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Research Article

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Quantification of the CVD/Stroke Risk Probability Due to the Extra Input of an Adjustment Factor of Glycemic Variability or Glucose Fluctuation Using Three Years of the Continuous Glucose Monitoring Sensor Device Collected Data Based on GH-Method: Math-Physical Medicine (No. 456)

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Abstract

Since 2017, the author utilized his collected data of finger pierced glucoses 4x per day, along with data of 10 metabolism index (MI) categories including 4 medical conditions and 6 lifestyle details over the period of 9.5 years, from 2012 to 2021. This is to estimate his annual risk probabilities of having a stroke, cardiovascular disease, diabetic kidney disease, diabetic retinopathy, Alzheimer's disease, and certain cancers. Most of his research articles using the MI model have been published in various medical journals. The purpose of his previous risk assessment studies were aimed at determining his own risk reduction rates from improvements achieved to overall health conditions and MI, since he is a severe diabetes patient.

Starting on 5/5/2018, along with the finger glucoses, he collects 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. Currently, he has accumulated 3+ years of sensor glucose data; therefore, he has enhanced his research work using his collected sensor glucose data.

Especially with 96 glucose data per day, he is now able to study the phenomenon of glucose excursion easily i.e., glucose fluctuation (GF), vibration, or oscillation. The medical community has used the term glycemic variability (GV) to describe glucose excursion involving various defined GV equations which have produced somewhat inconclusive statements. The author believes that the word "variability" could mean many things; therefore, he decided to apply the same basic concept of glucose excursion without the other defined GV equations, in order to deeply understand and precisely describe the basic biophysical phenomenon of "glucose excursion" using GF. Furthermore, in this article, to better view waveform similarity, in addition to daily data, he utilizes the 90-days moving average daily glucose known as "eAG", and his daily GF, defined as the maximum glucose minus the minimum glucose within a day, as the basis of his analysis.

Many research publications have covered the importance and impact of GV on diabetic macro-vascular and micro-vascular complications (References 16 and 17). In those publications, it has been defined and "***qualitatively*** proven" that GF does impact both macro-vascular system such as heart and brain and micro-vascular system involving the kidneys, feet, eyes, nerves, etc. This article offers some ***quantitative*** proof of GF impact on the risk of having a CVD/Stroke.

In order to include GF into the calculation of CVD risk probability, the author first created a simple equation of CVD risk adjustment through an amplification factor (+ or - value) which is defined as follows:

GF Adjustment Equation
GF % =(eAG+(GF-95.59))/eAG

The value of "GF-95.59" could be either positive or negative depending on whether the daily GF value is either higher or lower than 95.59 mg/dL which is his average GF value over 3-years (5/5/2018 - 5/4/2021). In Reference No. 19, ***"In most humans, the glucose varies from about 82 mg/dl to 110 mg/dL, and the mid-point GF value is around 96 mg/dL".*** In other words, the author's average GF value happens to be in line with "most of other humans".

Finally, he calculates his risk probability of having a "CVD/

Stroke from MI plus GF" by multiplying the existing "CVD from MI" with this "GF adjustment factor".

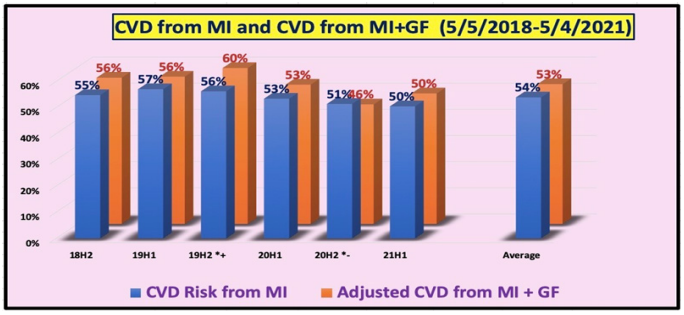
Over the past 3-years with 6-months sub-periods, the author's average risk probability of having a CVD/Stroke when including the GF factor would be ~1% lower than excluding the GF factor i.e., CVD risk using MI only.

Specifically, the three sub-periods are worthy of additional research for their causes. In the sub-period of 19H2 (5/5/2019 - 11/4/2019), the CVD risk with GF is 4% higher than without GF. This was due to his lifestyle of frequent business travel to attend many international conferences which not only raised the sensor eAG but increased his GF noticeably.

During the sub-period of 20H2 (5/5/2020 - 11/4/2020), the CVD risk with GF is 5% lower than without GF. This was due to his quiet and peaceful lifestyle during COVID-19 quarantine, which not only reduced his sensor eAG but also decreased his GF significantly.

The most recent sub-period of 21H1 (11/5/2020 - 5/4/2021) is valuable to investigate as well. Although his CVD risk from MI was reduced by 1% from 51% in 20H2 (5/5/2020 - 11/4/2020) down to 50% in 21H1 due to his overall improvement on his MI, he began conducting various food and meal experiments on his body which increased the GF values.

In summary, the glucose fluctuation element or GF contributes to some degree on the risk of having a CVD or Stroke i.e., macro-vascular diseases. This article provides quantitative proof on this specific cardiology subject.



Introduction

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Finally, he calculates his risk probability of having a "CVD/Stroke from MI plus GF" by multiplying the existing "CVD from MI" with this "GF adjustment factor".

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 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.

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). *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 72% for GF and 28% for eAG.
3. He then uses the following GF-influenced eAG equation:

GF-influenced eAG = (0.28*eAG + 0.72*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.
6. The above-described GF-influence HbA1C equation is acceptable in analyzing diabetes; however, he needs to delve deeper when researching major diabetic complications such as CVD or stroke. He needs to decouple GF from the concept of "mean values" such as HA1C or modified HbA1C formula. This investigation led him to this research article.

Results

In Figure 1, the upper diagram shows the Equation of GF Adjustment amplification/reduction factor on CVD/stroke risk assessment:

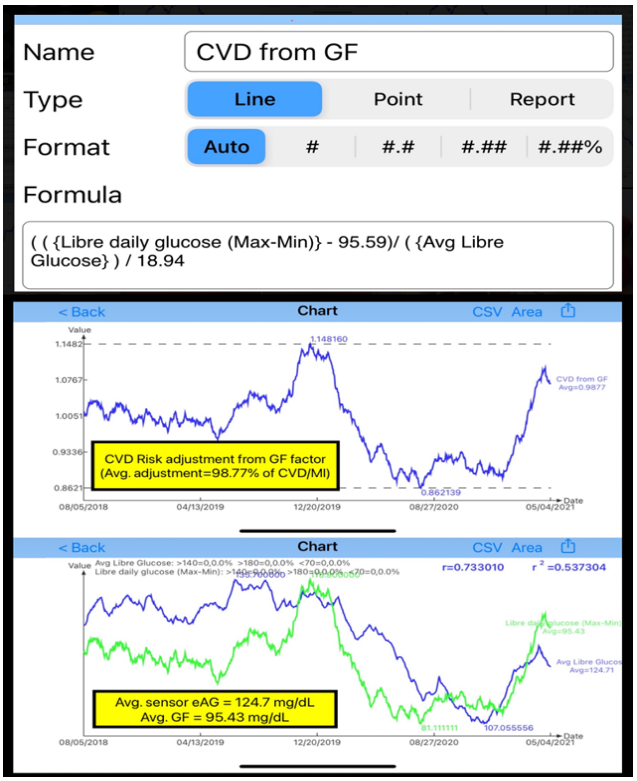

Figure 1: Equation and 3-year curve of adjusted GF on CVD risk, and sensor eAG, GF from 5/5/2018 to 5/4/2021

CVD risk change due to GF factor
= ((Sensor GF - 95.59) / Sensor eAG) / 18.94

The middle diagram reveals the range of GF adjustments within the range of 86% to 115% with an average value of 98.77%. Any percentage higher than 100% is an amplification effect and lower than 100% is a reduction effect from the original calculated CVD/Stroke risk using MI only.

The lower diagram reflects his average eAG as 125 mg/dL and GF as 95 mg/dL, which provides some fundamental information for this analysis work.

Figure 2 depicts the average GF adjustment percentage on CVD/Stroke risk of the 6-months sub-periods. As stated previously, when a sub-period's percentage is higher than 100%, then it is an amplification effect. When it is lower than 100%, then it is a reduction effect from the original calculated CVD/Stroke risk using MI only (without GF).

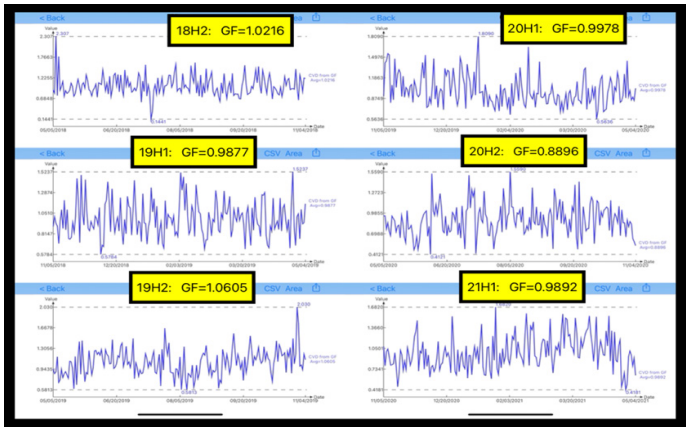

Figure 2: Calculated GF adjustment factor on CVD/Stroke risk probabilities of six half-year period during 5/5/2018-5/4/2021

18H2: GF % = 102%
19H1: GF % = 99%
19H2: GF % = 106%
20H1: GF % = 100%
20H2: GF % = 89%
21H1: GF % = 99%

This percentage table has dictated the moving trend of CVD/Stroke risk including GF factor.

Figure 3 illustrates the data table of the "GF adjustment equation":

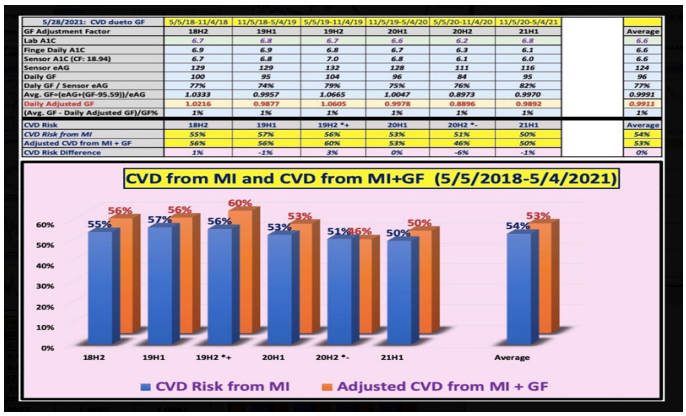

Figure 3: Data table of "GF adjustment equation": GF % =(eAG+(GF-95.59))/eAG, and differences between CVD risk from MI vs. CVD risk from MI+GF

GF % =(eAG+(GF-95.59))/eAG

It also shows the graphic differences between the CVD risk from MI (without GF) vs. CVD risk from MI+GF (with GF). The detailed explanation of this conclusive figure can be found in conclusion section.

Conclusion

Over the past 3-years with 6-months sub-periods, the author's average risk probability of having a CVD/Stroke when including the GF factor would be ~1% lower than excluding the GF factor i.e., CVD risk using MI only.

Specifically, the three sub-periods are worthy of additional research for their causes. In the sub-period of 19H2 (5/5/2019 - 11/4/2019), the CVD risk with GF is 4% higher than without GF. This was due to his lifestyle of frequent business travel to attend many international conferences which not only raised the sensor eAG but increased his GF noticeably.

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