

# The Role of NF- $\kappa$ B and HIF-1 $\alpha$ in the Formation of Deep Vein Thrombosis

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## Abstract

Deep vein thrombosis (DVT) remains a significant clinical challenge, with complex underlying pathophysiological mechanisms. Among the myriad factors contributing to DVT, the transcription factors NF- $\kappa$ B and HIF-1 $\alpha$  have been increasingly recognized for their roles. This study aims to deepen the understanding of NF- $\kappa$ B and HIF-1 $\alpha$  in the pathogenesis of DVT and explore potential therapeutic implications. This research investigates the expression of NF- $\kappa$ B and HIF-1 $\alpha$  in patients with DVT compared to a healthy control group, utilizing ELISA techniques for quantification. The results of the study showed that the expression of NF- $\kappa$ B and HIF-1 $\alpha$  in the blood samples of patients with DVT was significantly higher than that of normal subjects, and the difference was statistically significant ( $P < 0.001$ ). This study highlights the significantly elevated levels of NF- $\kappa$ B and HIF-1 $\alpha$  in the peripheral blood of DVT patients, suggesting their critical roles in inflammation and hypoxia regulation, with potential for future research into their mechanisms and therapeutic applications.

## Keywords

DVT, NF- $\kappa$ B, HIF-1 $\alpha$ , Inflammation, Biomarker

## 1. Introduction

Deep Vein Thrombosis (DVT) is a common vascular disorder characterized by the formation of blood clots in the deep veins, particularly those of the lower limbs. DVT not only causes symptoms such as pain, swelling, and erythema but can also lead to severe complications, such as pulmonary embolism, which poses a potential fatal risk in clinical settings [1]. The annual incidence rate of DVT is estimated to be about 1 to 2 cases per 10,000 people, increasing with age.

The formation of DVT is a complex multifactorial process involving reduced blood flow, endothelial damage, and a hypercoagulable state—collectively known as Virchow's triad [2]. Additionally, inflammatory responses play a key role in the pathogenesis of DVT. Inflammation not only directly affects endothelial function but also promotes thrombosis by activating coagulation factors in the blood [3]. NF- $\kappa\beta$  is a crucial transcription factor involved in regulating inflammation, immune responses, and cell survival, among other biological processes. In DVT-related research, the activation of NF- $\kappa\beta$  has been found to induce the expression of various inflammatory cytokines and cell adhesion molecules, which are critical factors in endothelial dysfunction and thrombus formation [4]. HIF-1 $\alpha$  is another important transcription factor that regulates gene expression under hypoxic conditions. In the thrombosis setting, HIF-1 $\alpha$  facilitates cellular adaptation to hypoxia, playing a central role in maintaining cell survival and function [5]. Additionally, HIF-1 $\alpha$  has been found to regulate the expression of certain coagulation and fibrinolysis-related genes, indirectly participating in the thrombosis process [6].

Recent studies have begun to unveil the specific roles of NF- $\kappa\beta$  and HIF-1 $\alpha$  in DVT formation, revealing their mechanisms in various cell types including endothelial cells, leukocytes, and platelets [7]. NF- $\kappa\beta$  activates the expression of multiple cytokines and chemokines under inflammatory conditions, promoting the recruitment and activation of inflammatory cells, which further exacerbate endothelial damage and thrombus formation. In contrast, HIF-1 $\alpha$  is activated under hypoxic conditions, influencing the cellular metabolism and functions involved in thrombus formation through its adaptive responses to hypoxia [5].

Although current understanding of the roles of NF- $\kappa\beta$  and HIF-1 $\alpha$  in DVT formation is preliminary and mostly descriptive, future research needs to explore the specific molecular mechanisms of these transcription factors in different cell types, and how these mechanisms interact to promote thrombosis. Additionally, exploring potential therapeutic strategies based on these transcription factors could provide new insights for the prevention and treatment of DVT. This research aims to provide a new perspective on understanding the molecular mechanisms of deep vein thrombosis formation and to explore potential therapeutic targets, offering theoretical basis and treatment strategies for clinical practice.

## 2. Materials and Methods

### 2.1. Research Population

All study subjects were required to obtain full informed consent, and the study was subject to approval by the hospital ethics committee. Case group: 50 patients with lower extremity deep vein thrombosis who were hospitalized in the First Affiliated Hospital of Bengbu Medical University from January 2023 to December 2023 were selected, and the diagnostic criteria for lower extremity deep vein thrombosis were adopted from the third edition of the 2017 Chinese Guidelines for the Diagnosis and Treatment of Deep Vein Thrombosis. The exclusion criteria were patients with thrombosis during pregnancy, combination of malignant

tumor or hematologic disease. Control group: 50 healthy people who underwent physical examination at the health examination center of the First Affiliated Hospital of Bengbu Medical University in the same period were selected.

## 2.2. NF- $\kappa$ B and HIF-1 $\alpha$ Expression Measurement

Case group: fasting for 12 hours, 10 ml of peripheral menstrual blood was added into EDTA anticoagulation tubes from 06:00 to 08:00 the next morning; control group: blood specimens were taken on the day of medical examination. The collected blood specimens were frozen and stored in an ultra-low temperature refrigerator at  $-80^{\circ}\text{C}$ . The blood specimens of the case group and control group were tested by ELISA kit and recorded.

## 2.3. Statistical Analysis

The data in this study were analyzed using SPSS 26.0 statistical software. Measurement data were summarized as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ), and comparisons between two groups were performed using the t-test. Count data were presented as [n (%)] and analyzed using the  $\chi^2$  test for comparisons between groups. A p-value of less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. General Characteristics of the Study Population

As **Table 1** showed that the study population consisted of 21 males and 29 females in the case group, with an age range of 28 to 73 years, and 23 males and 27 females in the control group, with an age range of 29 to 75 years. No significant differences were found between the two groups in terms of gender and age ( $P > 0.05$ ).

**Table 1.** General characteristics of the study population.

Characteristics	Case group	Control group	$t/\chi^2$	$P$	
Gender [N (%)]	Male	21 (42)	23 (46)	0.16	0.69
	Female	29 (58)	27 (54)		
Years ( $\bar{x} \pm s$ )	49.66 $\pm$ 12.23	46.14 $\pm$ 10.96	1.52	0.13	

### 3.2. The Expression of NF- $\kappa$ B and HIF-1 $\alpha$

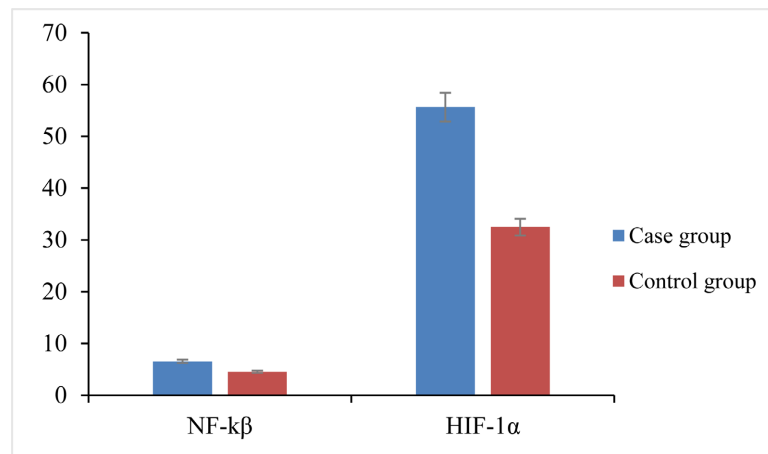
The expression of NF- $\kappa$ B and HIF-1 $\alpha$  were measured by ELISA in both groups. A t-test was performed on the concentration values measured by ELISA. **Table 2** and **Figure 1** illustrated that NF- $\kappa$ B and HIF-1 $\alpha$  expression were significantly higher in blood samples from patients with DVT than in normal subjects, and the difference was statistically significant ( $P < 0.001$ ).

## 4. Discussion

This study finds that the levels of NF- $\kappa$ B and HIF-1 $\alpha$  in the peripheral blood of patients with DVT are significantly higher than those in healthy controls. These

**Table 2.** The expression of NF- $\kappa$  $\beta$  and HIF-1 $\alpha$  in two groups.

Group	NF- $\kappa$ $\beta$ ( $\mu$ g/ml)	HIF-1 $\alpha$ (pg/ml)
Case group	6.54 $\pm$ 2.53	55.63 $\pm$ 13.35
Control group	4.53 $\pm$ 1.82	32.46 $\pm$ 8.67
<i>t</i>	4.56	10.29
<i>P</i>	<0.001	<0.001

**Figure 1.** Comparison of the level of serum NF- $\kappa$  $\beta$  and HIF-1 $\alpha$  expression between the case and control groups (NF- $\kappa$  $\beta$ :  $\mu$ g/ml, HIF-1 $\alpha$ : pg/ml).

results offer a deeper understanding of thrombus formation and progression, highlighting the crucial roles of these biomarkers in DVT pathology.

#### 4.1. Role of NF- $\kappa$ $\beta$ in Thrombosis

NF- $\kappa$  $\beta$  is a critical transcription factor involved in regulating immune and inflammatory responses [8]. Under normal conditions, NF- $\kappa$  $\beta$  exists in the cytoplasm bound to an inhibitor. Upon activation, it translocates to the nucleus to regulate the expression of various inflammation-related genes, including those encoding cytokines, chemokines, and adhesion molecules [9].

In thrombus formation, NF- $\kappa$  $\beta$  activation can be triggered by factors such as changes in blood flow dynamics, endothelial injury, and local inflammation [10] [11]. This activation not only amplifies the inflammatory response but also potentially exacerbates thrombus formation. The elevated NF- $\kappa$  $\beta$  levels observed in DVT patients suggest a heightened inflammatory state, which could contribute to the stabilization and growth of the thrombus.

#### 4.2. Role of HIF-1 $\alpha$ in Thrombosis

HIF-1 $\alpha$  is a transcription factor that is primarily activated in response to hypoxia. It regulates the expression of genes related to hypoxia responses, such as VEGF (vascular endothelial growth factor) [12] and EPO (erythropoietin), promoting angiogenesis, erythropoiesis, and metabolic adaptation [13] [14]. Local hypoxia is

a common occurrence in thrombus formation, especially in areas with reduced blood flow or vascular occlusion.

The elevation of HIF-1 $\alpha$  in DVT patients indicates that hypoxic conditions are present and that the hypoxic response has been activated. HIF-1 $\alpha$  not only serves as a marker of hypoxia but may also play a direct role in thrombus formation and development. For instance, HIF-1 $\alpha$  can stimulate endothelial cells to produce more VEGF, which promotes angiogenesis and repair but might also disrupt local blood flow and exacerbate thrombus growth [15].

### 4.3. Interaction Between NF- $\kappa$ B and HIF-1 $\alpha$

There may be an interaction and synergistic effect between NF- $\kappa$ B and HIF-1 $\alpha$  [16] [17]. Under hypoxic conditions, NF- $\kappa$ B can activate the expression of HIF-1 $\alpha$ , further enhancing the hypoxic response [18]. Conversely, HIF-1 $\alpha$  activation might influence inflammatory responses by modulating NF- $\kappa$ B pathways [19]. This interaction could exacerbate the inflammatory and hypoxic conditions in DVT, creating a vicious cycle.

### 4.4. Clinical Implications

The study results suggest that NF- $\kappa$ B and HIF-1 $\alpha$  could be significant clinical biomarkers for DVT [20]. Their elevated levels reflect severe inflammation and hypoxia in these patients, which are closely related to thrombus formation and progression. Thus, these biomarkers not only help assess the severity of the condition but might also serve as new therapeutic targets.

Monitoring NF- $\kappa$ B and HIF-1 $\alpha$  levels could enhance the understanding of the patient's pathological state and aid in developing more precise treatment strategies. Targeting NF- $\kappa$ B and HIF-1 $\alpha$  may help alleviate inflammation and improve hypoxia, potentially reducing thrombus formation and recurrence.

## 5. Conclusion

This study reveals that NF- $\kappa$ B and HIF-1 $\alpha$  levels in the peripheral blood of DVT patients are significantly elevated compared to healthy controls. These findings underscore the important roles of NF- $\kappa$ B and HIF-1 $\alpha$  in DVT pathology, likely through their regulation of inflammation and hypoxia. Future research should further explore the mechanisms underlying these biomarkers and assess their potential as therapeutic targets. Additionally, monitoring NF- $\kappa$ B and HIF-1 $\alpha$  levels could provide new tools for clinical management, facilitating personalized treatment approaches and improving patient outcomes.

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### Ethics Approval and Consent to Participate

The study adhered to the Declaration of Helsinki and received approval from the Institutional Review Board of the Natural Science Key Program of Bengbu Medical University (2021byzd119). All participants provided informed consent.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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