

High factor VIII levels and arterial thrombosis: illustrative case and literature review

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Abstract: Thrombotic disorders are one of the most common causes of morbidity and mortality in developing and developed countries. Several well-known genetic traits underlie predisposition to venous thrombosis. In particular, high factor VIII levels are a risk factor for venous thrombosis and coronary artery disease (CAD). However, similar insight into the genetic component of arterial thrombosis predisposition has not materialized fully, despite considerable effort. The authors present an illustrative case of a 32-year-old Saudi Arabian patient with peripheral arterial thrombosis whose only identifiable risk factor were high factor VIII levels. We also provide a comprehensive review of the current state of knowledge concerning the role of high factor VIII levels in determining the risk of arterial thrombosis or ischemic heart disease (IHD). We conclude that high factor VIII levels are a risk factor for thrombosis, with a greater impact on venous than on arterial thrombosis. However, due to a lack of international consensus on methods for the laboratory testing of factor VIII levels in plasma, we would not currently recommend the measurement of factor VIII levels as part of routine thrombophilia screening.

Keywords: blood group, genetic risk factors, ischemic heart disease, thrombophilia, myocardial infarction, von Willebrand factor

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Background

Thrombotic disorders are one of the most common causes of morbidity and mortality in developing and developed countries.¹ They are broadly classified into venous thrombosis and arterial thrombosis, comprised of deep-vein thrombosis and pulmonary embolism, or ischemic heart disease (IHD) and ischemic stroke (IS), respectively. Certain distinctions exist between thrombotic events in the venous and arterial systems, the most basic of which is that they are characterized by platelet-rich *versus* fibrin-rich thrombi, respectively. Thus, arterial thrombosis has historically been treated with agents that prevent platelet aggregation and venous thrombosis with agents that target coagulation factors. However, increasing evidence suggests that there may be some degree of overlap in the pathogenesis of these two conditions². Indeed, the effectiveness of anticoagulants including warfarin and

other vitamin K antagonists has been demonstrated in the secondary prevention of the formation of fibrin-rich thrombi in patients with atrial fibrillation, peripheral artery disease and myocardial infarction (MI).³

The pathogenesis of arterial thrombosis includes genetic and environmental factors including smoking, hypertension, hyperlipidemia, obesity, diabetes, and a positive family history are among the list of well-established risk factors.^{4,5} However, despite significant progress in the characterization of predisposing mutations for venous thromboembolism (VTE), studies that have attempted to elucidate genetic risk factors that contribute to the development of arterial thrombosis have generated conflicting results and as yet the factors remain undetermined. For example, although a high factor VIII level predicts the occurrence of episodes of venous thrombosis,^{6,7}

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its role in the pathogenesis of arterial thrombosis remains unclear.

In this review, we firstly present an illustrative case of a 32-year-old patient with high factor VIII levels that are the cause of peripheral arterial thrombosis and MI, which is only one of a few such cases published to date. We then review the current state of knowledge concerning the role of high factor VIII levels in determining the risk of arterial thrombosis or IHD. Finally, we discuss whether we should screen patients with thrombosis for high factor VIII levels and discuss the advantages and disadvantages of measuring factor VIII levels in routine clinical practice.

Clinical case

A 32-year-old male was referred to the hematology clinic in September 2018 due to complaints of intermittent claudication caused by severe physical inactivity (he had walked approximately 500m over a 12-month period). Two weeks prior to referral, he had experienced a transient ischemic attack of stable angina. He was taking no medication at the time of referral.

Patient history

In February 2013 the patient had anterior-wall MI at 27 years of age. On cardiac catheterization, the left anterior descending artery was obstructed with a thrombus that progressed distally. A percutaneous coronary intervention was not performed.

Environmental risk factors for arterial disease were initially negative according to the investigations at the time. A typical thrombophilia screen, conducted in March 2013, for activated protein C resistance, antithrombin III, protein S, anti-cardiolipin antibody, lupus anticoagulant, cholesterol, and fibrinogen revealed negative results. The patient received dual anti-platelet therapy (DAPT) for 6 months (aspirin + clopidogrel) with prescription of aspirin for a further 1-year period. The patient discontinued the medication without the physician's discretion despite experiencing several arterial thrombi while on DAPT.

In October 2014, at 28 years of age, the patient had left-sided hemiplegia and was diagnosed with IS. No thrombectomy was performed, and the patient did not receive fibrinolytic therapy because they did not arrive at the hospital within the required onset-to-treatment time (recommended within the first 4.5h). The patient was started

immediately on aspirin 300 mg daily for 2 weeks. The peripheral pulse in the left leg was impaired. Unfortunately, no further investigation of the weak peripheral pulse was carried out at this time. The patient then commenced warfarin 6 mg daily (due to previous episodes of arterial thrombosis) with a therapeutic international normalized ratio of 2–3, for a 12-month period from November 2014 to November 2015.

Diagnostic assessment

In September 2018 the patients complete blood count was normal, and there was no evidence of any myeloproliferative disorders. A more extensive thrombophilia screen was performed in December 2018, which revealed an elevated level of factor VIII at 365% (normal range 50–200%),⁶ that was confirmed on two further occasions 3 months apart. The patient was not taking warfarin at the time of the factor VIII tests. The results of liver function test were within normal limits. The patient was diagnosed at age 32 years with acute coronary syndrome (ACS).

Therapeutic intervention

The patient was instructed to take the oral anticoagulant warfarin indefinitely and was advised to make certain lifestyle changes, in particular, to exercise regularly.

Review

Although there is an exponential increase in the risk of both arterial and venous thrombotic events with age,^{1,4} some individuals are genetically predisposed to thrombotic events and are commonly referred to as having inherited thrombophilia or a hypercoagulable state.⁸

Genetic risk factors for thrombophilia

The genetic risk factors underlying predisposition to venous thrombosis are well-described⁹ and includes the Factor V Leiden variant (*F5* 1691G>A; rs6025),¹⁰ one of the most common mutations responsible for inherited thrombophilia. In addition, high factor VIII levels have been documented to be a risk factor for venous thrombosis and coronary artery disease (CAD).¹¹

The global phenomenon of an aging population means that the determination of genetic

predisposition to arterial thrombosis is becoming increasingly important. Considerable attention has been focused on testing the common genetic variants for VTE as predisposing factors for arterial thrombosis. However, large studies, including the Physician's Health Study,¹² failed to observe an effect for VTE-predisposing genetic variants as risk factors for arterial thrombosis, including MI and stroke, although this study only studied *F8* mutations. Although the published data is mainly epidemiological, high factor VIII levels appear to have a greater impact on venous *versus* arterial thrombosis. In general, there appears to be little overlap between the genetic risk factors associated with arterial *versus* venous thrombosis.¹³ This is not entirely unexpected because the pathophysiology in arterial disease is different and both genetic and environmental risk factors interact to contribute to the development of arterial thrombosis.^{4,5}

Until recently, the genetic basis for arterial thrombosis was poorly characterized. However, advances in DNA sequencing techniques are permitting the comprehensive investigation of the genetic basis for MI, IS, and arterial thrombosis. For example, the association between genetic variants of different blood coagulation factors and arterial thrombosis are emerging from genome-wide association studies (GWAS), that have the advantage over prospective studies by detecting even modest

genetic effects as well as identifying novel causative links between atherothrombotic disease and previously unrelated genes.

Association between coagulation factors and arterial thrombosis

Genetic variants that alter the production, activity, or metabolism of specific coagulation factors can affect hemostasis and coagulation and predispose the mutation carriers to atherothrombotic or thromboembolic events, or both. To date, the most consistent associations with arterial thrombotic disorders from large epidemiologic studies have been observed for variation in levels of factor VII and fibrinogen.¹⁴

Several GWAS have identified novel genetic loci associated with either altered levels of coagulation factors or an increased risk of atherothrombotic disease.¹⁵ Specifically, the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) GWAS identified altered factor VIII levels among 23,000 European participants with genetic variants of the genes *SCARA5*, *STXBP5*, and *STAB2*.¹⁶ Similarly, mutations in the gene encoding the ER-Golgi chaperone *ERGIC-53* were shown to cause lower levels of both factors V and VIII.¹⁷ The genetic variants identified as contributing to arterial thrombosis risk are summarized in Table 1.

Table 1. Genetic variants of coagulation factors associated with increased risk of arterial thrombosis (reviewed in Voetsch and Loscalzo¹⁴).

Gene	Phenotype	Association
<i>F13A1</i>	Increased factor XIII activation by thrombin	Protective effect for MI and IS. ^{18,19}
<i>VWF</i> , for example, Thr789Ala	High vWF levels	Increased risk of atherothrombotic disease. ²⁰
<i>THBD</i> , for example, Ala455Val, Ala25Thr	Decreased thrombomodulin levels	Increased risk of MI. ^{21,22}
<i>CBS</i>	Deficiency of the enzyme cystathionine β -synthase (homocystinuria)	Increased risk of atherosclerosis and arterial thrombosis, including stroke. ²³
<i>F7</i> , for example, Arg353Gln, the HVR4 polymorphism, 401G/T, -402G/A, -59T/G, -32A/C	High levels of factor VII	Higher risk of death from CHD. ²⁴
<i>FGB</i> , for example, Arg448Lys, <i>BclI</i> , -148C/T, -455G/A (<i>HaellI</i>), and -854G/A polymorphisms	High levels of fibrinogen	Increased risk of death from CHD. Increased risk of MI, IS, and peripheral vascular disease. ^{25,26}
<i>PIA</i> , for example, Leu33Pro	Lower levels of glycoprotein IIIa	Reduced risk of arterial thrombosis. ^{26,27}

CHD, coronary heart disease; IS, ischemic stroke; MI, myocardial infarction; vWF, von Willebrand factor.

Association between factor VIII levels and arterial thrombosis

Factor VIII, which circulates in plasma with von Willebrand factor (vWF) in an inactive form, is an important endogenous factor in the coagulation pathway. When activated, it acts on platelet membranes as an enzymatic co-factor for activated factor IX (FIXa), promoting the conversion of factor X to its activated form (Xa) and triggering a series of downstream reactions that lead to the formation of fibrin and a blood clot or thrombus.

For many years, the bleeding disorder hemophilia A has been associated with deficiency of factor VIII. The Leiden Thrombophilia Study was the first to report that high factor VIII levels were a risk factor for VTE⁶ (we refer the reader to a review of the case-control studies that associate high factor VIII levels with predisposition to VTE²⁸), and the first report of an association between CAD and factor VIII levels was published as early as 1962.²⁹ Further evidence from 1989 suggested that low levels of factor VIII in plasma may be protective against IHD,³⁰ and patients with hemophilia A (with a factor VIII deficiency) are well-reported as having decreased mortality for IHD than the matched population.^{30,31} The suggested genetic link between factor VIII levels and the pathogenesis of arterial thrombosis was supported by results from a retrospective study of 177 patients with high factor VIII levels. This study found that 40% of the patient's first-degree relatives also had levels above the 75th percentile of the normal population, and both the patients and their relatives with high plasma factor VIII levels had an increased risk of MI and peripheral arterial thrombosis.³² Similarly, a multivariate analysis of 288 white European patients compared with 313 healthy European controls reported elevated factor VIII levels as a significant independent risk factor for MI.³³ In combination, this data led Kamphuisen to estimate that factor VIII levels >123 IU/dl account for 4% of all cases of arterial thrombosis.²⁸

Several large prospective studies appear to confirm that elevated VIII plasma levels are an independent risk factor for MI, IHD or both. These studies include the Cardiovascular Health Study (5888 subjects), that associated high factor VIII levels with cardiovascular disease and mortality in older men;³⁴ the Caerphilly Heart Study (1423

subjects), that found that 8.9% of patients with IHD had factor VIII levels exceeding 123 IU/dl,³⁵ and the Northwick Park Heart Study (1393 subjects), that observed that an increase of one standard deviation in factor VIII levels increased the risk of IHD in men aged 40–64 years by 28%.³⁶ The Atherosclerosis Risk in Communities (ARIC) Study (14,713 patients) also described an independent association between high factor VIII levels and an increased risk of IS.³⁷

From these published results, we conclude that there is evidence to suggest strong independent associations between high factor VIII levels and an increased risk of arterial thrombosis, although the causality of this association can be questioned. However, a 2009 study in a baboon model successfully used an anti-factor VIII antibody to moderately inhibit factor VIII activity and significantly reduce thrombus development in this animal model, supporting the existence of such causality.³⁸

Genetic determinants of factor VIII levels

Factor VIII circulates in the plasma as part of a stable complex with vWF, that inhibits its proteolytic degradation. The key determinants of factor VIII levels in plasma are vWF levels and the ABO blood group,³⁹ both of which are also independent predictors of factor VIII half-life.⁴⁰ Blood group O is associated with an average of 31.5 IU/dl and 22.4 IU/dl lower levels of vWF and factor VIII, respectively.³⁹ Specifically, a single nucleotide polymorphism in the ABO locus (rs505922) was associated with factor VIII levels in a genetic study of over 50,000 patients and its association with the risk of IS was confirmed.⁴¹

Although individuals with blood group AB have the highest vWF levels,⁴² the genetic factors that regulate vWF levels still need to be determined. However, there is evidence for familial clustering of both high vWF levels and high factor VIII levels (>150 IU/dl),³⁹ with 86% of individuals from thrombophilic families belonging to blood group non-O.⁴³ Importantly, the familial aggregation of factor VIII levels persisted after adjustment for blood group, vWF levels, and age,³⁷ and high factor VIII levels remained associated with IHD after adjustment for blood group in prospective studies.³⁸ Therefore, it is likely that elevated factor VIII and vWF levels both contribute to an

Table 2. Environmental determinants of high factor VIII levels.

Risk factors	Reference
Age	Roth et al., ¹ Conlan et al., ⁴⁷ Balleisen et al. ⁴⁸
Smoking	Yusuf et al., ⁴ Balleisen et al. ⁴⁸
Exercise	Kopitsky et al. ⁴⁹
Stress	Austin et al. ⁵⁰
Pregnancy	Bloom ⁵¹
Surgery	Austin et al., ⁵⁰ Bloom ⁵¹
Acute phase reaction (i.e. inflammation)	Bloom ⁵¹
Hypertension	Yusuf et al., ⁴ Previtali et al. ⁵
Hyperlipidemia	Yusuf et al., ⁴ Assmann et al. ³⁴
Obesity	Yusuf et al., ⁴ Previtali et al., ⁵ Kopitsky et al. ⁴⁹
Diabetes/high levels of glucose	Yusuf et al., ⁴ Previtali et al., ⁵ Balleisen et al. ⁴⁸
Hyperthyroidism	Bloom ⁵¹

increased risk of arterial thrombosis, independently of one another and of blood group.

With the exception of the influence of the ABO blood group, the molecular basis of high factor VIII levels is not fully understood, although both genetic (Table 1) and acquired factors (Table 2) are believed to contribute. The *F8* gene is located on chromosome Xq24, and various mutations have been shown to impact the mRNA or protein levels, half-life of factor VIII, or both, including large indels and numerous point mutations.^{44,45} Specifically, 40–50% of individuals with severe cases of hemophilia A harbor the intron-22 inversion, and 1–5% harbor the intron-1 inversion of *F8*, both leading to low levels of factor VIII in plasma.⁴⁶

Thrombosis in the Saudi Arabian population

There is a rapidly growing body of literature on the relationship between the hemostatic system, the environment, and arterial thrombosis.⁵² For example, one study reported that female smokers who harbored the Factor V Leiden mutation had a significantly higher risk of MI odds ratio [(OR) 3.6] compared with nonsmoking carriers of the variant (OR 2.4).⁵³ Similarly, the prothrombin *20210A* variant was associated with a >40-fold

increase in the risk of MI in smokers compared with 4-fold for nonsmoking carriers.⁵⁴ These examples and many others are indicative of how known environmental risk factors can interfere with genetic predisposition.^{4,5}

Perhaps the most significant nongenetic risk factor to thrombosis is age, with an exponential increase in the risk of both arterial and venous thrombotic events with increasing age.⁵⁵ Indeed, the plasma concentrations of many coagulation factors increase progressively with age, including vWF, factors V, VII, IX, and fibrinogen.^{47,56,57} Specifically, the plasma levels of factor VIII can reach higher than 200 U/dl in individuals aged 70 years and over,⁵⁸ with an average rise of 5–6 IU/dl per decade.^{39,47}

In addition, population studies have shown that factor VIII levels demonstrate a wide range of inter-individual variation and that ethnicity can have an influence on factor VIII plasma levels.⁵⁹ For example, African Americans have significantly higher levels of factor VIII and vWF compared with Caucasians.⁶⁰ A study in 110 Saudi Arabian patients of mutations in the *F8* gene associated with low levels of factor VIII (the patients were undergoing treatment for hemophilia A) revealed that 15 patients harbored

inv-22, 2 patients harbored inv-1, and 5 patients harbored point mutations. These included c.409A>C, p. (T137P) in exon 4 in two patients, as well as two novel mutations: a missense mutation c.355G>C, p. (A119P) in exon 3 and a frameshift mutation c.6482delC (P2161Lfs × 25) in exon 23, both with predicted deleterious effects on the structure and function of the factor VIII protein, and thus on plasma levels.⁶¹

There is an alarming rise in the number of young patients with MI in Saudi Arabia,^{62,63} where the mean age for cardiovascular disease (CVD) incidence was reported to be 8–11 years lower than in European countries.^{63,64} In Saudi Arabia and other Gulf countries, approximately 50% of deaths in people aged under 70 years were attributable to CVD, compared with only 25% in Western countries.^{62,64} Thus, concerted efforts are currently being made in Saudi Arabia to register thrombotic events *via* the Saudi Thrombosis and Familial Thrombophilia (S-TAFT) Registry,⁶⁵ and coronary events, with the Project for Assessment of Coronary Events (SPACE) registry.⁶³

Although genetic background plays an important role in influencing thrombophilia, environmental influences may also account for a rise in MI in Saudi Arabia, and other countries, in recent years.^{9,62,66} A systematic review on the prevalence of CVD and its associated risk factors among the adult population in Gulf countries revealed high levels of obesity among women in this region⁶² and, in addition, the incidence of hypertension in the adult population was reportedly high.⁶⁶ However, a significant proportion of arterial and venous thrombotic episodes, especially among young individuals, occur without a plausible explanation.⁶⁷ To date, limited studies have been carried out on the thrombophilia status among the Saudi population, with a lack of large association studies to assess the genetic risk specific for this population. This case report reveals that a high factor VIII level is the only identifiable risk factor of peripheral arterial thrombosis, contributing to MI, stroke, and ACS in this young Saudi Arabian patient.

Should high factor VIII levels be analyzed in routine thrombophilia screens for patients with arterial thrombosis?

Molecular testing of the *F8* gene is difficult due to its large size (26 exons) and, to date, the impact

of specific factor VIII mutations on the incidence of arterial thrombosis still needs to be determined. In general, there is not enough convincing evidence on the prognosis of specific genetic variants associated with elevated factor VIII levels for the molecular testing of patients with atherothrombotic disease to be valuable or cost effective outside of specific investigations.

However, given the reported strong independent associations between high factor VIII levels and the risk of arterial thrombosis described in this review, the issue arises as to whether patients with atherothrombotic disease should be routinely tested for elevated factor VIII levels. This question is particularly pertinent given that a high level of factor VIII is not only a risk factor for the first thrombotic event, but also for recurrent events.⁵⁷ Thus, patients identified as having elevated levels may require prolonged anticoagulant treatment to prevent further thrombotic events.

Before the routine clinical screening of patients with arterial thrombosis for high factor VIII levels can be incorporated into clinical practice, first it is important to ensure that the analyses for plasma factor VIII levels, typically measured by enzyme-linked immunosorbent assay, are sensitive, accurate, and reproducible, as considerable variation has been reported.⁶⁸

Second, the scientific community must agree on how to interpret the plasma level results. Should cutoff values be used, and how should such values be interpreted in terms of the risk of the first thrombotic event compared with the risk of recurrent events? Would one set of cutoff values be applicable to all populations, because it is well-known that inter-individual factor VIII plasma levels are highly variable and vary among different ethnicities? In addition, the impact of environmental factors on plasma levels of factor VIII would need to be taken into consideration, as levels may be altered in individuals with conditions including diabetes, anemia, and obesity.

Another important question is the timing of measurement of factor VIII levels. Standard laboratory guidelines suggest that factor VIII measurement should be postponed until at least 4–6 weeks after the discontinuation of anticoagulant/thrombolytic therapies,⁶⁹ at least 6 weeks after giving birth, and at least 6 months after an

acute thrombotic event, and the analysis would need to be repeated after 3–6 months to confirm that plasma levels are elevated.⁷⁰ This is of particular importance in the case of therapy with vitamin K antagonists, including warfarin, which are associated with higher factor VIII levels and thus may lead to the overestimation of plasma levels.⁷¹

Finally, hematologists must agree on an appropriate treatment for patients with atherothrombotic disease identified as having elevated factor VIII levels in order to reduce plasma levels and prevent further episodes. Of note, there is little consensus in the literature about the management of patients who have suffered a first arterial thrombotic event.

Although the routine testing for high factor VIII levels could be useful in detecting individuals at high-risk of developing atherothrombotic events (first or recurrent), the prognostic value of such levels in relation to an estimate of the individual's risk of thrombosis needs to be determined. In combination, there are still too many unanswered questions for the current recommendation for the measurement of factor VIII levels in routine thrombophilia screening for patients with arterial thrombosis.

Conclusion

Genetic abnormalities that compromise hemostasis or coagulation can predispose to premature thromboembolic and atherothrombotic events. Although the published data is mainly epidemiological, we can conclude that high factor VIII levels are an independent risk factor for thrombosis, with a greater impact on venous than on arterial thrombosis. To date, several genetic factors have been described for the variation in factor VIII levels, most importantly the ABO blood group that acts through vWF levels. Other genetic loci associated with high factor VIII levels are poorly described and the molecular basis of high factor VIII levels is only partially known. However, increasingly sophisticated sequencing and molecular studies of atherothrombotic disease are improving our understanding of the genetic predisposition to arterial thrombosis. A growing number of genes and specific variants that contribute to arterial disease risk are being identified. Of interest, the majority of these are distinct from those involved in venous thrombosis. However,

arterial thrombosis is a complex disease, with interactions between variants of many different genes and noninherited environmental factors.

Due to the exponential increase in the risk of arterial and venous thrombotic events with age, and the global phenomenon of an aging population, the determination of genetic predisposition to arterial thrombosis is becoming increasingly important. Further studies will be essential in understanding how the analysis of elevated factor VIII levels could be useful in identifying a specific subset of patients who are at increased risk for developing recurrent thrombotic events. Despite the progress in determining the genetic determinants of factor VIII levels, we would not currently recommend their analysis as part of routine thrombophilia screening. However, we urge experts to commence discussions in order to build international consensus and to develop guidelines for its inclusion in the near future.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Informed consent

The patient has read and approved the contents of this case report and given written informed consent for its publication.

Ethics statement

This case report received exemption for ethical approval by King Saud University College of Medicine's Research Board. Ethics approval is not required for the publication of case reports if the data contained in it was retrospectively obtained and anonymized, and the patient was treated according to standard hospital procedures, as was the case for this report.

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