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Application of Perturbation Theory on Risk Assessments in Predicting Coronary Vascular Disease, Chronic Kidney Disease, and Diabetic Retinopathy using a Perturbation Factor of Combined Metabolism Index & Glucose Fluctuation over a Period of 11.5 years based on GH-Method: Math-Physical Medicine (No. 481)

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Abstract

Recently, the author read an article published in the journal of Cardiovascular Diabetologist on July 4, 2020, and selected the following excerpt:

"Although Glycemic variability (GV) remains yet no consensus, accumulating evidence has suggested that GV, representing either short-term (with-day and between-day variability) or long-term GV, was associated with an increased risk of diabetic macro-vascular and microvascular complications, hypoglycemia, mortality rates and other adverse clinical outcomes."

Due to his personal preference, he uses the term of "GF" instead of "GV" in his medical research work due to GF's non-ambiguity of definition and ease-of-calculation from glucose data directly. In addition, the within-day GF and between-day GF are incorporated in his ***combined GF model****.*

Of course, the advantages of using GF has become easier due to the wide acceptance of the continuous glucose monitor (CGM) sensor device for diabetes patients in recent years. Due to the initial commercial availability in late 2014, the author could only start using the CGM device on 5/5/2018. Therefore, all of his calculated GF values between 1/1/2010 and 5/4/2018 in this article are best-guesstimated.

In his earlier articles, No. 477 and No. 478, he has defined a combined arithmetic formula for glucose fluctuations (GF) which includes five glucose components: sensor daily glucose (eAG), daily GF over 24 hours (daily GF), PPG GF over 3 hours (PPG-3 GF), PPG GF over 2 hours (PPG-2 GF), and FPG GF over 7 hours (FPG GF).

This simple arithmetic formula of his newly defined "Combined GF" is:

Combined GF
= ((eAG/120) + (daily GF/85) + (PPG 3-hours GF/70)*(9/24) + (PPG 2-hours GF/30)*(6/24) + (FPG GF/35)*(7/24)) / 5

He has further calculated individual risk probability of having different kind of diabetic complications (DC) over a long period of time which was based on an overall metabolism index (MI). This overall MI model consists of 10 general categories and 500 elements which include both medical conditions and lifestyle management details. The DC include but are not limited to cardiovascular disease (CVD), coronary heart disease (CHD), stroke, chronic kidney disease (CKD), hypothyroidism, diabetic bladder infection, diabetic fungal infection, diabetic constipation, diabetic retinopathy, diabetic neuropathy (DR), foot ulcer, etc.

However, recently in 2021, he introduces the influences from GF instead of considering the average glucose only, such as the HbA1C value, into his risk assessments. In other words, by including the extra influential factor of a combined GF score into his existing MI-based risk assessment models, he expects to see more and wants to deeply understand the risks of having diabetic complications. In this article, he only selects three DC, which are CVD, CKD, and DR, for his investigation.

In this specific article, he chooses only three DC cases, which are CVD, CKD, and DR. He also applies the perturbation factor of

combined MI with GF to calculate three corresponding perturbed curves and finally conduct three comparison studies between the original curves and perturbed curves.

In summary, all three sets of curves, original risk curve versus perturbed curve, have extremely high and identical correlation coefficients (99%) using the combined factor of MI+GF (i.e. 77% of MI + 23% of GF) as the perturbation factor.

This phenomenon can be observed clearly in the graphic diagram. It includes the three original DC risk curves versus the three perturbed DC risk curves as being nearly on top of each other with small deviations around Y2011-Y2012. Therefore, from a math-physical viewpoint, this means that the perturbation theory is quite useful in deriving highly accurate "approximate" risk probabilities in having CVD, CKD, and DR caused by diabetes.

Introduction

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Methods

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. The second paper, No. 387 outlines the history of his personalized diabetes research, various application tools, and the differences between biochemical medicine (BCM) approach versus the MPM approach. The third paper, No. 397 depicts a general flow diagram containing ~10 key MPM research methods and different tools.

In short, the author studies and analyzes various digital footprints of human disease's biophysical phenomena using academic tools he has learned about mathematics, physics, engineering, and computer science.

The Author'S Diabetes History

The author was a severe type 2 diabetes patient since 1996. He weighed 220 lb. (100 kg) at that time. By 2010, he still weighed 198 lb. with an average daily glucose of 250 mg/dL (HbA1C at 10%). During that year, his triglycerides reached to 1161 (high risk for CVD and stroke) and albumin-creatinine ratio (ACR) at 116 (high risk for chronic kidney disease). He also suffered from five cardiac episodes within a decade. In 2010, three independent physicians warned him regarding the needs of kidney dialysis treatment and future high risk of dying from his severe diabetic complications.

In 2010, he decided to self-study endocrinology with emphasis on diabetes and food nutrition. During 2015 and 2016, he developed four mathematical prediction models related to diabetes conditions: weight, postprandial plasma glucose (PPG), fasting plasma glucose (FPG), and HbA1C (A1C). Through using his developed mathematical MI model and the other four glucose prediction

tools, by the end of 2016, his weight was reduced from 220 lbs. (100 kg) to 176 lbs. (89 kg), waistline from 44 inches (112 cm) to 33 inches (84 cm), average finger-piercing glucose from 250 mg/dL to 120 mg/dL, and A1C from 10% to ~6.5%. One of his major accomplishments is that he no longer takes any diabetes related medications since 12/8/2015.

In 2017, he had achieved excellent results on all fronts, especially his glucose control. However, during the pre-COVID period, including both 2018 and 2019, he traveled to ~50 international cities to attend 65+ medical conferences and made ~120 oral presentations. This hectic schedule inflicted damage to his diabetes control caused by stress, dinning out frequently, post-meal exercise disruption, jet lag, along with the overall negative metabolic impact from the irregular life patterns; therefore, his glucose control was somewhat affected during the two-year traveling period of 2018-2019.

He started his self-quarantined life on 1/19/2020. By now, 7/15/2021, his weight was further reduced to ~165 lbs. (BMI 24.4) and his A1C was at 6.2% without any medications intervention or insulin injection. In fact, with the special COVID-19 quarantine lifestyle since early 2020, not only has he written more than 200 new research articles and published a total of 400 medical papers in various medicine and engineering journals, but he has also achieved his best health conditions for the past 26 years. These achievements are resulted from his non-traveling, low-stress, and regular daily life routines. Of course, his in-depth knowledge on chronic diseases, sufficient practical lifestyle management experiences, and his own developed high-tech tools have also contributed to his excellent health improvements.

On 5/5/2018, he applied a continuous glucose monitoring (CGM) sensor device on his upper arm and checks his glucose measurements every 5 minutes for a total of 288 times each day. He has maintained the same measurement pattern to present day. However, in his research work, he decides to use the 15-minute sensor collected glucoses (96 data per day) due to its high accuracy and lower cost on computations.

During the past 11.5 years, he has continuously investigated, studied, and analyzed his collected more than 2 million data regarding his health status, medical conditions, and lifestyle details. He applies his physics knowledge, engineering models, mathematical tools, and computer programming to conduct his medical research work. His entire medical research work is based on the aims of achieving both "high ***precision***" with "***quantitative*** proof" in the bio-medical findings, not just through linguistic expressions with qualitative words, vague statements, or complex medical terminologies. His personal goal is aimed at saving his own life through research, and then helping family members along with other patients through distributing his knowledge learned and experiences gained from his 11.5 years medical research work to combat these chronic diseases and complications at the root-cause level.

It should be noted that the author uses a CGM sensor device which adopts the flash glucose monitoring (FGM) method. The following is an excerpt from diaTribe Learn (diatribe.org):

Flash Glucose Monitoring

What It Does: Flash Glucose Monitoring (FGM) is the newest method of glucose testing that is seen as a hybrid between meters and CGMs. The Abbott FreeStyle Libre is currently the only flash glucose monitoring product available, and it is currently only approved in Europe. In Flash Glucose Monitoring, patients have a sensor inserted on their upper arm and a separate touchscreen reader device. When the reader device is swiped close to the sensor, the sensor transmits both an instantaneous glucose level and eight-hour trend graph to the reader. This allows people to get individual blood sugar readings (like BGM) and trend information (like CGM). However, unlike CGM, FGM does not have hypo- or hyperglycemia alarms and will only provide a trend graph if it has been swiped in the past eight hours.

The FreeStyle Libre system does not require fingerstick calibration, so users can dose insulin based on its readings (except for when hypoglycemic, when glucose levels are rapidly changing, or when symptoms don't match the system's readings)."

Diabetic Complication Risk Model based on Overall Metabolism

In 2014, the author applied topology concept, finite-element engineering technique, and nonlinear algebra operations to develop a complex mathematical model of metabolism. This model contains 10 categories, including four output categories (weight, glucose, blood pressure, and lipids), and six input categories (food, water intake, exercise, sleep, stress, and routine life patterns). These 10 categories are comprised of approximately 500 detailed elements. He also defined two new parameters: metabolism index or MI, as the combined score of the above 10 metabolism categories and 500 elements along with the general health status unit (GHSU), as the 90-days moving average value of MI. Since 2012, he has collected more than 2 million data of his own biomedical conditions and personal lifestyle details.

Following the mathematical metabolism model, he further developed a series of models regarding diabetic complications which contain some detailed equations to predict his risk probabilities of having a stroke, CVD, chronic kidney diseases (CKD), and pancreatic beta-cells self-recovering assessment. These risk assessment models include a patient's baseline data including age, race, gender, family genetic history, medical history, and bad habits which contribute approximately 20% to the total risk. Furthermore, it also includes the following two major areas each with a 40% contribution:

(1) Medical conditions - individual M1 through M4 which include obesity, diabetes, hypertension, hyperlipidemia and others. It should be emphasized here that diabetes (i.e., glucose) alone contributes about 20% of the total risk.

(2) Lifestyle details - individual M5 through M10 which affect medical conditions.

In addition, he also uses his defined two terms, MI and GHSU, as a combined score of M1 through M10 and 90-days moving average MI, for his calculation. Of course, all of these 10 metabolism

factors (m1 through m10) are inter-related. The "break-even line" between heathy state and unhealthy state for both MI and GHSU is 0.735 or 73.5%.

With this mathematical risk assessment model, he can obtain three separate risk probability percentages associated with each of the three calculations mentioned above. As a result, this model would offer a range of the risk probability predictions of having a diabetic complication based on the patient's metabolic disorder conditions, unhealthy lifestyles, and the combined impact on the body.

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. These three references have cited 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. References 1 focuses on comparison of many published GV articles. Reference 2 concentrates on algorithm, method and firmware design of a web-based APP software for calculating GV values.

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 hyper-*

glycemia (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 β-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 β-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 (3) and the pancreatic β-cell."*

The author read an interesting article published in the Cardiovascular Diabetologist on July 4, 2020: "Glycemic variability: adverse clinical outcomes and how to improve it?" and selected the following excerpt:

"Glycemic variability (GV), defined as an integral component of glucose homoeostasis, is emerging as an important metric to consider when assessing glycemic control in clinical practice. ***Although it remains yet no consensus, accumulating evidence has suggested that GV,*** *representing either short-term (with-day and between-day variability) or long-term GV,* ***was associated with an increased risk of diabetic macro-vascular and microvascular complications, hypoglycemia, mortality rates and other adverse clinical outcomes.***

Glycemic variability (GV), referring to oscillations in blood glucose levels, is usually defined by the measurement of fluctuations of glucose *or other related parameters of glucose homoeostasis over a given interval of time (i.e., within a day, between days or longer term).* ***Although HbA1c was traditionally considered as the gold standard for assessing glycemic control, GV is a more meaningful measure of glycemic control than HbA1c in clinical practice, and is without doubt now being recognized.*** *Despite its clinical significance, there is no consensus on the optimum method for characterizing GV.*

GV and diabetic macrovascular and microvascular complications
Given that the limitations of HbA1c measurements, growing evidence demonstrated that GV was a significant and clinically meaningful glycemic metric and had drawn attention for its effects on adverse clinical outcomes, including diabetic macro-vascular and microvascular complications, hypoglycemia and mortality *(Table 2). There is considerable evidence to support the negative role of GV in the development of diabetic macro-vascular and microvascular complications.*

GV and hypoglycemia

Hypoglycemia is the major impediment to therapy in diabetes. While HbA1c remains widely used as a measure of mean glycemia, it may not be the best marker for predicting hypoglycemia. The consolidated evidence to date supported the importance of GV with respect to predicted risk of hypoglycemia. Zinman et al. concluded that ***higher day-to-day FPG variability was associated with increased risks of severe hypoglycemia and all-cause mortality.***

GV and mortality

A number of studies verified that GV was not only associated with the risk of diabetes-related complications and hypoglycemia, but also simultaneously related to the high incidence of mortality. Interestingly, several studies proposed an independent association of GV with mortality. ***Clinical data indicated that FPG variability might be an important predictor of mortality, particularly for those with their glycemic status uncontrolled. Besides, in hospitalized patients, increased GV was associated with a higher rate of mortality.*** *Recently, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,* ***researchers found that HbA1c variability was a strong predictor of all-cause mortality, and this observation was more remarkable in older people with diabetes.***

In addition to the above adverse clinical outcomes, ***GV was also reported to be associated with depressive symptoms, cognitive disorder and even cancer.*** *In the Israel Diabetes and Cognitive Decline (IDCD) study, GV measured as the SD of HbA1c increased the risk of depressive symptoms. A Taiwan diabetes study explored the relationship between GV and the incidence of Alzheimer disease (AD) in patients with type 2 diabetes mellitus, finding that* ***GV had a worse impact on AD and might be significant predictors for AD.*** *More importantly, recent study demonstrated that HbA1c variability was a potential risk factor for later tumorigenesis in patients with diabetes, which might be mediated by oxidative stress or hormone variability.*

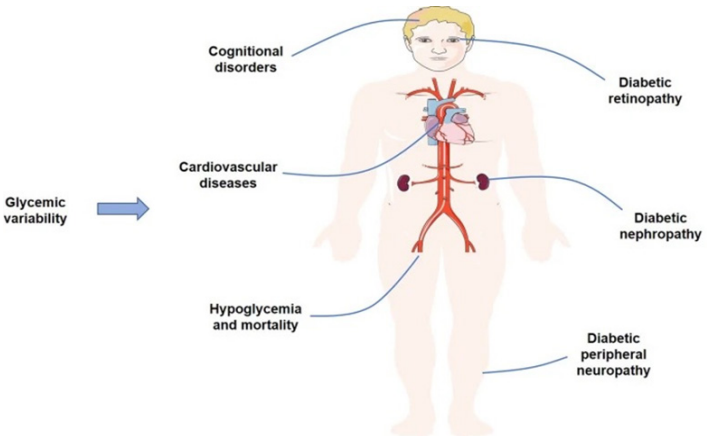

Figure 2: The effects of glycemic variability on the adverse clinical outcomes.

GV has been identified to be closely associated with the risk of adverse clinical outcomes and provides a better predictor of such complications. However, it still lacking a clear universal definition and different indices have been proposed to evaluate it. With the availability of CGM in clinical practice, the assessment of GV became not only possible but also required. *Also, CGM was frequently superior to continuous subcutaneous insulin infusion and could guide individuals' therapeutic changes to reduce GV, hypoglycemia and CVD.* ***A recent study reported that "flash glucose monitoring", a new approach to glucose monitoring, has a long sensor lifetime of 14 days and emerged as a practical solution to the glucose monitoring.*** *Meanwhile, a real-world data from Spain indicated that flash glucose monitoring allowed frequent glucose checks and reduced GV, as well as hypoglycemia. Consequently, in order to provide a more comprehensive assessment of GV, the new approach of glucose monitoring is advocated to adopt in clinical practice.* ***Future developments in new technologies, such as CGM systems and flash glucose monitoring, and indices for better deciphering and defining GV should contribute to improve understanding of the clinical relevance of GV in the management of diabetes****.*

Although GV had drawn attention for its effects on diabetic macrovascular and microvascular complications, hypoglycemia and mortality, several studies have shown conflicting results. Caprnda et al. failed to show the association between diabetic complication and GV in patients with type 2 diabetes.Furthermore, in the Diabetes Control and Complications Trial, within-day GV, as determined from quarterly glucose profiles, did not play an explicit role in the development of microvascular complications. However, ***we found that these results employed the 7-point glucose profiles, which might be insufficient to characterize GV correctly when compared with CGM.*** *Thus, these negative results may not necessarily disprove the importance of GV in the development of diabetic complications. Additionally, the mechanisms linking GV and related complications risk remained unclear.* ***Recent studies corroborated that GV was correlated with oxidative stress or erythrocyte membrane stability, emphasizing its participation in the pathogenesis of related complications.*** *Further prospective research to explore the explicit mechanisms linking GV and related complications is warranted.*

Finally, setting clear definitions and taking ***potential beneficial measures for addressing GV is essential. Further research in these domains will contribute to blood glucose control and management."***

Glucose Fluctuations or GF

The concept and practice of glycemic variability (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*.

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 are 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 an extended period, such as years. The reason is that until recently, after 2016-2017, the continuously glucose monitored (CGM) sensor devices became available to 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 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" result into "garbage outputs" which fits the common expression in computer science industry of "garbage in and garbage out".

Based on the above-mentioned theoretical and technical viewpoints, the author decided to conduct his study on "just" applying the ***basic concept*** of glycemic variability (i.e., glucose fluctuation between peak and nadir), and without touching certain created terms or derived formulas by some research doctors described in some of their publications. However, the author further combined the primary characteristics of ***wave theory***, e.g. frequency, amplitude, and wavelength along with the concept of ***energy theory*** to include the estimated energy associated with the glucose fluctuations.

He opted to abandon the usage of this term of "glycemic variability or GV" and directly utilize the term of "glucose fluctuations (GF)" in his research work where GF equals to the value of maximum glucose minus minimum glucose. Not only does the simpler definition and form of GF provide a straightforward interpretation and easier comprehension to be applied by both physicians and patients, but it also fully represents the meaning of glycemic variabil-

ity. The word "variability" can involve and signify many various things to different people.

GV or GF can indeed be applied to many clinical cases of greater mortality for those in intensive care unit or at-home, ***increased rate and risk of diabetes complications,*** *and postprandial beta-cell dysfunction (insulin health).*

Input Data and Formula of GF

The author has collected 288 glucose data per day (every 5 minutes) and extracted 96 Glucose data per day (every 15 minutes) from the CGM sensor device and then entered them into his computer software since 5/5/2018. He has chosen 11.5 years (1/1/2010-7/16/2021) for this specific analysis project. Due to the commercial availability in late 2014, the author could only start using a CGM device on 5/5/2018. Therefore, all of his GF values between 1/1/2010 and 5/4/2018 in this article's calculation are best-guesstimated.

In addition to his daily sensor glucose, eAG, for this particular study, he calculates four additional sets of his GF values (maximum glucose minus minimum glucose): daily GF, PPG GF within 3-hour duration, PPG GF within 2-hour duration, and FPG GF within 7-hour duration (from midnight to 7am). This effort results into a total of 4,668 GF data each day. The reason he selects these two sets for PPG GF is that their waveforms are different. The impacts from both food and exercise on glucose would last longer in the blood system than the conventional thinking of two hours. In general, the two-hour waveform is similar to a mountain shape with its peak around 60-minutes and trough at either 0-minute or 120-minutes. However, the three-hour waveform will either have a continuously drop-downward shape from the second hour into the third hour or behaving with a slightly tilt-upward shape at times. Therefore, their GF values are different and the PPG 3-hour GF is usually bigger than the PPG 2-hour GF.

The simple arithmetic formula of his "Combined GF" is:

Combined GF
= ((eAG/120) + (daily GF/85) + (PPG 3-hours GF/70)*(9/24) + (PPG 2-hours GF/30)*(6/24) + (FPG GF/35)*(7/24)) / 5

Perturbation Theory of Quantum Mechanics or Modern Physics

The author applies the first-order interpolation perturbation method to obtain his "perturbed PPG" waveforms based on one selected carbs/sugar intake amount functioning as the perturbation factors, which is the "Slope". He uses the "measured PPG" waveform as his reference or baseline waveform.

The following polynomial function is used as the perturbation equation:

A = f(x)
= A0 + (A1*x) *+ (A2*x**2)+(A3*x**3) + ... + (An*x**n)*

Where A is the perturbed glucose, Ai is the measured glucose, and ***x is the perturbation factor*** *based on a chosen carbs/sugar intake amount.*

For this particular study, he choose his ***Ai as A1, where i=1.*** In this way, the above equation can then be simplified into the first-order perturbation equation as follows:

A = f(x) = A0 + (A1*x)

Or the first-order interpolation perturbation equation can also be expressed in the following general format:

A i = A1 + (A2-A1)*(slope 1)

Where:
A1 = original risk A at year 1
A2 = advanced risk A at year 2
(A2-A1) = (Risk A at Year 2 - Risk A at Year 1)

The perturbation factor or ***Slope*** is an arbitrarily selected parameter that controls the size of the perturbation. The author has chosen a function of HbA1C value, as his perturbation factor or slope, which is further defined below:

In this particular study, he would like to ***use the "perturbation factor" as the combined factor of 77% of MI and 23% of GF.***

He selects the lowest value of the combined MI+GF as the low-bound value and the highest value of the combined MI+GF as the high-bound value, while using their mid-point value as his selected value.

Then the "slope" becomes:

Slope
= (Selected value - Low-bound value) / (High-bound value - Low-bound value)

Therefore, his slope or perturbation factor value has been calculated as:

Slope from combined MI+GF
= (mid - low) / (high - low)
= 0.50 or 50%

Results

Figure 1 shows the supporting data table of the original risk data and perturbed risk data. The calculation of the three extremely high correlation coefficients is 99% for the three individual DC risks.

	Risk	Perturbed		Risk	Perturbed		Risk	Perturbed	Perturbation Factor	Combined
Year	CVD - MI	CVD - Pert.	Year	CKD - MI	CKD - Pert.	Year	DR - MI	DR - Pert.	Year	MI+GF
Y2010	100%	100%	Y2010	100%	100%	Y2010	100%	100%	Y2010	100%
Y2011	82%	91%	Y2011	92%	96%	Y2011	83%	92%	Y2011	81%
Y2012	77%	80%	Y2012	84%	88%	Y2012	71%	77%	Y2012	70%
Y2013	72%	75%	Y2013	72%	78%	Y2013	66%	69%	Y2013	71%
Y2014	67%	70%	Y2014	66%	69%	Y2014	63%	65%	Y2014	61%
Y2015	63%	65%	Y2015	61%	63%	Y2015	60%	62%	Y2015	51%
Y2016	59%	61%	Y2016	55%	58%	Y2016	56%	58%	Y2016	48%
Y2017	55%	57%	Y2017	54%	55%	Y2017	54%	55%	Y2017	46%
Y2018	53%	54%	Y2018	55%	54%	Y2018	56%	55%	Y2018	45%
Y2019	50%	51%	Y2019	55%	55%	Y2019	55%	56%	Y2019	46%
Y2020	48%	49%	Y2020	52%	53%	Y2020	54%	54%	Y2020	40%
Y2021	45%	46%	Y2021	52%	52%	Y2021	52%	53%	Y2021	41%
Average	64%	67%	Average	66%	68%	Average	64%	64%	High (MI+GF)	100%
Accuracy		97%	Accuracy		97%	Accuracy		100%	Low (MI+GF)	40%
Correlation		99%	Correlation		99%	Correlation		99%	Selected (MI+GF)	70%
7/17/21									Slope:	50%

Figure 1: Data table of original MI-based DC risk versus perturbed DC risk

The upper diagram in Figure 2 illustrates the two CVD risk curves of original MI-based curve versus perturbed CVD risk curve using the mid-point value of (77%MI+23%GF) as the perturbation factor. Its perturbation prediction accuracy is 97% and corresponding correlation coefficient is 99%.

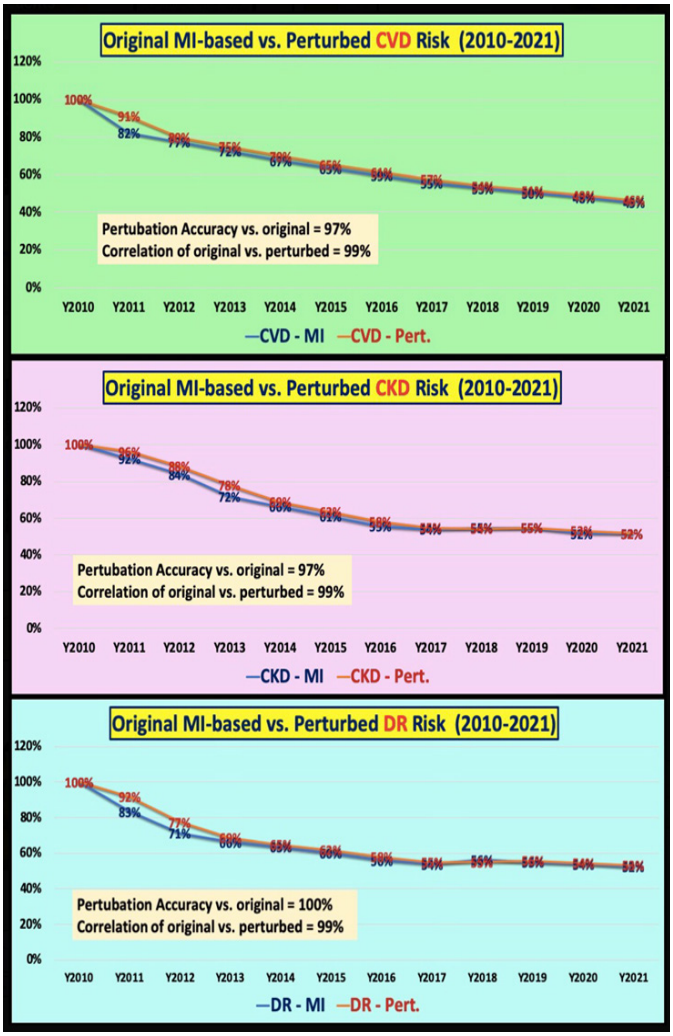

Figure 2: Three risk curves (CVD, CKD, DR) of original MI-based risk versus perturbed risk

The middle diagram in Figure 2 reveals two CKD risk curves of original MI-based curve versus perturbed CKD risk curve using the mid-point value of (77%MI+23%GF) as the perturbation factor. Its perturbation prediction accuracy is 97% and corresponding correlation coefficient is 99%.

The bottom diagram in Figure 2 depicts the two DR risk curves of original MI-based curve versus perturbed DR risk curve using the mid-point value of (77%MI+23%GF) as the perturbation factor. Its perturbation prediction accuracy is 100% and corresponding correlation coefficient is 99%.

Conclusions

In summary, all three sets of curves, original risk curve versus perturbed curve, have extremely high and identical correlation coefficients (99%) using the combined factor of MI+GF (i.e. 77% of MI + 23% of GF) as the perturbation factor.

This phenomenon can be observed clearly in the graphic diagram. It includes the three original DC risk curves versus the three perturbed DC risk curves as being nearly on top of each other with small deviations around Y2011-Y2012. Therefore, from a math-physical viewpoint, this means that the perturbation theory is quite useful in deriving highly accurate "approximate" risk probabilities in having CVD, CKD, and DR caused by diabetes [1-4].

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