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Research Article

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Relationships of Cardiovascular Disease Risks and Four Biomarkers of Insulin Resistance Via FPG and TyG, Glycemic Control Via HbA1c, Inflammation Via Hyperglycemia Intensity Using Viscoplastic Energy Model of GH-Method: Math-Physical Medicine (No. 973, VMT #372, 11/27/2023)

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Abstract

In a 2021 study, approximately 30% of US coronary artery disease patients and, according to BMC Public Health, an average of 30% (14% - 46%) of UK stroke patients had diabetes. The interplay of food quality, meal portion control, and consistent exercise significantly influences body weight—a crucial factor in the progression of type 2 diabetes (T2D).

T2D is characterized by three key biomarkers: insulin resistance (indicated by both morning fasting glucose - FPG and triglyceride- glucose index - TyG), averaged glycemic control (averaged daily glucose - eAG and quarterly glycemic control - HbA1c), and hyperglycemia damage control (hyperglycemia intensity - HyGI).

Both HbA1c and eAG are averaged values, providing limited insight into insulin resistance situations and inadequate representation of damage caused by hyperglycemia. In this study, the author characterized his insulin resistance (IR) with the following formula:
IR = ((FPG/90) + (TyG/10)) / 2
Here, TyG and HyGI are defined as follows:
TyG = ln (fasting triglycerides multiplied by fasting glucose) / 2

A TyG value exceeding 4.49 suggests insulin resistance, while a value surpassing 8.5 indicates nonalcoholic fatty liver disease.

HyGI = (averaged glucose above 180 mg/dL) multiplied by (occurrence frequency of glucose above 180 mg/dL)

In summary, *the traditional statistical analysis reveals strong correlations (80% to 93%) between the author's cardiovascular disease (CVD) annual risk and his four biomarkers, aligning with his previous research findings. This study identifies four significant correlations:*

- ***CVD vs. IR: 80%***
- ***CVD vs. HyGI: 81%***
- ***CVD vs. A1C: 80%***
- ***CVD vs. BW: 93%***

Additionally, the author uses the space-domain viscoplastic energy (SD-VMT) method to uncover hidden relationships and dynamics (i.e. energies) between these four biomarkers and his 11 years of annual CVD risks. This SD-VMT energy results reveal four contribution margins on CVD risks from four biomarkers:

- ***Energy from IR: 25%***
- ***Energy from HyGI: 29%***
- ***Energy from A1C: 25%***
- ***Energy from BW: 21%***

Key Message

The author's T2D conditions and overweight are indeed linked to his CVD risks. Despite representing only 2% of the glucose dataset, the HyGI (hyperglycemia intensity) contributes 29% of the total energy impact (or inflammation damages) on his CVD risks. Insulin resistance, and averaged glycemic value of A1c are secondary significant factors at 25% each, with body weight contributing the least at 21% in this 11-years CVD case study.

1. Introduction

In a 2021 study, approximately 30% of US coronary artery disease patients and, according to BMC Public Health, an average of 30% (14% - 46%) of UK stroke patients had diabetes. The interplay of food quality, meal portion control, and consistent exercise significantly influences body weight—a crucial factor in the progression of type 2 diabetes (T2D).

T2D is characterized by three key biomarkers: insulin resistance (indicated by both morning fasting glucose - FPG and triglyceride- glucose index - TyG), averaged glycemic control (averaged daily glucose - eAG and quarterly glycemic control - HbA1c), and hyperglycemia damage control (hyperglycemia intensity - HyGI). ***Both HbA1c and eAG are averaged values, providing limited insight into insulin resistance situations and inadequate representation of damage caused by hyperglycemia.***

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2. Biomedical Information

The following sections contain excerpts and concise information drawn from multiple medical articles, which have been meticulously reviewed by the author of this paper. The author has adopted this approach as an alternative to including a conventional reference list at the end of this document, with the intention of optimizing his valuable research time. It is essential to clarify that these sections do not constitute part of the author's original contribution but have been included to aid the author in his future reviews and offer valuable insights to other readers with an interest in these subjects.

3. Pathophysiological Interpretation of Triglyceride-Glucose Index (TyG)

The TyG index, or Triglyceride- glucose index, is an emerging marker used to evaluate insulin resistance and non-alcohol fatty liver disease (NFLD) conditions. It is calculated based on fasting levels of triglycerides (TG) and glucose, using the following formula:

TyG = ln (fasting triglycerides ×
fasting glucose) / 2
or
TyG = (ln(fasting triglycerides) + ln(fasting glucose)) / 2

Several studies have suggested a strong relationship between the TyG index and various metabolic and cardiovascular conditions, including obesity, inflammation, and insulin resistance.
Now let's go through these complex pathophysiological relationships between the TyG index and obesity, inflammation, insulin resistance, and triglycerides:

3.1 TyG and Obesity: Obesity is typically associated with a state of insulin resistance. The adipose tissue in individuals with obesity tends to have an increased release of free fatty acids, which can lead to increased production of glucose and triglycerides, hence the elevation of the TyG index. Furthermore, obesity-associated inflammation can impair insulin signaling, leading to both insulin resistance and hyperinsulinemia. Therefore, a higher TyG index is often seen in people with obesity.

4. Let us Explain Above Statement Deeper and More

The relationship between the TyG index and obesity is complex and multifaceted. Obesity, particularly visceral obesity, is associated with an increased amount of adipose tissue. This adipose tissue can secrete a variety of substances known as adipocytokines (like leptin and adiponectin), which can influence glucose and lipid metabolism. In obesity, there is a state of adipocytokine imbalance, often with increased leptin and reduced adiponectin, leading to insulin resistance. Furthermore, the excessive adipose tissue can cause an over-release of free fatty acids into the bloodstream, which get taken up by the liver and contribute to the production of triglycerides, thus increasing the TyG index. *In this article, the author uses his body mass index* ***(BMI) = weight / (height * height,*** *to represent his obesity condition. Sometime, he used* ***waistline length and hipline length ratio (WHR)*** *to represent his obesity condition.*

4.1 TyG and Inflammation: Chronic inflammation is a key component of metabolic syndrome, and this can be triggered by obesity and insulin resistance. Inflammatory cytokines can disrupt the normal functioning of insulin, leading to insulin resistance. Also, inflammation can stimulate the production of triglycerides, contributing to a higher TyG index.

5. Let us Explain Above Statement Deeper and More

Chronic inflammation, often present in obesity, plays a significant role in the pathogenesis of insulin resistance. The inflammation induces the production of several pro-inflammatory cytokines (such as TNF-alpha, IL-6), which can impair insulin signaling.

This disturbance of the insulin pathway results in less glucose being taken up by cells and more remaining in the blood, thereby contributing to a higher TyG index. Also, inflammation can trigger the release of stress hormones that promote lipolysis, the breakdown of fats leading to increased triglycerides, further raising the TyG index. *In this article,* ***the author uses his hypoglycemia intensity (HyGI) = averaged hyperglycemia***

(>180 mg/dL) * frequency % of hyperglycemia happening occurrence, to represent his inflammation condition.

5.1 TyG and Insulin Resistance: The TyG index has been found to be a reliable marker of insulin resistance. Insulin resistance is a state in which cells fail to respond normally to insulin, leading to elevated blood glucose levels. Over time, the pancreas beta cells produces more insulin to compensate, leading to hyperinsulinemia. This can promote the synthesis of triglycerides, raising both the components used to calculate the TyG index. Triglycerides are a type of fat (lipid) found in your blood. When you eat, your body converts any calories it doesn't need to use right away into triglycerides, which are stored in fat cells. High triglyceride levels could be an indicator of a condition that increases the risk of heart disease, including obesity and metabolic syndrome, both of which can be related to insulin resistance (IR). The triglycerides themselves form part of the TyG index, and so an increase would result in a higher TyG score.

6. Let us Explain Above Statement Deeper and More

Insulin resistance (IR) is a central component in the relationship between the TyG index and metabolic disorders.

When cells become resistant to the effects of insulin, the hormone can no longer effectively regulate glucose and lipid metabolism. The body compensates by producing more insulin, which can exacerbate the situation by increasing triglyceride synthesis in the liver. This scenario results in both higher glucose and triglyceride levels - the two factors used to calculate the TyG index, thereby leading to an increased index.

Fasting plasma glucose in early morning (FPG) is one of the best and a convenient biomarker indicating a person's health state of pancreatic beta cells since FPG is not under the influences from both food and exercise night sleep.

6.1 TyG and Triglycerides: Triglycerides (TG) are a type of fat (i.e. lipid) found in our blood. When we eat, our body converts any calories it doesn't need to use right away into triglycerides, which are stored in our fat cells. High triglyceride levels could be an indicator of a condition that increases the risk of heart disease, including obesity and metabolic syndrome, both of which can be related to insulin resistance. The triglycerides themselves form part of the TyG index, and so an increase of TG would result in a higher TyG score.

7. Let us Explain Above Statement Deeper and More

The relationship between TyG and triglycerides (TG) is direct, given that triglycerides are part of the calculation for the TyG index.

When insulin resistance occurs, it can disrupt the normal metabolic processes, leading to hypertriglyceridemia. High levels of circulating triglycerides indicate the presence of excessive very low-density lipoproteins (VLDL), a type of lipoprotein produced by the liver when there is excessive free fatty acid influx, often secondary to insulin resistance.

8. Pathophysiological Explanations of Insulin Resistance (IR) Versus Fasting Plasma Glucose (FPG) and Triglyceride-Glucose Index (TyG)

Insulin resistance refers to impaired cellular response to insulin, hindering glucose uptake. Elevated fasting plasma glucose (FPG) is a measure of high blood sugar levels after overnight fasting, indicating impaired glucose regulation. The Triglyceride-glucose index (TyG) combines fasting triglycerides and glucose levels, offering insights into insulin resistance and metabolic abnormalities. Insulin resistance may contribute to both elevated FPG and TyG, reflecting dysregulated glucose metabolism and lipid abnormalities. Understanding these biomarkers aids in assessing metabolic health and diabetes risk.

In this study, the author characterized his insulin resistance (IR) with the following formula:
IR = ((FPG/90) + (TyG/10)) / 2
This representation incorporates influences from both FPG and TyG.
To elaborate, approximately two- thirds of the weight in this formula is attributed to FPG (FPG plus the natural logarithm of FPG), while about one-third is assigned from triglycerides (actually, the natural logarithm of TG).

9. MPM Background

To learn more about his developed GH-Method: math-physical medicine (MPM) methodology, readers can read the following three papers selected from his published 760+ papers.

The first paper, No. 386 (Reference 1) describes his MPM methodology in a general conceptual format. The second paper, No. 387 (Reference 2) 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 (Reference 3) depicts a general flow diagram containing ~10 key MPM research methods and different tools.

10. The Author's Diabetes History

The author was a severe T2D patient since 1995. He weighed 220 lb. (100kg) 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 1161 (high risk for CVD and stroke) and his 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 need for kidney dialysis treatment and the future high risk of dying from his severe diabetic complications.

In 2010, he decided to self-study endocrinology with an emphasis on diabetes and food nutrition.
He spent the entire year of 2014 to develop a metabolism index (MI) mathematical model. During 2015 and 2016, he developed four mathematical prediction models related to diabetes conditions: weight, PPG, fasting plasma glucose (FPG), and HbA1C (A1C). Through using his developed mathematical metabolism index (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 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, dining out frequently, post-meal exercise disruption, and 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 COVID-19 self- quarantined life on 1/19/2020. By 10/16/2022, his weight was further reduced to ~164 lbs. (BMI 24.22) and his A1C was at 6.0% without any medication intervention or insulin injection. In fact, with the special COVID-19 quarantine lifestyle since early 2020, not only has he written and published ~500 new research articles in various medical and engineering journals, but he has also achieved his best health conditions for the past 27 years. These achievements have resulted from his non-traveling, low-stress, and regular daily life routines. Of course, his in- depth knowledge of 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. Furthermore, he extracted the 5- minute intervals from every 15-minute interval for a total of 96 glucose data each day stored in his computer software.

Through the author's medical research work over 40,000 hours and read over 4,000 published medical papers online in the past 13 years, he discovered and became convinced that good life habits of not smoking, moderate or no alcohol intake, avoiding illicit drugs; along with eating the right food with well- balanced nutrition, persistent exercise, having a sufficient and good quality of sleep, reducing all kinds of unnecessary stress, maintaining a regular daily life routine contribute to the risk reduction of having many diseases, including CVD, stroke, kidney problems, micro blood vessels issues, peripheral nervous system problems, and even cancers and dementia. In addition, a long-term healthy lifestyle can even "repair" some damaged internal organs, with different required time-length depending on the particular organ's cell lifespan. For example, he has "self-repaired" about 35% of his damaged pancreatic beta cells during the past 10 years.

11. Energy Theory

The human body and organs have around 37 trillion live cells which are composed of different organic cells that require energy infusion from glucose carried by red blood cells; and energy consumption from labor- work or exercise. When the residual energy (resulting from the plastic glucose scenario) is stored inside our bodies, it will cause different degrees of damage or influence to many of our internal organs.

According to physics, energies associated with the glucose waves are proportional to the square of the glucose amplitude. The residual energies from elevated glucoses are circulating inside the body via blood vessels which then impact all of the internal organs to cause different degrees of damage or influence, e.g. diabetic complications. Elevated glucose (hyperglycemia) causes damage to the structural integrity of blood vessels. When it combines with both hypertension (rupture of arteries) and hyperlipidemia (blockage of arteries), CVD or Stroke happens. Similarly, many other deadly diseases could result from these excessive energies which would finally shorten our lifespan. For an example, the combination of hyperglycemia and hypertension would cause micro-blood vessel's leakage in kidney systems which is one of the major cause of CKD.

The author then applied Fast Fourier Transform (FFT) operations to convert the input wave from a time domain into a frequency domain.

The y-axis amplitude values in the frequency domain indicate the proportional energy levels associated with each different frequency component of input occurrence.

Both output symptom value (i.e. strain amplitude in the time domain) and output symptom fluctuation rate (i.e. the strain rate and strain frequency) are influencing the energy level (i.e. the Y-amplitude in the frequency domain).

Currently, many people live a sedentary lifestyle and lack sufficient exercise to burn off the energy influx which causes them to become overweight or obese. Being overweight and having obesity leads to a variety of chronic diseases, particularly diabetes. In addition, many types of processed food add unnecessary ingredients and harmful chemicals that are toxic to the bodies, which lead to the development of many other deadly diseases, such as cancers. For example, ~85% of worldwide diabetes patients are overweight, and ~75% of patients with cardiac illnesses or surgeries have diabetes conditions.

In engineering analysis, when the load is applied to the structure, it bends or twists, i.e. deform; however, when the load is removed, it will either be restored to its original shape (i.e, elastic case) or remain in a deformed shape (i.e. plastic case). In a biomedical system, the glucose level will increase after eating carbohydrates or sugar from food; therefore, the carbohydrates and sugar function as the energy supply. After having labor work or exercise, the glucose level will decrease. As a result, the exercise burns off the energy, which is similar to load removal in the engineering case. In the biomedical case, both processes of energy influx and energy dissipation take some time which is not as simple and quick as the structural load removal in the engineering case. Therefore, the age difference and 3 input behaviors are "dynamic" in nature, i.e. time- dependent. *This*

time-dependent nature leads to a "viscoelastic or viscoplastic" situation. ***For the author's case, it is "viscoplastic" since most of his biomarkers are continuously improved during the past 13-year time window.***

Time-Dependent Output Strain and Stress of (Viscous Input*Output Rate)

Hooke's law of linear elasticity is expressed as:

Strain (ε: epsilon)
= Stress (σ: sigma) / Young's modulus (E)
For biomedical glucose application, his developed linear elastic glucose theory (LEGT) is expressed as:

PPG (strain) = carbs/sugar (stress)
**** GH.p-Modulus (a positive number) + post-meal walking k-steps * GH.w-Modulus (a negative number)***
Where GH.p-Modulus is reciprocal of Young's modulus E.
However, in viscoelasticity or viscoplasticity theory, the stress is expressed as:

Stress
= viscosity factor (η: eta) * strain rate (dε/dt)
Where strain is expressed as Greek epsilon or ε.

In this article, in order to construct an "ellipse-like" diagram in a stress- strain space domain (e.g. "hysteresis loop") covering both the positive side and negative side of space, he has modified the definition of strain as follows:

Strain
= (body weight at certain specific time instant)
He also calculates his strain rate using the following formula:

Strain rate
= (body weight at next time instant)
(body weight at present time instant)

The risk probability % of developing into CVD, CKD, Cancer is calculated based on his developed metabolism index model (MI) in 2014. His MI value is calculated using inputs of 4 chronic conditions, i.e. weight, glucose, blood pressure, and lipids; and 6 lifestyle details, i.e. diet, drinking water, exercise, sleep, stress, and daily routines. These 10 metabolism categories further contain ~500 elements with millions of input data collected and processed since 2010. For individual deadly disease risk probability %, his mathematical model contains certain specific weighting factors for simulating certain risk percentages associated with different deadly diseases, such as metabolic disorder- induced CVD, stroke, kidney failure, cancers, dementia; artery damage in heart and brain, micro-vessel damage in kidney, and immunity-related infectious diseases, such as COVID death.

Some of explored deadly diseases and longevity characteristics using the ***viscoplastic medicine theory (VMT)*** include stress relaxation, creep, hysteresis loop, and material stiffness, damping effect ***based on time-dependent stress and strain*** which are different from his previous research findings using ***linear elastic glucose theory (LEGT) and nonlinear plastic glucose theory (NPGT).***

12. Results

Figure 1 shows data table, Time- domain curves and SD-VMT energies.

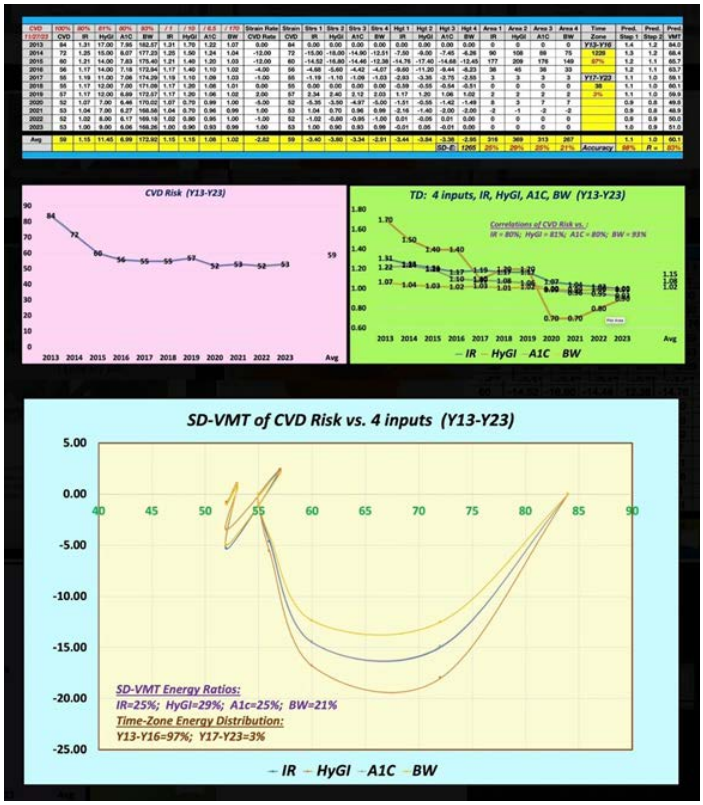

Figure 1: Data table, Time-domain curves and SD-VMT energies

13. Conclusions

In summary, the traditional statistical analysis reveals strong correlations (80% to 93%) between the author's cardiovascular disease (CVD) annual risk and his four biomarkers, aligning with his previous research findings. This study identifies four significant correlations:

- ***CVD vs. IR: 80%***
- ***CVD vs. HyGI: 81%***
- ***CVD vs. A1C: 80%***
- ***CVD vs. BW: 93%***

Additionally, the author uses the space-domain viscoplastic energy (SD-VMT) method to uncover hidden relationships and dynamics (i.e. energies) between these four biomarkers and his 11 years of annual CVD risks. This SD-VMT energy results reveal four contribution margins on CVD risks from four biomarkers:

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14. Key Message

The author's T2D conditions and overweight are indeed linked to his CVD risks. Despite representing only 2% of the glucose dataset, the HyGI (hyperglycemia intensity) contributes 29% of the total energy impact (or inflammation damages) on his CVD risks. Insulin resistance, and averaged glycemic value of A1c are secondary significant factors at 25% each, with body weight contributing the least at 21% in this 11-years CVD case study.

References

For editing purposes, majority of the references in this paper, which are self-references, have been removed for this article. Only references from other authors' published sources remain. The bibliography of the author's original self-references can be viewed at www.eclairemd.com. Readers may use this article as long as the work is properly cited, and their use is educational and not for profit, and the author's original work is not altered.

For reading more of the author's published VGT or FD analysis results on medical applications, please locate them through platforms for scientific research publications, such as ResearchGate, Google Scholar, etc.