



# Tissue Factor Levels Used as Coagulation Biomarkers in Diabetic and Hypertensive Patients

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## Abstract

**Background:** Tissue factor is a key initiator of the clotting process, and elevated levels are associated with abnormal thrombogenesis. Patients with chronic conditions like diabetes and hypertension may exhibit increased tissue factor concentrations, which can lead to serious complications. This study aims to determine tissue factor levels among diabetic patients, diabetics with uncontrolled hypertension, and healthy volunteers, to explore the potential of tissue factor as a diagnostic biomarker. **Methods:** Tissue factor concentrations were measured using enzyme-linked immunosorbent assay (ELISA), and glycated hemoglobin type 1A (HbA1c) levels were estimated with the Cobas instrument. The study population included diabetic patients, diabetics with uncontrolled hypertension, and healthy volunteers. Statistical analysis was performed using SPSS version 26, with comparisons made between the groups. **Results:** The results showed significantly higher tissue factor concentrations in patients compared to healthy volunteers. The mean tissue factor level in patients was 100.12 ( $\pm 26.92$ ) pg/mL, while in healthy volunteers, it was 59.17 ( $\pm 19.24$ ) pg/mL ( $p < 0.001$ ). Diabetic patients with elevated HbA1c levels had higher tissue factor concentrations compared to healthy volunteers (mean

HbA1c: 6.95 ( $\pm 1.853$ )% vs. 4.28 ( $\pm 0.327$ )%). Moreover, patients with both diabetes and hypertension had the highest tissue factor levels, with a mean of 130.89 ( $\pm 14.33$ ) pg/mL ( $p < 0.001$ ). No significant differences in tissue factor levels were observed based on gender or age ( $p > 0.05$ ). **Conclusion:** Elevated tissue factor levels were observed in patients with diabetes and hypertension, particularly in those with poorly controlled conditions. This elevation suggests an increased risk of coagulation disorders, potentially affecting vital organs such as the heart, brain, and kidneys. Tissue factor could serve as a valuable diagnostic biomarker, allowing for early intervention in patients at risk of developing serious complications.

**Keywords:** Tissue Factor (TF), Diabetes Mellitus (DM), Hypertension (HT), Coagulation Cascade, Cardiovascular Disease (CVD)

## Introduction

Tissue factor (TF) is the most potent initiator of the coagulation cascade and plays a critical role in hemostasis. Several studies have demonstrated that individuals with poorly managed diabetes exhibit elevated TF levels, which is released when cardiovascular risk factors such as diabetes and hypertension damage the endothelium, leading to thrombus formation in the arteries (Grover & Mackman, 2020; Witkowski et al., 2020).

Diabetes mellitus (DM), characterized by high fasting blood sugar and elevated glycated hemoglobin (HbA1c), causes extensive macrovascular and microvascular damage, resulting in multiple organ dysfunctions (Schneider, 2023). Recent research in Kirkuk City, Iraq, has revealed significant changes in the hematological

**Significance** | This study determined elevated Tissue Factor levels as a potential biomarker for thrombotic risk in diabetic and hypertensive patients.

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parameters of diabetic patients, suggesting an increased sensitivity to parasitic infections (Ahmed et al., 2023). Vascular complications, such as atherosclerosis, are the leading causes of mortality in diabetes, reflecting the consequences of endothelial dysfunction (Moreno & Fuster, 2004). Circulating TF, generated from platelets, lymphocytes, and endothelial cells, is significantly elevated in patients with diabetes mellitus (Zhang et al., 2020). Both type 1 and type 2 diabetes are associated with physiological changes affecting hemostasis, leading to a hypercoagulable state (Sobczak & Stewart, 2019). Patients with persistent hyperglycemia, particularly those with poor glycemic control, are at the highest risk of developing various vascular coagulopathies, as evidenced by a recent study showing shorter prothrombin time in diabetic individuals compared to healthy controls (Bryk-Wiązania & Undas, 2021). Fortunately, some antidiabetic medications, such as metformin, have been shown to reduce the activity of coagulation factors (Witkowski et al., 2021).

Hypertension (HT), defined as a systolic blood pressure (SBP) greater than 140 mmHg or a diastolic blood pressure (DBP) above 90 mmHg, is characterized by functional and structural changes in arterial flexibility, leading to increased peripheral vascular resistance (Tsao et al., 2022). Recent European guidelines suggest that clinic blood pressure levels above 140/90 mmHg necessitate pharmacological intervention (Grassi, 2024). In Iraq, like in many developing countries, hypertension prevalence is rising, driven by unhealthy diets, sedentary lifestyles, obesity, hyperglycemia, hypercholesterolemia, and smoking (Mousa et al., 2022). HT affects endothelial function through increased oxidative stress and inflammation, leading to elevated TF activity, which is considered a risk factor for vascular thrombotic disorders (Savoia et al., 2011).

This study aims to investigate the levels of human tissue factor in patients with diabetes and hypertension, particularly in those with poorly controlled blood sugar and blood pressure.

## 2. Methods and Materials

### 2.1 Study Setting and Population

The study was conducted at Gulan Public Hospital in Akre District, Duhok City, Kurdistan Region, Iraq. A total of 244 patients, comprising 124 males and 120 females, were enrolled alongside 80 health volunteers (40 males and 40 females). Both patient and control groups were divided into five distinct age categories, as detailed in Table 1, which presents their frequencies and percentages. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of Gulan Public Hospital, Akre District, Duhok City, Kurdistan Region, Iraq. Prior to enrollment, all participants, including the 244 patients (124 males and 120 females) and 80 health volunteers (40 males and 40 females), were fully informed about the study's objectives, procedures, potential

risks, and benefits. Written informed consent was obtained from each participant or their legal guardians where necessary.

Participants were assured of the confidentiality and anonymity of their data. All data collected was securely stored and used solely for research purposes, with access restricted to authorized personnel only. The study adhered to all relevant local and international guidelines for human research, ensuring the rights, safety, and well-being of the participants were fully protected. Furthermore, participants were informed of their right to withdraw from the study at any time without any negative consequences to their medical care or standing with the hospital.

Care was taken to minimize any discomfort or risk associated with the study procedures, and no invasive interventions beyond routine clinical practice were performed. All collected data was de-identified prior to analysis to maintain participant privacy.

### 2.2 Sample Collection and Preparation

Blood samples were obtained from all participants. After allowing the blood to clot for two hours at room temperature, the samples were centrifuged at 2000 g for 20 minutes. The serum was then carefully separated and stored at -30°C for subsequent analysis. Tissue Factor (TF) levels were measured in both diabetic and hypertensive patients, as well as in healthy control subjects. Participants were excluded from the study if they had a history of alcohol consumption, renal or hepatic disorders, or were using medications that could influence coagulation.

### 2.3 Measurement of Biomarkers

TF antigen levels were assessed using an enzyme-linked immunosorbent assay (ELISA). The analysis was conducted using the Biotek kit (USA) and the ELISA kit for human TF from ELK Biotechnology (Cat: ELK9399, USA). Additionally, glycated hemoglobin (HbA1c) levels were measured using the Cobas analyzer from Roche (USA).

### 2.4 Statistical Analysis

All statistical analyses were performed using SPSS software, version 26. Descriptive statistics for continuous variables are reported as mean  $\pm$  standard deviation (SD), while categorical variables are presented as frequencies and percentages. For between-group comparisons, independent t-tests were used for continuous variables, and chi-square tests were applied for categorical variables. One-way ANOVA was used for multiple comparisons within groups. A p-value of less than 0.05 was considered statistically significant.

## 3. Results and Discussions

The study involved participants undergoing two critical biochemical tests: HbA1c, which evaluates a diabetic patient's blood sugar control over time, and human tissue factor (TF). Before participation, patients with diabetes and hypertension were diagnosed by specialists in internal medicine and cardiology. The

**Table 1.** General characteristics of the study population, including gender, age groups, and the mean with standard deviation

		Cases Number= 244			Control Number= 80		
Variables		Mean and (±SD)	Number (No.)	(%)	Mean and (±SD)	Number (No)	Percentage %
Age in (Years)		48(±12.75)			31.62(±11.74)		
Age group (years)	<= 20		13	5.4		10	25.0%
Age group (years)	21 - 30		18	7.5		10	25.0%
Age group (years)	31 - 40		36	14.7		11	27.5%
Age group (years)	41 - 50		87	35.6		5	12.5%
Age group (years)	51+		90	36.8		4	10.0%
Sex (Gender)	(Male)		(124)	50.8		(40)	50%
	(Female)		(120)	49.2		(40)	50%

**Table 2.** Biochemical characteristics of participants, including HbA 1c and human TF tests

	Cases (No=244)	Control (No=40)	
(Variables)	Mean (±SD)	Mean (±SD)	(P-value)
TF (picogram/milliliter)	100.12 (±26.92)	59.17 (±19.24)	P<0.001
HbA1c%	6.95 (±1.853)	4.28 (±0.327)	P<0.01

A T-test was conducted with a p-value < 0.05 indicating significance

**Table 3.** Showing TF concentrations in different age groups of patients

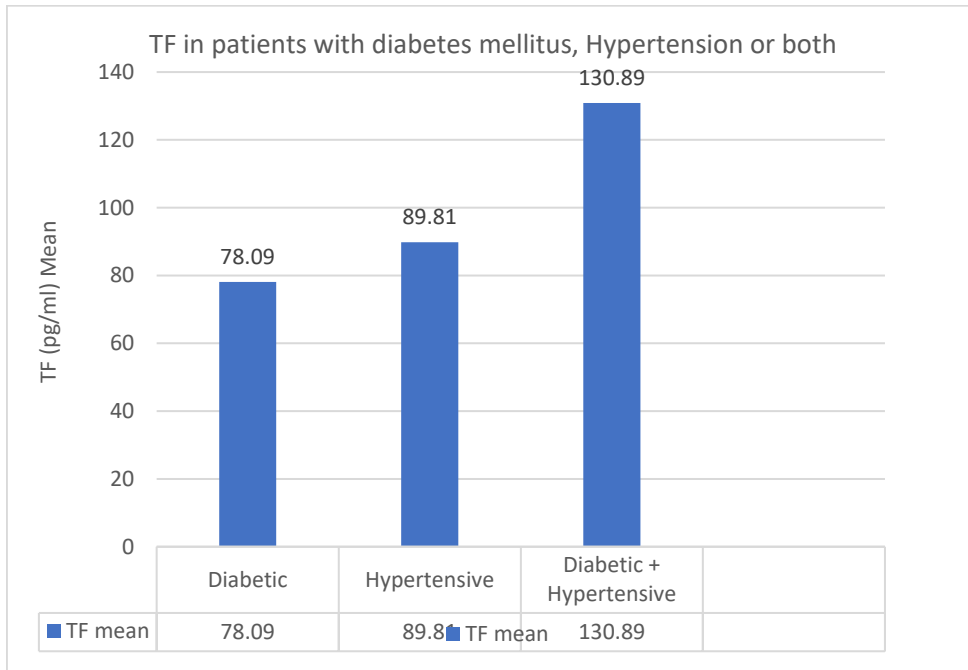
Age Group /(Years)	Number of Samples	TF Mean (±SD)	P-value
<= 20	13	76.00	P>0.05
21 - 30	18	91.17 (±6.177)	
31 - 40	36	81.66 (±14.05)	
41 - 50	87	105.20 (±28.36)	
51+	90	102.80 (±30.29)	
<b>Total</b>	244		

ANOVA test was Utilized p-value < 0.05 is significant

**Table 4.** Tissue factor in patients with Diabetes Mellitus and Hypertension

Patient case	Number of cases	TF Mean (±SD) ((picogram/milliliter))	P-value
Diabetes	103	78.09 (±8.76)	P<0.001
Hypertension	50	89.81 (±12.76)	
Diabetes + Hypertension	91	130.89 (±14.33)	

The ANOVA test was used; p-value < 0.05 indicates significance.



**Figure 1.** The histogram shows the substantial rise of TF in patients with diabetes, hypertension individually, and diabetes and hypertension combined

results indicated levels of HbA1c and TF in diabetic patients compared to healthy subjects, as illustrated in Table 1.

Human TF levels were measured across five age groups, with the majority of patients who visited the hospital being in their fourth or fifth decade of life, as shown in Table 3. The enrolled patients previously diagnosed with diabetes, hypertension, or both underwent the TF test to facilitate comparisons among all cases, as detailed in Table 4 and Figure 1.

The study's findings showed that most patients with diabetes and hypertension who visited the hospital were in their forties and fifties, suggesting that these chronic disorders are associated with aging. Similar findings were reported in a study conducted in Baghdad, Iraq (Hammood Hussein, Habeeb Rasool, Mohammed Taha, & Dakel Hussein, 2022). To understand the effects of chronic diseases like diabetes and hypertension on coagulation, including clot formation within blood vessels and potential complications, significant biochemical tests, such as TF and HbA1c estimations, were conducted on both diabetic patients and healthy volunteers. TF was measured in the blood serum of participants, revealing elevated TF levels in patients with diabetes and hypertension compared to healthy controls, consistent with previous research findings (Yigitbasi, Alagoz, Yigit, Emekli, & Cakici, 2021). Additionally, higher TF levels were found in patients with poorly controlled diabetes and hypertension than in those with better control, which aligns with multiple studies demonstrating elevated TF levels in diabetics, particularly those with high HbA1c levels (Bozkaya et al., 2023; Soma, Swanepoel, & Pretorius, 2017).

Moreover, Ghaleb et al. (2021) found that patients suffering from both diabetes and hypertension had significantly higher TF levels than those with either condition alone. In this study, no significant differences in human TF levels were observed based on age or gender, which corroborates findings from other studies (Ahmed et al., 2021). Steffel et al. (2021) also concluded that individuals with cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and smoking, as well as those experiencing acute coronary syndromes, tend to have increased TF levels.

It is worth noting that different commercial ELISA kits may yield varying results for TF concentration estimations. However, research using an ELISA kit (Quantikine) demonstrated results similar to those found in this study when determining TF levels in healthy controls (Moreno & Fuster, 2004).

Diabetes and hypertension are major risk factors for cardiovascular disease, often contributing to increased morbidity and mortality. Cardiovascular complications in patients with diabetes, hypertension, or both are driven by several pathological mechanisms, including a hypercoagulable state, especially in cases with poor management. As discussed earlier, tissue factor (TF) plays a crucial role in coagulation, and elevated levels of TF in the blood can lead to severe ischemic conditions. Therefore, human TF

could serve as a valuable diagnostic biomarker for identifying hypertensive diabetic patients at greater risk of thrombosis, aiding in the prevention of abnormal coagulation. Moreover, effective medical interventions and tight control of hypertension and diabetes can help reduce TF levels and minimize thrombotic complications.

### Conclusion

This study highlights the significant role of tissue factor (TF) in the pathogenesis of cardiovascular complications among patients with diabetes and hypertension. Elevated TF levels were observed in patients with poorly controlled diabetes and hypertension, indicating a hypercoagulable state that predisposes them to thrombotic events. The findings align with previous research, which shows that TF, as a potent initiator of the coagulation cascade, is closely linked to endothelial dysfunction and increased cardiovascular risk. Given the elevated TF levels in hypertensive diabetic patients, TF may serve as a promising diagnostic biomarker for identifying individuals at higher risk of thrombosis. Consequently, early intervention and stringent management of blood glucose and blood pressure levels are critical in reducing TF levels and minimizing thrombotic complications. Further studies are warranted to explore the potential of TF as a therapeutic target and to evaluate the impact of different interventions on TF levels and cardiovascular outcomes in this patient population.

### Author contributions

W.H.S. researched title suggestions, prepared the proposal, drafted the manuscript, and revised it. Z.M.M. collected samples and presented ideas. M.R.A. analyzed the results and proofread them. S.G.O. performed laboratory techniques, conducted analyses, and proofread the manuscript.

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### Competing financial interests

The authors have no conflict of interest.

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