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Original Research

Changes in thyroid function parameters 3 months after allogeneic and autologous hematopoietic stem cell transplantation in children

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Abstract

Background: Thyroid dysfunction (hypo- and hyperthyroidism) has been reported as a late effect after hematopoietic stem cell transplantation (HSCT) in children. Short-term effects of HSCT on thyroid function parameters are, however, unclear.

Methods: We prospectively evaluated thyroid function parameters before and 3 months after HSCT in all children (<21 years) who underwent HSCT during a 2-year period in the Princess Máxima Center, the Netherlands.

Results: Among 72 children, none had thyroidal hypothyroidism or hyperthyroidism 3 months after HSCT. Changes in thyroid function parameters (either aberrant thyroid-stimulating hormone [TSH] or free thyroxine [FT4] concentrations) were found in 16% before and in 10% 3 months after HSCT. Reverse triiodothyronine (rT3) was found elevated in 9.3% before and in 37% 3 months after HSCT, which could be related to poor physical condition. An individual decline in FT4 concentration of ≥20% was found in 10.5% (6/57) 3 months after HSCT.

Conclusion: In conclusion, thyroidal hypo- and hyperthyroidism are very rare 3 months after HSCT. These results indicate that surveillance for hypo- and hyperthyroidism may start later in time. The changes in thyroid function parameters found 3 months after HSCT might reflect euthyroid sick syndrome.

Keywords: hematopoietic stem cell transplantation, thyroid dysfunction, pediatrics

Significance

Thyroid function parameters were evaluated after the first 3 months following hematopoietic stem cell transplantation (HSCT). No clinically relevant hypo- or hyperthyroidism was found after 3 months requiring intervention. These results are reassuring and may imply that surveillance for hypo- and hyperthyroidism may be unnecessary shortly after HSCT. The changes in thyroid function parameters found 3 months after HSCT may reflect the presence of euthyroid sick syndrome (ESS) and poor physical condition.

Introduction

Hematopoietic stem cell transplantation (HSCT) has become an important treatment modality to improve the prognosis for several benign and malignant childhood diseases.[1] Adverse effects of HSCT, however, have been described on the endocrine system, including thyroid dysfunction.[1,2]

Thyroid hormones are essential during childhood.[3,4] Hypothyroidism may result in fatigue, declining growth, mental retardation in the young, and constipation, and it has cardiovascular consequences.[5] Hyperthyroidism may cause tachycardia, growth acceleration, fatigue, diarrhea, and emotional imbalances.[6]

Hypo- and hyperthyroidism have been reported to occur as adverse late effects of childhood cancer treatment, as well as following HSCT,[6] especially after treatment with busulfan or melphalan[7,8] and radiotherapy[9] or due to autoimmune

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disease following allogeneic HSCT.[10] Signs and symptoms of thyroid dysfunction can be overlooked in children; therefore, surveillance for thyroid function is advocated after cancer treatment and HSCT. In this regard, not only thyroid function parameters outside the reference ranges may be of clinical importance, but, as was shown in childhood cancer survivors following cranial irradiation, a decline in free thyroxine (FT4) concentration of >20% can be clinically relevant,[11,12] even when FT4 is still within normal reference ranges.

Previous studies showed a prevalence of hypothyroidism after HSCT ranging from 10.0%-22.3%, occurring after a median of 1.8-5.3 years,[8,13-15] with increased risk after total body irradiation (TBI) as conditioning and younger age at the time of HSCT.[9] The prevalence of hypo- or hyperthyroidism was reported in 12.6%, 22.5%, and 34.0% at 5, 10, and 15 years post-HSCT, respectively.[13] The minimum time between HSCT and the occurrence of hypo- or hyperthyroidism is uncertain. Some studies already reported thyroid dysfunction 4 months after HSCT.[10,16] Currently, there is no agreement on the timing of surveillance of thyroid dysfunction after HSCT, as screening has been advised starting from 3 months to 1 year after HSCT.[8,17-19]

In children undergoing HSCT, thyroid hormone metabolism may also change due to supportive care drugs (eg, decrease in thyroid-stimulating hormone [TSH] concentration due to corticosteroids) or as a consequence of an adaptation mechanism of the body to severe illness, called the "euthyroid sick syndrome" (ESS).[20] In this situation, secretion of other pituitary hormones may also be distorted such as gonadotropins (leading to amenorrhea) and growth hormones (GH) (leading to low insulin-like growth factor [IGF-1] concentrations).[21] In ESS, changes in thyrotropin-releasing hormone (TRH) metabolism and deiodinase activity[22,23] result in low–normal TSH and low FT4 and free triiodothyronine (FT3) with increased reverse triiodothyronine (rT3) concentration. Euthyroid sick syndrome is considered to be a physiological adaptation mechanism that does not require thyroxine treatment.[24] It may be hypothesized that having aberrant thyroid function parameters for a prolonged time during recovery from HSCT in childhood has clinical consequences.

As euthyroidism is important for optimal recovery after HSCT, we first questioned whether thyroid dysfunction occurs shortly after HSCT. Second, we questioned whether thyroid function parameters are aberrant 3 months after HSCT and, if so, their relation to clinical well-being and whether such changes have clinical relevance. These questions prompted us to perform a prospective study evaluating thyroid function parameters before and 3 months after HSCT in children.

Methods

Patients

During a 2-year period (January 2020 to April 2022), thyroid function parameters in all children (<21 years) who underwent HSCT (allogeneic or autologous) in the Princess Máxima Center for Pediatric Oncology were measured before and 3 months after HSCT. Children known with previous thyroid disease, Down syndrome, a thyroid cancer predisposition syndrome, a history of neck irradiation, and meta-iodobenzylguanidine (MIBG) treatment and children with a brain tumor in the hypothalamic–pituitary (HP) region were excluded from this study. In total, 76 children were assessed for eligibility; 2 children were excluded, and 2 children did not consent to the study (Figure 1). Informed consent was obtained from 72 children (97% of eligible children).

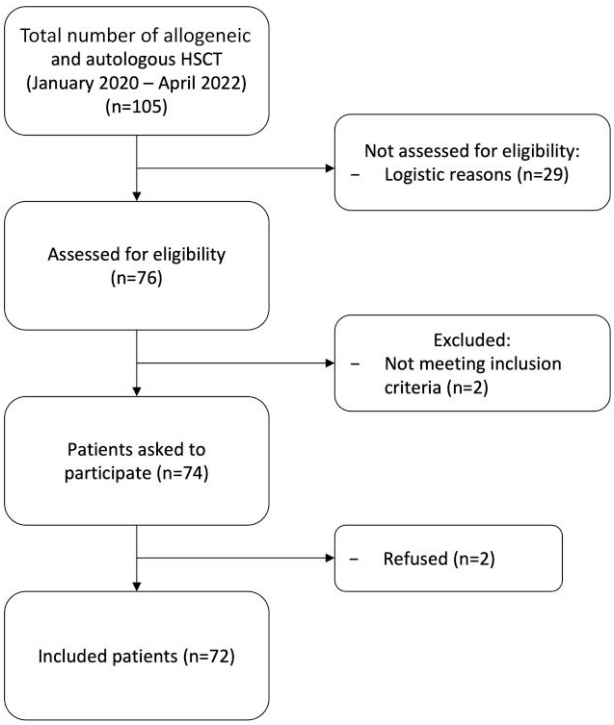

Figure 1. Flowchart included children (THYRO-Dynamics study).

Ethics

The research protocol was approved by the medical ethics committee of the Princess Máxima Center (NedMec, NL69960.041.19) and conducted in accordance with the principles of the Declaration of Helsinki. For ethical reasons, blood samples for the study were only taken if simultaneous sampling for clinical reasons was necessary. Informed consent was obtained from all children and/or their parents and/or legal representatives.

Data collection

Thyroid function parameters TSH, FT4, rT3, and IGF-1 and anti-thyreoperoxidase (anti-TPO) concentrations were measured before HSCT (−100-0 days before HSCT) and at 3 months after HSCT (60-160 days after HSCT). The results of the laboratory investigations were interpreted by the treating physician. As this was a descriptive study, no interventions were done. However, in case of aberrant thyroid function tests requiring further evaluation or intervention (FT4 concentrations below the reference range or TSH values > 10 mU/L), children were referred to the pediatric endocrinologist.

Clinical data on anthropometrics (height, weight, and body mass index [BMI]) and general well-being (body temperature, vomiting, nutritional status, and overall physical condition) were abstracted from children's electronic medical records on the day of blood sampling. Physical condition was categorized into "good" (no complaints), "medium" (moderate complaints, "not feeling well" or "feeling tired"), or "poor" (severe complaints or "feeling ill"), as noted by the health care provider/nurse.

Laboratory assays

A description of the laboratory assays is shown in Appendix S1. Reference values are shown in Table 1.

Definitions and statistics

Thyroidal hypothyroidism was defined as TSH concentration > reference interval (5.0 mU/L) at diagnosis or 3 months after diagnosis. The severity of thyroidal hypothyroidism was defined as mild (TSH > 5 mU/L, FT4 within the reference range), moderate (TSH > 10 mU/L, FT4 within reference ranges), or severe (TSH > 10 mU/L, FT4 < reference range). Thyroidal hyperthyroidism was defined as suppressed TSH in combination with FT4 within the reference range (mild) or suppressed TSH in combination with FT4 above the reference range (severe). Hypothalamic–pituitary hypothyroidism (central hypothyroidism) was defined as non-elevated TSH concentration in combination with FT4 concentration below the reference range and non-elevated rT3. Euthyroid sick syndrome was defined as FT4 concentration < reference range in combination with elevated rT3 concentration. The severity of ESS was defined as mild (FT4 9-10 pmol/L), moderate (FT4 7-9 pmol/L), or severe (FT4 < 7 pmol/L).

Data are presented as mean ± SD or median (range) for continuous data, depending on the distribution. Data are presented as percentages for categorical variables. Differences between groups were examined by unpaired Student's *t*-tests for normally distributed continuous data and Mann–Whitney *U* tests for continuous data with a skewed distribution. For categorical data, χ^2 tests or Fisher's exact tests (if the assumptions for χ^2 were violated) were used. Between time points, differences were evaluated by paired Student's *t*-tests for continuous data with a normal distribution and Wilcoxon matched-pair signed rank tests for continuous data with a skewed distribution. To assess violation of normality distribution, QQ plots of the residuals and Shapiro–Wilk's tests were used. For analysis of changes in thyroid hormone concentrations, only paired blood samples were used. The Pearson correlation coefficient was calculated to measure the strength of a linear association between 2 continuous variables. Analyses were performed by using SPSS version 27.0. *P*-values of <.05 were considered statistically significant.

Results

Patient characteristics

Among 72 included children, 42 (58%) were diagnosed with leukemia (Table 2). Sixty-eight (94%) children underwent allogeneic HSCT, and 5 had already undergone ≥1 previous HSCT. The median age at HSCT was 10.2 years (0.2-20.4 years), and 60% were male. Three children (4.2%) were deceased within 3 months after HSCT.

Thyroid function parameters

Hypo- and hyperthyroidism

In Table 1, median plasma concentrations of thyroid function parameters are shown.

Before HSCT, TSH and FT4 were both measured in $n = 68$ children. Of these, 84% (64/68) had both the TSH and FT4 concentrations within reference ranges. One child (1/68; 1.5%) had mild thyroidal hypothyroidism before HSCT. None were found to have hyperthyroidism before HSCT.

Table 1. Median plasma concentration of thyroid function parameters measured before HSCT and 3 months after HSCT.

Thyroid function parameters	Before HSCT Concentration mIU/L Median (range) (# samples)	3 months after HSCT Concentration mIU/L Median (range) (# samples)	*P*-value
TSH (0.30-5.00 mIU/L)	2.20 (0.44-5.20) ($n = 68$)	2.50 (0.49-5.80) ($n = 60$)	.206
FT4 (10-22 pmol/L)[a]	15 (9-20) ($n = 69$)	15 (8-24) ($n = 59$)	.143
rT3 (0.098-0.218 ng/mL)	0.15 (0.08-1.65) ($n = 44$)	0.20 (0.11-0.40) ($n = 39$)	.012
IGF-1 (nmol/L, age and sex specific)	22.50 (2.30-53.60) ($n = 66$)	21.80 (2.30-74.20) ($n = 60$)	.119
IGF-1 SDS[b]	0.06 (−2.22-2.41) ($n = 62$)	0.03 (−2.47-3.03) ($n = 53$)	.196

P-value: for analysis of changes in thyroid hormone concentrations, only paired blood samples (diagnosis and 3 months after diagnosis) were used (TSH: $n = 58$; FT4: $n = 57$; rT3: $n = 24$; IGF-1: $n = 55$; IGF-1 SDS: $n = 48$). Abbreviations: FT4, free thyroxine; HSCT, hematopoietic stem cell transplantation; IGF-1, insulin-like growth factor; rT3, reverse triiodothyronine; TSH, thyroid-stimulating hormone. [a]Dependent on age: 20 days-3 years: 12-21 pmol/L; 3-5 years: 10-19 pmol/L; 5-19 years: 11-20 pmol/L; >19 years: 10-22 pmol/L. [b]IGF-1 SDS of children <6 months of age are not presented on the electronic patient chart; data could not automatically be retrieved.

Table 2. Baseline characteristics of 72 children undergoing HSCT.

Baseline characteristics	
Age at HSCT (years) (median, range)	10.2 (0.2-20.4)
Male/female (%)	43/29 (60/40)
Diagnosis	
Leukemia	42 (58%)
ALL	21 (29%)
AML	16 (22%)
CML	2 (2.8%)
Other[a]	3 (4.2%)
Myelodysplastic syndrome	6 (8.3%)
Lymphoma	4 (5.6%)
Severe aplastic anemia	4 (5.6%)
Fanconi anemia	5 (6.9%)
Hurler syndrome	5 (6.9%)
Other[b]	6 (8.3%)
Type of stem cell transplantation	
Autologous	4 (5.6%)
Allogeneic	68 (94%)
TBI (conditioning regimen)	22/72 (31%)
Mean BMI SDS (±SD)	
Before HSCT	0.52 (1.37)
3 months after HSCT	0.21 (1.41)

Abbreviations: HSCT, hematopoietic stem cell transplantation; ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; TBI, total body irradiation; BMI, body mass index. [a]Including juvenile myelomonocytic leukemia and acute bilineage leukemia. [b]Including Wolman disease, juvenile dermatomyositis, teratoid rhabdoid tumor, Diamond–Blackfan anemia, medulloblastoma, and Ewing sarcoma.

Three (4.4%; 3/68) showed decreased FT4 concentrations (9, 10, and 11 pmol/L) with non-elevated TSH concentrations.

Reverse T3 in combination with TSH and FT4 had been measured in 43 children before HSCT. In 2 out of 43 children

(2.8%), FT4 was below reference ranges with non-elevated TSH and non-elevated rT3; they were considered to have central hypothyroidism (diagnoses: acute lymphatic leukemia [ALL] [$n = 1$], acute myeloid leukemia [AML] [$n = 1$]). In 1 patient with decreased FT4 and non-elevated TSH concentrations, rT3 was not measured.

All values were discussed with the pediatric endocrinology department. None of the children were started on thyroid hormones.

Three months after HSCT, TSH and FT4 combined were measured in 59 children. The TSH and FT4 concentrations within reference ranges were found in 90% (53/59) of children. None had thyroidal hypo- or hyperthyroidism. Two (3.4%; 2/59) children (with normal FT4 before HSCT) showed decreased FT4 concentrations (10 and 8 pmol/L) with non-elevated TSH concentrations. Four children (6.8%; 4/59) showed elevated FT4 concentrations (median 23 pmol/L, range 21-24 pmol/L) with TSH concentrations within the reference range.

Euthyroid sick syndrome

The prevalence of ESS was determined in children in whom simultaneous measurements of TSH, FT4, and rT3 were available. Before HSCT, no ESS was found in 43 children in whom these measurements were available. Three months after HSCT, in 1 of 38 children in whom FT4, TSH, and rT3 had been measured simultaneously (2.6%; 1/38), (moderate) ESS was found.

Overall, 3 months after HSCT, the median concentration of rT3 significantly increased (0.15 ng/mL [0.08-1.65] to 0.20 ng/mL [0.11-0.40]; $P = .012$) (Table 1). No significant correlation was found between the FT4 and rT3 concentrations before or 3 months after HSCT (before HSCT: $r = 0.16$, 95% CI −0.95-0.97; after HSCT: $r = 0.30$, 95% CI −0.95-0.97). However, a significant negative correlation was found between TSH and rT3 ($r = -0.37$, 95% CI −0.61-−0.06) 3 months after HSCT. Additionally, no significant correlation was found between age at HSCT and FT4 or rT3 concentrations 3 months after HSCT.

An isolated rT3 elevation (with no decrease in FT4 and non-elevated TSH) was found in 9.3% (4/43) and 37% (14/38) of the children before and 3 months after HSCT, respectively. Children with isolated elevated rT3 concentrations 3 months after HSCT showed a median increase of FT4 in this period of +27% compared to +5.9% in others ($P = .077$). No other differences were found between children with elevated rT3 levels 3 months after HSCT compared to those without underlying disease or any administered chemotherapy groups, corticosteroids (Table 3), or BMI (Table 1).

Dynamics of thyroid function parameters

Overall, no significant differences were found in median FT4, TSH, or IGF-1 concentrations 3 months after HSCT when compared to before HSCT (Table 1). No correlation between IGF-1 standard deviation score (SDS) and rT3 concentrations was found 3 months after HSCT ($r = 0.13$, 95% CI 0.22-0.44).

A paired TSH and FT4 measurement was available for 57 children. The median difference in FT4 concentration between the 2 time points was +5.0%. A decline in FT4 3 months after HSCT of 10%, 20%, and 30% was found in 30% (17/57), 11% (6/57), and 3.5% (2/57) of children, respectively.

Table 3. Overview of groups of chemotherapeutic agents and corticosteroids administered in children undergoing HSCT.

Chemotherapy groups	Thyroid hormone measurement before HSCT $n = 68$		Thyroid hormone measurement +3 months after HSCT $n = 59$	
	Cumulative *n* (%)	<7 days *n* (%)	Cumulative *n* (%)	<7 days *n* (%)
Alkylating agents	29 (43)	0 (0)	57 (97)	0 (0)
Busulfan	3 (4.4)	0 (0)	21 (37)	0 (0)
Melphalan	0 (0)	0 (0)	3 (5.3)	0 (0)
Antimetabolites	47 (69)	1 (1.5)	57 (97)	0 (0)
Anthracyclines/ antineoplastic antibiotics	35 (52)	0 (0)	28 (48)	0 (0)
Asparaginase	22 (32)	0 (0)	19 (33)	0 (0)
Platinum agents	2 (2.9)	0 (0)	1 (1.7)	0 (0)
Protein kinase inhibitors	10 (15)	8 (12)	5 (8.5)	2 (3.4)
Topoisomerase inhibitors	30 (44)	0 (0)	33 (56)	0 (0)
Vinca alkaloids	26 (38)	1 (1.5)	21 (36)	0 (0)
Immunotherapy	19 (28)	2 (2.9)	22 (37)	1 (1.7)
CAR-T cell infusion	11 (16)	0 (0)	11 (19.3)	NA
Corticosteroids[a]	**<48 h *n* (%)**		**<48 h *n* (%)**	
	1 (1.5)		17 (29)	

Chemotherapeutic agents or corticosteroids (Appendix S2) administered prior to transplant and at the first measurement as well as at the second measurement 3 months after HSCT (the latter including the conditioning regimen). Abbreviations: HSCT, hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor (CAR) T cell therapy; NA, not applicable.
[a]Including corticosteroids used as graft versus host disease (GVHD) prophylaxis, anti-inflammatory drugs, or anti-emetic drugs.

Anti-TPO concentrations

Anti-TPO was measured in 59 children pre-transplant. Two children (3.4%) had elevated anti-TPO concentrations before HSCT compared to none of the children after HSCT. One of the 2 children with elevated pre-transplant anti-TPO concentrations had a decreased FT4 concentration after 3 months with a normal TSH concentration.

Chemotherapy, corticosteroids, and TBI

Table 3 provides an overview of the groups of chemotherapy that had been administered to the children in whom thyroid hormones were measured. Three months after HSCT, 21 (37%) and 3 (5.3%) children had received busulfan or melphalan, respectively. Corticosteroids had been administered to 1 child <48 h before the first thyroid hormone measurement, while 3 months after HSCT, 17/59 (29%) children had received corticosteroids <48 h. In these 17 children, FT4 concentrations were higher ($P < .001$) and TSH concentrations were lower ($P < .001$) compared to those not receiving corticosteroids <48 h before thyroid hormone measurement. Reverse T3 concentrations did not differ between the 2 groups. Total body irradiation (12 Gy) had been part of the conditioning regimen in 31% of the children. The FT4, TSH, and rT3 concentrations of these irradiated children were comparable with non-irradiated children 3 months after HSCT.

General well-being and anthropometrics

Before HSCT, 15%, 16%, and 13% of the children reported symptoms of pain, symptoms of nausea/vomiting, and the presence of fever on the day of blood sampling, respectively. Physical condition was scored as "medium" in 35% of the children and "poor" in 1 child. Three months after HSCT, symptoms of nausea/vomiting, pain, and fever were reported in 24%, 25%, and 3.5%, respectively. Physical condition "medium" and "poor" were scored in 49% and 1.7% of the children 3 months after HSCT. Children with elevated rT3 concentrations 3 months after HSCT scored significantly more often "medium" or "poor" on physical condition compared to those without elevated rT3 concentrations (11/14 [79%] vs 10/24 [42%] [$P = .043$]). The mean BMI SDS before HSCT was 0.52 ± 1.37 (which significantly decreased to 0.21 ± 1.41) ($P = .004$). No correlation was found between BMI SDS and TSH, FT4, or rT3 at both time points.

Discussion

This prospective study of a 2-year cohort of children treated with HSCT in the Princess Máxima Center enabled us to evaluate thyroid function parameters after the first 3 months following HSCT. We did not find any clinically relevant hypo- or hyperthyroidism after 3 months requiring intervention. These results are reassuring and may imply that surveillance for hypo- and hyperthyroidism may be unnecessary shortly after HSCT. However, we did find an individual decline in FT4 of ≥20% after 3 months in 11% of the children. The period of time of this FT4 decline or whether such a severe FT4 decline has clinical consequences on growth, bone health, or muscle development in these children is uncertain and may be studied in future cohorts with longer follow-up time. Due to the fact that the decline in FT4 must be considered adaptive, we do not recommend treatment of this decline with levothyroxine.

Baseline assessment of thyroid function pre-transplant is the standard of care, which is of relevance, considering the importance of having adequate thyroid function during HSCT, and enables assessing changes in the thyroid function during follow-up. The results of our study illustrate that thyroid function tests after 3 months may not be necessary. The baseline thyroid function tests should, in our opinion, remain the standard of care.

The high percentage of children developing elevated rT3 concentrations in combination with the significant negative correlation between TSH and rT3 3 months after HSCT underlines the possible presence of ESS in this group.[25] The presence of ESS can be expected in light of the intensive treatment that these children have undergone and in the setting of immune dysregulation with an inflammatory milieu that may impair organ function and tissue damage with, among others, mucositis and feeding problems. In line with this, we found that elevated rT3 concentrations were associated with "medium and poor" physical condition.

Our results illustrate that the determination of rT3 in these situations, as mentioned above, may serve as an objective marker of physical condition. Furthermore, the determination of rT3 may be helpful in clinical care when thyroid function tests suggest central hypothyroidism with low FT4 and non-elevated TSH concentrations. In such situations, rT3 will be normal–low in case of central hypothyroidism but will be elevated in case of ESS. In case of ESS, it is not recommended to treat with thyroid hormones.[24] It may be important to note that in many institutions, the determination of the rT3 concentration often takes a few days, which may be a limitation in the practical utility of rT3 as a discriminator between central hypothyroidism and ESS.

Children suffering from prolonged severe illness have been shown to present with low total T4 and FT4 concentrations.[26] For this reason, we had expected that since higher rT3 concentrations and "medium and poor" physical condition were associated, the FT4 concentrations of children with elevated rT3 concentrations would have been lower. No significant correlation between rT3 and FT4 was, however, found in children with elevated rT3 concentrations. This may be explained by the fact that circulating FT4 concentrations may transiently rise during the acute phase of illness and normalize during recovery.[27] Another explanation for the non-decreased FT4 concentrations might be that TRH metabolism had already been restored, but during severe illness, the deiodinase activity was altered, resulting in elevated rT3 concentrations. Unfortunately, T3 concentrations were not available; thus, the T3/rT3 ratio, used to define ESS,[24] could not be determined.

Next to illness, age is also known to influence rT3 and FT4 concentrations, with higher rT3 and FT4 concentrations in younger children.[28] In our cohort, no significant correlation of age with rT3 or FT4 concentrations could be found.

The changes in thyroid function parameters may, alternatively to ESS, be explained by the administration of drugs, such as corticosteroids.[29] In our cohort, 29% of the children had received corticosteroids <48 h of thyroid hormone measurement 3 months after HSCT, although no significant difference in median rT3 concentrations was found between children given corticosteroids <48 h before thyroid hormone measurement and those not.

During severe illness, the body is in a catabolic state.[30] This catabolic state has been linked not only to changes in thyroid function parameters but also to other pituitary hormones, such as adrenocorticotropic hormone (ACTH) and GH. Due to reduced pulsatile secretion of GH, IGF-1 levels may diminish. In our cohort, as well as in the children with elevated rT3 concentrations, IGF-1 SDS remained stable 3 months after HSCT. The administration of corticosteroids might have influenced these results since corticosteroids have been described to increase IGF-1 concentrations due to corticosteroid-induced insulin resistance.[31] Alternatively, IGF-1 levels may already have improved after a catabolic state due to illness, with a more prolonged time for recovery of rT3.

Development of autoimmune thyroiditis after HSCT has been reported.[32,33] We questioned whether autoimmune thyroiditis already occurs 3 months after HSCT; however, this was not seen. Interestingly, none of the children showed elevated anti-TPO levels 3 months after HSCT. This might be explained by the fact that HSCT may induce a "resetting" or replacement of the dysfunctional immune system in children with autoimmune disease.[34]

In this unique cohort, we studied the short-term effects of HSCT on thyroid function parameters in children. The strengths of this study are the relatively large cohort of children and the systematic biochemical measurements before and 3 months after HSCT. Also, the measurement of rT3 concentrations in addition to TSH and FT4 has given insight into the relation between poor physical condition and the dynamics of thyroid function parameters.

The fact that only 72% of all the children undergoing HSCT were assessed for eligibility may be considered a limitation. However, this seemed to be due to logistic reasons, making selection bias unlikely. Secondly, although thyroid function parameters were evaluated in 72 children, a paired TSH and FT4 measurement before and after 3 months was only available for 80% of the children due to ethical reasons (blood samples were only taken if simultaneous sampling for clinical reasons was necessary). Also, rT3 concentrations were only available in 65% of the children and T3 measurements were not available. Lastly, the scoring of physical condition was done using 3 categories, which may have been subjective and not detailed.

In conclusion, this study shows that hypo- and hyperthyroidism are exceedingly rare in children 3 months after HSCT and that surveillance for thyroid dysfunction may start later in time, eg, at 6 months after HSCT.[8] Starting surveillance earlier may even result in a large number of false-positive results, as children may have aberrant thyroid function parameters caused by ESS in which thyroid hormone treatment is not indicated. The fact that both a decline in FT4 concentration of ≥20% was seen in 11% of children and elevated rT3 concentrations were frequently found 3 months after HSCT may reflect the presence of ESS and poor physical condition. Reevaluation of these findings 1 year after HSCT might give insight into the trend of thyroid function parameters and clinical consequences.

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Supplementary material

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Data availability

The data that support the findings of this study are available from the corresponding author upon request.

References

1. Bazinet A, Popradi G. A general practitioner's guide to hematopoietic stem-cell transplantation. *Curr Oncol*. 2019;26(3):187-191. https://doi.org/10.3747/co.26.5033
2. Lee YJ, Lee HY, Ahn MB, *et al*. Thyroid dysfunction in children with leukemia over the first year after hematopoietic stem cell transplantation. *J Pediatr Endocrinol Metab*. 2018;31(11):1241-1247. https://doi.org/10.1515/jpem-2018-0162
3. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. *Endocr Rev*. 2010;31(2):139-170. https://doi.org/10.1210/er.2009-0007
4. Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. *J Neuroendocrinol*. 2008;20(6):784-794. https://doi.org/10.1111/j.1365-2826.2008.01733.x
5. Leung AKC, Leung AAC. Evaluation and management of the child with hypothyroidism. *World J Pediatr*. 2019;15(2):124-134. https://doi.org/10.1007/s12519-019-00230-w
6. Lebbink CA, Waguespack SG, van Santen HM. Thyroid dysfunction and thyroid cancer in childhood cancer survivors: prevalence, surveillance and management. *Front Horm Res*. 2021;54:140-153. https://doi.org/10.1159/000513805
7. Sanders JE, Hoffmeister PA, Woolfrey AE, *et al*. Thyroid function following hematopoietic cell transplantation in children: 30 years' experience, 2009. Available from: http://ashpublications.org/blood/article-pdf/113/2/306/1455389/zh800209000306.pdf
8. de Kloet LC, Bense JE, van der Stoep MYEC, *et al*. Late endocrine effects after hematopoietic stem cell transplantation in children with nonmalignant diseases. *Bone Marrow Transplant*. 2022;57(10):1564-1572. https://doi.org/10.1038/s41409-022-01755-x
9. Berger C, Le-Gallo B, Donadieu J, *et al*. Late thyroid toxicity in 153 long-term survivors of allogeneic bone marrow transplantation for acute lymphoblastic leukaemia. *Bone Marrow Transplant*. 2005;35(10):991-995. https://doi.org/10.1038/sj.bmt.1704945
10. Slatter MA, Gennery AR, Cheetham TD, *et al*. Post-transplant complications thyroid dysfunction after bone marrow transplantation for primary immunodeficiency without the use of total body irradiation in conditioning. *Bone Marrow Transplant*. 2004;33(9):949-953. https://doi.org/10.1038/sj.bmt.1704456
11. van Iersel L, Xu J, Potter BS, *et al*. Clinical importance of free thyroxine concentration decline after radiotherapy for pediatric and adolescent brain tumors. *J Clin Endocrinol Metab*. 2019;104(11):4998-5007. https://doi.org/10.1210/jc.2019-00539
12. Taylor PN, Razvi S, Pearce SH, Dayan CM. A review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab*. 2013;98(9):3562-3571. https://doi.org/10.1210/jc.2013-1315
13. Cattoni A, Molinari S, Gaiero A, *et al*. Thyroid disorders following hematopoietic stem cell transplantation in childhood: impact of conditioning regimen on thyroid dysfunction, volume changes, and occurrence of nodules. *Transplant Cell Ther*. 2022;28(8):506.e1-506.e12. https://doi.org/10.1016/j.jtct.2022.05.040
14. Wang YM, Howell JC, Grimley MS, Lane A, Davies SM, Myers KC. Incidence of thyroid dysfunction in children after HSCT with reduced intensity conditioning (RIC) or myeloablative conditioning (MAC). *Pediatr Transplant*. 2021;25(3):e13983. https://doi.org/10.1111/petr.13983
15. Figueiredo AA, Cavaco D, Damásio I, *et al*. Endocrine complications after hematopoietic stem cell transplantation during childhood—results from a close follow-up in a cohort of 152 patients. *Clin Endocrinol (Oxf)*. 2023;98(2):202-211. https://doi.org/10.1111/cen.14826
16. Al-Fiar FZ, Colwill R, Lipton JH, Fyles G, Spaner D, Messner H. Abnormal thyroid stimulating hormone (TSH) levels in adults following allogeneic bone marrow transplants. *Bone Marrow Transplant*. 1997;19:(10)1019-1022. https://doi.org/10.1038/sj.bmt.1700771
17. Bhatia S, Armenian SH, Landier W. How I monitor long-term and late effects after blood or marrow transplantation. *Blood*. 2017;130(11):1302-1314. https://doi.org/10.1182/blood-2017-03-725671
18. Ishiguro H, Yasuda Y, Tomita Y, *et al*. Long-term follow-up of thyroid function in patients who received bone marrow transplantation during childhood and adolescence. *J Clin Endocrinol Metab*. 2004;89(12):5981-5986. https://doi.org/10.1210/jc.2004-0836

19. Muller I, Moran C, Lecumberri B, *et al.* European Thyroid Association guidelines on the management of thyroid dysfunction following immune reconstitution therapy. *Eur Thyroid J*. 2019;8(4):173-185. https://doi.org/10.1159/000500881
20. Chopra IJ. Euthyroid sick syndrome: is it a misnomer? *J Clin Endocrinol Metab*. 1997;82(2):329-334. https://doi.org/10.1210/jcem.82.2.3745
21. van den Berghe G. Endocrine evaluation of patients with critical illness. *Endocrinol Metab Clin North Am*. 2003;32(2):385-410. https://doi.org/10.1016/S0889-8529(03)00005-7
22. Duntas LH, Nguyen TT, Keck FS, Nelson DK, DiStefano JJ. Changes in metabolism of TRH in euthyroid sick syndrome. *Eur J Endocrinol*. 1999;141(4):337-341. https://doi.org/10.1530/eje.0.1410337
23. van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid*. 2014;24(10):1456-1465. https://doi.org/10.1089/thy.2014.0201
24. Fliers E, Boelen A. An update on non-thyroidal illness syndrome. *J Endocrinol Invest*. 2021;44(8):1597-1607. https://doi.org/10.1007/s40618-020-01482-4
25. van den Berghe G, de Zegher F, Veldhuis JD, *et al.* Thyrotrophin and prolactin release in prolonged critical illness: dynamics of spontaneous secretion and effects of growth hormone-secretagogues. *Clin Endocrinol (Oxf)*. 1997;47(5):599-612. https://doi.org/10.1046/j.1365-2265.1997.3371118.x
26. Mebis L, van den Berghe G. Thyroid axis function and dysfunction in critical illness. *Best Pract Res Clin Endocrinol Metab*. 2011;25(5):745-757. https://doi.org/10.1016/j.beem.2011.03.002
27. Michalaki M, Vagenakis AG, Makri M, Kalfarentzos F, Kyriazopoulou V. Dissociation of the early decline in serum T3 concentration and serum IL-6 rise and TNF in nonthyroidal illness syndrome induced by abdominal surgery. 2001. Available from: https://academic.oup.com/jcem/article/86/9/4198/2848800
28. Lem AJ, de Rijke YB, van Toor H, de Ridder MAJ, Visser TJ, Hokken-Koelega ACS. Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. *J Clin Endocrinol Metab*. 2012;97(9):3170-3178. https://doi.org/10.1210/jc.2012-1759
29. Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. *Best Pract Res Clin Endocrinol Metab*. 2009;23(6):793-800. https://doi.org/10.1016/j.beem.2009.08.003
30. Elijah IE, Branski LK, Finnerty CC, Herndon DN. The GH/IGF-1 system in critical illness. *Best Pract Res Clin Endocrinol Metab*. 2011;25(5):759-767. https://doi.org/10.1016/j.beem.2011.06.002
31. Ramshanker N, Aagaard M, Hjortebjerg R, *et al.* Effects of prednisolone on Serum and tissue fluid IGF-I receptor activation and post-receptor signaling in humans. *J Clin Endocrinol Metab*. 2017;102(11):4031-4040. https://doi.org/10.1210/jc.2017-00696
32. Sklar C, Boulad F, Small T, Kernan N. Endocrine complications of pediatric stem cell transplantation. *Front Biosci*. 2001;6(5):g17-g22. https://doi.org/10.2741/A714
33. Au WY, Lie AK, Kung AW, Liang R, Hawkins BR, Kwong YL. Post-transplant events. Autoimmune thyroid dysfunction after hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;35(4):383-388. https://doi.org/10.1038/sj.bmt.1704766
34. Achini-Gutzwiller FR, Snowden JA, Corbacioglu S, Greco R; Parties TEAD (ADWP) and PD (PDWP) W. Haematopoietic stem cell transplantation for severe autoimmune diseases in children: a review of current literature, registry activity and future directions on behalf of the autoimmune diseases and paediatric diseases working parties of the European Society For Blood and Marrow Transplantation. *Br J Haematol*. 2022;198:24-45.