Mathematical Modeling of Type -2 Diabetes Mellitus as a Risk Factor for Cancer

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Abstract. Diabetes, a fifth leading disease in terms of causing death, is a complex syndrome, characterized by the altered metabolism of proteins, fats, and carbohydrates result in the raising of blood glucose level to more than 180 mg/dl cause a condition called Hyperglycemia. Many shreds of evidence are suggesting the positive relationship between diabetes and cancer means diabetic patients are more prone to cancer. Risk factors associated with type 2 diabetes and cancer share some common pathophysiologies as well as treatments and thus type-2 diabetes mellitus may be a predisposing factor for Cancer. The work proposes a generalized mathematical model whose numerical solution depicts the risk of cancer to the one having type-2 diabetes mellitus. In type-2 diabetes, the body neglects to react to the insulin produced by the body itself. A system of differential conditions is utilized for depicting these changes. This model incorporates the concentration of glucose, insulin and cancer growth cells. Taking everything into account, the possibility of having cancer is more in the individuals having long-standing type-2 diabetes than those who do not have diabetes. In the work, we propose a numerical model for the risk of disease to a patient having type 2 diabetes mellitus for quite a while.

Index Terms: Cancer, Glucose, Insulin, Mathematical model, Type-2 diabetes.

1. Introduction

Diabetes Mellitus is the recurring metabolic disorder of fats, proteins and carbohydrates. It is the disorder of metabolism which causes polyuria (overabundance pee with high sugar), polydipsia (excessive thirst) and polyphagia (overabundance hunger), signalized by the elevated levels of blood sugar in the body, leading to the condition of hyperglycemia (more than 180 mg/dl of blood glucose level) after the intake of any kind of meal [1*]. When the food is consumed by an individual, body’s beta cells start secreting insulin. Insulin causes the lowering of blood sugar concentration by increasing the rate of blood glucose uptake [2*]. The β-cells in pancreas start to release insulin. This insulin helps body cells to use or store the glucose from the blood. But if the calorie intake is more than sufficient then it increases adiposity. Increased adiposity leads to increased insulin resistance. Oxidative stress and high concentration of reactive oxygen species is also the cause of diabetes. Diabetes derived from
Greek word meaning “siphon” and Mel from Latin meaning “honey” providing Diabetes mellitus a literal meaning- “siphoning off sweet water” [3*].

In obese, insulin is less effective to stimulate glucose uptake comparative to non-obese. Due to increased insulin resistance β-cells in pancreas secret more insulin, but the body is unable to process the insulin and blood glucose level rises. So, type 2 diabetes is mainly characterized by hyperinsulinemia and hyperglycemia.

The possibility of having cancer is more in the people having long-standing (over 5 years) type 2 diabetes than in people who do not have diabetes [12]. Type 2 diabetes (insulin-independent diabetes) means where cells do not respond to the insulin or cells develop resistance to insulin. Due to insulin resistance, pancreas recognizes high levels of blood glucose, thereby, producing more insulin to compensate high blood glucose levels. The process of secreting more and more insulin continues and over time exhaustion of pancreas occurs which no longer capable of fulfilling the demand of releasing insulin, resulting in rise in blood glucose levels.

There is the increase in insulin concentration due to both obesity and early-stage type 2 diabetes, known as basal hyperinsulinemia. The type 2 diabetic patients have more tendencies to acquire cancer than the non-diabetic patients.

There is a positive relationship between insulin and IGF-I. The IGF system comprises two ligands (IGF-I and IGF-II) with two receptors (IGF-I R and IGF-II R) and six high-affinity binding proteins with several binding proteins proteases [10]. IGF-I has a significant role in cell growth and development (normal as well as abnormal cells) and it is also very necessary for cell cycle progression. A person having hyperinsulinemia has decreased IGF binding protein level and increased free IGF-I level [1], [2]. Thus, the increased IGF-I level due to hyperinsulinemia may inhibit apoptosis of transformed and abnormal cells. Hyperinsulinemia can cause cancer development through ligand by binding with the insulin receptor [3], [13]. It may be affected indirectly by increasing circulating IGF-I levels [15]. Hyperinsulinemia may influence tumour growth directly by its effect on the insulin receptor and IGF-I receptor [8]. It also causes increased hepatic IGF-I production indirectly by increasing hepatic growth hormone receptor (GHR) levels [9]. Due to increased IGF-I, cell proliferation rate is increased [5]. IGF-I have the same effect on normal and abnormal cells. So, sometimes cell proliferation rate of abnormal cells increases. If this rate increases, then the number of cells in that part of the body increases rapidly that causes cancer. IGF-I plays an important role in several functions of both neuronal and non-neuronal cells. It activates multiple signaling pathways including Akt kinase that is necessary for cell survival. Akt is protein kinase B (Serine /Threonine) that has a very important role in the insulin signaling pathway [17]. It is a powerful signaling molecule. The two important features of Akt are: it helps in the growth or proliferation of cells, and it prevents apoptosis [18]. If it increases in excess amount, then its function becomes dangerous to the body. It helps in cell proliferation. So it supports cancer cell proliferation and also prevents apoptosis of cancer cells. Due to this, the probability of getting cancer in the body of type 2 diabetic patients is higher. It has already been proved in the previous studies [2] but in this work, mathematical model is created for easy understanding of this complication in a type-2 diabetic patient. A new factor IGF-I is also included in the model that has not been previously used in diabetes mathematical models.

The purpose of this model construction is to provide an explanation of a certain observation with an aim of making predictions and facilitating decisions. Mathematical models are quite popular in scientific community, applied in various fields and constructed for specific goal to provide premises for better decision making.

The proposed mathematical model has been reformed to study the effects caused due to type -2 diabetes mellitus among different parameters including glucose concentration, insulin concentration, cancer cells. The stability of the system of equations has been analyzed by using Routh-Hurwitz stability criterion and found that the given system is stable (globally stable). A patient having diabetes is significantly in higher danger of cancer compared to non-diabetic. The mortality rate due to cancer is higher in patients having diabetes in comparison to non-diabetics [14].
2. Mathematical model

2.1. For Glucose Concentration

The principal factor that effects rate of glucose production and uptake is the level of glucose and insulin in the blood [11].

\[ \frac{dG}{dt} = R_0 - (E_{G0} + S_I I)G \]  

(1)

\[ R_0 = P_0 - U_0 \]

\[ E_{G0} = E_{G0P} + E_{G0U} \]

\[ S_I = S_{IP} + S_{IU} \]

\[ G - \text{“Concentration of glucose in blood”} \]

\[ R_0 - \text{“The rate of production at zero glucose”} \]

\[ P_0 - \text{“Rate of glucose production”} \]

\[ U_0 - \text{“Rate of glucose uptake”} \]

\[ E_{G0} - \text{“The net glucose effectiveness at zero insulin”} \]

\[ E_{G0P} - \text{“Glucose effectiveness at zero insulin for uptake/production”} \]

\[ E_{G0U} - \text{“Glucose effectiveness at zero insulin for uptake”} \]

\[ S_I - \text{“Total insulin sensitivity”} \]

\[ S_{IP} - \text{“Insulin sensitivity for production”} \]

\[ S_{IU} - \text{“Insulin sensitivity for uptake”} \]

2.2. For Insulin Concentration

The insulin secretion rate from pancreatic \( \beta \)-cells is a sigmoidal function of glucose concentration. It is considered that all \( \beta \)-cells secrete insulin at the same maximal rate [11].
\[
\frac{dI}{dt} = \beta \sigma \frac{G^2}{\alpha + G^2} - kI
\]  

(2)

I - “Concentration of insulin in blood”

\[\beta\] - “Mass of pancreatic \(\beta\)-cells”

\[\sigma\] - “Maximal rate of secreting insulin by \(\beta\)-cells”

\[
\frac{G^2}{\alpha + G^2}
\] - “Hill function with co-efficient 2 describing a sigmoid ranging from 0 to 1, which reaches half of its maximum value at \[G = \alpha^{\frac{1}{2}}\],

\[k\] - “Clearance constant that represents the combined insulin uptake”

2.3. For Cancer Cell Concentration

The rate of change of cancer cells is defined as:

\[
\frac{dC}{dt} = \lambda C \left(1 - \frac{C}{\mu}\right) + I_{IGF-I}
\]  

(3)

Where \(C\) - No. of Cancer cells

\[\lambda\] - “Population growth rate”

\[\mu\] - “Carrying capacity”

\[I_{IGF-I}\] - “Insulin like growth factor-I (IGF-I)”

3. Numerical values

Table 1: Parameter values (Topp. B. [11], Enderlin H. [4] and Revathidevi S [18])

| Parameter | Value | Unit |
|-----------|-------|------|
| \(R_0\)  | 864   | mgdl^{-1}d^{-1} |
| \(E_{in}\) | 1.44  | d^{-1} |
| \(S_1\)  | 0.72  | mlU^{-1}d^{-1} |
| \(G_0\)  | 100   | mgdl^{-1} |
| \(I_0\)  | 1.5   | \muUml^{-1} |
| \(\sigma\) | 43.2  | \muUml^{-1}d^{-1} |
| \(\alpha\) | 20000 | mg^{2}dl^{-2} |
| \(\beta\) | 150   | mg |
| \(k\)    | 432   | d^{-1} |
By considering these values, stability of the proposed model has been analyzed in the next section.

4. Stability analysis of the model
To analyze the stability of the model, eigen values of the system of equations has been calculated and checked them by using Routh-Hurwitz condition.

\[ J = AX \]

\[
J = \begin{bmatrix}
-E_{GF} - S, I & 0 & 0 \\
\beta \sigma \frac{G_0}{\alpha + G_0} - k & 0 & 0 \\
0 & I_{GF} & \lambda \left(1 - \frac{C_0}{\mu}\right)
\end{bmatrix}
\]

Where, \( J \)= Jacobian matrix;

\[ A = \begin{bmatrix}
-E_{GF} - S, I & 0 & 0 \\
0 & 0 & I_{GF} \lambda \left(1 - \frac{C_0}{\mu}\right)
\end{bmatrix}
\]

Substituting the numerical values,

\[
J = \begin{bmatrix}
-2.52 - \lambda & 0 & 0 \\
0.00324 & -432 - \lambda & 0 \\
0 & 300 & -11.10 - \lambda
\end{bmatrix}
\]

The characteristic equation is defined as:

\[
\operatorname{Det}(A - \lambda I) = 0
\]

\[
\begin{vmatrix}
-2.52 - \lambda & 0 & 0 \\
0.00324 & -432 - \lambda & 0 \\
0 & 300 & -11.10 - \lambda
\end{vmatrix} = 0
\]

\[
\lambda^3 + 445.62 \lambda^2 + 5911.812 \lambda + 12083.9 = 0
\]

The eigen values of above system of equations are:

\[
\lambda_1 = -2.52, \quad \lambda_2 = -432.00 \quad & \quad \lambda_3 = -11.10
\]

By Routh-Hurwitz condition if the eigen values are having all negative real parts the system is locally asymptotically stable.

Table 2. (Routh Hurwitz Table)
As the number of sign changes in the first column of Routh table is zero. Therefore, by Routh Hurwitz criteria the system is stable. Now Routh Hurwitz Stability Criteria is applied again to check the necessary and sufficient condition of stability of the system.

4.1. For necessary condition
As there is no sign change in the coefficients of characteristic equation. Thus necessary condition for a system to be stable is satisfied.

4.2. For sufficient condition
\[ a_6a_3 - a_4a_2 < 0 \]
or \[ (1)(12083.9) - (445.62)(5911.812) < 0 \]

Hence by Routh Hurwitz criteria, sufficient condition is also satisfied.

So, the system is completely stable. The proposed model based on the said parameters is stable and has further applications in real world situations.

5. Numerical result

![Graph](image)

**Figure 1:** ‘The variation of cancer cells with respect to time (in days) for different values of IGF-I’.

In the figure 1, two lines are shown for increasing cancer cells with increasing days at two different values of IGF-I. The dashed line presents change in number of cancer cells at 300 ng/ml of IGF-I for a type-2 diabetic person while the solid line presents change in number of cancer cells at 50 ng/ml of IGF-I.
5. Conclusion

The numerical solution for cancer cells has been discussed through graphs. Results indicating the more chances of having cancer (increased number of cancerous cells) in persons having type 2 diabetes. The reason behind it is improper control of beta-pancreatic cells to release insulin. Increased level of insulin (due to insulin resistance) caused the secretion of IGF-I in the liver more than it is desired. High levels of IGF-I causes growth of cancerous cells. That's why a diabetic patient is at higher risk or more prone to acquiring cancer as compared to non-diabetic one. From the results, it comes to know that the parameter like cancer cells increases in the case of type 2 diabetic patients in comparison to a non-diabetic patient. The reason for increased cancerous cells in type-2 diabetes is that a number of cancer cells may be lifted in type 2 diabetic patients if the proper control of insulin secreted by pancreatic β-cells is not done at the proper time. Due to the increase of insulin resistivity, the quantity of insulin increases which causes the secretion of IGF-I in liver more than it requires by our body. This heavy amount of IGF-I causes the growth of cancer cells. So, a type-2 diabetic patient is at higher risk of acquiring cancer in comparison to a non-diabetic patient.

6. References

[1] Brismar KE, Fernqvist-Forbes E, Wahren JO, Hall KE. Effect of insulin on the hepatic production of insulin-like growth factor-binding protein-1 (IGFBP-1), IGFBP-3, and IGF-I in insulin-dependent diabetes. The Journal of Clinical Endocrinology & Metabolism. 1994 Sep 1; 79(3):872-8.

[2] Cohen DH, LeRoith D. Obesity, type 2 diabetes, and cancer: the insulin and IGF connection. Endocrine-related cancer. 2012 Oct 1;19(5):F27-45.

[3] Duan W, Shen X, Lei J, Xu Q, Yu Y, Li R, Wu E, Ma Q. Hyperglycemia, a neglected factor during cancer progression. BioMed research international. 2014;2014.

[4] Enderling H, AJ Chaplain M. Mathematical modeling of tumor growth and treatment. Current pharmaceutical design. 2014 Sep 1;20(30):4934-40.

[5] Gallagher EJ, LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. Annals of the New York Academy of Sciences. 2011 Dec;1243(1):54-68.

[6] Gupta R, Kumar D. Hypertension and coronary heart disease risks for a type ii diabetic patient with or without intake of alcohol: A Mathematical Model. Advanced Science, Engineering and Medicine. 2017 Sep 1;9(9):709-12.

[7] Gupta R, Kumar D. Numerical model for glucose metabolism for various types of food and effect of physical activities on type 1 diabetic patient. Applied Mathematics, 2017, 7(2):19-22.

[8] Johnson JA, Pollak M. Insulin, glucose and the increased risk of cancer in patients with type 2 diabetes. Diabetologia. 2010 Oct 1;53(10):2086-8.

[9] Qiu H, Yang JK, Chen C. Influence of insulin on growth hormone secretion, level and growth hormone signalling. Sheng Li Xue Bao. 2017 Oct 25;69(5):541-56.

[10] Tian D, Kreeger PK. Analysis of the quantitative balance between insulin-like growth factor (IGF)-1 ligand, receptor, and binding protein levels to predict cell sensitivity and therapeutic efficacy. BMC systems biology. 2014 Dec 1;8(1):98.

[11] Topp B, Promislov K, Devries G, Miura RM, Finegood DT. A model of b-cell mass, insulin, and glucose kinetics: pathways to diabetes. Journal of theoretical biology. 2000;206(4):605-19.

[12] Vigneri P, Frasca F, Sciaccia L, Pandini G, Vigneri R. Diabetes and cancer. Endocrine-related cancer. 2009 Dec 1;16(4):1103-23.

[13] Vigneri R, Goldfine ID, Frittitta L. Insulin, insulin receptors, and cancer. Journal of endocrinological investigation. 2016 Dec 1;39(12):1365-76.

[14] Xu CX, Zhu HH, Zhu YM. Diabetes and cancer: Associations, mechanisms, and implications for medical practice. World journal of diabetes. 2014 Jun 15;5(3):372-380.
[15] Yehuda Handelsman, M.D., Bloomgarden, Z.T., Dagogo-Jack, S., Daniel Einhorn, M.D., Garber, A.J., George Grunberger, M.D., Gagel, R.F., Lebovitz, H.E., McGill, J.B. and Hennekens, C.H., Diabetes and cancer-an aace/ace consensus statement. Endocrine Practice, 2013, 19(4):675-693.

[16] Colako, O., B. Taskiran, and Gül Colako. "Serum insulin like growth factor-1 (IGF-1) and insulin like growth factor binding protein-3 (IGFBP-3) levels in liver cirrhosis." Turk J Gastroenterol 18, no. 4, 2007, 245-249.

[17] Zheng WH, Quirion R. Insulin-like growth factor-1 (IGF-1) induces the activation/phosphorylation of Akt kinase and cAMP response element-binding protein (CREB) by activating different signaling pathways in PC12 cells. BMC neuroscience. 2006, 1;7(1):51.

[18] Revathidevi S, Munirajan AK. Akt in cancer: mediator and more. In Seminars in cancer biology 2019, Academic Press.