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The Contribution of Glycemic Variability or Glucose Fluctuation in Risk Probability for Various Diabetic Complications Using Three Years of Continuous Glucose Monitor Sensor Data Based on GH-Method: Math-Physical Medicine (No. 451)

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Abstract

The author utilized his collected data of finger pierced glucose (4x per day), along with data of 10 metabolism categories including 4 medical conditions and 6 lifestyle details over the period of 9 years, from 2012 to 2020, to estimate his annual risk probabilities of having a stroke, cardiovascular disease, diabetic kidney disease, diabetic retinopathy, Alzheimer's disease, and certain cancers. His research articles have been published in various medical journals. The purpose of the several risk assessment studies aimed at studying his own risk reduction rates from improvements achieved on the overall health conditions, especially type 2 diabetes. Starting from 5/5/2018, along with the finger glucose, he collected 96 data of glucose values per day for 1,095 days using a continuous glucose monitor (CGM) sensor device for a total of ~105,120 glucose data. He observed the three-year period from 5/5/2018 through 5/4/2019 that his average daily sensor glucose (124.4 mg/dL) is 12% higher than his average daily finger glucose (110.9 mg/dL. Currently, he accumulated three full years of glucose data; therefore, he has modified his input data for the glucose category. Especially, with 96 glucose data per day, he is able to study the glucose excursion easily i.e., glucose vibration, glucose oscillation, or glucose fluctuation (GF). The medical community has used the terminology of glycemic variability (GV) for glucose excursion and involved a few different but inconclusive GV equations. The author believes that variability means many things; therefore, he decided to apply the same basic concept of glucose excursion without applying the defined GV equations, in order to describe the biophysical phenomenon of glucose excursion. However, he chose GF in his diabetes research work. Furthermore, in this article, for a better viewing of wave form similarity, in addition to daily data, he uses the 90-days moving average daily glucose data, where he uses the term eAG, and his daily GF, defined as maximum glucose minus minimum glucose within a day, as his base of calculation. Many research publications cover the impact of GV on diabetic macro-vascular and micro-vascular complications. In order to include GF into the calculation, he has defined an effective eAG as follows: Effective eAG = (29% eAG + 71% GF). The weight between 71% for GF and 29% for eAG comes directly from the energy analysis results of frequency domain (FD) data which are transformed from wave analysis results of the time domain (TD) data for eAG and GF through the Fast Fourier Transform (FFT) operation. In summary, there are six key observations: (1) Over three years, the average daily GF (96 mg/dL) is 77% of the average daily eAG (124 mg/dL). However, both eAG and GF have maintained high waveform shape similarity with a high correlation coefficient of 73%. This indicates that when eAG is high, most likely GF is high as well; therefore, both eAG and GF would be out of control simultaneously. (2) After FFT operation, the ratio of both FD amplitude and total area underneath the frequency curve between eAG and GF is 71% vs. 29%. This implies that glucose excursion or GF may generate more excessive and unnecessary energy than the average glucose eAG. The bad energy associated with GF causes damage to the internal organs, including brain, heart, kidney, bladder, eyes, feet, thyroid, etc. (3) Through comparison, the author's bold definition of GF-influenced eAG equals to the combination of 29% weight from eAG and 71% weight from GF offers acceptable proof on its biophysical validity via mathematical expressions. For example, 84% correlation with his sensor HbA1C, 86% correlation with his sensor eAG and all of their peaks occurred in the second half of 2019. (4) In comparison with metabolism index (MI), his defined GF-influenced eAG has a lower yet high enough correlation of 62%, where MI's peak occurred in early 2019. This observation is due to the diabetes conditions (glucose) which are only one out of ten categories of metabolism. (5) The author takes the effective eAG to be divided by a conversion factor of 15.5 to achieve his weighted HbA1C with strong GF influence inside. He then compares this GF-influenced HbA1C against his lab-tested HbA1C and ADA defined A1C equation of (eAG+46.7)/28.7. The results show that his GF-influenced A1C has 97% prediction accuracy, while the ADA HbA1C has only 91% prediction accuracy. Both GF-influenced A1C and ADA A1C have 62% correlation with lab-tested A1C. (6) The conclusion from this study is that GF (i.e., glycemic variability) has a clear relationship and direct impact on most diabetic complications. From examining the waveform of this GF-influenced eAG, we can clearly see the risk probabilities of having diabetic complications along the time scale. For example, his risk has reached to the highest level near the end of 2019 due to his extremely busy schedule of attending many international medical conferences which brought along his higher risks of having various diabetic complications.

Keywords: Metabolism; Glycemic variability; Glucose fluctuation; Diabetic complications; Glucose

Abbreviations: CGM: continuous glucose monitor; GF: glucose fluctuation; GV: glycemic variability; FD: frequency domain; TD: time domain; FFT: Fast Fourier Transform; MI: metabolism index; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; HbA1C: glycated hemoglobin

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1. INTRODUCTION

The author utilized his collected data of finger pierced glucose (4x per day), along with data of 10 metabolism categories including 4 medical conditions and 6 lifestyle details over the period of 9 years, from 2012 to 2020, to estimate his annual risk probabilities of having a stroke, cardiovascular disease, diabetic kidney disease, diabetic retinopathy, Alzheimer's disease, and certain cancers. His research articles have been published in various medical journals. The purpose of the several risk assessment studies aimed at studying his own risk reduction rates from improvements achieved on the overall health conditions, especially type 2 diabetes[1,2].

Starting from 5/5/2018, along with the finger glucose, he collected 96 data of glucose values per day for 1,095 days using a continuous glucose monitor (CGM) sensor device for a total of ~105,120 glucose data. He observed the three-year period from 5/5/2018 through 5/4/2019 that his average daily sensor glucose (124.4 mg/dL) is 12% higher than his average daily finger glucose (110.9 mg/dL. Currently, he accumulated three full years of glucose data; therefore, he has modified his input data for the glucose category. Especially, with 96 glucose data per day, he is able to study the glucose excursion easily i.e., glucose vibration, glucose oscillation, or glucose fluctuation (GF)[3]. The medical community has used the terminology glycemic variability (GV) for glucose excursion and involved a few different but inconclusive GV equations. The author believes that variability means many things; therefore, he decided to apply the same basic concept of glucose excursion without applying the defined GV equations, in order to describe the biophysical phenomenon of glucose excursion. However, he chose GF in his diabetes research work. Furthermore, in this article, for a better viewing of wave form similarity, in addition to daily data, he uses the 90-days moving average daily glucose data, where he uses the term eAG, and his daily GF, defined as maximum glucose minus minimum glucose within a day, as his base of calculation[4-6].

Many research publications cover the impact of GV on diabetic macro-vascular and micro-vascular complications. In order to include GF into the calculation, he has defined an effective eAG as follows:

Effective eAG = (29% eAG + 71% GF)

The weight between 71% for GF and 29% for eAG comes directly from the energy analysis results of frequency domain (FD) data which are transformed from wave analysis results of the time domain (TD) data for eAG and GF through the Fast Fourier Transform (FFT) operation.

2. METHODS

2.1 Glucose and HbA1C

Using signal processing techniques, the author identified approximately 20 influential factors of physical behaviors for glucose. From these 20 factors, he further outlined the following six most prominent conclusions for his glucose and HbA1C values:

(1) The CGM sensor based A1C variances have the following contributions: 29% from fasting plasma glucose (FPG), 38% from postprandial plasma glucose (PPG), and 33% from between meals and pre-bedtime periods. Therefore, all of the three segments contributed to HbA1C value almost equally.

(2) FPG variance due to weight change with ~77% contribution.

(3) Colder weather impact on FPG with a decrease of each Fahrenheit degree caused 0.3 mg/dL decrease of FPG.

(4) PPG variance due to carbs/sugar intake with ~39% weighted contribution on PPG.

(5) PPG variance due to post-meal walking with ~41% weighted contribution on PPG.

(6) Warm weather impact on PPG with an increase of each Fahrenheit degree caused 0.9 mg/dL increase of PPG[7-10].

It is common knowledge that HbA1C is closely connected to the average glucose for the past 90 days. Actually, the average human red blood cells (RBC), after differentiating from erythroblasts in the bone marrow, are released into the blood and

survive in circulation for approximately 115 days. He has adopted the 120-days model in his previous sensor HbA1C studies, but he uses the 90-days model in this particular study. It should also be pointed out that, he has used the CGM collected sensor glucose and calculated the HbA1C to compare against his collected nine lab-tested HbA1C data, while the lab A1C data contained a large margin of error due to various reasons[11-15].

2.2 GF and diabetic complications

The following are excerpts from references[16,17]:

"From reference 16: Diabetes mellitus is a world-wide health issue with potential for significant negative health outcomes, including microvascular and macrovascular complications. The relationship of hemoglobin HbA1c and other glycosylation end products (AGEs) to these complications, particularly microvascular disease, is well understood. More recent evidence suggests that glycemic variability may be associated with diabetes macrovascular complications. As HbA1c is better representative of average glucose levels and does not account as well for glycemic variability, hence new methods to assess and treat this variability is needed to reduce incidence of complications.

From reference 17: Few physicians recognized that only 6.6% of the variation in risk of retinopathy for the entire study cohort was explained by the difference in the treatment groups, although it was widely appreciated that nearly all of this treatment group effect was explained by differences in the mean level of HbA1C over time. The trial results also considered the instantaneous risk of retinopathy (i.e., whether a patient would develop retinopathy at a particular point in time during the study) rather than eventual risk of retinopathy (whether a patient would develop retinopathy over his or her entire life). However, this latter outcome is not feasible to study because it would require lifetime follow-up of patients.

Similarly, HbA1C and duration of diabetes (glycemic exposure) explained only about 11% of the variation in retinopathy risk for the entire study population, suggesting that the remaining 89% of the variation in risk is presumably explained by other factors independent of HbA1C. Given the magnitude of the effect of unmeasured elements in the Diabetes Control and Complications Trial, identification of these elements is critically important for designing more effective therapy for type 1 diabetes.

What factors not captured by HbA1C measurements might explain the remaining 89% of microvascular complications risk? Possible factors unrelated to blood glucose levels include genetics, environmental toxins, and metabolic consequences of abnormal insulinization such as increased free fatty acid levels. Possible factors related to blood glucose levels most likely reflect the fact that since HbA1c represents the time-averaged mean level of glycemia, it provides no information about how closely the fluctuations of blood glucose levels around that mean mimic the normal narrow range of blood glucose excursion. In addition, patients with identical HbA1C values differ significantly in amplitude and duration of glycemic spikes."

2.3 GF-influenced eAG study

In this study, he applied the following procedures to calculate and analyze GF-influenced risk of diabetic complications:

(1) He collects his daily average CGM sensor glucose and calculates where he uses the abbreviation eAG and average glucose fluctuation (maximum glucose minus minimum glucose) with the abbreviation GF.

(2) Using FFT operation, he transforms his TD waves into FD waves. He then calculates the ratio of either FD y-axis amplitude or total area underneath the FD curve between eAG and GF. He identified the spilt as 71% for GF and 29% for eAG.

(3) He then uses the following GF-influenced eAG equation:
GF-influenced eAG = (0.29*eAG + 0.71*GF)

(4) He compares the data and waveform of this GF-influenced eAG against his collected sensor eAG, sensor A1C, and MI.

(5) Using his collected 9 lab-tested HbA1C data, he selects 9 HbA1C values from using his calculated GF-influenced A1C data and the ADA A1C equation derived data. Through the comparison from these three datasets, he

calculates the prediction accuracies and correlation coefficients.

3. RESULTS

The left diagram in Figure 1 shows the original input data of both eAG and GF from the CGM sensor collected dataset, while the right diagram reflects the FFT converted FD waveforms. Over three years, the average daily GF (96 mg/dL) is 77% of the average daily eAG (124 mg/dL); however, both eAG and GF have maintained high waveform shape similarity with a high correlation coefficient of 73%. This indicates that when eAG is high, most likely GF is high as well, where eAG and GF would be out of control simultaneously.

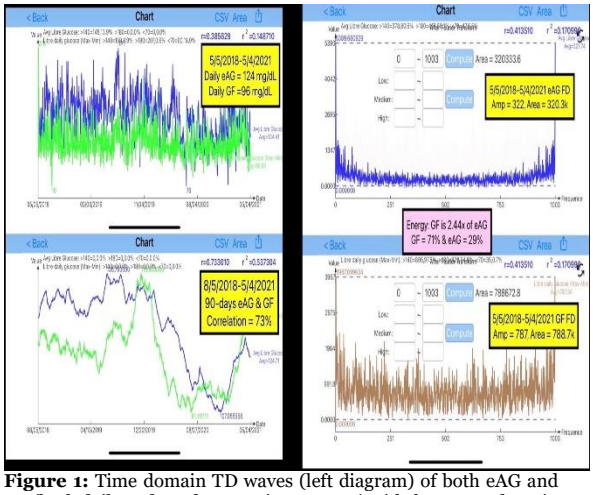

Figure 1: Time domain TD waves (left diagram) of both eAG and GF (both daily and 90-days moving average) with frequency domain FD waves (right diagram) showing both FD amplitude and FD area split ratio of 79% GF vs. 21% eAG.

After the FFT operation, the ratio of FD amplitude and total area underneath the frequency curve between eAG and GF is 71% vs. 29%. This signifies that glucose excursion or GF may generate more excessive and unnecessary energy than the average glucose eAG. The bad energy associated with GF causes damage to the internal organs, including brain, heart, kidney, bladder, eyes, feet, thyroid, etc.

The right diagram in Figure 2 reveals the equation and curve of GF-influenced eAG, while the left diagram is the comparison of GF-influenced eAG against sensor eAG, sensor A1C, and metabolism index (MI).

Through comparison, the author's defined GF-influenced eAG which includes 29% contribution from eAG and 71% contribution from GF offers the needed biophysical validity via mathematical operations. For example, 84% correlation with his sensor HbA1C and 86% correlation with his sensor eAG, where all of the peaks occurred in the second half of 2019. In comparison with the MI, his defined GF-influenced eAG has a less yet high enough correlation coefficient of 62%, where MI's peak occurred in early 2019. This different peak occurrence time is due to diabetes being only one of ten categories in his metabolism definition.

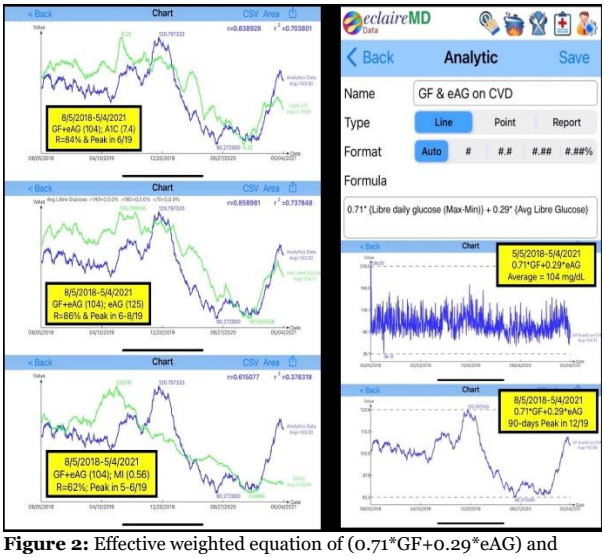

Figure 2: Effective weighted equation of (0.71*GF+0.29*eAG) and shape similarity comparisons vs. sensor A1C, sensor eAG, and metabolism index (left diagram) during period of 8/5/2018-5/4/2021.

Figure 3 depicts the HbA1C comparison between the lab-tested A1C vs. the following two HbA1C equations in the 9 lab-test dates:

(1) Predicted HbA1C = (29% eAG + 71% GF) / 15.5

(2) ADA defined A1C = (eAG + 46.7) / 28

He divides his GF-influenced eAG by a conversion factor of 15.5 in order to achieve a near-perfect match with his lab-tested average A1C value. He then compares this GF-influenced HbA1C against his lab-tested HbA1C and the ADA defined A1C equation of (eAG+46.7)/28.7. The results show that his GF-influenced A1C has 97% of prediction accuracy while the ADA HbA1C has only 91% of prediction accuracy. Both the GF-influenced A1C and ADA A1C have 62% of correlation with lab-tested A1C.

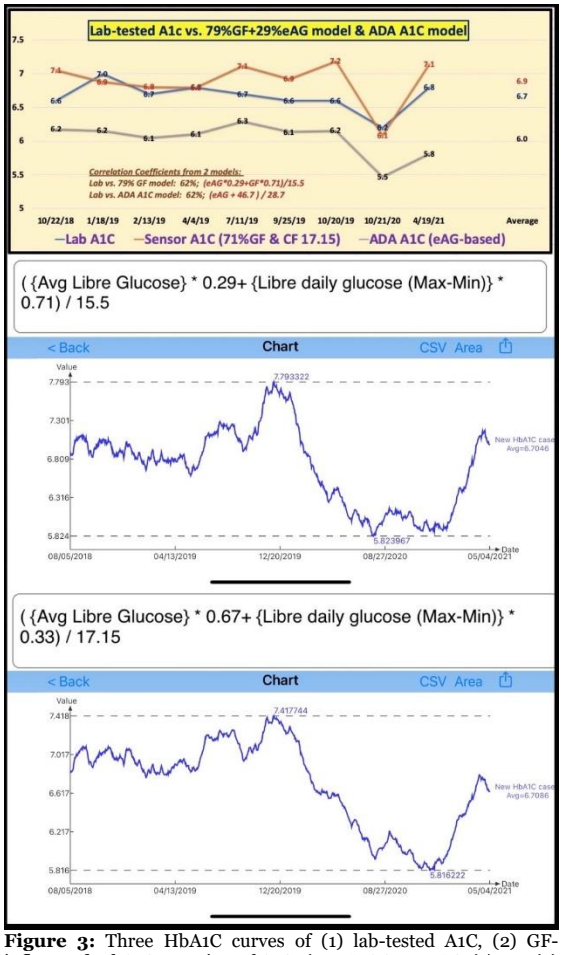

Figure 3: Three HbA1C curves of (1) lab-tested A1C, (2) GF-influenced HbA1C equation of A1C=(0.29*eAG+0.72*GF)/15.5, (3) ADA defined equation A1C=(eAG+46.7)/28.7.

4. CONCLUSION

In summary, there are six key observations:

(1) Over three years, the average daily GF (96 mg/dL) is 77% of the average daily eAG (124 mg/dL). However, both eAG and GF have maintained high waveform shape similarity with a high correlation coefficient of 73%. This indicates that when eAG is high, most likely GF is high as well; therefore, both eAG and GF would be out of control simultaneously.

(2) After FFT operation, the ratio of both FD amplitude and total area underneath the frequency curve between eAG and GF is 71% vs. 29%. This implies that glucose excursion or GF may generate more excessive and unnecessary energy than the average glucose eAG. The bad energy associated with GF causes damage to the internal organs, including brain, heart, kidney, bladder, eyes, feet, thyroid, etc.

(3) Through comparison, the author's bold definition of GF-influenced eAG equals to the combination of 29% weight from eAG and 71% weight from GF offers acceptable proof on its biophysical validity via mathematical expressions. For example, 84% correlation with his sensor HbA1C, 86% correlation with his sensor eAG, and all of their peaks occurred in the second half of 2019.

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(5) The author takes the effective eAG to be divided by a conversion factor of 15.5 to achieve his weighted HbA1C with strong GF influence inside. He then compares this GF-influenced HbA1C against his lab-tested HbA1C and ADA defined A1C equation of (eAG+46.7)/28.7. The results show that his GF-influenced A1C has 97% prediction accuracy, while the ADA HbA1C has only 91% prediction accuracy. Both GF-influenced A1C and ADA A1C have 62% correlation with lab-tested A1C.

(6) The conclusion from this study is that GF (i.e., glycemic variability) has a clear relationship and direct impact on most diabetic complications. From examining the waveform of this GF-influenced eAG, we can clearly see the risk probabilities of having diabetic complications along the time scale. For example, his risk has reached to the highest level near the end of 2019 due to his extremely busy schedule of attending many international medical conferences which brought along his higher risks of having various diabetic complications.

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