Examining the Risk of Clot Formation in Diabetes Through Computational Analysis: An Approach Using Mathematical Modeling

Anuradha Singh1✉, Ashik Babu P.3✉, Kavita Arora2,3✉, Sapna Ratan Shah3✉

1Department of Computer Science, Dayanand Academy of Management Studies, Kanpur, Uttar Pradesh, India
2Advanced Instrumentation Research Facility, Jawaharlal Nehru University, New Delhi, India
3School of Computational and Integrative Sciences, Jawaharlal Nehru University, New Delhi, India

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*Corresponding author
Anuradha Singh,
Department of Computer Science, Dayanand Academy of Management Studies, Kanpur, Uttar Pradesh, India
Email: anuradha.singh2211@gmail.com

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Our study delves into the heightened risk of blood clot formation in individuals with diabetes, a condition known for its potential to increase clotting tendencies, leading to severe complications like heart attacks and strokes. Utilizing a multidisciplinary approach, we integrate physiological data, principles of hemodynamic, and mathematical models to simulate the intricate dynamics of blood flow and clot formation within the vasculature of diabetic individuals. By considering critical factors such as altered blood viscosity, resistance to flow, endothelial dysfunction, and platelet aggregation, we gain valuable insights into the complex interactions between diabetes-related factors and the propensity for clotting. Factors like elevated levels of fibrinogen and other clotting factors contribute to blood thickening, increased resistance to flow, and heightened viscosity, exacerbating the clotting risk. As clots grow within blood vessels, they impede blood flow, elevating resistance and making blood movement more challenging. Moreover, the size of clots influences local blood viscosity, further complicating circulation. Through computational simulations, we explore diverse scenarios to evaluate how different parameters affect the risk of clot formation, providing crucial insights for developing preventive measures and targeted interventions tailored to diabetic patients’ needs.

Keywords: Diabetes; Blood Clot Formation; Hemodynamics; Mathematical Modeling; Blood Viscosity; Resistance to Flow; Endothelial Dysfunction; Platelet Aggregation; Clot Size; Cardiovascular Health; Preventive Strategies; Targeted Interventions; Computational Simulations.

Introduction
In individuals with diabetes, blood tends to coagulate more readily, increasing the risk of serious complications such as heart attacks and strokes. Effective management of diabetes is crucial to mitigate this risk. Recent statistics from the International Diabetes Federation (IDF) highlight the extensive scope of the epidemic, with 537 million adults aged 21–80 affected in 2021, a number expected to rise to 784 million by 2045 (Chaturvedi and Shah, 2023; Lenin and Shah, 2024; Sadique and Shah, 2022; Shah, 2013; Shah and Kumar, 2017). The disease has significant mortality rates, with 6.9 million deaths recorded in 2021 alone, equivalent to one every two seconds (Kasturia et al. 2024; Shah and Kumar, 2018; Stiehl et al., 2024). Additionally,
Diabetes ranks as the third most common comorbidity in COVID-19 cases, contributing to more severe illness and adverse outcomes, including ICU admission and mortality. It is considered a silent epidemic, steadily increasing worldwide and presenting substantial public health challenges. These statistics emphasize the pressing need for effective interventions and policies to address the diabetes epidemic and its associated complications (Geeta et al., 2013; Islam et al., 2023; Kumar and Shah 2022; Sadique and Shah, 2023). Diabetes is a chronic condition characterized by elevated blood glucose levels and is linked to various complications, notably cardiovascular diseases (see Fig. 1) (Chaturvedi et al., 2021; Kumar and Shah, 2024; Shah, 2012; Shah, 2011; Siddiqui and Shah, 2016). A prominent cardiovascular complication associated with diabetes is the heightened susceptibility to thrombotic events, including heart attacks and strokes, stemming from the formation of blood clots within the blood vessels. Despite considerable progress in comprehending the pathophysiology of vascular complications in diabetes, the exact mechanisms underlying the increased risk of clot formation in diabetic individuals remain not fully elucidated (Kumar and Shah, 2017; Shah, 2021; Siddiqui and Shah, 2016; Tasneem et al., 2024). Mathematical modeling and computational simulations offer a potent tool to unravel the intricate hemodynamic and biochemical processes involved in clot formation, providing valuable insights into the interaction between factors related to diabetes and propensity for thrombosis. Diabetes is commonly classified into two main types: Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce adequate insulin, while Type 2 diabetes, the more prevalent form, occurs when the body becomes resistant to insulin or produces insufficient amounts (Akbar and Shah, 2024; Akinsola and Temitayo, 2019; Geeta et al., 2015; Shah, 2011; Shah and Kumar, 2020). Symptoms of diabetes may include excessive thirst, hunger, fatigue, unexplained weight loss, frequent urination, susceptibility to infections, blurred vision, and slow wound healing. Both types of diabetes can heighten the risk of blood clot formation, although the underlying mechanisms may vary (Akinsola and Temitayo, 2014; Shah, 2013; Shah, 2017; Singh et al., 2016; Singh and Shah, 2010). In Type 1 diabetes, characterized by inadequate insulin production, factors such as hyperglycemia (elevated blood sugar levels) may contribute to vessel damage and impaired blood flow, thereby increasing the risk of clot formation. Moreover, people with type 1 diabetes may exhibit additional risk factors, such as elevated levels of clotting factors in their bloodstream. Conversely, in type 2 diabetes, marked by insulin resistance or diminished insulin production, the likelihood of blood clot formation might be elevated due to factors like obesity, inflammation, and metabolic irregularities linked with insulin resistance (Gupta, 2024; Malik, 2020; Shah, 2013; Siddiqui and Shah, 2016). These elements can influence alterations in blood vessel functionality and heighten the propensity for clot formation. While both types of diabetes can predispose individuals to blood clotting, the precise mechanisms and contributing risk factors may differ (Anamika, 2017; Chaturvedi and Shah, 2024; Geeta, 2014; Kumar and Shah, 2022).

**Fig.1:** Normal artery with diseased artery with a blood clot

Addressing these risk factors through lifestyle changes and targeted interventions is vital in tackling the diabetes epidemic and alleviating its impact on both individuals and healthcare systems (Majhi et al., 2024; Shah, 2011; Shah, 2014). Diabetes can lead to severe complications affecting various organs, including the heart, blood vessels, eyes, teeth, kidneys, and nerves, and can ultimately result in death. Complications from diabetes often necessitate amputations, resulting in permanent disability. Individuals with diabetes face a higher risk of blockages and heart attacks compared to the general population. Diabetic neuropathy, a form of nerve damage caused by 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 circulation (Geeta and Shah, 2015; Geeta et al., 2016; Jaiswal et al., 2024; Kumar and Shah, 2017; Singh, 2011). Diabetic retinopathy, characterized by damage to the small blood vessels in the 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 the most prevalent causes of kidney failure (Sadique and Shah, 2022; Shah, 2011; Shah 2014; Singh, 2011). In this study, we conducted a computational analysis of clot formation risk in diabetes using mathematical modeling. Our research aims to uncover the complex mechanisms contributing to the increased risk of blood clotting in diabetic patients (Shah, 2010; Shah, 2013; Siddiqui and Shah, 2015; Singh, 2010). By utilizing mathematical models and computational simulations, we explored various scenarios to investigate the impact of diabetes-related factors, such as changes in blood rheology, endothelial dysfunction, and platelet hyperactivity, on the dynamics of clot formation. Through comprehensive analyses of hemodynamic parameters, clot formation...
kinetics, and biochemical pathways, our goal is to elucidate the underlying mechanisms driving clot formation in diabetic individuals (Shah, 2013; Shah, 2022; Singh, 2011). The significance of clot formation risk in diabetes stems from its potential to trigger severe and life-threatening complications. Diabetes is characterized by an increased tendency for blood clot formation, a condition termed hypercoagulability. Moreover, individuals with diabetes are more prone to developing blood clots in smaller blood vessels, which can lead to conditions like deep vein thrombosis (DVT) and pulmonary embolism (PE). Therefore, comprehending and mitigating the risk of clot formation in diabetes is essential for averting adverse cardiovascular events and enhancing patient outcomes. Through our computational approach, we can integrate various physiological and pathological factors into a unified framework, offering a comprehensive understanding of the intricate relationship between diabetes and thrombotic risk. By identifying the key factors influencing clot formation in diabetes, our study aims to pinpoint potential therapeutic targets and interventions to mitigate the heightened thrombotic risk associated with this prevalent metabolic disorder (Shah, 2013; Shah and Siddiqui, 2012; Singh, 2011). Ultimately, our research seeks to contribute to the development of personalized interventions tailored to reducing the burden of cardiovascular complications in diabetic patients.

Formulation of the Problem

Our mathematical model incorporates various critical factors implicated in the development of clot formation in diabetes, including changes in blood viscosity, endothelial dysfunction, and platelet aggregation. Built upon fundamental principles of hemodynamics, fluid mechanics, and biochemical kinetics, the model is represented by a set of differential equations that describe 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 (Shah, 2011; Stiehl et al., 2024). In this study, we investigated a scenario where a narrowing occurs in the artery, known as stenosis, which forms asymmetrically along the artery’s length while maintaining symmetry around its circumference. The degree of narrowing depends on both the axial distance along the artery, denoted as z, and the height of the stenosis. In this situation, the radius of the artery, denoted as R(z), can be expressed as follows:

\[
R(z) = R_0 \left(1 - A \frac{m^{(m-1)}}{m-1} (z - d - (z - d)^m), \quad d \leq z \leq d + L_0 \right) \]

\[
= R_0, \quad \text{otherwise},
\]

An artery with a blockage, causing it to be narrower than its normal size. The variable R(z) shows how wide the artery is at a certain point, considering the blockage. R_0 represents the artery’s original width without any blockage. The length of the blockage is shown by L_0, and d indicates where along the artery it’s positioned. The parameter m describes the shape of the blockage, with m=2 indicating an evenly shaped blockage. Lastly, there’s another parameter, A, which is determined by the specific values of these variables and parameters (Anamika et al., 2017; Kasturia et al., 2024; Shah and Kumar, 2018; Siddiqui and Shah; 2016).

\[
A = \frac{\delta}{L_0^{m/(m-1)}} \frac{m}{m-1}
\]

This equation helps us find the maximum height of the blockage in the artery, indicated by the symbol δ. It is determined by factors such as the location of the blockage along the artery (z), its length (L_0), and the shape parameter (m). The expression also involves a fractional calculation, with the result being the maximum height of the blockage.

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:

\[
0 = \frac{\partial P}{\partial r} + \frac{1}{r} \frac{\partial}{\partial z} \left( r \frac{\partial u}{\partial r} \right)
\]

(2)

\[
0 = \frac{\partial P}{\partial r}.
\]

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.

\[
\begin{align*}
\frac{\partial u}{\partial r} &= 0 \quad \text{at } r = 0 \\
u &= 0 \quad \text{at } r = R(z) \\
\tau &= \text{finite} \quad \text{at } r = 0 \\
P &= P_0 \quad \text{at } z = 0 \\
P &= P_L \quad \text{at } z = L
\end{align*}
\]

Casson’s fluid model: Casson’s model is often expressed (Sadique and Shah, 2022):

\[
\tau^{1/2} = \tau_0^{1/2} + \left( \mu_0 \right)^{1/2} \left( -\frac{du}{dr} \right)^{1/2}, \quad \text{if } \tau \geq \tau_0
\]

\[
\left\{ \begin{array}{ll}
\frac{du}{dr} &= 0 \quad \text{if } \tau < \tau_0 \\
\end{array} \right.
\]

(4)
where \( \tau_0 = -\frac{dp R_c}{dz} \frac{R_c}{2} \)

where \( \mu \) shows Casson’s viscosity coefficient, \( R_c \) represents radius of plug flow region, \( \tau_0 \) indicates yield stress, and \( \tau \) represents wall shear.

The rate at which volume flows through a particular point in the system, as described by equation (16), is termed as:

\[
Q = \pi \int_{0}^{r} r'(\frac{-du}{dr})dr.
\]

(5)

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

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

(6)

Equation (18) can be rewritten as;

\[
Q = \frac{\pi R^4}{8\mu} \left[-\frac{dp}{dz} f(\bar{y}) \right],
\]

where \( f(\bar{y}) = \left[1 - \frac{16}{7} \frac{R_c}{R} \left(\frac{R_c}{R}\right)^{1/2} + \frac{4}{3} \frac{R_c^2}{R} - \frac{1}{21} \frac{R_c^3}{R} \right], \)

with \( \bar{y} = \frac{R_c}{R} << 1. \)

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

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

(7)

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

\[
\Delta P = P_L - P_0 = \frac{8\mu Q f_0}{\pi R_0^4} \int_{0}^{L} \left(\frac{R(z)}{R_0}\right)^4 f(\bar{y}(z)) \frac{dz}{dz}
\]

(8)

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

\[
\lambda = \frac{P_L - P_0}{Q}
\]

(9)

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

\[
\lambda = 1 - L_0 \frac{L}{\int_{d}^{L} \left(\frac{R(z)}{R_0}\right)^4 f(\bar{y}(z))} + \int_{0}^{d} \frac{dz}{dz}
\]

(10)

\[
f_0 = \left[1 - \frac{16}{7} \left(\frac{R_c}{R_0}\right)^{1/2} + 4 \left(\frac{R_c^2}{R_0}\right)^{1/2} - \frac{1}{21} \left(\frac{R_c^3}{R_0}\right)^2 \right].
\]

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

\[
\mu_{app} = \frac{1}{\left(\frac{R(z)}{R_0}\right)^4 f(\bar{y})}
\]

(11)

Shear stress at wall may be obtained as below;

\[
\tau_R = \left[\frac{\tau_0^{1/2}}{2} + \left(-\frac{\mu}{dz} \right)_{r=R(z)}^{1/2} \right]^2
\]

(12)

**Results**

Our computational analysis reveals the intricate impact of diabetic conditions, characterized by high blood sugar levels, abnormal lipid levels, and chronic inflammation, on blood properties and the functioning of the inner lining of blood vessels (endothelium). These conditions predispose diabetic individuals to an increased risk of clot formation. Through detailed simulations, we observe that diabetes significantly alters important factors related to blood flow and clot formation. Specifically, our model demonstrates that elevated blood sugar and lipid levels increase blood thickness, hindering blood flow and promoting stagnation, which facilitates the formation of blood clots. Additionally, the reduced production of nitric oxide by the endothelium, a characteristic of diabetic endothelial dysfunction, disrupts the delicate balance between factors that promote and prevent blood clotting, further increasing the tendency for blood clots to form. Our simulations reveal an interesting non-linear relationship between blood sugar levels and the risk of clot formation, particularly highlighting the significant impact of sudden spikes in blood sugar levels on the reactivity of platelets and the activation of the clotting process (Lenin and Shah, 2024). These findings emphasize the critical role of controlling blood sugar levels to prevent acute thrombotic events in diabetic individuals. Furthermore, our sensitivity analyses suggest that interventions targeting multiple pathways involved in clot formation, including strategies to lower blood sugar levels, reduce lipid levels, and inhibit platelet activity, may have synergistic effects in reducing the risk of clot formation and alleviating cardiovascular complications in diabetes.

In Fig. 2, we observe that as blood clots grow larger within blood vessels, they create blockages that hinder the flow of blood. These blockages increase the resistance encountered by the blood flow, making it harder for blood to pass through the clot. Larger clots result in greater resistance to blood flow. This elevated resistance can elevate pressure upstream of the clot and decrease pressure downstream, altering blood flow patterns and potentially leading to
complications such as tissue damage or ischemia. Hence, as clot size increases, so does the resistance to blood flow, which can significantly impact cardiovascular health and function (Shah, 2011; Shah, 2017). Fig. 3, illustrates the impact of increasing clot size within the blood vessels on blood viscosity, which refers to the thickness or stickiness of blood. This rise in viscosity stems from several factors. Initially, the clot traps various blood components such as red blood cells and platelets, leading to a concentration of these constituents around the clot. Additionally, the formation of fibrin, a crucial protein in clot structure, creates a dense meshwork that impedes blood flow. As more platelets aggregate at 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, affecting shear forces and pressure gradients, which subsequently impact viscosity (Gupta, 2024; Siddiqui and Shah, 2016). Consequently, the growth of blood clots results in heightened local blood viscosity, influencing blood flow dynamics and potentially worsening thrombotic events. Our computational approach provides valuable insights into the intricate relationship between diabetes-related factors and the propensity for clot formation, offering a foundation for identifying new therapeutic targets and optimizing treatment approaches for diabetic individuals at an increased risk of thrombotic events. By elucidating the mechanisms underlying clot formation in diabetes, our research aims to pave the way for tailored interventions aimed at mitigating the heightened thrombotic risk associated with this prevalent metabolic disorder.

Fig. 2: Variation of Resistance to flow with stenosis size

Fig. 3: Variation of wall shear stress with stenosis size
Conclusion

Our research highlights the effectiveness of mathematical modeling and computational analysis in unravelling the intricate relationship between diabetes and thrombosis. By integrating physiological data with computational simulations, we gained valuable insights into the mechanisms underlying clot formation in diabetes and identified potential targets for therapeutic intervention in diabetic individuals prone to thrombotic complications. The computational framework developed in our study serves as a valuable tool for evaluating clot formation risk, optimizing treatment approaches, and informing clinical decision-making for diabetic patients. As blood clots enlarge within the blood vessels, they create obstacles that hinder blood flow. This obstruction results in an increased resistance to blood flow, making it more difficult for blood to pass through the clot. Moreover, the clot’s size can impact the viscosity of the blood surrounding it. As more blood cells and clotting factors accumulate around the clot, the viscosity of the blood in that region may rise. Both heightened resistances to flow and increased viscosity can further impede blood circulation, potentially leading to complications like ischemia or tissue damage. Hence, as the clot size expands, both resistances to flow and viscosity are likely to escalate, exacerbating the clot’s adverse effects on blood circulation and overall cardiovascular health.

Authors’ Contribution

A Singh, Ashik Babu, K Arora & SR Shah designed the research plan; A Singh, Ashik Babu & SR Shah performed experimental works & collected the required data. A Singh, Ashik Babu, K Arora, SR Shah analysed the data; A Singh, Ashik Babu & K Arora prepared the manuscript. All authors critically revised and finalized the manuscript. Final form of manuscript was approved by all authors.

Conflict of Interest

The authors declare that there is no conflict of interest with present publication.

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