

Deep Vein Thrombosis Secondary To Graves' Disease—A Case Report

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Abstract

Deep vein thrombosis (DVT) is the formation of a blood clot within a deep vein, most commonly the legs. The incidence of a first venous thrombosis is 1–3 per 1000 persons per year, around two-thirds manifest as DVT of the leg, and one-third as pulmonary embolism (PE). Graves' disease, also known as toxic diffuse goiter, is an autoimmune disease that affects the thyroid which frequently results in and is the most common cause of hyperthyroidism, often results in an enlarged thyroid. The disorder results from an antibody, called thyroid stimulating immunoglobulin (TSI), that has a similar effect to thyroid stimulating hormone (TSH) which cause the thyroid gland to produce excess thyroid hormone. Graves' disease will develop in about 0.5% of males and 3% of females, approximately 7.5 times more often in women than men. Various changes in the coagulation-fibrinolytic system have been described in patients with an excess thyroid hormones particularly procoagulant and antifibrinolytic effects. Review analysis confirmed that clinically overt hyperthyroidism modify the coagulation-fibrinolytic balance, indicating that thyroid hormone excess is the probable main pathophysiological mechanism. Patients with overt hyperthyroidism appear to have an increased risk of thrombosis. Here we present a case of right sided leg swelling due to deep vein thrombosis with Grave's disease. A 30 year old lady admitted in tertiary care hospital with right sided leg swelling for 25 days and protrusion of both eyes for 3 months. Swelling was sudden in onset, painful, red in colour, which involved almost whole right lower limb and it was associated with venous engorgement. Physical examination revealed patient was ill looking, mildly anaemic, tachycardic, normotensive, severe pitting edema on right leg but left was normal. Thyroid gland was diffusely enlarged. She had bilateral exophthalmos with presence of lid retraction and lid lag. Examination of Lower limbs revealed swollen whole right lower limb with engorged veins in the upper part of thigh with raised local temperature, calf muscle tenderness and positive Homan's sign on right side. The purpose of this case report is to establish that Graves' disease is the cause of DVT in this patient.

CBMJ 2016 January: Vol. 05 No. 01 P: 33-41

Key words: Leg swelling, DVT, Graves' disease.

Introduction

Venous thrombosis is the result of occlusive clot formation in the veins. It occurs mainly in the deep veins of the leg called deep vein thrombosis (DVT), from which parts of the clot frequently embolize to the lungs causing pulmonary embolism (PE).¹ In 1856, German pathologist Rudolf Virchow postulated the interplay of three processes resulting in venous thrombosis, now known as Virchow's triad: a decreased blood flow rate (venous stasis), increased tendency to clot (hypercoagulability), and changes to the blood vessel wall.⁴³ DVT formation typically begins inside the valves of the calf veins, where the blood is relatively oxygen deprived, which activates certain biochemical pathways. Fewer

than 5% of all venous thromboses occur at other sites. Venous thrombosis is common

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and often occurs spontaneously, but it also frequently accompanies medical and surgical conditions, both in the community and the hospital. The symptoms of venous thrombosis are nonspecific, and therefore the clinical diagnosis is difficult and requires objective testing by imaging. Major complications of thrombosis include a disabling post-thrombotic syndrome and death due to fatal PE. Treatment with anticoagulants should be prompt and adequate. Many risk factors for thrombosis are known, all of them related either to immobilization or to hypercoagulability. While it has no utility to assess the risk factor status after thrombosis has occurred, several acquired risk factors are so strong that they warrant prophylactic anticoagulation, in both those with and without a history of thrombosis. Detailed guidelines for primary prevention are available. Venous thrombosis tends to recur.⁴⁴⁻⁵⁰

The risk factors for a first venous thrombosis are not the same as for recurrent venous thrombosis and to a large extent are unknown. Individuals from families with inherited thrombophilia tend to develop thrombosis at a young age and to have frequent recurrences.⁹⁻³⁰

The incidence of a first venous thrombosis is 1–3 per 1000 persons per year. Around two-thirds manifest as DVT of the leg, and one-third as PE. Up to half of patients with PE have no signs of DVT. From 1–10% of venous thromboses prove fatal, with deaths predominantly, but not exclusively, among the elderly or in patients with severe underlying disease, notably cancer. The incidence of venous thrombosis is exponentially related to age, where a rule of 10 applies: in children the incidence is 1 per 100,000 per year; in young adults, 1 in 10,000 per year; in the middle-aged, 1 per 1000 per year; in the elderly the incidence is 1% per year, up to nearly 10% per year in the very oldest. The recurrence rate of venous thrombosis is 3–10% per year.²⁻⁵

The causes of thrombosis can be divided into those associated with immobilization, which are usually acquired, and those associated

genetic or acquired. Venous thrombosis is a multi causal disease that occurs when several risk factors are present simultaneously in a particular combination. Often, long-term risk factors, e.g., genetic defects, are joined by short-term acquired factors. While many factors simply add to the risk, contributing to an individual's "thrombosis potential," some factors may interact synergistically, when the combination adds more to the risk than the sum of the separate contributions of the risk factors e.g., factor V Leiden and oral contraceptive use.

Several acquired risk factors are very strong, causing thrombosis in several percent of those afflicted, which implies a relative risk of 50. These are orthopedic, neurosurgical, and major abdominal interventions; major trauma with multiple fractures; central venous catheters; and metastasized cancer, particularly adenocarcinomas. Moderate risk factors are antiphospholipid antibody syndrome, puerperium, prolonged bed rest, and nonmetastasized cancers; pregnancy, oral contraceptive use, hormone replacement therapy, obesity, and long-distance travel are mild risk factors, with a two- to fivefold increased risk.^{1,4}

Homozygous protein C or protein S deficiency leads to potentially fatal purpura fulminans directly after birth, while homozygous antithrombin deficiency is not compatible with life. These are exceedingly rare, except in communities with a high frequency of consanguinity. Heterozygous antithrombin deficiency and homozygous factor V Leiden are the strongest genetic risk factors, increasing the risk of thrombosis 20- to 50-fold. Heterozygous protein C and protein S deficiencies are moderate contributors to risk, with a relative risk of 10. Other genetic factors that are associated with venous thrombosis are either mild and increase the risk two- to fivefold (as is the case for factor V Leiden, prothrombin 20210A, and non-O blood groups) or have negligible effects on risk that are only of academic interest (MTHFR 677T, factor V HR2, FXIII val34leu, PAI-1 4G/5G).² Mildly increased risks are also present for

abnormalities in the coagulation system of which the origin is unclear, such as elevated levels of procoagulant factors (fibrinogen, II, von Willebrand factor, VIII, IX, X, and XI) and antifibrinolytic factors (TAFI), and low levels of anticoagulant factors (TFPI).^{5,8}

Graves' disease, also known as toxic diffuse goiter, is an autoimmune disease that affects the thyroid.¹³ It frequently results in and is the most common cause of hyperthyroidism.¹⁴ It also often results in an enlarged thyroid.¹³ Signs and symptoms of hyperthyroidism may include irritability, muscle weakness, sleeping problems, a fast heartbeat, poor tolerance of heat, diarrhea, and weight loss. Other symptoms may include thickening of the skin on the shins, known as pretibial myxedema, and eye bulging, a condition caused by Graves' ophthalmopathy.¹³ About 25% to 80% of people with the condition develop eye problems.^{13,15} The exact cause is unclear; however, it is believed to involve a combination of genetic and environmental factors.¹⁶ A person is more likely to be affected if they have a family member with the disease.¹³ If one twin is affected there is a 30% chance the other twin will also have the disease.¹⁷ The onset of disease may be triggered by stress, infection, or giving birth.¹⁵ The disorder results from an antibody, called thyroid stimulating immunoglobulin (TSI), that has a similar effect to thyroid stimulating hormone (TSH). These TSI antibodies cause the thyroid gland to produce excess thyroid hormone.¹³ The diagnosis may be suspected based on symptoms and confirmed with blood tests and radioiodine uptake.^{13,15} Typically blood tests show a raised T_3 and T_4 , low TSH, increased radioiodine uptake in all areas of the thyroid, and TSI antibodies.¹⁵ Graves' disease will develop in about 0.5% of males and 3% of females.¹⁴ It occurs about 7.5 times more often in women than men.¹³ Often it starts between the ages of 40 and 60 but can begin at any age.¹⁷ It is the most common cause of hyperthyroidism in the United States (about 50% to 80% of cases).^{13,15} The condition is named after Robert Graves who described it

in 1835. Review of research papers indicates significantly positive correlation with DVT. Cerebral venous thrombosis (CVT) is a distinct cerebrovascular condition that has an estimated incidence between 0.5 and 1% of all strokes in the general population.⁸ Hyperthyroidism is a predisposing factor for CVT in 1.7% of patients.^{8,10} Indeed, because of its procoagulant and antifibrinolytic effects, hyperthyroidism is a known prothrombotic condition,^{9,12} that has been considered an independent risk factor for sinus thrombosis.¹³ A thorough review of the literature resulted in 20 case reports describing CVT due to hyperthyroidism.⁸

Case Report

Mrs. Shathi 30 years old lady nonsmoker, normotensive, non diabetic hailing from Sherpur, Mymensingh got admitted in the department of medicine, Community Based Medical College Hospital, Bangladesh with the complaints of pain and swelling in the right lower limb for 25 days (Fig 1, 2). Swelling was sudden in onset, painful, red in colour, which involved almost whole right lower limb. It was associated with venous engorgement with no genital and abdominal swelling, fever and skin tightness and also not associated with lower limb joint such as knee joint and elbow joint. On query, she had no history of abdominal and pelvic surgery, paresis or prolonged immobilisation of affected side of the body, or anasarca. General examination revealed patient was ill looking, mildly anaemic, severe pitting edema on right leg but left was normal, non-icteric. Her pulse 110 beats/minute, BP 120/80 mm of Hg. Thyroid gland was soft and mild diffuse enlargement (Fig 3) present with no regional lymphadenopathy and bruit. Eye examination revealed presence of bilateral exophthalmos with presence of lid retraction (Fig 4) and lid lag. On examination of Lower limbs revealed swelling present in the whole right lower limb. Engorged veins present in the upper part of thigh with increased local temperature, calf muscles was tender and Homan's sign positive on right side. Flexion movement restricted in the right knee and ankle joint. Left lower limb was

normal on examination. Rest of the systems revealed no abnormalities.

Complete blood count revealed Hb% 9.6 g/dl, ESR 120 mm in 1st hour, total count of WBC 9700/cumm, differential count was within normal limit, random blood sugar 5.6 mmol/l, urine routine examination normal, serum creatinine 1.2 mg/dl, C-reactive protein 12.0 mg/dl (normal <6mg/dl), thyroid function test : TSH – 0.14 mIU/ml (normal value 0.3 – 5 mIU/ml), FT3 – 18.84 fmol/ml (normal - 3.5-8.56), FT4 – 39.82 fmol/ml (normal - 8.56-25.6), High resolution ultrasonogram showed mild diffusely enlarged thyroid gland, thyroid scan revealed enlarged thyroid with increased diffuse uptake of radiotracer concentration, color doppler ultrasound of both lower Limbs showed revealed normal arterial system, venous system - extensive DVT is seen involving right CFV, SFV, POPV, PTV&GSV but normal venous flow is seen through all the major veins of left limb(Fig 5). Sonological comment was extensive DVT on right lower limb. Prothrombin Time 13 sec INR : 1.9, ECG showed sinus Tachycardia. Based on the investigations patient started low molecular weight heparin(LMWH) at a dose of 40 mg subcutaneous twice daily 12 hours apart and warfarin at an initial dose of 5 mg, oral carbimazole 45 mg in three divided doses, propranolol 40 mg three times daily. She improved symptomatically and swelling was reduced with time. Patient was on maintenance oral warfarin therapy and following in outpatient department. Other supportive management was given.

Patient was on adequate dose of carbimazole and compliant to her medications. On further follow up she did not show any such episode, swelling has been subsided significantly.



Figure 1. Swollen right thigh

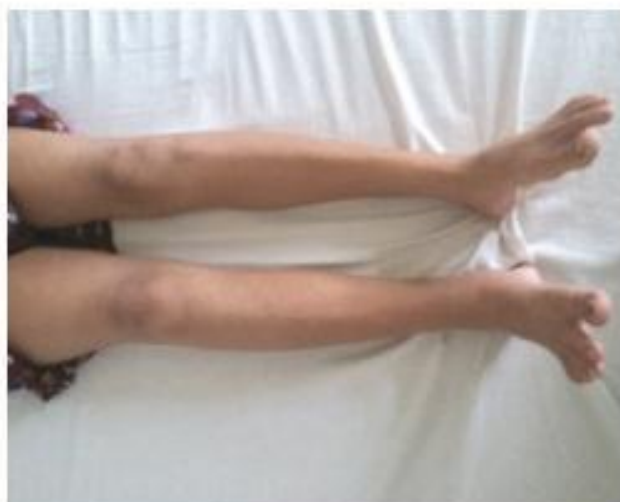


Figure 2. Swollen right lower limb

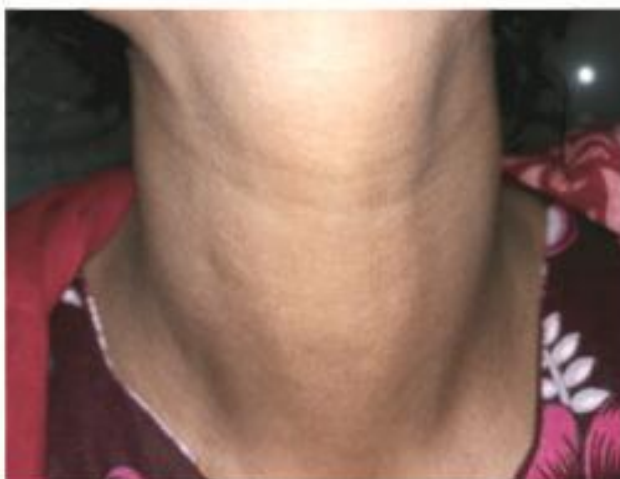


Figure 3. Diffuse enlargement of thyroid gland



Figure 4. Bilateral exophthalmos with lid retraction



Figure 5. Colour doppler study of both lower limb

Discussion

This patient presented a right deep venous thrombosis due to Graves' disease. DVT occurs 1-3 per 1000 persons per year, two-thirds of which are DVT of legs and one-third manifests as PE.⁸ Hyperthyroidism has been reported to be a predisposing factor for DVT.¹⁰ The link between the hemostatic system and thyroid diseases has been investigated about

a century ago. Both subclinical as well as overt hyperthyroidism is found to be associated with coagulation abnormalities. Globally, these disorders involve both primary and secondary hemostasis. Overt hyperthyroidism has emerged to have an increased risk of thrombotic events. However whether hyperthyroidism is a true risk factor for hypercoagulable state is not yet well proven and it is also not done in the thrombophilia workup. Hyperthyroidism is associated with increased levels of factor VII and vWF. These complications are rare and was demonstrated in case reports only.⁶ Hyperthyroidism when untreated or inadequately treated leads to various complications of body systems. Hyperthyroidism, per se is also a risk factor for development of many diseases. Arterial or venous thrombosis is one of the rare complications where hyperthyroidism is implicated as a risk factor.⁷ Hyperthyroidism is a prothrombotic state because of its procoagulant and antifibrinolytic effects.⁹ Higher fibrinogen, higher F VIII and plasminogen activator inhibitor-1 and lower protein C is typically found in patients with hyperthyroidism.

Since F VIII promotes while protein C inhibits thrombin production, these changes are responsible for hypercoagulability [1]. In addition, there is also a shift towards reduced plasminogen activation, which is responsible for the antifibrinolytic effect.^{8,9} Hyperthyroidism also induces elevation of von Willebrand factor, which is associated with an enhanced platelet function and, therefore, with a shortened clotting time.¹² Hyperthyroidism is not a widely recognized association with venous thromboembolism (VTE) and thyroid function test is certainly not a routine test in thrombophilia screening.^{7,19-21} However, various changes in the coagulation pathway and platelet function that can predispose to VTE have been described in patients of hyperthyroidism. In particular, a number of case reports have documented acute venous thrombosis complications in patients with overt hyperthyroidism.²² Verberne et al. reported a

case of a young woman with severe thyrotoxicosis and concurrent cerebral venous sinus thrombosis.²³⁻²⁵ Dharmshaktu et al reported a case of 35 year old male patient who presented with hyperthyroidism and recurrent DVT with raised factor VIII level.⁷ A possible cause for this is persistent elevation of factor VIII levels which has been shown to be independently associated with both first and recurrent venous thrombosis.²⁴

So the most biologically plausible mechanism for a causal link between hyperthyroidism and VTE is related to significant but reversible elevation of factor VIII. An indirect effect of hyperthyroidism via the beta adrenergic receptors is also a possible theory.²⁶ Stuijver et al. found that thyrotoxicosis shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state with a rise in factors VIII and IX, fibrinogen, von Willebrand factor, and plasminogen activator inhibitor-1.²⁷ This was observed in endogenous and exogenous thyrotoxicosis, and in subclinical as well as overt hyperthyroidism. Studies have documented sustained but transient elevation of factor VIII and vonWillebrand factor (vWF) activity in patients with overt hyperthyroidism. The elevation in factor VIII and vWF resolved over few weeks of treatment suggesting a direct role of hyperthyroidism in elevation of factor VIII and vWF activity.²⁸ Erem et al. showed statistically significant elevations in vWF, factor IX, antithrombin III, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) levels, and reduction in factor X and tissue plasminogen activator (tPA) levels in hyperthyroid subjects when compared to their euthyroid controls. vWF, PAI-1, and tPA are among the important endothelium derived proteins, and hence they suggested that hyperthyroid patients may experience vascular endothelial dysfunction with decreased fibrinolytic activity in the blood.²⁶ Burggraaf et al. similarly showed that hyperthyroid patients with Grave's disease had significantly altered levels of endothelium-associated proteins, and these changes were corrected after patients became euthyroid with therapy.²⁸ There is

paucity of literature describing the incidence of VTE in patients with thyrotoxicosis.⁷

After carefully reviewing the literature, published 36 case-control and cohort studies that evaluated the effects of hyperthyroidism and hypothyroidism on the coagulation-fibrinolytic system, we found hormones directly influence both primary and secondary hemostasis.⁵¹ In particular, a possible increased risk of sinus and cerebral vein thrombosis has been reported in clinically overt hyperthyroidism.⁵² Several in vivo studies have been performed to elucidate the pathophysiology of bleeding and thrombotic events in overt thyroid dysfunction. Recent research focused on subclinical disorders. Four main conclusions can be drawn from the summarized coagulation-fibrinolysis results. First, thyroid dysfunctional diseases, hypothyroidism and hyperthyroidism, overt and subclinical, alter the coagulation-fibrinolytic balance. The overall coagulation and fibrinolytic effect in medium quality studies is shown in Table 1. Published case reports suggest a clinical relevance, but prospective clinical studies are absolutely lacking. Second, clinically overt hypothyroidism and hyperthyroidism modify the hemostatic balance in opposite directions. This supports the assumption that thyroid hormone excess and deficit are the main mechanisms of a hypercoagulable and hypocoagulable state, respectively. The complex hemostatic balance can be influenced by autoimmune mechanisms, such as idiopathic thrombocytopenic purpura, secondary antiphospholipid syndrome, or acquired hemophilia, but these occur rarely. The hypercoagulable and hypocoagulable states are probably independent of the underlying pathophysiology of thyroid disease. In the past, other hypotheses have been postulated to explain coagulation abnormalities in thyroid patients, such as endogenous arginine vasopressin and adrenergic system imbalance, but these have never been proven.^{53,54} Third, the concept of a hypercoagulable state in subclinical

hypothyroidism cannot be supported by the present analysis. A possible increased risk of myocardial infarction in patients with subclinical hypothyroidism suggested a prothrombotic effect.⁵⁵ Fourth, few coagulation test abnormalities have been described in subclinical hyperthyroidism and hypothyroidism. Only one study, of low quality, extensively investigated coagulation-fibrinolytic abnormalities in subclinical hyperthyroidism.⁵⁶

Many physicians still ignore the existing relationship between thyroid hormones and the coagulation system. It is important for clinicians to realize that hemostaic balance can be affected by thyroid dysfunction, as well as hepatic, renal, and other systemic diseases.⁶ No causes other than Graves' disease were identified to explain the hypercoagulable state in our patient. Given the known effects of hyperthyroidism on coagulation and platelet function, we believe that this was the probable cause of the deep vein thrombosis.

Table1. Overall coagulation and fibrinolytic changes in medium quality studies.⁶

Parameters	No. of studies	Hypo	Hyper	Sub. hypo	Sub. hyper
General hemostatic tests					
Bleeding time	4	↑	↓	=	
aPTT	2	↑		=	
PT	2	↑		=	
Clotting time	2	↑		=	
Prothrombin fragment 1-2					
Coagulation tests					
IVIII:C	4	↓ or =		↓	
vWf:Ag	6	↓	↑ or =	↓	
vWf:C	2	↓		↓	↑
vWf ristocetin	2	↓		↓	
Fibrinogen	6	↓ or =	↑ or =		↑
Ristocetin agglutination	2	↓	=		
Fibrinolytic tests					
t-PA:Ag	2		=	↑ or =	
t-PA:C	1		↓		
PAI-1	2		↑		
Plasminogen	1		=		
α2 antiplasmin	1				
Plasmin-antiplasmin complex	1				

Conclusion

We describe a 30-year-old female patient with a right lower limb deep venous thrombosis as the presenting symptoms of Graves' disease. A concise survey of the literature shows that this localization has not been described before in patients with Graves' disease without other risk factors. Hypercoagulable findings clearly demonstrate the importance of early recognition and follow-up of subclinical and overt hyperthyroidism, since it is a known independent risk factor for DVT although rare. Early diagnosis and treatment may prevent serious complications such as PE and chronic venous insufficiency.

References

- 1 Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL (eds): *Harrison's Principles and Practice of Internal Medicine*, 16th ed. USA, McGraw-Hill, 2005.
- 2 Colman RW et al (eds): *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 2006.
- 3 Prandoni P: Links between arterial and venous disease. *J Intern Med* 262:341, 2007 [PMID: 17697155]
- 4 Rosendaal FR: Venous thrombosis, a multicausal disease. *Lancet* 353:1167, 1999 [PMID: 10209995]
- 5 The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126(3 Suppl):167S, 2004
- 6 Squizzato A, Romualdi E, Buller HR, Gerdes VEA. Clinical review: Thyroid dysfunction and effects on coagulation and fibrinolysis: a systematic review. *J of Clin Endocrinol and Metab* 2007; 92(7): 2415-2420.
- 7 Dharmshaktu P, Garg A, Dhanwal D, Gupta N. Recurrent deep vein thrombosis presenting in a patient with overt hyperthyroidism. *Endocrinology studies* 2014;4: 5096-97.
- 8 Hermans Ellen, Marien Peter, De Deyn PP. Sinus sogmoideus thrombosis secondary to Grave's disease: a case description. *Case Rep Neurol* 2011;3:203-209. DOI: 10.1159/000331448.
- 9 Horne MK, Singh KK, Rosenfeld KG, Wesley R, Skarulis MC, Merryman PK, et al: Is thyroid hormone suppression therapy prothrombotic? *J Clin Endocrinol Metab* 2004;89:4469-4473.
- 10 Saposnik G, Barinagarrementeria F, Brown RD, Bushnell CD, Cucchiara B, Cushman M, et al: Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42:1158-1192.
- 11 Weetman AP: Graves' disease. *N Eng J Med* 2000; 343:1236-1248.

- 12 Homoncik M, Gessl A, Ferlitsch A, Jilma B, Vierhapper H: Altered platelet plug formation in hyperthyroidism and hypothyroidism. *J Clin Endocrinol Metab* 2007;92:3006-3012.
- 13 "Graves' Disease". www.niddk.nih.gov. August 10, 2012. Retrieved 2015-04-02.
- 14 "Management of graves disease: A review". *JAMA*. 314 (23): 2544-2554. 2015-12-15. doi:10.1001/jama.2015.16535. ISSN 0098-7484.
- 15 Brent, Gregory A. (Jun 12, 2008). "Clinical practice. Graves' disease". *The New England Journal of Medicine*. 358 (24):2594 - 2605. doi: 10.1056/NEJMcpr0801880. ISSN 1533-4406. PMID 18550875.
- 16 Menconi, F; Maroccoli, C; Marinò, M (2014). "Diagnosis and classification of Graves' disease.". *Autoimmunity reviews*. 13 (4-5): 398- 402. doi:10.1016/j.autrev.2014.01.013. PMID 24424182.
- 17 Nikiforov, Yuri E.; Biddinger, Paul W.; Nikiforova, Lester D.R.; Biddinger, Paul W. (2012). *Diagnostic pathology and molecular genetics of the thyroid* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 69. ISBN 9781451114553.
- 18 Tomer Y, Davies T (1993). "Infection, thyroid disease, and autoimmunity" (PDF). *Endocr Rev*. 14 (1): 107-20. doi:10.1210/er.14.1.107. PMID 8491150.
- 19 Maes J, Michotte M, Velkeniers B, et al. Hyperthyroidism with increased factor VIII procoagulant protein as a predisposing factor for cerebral venous thrombosis. *J Neurol Neurosurg Psychiatry* 2002;73:456-9.
- 20 Squizzato A, Romualdi E, Buller HR, Gerdes VE. Clinical review: thyroid dysfunction and effects on coagulation and fibrinolysis: a systematic review. *J Clin Endocrinol Metab* 2007;92:2415-20.
- 21 Rogers JS, Shane SR, Jencks FS. Factor VIII activity and thyroid function. *Ann Intern Med* 1982;97:713-6.
- 22 Franchini M, Lippi G, et al. Hyperthyroidism and venous thrombosis: a casual or causal association? A systematic literature review. *Clin Appl Thromb Hemost* 2011;17:387-92.
- 23 Verberne HJ, Fliers E, Prummel MF, et al. Thyrotoxicosis as a predisposing factor for cerebral venous thrombosis. *Thyroid* 2000;10:607-10. 6. Koster T, Blann AD, Briet E, et al. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deepvein thrombosis. *Lancet* 1995;345:152-5.
- 24 Kyrle PA, Minar E, Hirschl M, et al. High plasma levels of Factor VIII and the risk of recurrent venous thromboembolism. *N Eng J Med* 2000;343:457-62.
- 25 Erem C, Ersoz HO, Karti SS, et al. Blood coagulation and fibrinolysis in patients with hyperthyroidism. *J Endocrinol Invest* 2002;25:345-50
- 26 Stuijver DJ, Van Zaane B, Romauldi E. The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors: a systematic review and meta-analysis. *Thromb Homeostasis* 2012;108:1077-88.
- 27 Burggraaf J, Lalezari S, Emeis JJ, et al. Endothelial function in patients with hyperthyroidism before and after treatment with propranolol and thiamazol. *Thyroid* 2001;11:153-60.
- 28 Scarvelis D, Wells P (2006). "Diagnosis and treatment of deep-vein thrombosis". *CMAJ*. 175 (9):1087-92. doi:10.1503/cmaj.060366. PMC 1609160. PMID 17060659.
- 29 Bates SM, Jaeschke R, Stevens SM, et al. (2012). "Diagnosis of DVT: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines". *Chest*. 141 (suppl 2): e351S-e418S. doi:10.1378/chest.11-2299. PMC 3278048. PMID 22315267.
- 30 Owings JT (2005). "Management of venous thromboembolism". *ACS Surgery, American College of Surgeons*. Retrieved 16 January 2012.
- 31 Barham K, Shah T; Shah (2007). "Images in clinical medicine: Phlegmasia cerulea dolens". *N Engl J Med*. 356 (3): e3. doi: 10.1056/NEJMimc 054730. PMID 17229945.
- 32 Martinelli I, Bucciarelli P, Mannucci PM (2010). "Thrombotic risk factors: Basic pathophysiology". *Crit Care Med*. 38 (suppl 2): S3-S9. doi:10.1097/CCM.0b013e3181c9cbd9. PMID 20083911.
- 33 Bovill EG, van der Vliet A (2011). "Venous valvular stasis-associated hypoxia and thrombosis: What is the link?". *Annu Rev Physiol*. 73: 527-45. doi:10.1146/annurev-physiol-012110-142305. PMID 21034220.
- 34 Reitsma PH, Versteeg HH, Middeldorp S (2012). "Mechanistic view of risk factors for venous thromboembolism". *Arterioscler Thromb Vasc Biol*. 32 (3): 563-8. doi:10.1161/ATVBAHA.111.242818. PMID 22345594.
- 35 Lijfering WM, Rosendaal FR, Cannegieter SC (2010). "Risk factors for venous thrombosis - current understanding from an epidemiological point of view". *Br J Haematol*. 149 (6): 824-33. doi:10.1111/j.1365-2141.2010.08206.x. PMID 20456358.
- 36 Wong P, Baglin T (2012). "Epidemiology, risk factors and sequelae of venous thromboembolism". *Phlebology*. 27 (suppl2):2- 1. doi:10.1258/phleb.2012.012S31. PMID 22457300.
- 37 Mantha, S.; Karp, R.; Raghavan, V.; et al. (2012). "Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: A meta-analysis". *BMJ*. 345: e4944. doi:10.1136/bmj.e4944. PMC 3413580. PMID 22872710.
- 38 Turpe AGG (March 2008). "Deep venous thrombosis". *The Merck's Manuals Online Medical Library*. Merck.
- 39 Zöller B, Li X, Sundquist J, et al. (2012). "Risk of pulmonary embolism in patients with autoimmune disorders: A nationwide follow-up study from Sweden". *Lancet*. 379 (9812): 244-9. doi:10.1016/S0140-6736(11)61306-8. PMID 22119579.
- 40 Stephens, MB (Feb 1, 1997). "Deep venous thrombosis of the upper extremity.". *American family physician*. 55 (2): 533-9. PMID 9054222.
- 41 Jenkins PV, Rawley O, Smith OP, et al. (2012). "Elevated factor VIII levels and risk of venous thrombosis". *Br J Haematol*. 157(6): 653-63. doi:10.1111/j.1365-2141.2012.09134.x.PMID 22530883.
- 42 "What is deep vein thrombosis?". *National Heart, Lung, and Blood Institute*. 28 October 2011. Retrieved 26 July 2012.
- 43 López JA, Chen J (2009). "Pathophysiology of venous thrombosis". *Thromb Res*. 123 (suppl 4): S30-S34. doi: 10.1016/S0049-3848(09)70140-9. PMID 19303501.

- 44 National Institute for Health and Clinical Excellence. Clinical guideline 144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. London, 2012.
- 45 Kahn SR, Lim W, Dunn AS, et al. (2012). "Prevention of VTE in nonsurgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines". *Chest*. 141 (suppl 2): e195S–e226S. doi:10.1378/chest.11-2296. PMC 3278052. PMID 22315261.
- 46 Strijkers RH, Cate-Hoek AJ, Bukkems SF, et al. (2011). "Management of deep vein thrombosis and prevention of post-thrombotic syndrome". *BMJ*. 343: d5916. doi:10.1136/bmj.d5916. PMID 22042752.
- 47 Anderson, Cathy M.; Overend, Tom J.; Godwin, Julie; Sealy, Christina; Sunderji, Aisha (2009). "Ambulation after Deep Vein Thrombosis: A Systematic Review". *Physiotherapy Canada*. 61 (3): 133–140. doi:10.3138 / physio.61.3.133. ISSN 0300-0508.
- 48 Watson L, Broderick C, Armon MP (23 Jan 2014). "Thrombolysis for acute deep vein thrombosis". *Cochrane Database Syst Rev*. 1: CD002783. doi:10.1002/14651858.CD002783.pub3. PMID 24452314.
- 49 Bagot CN, Arya R (2008). "Virchow and his triad: A question of attribution". *Br J Haematol*. 143 (2): 180–9. doi : 10.1111/j.1365-2141.2008.07323.x. PMID 18783400.
- 50 Squizzato A, Gerdes VEA, Ageno W, Buller HR 2006 The coagulation system in endocrine disorders: a narrative review. *Intern Emerg Med*, in press
- 51 Squizzato A, Gerdes VEA, Brandjes DPM, Buller HR, Stam J 2005 Thyroid diseases and cerebrovascular disease. *Stroke* 36:2302–2310
- 52 Rogers II JS, Stanley RS 1983 Factor VIII activity in normal volunteers receiving oral thyroid hormone. *J Lab Clin Med* 102:444–449
- 53 Jawadi MH, Ho L, Dejong DC 1984 Effect of TRH on plasma arginin vasopressin. *Horm Res* 19:91–96
- 54 Chadarevian R, Bruckert E, Ankri A, Beucler I, Giral P, Turpin G 1998 Relationship between thyroid hormones and plasma D-dimer levels. *Thromb Haemost* 79:99–103
- 55 Chadarevian R, Bruckert E, Leenhardt L, Giral P, Ankri A, Turpin G 2001 Components of the fibrinolytic system are differently altered in moderate and severe hypothyroidism. *J Clin Endocrinol Metab* 86:732–737
- 56 Erem C 2006 Blood coagulation, fibrinolytic activity and lipid profile in subclinical thyroid disease: subclinical hyperthyroidism increases plasma factor X activity. *Clin Endocrinol (Oxf)* 64:323–329.