Mathematical Modelling and Computer Analysis of Diabetes to Develop Novel Index for Diagnosis and Risk Prediction of Pathogenesis

Kazumi Omata(✉)

Center for Clinical Sciences, National Center for Global Health and Medicine,
1-21-1 Toyama, Shinjuku, Tokyo 162-0052, Japan
komata@hosp.ncgm.go.jp

Abstract. A simple model for diabetes has been considered and represented mathematically in terms of reaction rate equations. The diabetic states determined by the relative intensities of reaction parameters included in the model have been investigated by numerical calculations. This mathematical model could realize the diabetic and non-diabetic states, namely, the change in states according to dietary intake, insulin secretion, and physical activity. Based on these analyses, it has been proposed that, if the parameter set in the model was evaluated for individuals and saved as a clinical database, it could be used for diagnosis, treatment, and risk prediction for diabetes pathogenesis.

Keywords: Mathematical modelling · Diabetes · Disease risk

1 Introduction

The morbidity of diabetes has been expanding worldwide during these decades, evoking the necessity of measures to this disease. The index of the modern standard diagnosis for diabetes are the blood glucose level, glycated hemoglobin (HbA1c), glycoalbumin (GA), C-peptide index, body mass index (BMI), abdominal circumference and so on. The genomic medicine is in progress for identifying overall diabetes-relating genes as an end in view, and thereby implementing personalized medicine and risk prediction of diabetes pathogenesis. In this context, the present study has proposed another type of index by mathematical modelling and computer analysis of a simple metabolic system that regulates carbohydrate metabolism. It is distinctive of this novel type of index that the index does not represent extensive variables indicating amount of substance such as blood glucose but intensive variables indicating metabolic ability of a person.

2 Simple Metabolic Model for Diabetes

Figure 1 illustrates a metabolic model for diabetes. The insulin is secreted into blood, following increase in blood glucose, and promotes taking glucose into adipocytes. However, excessive dietary intake gives rise to hypertrophy of adipocytes, and the

T. Ahram et al. (Eds.): IHIET 2020, AISC 1152, pp. 440–444, 2020.
https://doi.org/10.1007/978-3-030-44267-5_66

enlarged adipocytes induce the secretion of inflammatory cytokines [1, 2]. These cytokines hinder the function of insulin, leading to inability of taking glucose into adipocytes (insulin resistance) [2] and decrease in one's weight. In addition, long-time duration of high blood-glucose state is responsible for disorder of insulin secretion (glucotoxicity) [3]. Diabetes develops via such processes.

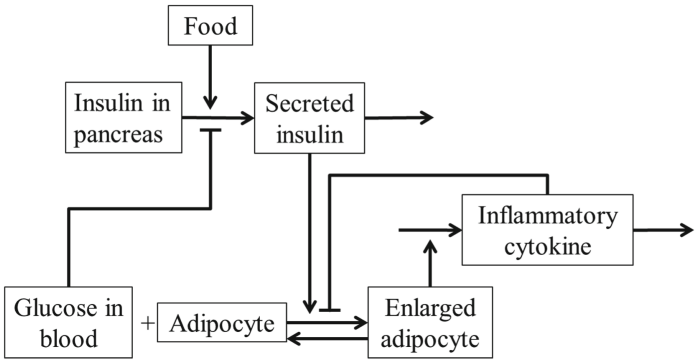

Fig. 1. Model of insulin resistance, glucose toxicity, and diabetes. The laterally directed arrows describe reactions or changes, and the vertical arrows denote activation of reactions. The T-shape symbols denote inhibition.

3 Mathematical Modelling

The processes shown in Fig. 1 can be described as reactions and written as

$$\mathrm{G} + \mathrm{f} + \mathrm{S} \rightleftharpoons \mathrm{X} \rightarrow \mathrm{F} + \mathrm{S} \tag{1}$$

$$\mathrm{S} + \mathrm{I} \rightleftharpoons \mathrm{Y} \tag{2}$$

$$\mathrm{i} + \mathrm{F} \rightleftharpoons \mathrm{Z} \rightarrow \mathrm{I} + \mathrm{F} \tag{3}$$

where G, S, f, F, i, and I denote the amount of blood glucose, insulin, the mass of normal and enlarged adipocytes, and the amount of unreleased and released inflammatory cytokines, respectively, and X, Y, and Z are transient products.

These reactions are written mathematically in terms of rate equations; namely, the time evolution of these variables are described by differential equations [4–6]. Here, the rate equations are approximated by functions of the Michaelis-Menten type which is known as a model for enzyme kinetics, and written as

$$\dot{G} = k_G - \frac{\sigma_T k_a G f}{(1 + k_a G f + k_b I)}, \tag{4}$$

$$\dot{F} = \frac{\sigma_T k_a G f}{(1 + k_a G f + k_b I)} - k_F F \tag{5}$$

$$\dot{I} = \frac{i_T k_c F}{(1 + k_c F)} - k_I I \tag{6}$$

where k_a, k_b, k_c, k_F, and k_I denote parameters obtained from reaction rates, and we assume that the amounts of secreted insulin, adipocytes, and unreleased inflammatory cytokines are constant, i.e., $S(t) = \sigma_T$, $f(t) + F(t) = f_T$, and $i(t) = i_T$.

Equations (4)–(6) provide the zero-growth isoclines (nullclines):

$$k_a G f = \frac{k_G}{\sigma_T - k_G}(k_b I + 1) \tag{7}$$

$$k_a G f = \frac{k_F k_I I (k_b I + 1)}{-k_I I (\sigma_T + k_F) + \sigma_T i_T} \tag{8}$$

The fixed point (I_0, G_0) obtained from the intersection of these nullclines is

$$(I_0, G_0) = \left(\frac{k_G i_T}{k_I (k_G + k_F)}, \frac{k_G (k_b I_0 + 1)}{(\sigma_T - k_G)(f_T - k_G / k_F)} \right) \tag{9}$$

This expression of the fixed point reveals that the relative intensities among k_G, k_F, and σ_T are important, determining the sign for the G_0 element of the fixed point, and the location in the variable space.

4 Diabetic States and Numerical Calculations

The expression of the fixed point, Eq. (9), provides non-diabetic and diabetic states, depending on the relative intensities of σ_T, k_G, f_T, and k_F. The qualitative features are classified into four cases.

Case I: $\sigma_T > k_G$ and $f_T > k_G/k_F$

When the dietary intake is normal and the insulin secretion is sufficient, the metabolic system stays in the. non-diabetic state. Figure 2 shows the G-I plane of the variable space. In Case I (Fig. 2(a)), the fixed point is located in the first quadrant (positive area) of the plane. It is found that the fixed point acts as an absorber for the trajectories (thin solid curves), (I(t), G(t)) where t denotes time. The trajectories approach the null cline, Eq. (7), and merge on it; then, they are eventually absorbed into the fixed point. This behavior on the G-I plane implies that the amounts of blood glucose and inflammatory cytokines are regulated to be finite values in the non-diabetic state.

Case II: $\sigma_T < k_G$ and $f_T > k_G/k_F$

When the dietary intake exceeds the supply of insulin, the diabetic state appears. The fixed point sinks under the G = 0 line so that the trajectories cannot approach the fixed point (Fig. 2(b)). Instead, they approach the nullcline Eq. (8) (thick solid line), and clime it from the right-hand side. This behavior represents that the blood glucose increases in the state of high-calory diet.

Case III: $\sigma_T > k_G$ and $f_T < k_G/k_F$

Despite normal dietary intake, if the decay rate of enlarged adipocytes k_F is small, the fixed point sinks under the G = 0 line. The trajectories assemble from the right and left sides, and climb upwards. It may be possible to consider that the small value of k_F indicates deficiency of physical activity.

Case IV: $\sigma_T < k_G$ and $f_T < k_G/k_F$

The worst case for a human occurs when the dietary intake exceeds the insulin secretion and the decay rate of enlarged adipocytes is small. In this case, the fixed point is located in the positive region of the G-I plane; however, it does not function as an absorber of the trajectories. The trajectories assemble and merge near the singular line (broken line) on which the denominator of the null cline Eq. (8) equals zero. Then, they climb along the singular line. This case also exhibits increase in blood glucose with time, i.e., pathogenesis of diabetes.

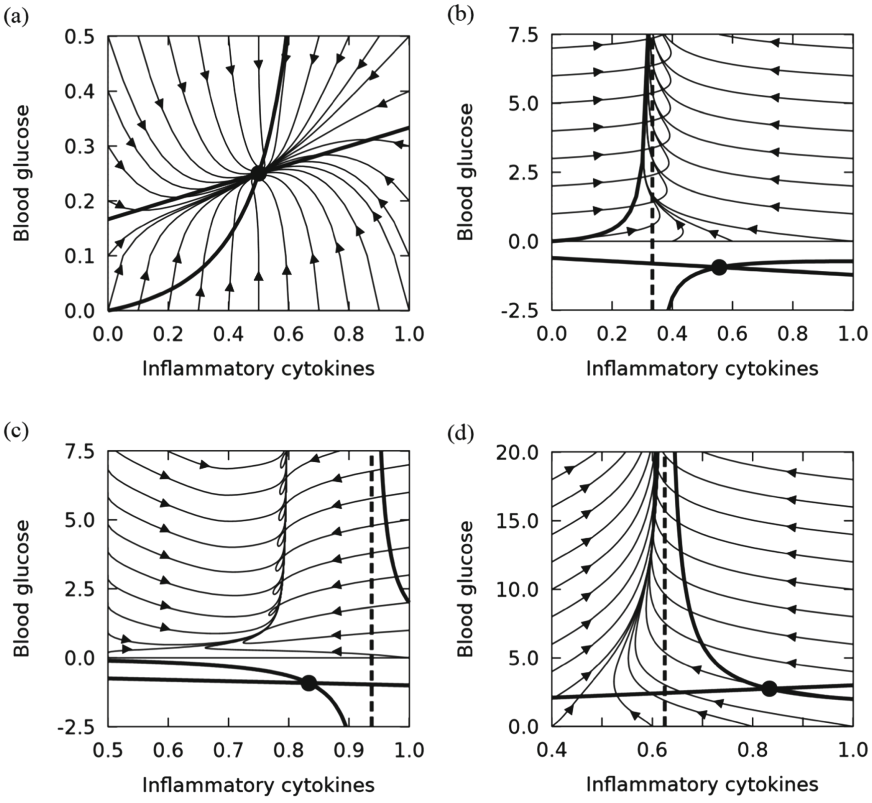

Fig. 2. Four types of diabetic states on the G-I plane of the variable space. The null clines and fixed points are shown by thick solid lines and solid circles, respectively. The broken lines are the singular lines on which the denominator of the null cline Eq. (8) equals zero. The trajectories calculated numerically are depicted by thin solid lines. The arrows on the trajectories indicate the direction of time evolution. The parameters are set to $k_A = k_B = k = k_I = 1.0$ and $f_T = 4.0$. (a) $\sigma_T > k_G$ and $f_T > k_G/k_F$: $(k_G, k_F, \sigma_T) = (1.0, 1.0, 3.0)$, (b) $\sigma_T < k_G$ and $f_T > k_G/k_F$: $(k_G, k_F, \sigma_T) = (0.5, 0.4\ 0.2)$, (c) $\sigma_T > k_G$ and $f_T < k_G/k_F$: $(k_G, k_F, \sigma_T) = (1.0, 0.2, 3.0)$, and (d) $\sigma_T < k_G$ and $f_T < k_G/k_F$: $(k_G, k_F, \sigma_T) = (3.0, 0.6, 1.0)$.

5 Index for Diabetes Diagnosis, Treatment, and Risk Assessment

The precise location of the fixed point must be determined by more quantitative evaluation of the parameters, (k_a, k_b, k_c, k_F, k_I), included in the rate equations. This parameter set may be used for diagnosis, treatment, and risk prediction for diabetes. Actual remedy targeting human would require to measure and evaluate these parameters in detail; they seem to be implemented by medical testing or biological experiments. For example, hypertrophy in adipocytes can be examined by periodic sampling of adipocytes, and thereby the variation rate for the hypertrophy can be evaluated. The variation rate for inflammatory cytokines can be also investigated in the same way. In addition, it is expected that, following such actual measurements, the mathematical model can be improved and updated, and vice versa.

The parameter set varies person to person, and therefore, statistical analyses of many private records for the parameter set would be very useful for diagnosis, treatment, and risk assessment. It is desirable that the results of the statistical analyses are saved as a clinical database so that not only hospitals but individuals can access it for medical purposes. Clearly, such a medical system could be applied to other diseases; an important point is the construction of mathematical models with good quality.

6 Concluding Remarks

The present study has considered a mathematical model for diabetes, and the diabetic states determined by the relative intensities of reaction parameters have been investigated by numerical calculations. It has been proposed that the parameter set could be used for risk prediction of diabetes as well as diagnosis and treatment.

This mathematical model is based on many simplifications, whereas it is better that rough estimates provide good suggestions than that too exact calculations reveal useless results. Interactions between mathematics and medicine would open up possibilities, providing novel types of therapy.

Acknowledgments. The author would like to thank Dr. Erika Sugito, Dr. Ryotaro Bouchi, and Dr. Takao Nammo for helpful suggestions.

References

1. Kahn, C.R.: Joslin's Diabetes Mellitus. Lippincott Williams & Wilkins, Philadelphia (2004)
2. Rodriguez, A., Ezquerro, S., Mendez-Jimenez, L., Becerril, S., Fruhbeck, G.: Revisiting the adipocyte: a model for integration of cytokine signaling in the regulation of energy metabolism. Am. J. Physiol. Endocrinol. Metab. **309**, E691–E714 (2015)
3. Luo, X., Wu, J., Jing, S., Yan, L.: Hyperglycemic stress and carbon stress in diabetic glucotoxicity. Aging Dis. **7**, 90–110 (2016)
4. Prigogine, I., Lefever, R.: Stability problems in cancer growth and nucleation. Comp. Biochem. Physiol. **67B**, 389–393 (1980)
5. Murray, J.D.: Mathematical Biology. Springer, Heidelberg (2002)
6. Novak, B., Tyson, J.: Design principles biochemical oscillators. Nat. Rev. **9**, 981–991 (2008)