The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors

A systematic review and meta-analysis

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Summary

Several coagulation and fibrinolytic parameters appear to be affected by thyroid hormone excess; however, the net effect on the haemostatic system remains unclear. We aimed to update our previous review and systematically summarise and meta-analyse the data by assessing the effects of thyrotoxicosis on the coagulation and fibrinolytic system *in vivo*. Data sources included MEDLINE (2006–2012), EMBASE (2006–2012), and reference lists. The sources were combined with our previous search containing studies from 1980–2006. Eligible studies were all observational or experimental studies. Two investigators independently extracted data and rated study quality. Weighted mean proportion and 95% confidence intervals were calculated and pooled using a fixed and a random-effects model. A total of 29 articles consisting of 51 studies were included, as in several articles more than one study was described. We included four intervention (before and after treatment in hyperthyroid patients), five cross-sectional (hyperthyroid subjects and euthyroid controls), and four experimental (before and after use of thyroid hormone in euthyroid subjects) medium/high quality studies for meta-analysis. We 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. This was observed in endogenous and exogenous thyrotoxicosis, and in subclinical as well as overt hyperthyroidism. We conclude that both subclinical and overt hyperthyroidism induce a prothrombotic state, which is therefore likely to be a risk factor for venous thrombosis.

Keywords

Thyrotoxicosis, hyperthyroidism, coagulation, fibrinolysis

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Introduction

Hyperthyroidism is associated with a hypercoagulable state (1, 2). Several coagulation and fibrinolytic parameters appear to be affected by thyrotoxicosis; elevated plasma levels of factor VIII (FVIII), factor IX (FIX), von Willebrand factor (VWF), and fibrinogen, and a reduced fibrinolytic activity due to increased levels of plasminogen activator inhibitor-1 (PAI-1) have been reported in both hyperthyroid patients and healthy subjects after taking thyroid hormones (1, 3–9). However, in a previous systematic review, we found the majority of these studies to have major methodological flaws (1). This left the net effect of thyroid hormone excess on the haemostatic system unclear. Moreover, the question as to whether thyrotoxicosis enhances the risk of venous thrombosis, and to which extent, still remains controversial.

In this review, we aimed to update our previous systematic review and systematically summarise and meta-analyse the data by assessing the effects of thyrotoxicosis on the coagulation and fibrinolytic system *in vivo* (1). For the interpretation of the results we will also discuss the recent studies on the relationship between (supra) physiological thyroid hormone levels and VTE.

Methods

Study identification

A computer-assisted search of the MEDLINE and EMBASE electronic databases from July 2006 to March 2012 was performed to identify published studies that evaluated the effect of thyroid hormone excess on the coagulation-fibrinolytic system. The following search terms were used for the MEDLINE search: "haemostasis, blood coagulation tests, blood coagulation, blood coagulation fac-

tors, blood coagulation disorders, thyroid diseases, thyroid hormones, thyroid dysfunction, thyroid receptors, thyroid hormone, hyperthyroidism". For the EMBASE database search, the terms "haemostasis, blood clotting, blood clotting test, blood clotting factor, blood clotting disorders, thyroid disease, thyroid hormone, thyroid hormone receptor, and hyperthyroidism" were used. Reference lists of all included studies were manually searched for other potentially eligible studies. All included studies were merged with the studies found in our previous search from January 1980 until June 2006 (1).

Inclusion criteria

Two investigators (D.S. and B.v.Z) performed the study selection independently. Main inclusion criterion was that the study had to evaluate the effect of thyrotoxicosis, overt and/or subclinical, on the coagulation-fibrinolytic system *in vivo*. The following study designs were allowed: 1) observational cross-sectional studies in which hyperthyroid individuals were compared to euthyroid controls or 2) observational intervention studies in which laboratory tests were performed before and after treatment to correct hyperthyroidism, or 3) experimental clinical trials in which euthyroid subjects received a thyroid hormone analogue to induce exogenous thyrotoxicosis. Case reports, case series, reviews, editorials, *in vitro*, and non-human studies were excluded. Moreover, studies on cancer patients (as cancer itself influences the coagulation system) and studies without statistical analysis were excluded. No language restrictions were initially applied to the search strategy, but only articles written in English, French, Spanish, German, Dutch, and Italian were evaluated. The two investigators independently reviewed titles and/or abstracts from the initial search to determine whether the inclusion criteria were satisfied. The full text of the study was obtained when an article could not be excluded with certainty. Decisions regarding inclusion were made separately, results were compared, and any disagreement was resolved by discussion. When multiple articles for a single study had been published, it was decided to use the latest publication and to supplement it, if necessary, with data from the earlier publications.

Quality assessment

The quality of randomised and non-randomised clinical trials was assessed in an extended version of the Delphi list (the Maastricht-Amsterdam list) (10, 11). The Newcastle-Ottawa Scale (NOS scale) for assessing quality of observational studies was used as a guide to assess study quality of cross-sectional and intervention studies (12). For summarising study validity, we adopted a simple Cochrane Collaboration approach (13). Three categories were therefore identified: high quality (low risk of bias), medium quality (moderate risk of bias), or low quality (high risk of bias). Quality of the included studies was assessed independently by the same two reviewers and any differences were resolved by consensus or the opinion of the third reviewer, if necessary. No attempts to mask for authorship, journal name or institution were made. Appendix 1 (available online at www.thrombosis-online.com) details the quality assessment and scoring system.

Statistical analysis

For each outcome and for each study we extracted the effect sizes comparing the exposed and control situations. This implies that in cross-sectional studies hyperthyroid patients and controls were compared, whereas in intervention studies pre- and post-treatment values were evaluated. In experimental trials, post- versus pre-exposure values, or post-intervention versus values without intervention, were compared. A positive effect size reflected higher values in the exposed situation (i.e. thyroid hormone excess), whereas a negative effect size reflected lower values in the exposed situation.

Results were expressed as standardised mean difference, i.e. the difference between the group means divided by the pooled standard deviation (14). If, instead of standard deviations (SD), standard errors of the mean (SEM) were provided, the SD based on the SEM and the number of subjects ($SEM = SD / \sqrt{n}$) was calculated. If, instead of SD, the 95% confidence interval (CI) was given, the SEM was calculated based on the z-score, the upper limit and the mean value (SEM = upper limit-mean/z-score). For those articles that did not report exact statistics, we only documented the authors' statements on the statistical difference per outcome using notations of statistical significant increase, statistical significant decrease or no statistical significant difference.

Data were categorised according to 1) study design and 2) subclinical and overt hyperthyroidism (in cross-sectional studies). These data were pooled using a fixed-effects model and comparing these findings with the results obtained using a random-effects model, in particular in case of significant statistical heterogeneity (15, 16). In case of high statistical heterogeneity, results using random-effects model are reported. Statistical heterogeneity was evaluated using the I2 statistic, which assesses the appropriateness of pooling the individual study results. The I2 value provides an estimate of the amount of variance across studies due to heterogeneity rather than chance. I2< 30% indicates mild heterogeneity, 30–50% moderate, and >50% severe heterogeneity. When heterogeneity was present, we repeated the analysis removing one study at time to assess the source of heterogeneity. All statistical calculations were performed using Review Manager 5.0 computer software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Results

Search results and included studies

Search results are summarised in ►Figure 1. From our previous search from January 1980 to June 2006, a total of 18 articles had been identified (3–6, 8, 17–29). Our new search identified a further 1,233 citations from the database and reference searches. Of these, 96 publications were considered potentially relevant. Forty case-reports and 31 reviews were excluded. Of the remaining articles, the full text was retrieved and assessed for eligibility. Six articles were further excluded based on an *in vitro* design (30), a study population aged below 18 years (31, 32), or involving cancer patients (33–35). Only 10 publications actually reported on the effect of thyrotoxicosis on haemostatic parameters and were therefore included in the present analysis (7, 9, 36–43). In addition, we included one previously excluded publication from before June 2006 as the previous review did not take exogenous thyrotoxicosis into account (44).

Taken together with the articles published before June 2006, a total of 29 articles were included.

In several articles, more than one study or study design was described. The 29 articles contained a total of 51 studies: seven experimental studies (thyroid hormones given to healthy subjects) and 44 observational studies. The latter consisted of 15 intervention studies (pre- versus post-treatment in hyperthyroid patients) and 29 cross-sectional studies (hyperthyroid patients versus euthyroid controls).

Characteristics of the included studies are summarised in ►Table 1.

Methodological quality of included studies

A detailed description of individual study quality is provided in Appendix 1 (available online at www.thrombosis-online.com). Five observational cross-sectional studies, and 4 observational in-

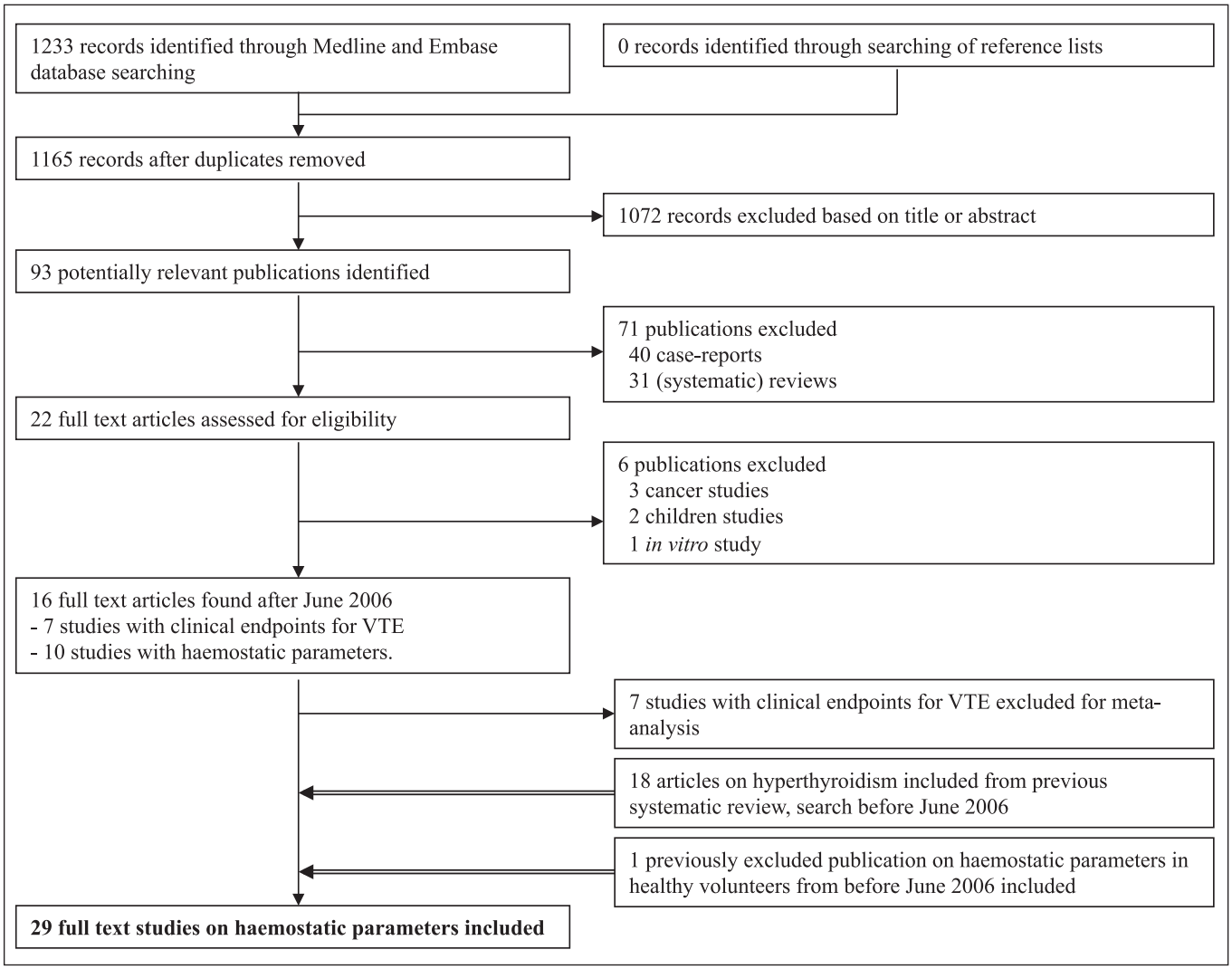

Figure 1: Flow chart of search strategy and selection. VTE, venous thromboembolism.

Table 1: Characteristics of included studies.

Author, year	Study design	Quality	Population (n)	Treatment or intervention	Blood sampling	Outcome parameters
Arnaout, 1992 (3)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (12) Euthyroid controls (15)	-	Before start of treatment	pFN, FVIII:C, vWF:Ag, AT-III α-1 antitrypsin:Ag
	B. Observational: Intervention	Low	Hyperthyroid patients (10)	Anti-thyroid treatment	Before treatment and after euthyroidism was achieved	pFN, FVIII:C, vWF:Ag, AT-III α-1 antitrypsin:Ag
Burggraaf, 2001 (17)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (14) Euthyroid controls (14)	-	Before start of treatment	F1+2, cFN, pFN, VWF:Ag, tPA:Ag, tPA:C, PAI-1:Ag, PAP, thrombomodulin, Plasminogen, α-2-antiplasmine, Fibrinogen:Ag,
	B. Observational: Intervention	Medium	Hyperthyroid patients (14)	Propranolol and thiamazol 10 mg 3 times a day and levothyroxine 100 ug starting dose	At time of diagnosis and after euthyroidism was achieved (at least 1 months after propranol was stopped)	F1+2, cFN, pFN, VWF:Ag, tPA:Ag, tPA:C, PAI-1:Ag, PAP, thrombomodulin, Plasminogen, α-2-antiplasmine, Fibrinogen:Ag,
Coban, 2006 (18)	Observational: Cross-sectional	Medium	Subclinical hyperthyroid patients (20) Euthyroid controls (20)	-	Before start of treatment	VWF:Ag
Dörr, 2005 (4)	A. Observational: Cross-sectional	Medium	General population of unselected patients divided into TSH<0.1 mU/l (11) compared to TSH 0.3–3.0 mU/l (3362)	-	-	Fibrinogen:Ag
	B. Observational: Cross-sectional	Medium	General population of unselected patients divided into TSH<0.3 mU/l (388) compared to TSH 0.3–3.0 mU/l (3362)	-	-	Fibrinogen:Ag
Erem, 2002 (5)	Observational: Cross-sectional	Low	Hyperthyroid patients (41) Euthyroid controls (20)	-	Before start of treatment	PT, APTT, Fibrinogen, FV:C, FVII:C, FVIII:C, FIX:C, FX:C, AT III:Ag, Protein C (%), Protein S, vWF:C, t-PA:Ag, PAI-1:Ag
Erem, 2006 (19)	Observational: Cross-sectional	Low	Subclinical hyperthyroid patients (20) Euthyroid controls (20)	-	Before start of treatment	Platelet count, MPV, PT, APTT Fibrinogen:Ag, D-Dimer, FV:C, FVII:C, FVIII:C, FIX:C, FX:C, AT-III:Ag, Protein C, Protein S, VWF:C,t-PA:Ag, PAI-1:Ag
Graninger, 1986 (20)	A. Observational: Cross-sectional	Low	Hyperthyroid women (27) Euthyroid women (30)	-	Before start of treatment	pFN, FVIII:Ag, AT-III:Ag
	B. Observational: Intervention	Medium	Healthy women (7)	25 ug T3 three times a day for 14 days	On day 4,7, 14 and 24 after start of treatment	pFN, FVIII:Ag, AT-III:Ag
Li, 1998 (6)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (14) Euthyroid controls (10)	-	Before start of treatment	vWF:Ag, t-PA:ag, PAI-1:Ag
	B. Observational: Intervention	Medium	Hyperthyroid patients (14)	Iodine radiotherapy	Before and 30 days after treatment	vWF:Ag, t-PA:ag, PAI-1:Ag
Liu, 1993 (21)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (35) Euthyroid controls (20)	-	Before treatment	VWF:Ag
	B. Observational: Intervention	Medium	Hyperthyroid patients (7)	Anti-thyroid treatment	Before treatment and after euthyroidism was achieved	VWF:Ag

Table 1: continued

Author, year	Study design	Quality	Population (n)	Treatment or intervention	Blood sampling	Outcome parameters
Marongiu, 1988 (22)	Observational: Cross-sectional	Low	Hyperthyroid patients (14) Euthyroid controls (25)	-	One time point	Fibrinopeptide Bβ 15–42 Fibrinogen:C
Marongiu, 1991 (23)	Observational: Cross-sectional	Low	Hyperthyroid patients (65) Euthyroid controls (58)	-	One time point	Fibrinopeptide a, GLP, MLP
Marongiu, 1991 (24)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (50) Euthyroid controls (14)	-	Before start of treatment	fibrinopeptide a, fibrinopeptide Bβ 15–42, Fibrinogen:C
	B. Observational: Intervention	Low	Hyperthyroid patients (40)	Methimazole or ^{131}I treatment	Before treatment and after euthyroidism was achieved	fibrinopeptide a, fibrinopeptide Bβ 15–42, Fibrinogen:C
Morishita, 1998 (25)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (15) Euthyroid controls (25)	-	Before start of treatment	vWF:Ag, thrombomodulin, Free TFPI, Total TFPI
	B. Observational: Intervention	Low	Hyperthyroid patients (10)	Antithyroid drugs	Before treatment and after euthyroidism was achieved	vWF:Ag, thrombomodulin, Free TFPI, Total TFPI
Myrup, 1995 (26)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (10) Euthyroid controls (15)	-	Before start of treatment	Platelets, Bleeding time, RIPA, Platelet aggregation (ADP/collagen)
	B. Observational: Intervention	Medium	Hyperthyroid patients (10)	Carbimazole	Before treatment and after euthyroidism was achieved	Platelets, Bleeding time, RIPA, Platelet aggregation (ADP/collagen), pFN, vWF:Ag, Fibrinogen:Ag, α-2 macroglobulin
Ozcan, 2003 (8)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (10) Euthyroid controls (16)	-	Before start of treatment	free TFPI, total TFPI, tPA:Ag, PAI-1:Ag
	B. Observational: Intervention	Low	Hyperthyroid patients (10)	Anti-thyroid therapy (not further specified)	Before treatment and after euthyroidism was achieved	free TFPI, total TFPI, tPA:Ag, PAI-1:Ag
Rogers, 1982 (27)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (22) Euthyroid controls (24)	-	Before start of treatment	FVIII:C, FVIII:Ag: FVIII:RiCo
	B. Observational: Intervention	Low	Hyperthyroid patients (10)	Levothyroxine, radioactive iodine, propylthiouracil	Before treatment and after euthyroidism was achieved	FVIII:C, FVIII:Ag: FVIII:RiCo
Rosc, 1998 (28)	Observational: Cross-sectional	Low	Hyperthyroid patients (33) Euthyroid controls (34)	-	Before start of treatment	t-PA:Ag, u-PA:Ag, PAI-1;Ag
Wahrenberg, 2002 (29)	A. Observational: Cross-sectional	Low	Hyperthyroid patients (10) Euthyroid controls (16)	-	Before start of treatment	PAI-1:C, PAI-1:Ag
	B. Observational: Intervention	Low	Hyperthyroid patients (10)	Anti-thyroid therapy for at least 8 weeks (not further specified)	Before treatment and after euthyroidism was achieved	PAI-1:C, PAI-1:Ag
Rogers, 1983 (44)	A. Experimental: Clinical trial	Medium	Healthy volunteers (14)	Levothyroxine (LT4) 0.6 mg daily	On day 1,7 and day 14	FVIII:C, FVIII:Ag: FVIII:RiCo
	B. Experimental: Clinical trial	Medium	Healthy volunteers (9)	Liothyronine 50 ug three times daily	On day 1 and 7	FVIII:C, FVIII:Ag: FVIII:RiCo

Table 1: continued

Author, year	Study design	Quality	Population (n)	Treatment or intervention	Blood sampling	Outcome parameters
Akinci, 2007 (36)	A. Observational: Cross-sectional	Low	Overt hyperthyroid patients (14) Euthyroid controls (26)	-	Before start of treatment	PAI-1:Ag, TAFI:Ag
	B. Observational: Cross-sectional	Low	SC hyperthyroid patients (15) Euthyroid controls (26)	-	Before start of treatment	PAI-1:Ag, TAFI:Ag
Akinci, 2011 (37)	A. Observational: Cross-sectional [b]	Low	Overt hyperthyroid patients (9) Euthyroid controls (18)	-	Before start of treatment	PAI-1:Ag, TAFI:Ag
	B. Observational: Cross-sectional [b]	Low	Subclinical hyperthyroid patients (10) euthyroid controsl (18)	-	Before start of treatment	PAI-1:Ag, TAFI:Ag
	C. Experimental: Clinical trial	Medium	Premenopausal women with benign thyroid nodules (20)	Levothyroxine (LT4) suppression therapy	Before and one year after LT4 suppression therapy	PAI-1:Ag, TAFI:Ag
Brona, 2011 (38)	A Observational: Intervention [a]	Low	Overt hyperthyroid women (15)	Radioiodine therapy	Before treatment, and between 12–16 weeks after treatment	Fibrinogen:C, D-Dimer
	B. Observational: Intervention [a]	Low	Overt hyperthyroid women (15)	Radioiodine therapy	Before treatment, and between 24–28 weeks after treatment	Fibrinogen:C, D-Dimer
	C. Observational: Intervention [a]	Low	Subclinical hyperthyroid women (20)	Radioiodine therapy	Before treatment, and between 12–16 weeks after treatment	Fibrinogen:C, D-Dimer
	D. Observational: Intervention [a]	Low	Subclinical hyperthyroid women (20)	Radioiodine therapy	Before treatment and between 24–28 weeks after treatment	Fibrinogen:C, D-Dimer
Coban, 2008 (39)	Observational: Cross-sectional	Medium	SC hyperthyroid patients (36) Euthyroid controls (36)	-	One time point	Fibrinogen:C, D-Dimer
Demir, 2009 (40)	Experimental: Clinical trial [c]	High	Premenopausal women with benign thyroid nodules (30)	Levothyroxine (LT4) suppression therapy	Before and one year after start of LT4 suppression therapy	Fibrinogen :C, D-Dimer, vWF:C, Tissue Factor, t-PA:C, PAI-1:Ag, TFPI:Ag
Erem, 2009 (41)	Observational: Cross-sectional	Low	Hyperthyroid patients (30) healthy controls (25)	-	Before start of treatment	FV:C, Protein C, Protein S, TFPI:Ag, TAFI:Ag
Homoncik, 2007 (42)	A. Observational: Cross-sectional	Low	Overt hyperthyroid patients (30) Euthyroid controls (30)	-	One time point	Platelet count, PT, APTT, platelet aggregation (epinephrine), vWF:Ag, vWF-RiCo, FVIII:C
	B. Observational: Intervention [a]	Low	Overt hyperthyroid patients (30)	Thiamazole started with 60 mg/d adjusted depending on T4, T3 and TSH concentrations	At baseline and after therapy with thiamazole	platelet aggregation (epinephrine), vWF:Ag
Lippi, 2008 (7)	Observational: Cross-sectional	Medium	General population of unselected patients devided into TSH<0.2 (54) compared to TSH 0.2–2.5 (943)	–	Retrospective analysis of routine blood testing	APTT, PT, Fibrinogen:C

Table 1: continued

Author, year	Study design	Quality	Population (n)	Treatment or intervention	Blood sampling	Outcome parameters
Mohamed-Ali, 2008 (43)	A. Observational: Cross-sectional	Low	Overt hyperthyroid patients (30) Euthyroid controls (30)	-	Before start of treatment	Platelet count, PT, APTT, Fibrinogen:Ag
	B. Observational: Cross-sectional	Low	Subclinical hyperthyroid patients (30) Euthyroid controls (30)	-	Before start of treatment	Platelet count, PT, APTT, Fibrinogen:Ag
Van Zaane, 2010 (9)	A. Experimental: Randomised clinical trial [d]	High	Healthy volunteers (16)	Levothyroxine 0.3 mg/d or placebo for 14 days	At baseline and on day 14	VWF:Ag, FVIII:C, VWF:RiCo, PAI-1:Ag, Clot-lysis time
	B. Experimental: Randomised clinical trial [d]	High	Healthy volunteers (12)	Levothyroxine 0.45 mg/d or 0.6 mg/d depending on weight or placebo for 14 days	At baseline and on day 14	PT, APTT, Fibrinogen:Ag, VWF:Ag, VWF:RiCo (%), Factor II:C, FVII:C, FVIII:C,FIX:C, FX:C, protein C, APCsr, total protein S, free protein S, F1+2, ETP, PAI-1:Ag, PAP, D-dimer, Clot-lysis time

[a]Mean and/or SD estimated from figure. [b]Plasma samples of hyperthyroid and SC hyperthyroid patients were obtained from a previous study (Akinci, 2007). [c]SD estimated calculated from SEM (SD= SEM* vn). [d]Mean and SD calculated from original database. PT indicates protrombin time; APTT, activated partial thromboplastin time; ADP, adenosine 5′-diphosphate; RIPA, ristocetin platelet agglutination; F1+2, prothrombin fragment 1+2; pFN, plasma fibronectin; cFN, cellulair fibronectin; F, factor; Ag, antigen; C, activity; RiCo, ristocetin-cofactor activity; VWF, von Willebrand factor; ATIII, antithrombin III C; GPL, anti-cardiolipin antibody IgG; MLP, anti-cardiolipin antibody IgM; TFPI, tissue factor pathway inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; PAP plasmin-antiplasmin complexes; t-PA, tissue type-plasminogen activator; u-PA, urokinase-type plasminogen activator; PAI, plasminogen activator inhibitor; ETP, endogenous thrombin potential; APCsr, activated protein C sensitivity ratio.

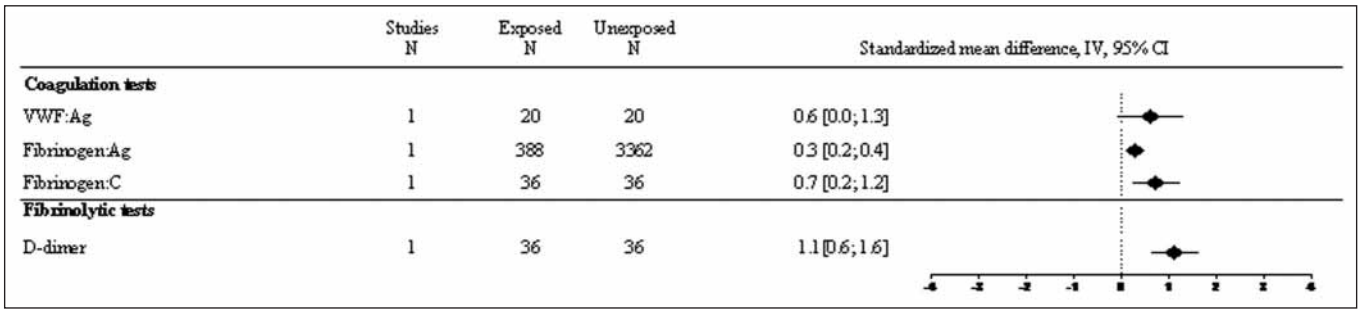

Figure 2: Haemostatic parameters for all medium-/high-quality cross-sectional studies: subclinical hyperthyroidism. VWF, von Willebrand factor; Ag, antigen; C, activity.

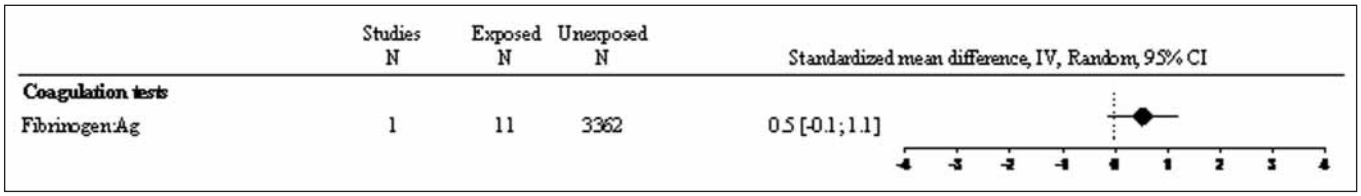

Figure 3: Haemostatic parameters for all medium-/high-quality cross-sectional studies: overt hyperthyroidism. Ag, antigen.

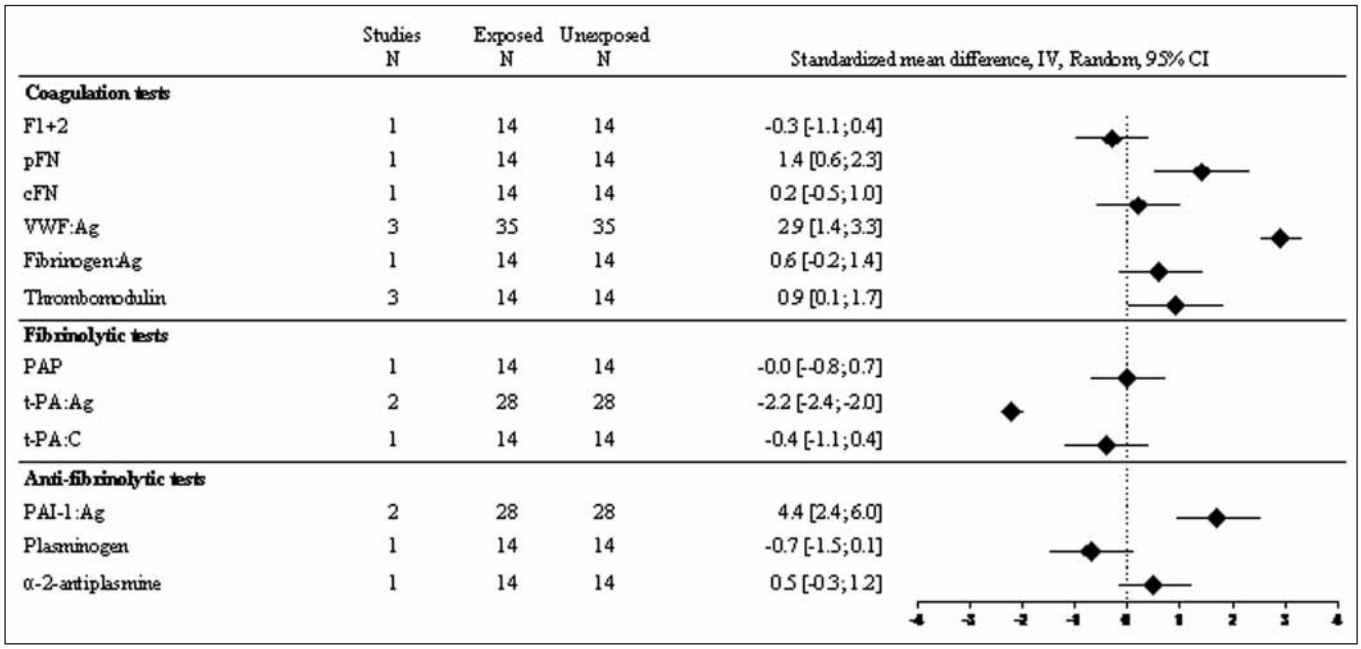

Figure 4: Haemostatic parameters for all medium-/high-quality observational intervention studies. F1+2, prothrombin fragment 1+2; pFN, plasma fibronectin; cFN, cellulair fibronectin; VWF, von Willebrand factor; Ag, antigen; C, activity; PAP plasmin-antiplasmin complexes; t-PA, tissue type-plasminogen activator; PAI, plasminogen activator inhibitor.

tervention studies of medium quality were identified. In the experimental studies, two high-quality studies and one medium-quality study were identified. The remaining studies were considered of low quality.

Outcome parameters

Data on coagulation and fibrinolytic tests of all studies (including low quality studies) are summarised in Appendix 2 (available online at www.thrombosis-online.com). The pooled results of all medium/high quality studies are summarised in ▶Figures 2–5.

Observational cross-sectional studies

Four medium quality studies involved subclinical thyrotoxicosis and only one study compared patients with overt hyperthyroidism to euthyroid controls. Levels of VWF, fibrinogen, and D-dimer were significantly increased in subclinical hyperthyroid individuals, whereas only fibrinogen levels were measured in overt hyperthyroid individuals and appeared to be slightly increased compared to euthyroid controls (▶Figs. 2 and 3).

Observational intervention studies

In the four medium quality studies, increased levels of plasma fibrinonectin, VWF, thrombomodulin and PAI-1, and decreased levels of tissue type-plasminogen activator (t-PA) were found during hyperthyroidism compared to the euthyroid state after normalisation of thyroid hormone levels by anti-thyroid agents (▶Fig. 4).

Experimental studies

Four studies investigated laboratory parameters in healthy volunteers taking thyroid hormone for a specific period of time. Thyrotoxicosis increased plasma levels of tissue factor, FVIII, FIX, VWF, fibrinogen, d-dimer, and PAI-1. For the remaining parameters, no univocal statistical differences were observed (▶Fig. 5).

Discussion

This meta-analysis shows that thyrotoxicosis shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state with a rise in FVIII, FIX, VWF, fibrinogen, and PAI-1. This was observed in both endogenous and exogenous thyrotoxicosis, and in subclinical as well as overt hyperthyroidism.

Several pathophysiological mechanisms have been suggested to underlie the relation between thyroid hormone excess and haemostasis. One of these mechanisms is the activation of the immune system in thyroid disease (45, 46). As we found an equal effect on haemostatic parameters in subclinical thyrotoxicosis compared to overt thyrotoxicosis, the role of the immune system on the haemostatic system may be relevant. However, similar alterations were observed in exogenous thyrotoxicosis in which auto-immunity

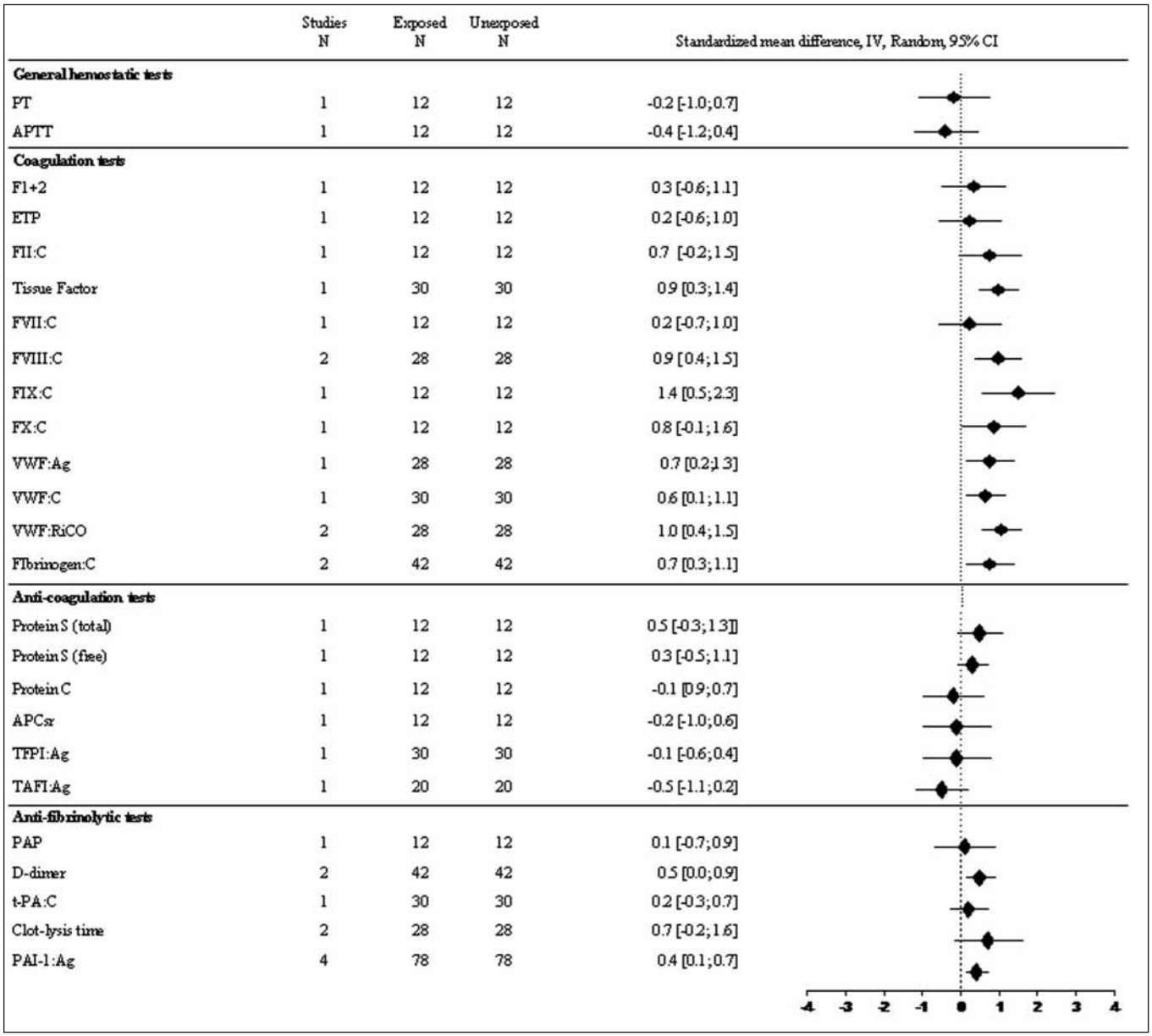

Figure 5: Haemostatic parameters for all medium-/high-quality experimental studies. PT, protrombin time; APTT, activated partial thromboplastin time; F1+2, prothrombin fragment 1+2; ETP, endogenous thrombin potential; F, factor; Ag, antigen; C, activity; VWF, von Willebrand factor; RiCo, ristocetin-cofactor activity; APCsr, activated protein C sensitivity ratio; TFPI, tissue factor pathway inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; PAP plasmin-antiplasmin complexes; t-PA, tissue type-plasminogen activator; PAI, plasminogen activator inhibitor.

does not come into play. This gives way for another possible mechanism involving the direct effect of thyroid hormones on the synthesis of coagulation and fibrinolytic proteins due to thyroid-receptor mediated upregulation of gene transcription in hepatic and endothelial cells (47, 48). As antibody concentrations have been found to decrease with anti-thyroid treatment, these two mechanisms might not be mutually exclusive, but together may result in a prothrombotic state with an increased risk of both venous and arterial thrombosis during thyrotoxicosis (49, 50).

Nowadays, thrombosis is known as a "multi-causal" disease in which multiple genetic or environmental risk factors coincide to push over a so-called 'thrombotic threshold'. If hyperthyroidism is a risk factor for venous thromboembolism (VTE), this will be clinically relevant both for the treatment and prevention of venous thrombosis as well as for the treatment of hyperthyroidism. It will be important for the distinction between provoked or unprovoked thrombosis and decisions on the duration of anticoagulant therapy. Moreover, it may lead to more vigilant monitoring for possible signs and symptoms of VTE in patients with recently diagnosed hyperthy-

Table 2: Clinical endpoint studies.

Author, year	Study design	Cohort; objective	Sample	Clinical endpoints	Conclusions
Danescu, 2009 (51)	Cohort	National Discharge Survey; to study the incidence of VTE in patients discharged from short stay hospitals in the united states between 1979 to 2005 with or without hyperthyroidism.	Cases: 633000 patients with hyperthyroidism[1] Controls: 908172 patients without thyroid dysfunction	PE & DVT	Hyperthyroidism is not associated with an increased risk of VTE.
Debeij, 2012 (52)	Nested case-control	To determine whether high levels of thyroid hormones are associated with an increased risk of venous thrombosis	Cases: 515 patients with venous thrombosis Controls: 1476 randomly selected age and sex-stratified controls	PE & DVT	The risk of VTE increases with higher levels of FT4 and shorter time between blood sampling and event.
Kootte, 2012 (53)	Cohort	Hospital records of three hospitals in the Netherlands between 2003 to 2009; to determine the risk of VTE in all patients with overt hyperthyroidism.	Cases: 587 patients with overt hyperthyroidism[2] Controls: none	PE & DVT	The incidence of VTE in patients with hyperthyroidism appears to be high.
Lin, 2010 (54)	Cohort	The Taiwan Longitudinal Health Insurance Database; to estimate the risk of PE among hyperthyroid patients compared with non-hyperthyroid patients.	Cases: 8903 patients with hyperthyroidism[1] Controls: 44515 patients without thyroid dysfunction.	PE	Patients with hyperthyroidism are at increased risk of PE.
Ramagopalan, 2011 (55)	Cohort	Three databases of linked statistical records of hospital admissions in England; to study the risk of VTE in patients admitted to the hospital with immune-mediated diseases.	Cases: 101402 individuals with thyrotoxicosis[1] Controls: 313716 individuals without thyrotoxicosis	PE & DVT	Graves' disease is associated with an increased risk of VTE.
Van Zaane, 2010 (56)	Case-control	To study the risk of VTE for different plasma levels of thyroid hormones and thyroid antibodies.	Cases: 190 patients with leg vein thrombosis Controls: 379 randomly selected gender-matched controls	DVT	The risk of VTE gradually rises with increasing levels of FT4.
Zoller, 2012 (57)	Cohort	The Swedish Hospital Discharge Register to study the risk of VTE after hospital admission for autoimmune disorders.	Cases: 50954 individuals with Graves' disease[1] Controls: total population of Sweden.	PE	Graves'disease is associated with a high risk of PE in the first year after hospital admission.

DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; FT4, free thyroxine. [1]Based on diagnostic codes. [2]Biochemically confirmed.

roidism, but could also be relevant for prophylactic strategies in hyperthyroid patients undergoing surgery or other interventions associated with a high risk of venous thrombosis. In recent years, a few studies on the relationship between hyperthyroidism or thyroid hormone levels and VTE have been published (▶ Table 2) (51–58). Four population-based follow-up studies explored the risk of VTE in individuals with, amongst others, hyperthyroidism (51, 54, 55–57). The diagnosis of hyperthyroidism was, however, solely based on diagnostic codes. A recently performed cohort study, performed by our group, included a small number of patients with biochemically confirmed overt hyperthyroidism (53). Two case-control studies investigated the risk of VTE associated with varying levels of thyroid hormone (52, 56). A rise in VTE risk was found with higher levels of thyroid hormone, yet only a small number of patients had thyroid levels above the upper end of the normal range. These studies mostly point towards an increased risk of VTE associated with hyperthyroidism. However, limitations due to study design and contradicting results drastically reduce the strength of evidence and do not allow for definitive conclusions to be drawn about the clinical relevance of the findings. Further prospective studies are needed to provide robust evidence on the VTE risk involved in hyperthyroidism, and subsequently the mechanisms behind this presumed relationship. Ideally, a prospective clinical study including consecutive patients with a well-defined degree of hyperthyroidism, with proven VTE as main outcome should be performed. In addition, further insight could be obtained by assessing the relation between thyroid hormone levels and venous thrombosis in patients already at high risk of venous thrombosis, such as patients undergoing major orthopaedic surgery.

Several limitations need to be addressed. Most importantly, the use of quality scoring in meta-analysis for observational studies is controversial. Also, the quality scoring is arbitrary. However, we do feel that it is the only way to gain insight on adequate study design and identify risks of bias. Even when combining the more recent studies (published after June 2006) with the older studies, only a limited number of medium and high-quality studies were found. As a result, most observed alterations have not been confirmed in other studies. However, we were able to confirm main alterations

in different study designs, and most low-quality studies provided similar results.

In conclusion, this meta-analysis showed consistent evidence of a hypercoagulable and hypofibrinolytic state in thyrotoxicosis. Well-designed studies with clinical outcomes are needed to provide more definitive data. Only then, the clinical relevance of these findings, especially in terms of prevention and treatment of venous thrombosis in hyperthyroid patients, can be determined.

Conflicts of interest

None declared.

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