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The GH-Method

Viscoelastic and Viscoplastic Glucose Theory (VGT #26): Investigation of the Relationships Between an Overall Metabolism Index and Type 2 Diabetes Utilizing HbA1C, Diabetic Nephropathy via Urinary Albumin-to-Creatinine Ratio, Along with Diabetic Retinopathy with Hypothyroidism Through Thyroid Stimulating Hormone Using Statistical Correlation Coefficient and VGT of GH-Method: Math-Physical Medicine (No. 607)

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Abstract

Over the past two years, the author self-studied certain biomarkers and their relationships with certain diabetic complications, such as albumin-to-creatinine ratio (ACR) for diabetic nephropathy, thyroid stimulating hormone (TSH) for hypothyroidism and diabetic retinopathy (DR). The medical papers he reviewed utilized statistical tools, including regression analysis, with input data collected from hundreds of different patients in hospitals (References 1-14). In this article, he uses his own collected data from the past ~9 years, where he applies a combined math-physical medicine tools, such as correlations (a statistics tool), viscoelastic and viscoplastic glucose theory (VGT, a physics tool) from engineering, and perturbation theory from quantum mechanics to investigate certain hidden behaviors of selected biomarkers, such as MI, HbA1C, ACR, TSH, and their associated diseases. Initially, he attempts to find relationships between two biomarkers, ACR and TSH. Although these two biomarkers belong to output variables of the human body, he tries to alter their roles with the following two assumptions: TSH influences ACR and ACR influences TSH. He then selects the metabolism index (MI) as the sole input variable of all outputs for endocrinological diseases, including diabetes, chronic kidney disease (CKD), and diabetic retinopathy (DR). The MI is an integrated value from 10 selected categories: weight, glucose, blood pressure, blood lipid, diet, exercise, stress, sleep, water intake, and daily life routines. Next, he utilizes the general health status unit (GHSU), which is the 90-days moving average value of MI for this analysis. The logic behind this decision is that MI, chronic disease biomarkers and lifestyle details, influences type 2 diabetes (T2D) which in turn impacts various diabetic complications, including CKD (ACR as biomarker), DR and hypothyroidism (TSH as biomarker). In summary, the research path from GHSU (or MI) to T2D, then from GHSU to ACR or CKD, and GHSU to TSH or DR. Along this biomedical pathway, the following six key findings are observed: (1) The correlation between GHSU and Daily A1C is 82% within a period from 5/29/2018 to 2/15/2022. But, the correlation between Daily A1C and lab-tested A1C is 74% over 16 discrete dates. Both correlations are quite high which indicates that the overall metabolism is indeed strongly influencing T2D conditions. (2) The correlation between GHSU and ACR is 74% (higher) while the correlation between GHSU and TSH is only 48% (lower and moderate). This means that the metabolism has a much stronger connection with ACR (related to kidney diseases), but it has a lesser degree of connectivity with TSH (related to DR and hypothyroidism). (3) The correlation between two outputs (symptoms), ACR and TSH, is a moderate 58%. This signifies that ACR and TSH are connected but not as strong as the connectivity between metabolism and T2D. (4) Using a viscoelastic perturbation model, his predicted lab-test HbA1C values in comparison with his lab-measured HbA1C values have 100% prediction accuracy with a very high correlation of 94%. This means that the viscoelastic perturbation model is quite practical on predicting T2D using metabolism (GHSU) as its input (or viscosity factor). (5) In comparing the four stress-strain diagrams from the following 4 VGT analyses, "TSH using ACR versus TSH using GHSU, and ACR using TSH versus ACR using GHSU". These 4 stress-strain diagrams only have

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two curve types which are dependent on the strain selection of either ACR or TSH, regardless of the input variable selection. The observed conclusion is that the stress-strain curve shapes have been determined by the strain (ε of x-axis) and strain rate (dε/dt). And, the selection of input variables as the viscosity factor (η) only changes the magnitude of the stress scale (σ of y-axis). (6) By judging the first line segment and the last line segment (two red-line segments) of the stress-strain diagram, the two first red-line segments reached their maximum strain values (ACR and TSH) which are close to the upper limits of the ACR and TSH biomarkers. However, the end segments almost return to their starting point locations. In addition, both ACR and TSH are time-dependent (i.e. their values change with time) which are shown with the existence of hysteresis loops. These observations have indicated a "pseudo-viscoelastic" behavior. In conclusion, metabolism does affect both T2D via HbA1C and diabetic nephropathy via ACR, but with a smaller amount of influences on DR and hypothyroidism via TSH. The viscoelastic glucose theory and the viscoelastic perturbation model have offered some practical assistance on discovering additional hidden behaviors of the biomarkers. Therefore, it is a useful tool for developing certain predicted biomarker values.

Keywords: Viscoelastic; Viscoplastic; Metabolism index; Type 2 diabetes; Diabetic nephropathy; Hypothyroidism; Thyroid stimulating hormone

Abbreviations: ACR: albumin-to-creatinine ratio; TSH: thyroid stimulating hormone; DR: diabetic retinopathy; MI: metabolism index; CKD: chronic kidney disease; GHSU: general health status unit; T2D: type 2 diabetes; HbA1C: hemoglobin A1C; MPM: math-physical medicine

1. INTRODUCTION

Over the past two years, the author self-studied certain biomarkers and their relationships with certain diabetic complications, such as albumin-to-creatinine ratio (ACR) for diabetic nephropathy, thyroid-stimulating hormone (TSH) for hypothyroidism, and diabetic retinopathy (DR). The medical papers he reviewed utilized statistical tools, including regression analysis, with input data collected from hundreds of different patients in hospitals (References 1-14). In this article, he uses his own collected data from the past ~9 years, where he applies combined math-physical medicine tools, such as correlations (a statistics tool), viscoelastic and viscoplastic glucose theory (VGT, a physics tool) from engineering, and perturbation theory from quantum mechanics to investigate certain hidden behaviors of selected biomarkers, such as MI, HbA1C, ACR, TSH, and their associated diseases.

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He then selects the metabolism index (MI) as the sole input variable of all outputs for endocrinological diseases, including diabetes, chronic kidney disease (CKD), and diabetic retinopathy (DR). The MI is an integrated value from 10 selected categories: weight, glucose, blood pressure, blood lipid, diet, exercise, stress, sleep, water intake, and daily life routines. Next, he utilizes the general health status unit (GHSU), which is the 90-days moving average value of MI for this analysis. The logic behind this decision is that MI, chronic disease biomarkers, and lifestyle details, influence type 2 diabetes (T2D) which in turn impacts various diabetic complications, including CKD (ACR as biomarker), DR, and hypothyroidism (TSH as biomarker).

2. METHODS

Note by the author: Generally speaking, T4 and T3 can exert negative feedback on TSH levels (high levels of T3/T4 decrease TSH release from the anterior pituitary, while low levels of T3/T4 increase TSH release). T3 is the predominant inhibitor of TSH secretion. However, A moderate inverse relationship was observed between TSH and T4 ($r = 0.73$), in contrast to TSH and T3 which showed comparatively poor relationships ($r = 0.41$ - 0.43).

2.1 Diabetes, CKD & DR

The author self-studied diabetes and its complications over the past 12 years. The following information is excerpts from multiple articles he has read and collected (References 1 through 14).

"Diabetes mellitus is a lifelong, incapacitating disease affecting multiple organs. Worldwide figures estimate that there were 422 million diabetic patients in 2014. The National Diabetes Statistics Report 2020 by the CDC in the USA also estimates that 34.2 million Americans, just over 1 in 10, have diabetes in 2020.

The American Diabetes Association (ADA) released research on March 22, 2018, estimating the total costs of diagnosed diabetes have risen to $327 billion in 2017 from $245 billion in 2012. This figure represents a 26% increase over a five-year period. The total estimated 2017 cost of diagnosed diabetes of $327 billion includes $237 billion in direct medical costs and $90 billion in reduced productivity.

The largest components of medical expenditures are:

- Hospital inpatient care (30% of the total medical cost)
- Prescription medications to treat complications of diabetes (30%)
- Anti-diabetic agents and diabetes supplies (15%)
- Physician office visits (13%)

People with diagnosed diabetes incur average medical expenditures of $16,752 per year, of which about $9,601 is attributed to diabetes (57% of total expenditures). On average, they have medical expenditures approximately 2.3 times higher than what expenditures would be in the absence of diabetes.

Diabetes is associated with devastating chronic complications including coronary heart disease and stroke (macro-vascular disease) as well as microvascular disorders leading to damage of the small blood vessels of the kidney (nephropathy), eye (retinopathy) and peripheral nerves (neuropathy). These complications impose an immense burden on the quality of life of the diabetes patients.

Note by the author: Hyperglycemia causes different degrees of damage to both macro and micro blood vessels as well as nerves which induces stroke, cardiovascular diseases (CVD), diabetic neuropathy or chronic kidney diseases (CKD), diabetic retinopathy (DR), etc.

Urinary albumin-to-creatinine ratio (ACR) is a biomarker of diabetic nephropathy (kidney complications) and microvascular damage. Metabolic-related traits are observationally associated with ACR, including glycemic, lipid, and adiposity traits. Specifically, insulin resistance (for example, two TyG biomarkers including logarithm of both TG and FPG) which are associated with elevated ACR levels and microvascular damage.

The thyroid-stimulating hormone (TSH aka thyrotropin or thyrotrophin) is produced by the pituitary gland. It works sort of like the master of the hormones, and rules the production of T3 and T4 from its control center. If you have too much TSH, it might mean that your thyroid gland isn't making enough T3 or T4. Remember, the TSH is supposed to stimulate the thyroid gland. But if the gland isn't responding, then we will have too much TSH in our system. On the other hand, if our TSH levels are too low, it may mean that our thyroid gland is making too much thyroid hormone. This excessive thyroid production could actually suppress the TSH to a low level.

My friend, Dr. Nelson Hendler, also advised the following:

"For evaluation of thyroid function, you need to consider not only the thyroid gland but the pituitary and immune system. So measurements of Thyroid Stimulating Hormone and T4 are not enough. You need to look at mitochondrial and autoimmune features seen in Hashimoto's thyroiditis.

#1 Thyroid Stimulating Hormone (TSH)
#2 Free T3 (Free Triiodothyronine)
#3 Free T4 (Free Thyroxine)
#4 Total T3
#5 Reverse T3 (Reverse Triiodothyronine)
#6 Sex Hormone Binding Globulin
#7 Thyroglobulin Antibodies (TGAb) & Thyroid Peroxidase Antibodies
#8 Thyroid Stimulating Immunoglobulins (TSI)
#9 Thyroid binding globulin."

Article of ACR and TSH:

Here is an excerpt of the article from a Saudi Arabia hospital, "Association of Serum Thyroid Stimulating Hormone and Free Thyroxine with Urinary Albumin Excretion in Euthyroid Subjects with Type 2 Diabetes Mellitus":

"Our study demonstrated that abnormalities in thyroid function occur in patients with T2DM and proteinuria. Specifically, TSH levels were higher and FT4 levels were lower in patients with albuminuric diabetic renal diseases (higher ACR). The interplays between thyroid and kidney have been recognized in many disease states. Thyroid dysfunction can influence kidney through the immune-mediated pathway and thyroid hormones [18]. The thyroid disorder and coincident nephropathy have been reported mainly in the patients presented with albuminuria [19,20]. In this situation, thyroid hormone may influence glomerular and tubular functions through pre-renal and intrinsic renal effects. Thyroid hormones influence renal development, kidney structure, renal hemodynamics, glomerular filtration rate, the function of many transport systems along the nephron and sodium and water homeostasis. These effects of thyroid hormone are due to direct renal actions and in part are mediated by cardiovascular and systemic hemodynamic effects that influence kidney function. Disorders of thyroid function have also been linked to development of immune mediated glomerular injury and alterations in thyroid hormones and thyroid hormone testing occur in patients with kidney disease.

The TSH level is often elevated in CKD in response to TSH from pituitary as a result of uremic effect [22]. In agreement to our study, patients with severely increased albuminuria has the worst HbA1c compared to NA

(normal albuminuria) and moderately increased albuminuria patients, 9.2 ± 2.1 versus8.6 ± 2.2 and 7.9 ± 2.1 respectively, $p < 0.0001$ [23]. TSH also loses its circadian rhythm along with compromised bioactivity due to poor glycosylation. The Wolffe Chaikoff effect has been cited as a causative phenomenon behind the rise of this disorder in diabetic kidney disease patients [24].

In agreement to our study, we found that patients with severely increased albuminuria were significantly have lower FT4 than patients with NA and moderately increased albuminuria, 15.3 ± 1.9 versus16.1 ± 2.5 and 15.4 ± 2.6 respectively, $p = 0.045$ [12]. The role of albuminuria is confirmed by the significant positive correlation between TSH and albuminuria, $r = 0.08$, $p = 0.01$ and nonsignificant negative correlation between FT4 and albuminuria, $r = -0.07$, $p = 0.2$. Proteinuria is a hallmark of renal diseases. Severe albuminuria results in hypoalbuminaemia. Albumin is the most abundant protein in serum and urine. In patients with albuminuria many other proteins beside albumin are lost in the urine. Among these are hormones and hormone-binding proteins. Several studies have documented urinary loss of thyroid hormones and thyroxin-binding globulin (TBG) in patients with albuminuria [25-28]. In patients with the nephrotic syndrome, loss of thyroid hormones may lead to low free thyroid hormone levels unless production is increased under the influence of TSH. Furthermore, loss of albumin and TBG may reduce the binding capacity for thyroid hormones, resulting in a decrease in total T4 concentrations.

We conclude that despite the limitations of this hospital-based retrospective study, high TSH and low FT4 levels are highly prevalent in cohort of Saudis with albuminuria and T2DM. The majority of our patients in our finding were predominantly females. These two observations remain to be validated by population-based studies.

Article of ACR using Mendelian Randomization (MR) method:

Professor Jessica Terrell has conducted a study regarding the ACR and published a paper: "A Mendelian Randomization Study Provides Evidence That Adiposity and Dyslipidemia Lead to Lower Urinary Albumin-to-Creatinine Ratio, a Marker of Microvascular Function".

Here is an excerpt from their paper:

"Here, we confirmed ACR as a marker of microvascular damage and tested whether metabolic-related traits have causal relationships with ACR. The association between ACR and microvascular function was tested in the SUMMIT study. Two-sample Mendelian randomization (MR) was used to infer the causal effects of 11 metabolic risk factors, including glycemic, lipid, and adiposity traits, on ACR. MR was performed in up to 440,000 UK Biobank and 54,451 CKDGen participants. ACR was robustly associated with microvascular function measures in SUMMIT. Using MR, we inferred that higher triglyceride (TG) and LDL cholesterol (LDL-C) levels caused elevated ACR. A 1 SD higher TG and LDL-C level caused a 0.062 (95% CI 0.040, 0.083) and a 0.026 (95% CI 0.008, 0.044) SD higher ACR, respectively. There was evidence that higher body fat and visceral body fat distribution caused elevated ACR, while a metabolically "favorable adiposity" phenotype lowered ACR. ACR is a valid marker for microvascular function. MR suggested that seven traits have causal effects on ACR, highlighting the role of adiposity-related traits in causing lower microvascular function.

The urinary albumin-to-creatinine ratio (ACR), a marker of diabetic nephropathy, is used as a proxy for damage to the systemic microcirculation (1) and predicts first myocardial infarction and mortality in those with diabetes, poststroke, and in the general population (2–4). There is evidence linking metabolic-related traits, including adiposity, dyslipidemia, and insulin resistance with elevated ACR levels and microvascular damage (5,6). It is well accepted that tight glucose control in patients with type 2 diabetes (T2D) reduces the risk of microvascular retinal complications (7,8), and there is evidence that adiposity per se is associated with increased ACR. For example, population studies suggest that microalbuminuria is associated with central adiposity (9), and results from the Framingham Heart Study show that visceral but not subcutaneous fat is associated with increased albuminuria (10). Not all evidence linking metabolic-related traits comes from

randomized control trials, and in absence of these, the next best evidence of causality comes from genetic studies using a technique known as Mendelian randomization (MR).

Mendelian randomization study:

The following is a simple explanation of the Mendelian randomization (MR) study from Wikipedia:

"Mendelian randomization (MR) is a method that allows one to test for, or in certain cases to estimate, a causal effect from observational data in the presence of confounding factors. From a statistical perspective, Mendelian randomization (MR) is an application of the technique of "instrumental variables" with genotype acting as an instrument for the exposure of interest. The method has also been used in economic research studying the effects of obesity on earnings, and other labor market outcomes. The accuracy of MR depends on a number of assumptions: That there is no direct relationship between the instrumental variable and the dependent variables, and that there are no direct relations between the instrumental variable and any possible confounding variables.

Article of "Free Triiodothyronine Levels Are Associated with Nephropathy in Euthyroid Patients with Type 2 Diabetes" by Jingcheng Wu, Xiaohua Li, and Yongde Peng:

"Objective. to investigate the association of thyroid function and diabetic nephropathy (DN) in euthyroid patients with type 2 diabetes.

Methods. A total of 421 patients were included in this cross-sectional study. Patients with urinary albumin-to-creatinine ratio (UACR) of ≥30 mg/g were defined as those suffering from DN.

Results. Of the 421 patients, 203 (48.2%) suffered from DN.

Conclusion. Serum FT3 levels are inversely associated with DN in euthyroid patients with type 2 diabetes, independent of traditional risk factors.

Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes mellitus and the leading cause of end-stage renal disease worldwide and accounts for a significant increase in morbidity and mortality in diabetic patients.

Several clinical studies show that thyroid dysfunction is related to renal disease. Moreover, recent studies on the euthyroid general population show that high normal levels of thyroid-stimulating hormone (TSH) and low normal levels of free triiodothyronine (FT3) are also associated with renal dysfunction, such as CKD and microalbuminuria.

Previous studies have shown a close interrelationship between thyroid hormone and DN. Type 2 diabetic patients with subclinical hypothyroidism (SCH) are associated with a high prevalence of DN in several studies.

eGFR was calculated using the equation of the Modification of Diet in Renal Disease: eGFR (mL/min/1.73 m2) = 186 × (serum creatinine (SCr)/88.4)−1.154 × (age)−0.203 × (0.742 if female).

Non-normally distributed variables, such as HbA1c, TG, TSH, and UACR, were natural log-transformed or arctan-transformed into approximately normal distributed data before correlation and regression analysis was conducted. The independent determinants of UACR were identified through multiple linear regression analysis. A two-tailed P value of <0.05 was considered statistically significant.

Among the 421 patients, 203 (48.2%) were diagnosed with DN. The patients with DN were older than those without DN. The patients with DN also experienced longer diabetic duration and exhibited higher BMI, SBP, and DBP, higher FPG, SCr, TG, and TC levels, and lower serum HDL-C and eGFR levels than those without DN. The patients with DN also showed a higher prevalence of hypertension and DR than those without DN. Furthermore, the patients with DN yielded significantly lower FT3 levels than those without DN. The former also showed higher TSH levels and lower FT4 levels than the latter; however, the obtained values were not statistically significant.

Thyroid hormone plays an important role in the growth, development, and physiology of the kidneys. Thyroid dysfunction causes

remarkable changes in renal blood flow, glomerular filtration rate, tubular secretory and absorptive capacity, electrolyte pumps, and kidney structure [16]. The results of previous studies suggest that overt and subclinical hypothyroidism are both associated with reduced eGFR and high prevalence of CKD and that these abnormalities can be normalized through thyroid hormone replacement therapy [2–5]. In a cross-sectional and multicentric study on patients with type 1 diabetes, Rodacki et al. found that patients with low normal TSH levels (0.4–2.5 mIU/L) are associated with a lower risk of renal failure than patients with SCH (TSH ≥ 4.5 mIU/L) and high normal TSH levels (2.5–4.4 mIU/L). The above two studies both suggest that low normal FT3 levels are independently associated with kidney diseases.

In summary, our study suggests that serum FT3 levels are inversely associated with DN in euthyroid patients with type 2 diabetes, which is independent of other risk factors."

Article of "An Association Between Subclinical Hypothyroidism (SCH) and Sight-Threatening Diabetic Retinopathy (STDR) in Type 2 Diabetic Patients" by Jin-Kui Yang, MD, PHD, Wei Liu, MD, and Yi-Bing Li, MD, PHD:

"To determine the relationship between subclinical hypothyroidism (SCH) and the prevalence of diabetic retinopathy in type 2 diabetic patients.

A total of 1,170 type 2 diabetic patients were screened for thyroid function. There were 127 type 2 diabetic patients with SCH and 200 randomly selected euthyroid type 2 diabetic patients selected. Those with more severe than moderate nonproliferative diabetic retinopathy were classified as having sight-threatening diabetic retinopathy (STDR).

The trend for severe retinopathy was significantly higher in the SCH group than in the euthyroid group ($\chi 2 = 20.43$, $P = 0.000$). SCH was associated with a greater prevalence of diabetic retinopathy, especially STDR. Even euthyroid patients with thyroid-stimulating hormone levels between 2.0 and <4.0 μIU/ml had a higher rate of STDR than those between 0.4 and <2.0 μIU/ml ($P = 0.008$).

Conclusions

Type 2 diabetic patients with SCH (high TSH) are associated with an increased risk of STDR.

Subclinical hypothyroidism (SCH) is defined as an asymptomatic state characterized by a normal serum thyroxin level and elevated serum concentration of thyrotropin (thyroid-stimulating hormone [TSH]). Patients with SCH sustain an obvious increase in cardiovascular event rates. Despite this, there is a distinct lack of relevant research into risk factors associated with microvascular complications in type 2 diabetes with SCH. In fact, only a single study conducted by Chen et al. has attempted to elucidate these issues. Yet this study focused predominantly on the issue of diabetic nephropathy, as defined solely by elevated microalbuminuria, rather than retinopathy.

SCH is a common endocrine disorder and has been reported to range from 4 to 10% in large general population screening surveys and has been found to be 4–17% in diabetic patients in previous studies.

SCH is an asymptomatic stage of hypothyroidism, but it is often complicated with endothelial dysfunction, including capillary and precapillary arterioles, manifested by thickening of the capillary basement membrane. Serum high-sensitive C-reactive protein levels in subjects with SCH were higher than control subjects. These changes lead to small vessel dysfunction, increasing the prevalence of retinopathy. The reference range for "normal" TSH has been the focus of considerable debate. Some clinicians have advocated reducing the upper limit of the normal reference interval for TSH to 2.5 or 3.0 mIU/l. Individuals in the 3.0–5.0 mIU/l TSH range are considered as possibly exhibiting the early signs of developing hypothyroidism, prompting continued monitoring. Our study supports this, since euthyroid patients with TSH levels between 2.0 and <4.0 μIU/ml demonstrated a higher rate of STDR than patients with levels between 0.4 and <2.0 μIU/ml.

Our findings suggest that type 2 diabetic patients with SCH demonstrated a higher prevalence of retinopathy than their non-SCH counterparts."

Article of "Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients" by H-S Chen, T-E J Wu, T-S Jap, R-A Lu, M-L Wang, R-L Chen, H-D Lin:

"Aims: The purpose of this study was to determine the relationship between subclinical hypothyroidism and prevalence of retinopathy and nephropathy, incident cardiovascular disease, and mortality in Type 2 diabetic patients without taking thyroid medication.

Methods: Serum thyrotropin and free thyroxine concentrations were measured in 588 Type 2 diabetic subjects in Taipei Veterans General Hospital, Taiwan. In a cross-sectional study, we examined the prevalence of retinopathy and nephropathy. In a longitudinal study, we examined the risk of cardiovascular disease events, cardiovascular mortality and total mortality in the 4-year follow-up.

Results: In the cross-sectional analysis, subclinical hypothyroidism was associated with a greater prevalence of diabetic nephropathy (odds ratio, 3.15 [95% CI, 1.48-6.69]) and did not show a high prevalence of diabetic retinopathy (odds ratio, 1.15 [95% CI, 0.59-2.26]) compare to euthyroid diabetics. During the 44.0 +/- 7.4 months of follow-up, 51 participants had cardiovascular events. The risk of cardiovascular events was significantly increased in Type 2 diabetics with subclinical hypothyroidism after adjustment for age, sex, A1C, other standard cardiovascular risk factors and medication (hazard ratio, 2.93; 95% CI, 1.15-7.48; P = 0.024), but it became nonsignificant after additional adjustment for urinary albumin-to-creatinine ratio (hazard ratio, 2.06; 95% CI, 0.67-6.36; P = 0.211). The rates of cardiovascular-related and total mortality did not significantly differ by thyroid status.

Conclusions: Type 2 diabetic patients with subclinical hypothyroidism are associated with an increased risk of nephropathy and cardiovascular events, but not with retinopathy. Our data suggest that the higher cardiovascular events in subclinical hypothyroidism with Type 2 diabetes may be mediated with nephropathy."

2.2 Input biomarker data of this study

The author was diagnosed with a severe metabolic disorder for over 25 years, including T2D (HbA1C at 10%), hyperlipidemia (TG at 1161 in 2010), hypertension (SBP 150, DBP 92), five cardiac episodes (during 1994-2008), kidney complications (ACR at 160 in 2010), foot ulcer (infected toe for over 3 months), diabetic retinopathy (microvascular complications), and hypothyroidism (TSH 6.32). His two calculated TyG values in 2010 were extremely high, TyG-A at 6.18 and TyG-B at 6.52. As a result, during the period of 2002 through 2010, he has suffered all of the known diabetic complications, including CVD, CKD, DR, neuropathy, etc., except for a stroke.

During the past 9 years, he has maintained a routine of having his medical examination conducted at the same medical laboratory or hospital quarterly. However, his main focus has been on controlling his diabetes conditions; therefore, he has paid more attention to his diabetes and glucose directly-related biomarkers, particularly HbA1C. For the past 9 years from 2013 to 2021, he has had 36 medical examinations which include 15 examinations containing ACR and TSH data. That is why he can only apply these 15 cases for this study. As a long-term patient of chronic diseases and a dedicated endocrinology research scientist, he concentrated on his health conditions first to save his own life. As a result, he is most familiar with his own body situations and health conditions through his 12 years of self-study on medicine and his persistent medical research efforts using his~3 million collected data.

This particular study period covers ~8 years, about 96 months, where he utilized 15 datasets of consistent biomarkers with an average of 6.4 months for each sub-period between two adjacent medical examinations. From a macro-viewpoint, all of these 15 biomarkers should be more or less stabilized (i.e., near-constant) during each sub-period of 6.4 months.

2.3 Pearson's correlation coefficient

The calculated results of the correlation coefficient (R) between ACR/TSH versus the

other 12 biomarkers used the formula in the following table from Wikipedia:

Pearson's correlation coefficient, when applied to a sample, is commonly represented by r_{xy} and may be referred to as the *sample correlation coefficient* or the *sample Pearson correlation coefficient*.[9] We can obtain a formula for r_{xy} by substituting estimates of the covariances and variances based on a sample into the formula above. Given paired data $\{(x_1, y_1), \ldots, (x_n, y_n)\}$ consisting of n pairs, r_{xy} is defined as:

$$r_{xy} = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2}\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2}} \quad \text{(Eq.3)}$$

where:

n is sample size

x_i, y_i are the individual sample points indexed with i

$\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$ (the sample mean); and analogously for $\bar{y}$

2.4 Viscoelasticity, viscoplasticity and perturbation model

The authors will not explain this subject in details due to his concerns of the size of this article. Instead, he will just list their associated key equations.

Normally, a system or a problem would have some input variables (causes or stressors) and some output variables (symptoms or behaviors). Usually, the researcher's job is to identify the relationship between the input variable (such as metabolism) and the output variable (such as glucose, ACR, or TSH) However, sometimes, certain situations requires the researcher to investigate the relationship between two inputs (metabolism and HbA1C) or between two outputs (ACR and TSH).

Nevertheless, in the theories of viscoelasticity and viscoplasticity, the author defines two equations at below:

Strain (ε)
= output or biomedical symptom;

Stress (σ)
= input or biomedical cause;

Stress (σ)
= (strain change rate) * (viscosity factor η)
= (dε/dt) * η

Note: For a more detailed description, please refer to the "consolidated method" section which is given at the beginning of the special issue.

3. RESULTS

Figure 1 shows two input data tables of selected biomarkers and their calculation results.

	<30mg/mmol			<4.0mU/L		
Date	ACR	ACR Stress	*ACR Area*	TSH	TSH Stress	*TSH Area*
8/9/13	19	0.0	256	3.02	0.0	152
2/5/14	28	56.9	-109	6.32	92.4	-15
8/20/14	23	-13.4	55	2.67	-84.0	47
8/6/15	18	-8.7	-7	1.74	-16.7	6
10/9/15	21	3.8	28	1.28	-9.7	0
9/1/16	13	-10.9	6	1.36	1.0	0
6/11/17	12	-1.5	7	1.45	1.1	3
9/12/17	15	6.2	0	2.05	9.0	5
1/26/18	15	0.0	0	2.64	8.9	2
10/22/18	15	0.0	78	2.92	4.2	1
4/4/19	22	22.3	-18	3.19	5.9	0
9/25/19	16	-16.3	-5	2.71	-7.7	47
10/21/20	17	5.3	-1	5.31	44.2	-2
4/23/21	16	-2.7	0	2.65	-42.6	-3
10/22/21	17	2.8	2	2.81	2.7	0
Data Average	17.8	2.9	*292*	2.81	0.59	*244*
Correlation (R)	ACR vs ACR			ACR vs TSH		
R = N/D	100%			58%		

2/16/22	Diabetes		Metabolism	
	Lab A1C	T2D Stress	GHSU	Predicted A1C
5/29/18	6.8	0.0000	0.5553	6.8
6/29/18	6.5	-0.1692	0.5640	6.3
10/22/18	6.6	0.0573	0.5733	6.7
1/18/19	7.0	0.2320	0.5799	7.2
2/12/19	6.7	-0.1733	0.5776	6.5
2/13/19	6.7	0.0000	0.5760	6.7
4/4/19	6.8	0.0599	0.5995	6.9
7/11/19	6.7	-0.0609	0.6090	6.6
9/25/19	6.6	-0.0571	0.5707	6.5
12/20/19	6.6	0.0000	0.5659	6.6
10/21/20	6.2	-0.2064	0.5161	6.0
1/28/21	6.1	-0.0509	0.5093	6.0
4/19/21	6.8	0.3516	0.5095	7.1
7/21/21	6.3	-0.2651	0.5410	6.0
10/22/21	6.0	-0.1587	0.5471	5.9
2/8/22	6.2	0.1028	0.5412	6.3
Average	6.5	0.0	0.6	6.5
Correlation	58%			94%

Figure 1: Data table of input biomarker values and calculation results.

Figure 2 displays time-domain of ACR, TSH, and GHSU*30 (upper diagram), spatial-domain of stress-strain diagram of HbA1C vs. GHSU (middle diagram), and predicted lab-tested HbA1C values using visco-perturbation model (lower diagram).

Figure 3 shows four stress-strain diagrams with only two types of curve shapes for both ACR versus TSH and GHSU respectively; and TSH versus ACR and GHSU respectively.

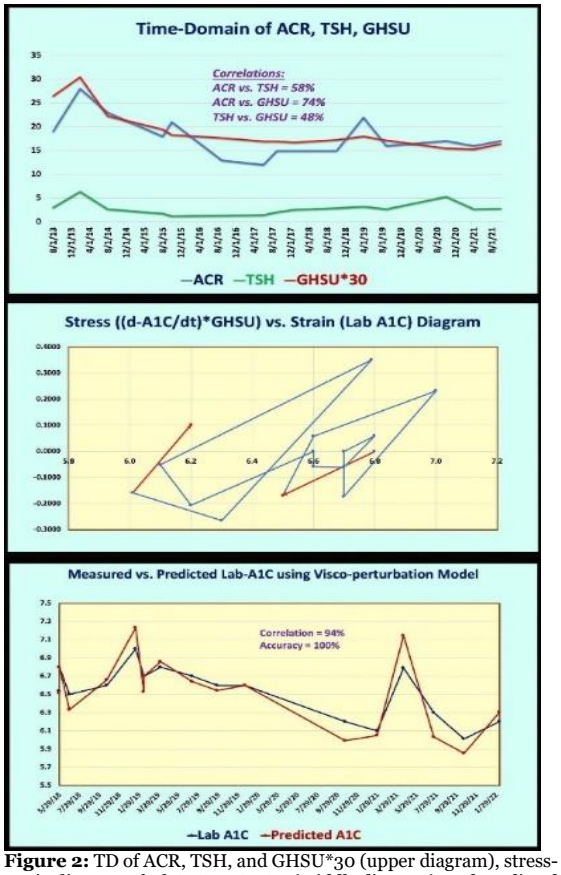

Figure 2: TD of ACR, TSH, and GHSU*30 (upper diagram), stress-strain diagram of HbA1C vs. GHSU (middle diagram), and predicted lab-tested HbA1C using visco-perturbation model (lower diagram).

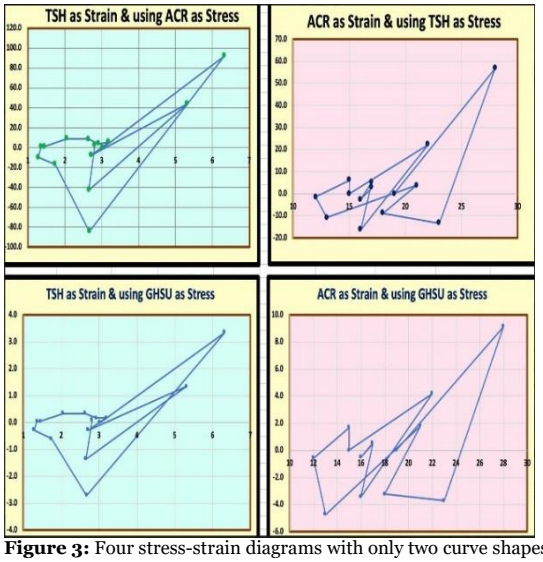

Figure 3: Four stress-strain diagrams with only two curve shapes.

4. CONCLUSION

In summary, the research path from GHSU (or MI) to T2D, then from GHSU to ACR or CKD, and GHSU to TSH or DR. Along this biomedical pathway, the following six key findings are observed:

(1) The correlation between GHSU and Daily A1C is 82% within a period from 5/29/2018 to 2/15/2022. But, the correlation between Daily A1C and lab-tested A1C is 74% over 16 discrete dates. Both correlations are quite high which indicates that the overall metabolism is indeed strongly influencing T2D conditions.

(2) The correlation between GHSU and ACR is 74% (higher) while the correlation between GHSU and TSH is only 48% (lower and moderate). This means that the metabolism has a much stronger connection with ACR (related to kidney diseases), but it has a lesser degree of connectivity with TSH (related to DR and hypothyroidism).

(3) The correlation between two outputs (symptoms), ACR and TSH, is a moderate 58%. This signifies that ACR and TSH are connected but not as strong as the connectivity between metabolism and T2D.

(4) Using a viscoelastic perturbation model, his predicted lab-test HbA1C values in comparison with his lab-measured HbA1C values have 100% prediction accuracy with a very high correlation of 94%. This means that the viscoelastic perturbation model is quite practical in predicting T2D using metabolism (GHSU) as its input (or viscosity factor).

(5) In comparing the four stress-strain diagrams from the following 4 VGT analyses, "TSH using ACR versus TSH using GHSU, and ACR using TSH versus ACR using GHSU". These 4 stress-strain diagrams only have two curve types which are dependent on the strain selection of either ACR or TSH, regardless of the input variable selection. The observed conclusion is that the stress-strain curve shapes have been determined by the strain (ε of the x-axis) and strain rate ($d\varepsilon/dt$). And, the selection of input variables as the viscosity factor (η) only changes the magnitude of the stress scale (σ of the y-axis).

(6) By judging the first line segment and the last line segment (two red-line segments) of the stress-strain diagram, the two first red-line segments reached their maximum strain values (ACR and TSH) which are close to the upper limits of the ACR and TSH biomarkers. However, the end segments almost return to their starting point locations. In addition, both ACR and TSH are time-dependent (i.e. their values change with time) which is shown by the existence of hysteresis loops.

These observations have indicated a "pseudo-viscoelastic" behavior.

In conclusion, metabolism does affect both T2D via HbA1C and diabetic nephropathy via ACR, but with a smaller amount of influence on DR and hypothyroidism via TSH. The viscoelastic glucose theory and the viscoelastic perturbation model have offered some practical assistance in discovering additional hidden behaviors of the biomarkers. Therefore, it is a useful tool for developing certain predicted biomarker values.

5. REFERENCES

1) Aljabri KS, Alnasser IM, Bokhari SA, Alshareef MA, Khan PM, et al. (2019) Association of Serum Thyroid Stimulating Hormone and Free Thyroxine with Urinary Albumin Excretion in Euthyroid Subjects with Type 2 Diabetes Mellitus. Int J Diabetes Clin Res 6:102.

2) Thyroid Disease and Diabetes. Diabetes Spectrum. 2002; 15(3):143-143.

3) Gary Gilles. Thyroid Disease and Diabetes. 2019.

4) Ladenson PW, Singer PA, Kenneth BA, et al. American Thyroid Association Guidelines for Detection of Thyroid Dysfunction. 2000.

5) Casanova F, Wood AR, Yaghootkar H, Beaumont RN, Jones SE, Gooding KM, Aizawa K, Strain WD, Hattersley AT, Khan F, Shore AC, Frayling TM, Tyrrell J. A Mendelian Randomization Study Provides Evidence That Adiposity and Dyslipidemia Lead to Lower Urinary Albumin-to-Creatinine Ratio, a Marker of Microvascular Function. Diabetes. 2020 May;69(5):1072-1082.

6) ADA-American Diabetes Association. The cost of diabetes.

7) de Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. J Am Soc Nephrol. 2006 Aug;17(8):2100-5.

8) Strickland AL, Rossetti HC, Peshock RM, Weiner MF, Nakonezny PA, McColl RW, Hulsey KM, Das SR, King KS. Urinary albumin to creatinine ratio as potential biomarker for cerebral microvascular disease. Curr Neurovasc Res. 2014;11(3):242-7.

9) Seliger SL, Salimi S, Pierre V, Giffuni J, Katzel L, Parsa A. Microvascular endothelial dysfunction is associated with albuminuria and CKD in older adults. BMC Nephrol. 2016 Jul 13;17(1):82.

10) de Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. J Am Soc Nephrol. 2006 Aug;17(8):2100-5.

11) Mohammedi K, Woodward M, Marre M, Colagiuri S, Cooper M, Harrap S, Mancia G, Poulter N, Williams B, Zoungas S, Chalmers J. Comparative effects of microvascular and macrovascular disease on the risk of major outcomes in patients with type 2 diabetes. Cardiovasc Diabetol. 2017 Jul 27;16(1):95.

12) Wu J, Li X, Tao Y, Wang Y, Peng Y. Free Triiodothyronine Levels Are Associated with Diabetic Nephropathy in Euthyroid Patients with Type 2 Diabetes. Int J Endocrinol. 2015;2015:204893.

13) Chen HS, Wu TE, Jap TS, Lu RA, Wang ML, Chen RL, Lin HD. Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. Diabet Med. 2007 Dec;24(12):1336-44.

14) Yang JK, Liu W, Shi J, Li YB. An association between subclinical hypothyroidism and sight-threatening diabetic retinopathy in type 2 diabetic patients. Diabetes Care. 2010 May;33(5):1018-20.

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Viscoelastic and Viscoplastic Glucose Theory Application in Medicine

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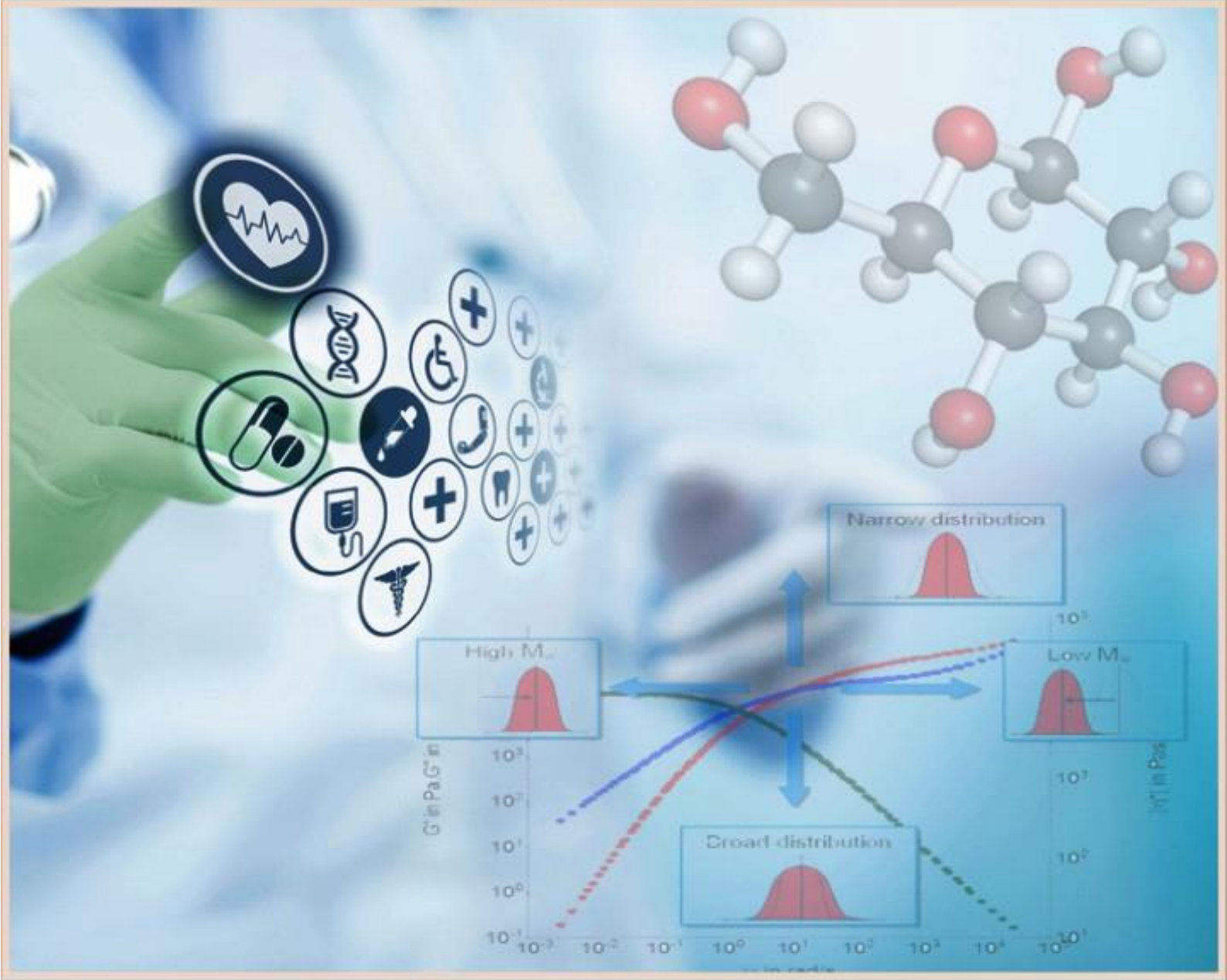

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