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Alteration of Coagulation Profiles in Hypothyroid Patients

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Background:

Hypothyroidism is an underactive thyroid gland that results in too little thyroid hormones in circulation causing a slowdown in metabolism, therefor hypothyroid modifies physiological process of primary and secondary hemostasis and may lead to a higher bleeding risk.

Objectives: The aim of this study is to assess the coagulation profiles [Prothrombin Time (PT), International Normalize Ratio (INR), Activated Partial Thromboplastin Time (PTT)] in patients with hypothyroidism.

Methodology: This is a case-control hospital-based study carried out at the National Cancer Institute – University of Gezira (NCI-UG), Wad Medani, Sudan from January to October 2020. A total of 100 (50 patients with hypothyroidism as cases (38.50 ± 10.46 years) matched with 50 normal healthy individuals as controls (35.52 ± 11.64 years) participated in this study. Two ml of venous blood sample was collected in a trisodium citrate container. Coagulation profiles (PT, INR, and PTT) were measured using a Coatron M4 coagulometer. SPSS computer program (v 21.0) was used for data analysis.

Results: The prolonged PTT account for 74%. The average PTT of cases (42.29 ± 7.22 sec) was higher than controls (32.67 ± 5.90 sec) giving highly statistically significant differences (P value = 0.000) between them. There were significant differences in PTT between mild and severe hypothyroidism (P value = 0.0470). PTT had significant positive correlation within TSH (P value = 0.048; r = 0.070) and significant negative correlation within T3 (P value = 0.000; r = - 0.490) and T4 (P value = 0.020; r = - 520; P value = 000).

Conclusion: The study concluded that PTT was significantly higher in a patient with hypothyroidism when compared to the control. PTT results showed there was a significant negative correlation between T3 and T4 levels and a significant positive correlation with TSH levels. So, PTT should be included as a follow-up routine test for patients with hypothyroidism.

Keywords: *Prothrombin time, International Normalized Ratio, Partial Thromboplastin Time, Hypothyroidism, Sudan.*

Introduction

Thyroid dysfunction is a group of disorders that affect the thyroid. Some of them have a companion change in structure and function, others have no effect (1). Thyroid hormone is required for the normal functioning of numerous tissues in the body. In healthy individuals, the thyroid gland predominantly secretes thyroxine (T4), which is converted into triiodothyronine (T3). T3 binds to the thyroid hormone receptor in the nucleus of cells, where it stimulates the turning on of genes and the production of specific proteins (2).

Thyrotropin-releasing hormone (TRH) is produced by the brain and stimulates the pituitary gland to create thyroid-stimulating hormone (TSH). TSH stimulates the thyroid gland to produce and secrete mainly T4 and, while smaller quantities of T3 are possible, alteration in the structure and function of this organ or pathways can result in hypothyroidism (3). Hypothyroid disorders may occur as a result of congenital thyroid abnormalities (thyroid deficiency at birth) or iodine deficiency. Hypothyroidism and endemic goitre are most commonly caused by a lack of iodine. In places of the world where dietary iodine is sufficient, the autoimmune disease Hashimoto's thyroiditis is the most common cause of hypothyroidism (chronic autoimmune thyroiditis). It is characterised by infiltration of the thyroid gland with T lymphocytes and autoantibodies against specific thyroid antigens such as thyroid peroxidase, thyroglobulin, and the TSH receptor (4).

Thyroid problems have been reported in over 110 countries in the world, with 1.6 billion people at risk and needing some form of iodine supplement. Most of these are in developing countries, Asia, Africa, and Latin America (5). More than one billion people are at risk of iodine deficiency worldwide, and 200 million have goiter. In many parts of Sudan, endemic goitre and iodine deficiency illnesses are severe health issues. The prevalence of goitre among school children was estimated to be 85% in the Darfur region in western Sudan, 74% in the Kosti area in the centre of Sudan, 13.5% in Port-Sudan in eastern Sudan, and 17% in the capital, Khartoum, and 22.3% in the southern Blue Nile area of Sudan (6). Thyroid disease is common, affecting around 2% of women and 0.2% of men in the UK. It has become clear that overt thyroid dysfunction is associated with significant morbidity, and people with hypothyroidism are more susceptible to bleeding (7).

In Sudan, a survey was done as early as in the last century to study goiter, which results from the effect of iodine deficiency and leads to poor manufacturing of thyroid hormones. This survey studies goitre in the people of Darfur. The survey included 17470 participants. The survey showed that 57% were goitrous and 18.5% of these had large goitres. Another study in Darfur showed that about 85% of schoolchildren were suffering from endemic goitre (8).

The presenting symptoms of hypothyroidism include fatigue, dysarthria, and dysphagia, sleep apnea, and swelling of the lower back. Constipation, fatigue, dry skin, hair loss, bradycardia, and confusion (9); The primary screening test to evaluate thyroid function measures TSH levels. The next step is to measure free T4 and free T3 (10).

Most of the coagulation abnormalities associated with thyroid disorder are consequences of the direct action of thyroid hormones on the synthesis of various hemostatic factors or derangement of immune function. However, these abnormalities suggest that patients suffering from hypothyroidism are at an increased risk of bleeding tendency (11).

The influence of thyroid hormone on the coagulation system Various abnormalities, ranging from preclinical laboratory abnormalities to severe haemorrhages or deadly thromboembolic episodes, have been recorded. Excess or shortage of thyroid hormones may have direct and indirect effects on platelet maturation and function, coagulation factor synthesis and activity, and blood viscosity, which may contribute to the pathogenesis of coagulopathies associated with thyroid illnesses. Many factors are responsible for maintaining the hemostatic balance and, among them, hormones directly influence both primary and secondary hemostasis. In particular, a bleeding tendency is often observed in hypothyroid patients. So, a prolongation of coagulation profiles means a decreased ability to stop bleeding and a tendency to bleed (12).

In Sudan, there is a paucity of data regarding the disorders of the coagulation system in people suffering from hypothyroidism. So, this study was undertaken to assess the coagulation system state during hypothyroidism.

Materials and Methods

The study was designed as a case-control hospital-based study and carried out at the National Cancer Institute – University of Gezira (NCI-UG), Wad Medani, Gezira State, Sudan during the period from January to October 2020. 50 Sudanese patients confirmed with hypothyroidism as cases (mean age 38.50 ± 10.46 years) the patient already diagnosed with hypothyroidism deepen on a normal range for TSH in most laboratories is (0.4 milliunits per liter (mU/L) to 4.0 mU/L) and 50 normal healthy individuals as control (mean age 35.52 ± 11.64 years) were participated in this study. Most of the cases were females (64%), 30% had family history of hypothyroidism. Mild cases account for 86% compared to 14% severe cases. Ethical approval was obtained from both the Research and Ethics Committees (REC) of the Ministry of Health, Gezira State and the Faculty of Medical Laboratory Sciences, University of Gezira, Sudan. Ethical permission was obtained from the National Cancer Institute—University of Gezira (NCI-UG). An informed consent form was signed by each participant.

After excluding the patient who is suffering from any disease that can affect coagulation profiles. A 2 mL venous blood sample was collected in a trisodium citrate container from each participant. Platelet poor plasma (PPP) was prepared by centrifugation of blood at 1200 – 2000 rpm for 15 minutes (13). Prothrombin Time (PT), International Normalized Ratio (INR), and Activated Partial Thrombin Time (PTT) were measured using a Coatron M4 coagulometer. The statistical package for social sciences (SPSS) computer programme (Version 21.0) was used to analyse the data.

Results

50 Sudanese patients confirmed with hypothyroidism as cases (mean age 38.50 ± 10.46 years) and 50 normal healthy individuals as control (mean age 35.52 ± 11.64 years) were participated in this study. Most of the cases were females (64%), 30% had family history of hypothyroidism. Mild cases account for 86% compared to 14% severe cases (Table 1).

Control (N = 50)	Cases (N = 50)	Factors
35.52 ± 11.64	38.50 ± 10.46	**Age (years)**
20 (40%)25 (50%)5 (10%)	18 (36%)25 (50%)7 (14%)	**Age group (years)**Less than 30 years30 – 50 yearsMore than 50 years
23 (46%)27 (56%)	18 (36%)32 (64%)	**Gender** Male Female
--	15 (30%)35 (70%)	**Family history** Yes No
--	43 (86%)7 (14%)	**Severity** Mild Severe

Table 1. *Demographic characteristics of study participants.*

The prolonged PTT account for 74% (Table 2).

Parameters	Normal	Prolonged
PT/ sec	33 (66%)	17 (34%)
INR	33 (66%)	17 (34%)
PTT/ sec	13 (26%)	37 (74%)

Table 2. *Frequency of coagulation profiles (PT, INR, and PTT) among cases.*

Parameters	Controls	Cases (N=50)	Mild (N=43)	Severe (N=7)	P value *	P value $

	(N=50)					
PT/ sec	15.03 ± 1.6	15.10 ± 1.8	15.1 ± 1.8	15.09 ± 2	0.85	0.98
INR	1.16 ± 0.2	1.14 ± 0.2	1.14 ± 0.2	1.14 ± 0.2	0.58	0.96
PTT/ sec	32.67 ± 5.9	42.29 ± 7.2	43.1 ± 4.4	37.28 ± 2.2	0.000	0.05

Table 3. *Comparison of coagulation profiles (PT, INR, and PTT) between control, case, mild and severe hypothyroidism*

*Case vs Control, $^{\$}$Mild VS Severe

The average PTT of cases (42.3±7.2sec) was higher than controls (32.67±5.9 sec) giving highly statistically significant differences (P value = 0.000) between them, there were significant differences in PTT between mild and severe hypothyroidism (P value = 0.0470) (Table 3).

Parameters	> 30 years (N=12)	30 – 50 years (N=25)	< 50 years (N=7)	P value *
PT/ sec	14.58 ± 1.64	15.29 ± 1.87	15.23 ± 2.40	0.823
INR	1.10 ± 0.14	1.16 ± 0.23	1.15 ± 0.20	0.821
PTT/ sec	43.00 ± 3.16	42.37 ± 7.28	41.46 ± 4.83	0.791

Table 4. *Comparison of coagulation profiles (PT, INR, and PTT) between age groups.*

There were no significant differences in PT, INR, and PTT between different age groups (P value = 0.823, 0.821, and 0.791 respectively) (Table 4).

Parameters	Males (N=9)	Females (N=41)	P value *
PT/ sec	15.01 ± 1.2	15.12 ± 1.9	0.856
INR	1.17 ± 0.2	1.13 ± 0.2	0.605
PTT/ sec	43± 5.4	42.13 ± 7.6	0.692

Table 5. *Comparison of coagulation profiles (PT, INR, and PTT) between gender.*

There were no significant differences in PT, INR, and PTT between different males and females (Table 5).

Parameters		TSH	T3	T4
PT/ sec	Correlation coefficient	0.005	- 0.039	- 0.060
	P value*	0.950	0.690	0.520
INR	Correlation coefficient	- 0.050	- 0.003	- 0.020
	P value*	0.590	0.960	0.870
PTT/ sec	Correlation coefficient	0.070	- 0.490	- 0.520
	P value*	0.048	0.000	0.000

Table 6. *Correlation between coagulation profiles (PT, INR, and PTT) and thyroid hormones.*

PTT had significant positive correlation within TSH (P value = 0.048; r = 0.070) and significant negative correlation within T3 (P value = 0.000; r = - 0.490) and T4 (P value = 0.020; r = - 520; P value = 000) (Table 6).

Discussion

Hypothyroidism is a clinical disorder that may occur as a result of primary gland failure or insufficient thyroid gland stimulation by the hypothalamus or pituitary gland, and can contribute to

hypertension, dyslipidemia, infertility, cognitive impairment, and affect all body metabolism. Autoimmune thyroid disease is the most common aetiology of hypothyroidism (14).

This study was a case-control study and was conducted at the National Cancer Institute, University of Gezira (NCI-UG) to study prothrombin time (PT), international normalised ratio (INR) and activated partial thromboplastin (PTT) among patients with hypothyroidism.

A total of 100 participants were included (50 normal participants as controls and 50 patients with hypothyroidism as cases). According to age group, the most common age range was 31–40 years old (36%). Hypothyroidism was more common among females (82%) than males (18%). Carle et al. (2006) reported that hypothyroidism was more common among females with a female/male incidence rate ratio of 5:3 and 7:3 for spontaneous hypothyroidism (Carle et al., 2006). Regarding family history of hypothyroidism, there were 15 (30%) participants who had family. Patients with severe hypothyroid were represented (14%) (TSH > 40 mu/L) in the study group compared to mild cases (86%) (TSH ≤ 40 mu/L) according to TSH results.

In this study, PTT levels among cases were significantly higher (43.08 ± 4.28 sec) than in the control group (32.67 ± 5.90 sec) (P. value 0.000). In contrast, PT and INR levels showed no significant difference between cases and the control group (15.0±1.6 sec) ((P. value 0.849 and 0.576 respectively). These findings disagree with previous case-control studies done in Sudan among hypothyroid patients were showed a significant decrease in PT and an insignificant change in PTT (15-17). Significant prolongation of PTT levels may be due to the effect of hypothyroidism on the activation and production of factor VIII and VWF (which is to act as a carrier for VIII).

The severity of hypothyroidism had no effect on coagulation parameters except PTT (P. value 0.047). Previous studies showed that patients with severe hypothyroidism displayed a bleeding tendency as reflected by higher levels of PTT, PT, and INR (18–19).

PTT results showed there was a significant negative correlation with TSH, T4, and T3 levels. PT and INR had an insignificant negative correlation with TSH, T4, and T3 levels.

Conclusion

The study concluded that PTT was significantly higher in patients with hypothyroidism when compared to controls. PTT results showed there was a significant negative correlation with T3 and T4 levels and a significant positive correlation with TSH levels. So, PTT should be included as a follow-up routine test for patients with hypothyroidism.

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