

CLINICAL REVIEW: Thyroid Dysfunction and Effects on Coagulation and Fibrinolysis: A Systematic Review

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Context: Various changes in the coagulation-fibrinolytic system have been described in patients with an excess or deficiency of thyroid hormones. The purpose of this systematic review is to summarize the effects of hyperthyroidism and hypothyroidism on these systems.

Evidence Acquisition: All published case-control or interventional cohort studies that evaluated the effects of hyperthyroidism and hypothyroidism on the coagulation-fibrinolytic system *in vivo* were identified by a computer-assisted search of the MEDLINE and EMBASE electronic databases. A scoring system was used to divide studies into three quality categories: high, medium, and low quality.

Evidence Synthesis: A total of 36 papers were included. Because in several papers more than one case-control study or both a case-control and intervention study were described, a total of 39 case-control

studies and 24 interventional cohort studies were analyzed. No high-quality study was identified. Three (7.7%) case-control and eight (33.3%) cohort studies were of medium quality. A total of 19 tests were investigated in the medium-quality studies. These tests revealed a hypocoagulable state for overt hypothyroidism and a hypercoagulable state for overt hyperthyroidism.

Conclusions: This analysis confirmed that clinically overt hyperthyroidism and hypothyroidism modify the coagulation-fibrinolytic balance, indicating that thyroid hormone excess or deficit is the probable main pathophysiological mechanism. Patients with overt hypothyroidism and overt hyperthyroidism appear to have an increased risk of bleeding and of thrombosis, respectively. (*J Clin Endocrinol Metab* 92: 2415–2420, 2007)

THE LINK BETWEEN the hemostatic system and thyroid diseases has been known since the beginning of the past century. The first clinical association was described in 1913, when Kaliebe reported an episode of cerebral vein thrombosis in a thyrotoxic patient (1). Several elements of the process of thrombus formation may be involved (2). Both thyroid dysfunction and autoimmunity may modify physiological processes of primary and secondary hemostasis and lead to bleeding or thrombosis. Idiopathic thrombocytopenic purpura, secondary antiphospholipid syndrome, or acquired hemophilia have been associated in individual cases with autoimmune thyroid disorders (3).

The influence of thyroid hormone on the coagulation-fibrinolytic system is mainly mediated by the interaction between the hormone and its receptors (4). Various abnormalities have been described, ranging from subclinical laboratory abnormalities to major hemorrhages or fatal thromboembolic events. The relationship between thyroid hormones and the coagulation system is, however, often ignored. One of the reasons could be that, although several *in vivo* abnormalities have been reported in patients with hypothyroidism and hyperthyroidism, most published studies focus on laboratory measurements, and good studies on the relationship between thyroid dysfunction and clinically manifest bleeding or thrombosis are lacking. In addition, a large number of studies have important methodological drawbacks, such as lack of a control group, small study size,

heterogeneity of cause and severity of thyroid dysfunction, and different laboratory assays.

Therefore, the purpose of this review is to summarize systematically the effects of excess or deficiency of thyroid hormone on the coagulation-fibrinolytic system *in vivo*, to generate well-founded hypotheses, and to give direction for future basic and clinical research on this topic.

Patients and Methods

Study identification

A computer-assisted search of the MEDLINE and EMBASE electronic databases up to July 2006 was performed to identify published studies that evaluated the effect of hyperthyroidism and hypothyroidism on the coagulation-fibrinolytic system.

The following search terms (medical subject heading terms and text words) were used for the MEDLINE search: hemostasis, blood coagulation tests, blood coagulation, blood coagulation factors, blood coagulation disorders, thyroid diseases, thyroid hormones, receptors thyroid hormone, hyperthyroidism, hypothyroidism. These terms were used for the EMBASE database search: hemostasis, blood clotting, blood clotting test, blood clotting factor, blood clotting disorders, thyroid disease, thyroid hormone, thyroid hormone receptor, hyperthyroidism, hypothyroidism.

Reference lists of all included studies were manually searched for other potentially eligible studies.

Inclusion criteria

Two investigators (A.S. and E.R.) independently performed the study selection. Main inclusion criterion was that the study has to evaluate the effect of dysfunctional thyroid diseases, hypothyroidism and hyperthyroidism, overt and/or subclinical, on the coagulation-fibrinolytic system *in vivo*. The following study designs were allowed: 1) case-control study or 2) cohort study in which an intervention was performed to correct hyperthyroidism or hypothyroidism and in which laboratory tests were performed before and after treatment.

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Case reports, case series, reviews, editorials, *in vitro*, and nonhuman studies were excluded. Moreover, studies on cancer patients (cancer itself influences the coagulation system) and studies without statistical analysis were excluded.

Studies in which thyroid functional status was not determined by thyroid hormone measurement were also excluded. For this reason, we excluded studies that were published before 1980 (5). No language restrictions were initially applied to the search strategy, but only papers 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 papers 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 same two investigators independently completed the assessment of study quality. Disagreement was resolved by consensus and by the opinion of a third reviewer, if necessary. Although the use of quality scoring systems or quality scales in observational studies is controversial (6), the Newcastle-Ottawa Scale for assessing quality of nonrandomized studies was adapted for use (7). This assesses the three broad areas of selection, comparability, and outcome or exposure, for cohort or case-control studies, respectively. For summarizing study validity, we adapted a simple Cochrane Collaboration approach for interventional studies (8). Three categories were therefore identified: high quality (low risk of bias), medium quality (moderate risk of bias), or low quality (high risk of bias).

The main items for case-control studies and their scoring were as follows: 1) definition of type of thyroid dysfunction (1 point was given if degree of thyroid dysfunction and underlying cause were registered and if the interval between thyroid hormone measurement and study enrollment was <48 h); 2) selection of patients (1 point was given if they were consecutive or clearly a representative series of cases); 3) definition of control group (1 point was given if thyroid hormones were measured or if an explicit statement of no history of thyroid disease was reported); 4) selection of control group (1 point was given if it was a community control group); and 5) comparability on the basis of the design or analysis (1 point was given if controls were age and sex matched or if there was an adequate adjustment for age and sex in the statistical analysis).

The main items for the cohort studies in which thyroid dysfunction was corrected and their scoring were as follows: 1) definition of type of thyroid dysfunction (1 point was given if degree of thyroid dysfunction and underlying cause were registered and if the interval between thyroid hormone measurement and study enrollment was <48 h); 2) selection of patients (1 point was given if they were consecutive or clearly a representative series of cases); 3) definition of euthyroid state after therapy (1 point was given if thyroid hormone measurement was repeated to define the euthyroid state; 2 or 1 points were given if 100% or >90% of patients were euthyroid, respectively, and interval between assessment of euthyroid state and coagulation test measurement was <48 h).

The scoring system defined the three quality categories as follows: a total of 5 points was for high-quality study; 4 points for a medium-quality study; and 3 or less for a low-quality one. Three was used as cutoff value for low quality, because, in these studies, the definition and selection of the populations, either cases or controls, or both, were believed to be inaccurate.

The quality assessment form is available on request.

No attempts to mask for authorship, journal name, or institution were made.

Data extraction

The same two reviewers independently completed the data extraction form. Disagreement was resolved by consensus and by the opinion of a third reviewer, if necessary. The following characteristics were col-

lected: 1) investigated thyroid dysfunction (hypothyroidism and/or hyperthyroidism, clinically overt and/or subclinical); 2) total number of enrolled cases and controls; 3) performed coagulation-fibrinolytic tests; 4) statistically decreased, increased, or no statistically difference of each test of cases *vs.* controls or before *vs.* after treatment.

Statistical analysis

Data for qualitative variables were presented as incidence rates (N, number, and percentage).

Results

The initial search strategy identified 4895 papers. A total of 158 publications were considered potentially eligible based on the title and/or abstract. Of these, 41 were excluded for language, 64 were written before 1980, and four were not available. We retrieved full copies of 49 potentially appropriate studies. After excluding 13 articles not meeting the prespecified inclusion criteria (9–21), a total of 36 were included in the final analysis (22–57). As summarized in Tables 1 and 2, several studies were designed as both a case-control and intervention study and explored different types of thyroid dysfunction. A total of 39 case-control studies and 24 interventional cohort studies were analyzed. If the authors clearly defined that the enrolled patients had a subclinical degree of thyroid dysfunction, in the column “Type of dysfunction,” we reported “subclinical;” otherwise, if the authors declared that they enrolled hypothyroid or hyperthyroid patients or they specifically declared that they enrolled only overt hypothyroid or hyperthyroid patients, we reported “hypothyroidism” or “hyperthyroidism.”

No high-quality study was identified. Three (7.7%) case-control and eight (33.3%) cohort studies were of medium quality. Table 3 summarizes the findings regarding the various elements of “Definition of thyroid dysfunction.” Only a few studies enrolled an optimal thyroid dysfunction population, mainly because most studies included a heterogeneous patient group with several underlying causes of thyroid dysfunction (autoimmune, postsurgical, *etc.*). Moreover, some authors did not enroll patients with the same degree of thyroid dysfunction (as reported above, some studies with overt hypothyroid or hyperthyroid patients included also patients with subclinical disease) and did not measure thyroid hormones at the same time of coagulation-fibrinolytic measurements. Few authors did not report the type of tested thyroid hormones, *i.e.* total or free T₄, total or free T₃, and TSH, on which they based laboratory diagnosis of thyroid dysfunction disease.

Table 4 summarizes the data on coagulation and fibrinolytic tests of the medium-quality studies. Supplemental Table 1 (published as supplemental data on The Endocrine Society’s Journals Online web site at <http://jcem.endojournals.org>) summarizes the coagulation and fibrinolytic effect for each thyroid dysfunction in all quality studies; also poor-quality ones can be provided.

The activated partial thromboplastin time, prothrombin time, and clotting time are general coagulation tests that evaluate time necessary to clot *in vitro*, whereas the bleeding time is a test in which the interaction between platelets and the vessel wall is reflected *in vivo*. Therefore, a prolongation of these tests means a reduced hemostatic response and a bleeding tendency. Factor VIII and von Willebrand factors are procoagulant factors.

TABLE 1. Individual study quality assessment of case-control study design

First author	Patients definition	Patients selection	Controls definition	Controls selection	Sex-age comparability	Score	Quality	Type of dysfunction	Ref.
Arnout									
(A)	0	0	0	0	0	0	Low	Hypo	22
(B)	1	0	0	0	0	1	Low	Hyper	
Burggraaf	1	0	1	0	1	3	Low	Hyper	23
Canturk	0	0	1	1	1	3	Low	Sub. hypo	24
Chaderevian	0	1	1	1	0	3	Low	Hypo	26
Chaderevian	0	0	1	1	0	2	Low	Hypo	25
Coban	1	0	1	1	1	4	Medium	Sub. hyper	28
Dorr									
(A)	0	1	1	1	1	4	Medium	Hypo	29
(B)	0	1	1	1	1	4	Medium	Hyper	
(C)	0	1	1	1	1	4	Medium	Sub. hyper	
Erem	0	0	0	0	0	0	Low	Hypo	32
Erem	0	0	0	0	1	1	Low	Hyper	31
Erem									
(A)	0	0	1	0	1	2	Low	Sub. hypo	30
(B)	0	0	1	0	1	2	Low	Sub. hyper	
Graninger	0	0	0	0	1	1	Low	Hyper	34
Guldiken	0	0	1	1	0	2	Low	Sub. hypo	35
Gullu									
(A)	1	0	1	0	0	2	Low	Hypo	36
(B)	1	0	1	0	0	2	Low	Sub. Hypo	
Gursoy									
(A)	0	0	1	0	1	2	Low	Hypo	37
(B)	0	0	1	0	1	2	Low	Sub. hypo	
Jorde	0	0	1	1	1	3	Low	Sub. hypo	38
Kventy	0	1	1	1	0	3	Low	Sub. hypo	39
Li	1	0	0	0	0	1	Low	Hyper	41
Liu	0	1	1	0	0	2	Low	Hyper	42
Marongiu	0	0	0	0	1	1	Low	Hyper	43
Marongiu	0	0	0	0	1	1	Low	Hypo	46
Marongiu	0	0	0	0	1	1	Low	Hyper	45
Marongiu	0	0	0	0	0	0	Low	Hyper	44
Myrup									
(A)	0	1	0	0	0	1	Low	Hypo	49
(B)	0	1	0	0	0	1	Low	Hyper	
Morishita	0	0	1	0	0	1	Low	Hyper	47
Muller	0	0	1	0	0	1	Low	Sub. hypo	48
Ozcan									
(A)	0	0	1	0	1	2	Low	Hypo	52
(B)	0	0	1	0	1	2	Low	Hyper	
(C)	0	0	1	0	1	2	Low	Sub. hypo	
Rogers II	0	0	0	0	0	0	Low	Hyper	54
Rosc	0	0	1	0	0	1	Low	Hyper	55
Wahrenberg	1	0	0	0	0	1	Low	Hyper	56
Yong	0	0	1	0	0	0	Low	Hypo	57
Total (%)	7 (17.9)	8 (20.5)	24 (61.5)	11 (28.2)	19 (48.7)				

Ref., Reference; hypo, hypothyroidism; hyper, hyperthyroidism; sub, subclinical.

A decreased plasma level or activity indicates a higher chance of bleeding, especially when levels are markedly reduced.

The fibrinolytic system is important to counterbalance the coagulation cascade. In general, increased fibrinolysis, for instance, by fibrinolysis-stimulating factors or by reduced anti-fibrinolytic factors, will result in a increased chance of bleeding. An increase of inhibitory factors, especially plasminogen activator inhibitor 1 level, has been associated with an increased risk of thrombotic complications (58).

In summary, the available evidence revealed four important changes: 1) thyroid dysfunction modifies the balance between coagulation and fibrinolysis; 2) coagulation tests revealed a hypocoagulable state for overt hypothyroidism and a hypercoagulable state for overt hyperthyroidism; 3) the hypothesis of a hypercoagulable state in subclinical hypothyroidism is not supported; and 4) few coagulation-fibrinolytic test abnormali-

ties have been described in subclinical hyperthyroidism and hypothyroidism.

Discussion

Many factors are responsible for maintaining the hemostatic balance, and, among them, hormones directly influence both primary and secondary hemostasis (59). In particular, a bleeding tendency is often observed in hypothyroid patients, and a possible increased risk of sinus and cerebral vein thrombosis has been reported in clinically overt hyperthyroidism (1). 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.

We conducted this systematic review to better define which

TABLE 2. Individual study quality assessment of interventional cohort study design

First author	Patients definition	Patients selection	All patients euthyroid at control	>90% euthyroid at control	Hormone measurement for euthyroid	Quality score	Study quality	Type of dysfunction	Ref.
Arnaout (A)	0	0	0	0	1	1	Low	Hypo	22
(B)	1	0	0	0	1	2	Low	Hyper	
Burggraaf	1	0	2	0	1	4	Medium	Hyper	23
Canturk	0	0	2	0	1	3	Low	Sub. hypo	24
Chadarevian	0	1	0	0	1	2	Low	Hypo	27
Erfurth	0	0	0	0	1	1	Low	Hypo	33
Gullu (A)	1	0	2	0	1	4	Medium	Hypo	36
(B)	1	0	2	0	1	4	Medium	Sub. hypo	
Levesque	0	0	0	0	1	1	Low	Hypo	40
Li	1	0	2	0	1	4	Medium	Hyper	41
Liu	0	1	2	0	1	4	Medium	Hyper	42
Marongiu	0	0	0	0	0	0	Low	Hyper	45
Morishita	0	0	0	0	1	1	Low	Hyper	47
Myrup (A)	0	1	2	0	1	4	Medium	Hypo	49
(B)	0	1	2	0	1	4	Medium	Hyper	
Nagasaki	0	1	2	0	1	4	Medium	Hypo	50
Nagasaki	0	1	2	0	1	4	Medium	Hypo	51
Ozcan (A)	0	0	0	0	0	0	Low	Hypo	52
(B)	0	0	0	0	0	0	Low	Hyper	
(C)	0	0	0	0	0	0	Low	Sub. hypo	
Palareti	0	0	0	0	0	0	Low	Hypo	53
Rogers II(A)	0	0	0	0	1	0	Low	Hypo	54
(B)	0	0	0	0	1	0	Low	Hyper	
Wahrenberg	1	0	0	0	1	2	Low	Hyper	56
Total (%)	6 (25)	6 (25)	10 (41.7)	0	19 (79.2)				

Ref., References; hypo, hypothyroidism; hyper, hyperthyroidism; sub, subclinical.

hypotheses on the relationship between dysfunctional thyroid disease and the coagulation-fibrinolytic system are well founded. For this purpose, we selected the better quality publications. Two arbitrary criteria were introduced for study selection and quality assessment. First, we excluded studies that were published before 1980. In 1963, Condliffe purified TSH, and, soon thereafter, Odell and Utiger both reported the first immunoassays for human TSH (5). In 1971, Mayberry and Hershman simultaneously described the TSH immunoassays for the diagnosis of hypothyroidism (5). Second, use of quality scoring in metaanalyses for observational studies is controversial (6, 60). For this reason, we adapted the Newcastle-Ottawa Scale to identify main biases in case and control selection and comparability and a simple Cochrane Collaboration approach for summarizing study validity (8). However, no high-quality case-control or interventional cohort studies could be identified. Study quality assessment elucidated a number of methodological weaknesses in the published thyroid-coagulation studies.

Additional information about the influence of thyroid hormones on coagulation comes from two intervention studies performed in healthy volunteers (9, 34). Unfortunately only

TABLE 3. Study quality assessment on "definition of dysfunctional thyroid patients": fulfilled item and subitems

	Case control (n = 39)	Cohort (n = 24)
Patients' definition	7 (17.9%)	6 (25.0%)
Reporting of		
Measured assay of thyroid hormones	37 (94.9%)	21 (87.5%)
Degree of thyroid dysfunction	31 (79.5%)	16 (66.7%)
Underlying cause	13 (33.3%)	10 (41.7%)
Brief interval (<48 h) between thyroid hormone measurement and study enrollment	26 (66.7%)	16 (66.7%)

a few tests were performed during administration of oral thyroid hormones in these studies, but a clear increase of factor VIII, von Willebrand antigen and activity, and tissue plasminogen activator antigen was observed. However, these studies only revealed the effect of relatively short period, 2 wk, of hyperthyroidism.

Given the large amount of studies performed on this topic, future studies should be of high quality to provide more definitive data. They should enroll consecutive patients with a well-defined degree of dysfunction (overt or subclinical), based on thyroid hormone measurement (TSH, free T_4 , and free T_3), with the same underlying cause (autoimmune, postsurgical, *etc.*); blood for coagulation-fibrinolytic tests and thyroid hormone measurements should be drawn the same day, no more than 48 h after starting drug therapy; the control group should be of the same community as cases, should have no history of thyroid disease, and thyroid hormones should be measured; in case of an interventional cohort study, tests should be repeated when all patients have reached an euthyroid state, defined by hormones measurements; and sex- and age-matched control group would be the optimal, but any possible confounder may be easily adjusted for in the analysis (interventional cohort study has an intrinsic perfect comparability).

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 4. Hypothyroidism and hyperthyroidism modify each group of coagulation-fibrinolytic tests. The effect is consistent across the three groups and support an increased risk of bleeding in hypothyroidism and an increased risk of throm-

TABLE 4. Overall coagulation and fibrinolytic changes in medium quality studies (23, 28, 29, 36, 41, 42, 49–51)

	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	1		=		
Coagulation tests					
fVIII:C	4	↓ or =		↓	
vWf:Ag	6		↑ or =		
vWf:C	2	↓			↑
vWfII:Ag	1		↑		
vWf ristocetin	2	↓		↓	
Fibrinogen	6	↓ or =	↑ or =		↑
Ristocetin agglutination	2	↓	=		
Fibrinolytic tests					
t-PA:Ag	2		↑ or =		
t-PA:C	1		=		
PAI-1	2		↑ or =		
Plasminogen	1		↓		
α 2 antiplasmin	1		↑		
Plasmin-antiplasmin complex	1		=		

hypo, Hypothyroidism; hyper, hyperthyroidism; sub, subclinical; aPTT, activated partial thromboplastin time; PT, prothrombin time; f, factor; C, activity, Ag, antigen; vWf, von Willebrand factor; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; ↑, increased; ↓, decreased; =, nonstatistically significant difference.

basis in hyperthyroidism. Even if some results are discordant, medium-quality studies may have a moderate risk of bias.

No definitive data are available to assess the degree of the hypocoagulable and hypercoagulable state in overt hypothyroidism and hyperthyroidism, respectively. 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 (9, 61).

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 (25, 26). Some of the studies in which this was suggested were also included in our review, but they were of low quality (25, 26).

Moreover, the role of the coagulation-fibrinolytic system in the pathophysiology of atherosclerosis and arterial thrombosis is still a matter of debate (62, 63)

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 (30).

Many physicians still ignore the existing relationship between thyroid hormones and the coagulation system. It is important for clinicians to realize that hemostatic balance can be affected by thyroid dysfunction, as well as hepatic, renal, and other systemic diseases.

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