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Special Issue

Diabetic Retinopathy Study *via* Metabolism Improvements and Chronic Diseases Medical Conditions Control of HbA1C, SBP, and Triglycerides (GH-Method: Math-Physical Medicine) (No. 247)

Hsu GC*

eclaireMD Foundation, USA

***Correspondence:** Gerald C Hsu, eclaireMD Foundation, USA

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Keywords: diabetic retinopathy, metabolism, chronic diseases, triglycerides, medicine

Abbreviations: HR: hazard ratio; CVD: cardiovascular disease; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; HbA1C: hemoglobin A1C; AI: artificial intelligence; SBP: systolic blood pressure

Introduction

The author used his own medical data to investigate the impact on his diabetic retinopathy condition and its risk probability percentage or hazard ratio (HR) over a period of 7-years.

Methods

The author suffered from type 2 diabetes (T2D) since 1996. By the year 2010, he experienced cardiovascular disease (CVD), renal complications, bladder infection, foot ulcer, thyroid disorder, and vision problems. In July of 2010, three of his physicians warned him that he would have 3–5 remaining years to live. Therefore, he decided to study and research diabetes and its complications to save his own life. For the past 10 years, he has spent 30,000 h on endocrinology with a specialty in diabetes and food nutrition.

The following timetable illustrates the focused area of each stage:

- 2000–2013 - Self-study diabetes and food nutrition, developing a data collection and analysis software
- 2014 - Develop a mathematical model of metabolism, using engineering modeling and advanced mathematics
- 2015 - Weight and fasting plasma glucose (FPG) prediction models, using neuroscience
- 2016 - Postprandial plasma glucose (PPG) and hemoglobin A1C (HbA1C) prediction models, using optical physics, artificial intelligence (AI), and neuroscience [1]
- 2017 - CVD and stroke research, using segmentation analysis and pattern analysis [2]
- 2018 - Complications due to micro-vascular research, for example, renal, bladder, and foot
- 2019 - Continuous glucose monitor (CGM) glucose big data analysis, using wave theory, energy theory, frequency domain analysis, quantum mechanics, and AI
- 2020 - Geriatrics, longevity, diabetic retinopathy, diabetic hyperthyroidism, the linkage between metabolism and immunity

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To date, he has collected ~2 million data regarding his medical conditions and lifestyle details. He has written 246 medical papers and made ~120 presentations at ~70 international medical conferences.

Under the leadership of American Diabetes Association (ADA), a group of 14 authors quoted 137 references to publish a long editorial article, "Perspectives in diabetes: diabetic retinopathy, seeing beyond glucose-induced microvascular disease" [3].

Here is an excerpt:

The diabetic retinopathy remains the leading cause of vision impairment and blindness. The risk of developing vision loss from diabetes is predicted to double over the next 3 decades.

The fundamental functions of retina are to capture photons, convert the photochemical energy into electric energy, integrate the resulting action potentials, and transmit them to the occipital lobe of the brain, where they are deciphered and interpreted into recognizable images. Although the retina is easily visible, it is, ironically, the only major tissue affected by diabetes that cannot be biopsied in human.

Established neurobiological principles can inform us how diabetes impairs vision, and metabolism knowledge may lead to new treatments. Retina physiology may underlie its vulnerability to diabetes. The combination of high metabolic demand and minimal vascular supply may limit the inner retina's ability to adapt to the metabolic stress of diabetes. The pathogenesis of diabetic retinopathy includes glucose-mediated microvascular damage. Although micro vascular changes are undeniably integral to retinopathy, the retina is a vascularized neural tissue, not a network of blood vessels. Diabetic retinopathy involves more than elevated glucose and micro vascular lesions. Plenty of evidence for neural retinal involvement in diabetic retinopathy have already been presented.

To the best of our knowledge, there is no evidence that a primary, selective defect in vascular cells is sufficient to cause diabetic retinopathy. Clearly, it is essential to treat both the vascular and neural elements of the retina to preserve vision.

Excess glucose (elevated HbA1C) is the primary culprit in the development and progression of diabetic retinopathy. However, disordered lipid (especially triglycerides) and protein metabolism are also linked to the central biochemical abnormality in all forms of impaired insulin action.

A paper titled "Risk factors associated with progression to referable retinopathy" was written and presented by Smith JJ et al. [4]:

This study was conducted in a dynamic cohort of 2,770 type 2 diabetes patients, recruited between April 2005 and July 2013 (~8 years) in Ireland. In this diabetic retinopathy paper, the authors demonstrated that higher current values of HbA1C, systolic blood pressure (SBP), and triglycerides were associated with increased risk of referral diabetic retinopathy.

Based on the findings from the long editorial article, the author conducted a study on his own diabetic retinopathy development and progression for the past 7-years (2013–2019). He has collected and further calculated the following data categories associated with his own medical conditions:

- Weight: 2 body weight, BMI
- Glucose: 1 FPG, 3 PPG, 1 daily A1C
- Blood pressure: SBP, DBP, pulse
- Lipid: triglycerides, HDL, LDL

The data for the top 3 categories were collected (weight, glucose, and BP) or calculated (*i.e.*, HbA1C, BMI, and predicted glucose) daily. However, his lipid results were obtained from 22 hospital lab-tests with an average testing period of every 4 months.

Initially, he listed his lab-tested triglycerides data, and then extracted data from both measured HbA1C and SBP from his stored database to match the actual dates of his lab-test for triglycerides (a total of 22 dates). In summary, 38,385 data of these 2,555 days (7-years) were used in this study.

Next, he selected the following medical conditions as his baseline conditions (*i.e.*, normal conditions) for his risk probability analysis.

- Triglycerides: 150 mg/dL
- SBP: 120
- HbA1C: 6.0%

Finally, he applied a linear regression analysis model with 7 different cases to conduct his numerical analysis.

In addition, he also applied the Cox proportional hazards regression model to conduct one more set of calculations. The Cox hazard model can be expressed as follows:

$h(t) = h_0(t) * \exp(b_1x_1+b_2x_2+...+b_nx_n)$

where h(t) is the expected hazard at time t, $h_0(t)$ is the baseline hazard and represents the hazard when all the predictors (or independent variables) x_1, $x_2...x_n$ are equal to zero. Notice that the predicted hazard (*i.e.*, h(t)), or the rate of suffering the event of interest in the next instant, is the product of the baseline hazard ($h_0(t)$) and the exponential function of the linear combination of the predictors. Thus, the predictors have a multiplicative or proportional effect on the predicted hazard.

Results

The figure (Figure 1) shows his records of triglyceride, SBP, and HbA1C, where his SBP curve is expressed with 90-days moving average data.

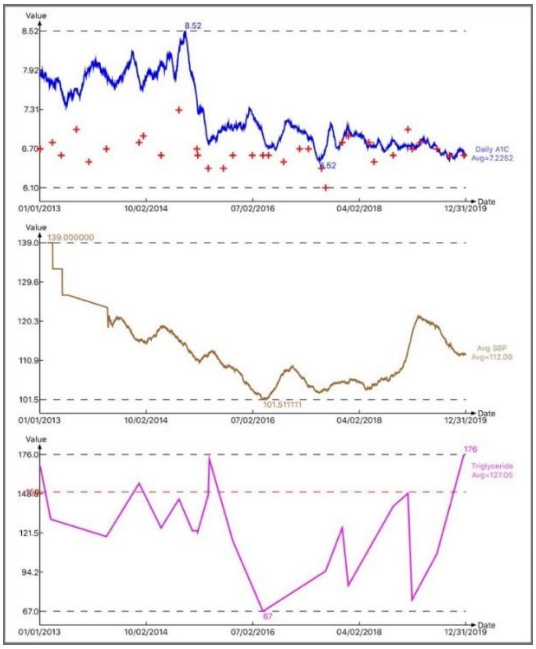

Figure 1: HbA1C, SBP, triglycerides during 2013–2019.

After he matches the dates of both HbA1C and SBP with the actual lab-test dates of triglycerides, he then normalized those daily medical values by using baseline or normal conditions. These original data and normalized results are shown in the figure (Figure 2).

The author could not find the contribution margins (*i.e.*, weighting factors) related to these 3 primary factors of diabetic retinopathy study (*i.e.*, A1C, SBP, and triglycerides) from the external references; therefore, he decided to conduct a sensitivity analysis by using a range of possible weighting factors. The figures (Figure 3, 4, 5, and 6) reflect the operational results and his 7 different cases of weighting factors.

Here is the list of these 7 different weighting factors:

- Case 1: triglycerides 33%, SBP 33%, A1C 33% (even distribution at 33% each)
- Case 2: triglycerides 30%, SBP 30%, A1C 40% (A1C is slightly heavier, 40%)
- Case 3: triglycerides 60%, SBP 20%, A1C 20% (triglyceride is the heaviest, 60%)
- Case 4: triglycerides 20%, SBP 60%, A1C 20% (SBP is the heaviest, 60%)
- Case 5: triglycerides 20%, SBP 20%, A1C 60% (A1C is the heaviest, 60%)
- Case 6: triglycerides 20%, SBP 30%, A1C 50% (A1C is heavier, 50%)
- Case 7: triglycerides 30%, SBP 36%, A1C 34% (using HR findings as a clue or source) [4]

The figure (Figure 6) is a simplified bar chart of risk probability % of these 7 cases.

Original Data				Standard %	150	120	6.0
Date	Trig.	SBP	HbA1C	Date	Trig.	SBP	HbA1C
1/4/13	168	139	7.83	1/4/13	1.12	1.16	1.31
3/8/13	131	139	7.74	3/8/13	0.87	1.16	1.29
2/5/14	119	124	7.86	2/5/14	0.79	1.03	1.31
8/20/14	156	116	7.77	8/20/14	1.04	0.97	1.30
12/30/14	125	119	8.02	12/30/14	0.83	0.99	1.34
4/16/15	145	116	8.20	4/16/15	0.97	0.97	1.37
7/6/15	123	112	7.85	7/6/15	0.82	0.93	1.31
8/4/15	123	111	7.39	8/4/15	0.82	0.93	1.23
10/9/15	148	112	6.79	10/9/15	0.99	0.93	1.13
10/15/15	173	113	6.78	10/15/15	1.15	0.94	1.13
3/4/16	116	109	6.98	3/4/16	0.77	0.91	1.16
9/1/16	67	102	6.91	9/1/16	0.45	0.85	1.15
9/12/17	95	104	6.81	9/12/17	0.63	0.87	1.14
12/20/17	125	106	6.89	12/20/17	0.83	0.88	1.15
1/26/18	85	105	7.01	1/26/18	0.57	0.88	1.17
10/22/18	140	107	6.84	10/22/18	0.93	0.89	1.14
1/18/19	149	113	6.74	1/18/19	0.99	0.94	1.12
2/12/19	75	117	6.77	2/12/19	0.50	0.98	1.13
7/11/19	107	109	6.72	7/11/19	0.71	0.91	1.12
12/20/19	176	113	6.64	12/20/19	1.17	0.94	1.11
Avarage	127	114.3	7.23	Avarage	0.85	0.95	1.20

Figure 2: Original data and normalized value of HbA1C, SBP, triglycerides of selected dates during 2013–2019.

From the figures (Figure 3, 4, 5, 6, and 7), we can observe the following conclusive phenomena:

1) Upper bound: Both case 5 (A1C 60%) and case 6 (A1C 50%) have the highest risk probability % (106–108%).
2) Middle bound: All of case 7 (Ireland HR case), case 1 (even distribution of 33% each), and case 2 (A1C 40%) are within a range of moderate risk probability % (100–102%).
3) Lower bound: Both case 3 (triglycerides 60%) and case 4 (SBP 60%) have the lowest risk probability % (94–98%).

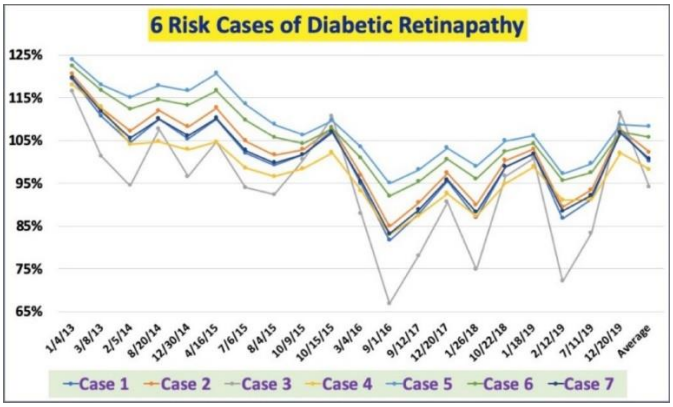

Figure 3: Time series line chart of diabetic retinopathy risk probability % of 7 cases.

Risk Case	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
1/4/13	119%	121%	116%	118%	124%	122%	120%
3/8/13	111%	113%	101%	113%	118%	117%	112%
2/5/14	105%	107%	94%	104%	115%	112%	106%
8/20/14	110%	112%	108%	105%	118%	115%	110%
12/30/14	105%	108%	97%	103%	117%	113%	106%
4/16/15	110%	113%	105%	105%	121%	117%	110%
7/6/15	102%	105%	94%	99%	114%	110%	103%
8/4/15	99%	102%	92%	97%	109%	106%	100%
10/9/15	102%	103%	101%	98%	106%	104%	102%
10/15/15	107%	108%	111%	102%	110%	108%	107%
3/4/16	95%	97%	88%	93%	103%	101%	95%
9/1/16	82%	85%	67%	83%	95%	92%	83%
9/12/17	88%	90%	78%	87%	98%	95%	89%
12/20/17	95%	97%	91%	93%	103%	101%	96%
1/26/18	87%	90%	75%	87%	99%	96%	88%
10/22/18	99%	100%	97%	95%	105%	102%	99%
1/18/19	102%	103%	101%	99%	106%	104%	102%
2/12/19	87%	89%	72%	91%	97%	96%	88%
7/11/19	91%	93%	83%	91%	100%	98%	92%
12/20/19	107%	108%	111%	102%	109%	107%	107%
Average	100%	102%	94%	98%	108%	106%	101%

Figure 4: Data table of diabetic retinopathy risk probability % of 7 cases.

Risk Case	Risk %	Trig.	SBP	A1C
Case 1	100%	33%	33%	33%
Case 2	102%	30%	30%	40%
Case 3	94%	60%	20%	20%
Case 4	98%	20%	60%	20%
Case 5	108%	20%	20%	60%
Case 6	106%	20%	30%	50%
Case 7	101%	30%	36%	34%
Case 7	HR	1.10	1.29	1.22

Figure 5: Table of contribution weighting factors and risk probability % of 7 cases.

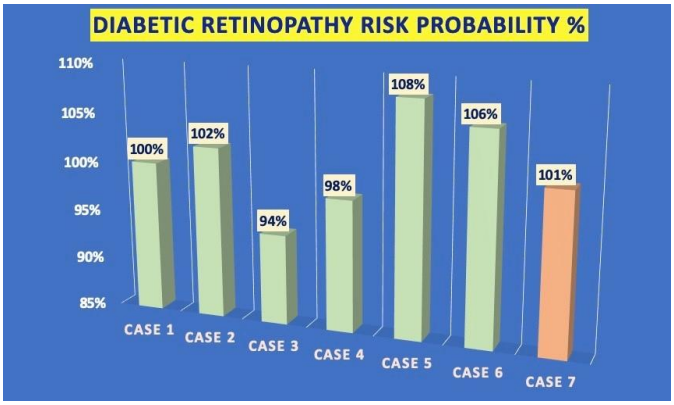

Figure 6: Bar chart of diabetic retinopathy risk probability % of 7 cases.

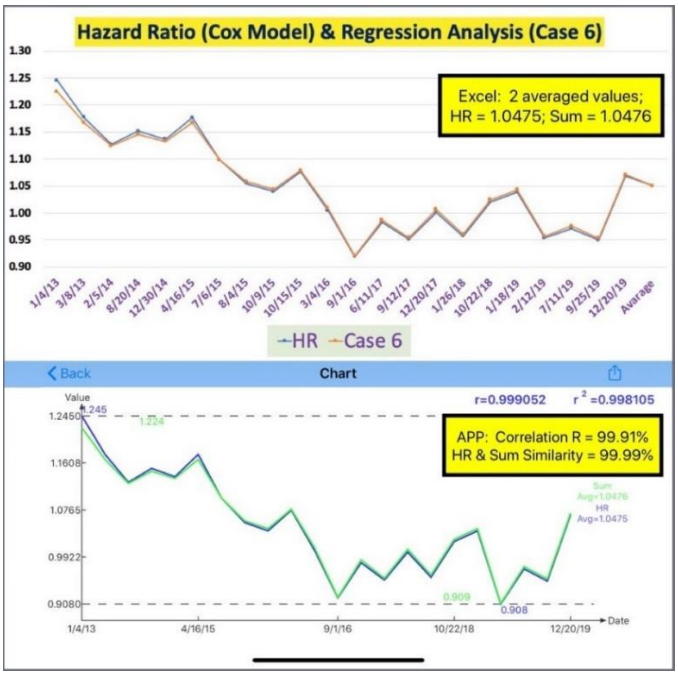

Figure 7: Comparison of case 6 between weighted risk probability (sum) % and HR model results.

Based on the author's medical data and personal feelings of his diabetic retinopathy conditions at different progression stages, the upper bound curves, case 5 and 6, seem to be closely matched with the situation of his real conditions. On the opposite, the lower bound, case 3 and 4, seem to be further apart from his real conditions.

Although lacking available medical test data, in general, he believes his overall diabetic retinopathy progression has slowed down for the past 7-years. His belief matched the trend of this set of curves.

Although both blood pressure and lipids share their responsibility of damaging the retina, based on this specific study, it seems that HbA1C plays a major role in his diabetic retinopathy conditions and developments.

In summary, he applied both linear regression analysis and Cox proportional hazards model to calculate his relative risk probability % and his HR using 0.366 as its baseline. The comparison of these two approaches can be seen in the figure (Figure 7). Although the absolute values are slightly different on certain test dates, these two curves have an extremely high correlation coefficient (99.991%). These slight numerical differences are a result of the HR model utilizing exponential operation of the risk % value. The most important thing is that they demonstrate the relative risk probability % and relative HR of an upper bound case 6 with an extremely high correlation.

Conclusion

From the diabetic retinopathy sensitivity regression analysis results, it appears that diabetes, in particular HbA1C, plays a more dominating role as the murderer, while both hypertension (SBP) and hyperlipidemia (triglycerides) play supporting roles as the accomplices. It is no wonder that the medical community calls it diabetic retinopathy! Nevertheless, the combination of these 3 chronic diseases may cause severe damage to the retina. Furthermore, diabetic retinopathy is not only a metabolic microvascular blood vessel issue but also a serious neuroscientific problem [3]. The author strongly agrees with this viewpoint. In his recent research work on glucose, he has identified the amounts for both fasting and postprandial glucose' production and timing are controlled by the brain and neuro-system. He has already proven previously that diabetes itself is also closely related to our brain and nervous system.

This study may shed some light on using an approach to strengthen metabolic conditions, a combination of HbA1C, SBP, and triglycerides to improve existing conditions of diabetic retinopathy in the patient [3].

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