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Research Article

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Comparison of Waves and Energies between the 3-Hours Versus 24-Hours of Glucose Fluctuation using 3+ Years of Continuous Glucose Monitoring Sensor Device Collected Data Based on GH-Method: Math-Physical Medicine (No. 457)

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Abstract

Since 2017, the author utilized his collected data of finger pierced glucoses 4x per day, along with the data of 10 metabolism index (MI) categories including 4 medical conditions and 6 lifestyle details over a 9.5-year period, from 2012 to 2021, to estimate his risk probabilities of having diabetic complications. They include macro-vascular and micro-vascular diseases such as cardiovascular disease, stroke, diabetic kidney disease, diabetic retinopathy, foot ulcer, Alzheimer's disease, and certain cancers. In addition to the mean value of glucoses, namely the average glucose such as HbA1C, the actual glucose excursion or glucose fluctuation (GF) has noticeable influences on these diabetic complications.

Starting from 5/5/2018, along with the finger glucoses, he collected 96 data of glucose values per day for 1,120 days using a continuous glucose monitoring (CGM) sensor device for a total of 107,520 glucose data. Thus far, he has accumulated 3+ years of sensor glucose data; therefore, he would like to enhance his medical research work by using them. Especially with 96 glucose data collected per day, he is now able to easily study the phenomenon of glucose excursion, glucose wave vibration, or glucose data oscillation. The medical community has used the term "glycemic variability (GV)" to describe the glucose excursion which involves several defined GV equations with some inconclusive findings. The author believes that the word "variability" could mean many things; therefore, he decided to apply the same basic concept of glucose excursion or GF without using the other defined GV equations in order to deeply understand and precisely describe the basic biophysical phenomenon of "glucose excursion".

The author has been utilizing glucose fluctuation known as "Daily GF or 24-hour GF" over a 24-hour period in his research work each day. The definition of GF is the maximum glucose (usually around 60-minutes after a meal) minus the minimum glucose (usually around 3am to 4am during sleep) within 24-hours or another selected time period. Recently, he noticed the extremely high and extremely low glucoses frequently occurring within a shorter duration of 3 hours. Therefore, he has inserted a new algorithm of computation into his software program to dynamically calculate the difference between the maximum glucose and the minimum glucose within the moving duration of 3 hours, at15-minute increments throughout the day. By the end of a day, the largest number of GF, which is defined as 3-hour GF, is selected and stored on the cloud server.

Furthermore, to obtain a better view of the glucose waveform shape's similarity, he utilizes the 90-days moving average of daily glucose which is named as eAG, along with the 24-hour GF, and daily 3-hour GF to serve as the basis of his analysis.

Many research publications have covered the importance and impact of GV or GF on diabetic macro-vascular and micro-vascular complications (References 16 and 17). In those publications, it has defined and also "qualitatively proven" that GF does impact the macro-vascular system, including the heart and brain, and micro-vascular system such as kidneys, feet, eyes, nerves, etc. This article offers some quantitative proof of GF impact on the risk of having diabetic complications. It also investigates the insignificant difference between 24-hour daily GF and 3-hour GF.

There are 4 developed equations of predicted HbA1C and used for subsequent calculations and presentation of results:

Finger A1C= finger eAG / 16.79

Sensor A1C-2= sensor eAG / 18.86

24-hour A1C-1= (sensor eAG * 0.29 + 24-hour GF * 0.71) / 15.75

3-hour A1C-1= (sensor eAG * 0.29 + 24-hour GF * 0.71) / 14.0

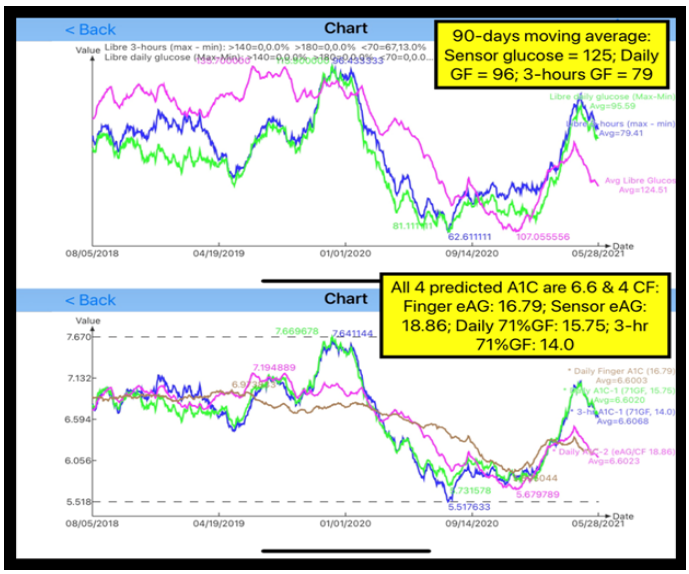
The above four HbA1C equations provide identical predicted A1C results of ~6.6% which is consistent with the average value in his previous 12 lab-tested A1C results from a ~3-year period from 5/5/2018 to 5/28/2021. Of course, the 4 conversion factors (4 different denominators in 4 A1C equations) comprise and contribute to the HbA1C prediction accuracy. Other than the 2 equations using finger eAG and sensor eAG, which are based on the common knowledge of HbA1C related to the average glucose values over the past 90 to 120 days period. He also makes a bold action of including the GF factor into his HbA1C estimations. The weight factors of 71% for GF and 29% for eAG are actually based on his glucose energy analysis results.

In summary, with four appropriate conversion factors (16.79, 18.86, 15.75, 14.0) and reasonable split between two weighing factors for GF (71%) and eAG (29%), his 4 defined HbA1C equations have yielded almost identical result of ~6.6, where his lab-tested results are 6.6%.

In addition, his finger eAG curve and sensor eAG curve have an extremely high correlation of 93%; likewise, his 3-hour A1C curve and 24-hour A1C curve also have an extremely high correlation of 98%. However, the waveform of A1C equations involving GF factor is more violent, higher wave oscillation, than the two equations using eAG only. This observation also explains why the mean value of a curve or dataset, such as HbA1C, does not reflect the true characteristics of wave vibration, such as GF.

The contribution of GF on a diabetes patient's complications is mentioned ***qualitatively*** in various published medical literature. However, the author could not locate any ***quantitative*** proof of the GF's contribution or involvement in diabetes and its complications. Therefore, he inserts the GF factor into his predicted HbA1C formulas using the split weighting factors based on associated energy ratios of eAG (29%) versus GF (71%).

From this article, it seems that the difference between the 24-hour GF and 3-hour GF is not as significant. Nevertheless, as a medical research scientist, he must examine all meaningful viewpoints and try varying approaches to pursue his research to understand GF more in depth. In general, the 3-hour GF and 24-hour GF are quite similar except for their average values which are different. The 24-hour average GF amplitude is 96 mg/dL which is similar to most people and its associated energy is 859, while the 3-hour average GF is 80 mg/dL and its associated energy is 821. These data provide a 20% difference of average glucose amplitude and a 5% difference of glucose associated energy level. However, in both time domain (TD) and frequency domain (FD), their correlations are extremely high from 84% to 96% for the 3-hour GF versus 24-hour GF.



Introduction

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at15-minute increments throughout the day. By the end of a day, the largest number of GF, which is defined as ***3-hour GF***, is selected and stored on the cloud server.

Furthermore, to obtain a better view of the glucose waveform shape's similarity, he utilizes the 90-days moving average of daily glucose which is named as ***eAG***, along with the ***24-hour GF***, and ***daily 3-hour GF*** to serve as the basis of his analysis.

Method

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 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.

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. Although the author has adopted a 120-days model in his previous sensor HbA1C studies, he uses the 90-days model in this particular study. It should also be pointed out that he utilized the CGM collected sensor glucose and calculated HbA1C to compare against his collected nine lab-tested HbA1C data, while the lab A1C data actually contained a large margin of error due to various reasons.

GF and Diabetic Complications

The following are excerpts from references 16 and 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."***

Glucose Fluctuation (GF)

Another excerpt regarding glucose and glucose fluctuation from reference 19 is listed below:

"A variety of stimulations and mechanisms tightly regulates blood sugar levels. This is important for metabolic homeostasis. Levels may fluctuate after fasting for long periods of time or an hour or two after food consumption. Despite this, the fluctuations are minor. Normal human blood glucose levels remain within a remarkably narrow range.

Blood Sugar Fluctuations

In most humans, this varies from about 82 mg/dl to 110 mg/dl (4.4 to 6.1 mmol/l) and the author takes the averaged glucose fluctuation from the mid-point value of 96 mg/dL. The blood sugar levels rise to nearly 140 mg/dl (7.8 mmol/l) or a bit more in normal humans after a full meal. In humans, normal blood glucose levels are around 90 mg/dl, equivalent to 5mM (mmol/l). Since the molecular weight of glucose, C6H12O6, is about 180 g/mol, when calculated, the total amount of glucose normally in circulating human blood is around 3.3 to 7g (assuming an ordinary adult blood volume of 5 liters)."

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 4 predicted HbA1C equations using GF and eAG:

4 predicted HbA1C results (~6.6) and 2 correlation coefficients: R=93% of finger eAG vs. sensor eAG with R=98% of 3-hour GF vs. 24-hour GF (4). He compares the data and waveform with GF-influenced and without GF-influenced HbA1C results against his lab-tested HA1C.

Results

Figure 1 shows the Time-domain (TD) glucose data and 90-days moving average glucose curve with frequency domain (FD) data chart of eAG, 24-hour GF, and 3-hour GF over an ~3-year period from 5/5/2018 to 5/28/2021.

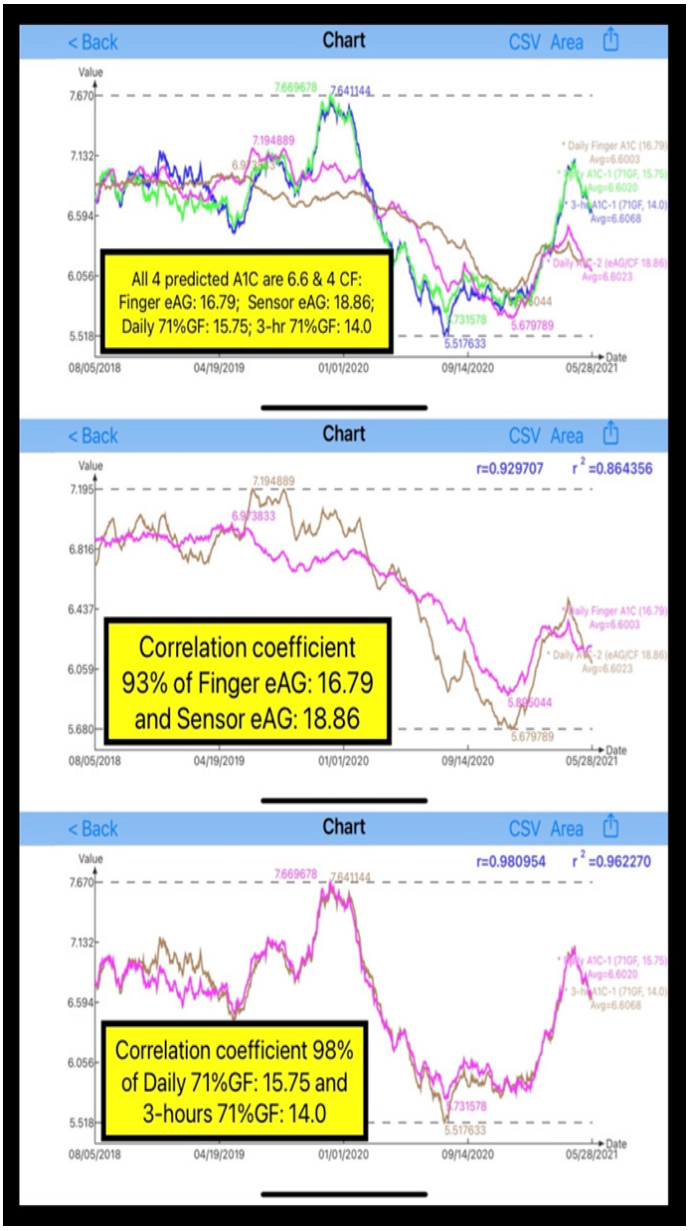
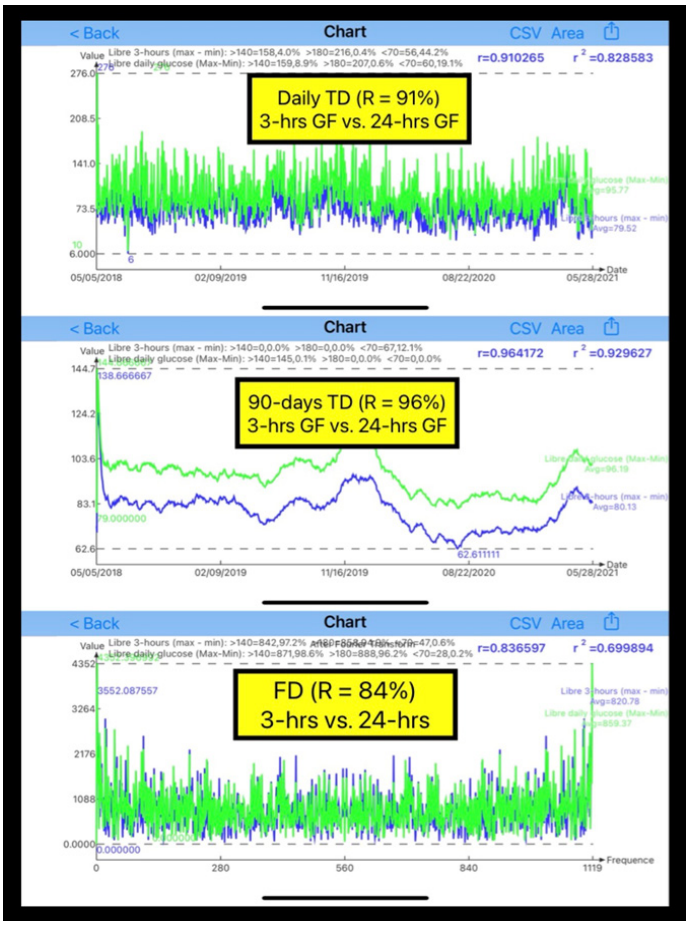


Figure 1: Time-domain (TD) data and 90-days moving average curve with frequency domain (FD) data of eAG, 24-hour GF and 3-hour GF

Daily eAG = 124 mg/dL
24-hour GF = 96 mg/dL
3-hour GF = 80 mg/dL
eAG energy = 341 (28-29%)
24-hr GF energy = 859 (72%)
3-hr GF energy = 821 (71%)

Figure 2 depicts 4 almost identical predicted HbA1C results at ~6.6%; and the following 2 extremely high correlation coefficients:



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The contribution factors (CF) used in the following 4 predicted A1C equations are:

Finger A1C: 16.79
Sensor A1C-2: 18.86
24-hour A1C-1: 15.75
3-hour A1C-1: 14.0

Figure 3 reflects the *Comparison between 3-hour GF and 24-hour GF in both TD and FD*. The moving average GF curves for the 3-hour and 24-hour have highly similar (96%) waveform shapes. Even in the daily GF data of TD, it has shown an extremely high 91% of correlation, and in the individual frequency components of FD, it a high 84% of correlation.

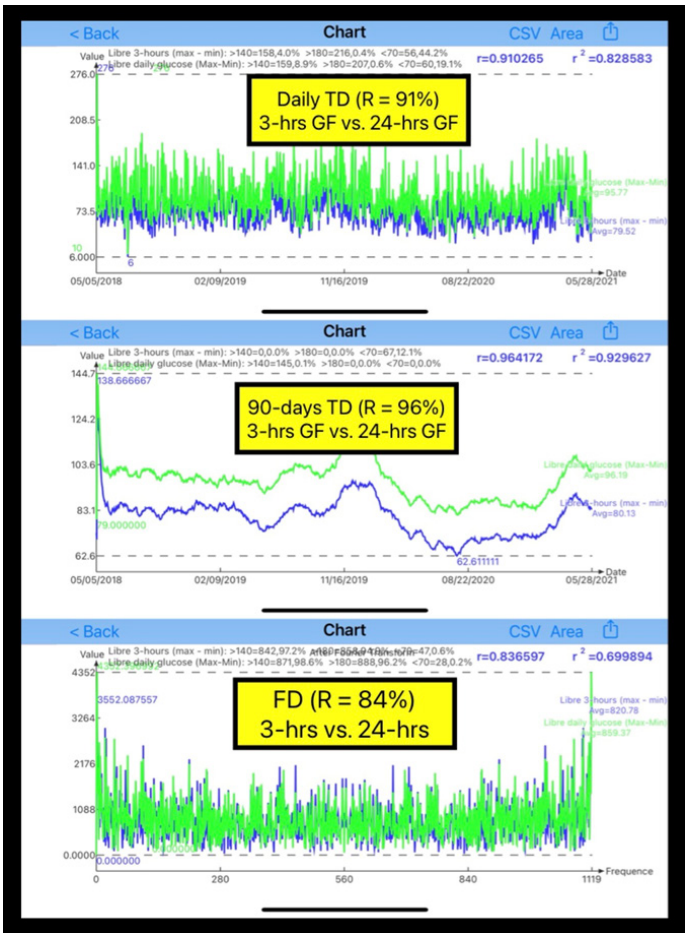

Figure 3: Comparison between 3-hour GF and 24-hour GF in both TD and FD

In Figure 4, the upper chart illustrates the composite diagrams of 90-days moving average curves of eAG, 3-hour GF, and 24-hour GF; whereas the lower chart reveals the composite diagrams of 4 predicted HbA1C curves of finger eAG, sensor eAG, 3-hours GF, and 24-hours GF (lower diagram)

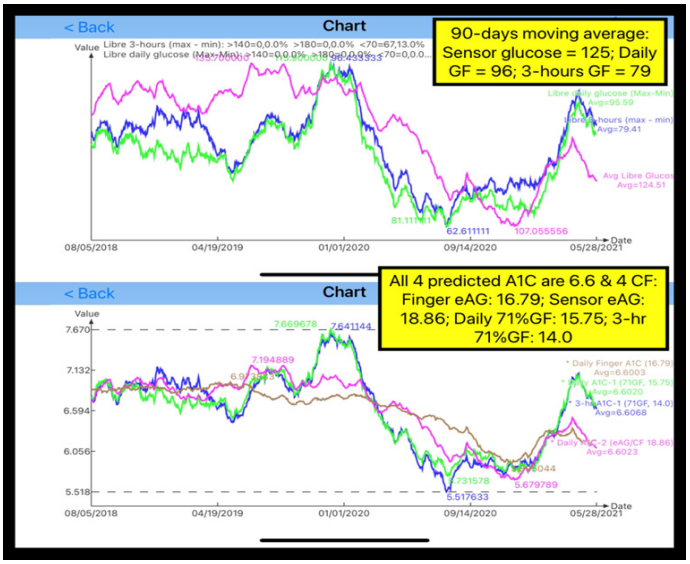

Figure 4: Composite diagrams of 90-days moving average curves of eAG, 3-hour GF, and 24-hour GF (upper diagram) along with 4 predicted HbA1C curves of finger eAG, sensor

Conclusion

Many research publications have covered the importance and impact of GV or GF on diabetic macro-vascular and micro-vascular complications (References 16 and 17). In those publications, it has defined and also "***qualitatively*** proven" that GF does impact the macro-vascular system, including the heart and brain, and micro-vascular system such as kidneys, feet, eyes, nerves, etc. This article offers some ***quantitative*** proof of GF impact on the risk of having diabetic complications. It also investigates the insignificant difference between 24-hour daily GF and 3-hour GF.

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