.

Figure 2 illustrates the graphic comparison among the values using the following three equations:

Equation 1 (average value 2.5) = 3.3% * eAG

Equation 2 (average value 2.4) = (GA by 3 formulas) / (HbA1C by 4 formulas)

Equation 3 (average value 2.7) = (GA by 3 formulas) / (lab-tested HbA1C)

The author developed a simple equation of 3.3% for GF/eAG that can describe the glucose fluctuation effectively and quickly.

4/28/21		5/5/18-11/4/18	11/5/18-5/4/19	5/5/19-11/4/19	11/5/19-5/4/20	5/5/20-11/4/20	11/5/20-4/27/21		9/20/20-12/20/20	1/20/21-4/20/21
GA / A1C Ratio Study		Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Average	Period Y20	Period Y21
	Lab A1C	6.7	6.8	6.7	6.6	6.2	6.8	6.6	6.2	6.8
	Finger A1C	6.9	6.9	6.8	6.7	6.3	6.1	6.6	6.0	6.2
	Sensor A1C	7.7	7.9	8.1	7.9	7.0	7.0	7.6	6.7	7.2
Daily averaged sensor glucose	eAG	128	129	132	128	111	116	124	107	120
GF = (Max. eAG - Min. eAG)	GF	100	95	104	96	84	96	96	85	106
	GF/eAG	78%	74%	79%	75%	76%	83%	77%	80%	89%
GA/A1C by 3.3% of GF/eAG	3.3% of GF/eAG	2.6	2.4	2.6	2.5	2.5	2.7	2.6	2.4	2.7
A1C 1 = (Sensor eAG / 17.13)	A1C by Hsu Equation	7.5	7.5	7.7	7.5	6.5	6.8	7.3	6.3	7.0
A1C 2 = (eAG+46.7)/28.7	A1C by ADA	6.1	6.1	6.2	6.1	5.5	5.7	6.0	5.4	5.8
A1C 3 = (eAG+77.3)/35.6	A1C by perinatology	5.8	5.8	5.9	5.8	5.3	5.4	5.7	5.2	5.5
A1C 4 = (eAg-36.5)/19.2	A1C by Isoda (Liver)	4.8	4.8	5.0	4.8	3.9	4.2	4.6	3.7	4.4
Avg. A1C from above 4	Avg. A1C from above 4	6.0	6.1	6.2	6.0	5.3	5.5	5.9	5.1	5.7
GA 1= (eAg-13)/6.6	GA by Isoda (Liver)	17.5	17.6	18.1	17.5	14.8	15.7	16.9	14.3	16.2
GA 2 = (Lab A1C-2.978)/0.216	GA by Inoue	17.0	17.7	17.0	16.8	14.9	17.6	16.8	14.9	17.6
GA 3 = (eAG-38.8)/6.2	GA by Isoda & Inoue	14.4	14.6	15.1	14.5	11.6	12.5	13.8	11.1	13.1
Avg. GA from above 3	Avg. GA from above 3	16.3	16.6	16.7	16.2	13.8	15.3	15.8	13.4	15.7
	Avg. A1C from above 4	6.0	6.1	6.2	6.0	5.3	5.5	5.9	5.1	5.7
	Avg. GA from above 3	16.3	16.6	16.7	16.2	13.8	15.3	15.8	13.4	15.7
GA/A1C by 3 & 4 formula	GA/A1C by 3 & 4 formula	2.7	2.7	2.7	2.7	2.6	2.8	2.7	2.6	2.8
	Lab A1C	6.7	6.8	6.7	6.6	6.2	6.8	6.6	6.2	6.8
	Avg. GA from above 3	16.3	16.6	16.7	16.2	13.8	15.3	15.8	13.4	15.7
GA/A1C by Lab	GA/A1C by Lab	2.5	2.4	2.5	2.5	2.2	2.3	2.4	2.2	2.3

Figure 1: Data table and formulas for calculating GA/A1C ratios and GF/eAG.

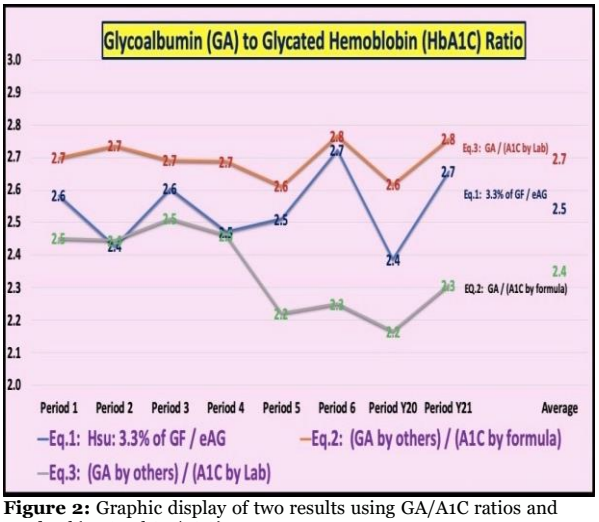

Figure 2: Graphic display of two results using GA/A1C ratios and result of (3.3% of GF/eAG).

4. CONCLUSION

The conclusive findings from this study are:

(1) Equation 1 of (Hsu equation = 3.3% of GF/eAG) has derived a result of 2.5 which is in the middle between the results of 2.4 from Equation 2 = (GA by formula / A1C by formula) and 2.7 from Equation 3 = (GA by formulas / lab-tested A1C). This observation proves that his simple equation of (3.3% of GF/eAG) directly comes from the CGM data

which offers an accurate ending result in terms of glucose vibration magnitude.

(2) Regardless of the data source for HbA1C, the GA value's computational formula is not simple to understand and easily available. However, they provide an upper bound and a lower bound of the results from using the Hsu equation.

From a practical viewpoint, diabetes patients have to go to a hospital, clinic, or medical laboratory in order to get their HbA1C and GA results. For patients wearing a CGMS device, the data can be automatically collected and analyzed. However, data collection and exhibition are one aspect (easier), while data process and data analysis are completely different matters (more difficult). That is why the author applied existing Bluetooth technology to automatically transmit his glucose data from a CGMS (at a time interval of every 5-minutes and every 15-minutes) device to the developed computer software on a smartphone and then process through his application equations to obtain various results. Furthermore, the concept of GF (glucose fluctuation magnitude between maximum and minimum) can actually offer an easier comprehension for both physicians and patients[20-22].

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Gerald C. Hsu

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