Coagulation profiles in hypothyroid and hyperthyroid female patients in Sudan

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ABSTRACT

الأهداف: لتقييم الإعتلالات التي تصيب جهاز تجلط الدم لدى النساء اللائي يعانين من أمراض الغدة الدرقية وذلك لمعرفة تأثيرها عليه.

الطريقة: أُجريت دراسة مقطعية في المركز القومي للعلاج بالأشعة والطب النووي – الخرطوم السودان. شملت الدراسة 30 مريضاً مصاب بنقص الغدة الدرقية السريري، و30 مريضاً مصاب بنقص الغدة الدرقية دون السريري، (19 منهم تحت العلاج ، 21 منهم قبل البدء في العلاج). أيضا شملت الدراسة 30 مريضاً مصاب بزيادة الغدة الدرقية السريري، و30 مريضاً مصاب بزيادة الغدة الدرقية دون السريري، (23 منهم تحت العلاج – 37 منهم قبل البدء في العلاج)، بالإضافة إلي 30 امرأة من الأصحاء الغير مصابين بأي من الأمراض كمجموعة ضبط للمقارنة. أجريت اختبارات زمن البروثرومبين (PT)، زمن الثرومبوبلاستين الجزئي (APTT)، مولد الفايبرين، وحساب الصفائح الدموية لكل العينات التي تم جمعها.

النتائج: أظهرت النتائج أن زمن البرثرمبين (PT) يقل بصورة ملحوظة عند المرضى الذين يعانون من نقص في الغدة الدرقية السريري (11.98±1.16)، ومرضى فرط نشاط الغدة الدرقية (12.02±1.29)، بالمقارنة مع مجموعة الضبط (14.4±1.15)، بينما يقل زمن الثرومبوبلاستين الجزئي (APTT) عند المرضى الذين يعانون من زيادة الغدة الدرقية السريري (28.52±6.27)، بالمقارنة مع مجموعة الضبط (32.44±2.97). علاوة على ذلك فان مستوى مولد الفايبرين في عينات الدم قد زاد كثيرا عند المرضى الذين يعانون من زيادة الغدة الدرقية السريري (352.2±161.36)، بالمقارنة مع مرضى فرط نشاط الغدة الدرقية (276.46±137.4).

خاتمة: تبين لنا في هذه الدراسة، إن تأثير أمراض الغدة الدرقية السريري على وظائف جهاز تجلط الدم بصورة متفاوتة، وأكثر من تأثير أمراض الغدة الدرقية دون السريري عليه. لم يكن لأعمار المرضى وخضوعهم للعلاج تأثير يذكر. تمت التوصية بإخضاع النساء اللائي يعانين من أمراض الغدة الدرقية السريري للفحص الكشفي لتجنب الاختلالات التي تحدث في هذا الجهاز وتجنب المضاعفات المترتبة على ذلك.

Objective: To evaluate disturbances in the coagulation system in female patients with thyroid disorders in order to assess the effects of thyroid diseases on coagulation parameters.

Methods: This study was conducted in Khartoum state, the national capital of Sudan from February 2007 and February 2008 The study included 30 patients with clinical hypothyroidism, and 30 patients with sub- clinical hypothyroidism (21 of them were recruited before starting the treatment). Also, the study included 30 patients with clinical hyperthyroidism, 30 with sub-clinical hyperthyroidism, (37 of them were recruited before starting the treatment) and 30 normal individuals as the control group. Prothrombin time (PT), activated partial thromboplastin time, fibrinogen level, and platelets count were performed in patients and control samples.

Results: A significantly decrease in PT was observed in hypothyroid patients, and hyperthyroid patients compared to the control group. Activated thromboplastin time was significantly decreased only in hyperthyroid patients, compared to the control group. Moreover, fibrinogen level was significantly increased in hyperthyroid patients compared to hypothyroid patients.

Conclusion: The study concluded that minor coagulation abnormalities were observed in both subclinical hypo- and hyperthyroidism compared to clinical hypo- and hyperthyroidism. Platelets count was also slightly decreased in both types of the disease. There was no significant effect of the treatment and age of such patients on the measured parameters. The study recommended to screen female patients with hypo- and hyperthyroidism for coagulation defect, to avoid the risk of such complications.

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Disturbances of thyroid function can usually be divided into thyroid hypo function (hypothyroidism) and thyroid hyper function (hyperthyroidism).[1,2] Hypothyroidism is a condition characterized by a deficiency of thyroid hormones that causes a generalized slowing of metabolic process.[3,4] Although not less than 5% of the world's population has goiters, and most of them (75%) live in the less developed countries where iodine deficiency is prevalent. The prevalence of subclinical hypothyroidism in the USA is approximately 4-8.5% and may be high as 20% in women older than 60 years, compared to approximately 85% prevalence of goiters detected in the region of Darfour in Sudan, mainly which is children.[5] Hyperthyroidism (thyrotoxicosis) occurs when excessive amount of thyroid hormones in the circulation affecting peripheral tissues, which lead to increase metabolic activities.[6] It is a common disorder in the United Kingdom where 2.7% of females and 0.5% of undiagnosed women carrying the disease. Moreover, the prevalence of "subclinical" hyperthyroidism is much higher than that of overt disease. In elderly, the frequency of hyperthyroidism ranges from 0.8-5.8 while sub-clinical hyperthyroidism constitutes 2.1% in over 65 years old.[7] Many coagulation abnormalities can be seen in patients with different thyroid diseases. Blood coagulation abnormalities in hyperthyroidism may lead to cerebral vein thrombosis (CVT) with mortality rates between 5% and 30%,[8] ischemic stroke without cardiac arrhythmias, and arterial fibrillation (AF), which occurs frequently in patients with hyperthyroidism and cardioembolic stroke.[9-11]

Cardiovascular mortality increased in clinical hypothyroidism as well as in overt and subclinical hyperthyroidism, and in association with predictors of cardiovascular or ventricular dysfunction. Further, important associations was identified for atherosclerosis and heart failure in individual with overt as well as sub-clinical hypothyroidism.[12,13] Most of the coagulation abnormalities associated with thyroid disorders are a consequence of the direct action of thyroid hormones on the synthesis of various hemostatic factors, or derangement of immune function. However, these abnormalities suggest that hyper-coagulable state is present in hyperthyroid patient, while patients suffering from moderate hypothyroidism are at increase risk of thrombosis contrasting with the bleeding tendency of those presenting severe hypothyroidism.[14] Thus, it is important to study coagulation profiles in Sudanese female patients to identify the etiology in order to limit these abnormalities as iodine deficiency is common, especially in western Sudan. Therefore, aims of the study are to measure the coagulation profiles [prothrombin time (PT), activated partial thrombo-plastin time (APTT), fibrinogen, and platelets) in patients with different thyroid diseases as well as to determine the effect of the onset, type of disease, age of patients, and the treatment on these parameters.

Methods. The design of the study is an observational cross-sectional. It was conducted in Khartoum State, the national capital of Sudan from February 2007 and February 2008. Samples were collected from females with thyroid disease attending the Radiation and Isotope Center in Khartoum, Sudan. The sample size was selected in a simple random manner. All males were excluded as well as females with malignancy or severe disease other than thyroidism. A total of 150 female patients were recruited for the study. Of them, 30 patients diagnosed as clinical hypothyroidism (T3 <60ng/dl, T4 <4.5µg/dl, and with clinical features of the disease) and 30 patients were sub-clinical hypothyroidism (decrease of T3 and T4 without clinical symptoms). The study also included 30 patients diagnosed as clinical hyperthyroidism (T3>220ng/dl, T4 >13µg/dl, and having clinical features of the disease) and 30 of the sub-clinical hyperthyroidism (elevation of T3 and T4 without clinical symptoms) in addition to the 30 healthy, non-hospitalized, adult females as the control group. Permission and consent from all patients as well as controls were taken. However, 1.8 ml and 2 ml blood of each patient and control was collected in a separate blood container containing 0.2 ml of tri-sodium citrate and 2.4 mg ethylene diamine tetraacetic acid (EDTA) anticoagulants. Patients and control citrated blood samples were prepared in a form of platelet poor plasma and used to perform PT, APTT, and fibrinogen estimation, while EDTA blood was used for platelets counting for each blood sample.

For counting platelets, blood samples were diluted in 1:20 1% ammonium as described by Cheesbrough.[15] Partial thromboplastin time, a screening test for the intrinsic clotting system, namely, factors XII, XI, IX, VIII, X, and V, prothrombin, and fibrinogen, and PT, a screening test for the extrinsic clotting system, namely, factors VII, X, and V, prothrombin and fibrinogen were conducted. These tests were conducted as described by Dacie and Lewis[16] using a commercial reagent (DiaMed Company, Turnhout, Belgium). For measuring the fibrinogen level, plasma was diluted to give low level of any inhibitors and then clotted with fibrinogen solution.

The test was also carried out as described by Dacie and Lewis[16] using a commercial reagent by DiaMed Company. Data were analyzed using Statistical Package for the Social Science (SPSS version 11.0) software. Non Parametric tests were mainly used for the abnormal distribution of the data.

Results. The study recruited 150 female patients. Of 60 patients with hypothyroidism 29 were under treatment and 21 were recruited prior to treatment. Sixty patients with hyperthyroidism (23 under treatment and 37 prior to treatment) and 30 normal individuals. Bleeding was observed in 8 patients with clinical hypothyroidism, one patient with subclinical hypothyroidism and in one patient with clinical hyperthyroidism. Bleeding is absent in patients with subclinical hyperthyroidism.

Table 1 shows the means of the coagulation tests among hyper- and hypothyroid patients as well as control group. As shown in **Table 2**, PT is significantly decreased in patients with hypothyroidism compared to the control group. Also, APTT is increased, while fibrinogen level and platelets count are decreased without statistical significance. **Table 3** shows that PT and APTT are significantly decreased in patients with hyperthyroidism compared to the control group. Also, fibrinogen level is increased, while platelets count was decreased in hypothyroidism patients compared to the control without statistical difference. **Table 4** illustrates the significant increase in the APTT, and significant decrease in fibrinogen level in hypothyroid patients less than in hyperthyroid patients. The table also illustrates the similarity of PT and platelets count

Table 1 - Means of the coagulation profiles among hypo and hyperthyroidism patients and control group.

Coagulation profiles	Hypothyroidism	Hyperthyroidism	Control group
	Mean ± SD		
PT	11.98±1.16	12.02±1.29	14.4±1.15
APTT	34.73±10.37	28.52±6.27	32.44±2.97
Fibrinogen	276.46±137.47	352.20±161.36	301.6±58.71
Platelets	200.85±61.77	192±52.53	205.64±60.21

PT - prothrombin time/seconds
APTT - activated partial thromboplastin time/second
Fibrinogen - concentration, mg/dl
Platelets - platelets count, × 10^3 cells/mm^3

Table 2 - Means and standard deviations (SD) of the coagulation profiles in hypothyroidism patients in relation to the control group.

Coagulation profiles	Hypothyroidism	Control group	*P*-value
	Mean ± SD		
PT	11.98±1.16	14.4±1.15	0.001
APTT	34.73±10.37	32.44±2.97	0.258
Fibrinogen	276.46±137.47	301.6±58.71	0.386
Platelets	200.85±61.77	205.64±60.21	0.752

PT - prothrombin time/seconds
APTT - activated partial thromboplastin time/second
Fibrinogen - concentration, mg/dl
Platelets - platelets count, × 10^3 cells/mm^3

Table 3 - Means and standard deviations (SD) of the coagulation profiles among hyperthyroidism patients in relation to control group.

Coagulation profiles	Hyperthyroidism	Control group	*P*-value
	Mean ± SD		
PT	12.02±1.29	14.4±1.15	0.001
APTT	28.52±6.27	32.44±2.97	0.004
Fibrinogen	352.20±161.36	301.6±58.71	0.131
Platelets	192±52.53	205.64±60.21	0.291

PT - prothrombin time/seconds
APTT - activated partial thromboplastin time/second
Fibrinogen - concentration, mg/dl
Platelets - platelets count, × 10^3 cells/mm^3

Table 4 - Means and standard deviations (SD) of the coagulation profiles in hypothyroid patients in relation to hyperthyroid patients.

Coagulation Profiles	Hypothyroidism	Hyperthyroidism	*P*-value
	Mean ± SD		
PT	11.98±1.16	12.02±1.29	0.879
APTT	34.74±10.37	28.52±6.27	0.001
Fibrinogen	276.46±137.47	352.20±161.36	0.010
Platelets	200.85±61.77	192.00±52.53	0.411

PT - prothrombin time/seconds
APTT - activated partial thromboplastin time/second
Fibrinogen - concentration, mg/dl
Platelets - platelets count, × 10^3 cells/mm^3

Table 5 - Means and standard deviations (SD) of the coagulation profiles in clinical and subclinical hypothyroidism.

Coagulation Profiles	Clinical Hypothyroidism	Subclinical Hypothyroidism	*P*-value
	Mean ± SD		
PT	11.93±1.18	12.05±1.15	0.724
APTT	36.14±10.41	32.75±10.24	0.268
Fibrinogen	271.43±116.32	283.5±165.62	0.768
Platelets	194.89±58.32	209.2±66.92	0.435

PT - prothrombin time/seconds
APTT - activated partial thromboplastin time/second
Fibrinogen - concentration, mg/dl
Platelets - platelets count, × 10^3 cells/mm^3

Table 6 - Means and standard deviations (SD) of the coagulation profiles in subclinical hypo and hyperthyroidism patients

Coagulation Profiles	Clinical Hyperthyroidism	Subclinical Hyperthyroidism	*P*-value
	Mean ± SD		
PT	11.92±1.14	12.07±1.39	0.644
APTT	29.88±6.94	27.84±5.81	0.185
Fibrinogen	365.21±192.65	344.76±142.49	0.624
Platelets	191.88±58.96	192.07±49.25	0.988

PT - prothrombin time/seconds
APTT - activated partial thromboplastin time/second
Fibrinogen - concentration, mg/dl
Platelets - platelets count, × 10^3 cells/mm^3

Table 7 - The effect of thyroid treatment on the coagulation profiles in patients with hypo and hyperthyroidism.

Coagulation profiles	Hypothyroidism		Hyperthyroidism	
	Under Treatment	Prior Treatment	Under Treatment	Prior Treatment
	Mean ± SD			
PT	11.97±1.18	12.00±1.15	11.92±1.06	12.08±1.44
APTT	35.21±10.39	34.00±10.57	28.42±7.39	28.57±5.53
Fibrinogen	285.00±133.83	263.42±145.55	351.54±167.38	352.63±159.48
Platelets	196.79±63.85	207.05±59.60	195.42±57.20	189.78±49.90

PT - prothrombin time/seconds, APTT - activated partial thromboplastin time/second
Fibrinogen - concentration, mg/dl, Platelets - platelets count, × 10^3 cells/mm^3

in both hypo- and hyperthyroid patients. As indicated in **Table 5**, PT, fibrinogen level, and platelets count are slightly decreased, while APTT is slightly increased in clinical hypothyroidism patients rather than in sub clinical hypothyroidism. **Table 6** shows that APTT and fibrinogen level are increased, PT, and platelets count are decreased in clinical hyperthyroidism patients less than in sub-clinical hyperthyroidism patients. There is no significant correlation between the 2 groups. **Table 7**, indicates the slight decrease of PT and fibrinogen level in under treatment hypo- and hyperthyroid patients compared to the untreated patients. There is no significant variation between the 2 groups. As presented in this table, APTT results were similar before and during treatment in both hypo- and hyperthyroid patients.

Discussion. Many factors are responsible for maintaining the hemostatic balance, and among them, hormones directly influence both primary and secondary homeostasis. The coagulation abnormalities in patients with thyroid deficiency are varied,[17] however, frequently the coagulopathy consists of a defect of primary hemostasis, which results in a bleeding tendency that is usually mild such as nose or gingival bleeding, menorrhagia, and easy bruising, however, it can rarely be severe hemorrhage following trauma or surgery.[18] Limited coagulation test abnormalities have been described in subclinical hyper and hypothyroidism patients.[17]

In the present study, the decrease of PT in patients with hypothyroidism was similar to that reported by Muller et al,[19] which could be explained by the increase of factor VII activity in subclinical hypothyroidism. These findings disagree with that documented by Ford and Carter,[20] who described low levels of plasma coagulation factor VII. Moreover, low fibrinogen level measured in the present study agreed to that reported by Graninger et al.[21] Normal platelets count in hypothyroid patients compared to the control group observed in this study was identical to that reported by Myrup et al.[22] Shortening PT and APTT and high fibrinogen level of hyperthyroid patients detected in the present study agree to that reported by Myrup et al.[22,23] Contrary, slightly low platelets count determined in patients with hyperthyroidism was consistent with the results obtained by Anselm et al,[24] who found a case of thrombocytopenia in patient with Grave's disease. No significant difference between clotting parameters of patients under treatment or prior to treatment. In the present context, 26.6% of clinical and 3.3% of sub-clinical hypothyroid patients were found to be suffering from bleeding, and the coagulation abnormalities was not affected by the age of patients.

We concluded that clinical hypo- and hyperthyroidism are associated with significant abnormalities in coagulation profiles, while subclinical hypo- and hyperthyroidism are associated with minor changes in clotting parameters. However, APTT is significantly increased in subclinical hyperthyroidism, while slight abnormalities were associated with platelets count in both overt and subclinical thyroid disorders. Moreover, coagulation parameters were not significantly affected by the treatment of both hypo- and hyperthyroidism. Therefore, coagulation screening is recommended in order to identify coagulation defect in patients with hypo- and hyperthyroidism, and thus, bleeding and thrombosis could be prevented. Although the study recruited adult females only, further studies are recommended to include adult males and children with thyroid disease.

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