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(REVIEW ARTICLE)

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# The process of blood coagulation in individuals with diabetes mellitus

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## Abstract

**Background:** Diabetes mellitus is a global health issue impacting around 382 million people worldwide. There is a growing number examining the impact of type 2 diabetes on alterations in the coagulation system. There are several factors that play a role in coagulation disorders. Understanding the molecular changes that occur in the coagulation process in diabetes patients can help in the development of more effective management strategies to prevent complications associated with blood coagulation.

**Objectives:** To assess the occurrence of blood coagulation in individuals with diabetes mellitus and identify the factors involved.

**Conclusion:** In individuals with diabetes, the blood coagulation process is disrupted at the molecular level due to the metabolic changes associated with the condition. Various factors contribute to coagulation disorders, including the activation of the renin-angiotensin system, inflammation, and oxidative stress.

**Keywords:** Diabetes Mellitus; Blood Coagulation; Literature Review; Coagulation Disorder; Type 1 Diabetes; Type 2 Diabetes

## 1. Introduction

Diabetes mellitus is a global health issue impacting approximately 382 million people worldwide, with an additional 316 million individuals exhibiting impaired glucose tolerance, putting them at high risk for the disease [1]. Diabetes mellitus is a chronic metabolic disease, with the number of cases anticipated to grow each year. It is increasingly becoming a global concern, affecting not just high-income countries. Therefore, there is a need for effective preventive, diagnostic, and treatment strategies [2].

Diabetes is classified into two types: type 1 and type 2. Type 1 diabetes mellitus is an autoimmune condition that leads to insulin deficiency due to the destruction of the insulin-producing beta cells in the pancreas. On the other hand, type 2 diabetes mellitus results from insulin resistance. The majority of diabetes cases are type 2 [2].

The blood clotting process occurs in a series of stages, during which coagulation factors are activated, ultimately leading to the formation of fibrin [3]. Coagulation factors, also known as blood clotting factors, are proteins present in blood plasma that play a key role in the clotting process. The purpose of blood clotting is to address vascular injury and prevent excessive bleeding, with the clotting process being confined to the area of injury [4].

Overall, there is a growing number examining the impact of type 2 diabetes on alterations in the coagulation system. Both insulin-resistant type 2 diabetes and chronic type 1 diabetes lead to heightened regulation of the fluid and cellular stages of thrombus formation and inflammation, which in turn raises the risk of cardiovascular complications [1].

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## 2. Material and methods

This research uses a Literature Review design with references to literature relevant to the topic and then written systematically. The study was conducted in May 2023. Data was obtained from journal sources, both national and international, between 2012 and 2023. Data was obtained from previous research using databases such as Google Scholar, PubMed, and several other relevant sources. The keywords we use in this literature review are Diabetes Mellitus at the molecular level and blood coagulation.

## 3. Results and discussion

According to the journals reviewed, several studies are relevant to the issues and objectives of this review. Research by Rhee and Kim [5] indicated that the formation of advanced glycation end-products (AGEs) in diabetic patients results from chronic elevated blood glucose levels. Some AGEs are also obtained through food intake. These AGEs are believed to be key contributors to the development of diabetes-related complications. They increase oxidative stress in the body and trigger inflammatory responses, which play a significant role in worsening vascular complications associated with diabetes. Various clinical and preclinical studies suggest that interventions targeting AGEs can help reduce and prevent these complications. Managing blood glucose levels, adopting a proper diet, and receiving medical treatment can serve as effective AGE interventions.

Research by Fiorentino *et al.* [6] found that diabetes mellitus is linked to a higher risk of cardiovascular disease. Hyperglycemia is a key factor in causing vascular damage in the heart, working through various mechanisms such as the activation of protein kinase C, polyol and hexosamine pathways, and the production of advanced glycation end products. These processes are connected to hyperglycemia-induced mitochondrial dysfunction and endoplasmic reticulum stress, which contribute to the buildup of reactive oxygen species (ROS). ROS can directly damage lipids, proteins, and DNA, as well as alter intracellular signaling pathways like mitogen-activated protein kinases and redox-sensitive transcription factors. This leads to changes in protein expression and irreversible oxidative modifications. The oxidative stress caused by hyperglycemia triggers endothelial dysfunction, which plays a crucial role in the development of both micro- and macrovascular diseases.

Research by Darenskaya *et al.* [7] highlighted a connection between oxidative stress and diabetes mellitus, with oxidative stress playing a dual role in both the manifestation and progression of related complications. Reactive oxygen species (ROS) contribute to one of the major complications of diabetes, endothelial dysfunction. Endothelial dysfunction is an independent risk factor for cardiovascular issues in diabetes and promotes the adhesion of leukocytes and platelets, thrombosis, and inflammatory reactions, all of which are key contributors to atherosclerosis. Short-term exposure to ROS in hyperglycemia selectively increases the expression of the iNOS gene, leading to higher levels of nitric oxide (NO). The simultaneous increase in NO and superoxide radicals promotes the formation of peroxynitrite, a potent oxidant that harms vascular tissue and can cause myocardial damage and disease. Various isoforms of NADPH oxidase (NOX) are found in monocytes, macrophages, and vascular cells, where they play both protective roles and contribute to endothelial dysfunction and inflammation.

Research by Mendivil *et al*. [8] found that an increased risk of type 2 diabetes was strongly linked to markers of early events in the development of atherosclerotic disease. These markers included endothelial activation (indicated by higher levels of sICAM-1), subclinical inflammation (evidenced by elevated hsCRP levels), impaired coagulation/thrombolysis (reflected in increased PAi-1 and tPA levels), and impaired suppression of adipose tissue lipolysis (shown by higher plasma free fatty acid levels). Preventive measures to curb the silent progression of cardiovascular disease should begin in early adulthood, particularly for ethnic groups that are more heavily affected by diabetes and cardiovascular disease.

Research by Domingueti [9] found that inflammation, endothelial dysfunction, and hypercoagulability are interconnected and play a crucial role in the development of vascular complications in diabetes patients. The study also noted that various biomarkers associated with endothelial function, inflammation, and coagulation, such as VWF, IL-6, TNF-α, D-dimer, and PAI-1, were elevated in diabetes patients with microvascular and macrovascular complications, including nephropathy and cardiovascular disease.

Research by Ighodaro [10] highlighted that oxidative stress plays a critical role in the onset and complications of diabetes. Furthermore, the accumulation of glyceraldehyde-3-phosphate, caused by the inhibition of glyceraldehyde-3-phosphate dehydrogenase by poly-ADP-ribose polymerase 1, is a key factor in oxidative stress associated with diabetes.

However, despite the significant role of oxidative stress in diabetes and its complications, the consumption of antioxidants does not prevent the onset of diabetes mellitus.

Research by Altalhi *et al*. [11] revealed that PAI-1 plays both physiological and pathological roles in health and disease, particularly in vascular disease with a focus on diabetes. The development of PAI-1 inhibitors offers an alternative strategy for managing hypofibrinolysis by targeting the underlying abnormality, rather than relying on current treatments that broadly inhibit cellular and/or acellular components of coagulation, which can increase the risk of bleeding. Creating PAI-1 inhibitors could pave the way for a new class of antithrombotic drugs in the future, potentially reducing vascular complications in diabetes.

## 4. Conclusion

In diabetes sufferers, the blood coagulation process experiences disturbances at the molecular level which is a result of metabolic changes that occur in diabetes. There are several factors that play a role in coagulation disorders, such as activation of the renin-angiotensin system, inflammation, and oxidative stress. Understanding the molecular changes that occur in the coagulation process in diabetes patients can help in the development of more effective management strategies to prevent complications associated with blood coagulation, such as vascular disease. Good control of blood sugar levels and the use of appropriate therapy to reduce activation of the renin-angiotensin system, inflammation and oxidative stress can be important steps in overcoming coagulation disorders in diabetes sufferers.

## Compliance with ethical stand*ards

*Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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