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Computational analysis of clot formation risk in diabetes: A mathematical modeling approach

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Abstract

Diabetes (Type 1 or Type 2) is a serious condition that can make blood clot more easily. This can cause heart attacks and strokes, which are very dangerous. Our approach integrates physiological data, hemodynamic principles, and mathematical equations to simulate blood flow dynamics and clot formation processes within the vasculature of diabetic individuals. By incorporating key factors such as altered blood viscosity, resistance to flow, endothelial dysfunction, and platelet aggregation, we obtained insights into the complex interplay between diabetes related factors and clotting propensity. Changes in blood composition, such as increased levels of fibrinogen and other clotting factors, can make blood thicker and more prone to clotting and the reason for increased resistance to flow and viscosity. As blood clots enlarge in blood vessels, they obstruct blood flow, increasing resistance. This makes blood movement harder. Clot size also affects nearby blood viscosity. Accumulating cells and clotting factors thicken blood, worsening circulation. Larger clots heighten flow resistance and viscosity, potentially causing issues like tissue damage. Thus, larger clots worsen blood flow and cardiovascular health. Through computational simulations, we explored various scenarios to assess the impact of different parameters on clot formation risk, thereby offering valuable insights for the development of preventive strategies and targeted interventions for diabetic patients.

Keywords
Clot formation, diabetes mellitus, Mathematical modeling, cardiovascular complications, Platelet aggregation.

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1 Introduction

In diabetes, blood tends to clot more easily, which can lead to serious problems like heart attacks and strokes. It is important to manage diabetes carefully to reduce this risk. Recent data from the International Diabetes Federation (IDF) underscores the alarming scale of the epidemic, with 537 million adults aged 21–80 living with diabetes in 2021, a number projected to soar to 784 million by 2045. The disease exacts a heavy toll, causing 6.9 million demise in 2021 alone, translating to one in every two seconds. Moreover, Diabetes ranks as the third most prevalent comorbidity in COVID-19 cases, leading to increased disease severity, and adverse outcomes, including admission in ICU and at last death. It is considered a silent epidemic, with its prevalence steadily increasing globally and posing significant public health challenges. All these statistics underscore the urgent need for effective interventions and policies to curb diabetes epidemic and its associated complications [1–4]. Diabetes is a chronic disorder characterized by high blood glucose levels and is associated with a myriad of complications, including cardiovascular diseases Figure.1. One of the major cardiovascular complications of diabetes is the increased risk of thrombotic events, such as myocardial infarction and stroke, attributed to the formation of blood clots within the vasculature [5–8]. Despite advances in understanding the pathophysiology of diabetic vascular complications, the precise mechanisms underlying the heightened clot formation risk in diabetic individuals remain incompletely understood [9–13]. Mathematical modeling and computational simulations offer a powerful approach to elucidate the complex hemodynamic and biochemical processes involved in clot formation, providing valuable insights into the interplay between diabetes related factors and thrombotic propensity [14–18]. Diabetes is commonly categorized into two primary types: Type 1 and Type 2. In Type 1 diabetes, pancreas doesn't produce enough insulin, while Type 2 diabetes, more prevalent form, arises when the body becomes resistant to insulin or doesn't produce sufficient amounts. Symptoms may include heightened thirst, hunger, fatigue, weight loss, frequent urination, infections, blurry vision, and slow wound healing [19–24]. Both type 1 and type 2 diabetes can increase the risk of blood clotting, but the mechanisms may differ between the two types. In type 1 diabetes, where the body does not produce enough insulin, the risk of blood clotting may be related to factors such as hyperglycemia (high blood sugar levels), which can lead to damage of blood vessels and impair blood flow. Additionally, individuals with type 1 diabetes may have other risk factors such as increased levels of clotting factors in the blood. In type 2 diabetes, which is characterized by insulin resistance or reduced insulin production, the risk of blood clotting may be higher due to factors such as obesity, inflammation, and metabolic abnormalities associated with insulin resistance. These factors can contribute to changes in blood vessel function and increased clot formation. Both types of diabetes can predispose individuals to blood clotting, but the specific mechanisms and risk factors may vary [10, 21].

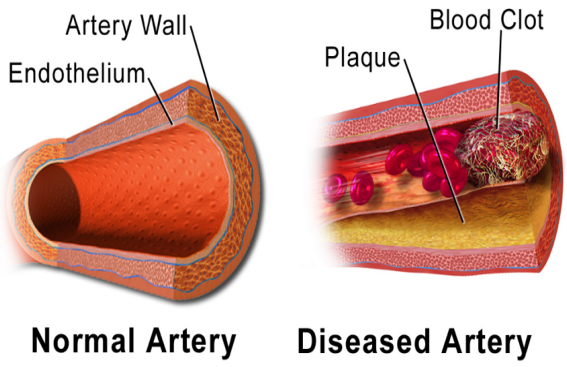

Figure 1: Normal artery with diseased artery with a blood clot.

Addressing these risk factors through lifestyle modifications and targeted interventions is crucial in combating the diabetes epidemic and reducing its burden on individuals and healthcare systems alike [25–30]. Diabetes can lead to severe complications that affect various parts of the body, including heart, blood vessels, eyes, teeth, kidneys, nerves, and may ultimately result in demise. Diabetic complications often necessitate amputations, causing permanent disability [31–36]. Diabetic patients has to face more higher risk of blockage and heart strokes compared to the general population. Diabetic neuropathy, a type of nerve damage resulting from high blood sugar levels, is another common complication, particularly affecting the feet and increasing the risk of foot ulcers, infections, and subsequent limb amputations, especially when combined with poor blood flow [37–42]. Diabetic retinopathy, characterized by hurting to the tiny blood vessels in retina, is a leading cause of blindness worldwide, affecting nearly one million individuals. Additionally, diabetic nephropathy, which damages the small blood vessels in the kidneys, leads to kidney disease and can eventually cause kidney failure, representing one of most prevalent causes for kidney failure [43–47]. In this study, we presented a computational analysis of clot forma-

tion risk in diabetes using a mathematical modeling approach. Our research aims to unravel the intricate mechanisms that contribute to the increased thrombotic risk in diabetic patients [48–51]. By leveraging mathematical models and computational simulations, we simulated various scenarios to explore the impact of diabetes related factors, such as altered blood rheology, endothelial dysfunction, and platelet hyperactivity, on clot formation dynamics. Through comprehensive analyses of hemodynamic parameters, clot formation kinetics, and biochemical pathways, we aim to elucidate the underlying mechanisms driving clot formation in diabetic individuals [52–56]. The significance of clot formation risk in diabetes lies in its potential to lead to severe and life-threatening complications. Diabetes is associated with an increased propensity for blood clot formation, a condition known as hypercoagulability. Additionally, diabetic individuals are more susceptible to developing blood clots in smaller blood vessels, leading to conditions like deep vein thrombosis (DVT) and pulmonary embolism (PE). Therefore, understanding and mitigating the risk of clot formation in diabetes is crucial for preventing adverse cardiovascular outcomes and improving patient outcomes. This computational approach allows us to integrate diverse physiological and pathological factors into a unified framework, providing a holistic understanding of the complex interplay between diabetes and thrombotic risk. By elucidating the key determinants of clot formation in diabetes, our study aims to identify potential therapeutic targets and strategies for mitigating the heightened thrombotic risk associated with this prevalent metabolic disorder [51, 57–60] ersonalized interventions aimed at reducing the burden of cardiovascular complications in diabetic patients.

2 Formulation of the problem

Our mathematical model incorporates several key factors implicated in the pathogenesis of clot formation in diabetes, including altered blood viscosity, endothelial dysfunction, and platelet aggregation. The model is based on fundamental principles of hemodynamics, fluid mechanics, and biochemical kinetics, represented by a system of differential equations describing the dynamics of blood flow and clotting processes within the vascular network. Parameters such as blood glucose levels, lipid profiles, and inflammatory markers are integrated into the model to capture the systemic effects of diabetes on vascular health [61, 62]. In this study, we considered, a scenario where a narrowing in the artery, known as stenosis, forms asymmetrically along the artery's length but maintains symmetry around its circumference. This narrowing depends on both the axial distance along the artery, denoted as z, and height of stenosis. In this situation, radius of artery, denoted as R(z), can be expressed as below:

$$\frac{R(z)}{R_0} = \begin{cases} 1 - [L_0^{(m-1)}x - x^m] & d \le z \le d + L_0, \\ 1 & \text{otherwise.} \end{cases} \tag{1}$$

where x =z-d.
In simpler terms, let's break down the equation. We are talking about an artery with a blockage, which reduces its radius compared to its original size. The variable R(z) represents the current radius of the artery with the blockage, while R0 represents its original, unobstructed radius. The length of the blockage is denoted by L0 and d indicates where along the artery it is located. The parameter m, which must be greater than or equal to 2, describes the shape of the blockage. When m=2, it means the blockage is axially symmetric. Finally, there is another parameter, A, which is determined by the specific values of these variables and parameters [10, 31, 36, 50].

$$A = \frac{\delta\, m^{m/(m-1)}}{R_0\, L_0^m\, (m-1)}$$

This equation helps us find the maximum height of the blockage in the artery, indicated by the symbol . It is determined by factors such as the location of the blockage along the artery (z), its length (L0), and the shape parameter (m). The expression also involves a fractional calculation, with the result being the maximum height of the blockage.

2.1 Conservation equation and boundary condition

The equation describing the steady, and fully-developed flow of blood in an artery, under the conditions of laminar flow and incompressibility, simplifies as:

$$0 = -\frac{\partial P}{\partial r} + \frac{1}{r}\frac{\partial (r\tau)}{\partial z}$$
$$0 = -\frac{\partial P}{\partial r} \tag{2}$$

The coordinates (z, r) represent the positional measurements, with z indicating the direction along the artery's axis, and r denoting measurements perpendicular to the artery's axis.

Coordinates (z, r) are used for pinpointing locations within artery. The coordinate z represents positions along the artery's length, while the coordinate r measures distances perpendicular to the artery's axis. This system allows for precise spatial referencing within the artery, aiding in the analysis of various phenomena occurring within its structure. The following conditions at the boundaries are applied to find the solution of the aforementioned equations.

$$\begin{cases} \frac{\partial u}{\partial r} = 0 & at\ r = 0 \\ u - 0 & at\ r = R(z) \\ \tau \text{ is finite} & at\ r = 0 \\ P = P_0 & at\ z = 0 \\ P = P_L & at\ z = L \end{cases} \quad (3)$$

2.2 Casson's fluid model

Casson's model is often expressed [16,27]:

$$\begin{cases} \tau^{1/2} = \tau_0^{1/2}(\mu)^{1/2}(-\frac{du}{dr})^{1/2}, & if\ \tau \geq \tau_0 \\ (\frac{du}{dr}), & if\ \tau < \tau_0 \end{cases} \quad (4)$$

with

$$\tau_0 = -(\frac{dp}{dz})\frac{R_c}{2}$$

where μ shows Casson's viscosity coefficient, Rc represents radius of plug flow region, 0 indicates yield stress, and represents wall shear. The rate at which volume flows through a particular point in the system, as described by equation (16), is termed as:

$$Q = \pi \int_0^R r(-\frac{du}{dr})dr \quad (5)$$

Upon integrating equation (17) with the assistance of equations (16) and (3), we obtain the following result:

$$Q = \frac{\pi R^4}{8\mu}(-\frac{dp}{dz})[1-\frac{16}{7}(\frac{R_c}{R})^{1/2}+\frac{4}{3}(\frac{R_c}{R})-\frac{1}{21}(\frac{R_c}{R})^4] \quad (6)$$

Equation (18) can be rewritten as;

$$Q = \frac{\pi R^4}{8\mu}(-\frac{dp}{dz})f(\bar{y})$$

with

$$f(\bar{y}) = [1 - \frac{16}{7}(\bar{y})^{1/2} + \frac{4}{3}(\bar{y}) - \frac{1}{21}(\bar{y})^4]$$

where

$$\bar{y} = \frac{R_c}{R} << 1$$

The pressure gradient, as derived from the equation above, can be expressed as below:

$$-\frac{dp}{dz} = \frac{8\mu Q}{\pi R^4 f(\bar{y})} \quad (7)$$

By integrating equation (19) with the boundary conditions, It is obtained:

$$\Delta P = P - P_0 = \frac{8\mu Q}{\pi R^4 f(\bar{y})} \int_0^L \frac{dz}{(R(z)/R_0)^4 f(y(\bar{z}))} \quad (8)$$

Resistance to flow, also known as resistive impedance, is represented by the symbol and is defined as below:

$$\lambda = \frac{P_L - P_0}{Q} \quad (9)$$

Resistance to flow, obtained from above equations as a reference, can be expressed as follows:

$$\lambda = 1 - \frac{L_0}{L} + \frac{f_0}{L}\int_0^{d+L_0} \frac{dz}{(R(z)/R_0)^4 f(y(\bar{z}))} \quad (10)$$

where

$$f_0 = [1 - \frac{16}{7}(\frac{R_c}{R})^{1/2} + \frac{4}{3}(\frac{R_c}{R}) - \frac{1}{21}(\frac{R_c}{R})^4]$$

Apparent viscosity (μ_{app}) is defined as below:

$$\mu_{app} = \frac{1}{(R(z)/R_0)^4 f(\bar{y})} \quad (11)$$

Shear stress at wall may be obtained as below;

$$\tau_R = [\tau_0^{1/2} + (-\mu\frac{du}{dr}) \quad (12)$$

3 Results

Our computational analysis unveils the intricate ways in which diabetic conditions, characterized by hyperglycemia, dyslipidemia, and chronic inflammation, exert profound effects on blood rheology and endothelial function, thereby predisposing diabetic individuals to heightened clot formation. Through detailed simulations, we observe that the diabetic milieu significantly alters key hemodynamic and biochemical parameters, creating a prothrombotic environment within the vasculature [34,50,52]. Specifically, our model demonstrates that increased blood viscosity, attributed to elevated levels of circulating glucose and lipids, impedes blood flow and promotes stasis, facilitating clot formation. Moreover, impaired endothelial nitric oxide production, a hallmark of diabetic endothelial dysfunction, disrupts the delicate balance between prothrombotic and antithrombotic factors, further exacerbating thrombotic propensity.

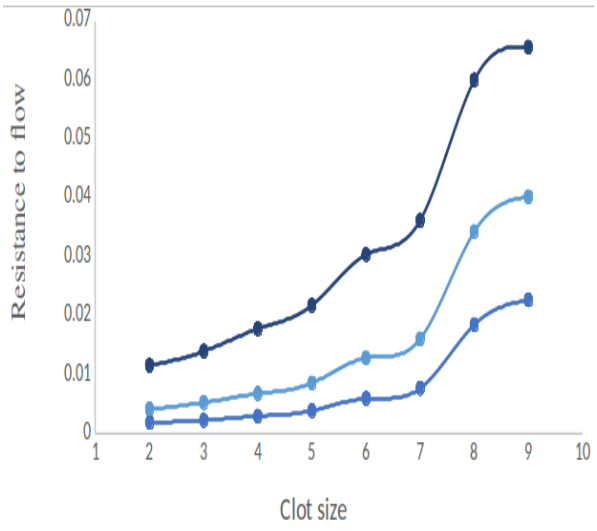

Figure 2: Resistance to flow with stenosis shape.

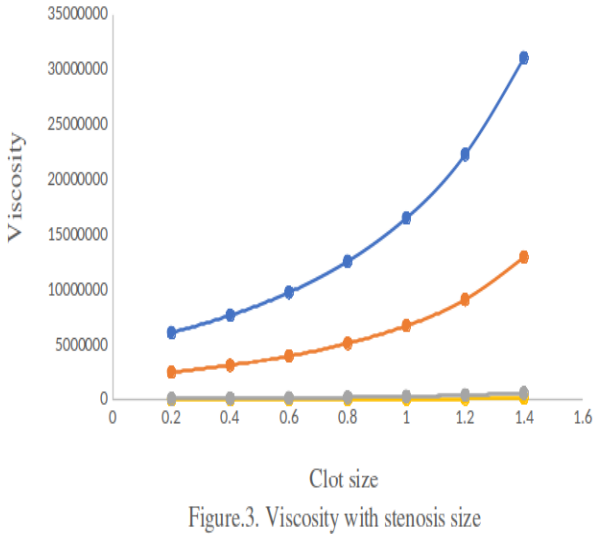

Figure 3: Viscosity with stenosis size.

Interestingly, our simulations elucidate a non-linear relationship between blood glucose levels and clot formation risk, with acute hyperglycemic spikes exerting particularly pronounced effects on platelet reactivity and activation of the clotting cascade. These findings underscore the importance of glycemic control in mitigating acute thrombotic events in diabetic patients. Additionally, our sensitivity analyses highlight the potential efficacy of multifaceted interventions targeting various pathophysiological pathways implicated in clot formation. By integrating blood glucose lowering strategies, lipid-lowering therapies, and antiplatelet agents, our model suggests synergistic effects in reducing clot formation risk and attenuating the burden of cardiovascular complications in diabetes [6,16,45,51]. Figure.2. show that as blood clots expand in size within the blood vessels, they create obstructions that impede the flow of blood. This obstruction results in an increase in resistance to blood flow, making it more difficult for the blood to move past the clot. The larger the clot, the greater the resistance it presents to the flow of blood. This increased resistance can lead to higher pressure within the blood vessel upstream of the clot and decreased pressure downstream, altering blood flow patterns and potentially causing complications such as ischemia or tissue damage. Therefore, as clot size increases, so does the resistance to blood flow, which can have significant implications for overall cardiovascular health and function. Figure.3. show that as blood clots grow larger within the vasculature, they exert significant effects on blood viscosity, the thickness or stickiness of blood. This increase in viscosity arises from several factors. First, the clot traps various blood components, including red blood cells and platelets, within its structure, leading to a concentration of blood constituents in the vicinity of the clot. Additionally, the formation of fibrin, a protein essential for clot structure, results in the creation of a dense meshwork that impedes blood flow [4,15,23,50]. As more platelets aggregate to the clot site, they further contribute to the viscosity of the surrounding blood. The obstruction caused by a larger clot alters the flow dynamics within the blood vessel, influencing shear forces and pressure gradients, which in turn affect viscosity. Ultimately, the growth of blood clots leads to an increase in local blood viscosity, impacting blood flow dynamics and potentially exacerbating thrombotic events. Overall, our computational approach offers valuable insights into the complex interplay between diabetes-related factors and thrombotic propensity, providing a framework for identifying novel therapeutic targets and optimizing treatment strategies for diabetic individuals at increased risk of thrombotic events [24,32,52]. By elucidating the underlying mechanisms driving clot formation in diabetes, our research aims to pave the way for personalized interventions aimed at mitigating the heightened thrombotic risk associated with this prevalent metabolic disorder.

4 Conclusion

Our study underscores the utility of mathematical modeling and computational analysis in elucidating the complex interplay between diabetes and thrombosis. By integrating physiological data and computational simulations, we provided mechanistic insights into the pathophysiology of clot formation in diabetes and identify potential therapeutic targets for mitigating thrombotic complications in diabetic individuals. The computational framework developed in this study offers a valuable tool for assessing clot formation risk, optimizing treatment strategies, and guiding clinical decision-making in diabetic patients. As blood clots grow larger within the blood vessels, they create obstructions that impede the flow of blood. This obstruction increases the resistance to blood flow, making it more challenging for blood to move past the clot. At the same time, the clot's size can also affect the viscosity of the blood in the vicinity of the clot. As more blood cells and clotting factors accumulate around the clot, the viscosity of the blood in that area can increase. Both increased resistance to flow and higher viscosity can further impede blood circulation, potentially leading to complications such as ischemia or tissue damage. Therefore, as the clot size increases, both resistance to flow and viscosity are likely to increase, exacerbating the clot's impact on blood circulation and overall cardiovascular health.

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