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Comparison of Energy Generated by Glucose Fluctuations Based on Two Clinical Cases Using Wave Theory, Fourier Transform, and Energy Theory of GH-Method: Math-Physical Medicine (No. 433)

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Abstract

In this article, the author investigates the energy differences associated with glucose fluctuations (GF) of two type 2 diabetes (T2D) patients in the year 2020. The extra energy generated through GF can be used as an influential factor in assessing a T2D patient's risk probability of having severe diabetic complications, including macro-blood vessels (i.e., arteries) related diseases, such as stroke and cardiovascular disease (CVD). Over the past 11 years, the author has continuously investigated, studied, and analyzed the collection of ~2 million data regarding his health status, medical conditions, and lifestyle details. He applies his physics knowledge, engineering models, mathematical tools, and computer science techniques to conduct his medical research work. His entire research is based on the aim of achieving high precision with quantitative proof in the biomedical findings, not just through linguistic expressions with qualitative words, vague statements, or complex medical terminologies. His personal goal is to save his own life through research and then assist family members and other patients through distributing his learned knowledge and experiences gained from the 11-years of medical research work to combat the diabetic complications at the root cause level. In summary, by calculating the GF associated energy using three different energy estimation methods for these two clinical cases, female patient and male patient, the results are listed below in the format of female and male: method 1: 9.4%, 9.2%, method 2: 12.5%, 7.5%, method 3: 12.5%, 7.5%. From above, we can draw the following four conclusions: (1) Overall, the female patient has generated more GF energy than the male patient. (2) Results from method 2 and method 3 are identical due to the specific definitions of the two GF energy methods which are almost identical. In fact, there is an exceedingly small difference because of numerical truncation. (3) Method 1 is based on the definition of the GF energy which equals the square of the GF magnitude. This is different from the other two methods which are derived from Fourier transform operation from a GF function in time-domain (TD) into a GF function in the frequency domain (FD). Furthermore, basic physics says that the energy associated with a wave is directly proportional to the square of the wave amplitude; but not equal to the square of the wave amplitude. In addition, the difference of GF energy using method 1 between the female patient and male patient is minuscule (~0.2%). This small difference is due to different ratios of GF dividing by glucose for measuring the glucose wave's relative fluctuation. The glucose fluctuation brings in extra energy that can damage the internal organs of a T2D patient, and therefore, increase the risks of having diabetic complications, such as a stroke, CVD, chronic kidney disease (CKD), etc.

Keywords: Glucose fluctuations; Type 2 diabetes; Cardiovascular disease; Stroke; Health

Abbreviations: GF: glucose fluctuations; T2D: type 2 diabetes; CVD: cardiovascular disease; TD: time-domain; FD: frequency domain; CKD: chronic kidney disease; MPM: math-physical medicine; GV: glycemic variability; HbA1C: hemoglobin A1c; CGM: continuous glucose monitoring; SMBG: self-monitored blood glucose; SD: standard deviation

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1. INTRODUCTION

In this article, the author investigates the energy differences associated with glucose fluctuations (GF) of two type 2 diabetes (T2D) patients in the year 2020.

The extra energy generated through GF is used as an influential factor in assessing a T2D patient's risk probability of having severe diabetic complications, including macro-blood vessels (i.e., arteries) related diseases, such as stroke and cardiovascular disease (CVD).

Over the past 11 years, the author has continuously investigated, studied, and analyzed the collection of ~2 million data regarding his health status, medical conditions, and lifestyle details. He applies his physics knowledge, engineering models, mathematical tools, and computer science techniques to conduct his medical research work. His entire research is based on the aim of achieving high precision with quantitative proof in the biomedical findings, not just through linguistic expressions with qualitative words, vague statements, or complex medical terminologies. His personal goal is to save his own life through research and then assist his family members and other patients by distributing his learned knowledge and experiences gained from 11-years of medical research work to combat the diabetic complications at the root cause level.

2. METHODS

2.1 MPM background

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

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

2.2 Other GV research work

There are many available articles regarding the subject of glycemic variability (GV), however, the author decided to include the following combined excerpt from the published articles[3-5]. These 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. These papers focus on the comparison of many published GV articles and algorithm, method, and firmware design of a web-based app software for calculating GV values[3,4].

Here is the combined excerpt:

"Several pathophysiological mechanisms were reported, unifying the two primary mechanisms: excessive protein glycation end products and activation of oxidative stress, which causes vascular complications. Intermittent high blood glucose exposure, rather than constant exposure to high blood glucose, has been shown to have deleterious effects in experimental studies. In the 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 the 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 postprandial plasma glucose (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 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 optimal glycemic control over and above standard glycemic parameters, such as blood glucose and HbA1c. Avoiding both hyperglycemia and hypoglycemia by careful use of self-monitored blood glucose (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 GV 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 CVD in diabetes. Percentages of hyperglycemia (levels between 126 and 180 mg/dl) and hypoglycemia (levels below 70.2 mg/dl) episodes should be used in the GV-related research. Mean amplitude of glycemic excursions (MAGE), together with mean and standard deviation (SD) is the most popular parameter for assessing GV 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 the use of GV 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 GV 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 reduce insulin resistance. This deterioration can be attributed to the progressive decline of ß-cell function. Even in subjects with well-controlled T2D, 70% of the variability of A1C can be explained by abnormalities in postprandial glucose. Chronic sustained hyperglycemia has been shown to exert deleterious effects on the ß-cells and the vascular endothelium. Monnier et al. and Brownlee and Hirsch have recently emphasized that another component of dysglycemia, i.e., GV, is even more important than chronic sustained hyperglycemia in generating oxidative stress and contributing to the development of secondary diabetes complications. In-vivo studies have convincingly demonstrated that hyperglycemic spikes induce increased production of free radicals and various mediators of inflammation, leading to dysfunction of both the vascular endothelium and the pancreatic ß-cell[3]."

2.3 Glucose fluctuations (GF)

The concept and practice of GV have existed since the clinical usage of CGM devices to monitor severe diabetes patients and insulin treatments in hospitals. Many medical papers have been published on GV; however, there is no universally accepted formula or equation for generally accepted applications[6-8].

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 SD from statistics. Although SD is widely used, it has limitations because the assumption of measured glucose data is normally distributed (similar to a Gaussian distribution), which is typically not the case for bio-waves and medical data. Besides, many research articles use glucose data collected within a few days from hospitalized patients rather than the use of glucose data collected over a long period, such as years, from outpatients. The reason is that until recently, after 2016-2017, the SMBG devices became available to diabetes out-patients to collect their own glucose data at home, instead of in the hospitals or clinic centers[9,10]. However, the tasks of glucose data transfer from a CGM device to a computer and then the necessary follow-on tasks of data processing, data management, and data analysis still remain a challenge, particularly for out-patients. Due to the lack of professional training and academic knowledge in this domain, most patients and clinical physicians have encountered difficulties with these tasks. Data without careful cleaning and proper preparation would create a situation of garbage inputs resulting in garbage outputs which fits the common expression in the computer science industry of "garbage in and garbage out".

Based on the above-mentioned theoretical and technical viewpoints, the author decided to conduct his study on just applying the basic concept of GV (i.e., glucose fluctuation between peak and nadir), and without touching certain terms or derived formulas described in some of those publications[11-13]. However, he 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 GF.

He finally decided to replace the term GV with glucose fluctuations (GF) where GF equals 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 GV. The word variability can involve and signify many various things to different people.

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

3. RESULTS

3.1 Two clinical cases of T2D patients

The female patient is 73 years old with a 23-year history of T2D and the male patient is 74 years old with a 26-year history of T2D. Both patients have hypertension and hyperlipidemia. The male patient has suffered several severe diabetic complications, including CVD, chronic kidney disease (CKD), retinopathy, hypothyroidism, etc.

During the entire year of 2020, both patients have applied a CGM sensor device on their upper arms and collected their glucose measurements every 15 minutes for a total of 96 times each day.

They live a quarantined lifestyle that is quiet, calm, without stress, with no travel, and no social contact with others due to their fears of the COVID-19 pandemic. As a result, their average glucose levels are lower than in the past years (111 mg/dL for female and 116 mg/dL for male). By the definition of diabetes, they fall in the normal category (lower than 120 mg/dL). This comparison study could not be performed at any other time period prior to 2021, since the female patient did not collect sufficient sensor glucose data.

In the year 2020, both patients have collected 96 glucose data per day (every 15 minutes) using a CGM sensor device, and then transferring them into customized computer software. Over the past year of 365 days, each patient has collected 35,040 glucose data with a combined 70,080 glucose data from the two patients which are used in this specific analysis project.

3.2 Three methods for estimated GF energy

The first method uses the square of Y-amplitude of GF (max-min of daily glucose) in the time-domain (TD).

The second method utilizes the Y-amplitude of GF in the frequency domain (FD).

The third method applies the Y-amplitude times the X-frequency component numbers to obtain the total area underneath the GF frequency curve in the FD.

Method 2 and method 3 would produce almost identical results. Method 1 would generate a similar energy curve's shape (i.e., with extremely high correlation coefficients) but there is some degree of numerical differences with both method 2 and method 3.

After obtaining the estimated energy data, they need to be normalized by a factor of 0.735 which is the dividing break-even line in his ready-developed metabolism model. The overall metabolism-based results continue to be the major players in his risk assessment models since disease-induced complications are based on the combination of chronic medical conditions and lifestyle details.

The metabolism-based CVD risk model is not utilized in this study because the female patient did not collect sufficient data to calculate her overall metabolism status. Therefore, in this article, its scope is limited to the rescinding of GF energy.

3.3 Graphic diagrams of results

Figure 1 shows the data table of input values and calculated results using three different energy methods to estimate the energy associated with GF influential factor. The actual physical interpretation from this data table can be summarized easily by the following two conclusive graphs.

Figure 2 depicts the input data of this study. The female patient has average daily glucose of 111 mg/dL and an average glucose fluctuation of 84 mg/dL. The male patient has average daily glucose of 116 mg/dL and an average glucose fluctuation of 87 mg/dL. The ratio of GF vs. glucose is 75.4% for female and 74.5% for male. If we take the square of these two values, we will get 56.9% for female and 55.6% for male. The female's GF energy via method 1 is slightly higher than the male's GF energy.

There is no information available for the standard break-even level of GF. Therefore, the author uses 120 mg/dL as the break-even standard for glucose and 80 mg/dL as the break-even standard for GF. In other words, the glucose wave would vibrate between 80 mg/dL and 160 mg/dL. Of course, this GF value of 80 mg/dL is debatable and subject to further investigation.

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CVD Risk with GF inputs	Female	Male	Male/Female	Ideal Case
No. of Days/Frequencies	365	365	100%	
Avg Daily Glucose	111	116	105%	120
Glucose Fluctuation (Max-Min)	84	87	104%	80
Fluctuation / Glucose	75.4%	74.5%	99%	67%
CVD Risk with GF inputs (Energy 1)	Female	Male	Male/Female	Ideal Case
SQ of (Fluctuation/Glucose)	56.9%	55.6%	98%	44%
Eneegy of Glucose (SQ of Gluc)	12301	13502	110%	14400
Eneegy of Fluctuation (SQ of Fluc)	6997	7503	107%	6400
Fluc Enegy /Glucose Energy	56.9%	55.6%	98%	44%
(Period/Ideal) of (Fluc.E/Gluc.E): (Eneegy 1)	1.2799	1.2503	98%	1.0000
Normalize to 0.735	0.941	0.919	98%	0.735
10% of Normaized Fluc Eneegy	0.094	0.092	98%	0.074
CVD Risk via GF (Energy 1)	9.4%	9.2%	98%	9.3%
CVD Risk with GF inputs (Energy 2)	Female	Male	Male/Female	Ideal Case
FD-Y magnitude: (GF Eneegy 2)	694	413	60%	407
Normalize to 0.735	1.254	0.746	60%	0.735
10% of Normaized Fluc Eneegy	0.125	0.075	60%	7%
CVD Risk via GF (Energy 2)	12.5%	7.5%	60%	#REF!
CVD Risk with GF inputs (Energy 3)	Pre-Virus	Virus	Virus/Pre-Virus	Ideal Case
FD-Y magnitude: (GF Eneegy 3)	251841	150926	60%	148017
Normalize to 0.735	1.2506	0.7494	60%	0.735
10% of Normaized Fluc Eneegy	0.1251	0.0749	60%	0.074
CVD Risk via GF (Energy 3)	12.5%	7.5%	60%	7.4%

Figure 1: Data table of GF associated energy using three different GF energy methods.

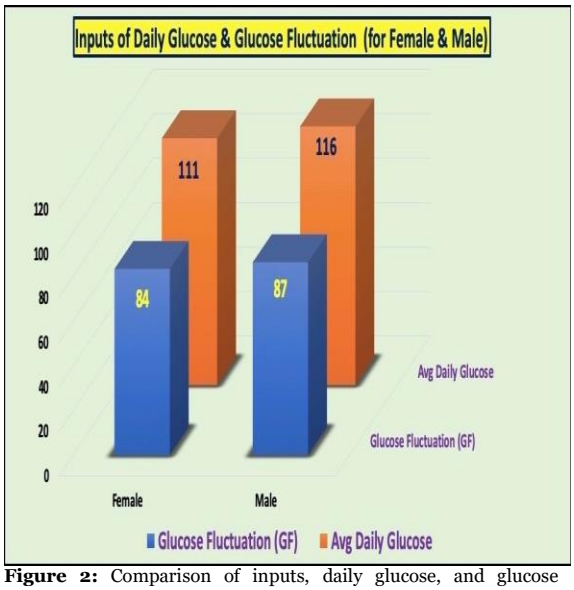

Figure 2: Comparison of inputs, daily glucose, and glucose fluctuation for female vs. male.

Figure 3 reveals the GF energy results using three different energy methods, for both female and male patients.

The three energy methods are method 1 (square of GF Y-magnitude in the TD), method 2 (GF Y-magnitude in the FD), and method 3 (GF area underneath the GF curve in the FD).

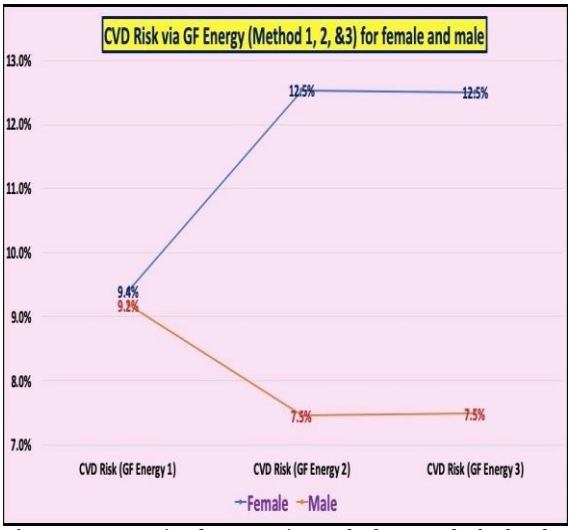

Figure 3: GF associated energy using methods 1, 2, and 3 for female vs. male.

Here are the key findings:

(1) The female's energy associated with GF is higher than the male's GF energy (the blue line of female is higher than the orange lineof male).
(2) The difference between female and male is only 0.2% based on the results from using method 1. This is due to the square of fluctuation divided by glucose, where they are very close to each other, 56.9% for female and 55.6% for male.
(3) Results of method 2 are identical with method 3 (12.5% for female and 7.5% for male).

4. CONCLUSION

In summary, by calculating the GF associated energy using three different energy estimation methods for these two clinical cases, female patient and male patient, the results are listed below in the format of female and male:

Method 1: 9.4%, 9.2%, method 2: 12.5%, 7.5%, method 3: 12.5%, 7.5%

From above, we can draw the following conclusion:

(1) Overall, the female patient has generated more GF energy than the male patient.
(2) Results from method 2 and method 3 are identical due to the specific definitions of the two GF energy methods which are almost identical. In fact, there is an exceedingly small difference because of numerical truncation.

(3) Method 1 is based on the definition of the GF energy which equals the square of the GF magnitude. This is different from the other two methods which are derived from Fourier transform operation from a GF function in the TD into a GF function in the FD. Furthermore, basic physics says that the energy associated with a wave is directly proportional to the square of the wave amplitude; but not equal to the square of the wave amplitude. In addition, the difference of GF energy using method 1 between the female patient and male patient is minuscule (~0.2%). This small difference is due to different ratios of GF divided by glucose for measuring the glucose wave's relative fluctuation.

The glucose fluctuation brings in extra energy that can damage the internal organs of a T2D patient, and therefore, increase the risks of having diabetic complications, such as a stroke, CVD, CKD, etc.[14,15].

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