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Relationship between thyroid hormone levels in euthyroid patients before HSCT and time to achieve neutrophil and platelet engraftment: an analytical cross-sectional study

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Abstract

Introduction: The time to reach neutrophil (NE) and platelet engraftment (PE) in hematopoietic stem cell transplantation (HSCT) is one of the most important factors indicating transplantation survival. The aim of this study was to investigate the relationship between thyroid hormone levels before HSCT and the time to achieve NE and PE.

Material and methods: The relationship between thyroid hormone levels before HSCT, age, gender, type of HSCT, type of disease and cluster of differentiation 34+ (CD34+) cell count and the number of days to reach NE and PE was examined in 37 clinically and laboratorially euthyroid patients.

Results: An odds ratio (OR) of >6 was observed in the probability of time to NE >10 days in patients with thyroid-stimulating hormone (TSH) >2.89 mU/L in the upper normal range (UNR) and male patients, also in the probability of time to PE >15 days in patients with TSH >2.89 mU/L in the UNR. Statistically significant *p*-value and confidence interval were found in the probability of time to NE >10 days in male patients (OR = 8.58, *p*-value = 0.036) and time to PE >15 days in patients with TSH >2.89 mU/L in the UNR (OR = 14.32, *p*-value = 0.041).

Conclusions: Treatment with low dose levothyroxine can be cautiously recommended to achieve TSH to ≤2.8 mU/L in the lower normal range before performing HSCT in euthyroid patients, which will reduce the times to NE and PE and help earlier discharge of patients.

Key words: neutrophil engraftment, platelet engraftment, HSCT, thyroid function, TSH, free T4

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Introduction

The most common indications of allogeneic hematopoietic stem cell transplantation (HSCT) include bone marrow failure syndromes and leukemia and, in the case of autologous HSCT, multiple myeloma and relapsed/refractory lymphoma [1]. Autologous HSCT refers to the replacement of the hematopoietic system by the patient's hematopoietic stem cells, which is used to treat acquired bone marrow failure and blood malignancies. Allogeneic HSCT means

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the replacement of the hematopoietic system by another person's hematopoietic stem cells. The three sources of stem cells are bone marrow (BM), peripheral blood stem cells (PBSC), and cord blood (CB) [2]. Two important factors affecting engraftment are graft source and HSCT conditioning regimen [3].

The main goal for effective and long-term hematopoiesis is engraftment after HSCT, which is the most important criterion for long-term survival. Engraftment is the process by which HSCs in the BM find their way to proliferate and produce all hematopoietic subcellular cells [producing white blood cells (WBCs), red blood cells (RBCs), and platelets] and releasing them into the peripheral blood [4]. NE is equivalent to the first day of three consecutive days when neutrophil counts reach above 500 × 10^6/L absolute neutrophil count (ANC) and platelet engraftment (PE) is considered equivalent to the first day of three consecutive days when the platelet counts reach >20 × 10^9/L without platelet transfusion for seven consecutive days [5–7].

In a study by Ali et al. of 90 autografted patients, it was stated that the first day of reaching ANC 500 × 10^6/L could be considered equivalent to the definition of NE and it is not necessary to have neutrophils above 500 × 10^6/L for three consecutive days [8]. Rihn et al. [9], in support of Ali et al.'s [8] suggestion of changing the definition of myeloid engraftment, equated the first day of neutrophil count as engraftment in order to discontinue prophylactic antibiotics earlier. In a large study of 1,268 children with acute leukemia in remission, the results of single-unit CB transplantation engraftment with a myeloablative conditioning regimen showed an average NE time of 25 days (range 11–108) in children and 23 days (range 11–116) in adults [10]. The time to reach NE and PE in HSCT with a PBSC source was shorter than BM, which was longer for a CB source [11, 12].

Most complications after HSCT are related to the endocrine system, and total body irradiation (TBI) is mainly responsible for endocrinopathies after HSCT [1]. Thyroid dysfunction is one of the most well-known late-onset complications of allogeneic HSCT. Due to the importance of this issue, and the high probability of thyroid dysfunction occurring in the postoperative period, long-term follow-ups of thyroid tests as annual laboratory tests and thyroid examinations are recommended. The factors associated with an increased risk of hypothyroidism after HSCT are TBI, immunosuppression, and thyroid-specific autoantibodies. Hyperthyroidism is less prevalent than hypothyroidism after HSCT. Previous TBI, female gender, chronic graft-versus-host disease (GvHD), and age <20 years during HSCT increase the risk of secondary thyroid cancer [13]. Complications such as persistent low T3 syndrome, chronic thyroiditis, subclinical hypo- or hyperthyroidism, and thyroid carcinoma, with a prevalence of c.30%, can continue for years after HSCT (mostly allogeneic) [14].

In a 6-year retrospective cohort study of 108 patients with normal thyroid function tests (TFT) before HSCT, disrupted thyroid tests were observed in 29% of those who underwent TBI during the conditioning regimen (in 61% of patients in the first year after transplantation and in 20% of patients in the second year). In this study, female gender, allogeneic transplantation, and TBI-based conditioning regimen were associated with a higher risk of thyroid disorders [15]. Because thyroid dysfunction is much more likely to occur after HSCT, it is recommended to check thyroid tests before and after HSCT for early diagnosis and timely treatment [16–19].

The shorter time to reach neutrophil engraftment (NE) and PE in allogeneic non-myeloablative HSCT compared to any standard myeloablative conditioning was first demonstrated by Slavin et al. [20]. One of the known causes of delayed (i.e. about five weeks compared to three weeks) engraftment is ABO mismatched HSCT [21]. In their study, Davies et al. [22] showed the important role played by human leukocyte antigen (HLA) matching in accelerating engraftment time. Thyroid function remains almost intact in patients treated with conditioning alone, and the incidence of compensated hypothyroidism is higher in patients receiving single-dose TBI (30–60%) [23]. In a follow-up study 28 years after HSCT of 791 patients, hypothyroidism was the most common thyroid disorder [24]. Long-term monitoring of thyroid function tests is recommended in children and in adults who have undergone HSCT [24, 25].

The aim of this study was to investigate the relationship between thyroid hormone levels before HSCT and the time to achieve NE and PE.

Material and methods

This cross-sectional analytical study was performed on 37 transplanted patients in order to investigate the relationship between thyroid hormone levels before autologous and allogeneic HSCT and the time to reach NE and PE.

HSCT recipients were included in this study over one year from 10 June 2020 to 11 June 2021 in Shahid Ghazi Hospital in Tabriz, Iran. Blood sampling for thyroid function tests, including thyroid-stimulating hormone (TSH), free triiodothyronine (T3), and free thyroxine (T4), was performed by the enzyme-linked immunosorbent assay (ELISA) method three days before HSCT. The age range of patients was 20–64 years with a mean of 42.7 years which was within the normal distribution curve. None of the 37 HSCT recipients included in the study had overt thyroid dysfunction, including hypothyroidism or hyperthyroidism or euthyroid sick syndrome (ESS), nor had any history of thyroid medication use, and all had normal TSH (0.32–5.45 mU/L), T3 (1.4–4.2 pg/mL), and T4 (0.8–2 ng/dL) three days before HSCT. On physical examination, they were clinically euthyroid, and examination of the patients' thyroid tissue was

Table I. Hematopoietic stem cell transplantation (HSCT) recipients conditioning regimens detail based on underlying disease

HSCT type	Disease of recipients	Conditioning regimens
Autologous HSCT recipients	Multiple myeloma (MM)	Based on melphalan (average dose: 170 mg/daily/2 days)
	Hodgkin's disease (HD)	Etoposide (average dose: 500 mg), melphalan (average dose: 200 mg), lomustine (340 mg), and cytarabine (average dose: 500 mg)
	Non-Hodgkin lymphoma (NHL)	
	Wilms tumor	Carboplatin (450 mg/day), melphalan (150 mg/day) and VP-16 (300 mg/day)
Allogeneic recipients HSCT	Acute lymphoblastic leukemia (ALL)	Busulfan (average dose: 60 mg/QID/4 days) and cyclophosphamide (average dose: 4.5 g/daily/2 days)
	Acute myelogenous leukemia (AML)	
	Aplastic anemia (AA)	Anti-thymocyte globulin (ATG) (average dose: 175 mg/daily/3 days) and cyclophosphamide (average dose: 3.5 g/daily/dose)

QID – quarter in die

normal in size and consistency. All patients who underwent allogeneic transplantation were HLA matched because of having been transplanted from fully matched donors, and there was no ABO incompatibility in patients. The source of all allogeneic and autologous transplants in the studied patients was peripheral stem cells. None of the patients had radiation to the head and neck. In their past medical history (PMH), none of the patients had a history of autoimmune disease, and all had a negative anti-thyroid peroxidase (anti-TPO). None of the HSCT recipients had a TBI-based conditioning regimen. The recipients' conditioning regimens are set out in Table I.

The normal range of the TSH test was 0.32–5.45 mU/L with mean: 2.89 mU/L, of free T3: 1.4–4.2 pg/mL with mean: 2.8 pg/mL, and of free T4: 0.8–2 ng/dL with mean: 1.4 ng/dL based on ELISA. The CD34+ cell count of patients was in the range 0.42–9.2 × 10^6/kg. After HSCT, complete blood count (CBC)-H1 was checked daily, and after the first day of neutrophil counts that were above 500 × 10^6/L, if the neutrophil count remained above 500 × 10^6/L for three consecutive days, the first day of ANC 500 × 10^6/L was considered as NE, and PE was considered as the first day of three consecutive days when the platelet counts reached >20 × 10^9/L independence from platelet transfusion for at least seven days. The day of reaching NE was categorized as either less or more than 10 days, and the day of reaching PE was categorized as either less or more than 15 days. Also, the normal range of laboratory tests TSH (0.32–5.45 mU/L), free T3 (0.8–2 ng/dL), and free T4 (1.4–4.2 pg/mL) were categorized into two groups according to their mean value. The age of the patients was divided into two groups: 40 years and above and less than 40. Moreover, CD34+ cell count levels were categorized as ≤2 × 10^6/kg, 2–3 × 10^6/kg, and >3 × 10^6/kg.

Statistical analysis

Due to the normal distribution of data curves on reaching NE and PE, correlation analysis was performed using Pearson's chi-square test for the subgroup analysis and to test the differences in each of the mentioned nominal and string variables. Exact significance of two-sided p values was considered as $p \leq 0.05$.

To evaluate the relationship between thyroid function and the day of reaching NE and PE in connection with various clinical diseases, patients were evaluated in three categories: [leukemias including acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL); lymphomas including Hodgkin's disease (HD) and non-Hodgkin lymphoma (NHL); and multiple myeloma (MM)]. Aplastic anemia (AA) and solid tumor (Wilms tumor) were removed from the categories due to their small number (one patient each).

Moreover, univariate and multivariate regression analysis (simple and multiple logistic regression analyses) were performed for computing unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). In univariate analysis, each variable i.e. age, sex, TSH, free T3 and free T4, allogeneic or autologous HSCT type, various diseases of HSCT recipients, including solid tumor (Wilms tumor), NHL, MM, HD, AML, ALL and AA and CD34+ cell count of patients were all analyzed separately. The day of reaching NE and PE was considered the dependent variable. Adjusted ORs were obtained from multivariate statistical analysis of all variables, using the multiple linear regression model to reduce the confounding effect with a 95% CI. In multivariate analysis, a backward-elimination multiple logistic regression was performed to find the set of best predictors of NE and PE. SPSS software (IBM SPSS Statistics Version 26) was used for all statistical analysis.

Results

Descriptive results

Descriptive results related to 37 patients' data according to the classification of variables into nominal and string are shown in Tables II, III and IV. The range of time to reach NE varied between patients from 8–17 days, and to reach PE from 10–25 days. Mean days to reach NE and PE were 11.3 and 14.5 days, respectively. Mean thyroid function tests including TSH, free T4, and free T3 were 1.89 mU/L,

Table II. Descriptive results of variables

Parameter	N	Min–max	Median ± SD
NE [day]	37	8–17	11.3 ± 2.0
PE [day]	37	10–25	14.5 ± 3.3
TSH [mU/L]	37	0.2–4.2	1.89 ± 1.05
Free T4 [ng/dL]	37	0.7–2	1.15 ± 0.31
Free T3 [pg/mL]	37	1.2–4.2	2.53 ± 0.66
Age [years]	37	20–64	42.7 ± 10.98
CD34+ cell count [$\times 10^6$/kg]	37	0.42–9.2	2.9 ± 2.06
Valid N (listwise)	37		

N — number; min — minimum; max — maximum; SD — standard deviation; NE — neutrophil engraftment; PE — platelet engraftment; TSH — thyroid-stimulating hormone; T4 — thyroxine; T3 — triiodothyronine

Table III. Disease types in hematopoietic stem cell transplantation recipients

Type of disease	Frequency	Percent
AA	1	2.7
ALL	4	10.8
AML	3	8.1
HD	5	13.5
MM	15	40.5
NHL	8	21.6
Solid tumor	1	2.7
Total	37	100

AA — aplastic anemia; ALL — acute lymphoblastic leukemia; AML — acute myelogenous leukemia; HD — Hodgkin's disease; MM — multiple myeloma; NHL — non-Hodgkin lymphoma

1.15 ng/dL, and 2.53 pg/mL, respectively. The mean age of patients was 42.7 years. The mean CD34+ cell counts were 2.90 × 10^6/kg. According to the obtained results of standard deviation and mean of string variables such as days to NE, days to PE, TSH, free T4, and free T3 indicated normal data distribution, Pearson correlation analysis was performed (Table II).

37 patients with different diseases including 2.7% of patients (n = 1) AA, 10.8% (n = 4) ALL, 8.1% (n = 3) AML, 13.5% (n = 5) HD, 40.5% (n = 15) MM, 21.6% (n = 8) NHL, and 2.7% (n = 1) solid tumor (Wilms tumor) were included in the study (Table III).

AA and solid tumor patients were excluded from disease categorization due to there being only one AA patient and one solid tumor patient. Finally, the relationship between the time of NE and PE and thyroid hormone levels in three groups, including leukemia (AML and ALL) (20.0%), lymphomas (HD and NHL) (37.15%), and MM (42.9%), were analyzed. 54.1% (21) of patients were male and 45.9% (17) of patients were female. 21.6% (n = 8) of patients underwent allogeneic HSCT and 78.4% (n = 29) of patients underwent autologous HSCT (Table IV).

Table IV. Descriptive results of nominal variables

Variable	Validation	Type	Frequency	Percent
Sex	Valid	M	20	54.1
		F	17	45.9
		Total	37	100
HSCT type	Valid	Allogeneic	8	21.6
		Autologous	29	78.4
		Total	37	100
Disease	Valid	Leukemias	7	18.9
		Lymphomas	13	35.1
		MM	15	40.5
		Total	35	94.6
	Missing	System	2	5.4
	Total		37	100

HSCT — hematopoietic stem cell transplantation; M — male; F — female; M — multiple myeloma

Correlation analysis results

The results of the Pearson correlation test of nominal and string variables are shown in Table V. It should be noted that for string variables such as sex, HSCT type, disease type of HSCT recipients, and CD34+ cell count, a cross tab test and chi-square correlation, and for nominal variables such as days to reach NE, days to reach PE, TSH, free T4, free T3 and age, correlation, compare mean and a Pearson test were used.

Pearson correlation test showed that there was a very strong positive association between the mean days to reach NE (11.3 days) and the mean days to reach PE (14.5 days) (Pearson R: 0.808, p <0.001) and between the type of transplantation with the different diseases of transplant patients (Pearson R: 0.855, p <0.001). There was a moderately positive association between the mean days to reach NE (11.3 days) and the mean TSH level of patients (1.89 mU/L) (Pearson R: 0.445, p = 0.006). There was a weakly positive association between the type of transplantation and the mean age (42.7 years) of transplant patients (Pearson R: 0.349, p = 0.034). There was a moderately negative association between the CD34+ cell count and the mean age (42.7 years) of transplant patients (Pearson R: –0.413, p = 0.011). There was a weakly negative association between the mean TSH (1.89 mU/L) and the mean T4 level (1.15 ng/dL) of patients (Pearson R: –0.318, p = 0.055), and between the CD34+ cell count and the different diseases of transplant patients (Pearson R: –0.314, p = 0.058).

Table V. Results of Pearson correlation test for nominal and string variables

		Days to NE	Days to PE	TSH	Free T4	Free T3	Age	Sex	HSCT type	Disease	CD34+cell count
Days to NE	Pearson R*		0.808**	0.445**	–0.205	0.189	0.139	–0.303	0.001	–0.062	0.059
	Sig. (two-tailed)	–	< 0.001	0.006	0.223	0.264	0.411	0.068	0.996	0.717	0.729
Days to PE	Pearson R	0.808**	–	0.349**	–0.119	0.184	0.113	–0.099	–0.162	–0.293	0.149
	Sig. (two-tailed)	< 0.001	–	0.034	0.484	0.275	0.507	0.558	0.337	0.078	0.378
TSH	Pearson R	0.445**	0.349**	–	–0.318**	0.281	0.015	–0.163	0.236	0.294	0.015
	Sig. (two-tailed)	0.006	0.034	–	0.055	0.092	0.931	0.334	0.160	0.078	0.931
Free T4	Pearson R	–0.205	–0.119	–0.318**	–	0.142	0.108	0.137	0.113	0.097	–0.127
	Sig. (two-tailed)	0.223	0.484	0.055	–	0.403	0.525	0.417	0.507	0.567	0.453
Free T3	Pearson R	0.189	0.184	0.281	0.142	–	–0.132	0.099	–0.004	0.069	–0.090
	Sig. (two-tailed)	0.264	0.275	0.092	0.403	–	0.435	0.560	0.983	0.686	0.597
Age	Pearson R	0.139	0.113	0.015	0.108	–0.132	–	–0.105	0.349**	0.183	–0.413**
	Sig. (two-tailed)	0.411	0.507	0.931	0.525	0.435	–	0.537	0.034	0.279	0.011
Sex	Pearson R	–0.303	–0.099	–0.163	0.137	0.099	–0.105	–	–0.174	0.070	0.147
	Sig. (two-tailed)	0.068	0.558	0.334	0.417	0.560	0.537	–	0.302	0.681	0.387
HSCT type	Pearson R	0.001	–0.162	0.236	0.113	–0.004	0.349**	–0.174	–	0.855**	–0.314**
	Sig. (two-tailed)	0.996	0.337	0.160	0.507	0.983	0.034	0.302	–	<0.001	0.058
Disease	Pearson R	–0.062	–0.293	0.294	0.097	0.069	0.183	0.070	0.855**	–	–0.215
	Sig. (two-tailed)	0.717	0.078	0.078	0.568	0.686	0.279	0.681	<0.001	–	0.201
CD34+ cell count	Pearson R	0.059	0.149	0.015	–0.127	–0.090	–0.413**	0.147	–0.314**	–0.215	–
	Sig. (two-tailed)	o.729	0.378	0.931	0.453	0.597	0.011	0.387	0.058	0.201	–

*Correlation ratio; **correlation is significant at 0.05 level (two-tailed); NE – neutrophil engraftment; PE – platelet engraftment; TSH – thyroid stimulating hormone; T4 – thyroxine; T3 – triiodothyronine; HSCT – hematopoietic stem cell transplantation; Sig – significance

Regression analysis results

Adjusted and unadjusted results of the regression analysis of nominal and string variables are shown in Table VI in detail.

Unadjusted regression analysis results

The results of unadjusted OR calculation from univariate regression analysis showed male patients were 5.71 times more likely to achieve NE >10 days than female patients (OR = 5.71, 95% CI = 1.33, 24.62, *p*-value = 0.019) which were statistically significant at *p*-value and CI. Also, patients with TSH >2.89 mU/L were five times more likely to achieve PE >15 days (OR = 5, 95% CI = 0.82, 30.46, *p*-value = 0.081). PE >15 days was 4.11 times more likely to be achieved in patients with free T4 <1.4 ng/dL (OR = 4.11, 95% CI = 0.43, 39.48, *p*-value = 0.22). Patients with allogeneic HSCT were 3.17 times more likely to achieve PE >15 days than autologous HSCT (OR = 3.17, 95% CI = 0.62, 16.05, *p*-value = 0.164). Reaching PE >15 days was twice as likely in patients with leukemia as in patients with MM (OR = 2, 95% CI = 0.32, 12.33, *p*-value = 0.455). Moreover, patients with CD34+ cell count $\leq 2 \times 10^6$/kg were twice as likely to achieve NE >10 days than patients with a higher CD34+ cell count (OR: 2.06, 95% CI = 0.43, 9.8, *p*-value = 0.363) (Table VI).

Adjusted regression analysis results

According to the results of adjusted OR calculation obtained from multivariate regression analysis, the probability of

Table VI. Regression analysis results (adjusted and unadjusted) in detail

N [%]			Days to NE							Days to PE						
			N [%] ≤ 10 days 14 (37.8%)							N [%] ≤ 15 days 22 (59.45%)						
			N [%] > 10 days 23 (62.2%)							N [%] > 15 days 15 (40.55%)						
			Unadjusted				Adjusted			Unadjusted				Adjusted		
			OR	95% CI	p-value	Constant p-value	OR	95% CI	p-value	OR	95% CI	p-value	Constant p-value	OR	95% CI	p-value
TSH	≤2.89 mU/L	30 (81.08%)	Reference							Reference						
	>2.89 mU/L	7 (18.92%)	1.67	0.28, 10.03	0.577	0.277	6.44	0.25, 67.47	0.262	5	0.82, 30.46	0.081	0.074	14.32	1.88, 33.11	0.041
Free T4	≤1.4 ng/dL	31 (83.78%)	1.82	0.31, 10.58	0.506	1	1.26	0.12, 13.45	0.846	4.12	0.43, 39.48	0.22	0.142	3.61	0.15, 34.47	0.432
	>1.4 ng/dL	6 (16.22%)	Reference							Reference						
Free T3	≤2.8 pg/mL	29 (78.38%)	0.98	0.2, 4.94	0.982	0.484	0.63	0.09, 4.69	0.653	0.32	0.06, 1.6	0.164	0.484	0.19	0.02, 1.64	0.132
	>2.8 pg/mL	8 (21.62%)	Reference							Reference						
Age	>40 years	22 (59.46%)	1.17	0.3, 4.49	0.823	0.442	1.46	0.2, 10.73	0.708	1.04	0.27, 3.96	0.956	0.442	2.2	0.21, 22.66	0.506
	≤40 years	15 (40.54%)	Reference							Reference						
Sex	Male	20 (54.05%)	5.71	1.33, 24.62	0.019	0.469	8.58	1.15, 64.13	0.036	1.5	0.4, 5.66	0.55	0.232	1.04	0.17, 6.47	0.965
	Female	17 (45.95%)	Reference							Reference						
HSCT type	Allogeneic	8 (21.62%)	1.02	0.2, 5.13	0.982	0.198	3.3	0.21, 50.95	0.39	3.17	0.63, 16.05	0.164	0.1	5.67	0.38, 84.53	0.208
	Autologous	29 (78.38%)	Reference							Reference						
Disease	Leukemia	7 (20.0%)	0.9	0.14, 5.48	0.899					2	0.32, 12.33	0.455				
	Lymphoma	13 (37.15%)	1.5	0.31, 7.19	0.612	0.442	4.43	0.37, 52.87	0.24	0.67	0.14, 3.19	0.612	0.442	1.02	0.12, 8.65	0.99
	MM	15 (42.9%)	Reference							Reference						
CD34+ cell count	≤2 × 10^6/kg	15 (40.5%)	2.06	0.43, 9.8	0.363		1.44	0.18, 11.82	0.735	0.67	0.15, 3.01	0.598		0.57	0.07, 4.5	0.59
	2–3 × 10^6/kg	8 (21.6%)	0.75	0.13, 4.29	0.746	0.594	0.22	0.01, 4.65	0.328	1.33	0.23, 7.63	0.746	0.594	0.66	0.04, 12.67	0.784
	>3 × 10^6/kg	14 (37.8%)	Reference							Reference						
Constant						0.23			0.456				0.28			0.583

NE — neutrophil engraftment; PE — platelet engraftment; N — number; OR — odds ratio; CI — confidence interval; TSH — thyroid stimulating hormone; T4 — thyroxine; T3 — triiodothyronine; HSCT — hematopoietic stem cell transplantation; MM — multiple myeloma

reaching NE >10 days was 6.44 times higher in patients with TSH >2.89 mU/L (OR = 6.44, 95% CI = 0.25, 67.47, *p*-value = 0.262). Male patients were 8.58 times more likely to achieve NE >10 days than female patients (OR = 8.58, 95% CI = 1.15, 64.13, *p*-value = 0.036) which had statistically significant *p*-value and CI. Patients with allogeneic HSCT were 3.3 times more likely to achieve NE >10 days than autologous HSCT (OR = 3.3, 95% CI = = 0.21, 50.95, *p*-value = 0.390). Patients with lymphoma were 4.43 times more likely to achieve NE >10 days than MM (OR: 4.43, 95% CI = 0.37, 52.87, *p*-value = 0.240). Moreover, patients with a CD34+ cell count ≤2 × 10^6/kg were 1.44 times more likely to achieve NE >10 days than patients with a higher CD34+ cell count (OR: 1.44, 95% CI = 0.18, 11.82, *p*-value = 0.735).

Patients with TSH >2.89 mU/L were 14.32 times more likely to achieve PE in >15 days, which was statistically significant at p-value and CI (OR = 14.32, 95% CI = 1.88, 33.11, *p*-value = 0.041). Patients with free T4 <1.4 ng/dL were 3.61 times more likely to achieve PE >15 days (OR = = 3.61, 95% CI = 0.15, 34.47, *p*-value = 0.432). Patients with allogeneic HSCT were 5.67 times more likely to achieve PE >15 days than patients with autologous HSCT (OR = 5.67, 95% CI = 0.38, 84.53, *p*-value = 0.208).

The above results indicate the important effects of thyroid function, sex, the type of transplant, and the type of underlying disease on the time to reach NE and PE.

Furthermore, additional backward-elimination multiple logistic regression showed that disease type (OR = 2.14, 95% CI = 0.43, 10.73, *p*-value = 0.354) and gender (OR = 5.53, 95% CI = 1.18, 25.95, *p*-value = 0.030) were the best predictors of reaching NE, while the best predictors of reaching PE were TSH level (OR = 10.70, 95% CI = 1.02, 52.34, *p*-value = 0.048) and T3 level (OR = 0.20, 95% CI = 0.03, 1.38, *p*-value = 0.102).

Discussion

To date, no study has been performed to investigate the relationship between a particular range of normal thyroid function tests before HSCT and the time to reach NE and PE. Most of the available studies have been into the diagnosis of thyroid disease in the form of a long follow-up after HSCT. Showing that delayed NE and PE engraftment causes longer hospital stays, prolonged prophylactic antibiotics, and delayed discharges, makes clear the importance of achieving a shorter time to achieve NE and PE. The high prevalence of post-transplant thyroid complications suggests that early detection of these disorders based on risk factors before doing HSCT can greatly contribute to the quality of life of transplanted recipients [14, 26].

The National Guidelines for Hematopoietic Stem Cell Transplantation 2020 recommend annual checks for thyroid-stimulating hormone (TSH and T4) and thyroid-specific antibodies (anti-TPO) after HSCT [27]. In a 3-year follow-up of a cohort study of 41 patients undergoing autologous or allogeneic HSCT without irradiation, thyroid dysfunction was observed in 65.8% of patients, with subclinical hypothyroidism being the predominant type of thyroid disorder. High TSH with p <0.01 was also present in patients undergoing chemotherapy due to the underlying disease, and the study emphasized the importance of long-term follow-ups of thyroid tests after HSCT without considering the use or non-use of irradiation [28].

In our cross-sectional study with a small number of patients, patients with TSH <2.89 mU/L, female patients, and autologous transplantation patients achieved NE <10 days. Also, patients with TSH <2.89 mU/L, free T4 >1.4 ng/dL, age <40 years and autologous transplantation achieved PE <15 days. A moderately positive association was obtained by Pearson correlation test between the mean days to reach NE (11.3 days) and the mean TSH level of patients (1.89 mU/L) (Pearson R: 0.445, p = 0.006). This confirms that NE <10 days is reached in transplanted patients with TSH <1.89 mU/L.

Considering the results of the studies mentioned above regarding the high prevalence of hypothyroidism after HSCT and the need for replacement therapy with levothyroxine, along with the results of our study on prolonged NE and PE in patients with TSH >2.89 mU/L and free T4 <1.4 ng/dL, we suggest that the appropriate laboratory range of thyroid function before HSCT should be considered to be TSH <2.89 mU/L in LNR to reach NE <10 days, and free T4 >1.4 ng/dL in UNR to reach PE in less than 15 days.

Further clinical trials with low-dose levothyroxine are recommended before HSCT for euthyroid patients with TSH >2.89 mU/L in the UNR (especially in male patients, allogeneic transplantation recipients and lymphomas) and free T4 <1.4 ng/dL in the LNR compared to the control group to evaluate reducing the number of days to reach NE and PE. Also, future studies will determine whether there is an association between patients with normal upper TSH (>2.89 mU/L) and delayed NE and PE with a higher incidence of thyroid endocrinopathy in the post-transplant period.

Conclusions

Our cross-sectional study demonstrated NE >10 days in male patients, patients with lymphoma, and allogeneic HSCT recipients, and PE >15 days in allogeneic HSCT recipients. Also, our study findings based on NE >10 days in patients with TSH >2.89 mU/L and PE >15 days in patients with TSH >2.89 mU/L and free T4 <1.4 ng/dL show a significant relationship between the thyroid hormone levels of euthyroid patients and the number of days taken to reach NE and PE.

Authors' contributions

STT, NG contributed to design of study. STT and RD contributed to data collection and analysis. STT and NG drafted manuscript. All authors contributed to reading and approving final manuscript. RD analyzed data and interpreted it. All authors shared in writing manuscript and approving final version supervised by STT.

Conflicts of interest

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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