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Thyroid dysfunction during treatment with systemic antineoplastic therapy for childhood cancer: A systematic review

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ABSTRACT

Thyroid dysfunction is known to occur following radiotherapy or chemotherapy for childhood cancer. Thyroid dysfunction during treatment for childhood cancer has, however, not been studied extensively, although thyroid hormones are of utmost importance during childhood. This information is needed to develop adequate screening protocols and may be of special importance with upcoming drugs, such as checkpoint inhibitors, which are highly associated with thyroid dysfunction in adults. In this systematic review we have evaluated the occurrence and risk factors for thyroid dysfunction in children during treatment with systemic antineoplastic drugs, up to three months after the end of therapy. Two review authors independently performed the study selection, data extraction and risk of bias assessment of included studies. After an extensive search (January 2021), in total six heterogeneous articles were included, reporting on 91 childhood cancer patients with a thyroid function test during treatment with systemic antineoplastic therapy for childhood cancer. All studies had risk of bias issues. Primary hypothyroidism was found in 18% of children treated with high dose interferon-α (HDI-α) and in 0–10% after tyrosine kinase inhibitors (TKIs). Transient euthyroid sick syndrome (ESS) was common (in 42–100%) during treatment with systematic multi-agent chemotherapy. Only one study addressed possible risk factors, showing different types of treatment to increase the risk. However, the exact prevalence, risk factors and clinical consequences of thyroid dysfunction remain unclear. Prospective high-quality studies including large study samples are needed to longitudinally assess the prevalence, risk factors and possible consequences of thyroid dysfunction during childhood cancer treatment.

1. Introduction

Thyroid hormones are essential for normal development and growth in children and may be essential for adequate recovery from cancer treatment (Carter et al., 2014). In children with thyroid dysfunction energy level, height, weight, defecation, liver function, cardiac function, daily well-being and quality of life may all be affected. Symptoms of thyroid dysfunction may be non-specific and mimic complaints regularly observed by children (whether or not treated for cancer), such as fatigue and loss of energy, and may therefore be overlooked (Sinha and Yen, 2000). In childhood cancer survivors, primary hypothyroidism has been reported after radiotherapy to the neck and after chemotherapy (Sklar et al., 2000a; Brignardello et al., 2013; Hudson et al., 2013; Mostoufi-Moab et al., 2016). However, during childhood cancer

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treatment, much less studies have been performed on fluctuating thyroid hormone parameters while awareness of fluctuating thyroid hormone parameters during treatment may be relevant as an adequate thyroid hormone state is essential for daily quality of life. In addition, if cancer treatment is given for a prolonged period, optimal thyroid hormone levels are important for longitudinal growth, BMI and (in the young) cognitive development. Also, low thyroid hormones may be of influence on chemotherapy related toxicity such as vincristine-induced constipation or anthracycline-induced cardiotoxicity (Razvi et al., 2018; Shahid and Ashraf, 2022).

In children receiving cancer treatment, the hypothalamic-pituitary-thyroid system may be disrupted by the tumor itself (e.g., thyroid cancer or a brain tumor in the hypothalamic-pituitary region), by therapy such as systemic antineoplastic drugs and radiotherapy, by autoimmunity, and by ill-being or as consequence of "supportive care" drugs, such as steroids or anti-epileptics (Waguespack, 2019; Yılmaz et al., 2014).

The change in thyroid hormone parameters caused by "ill-being" is known as the euthyroid sick syndrome (ESS) (Chopra, 1997a). ESS is considered to be an adaptive state, explained by downregulation of the hypothalamic-pituitary axis resulting in a decrease of thyroid releasing hormone (TRH) and a decrease of deiodinases (D1 and D2), resulting in a decreased conversion of T4 to T3, without an increase in plasma TSH concentrations (Clement et al., 2016). Weight loss and caloric deprivation, as frequently observed during severe illness, may also cause ESS (Reinehr and Andler, 2002).

To distinguish "true" central hypothyroidism from ESS, the concentration of reverse T3 can be measured, which is lowered in case of hypothyroidism, but will be increased in case of ESS (de Vries et al., 2015). Changes in thyroid hormone parameters as a consequence of ESS are correlated with the degree of illness; low levels of T3 may be predictive for poor prognoses in several diseases (McIver and Gorman, 1997a).

Systemic antineoplastic therapy (e.g., HDI-α, TKIs, multi-agent chemotherapy, immunotherapy) may target the function of the thyroid gland directly due to toxicity or autoimmunity or target pathways which secondarily influence thyroid function (Yeung et al., 1998; Jannin et al., 2019). New antineoplastic drugs, such as checkpoint inhibitors, target cancer cells by enhancing the immune system which can lead to immune related adverse events. Checkpoint inhibitors are associated with a variety of thyroid hormone abnormalities in adult and childhood cancer patients: transient thyrotoxicosis due to thyroiditis; primary hypothyroidism as well as central hypothyroidism due to hypophysitis (Ferrari et al., 2018a; Abdel-Rahman et al., 2016; Merchant et al., 2016a; Haanen et al., 2022; Husebye et al., 2022).

Insight into the changes of thyroid hormone parameters and the occurrence of hypothyroidism, hyperthyroidism or ESS during treatment with systemic antineoplastic therapy is important to develop adequate screening and treatment protocols. True hypothyroidism and hyperthyroidism can be treated with medication, while the presence of ESS in children with cancer may aid the oncologist in improving supportive care or be related to illness itself.

For this reason, we conducted a systematic literature review to identify studies on the prevalence of thyroid dysfunction, the dynamics of thyroid hormone parameters over time, and risk factors for thyroid dysfunction during treatment with systemic antineoplastic drugs for childhood cancer.

2. Methods

2.1. Search strategy, inclusion criteria, data extraction, risk of bias assessment and analyses

We searched Cochrane Central Register of Controlled Trials (CENTRAL) (issue 1 2021 (searched January 14, 2021)) and MEDLINE in PubMed (1946 to January 14, 2021). In addition, we hand searched several conference proceedings and searched the reference lists of included articles and reviews. Search strategies are shown in **Appendix A.** We included all study designs measuring thyroid hormone parameters during childhood cancer (age 0–21 years at tumor diagnosis) and up to three months after the end of therapy (i.e., systemic antineoplastic drugs), except case reports and case series. Childhood cancer patients with known risk factors for thyroid dysfunction (131-I-MIBG, radiotherapy exposing the thyroid or pituitary gland, thyroid carcinoma, suprasellar intracranial tumors or Down syndrome) were excluded (Bull et al., 2011; Clement et al., 2013). Studies which included both children and adults were only included if > 90% were children. Searches, data extraction and risk of bias assessment (**Appendix B**) were performed by two independent reviewers. If discrepancies between reviewers could not be solved by discussion, final resolution was achieved by using a third-party arbitrator. We used the Wilson method to calculate the corresponding 95% confidence intervals (CIs) of the prevalences (Sargento, 2018).

2.2. Outcomes and definitions

Our primary outcomes were the percentage of patients who developed thyroid dysfunction (i.e., hyper, hypothyroidism or ESS) and the percentage of patients treated with thyroid hormone.

Our secondary outcomes were the change in thyroid hormone parameters (ΔTSH, ΔFT4, ΔT4, ΔT3, ΔrT3, ΔTBG (thyroxine-binding globulin) and IGF-1) and the change in anti-thyroid antibody (anti-thyroid peroxidase, thyroglobulin antibody and TSH receptor antibody). Our definitions were based on biochemistry reports. The exact definitions are shown in **Appendix C.**

3. Results

Our search revealed 3720 unique references after deduplication of 56 records. We screened titles and abstracts and excluded 3697 references clearly not meeting the eligibility criteria for this review. We assessed the remaining 23 references in full text of which six fulfilled all criteria for inclusion (Fig. 1). Reasons for exclusion of the 17 references were: use of radiotherapy or MIBG, majority of study population were adults, no separate results for malignancies or non-eligible study design (**Appendix E**). There might be overlap between two studies (Walia et al., 2020; Narayanan et al., 2013). Both studies included chronic myelogenous leukemia (CML) patients treated with imatinib in the same medical centre and they were written by partly the same authors. However, the

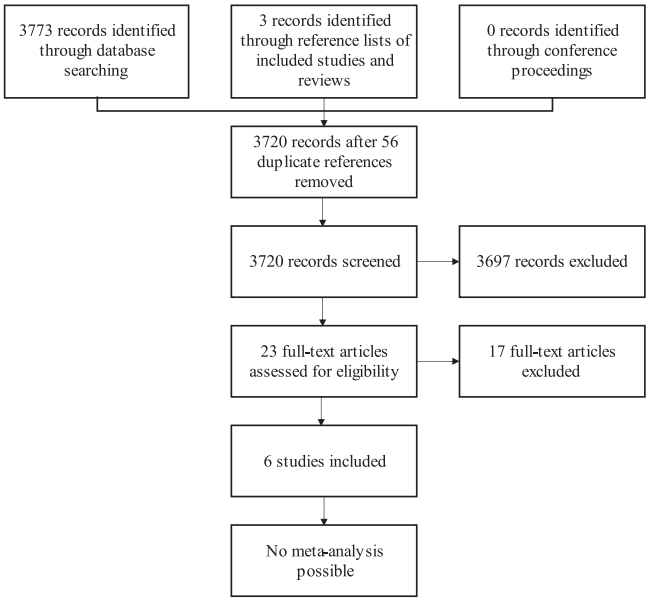

Fig. 1. Flow chart for inclusion and exclusion of studies.

study periods do not overlap, so both were included.

Of the six included studies, four studies described a cohort (Walia et al., 2020; Ferster et al., 1992; Heidemann et al., 1981; Van Santen et al., 2005) and two studies were cross-sectional studies (Narayanan et al., 2013; Chao et al., 2005). None of the studies had a control group. The total number of patients with thyroid function test in the studies was 91 (range nine to 20 patients per study). Patients were diagnosed with different types of childhood cancer.

Patients were treated with TKIs (imatinib) in two studies (Walia et al., 2020; Narayanan et al., 2013), HDI-α in one study (Chao et al., 2005) and with of multi-agent chemotherapy in three studies (Ferster et al., 1992; Heidemann et al., 1981; Van Santen et al., 2005).

In two studies patients did not receive previous systemic antineoplastic therapy (Ferster et al., 1992; Heidemann et al., 1981). In two studies patients were treated with TKIs for at least six months (Walia et al., 2020; Narayanan et al., 2013). In the other studies no information on previous treatment was provided.

Pre-existing thyroid disease was reported absent at study entry in two studies (Narayanan et al., 2013; Heidemann et al., 1981). One study reported a low serum T3 level before study entry in 22% of the patients (Ferster et al., 1992). The remaining three studies did not report on this.

The studies were heterogeneous regarding cancer type, therapy and definitions of thyroid dysfunction. Therefore, pooling of the results was not possible. We report outcomes separately for three categories of systemic antineoplastic drugs: HDI-α, TKIs and systemic multi-agent chemotherapy. More detailed study information is shown in **Appendix D.**

4. Risk of bias in included studies

4.1. Internal validity

In one study the risk of selection bias was high (Van Santen et al., 2005), in three it was low (Walia et al., 2020; Narayanan et al., 2013; Chao et al., 2005) and in the two remaining studies it was unclear (Ferster et al., 1992; Heidemann et al., 1981). In all studies, the risk of attrition and detection bias was low. Only one study conducted a multivariable analyses of risk factors for thyroid dysfunction (Van Santen et al., 2005); the risk of confounding was high (Fig. 2 and Appendix D).

4.2. External validity

Study groups were only well defined in two studies (Walia et al., 2020; Narayanan et al., 2013). Follow-up and outcome definitions were properly defined in five (Walia et al., 2020; Narayanan et al., 2013; Ferster et al., 1992; Heidemann et al., 1981; Chao et al., 2005) and four (Walia et al., 2020; Ferster et al., 1992; Heidemann et al., 1981; Van Santen et al., 2005) studies, respectively. The multivariable analysis in the study of van Santen (Van Santen et al., 2005) was well defined.

5. Primary (thyroidal) hypothyroidism

The prevalence of primary hypothyroidism was reported in five studies (Walia et al., 2020; Narayanan et al., 2013; Ferster et al., 1992; Heidemann et al., 1981; Chao et al., 2005) (Table 1). The study of Chao et al. reported hypothyroidism in two of the 11 patients (18%; 95%CI 5–48%) treated with HDI-α (Chao et al., 2005). One patient was diagnosed with hypothyroidism immediately after starting HDI-α, while the other was diagnosed at the end of therapy. The study did not provide any data about clinical symptoms of hypothyroidism, and we were unable to determine if the hypothyroidism was overt or subclinical.

Two studies reported primary hypothyroidism in patients treated for at least six months with the TKI imatinib (Walia et al., 2020; Narayanan et al., 2013). In the study of Narayanan et al., none of the 18 patients (0%; 95%CI 0–18%) developed hypothyroidism (mean duration of treatment with imatinib 3.6 years) (Narayanan et al., 2013). In the study of Walia et al. subclinical hypothyroidism was reported in two of the 20 patients (10%; 95%CI 3–30%) (mean duration of treatment with imatinib 6.1 years) (Walia et al., 2020).

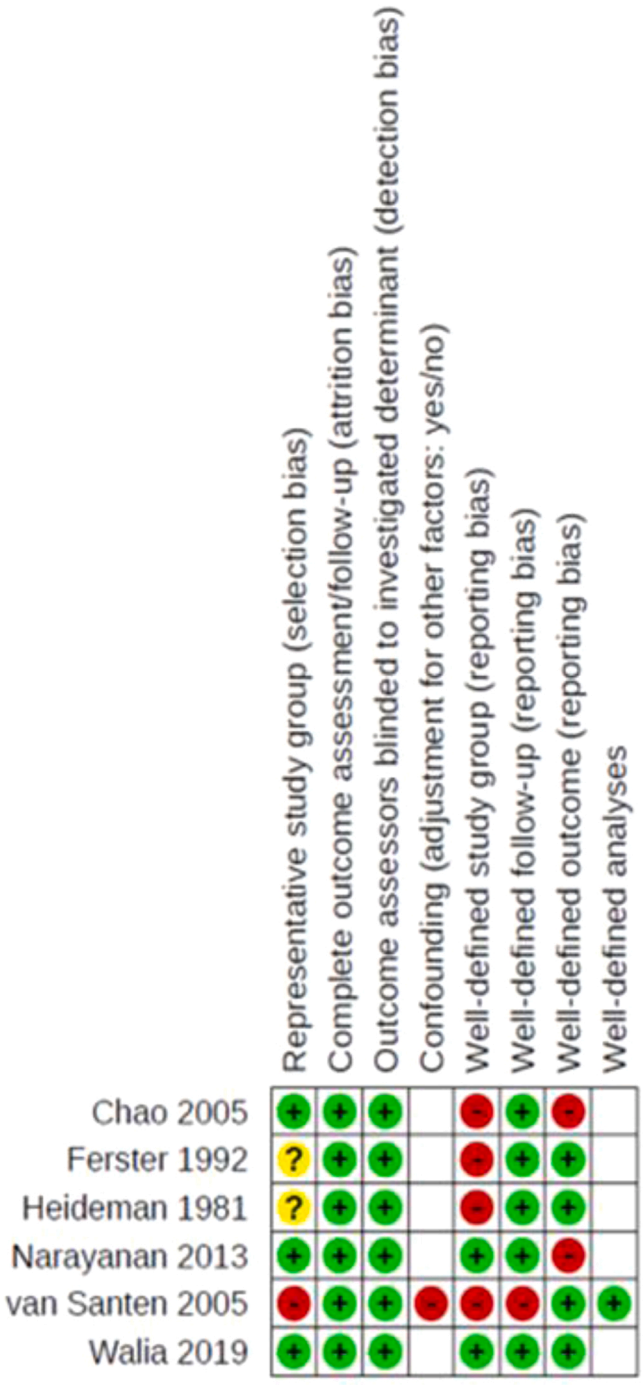

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

In the three studies with systemic multi-agent chemotherapy none of the patients developed primary hypothyroidism. In the study of Ferster et al. none of the nine patients (0%; 95%CI 0–30%) developed overt primary hypothyroidism after chemotherapy induction consisting of vincristine, daunorubicin, prednisolone and L-asparaginase (Ferster et al., 1992) and none of the seven patients (0%, 95%CI 0–35%) developed overt primary hypothyroidism during intensification therapy consisting of dexamethasone, vincristine, adriamycin and

Table 1
Overview of the prevalence of thyroid dysfunction (%).

Study	Patients	Treatment	Thyroid dysfunction	Prevalence (95% CI)
Chao 2005	Melanoma (n = 11)	High dose interferon-α	Primary hypothyroidism 1. Subclinical 2. Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	18% (95%CI 5–48%) NM NM NM 0% (95% CI 0–26%)
Narayanan 2013	CML (n = 18)	TKIs (imatinib)	Primary hypothyroidism 1. Subclinical 2. Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	0% (95% CI 0–18%) 0% (95% CI 0–18%) 0% (95% CI 0–18%) 0% (95% CI 0–18%) 0% (95% CI 0–18%)
Walia 2019	CML (n = 20)	TKIs (imatinib)	Primary hypothyroidism - Subclinical - Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	10% (95% CI 3–30%) NM 0% (95% CI 0–16%) 0% (95% CI 0–16%) 10% (95% CI 3–30%)
Heidemann 1981	ALL (n = 14, during multi-agent chemotherapy; n = 13, after 1–2 weeks multi-agent chemotherapy)	Multiagent chemotherapy Vincristine, daunorubicin, prednisonL -asparaginase	Primary hypothyroidism 1. Subclinical 2. Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	0% (95%CI 0–23%) during and after 1–2 weeks of chemotherapy 0% (95% CI 0–23%) during and after 1–2 weeks of chemotherapy 0% (95% CI 0–23%) 1–2 weeks after chemotherapy 64% (95% CI 39–84%) during chemotherapy NM
Fester 1992	ALL (n = 9, during induction n = 7, during intensification)	Multiagent chemotherapy Induction Vincristine, daunorubicin, prednisone,L -asparaginase Intensification Vincristine, dexamethasone, adriamycin, L-asparaginase	Primary hypothyroidism 1. Subclinical 2. Overt Primary hyperthyroidism 1. Subclinical 2. Overt ESS/central hypothyroidism Thyroid hormone treatment	NM, only mean TSH 0% (95% CI 0–30%) during induction 0% (95% CI 0–35%) during intensification NM, only mean TSH 0% (95% CI 0–30%) during induction 0% (95% CI 0–35%) during intensification 100% (95% CI 70–100%) on day 28 of induction 86% (95% CI 49–97%) on day 16 of intensification NM
Van Santen 2005	Solid tumors or leukemia (n = 19; 46 courses of chemotherapy)	Multiagent chemotherapy Alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinating compounds, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids	Primary hypothyroidism 1. Subclinical 2. Overt Primary hyperthyroidism ESS/central hypothyroidism Thyroid hormone treatment	NM, only mean TSH NM, only mean TSH NM, only mean TSH 42% (95% CI 1–64%) 0% (95% CI 0–18%)

Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; ESS, euthyroid sick syndrome; TKIs, tyrosine kinase inhibitors; TSH, thyroid stimulating hormone; CI, confidence interval; NM, not mentioned.

L-asparaginase. However, it was impossible to determine the incidence of subclinical hypothyroidism during chemotherapy because only mean TSH levels were available. In the study of Heidemann et al. none of the 14 patients (0%; 95%CI 0–22%) developed primary hypothyroidism during chemotherapy and none of the 13 patients (0%; 95%CI 0–23%) developed primary hypothyroidism after one to two weeks of chemotherapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase.

In the study of van Santen et al. the prevalence of primary hypothyroidism during and shortly after different kinds of chemotherapy (alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinum agents, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids) could not be calculated because only mean TSH levels were reported (Van Santen et al., 2005). However, the fact that mean TSH level decreased (mean TSH level before chemotherapy 1.4 mU/L versus 0.77 mU/L after chemotherapy) makes the development of primary hypothyroidism unlikely. Furthermore, this decrease of TSH was accompanied by an increase of rT3 (mean rT3 before chemotherapy 0.18 nmol/l versus 0.39 nmol/l after chemotherapy) suggesting the presence of ESS. In one of the 19 patients (5%; 95%CI 1–25%) TSH level was elevated after treatment with vincristine and asparaginase. However, this elevated TSH level was accompanied by an elevated T3 level and was therefore not considered a reflection of subclinical hypothyroidism.

6. Primary hyperthyroidism

The prevalence of hyperthyroidism was reported in four studies (Walia et al., 2020; Narayanan et al., 2013; Ferster et al., 1992; Heidemann et al., 1981) (Table 1). None of the 18 patients (0%; 95%CI 0–18%) treated with TKIs developed hyperthyroidism in the study of Narayanan et al (Narayanan et al., 2013). and none of the 20 patients (0%; 95%CI 0–16%) developed hyperthyroidism in the study of Walia et al (Walia et al., 2020).

In the three studies with systemic multi-agent chemotherapy, none of the nine patients (0%, 95%CI 0–30%) developed primary overt hyperthyroidism during induction chemotherapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase and none of the seven patients (0%; 95%CI 0–35%) developed overt hyperthyroidism during intensification therapy consisting of dexamethasone, vincristine, adriamycin and L-asparaginase in the study of Ferster et al. Because only mean TSH levels were available, it was impossible to determine the prevalence of subclinical hyperthyroidism.

In the study of Heidemann et al. none of the 14 patients (0%; 95%CI 0–22%) developed primary hyperthyroidism during chemotherapy and none of the 13 patients (0%; 95%CI 0–23%) developed primary (overt or subclinical) hyperthyroidism after one to two weeks of chemotherapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase.

In the study of van Santen et al. the prevalence of primary hyperthyroidism could not be determined because only mean TSH and mean total T4/T3 levels were available (Van Santen et al., 2005). However, after chemotherapy mean TSH levels showed a decline of 53% which was accompanied by a stable mean total T4 and a decline of 67% in mean total T3 concentration. Therefore, it is unlikely that patients developed primary hyperthyroidism.

7. Euthyroid sick syndrome (ESS) or central (secondary/hypothalamic-pituitary) hypothyroidism

In five of the six studies (Walia et al., 2020; Narayanan et al., 2013; Ferster et al., 1992; Heidemann et al., 1981; Van Santen et al., 2005), it was possible to calculate the percentage of patients with a decrease in thyroid hormones without an adequate increase in plasma TSH (Table 1). In the study of Narayanan et al. none of the 18 patients (0%; 95%CI 0–18%) treated with imatinib developed ESS or central hypothyroidism. In the study of Walia et al. none of the 20 patients (0%; 95%CI 0–16%) treated with imatinib developed ESS or central hypothyroidism (Walia et al., 2020).

In the study of Fester et al., in all nine patients (100%; 95%CI 70–100%) low levels of T3 and T4 were seen accompanied by a low TBG level suggesting TBG deficiency on day 28 of induction therapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase. Isolated low T3 or low T3 and low T4 was reported in six of the seven patients (86%; 95%CI 49–97%) on day 16 of intensification therapy consisting of dexamethasone, vincristine, adriamycin and L-asparaginase. In three out of these seven patients the TBG level was below the reference range. TSH levels were normal during the study.

In the study of Heidemann et al. nine of the 14 patients (64%; 95%CI 9–84%) developed a low FT4 compatible with ESS or central hypothyroidism within three weeks of chemotherapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase (Heidemann et al., 1981). In six of these nine patients with FT4 levels below the reference range the pituitary-thyroid axis was evaluated by TRH stimulation. All six patients had a normal TSH response after TRH administration before starting chemotherapy. However, after chemotherapy the TSH peak after administration of TRH was absent in all six patients suggesting central hypothyroidism. The prevalence of patients with a low total T4 and T3 could not be calculated because only mean T4 and T3 were mentioned. However, mean total T4, total T3 and TBG declined to below the reference range without a significant change in the TSH level during three weeks of chemotherapy consisting of vincristine, daunorubicin, prednisone and L-asparaginase.

In the study of van Santen et al. ESS (or central hypothyroidism) developed in eight of the 19 patients (42%; 95%CI 23–64%) after different types of chemotherapy (alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinum agents, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids) (Van Santen et al., 2005). ESS only developed after the administration of dexamethasone.

8. Treatment with thyroid hormone

Treatment with thyroid hormone was mentioned in four studies (Table 1) (Walia et al., 2020; Narayanan et al., 2013; Van Santen et al., 2005; Chao et al., 2005). Only the study of Walia et al. reported two patients out of 20 (10%; 95%CI 3–30%) who were diagnosed with subclinical hypothyroidism and received thyroid hormone treatment. In the three other studies, no patients received treatment.

9. Change in thyroid hormone parameters or antithyroid antibodies

Three of the six included studies (all with systemic multi-agent chemotherapy) reported on the change in thyroid hormone parameters during treatment with systemic multi-agent chemotherapy for childhood cancer (Table 2) (Ferster et al., 1992; Heidemann et al., 1981; Van Santen et al., 2005). A decrease in thyroid hormone parameters was reported in the study of Ferster et al. including nine patients: change in total T4 of − 61% (mean T4 10.1–3.96 ug/100 ml; $p < 0.001$), total T3 of − 53% (mean T3 134–57 ng/100 ml; $p < 0.001$), FT4 of − 51% (mean FT4 of 1.4–0.7 ng/100 ml; $p < 0.001$) and TBG of − 63% (mean 2.14–0.79 mg/100 ml; $p < 0.001$) between day one and day 28 of induction therapy consisting of vincristine, daunorubicin, prednisolone and L-asparaginase. Total T4, total T3 and TBG level were below the lower limit of normal on day 28 of the induction therapy in all patients. All thyroid hormone parameters reverted towards normal on day 35 of the chemotherapy course, after withdrawal of L-asparaginase and during tapering of prednisone. TSH levels were normal before the start of induction therapy and did not change during the study.

A decrease in thyroid hormone parameters was reported in the study of Heidemann et al. including 14 patients: change in total T4 of − 73%

Table 2
Change in thyroid hormone parameters in children treated with multi-agent chemotherapy.

STUDY	PATIENTS	CHEMOTHERAPY	ΔTSH, ΔFT4, ΔT4, ΔT3, ΔrT3, ΔTBG, ΔIGF-1
Heidemann 1981	ALL (n = 14)	Vincristine, daunorubicin, prednisolone,L -asparaginase	*Before* versus *during 3 weeks of chemotherapy* **TSH**: within reference range (no significant change) **T4: − 73%** (mean 10.7–2.9 ug/100 ml; $p < 0.001$) **T3: − 65%** (mean 0.99–0.35 ng/ml; $p < 0.001$) **TBG: − 73%** (mean 29.4–8.0 ug/ml; $p < 0.001$) On day 35 (after withdrawal L-asparaginase + tapering prednisolone) all thyroid hormone levels reverted towards normal
Ferster 1992	ALL (n = 9)	Vincristine, daunorubicin, prednisolone,L -asparaginase	*Day 1* versus *day 28 chemotherapy* **TSH:** percentage not mentioned (not significant) **T4: − 61%** (mean T4: 10.1–3.96 ug/ 100 ml; $p < 0.001$) **T3: − 53%** (mean T3: 134–57 ng/ 100 ml; $p < 0.001$) **TBG: − 63%** (mean TBG: 2.14–0.79 mg/ 100 ml; $p < 0.001$) 2–3 weeks after L-asparaginase all thyroid hormone levels normalized
Van Santen 2005	Solid tumor or leukemia (n = 19, 46 courses of chemotherapy)	Alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinating compounds, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids	*After course of chemotherapy* **TSH: − 53%** (mean TSH: 1.45–0.77 mU/ l; $p \leq 0.0001$) **T4:** no significant change **T3: − 67%** (mean T3: 2.4–1.6 nmol/l; $p \leq 0.0001$) **TBG** no significant change **rT3: + 217%** (mean rT3: 0.18–0.39 nmol/l; $p \leq 0.0001$) **IGF-1:** no significant change

Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; ESS, euthyroid sick syndrome; TKIs, tyrosine kinase inhibitors; TSH, thyroid stimulating hormone; free T4, FT4; total T4, T4; total T3, T3; thyroxine binding globulin, TBG; reverse T3, rT3.

(mean 10.7–2.9 ug/100 ml; $p < 0.001$), total T3 of − 65% (mean 0.99–0.35 ng/ml; $p < 0.001$), FT4 of 47% (mean 1.77–0.94 ng/100 ml; $p < 0.001$) and TBG of − 73% (mean 29.4–8.0 ug/ml; $p < 0.001$) during 3 weeks of chemotherapy consisting of vincristine, daunorubicin, prednisone and L-asparaginase (Heidemann et al., 1981). TSH levels remained within the reference ranges throughout the study. All thyroid hormone levels normalized one week after the last prednisone and two to three weeks after the last L-asparaginase.

The study of van Santen et al., including 19 patients reported a change in thyroid hormone parameters: decrease in TSH of − 53% (mean TSH 1.45–0.77 mU/l; $p \leq 0.0001$), T3 of − 67% (mean T3 2.4–1.6 nmol/l; $p \leq 0.0001$), rT3 + 217% (mean rT3 0.18–0.39 nmol/l; $p \leq 0.0001$) after a course of chemotherapy (alkylating agents, antineoplastic agents, antimetabolites, plant alkaloids, platinum agents, topoisomerase inhibitors, asparaginase, retinoids and corticosteroids) (Van Santen et al., 2005). Total T4, TBG, and IGF-1 were not affected. FT4 was not determined because of the possible interaction with the assay using heparin in the central venous catheters. **Appendix D** shows a complete overview of the reported changes in thyroid function parameters.

None of the studies reported on change of anti-thyroid antibodies. In the study of van Santen et al., in none of the 19 patients elevated concentrations of anti-TPO or anti-TG were found at baseline (Van Santen et al., 2005).

10. Multivariable risk factor analyses

Possible risk factors for change in thyroid hormone parameters were analysed in the study of van Santen et al. for the different subgroups of chemotherapy; for chemotherapy with or without dexamethasone and by cancer type (solid tumor versus leukemia) (Van Santen et al., 2005). Cancer type did not influence the thyroid hormone parameters during chemotherapy treatment.

In 39 courses of chemotherapy in which dexamethasone was administered the baseline TSH was significantly lower and the concentrations of rT3 and T4 were significantly higher at baseline compared to chemotherapy courses without dexamethasone. No differences were seen in baseline T3 and TBG level. After administration of dexamethasone significantly lower concentrations of plasma TSH and T3 and an increase in plasma rT3 were found. In the chemotherapy courses with administration of dexamethasone, T3 was lower after alkylating chemotherapy (β − 2.246 with 95%CI −1.06 to −0.59, p 0.000), antineoplastic agents (β − 0.447 with 95%CI −0.29 to −0.02, p 0.027), antimetabolites (β − 2.808 with 95%CI −1.26 to −0.68, p 0.000), cisplatin (β − 1.968 with 95%CI −1.15 to −0.54, p 0.000) and topoisomerase inhibitors (β − 0.385 with 95%CI −0.22 to −0.05 p = 0.002). The TBG level was lower in patients treated with topoisomerase inhibitors (β − 0.478 with 95%CI −0.16 to −0.22, p 0.012).

In seven courses of chemotherapy without dexamethasone administration an increase in plasma rT3 was found after the course of chemotherapy. The mean rT3 was lower in patients treated with asparaginase (β − 0.936 with 95%CI −1.52 to −0.92, p 0.000).

11. Discussion

This systematic review is, to our knowledge, the first review to analyse the change in thyroid hormone parameters in childhood cancer patients treated with systemic antineoplastic therapy.

While the number of studies is small, the six studies included report on 91 childhood cancer patients and illustrate that changes in thyroid hormone parameters are commonly seen in children treated with systemic antineoplastic therapy, although the exact number varies.

The wide variation in prevalence of thyroid dysfunction during treatment with systemic antineoplastic therapy for childhood cancer, especially ESS, is related to the differences in definitions used for thyroid dysfunction and it may reflect the large heterogeneity of included studies mainly regarding the type of childhood cancer and type of systemic antineoplastic therapy.

Antineoplastic therapy can affect thyroid hormone parameters in different ways. Antineoplastics can target the thyroid gland directly or indirectly by affecting TSH, TBG and deiodinase enzymes (Clement et al., 2016; Sargento, 2018; Van Santen et al., 2005; Porcelli et al.,

2023). Because of the heterogeneity in systemic antineoplastics and the different underlying mechanism in affecting the thyroid hormone parameters we reported the outcomes separately for HDI-α, TKIs and multi-agent systemic chemotherapy.

Only one study performed a multivariate analysis to identify risk factors for aberrant thyroid function parameters (Van Santen et al., 2005). Cancer type did not influence the thyroid function parameters during chemotherapy treatment. In the chemotherapy courses with dexamethasone the mean T3 levels were lower and the rT3 increased after the course of chemotherapy probably reflecting ESS.

Unfortunately, an international definition of ESS is lacking and the wide biochemical criteria for ESS overlap the criteria for central hypothyroidism. The distinction between ESS and central hypothyroidism can be made by determining rT3 or performing a TRH test (McIver and Gorman, 1997b; Chopra, 1997b). In the clinical setting, the distinction between ESS and central hypothyroidism is based on the clinical pre likelihood by identifying risk factors for ESS or central hypothyroidism (e.g., malnourishment or admission to intensive care versus (supra) sellar tumor or cranial radiotherapy) whether or not in combination with the rT3 level. Due to lack of rT3 measurements, it was impossible to distinguish ESS from central hypothyroidism in most of the reviewed studies. Only in the study of van Santen et al. rT3 was analysed and in the study of Heidemann et al. a TRH test was performed making differentiation between ESS and central hypothyroidism possible (Heidemann et al., 1981; Van Santen et al., 2005).

Although differentiation between ESS and central hypothyroidism was biochemically not possible in all studies it is likely that in most cases the aberrant thyroid parameters are caused by ESS because patients at risk for central hypothyroidism were excluded in our review. The fact that ESS only developed in chemotherapy courses in which dexamethasone was administered is suggestive for an important role for corticosteroids in the development of ESS. Corticosteroids are known to have different effects on thyroid hormone parameters: administration of glucocorticosteroids suppress the secretion of TSH, inhibits the synthesis of TBG and inhibits the conversion of T4 into T3 (de Vries et al., 2015). In the study of Heidemann et al. in six of the nine patients with ESS or central hypothyroidism an additional TRH test was performed (Heidemann et al., 1981). All six patients had a blunted TSH response after TRH administration. The authors hypothesised that L-asparaginase and corticosteroids can result in transient central hypothyroidism.

Because the effect of antineoplastic drugs may be different in children and adults, we specifically sought studies performed in children with cancer.

HDI-α is a recombinant cytokine with direct antitumor as well as indirect immune mediated antitumor activity. Thyroid dysfunction is immune mediated and is a common side effect of HDI-α. In adult patients, primary hypothyroidism has been reported in 2.4–19% of patients treated with HDI-α. The incidence is higher in patients with pre-existing thyroid autoimmunity (Carella et al., 2004a; Torino et al., 2013a). Thyroiditis, mostly mild and transient, is reported in 2–3% of adult patients treated with HDI-α and may be followed by hypothyroidism. Graves hyperthyroidism has also been described. Thyroid dysfunction may recover after withdrawal of HDI-α, although hypothyroidism is persistent in most patients (Carella et al., 2004a; Torino et al., 2013a). In our reviewed study (Chao et al., 2005) the prevalence of HDI-α-induced hypothyroidism of 18% is comparable to the adult literature.

In adult patients, hypothyroidism is a common side effect of TKIs and is reported in 0–100% of patients depending on the type and duration of TKI. TKI induced thyroid dysfunction is more common in females and older patients (Walia et al., 2020; Narayanan et al., 2013; Porcelli et al., 2023). TKIs have an antitumor effect by inhibiting proteins involved in the signalling pathways of cell survival and angiogenesis. The exact mechanism of TKI induced thyroid dysfunction is not completely understood but is probably due to vascular damage leading to a (mild) destructive thyroiditis followed by hypothyroidism. Increased autoimmunity could also play a role. The transient thyroiditis is seen in 0–83% of adult patients and is often followed by hypothyroidism (Walia et al., 2020; Narayanan et al., 2013; Porcelli et al., 2023). TKIs also alter the deiodinases; decreased type II deiodinase activity leads to a lower T3 and increased type III deiodinase activity leads to higher rT3 and T2 levels. Finally, some TKIs (e.g. imatinib) inhibit the MCT8 transporter, which is necessary to transport T3 across the cell membranes into the cells. It is unclear if hypothyroidism is reversible after withdrawal of TKIs (Jannin et al., 2019; Torino et al., 2013b; Carella et al., 2004b; Illouz et al., 2014; Sutcliffe et al., 1981a).

The prevalence range of TKI-induced primary hypothyroidism in adult patients is larger than the prevalence of 0–10% in our reviewed studies and our reviewed studies did not report any patient with thyrotoxicosis probably due to the small number of patients (Walia et al., 2020; Narayanan et al., 2013).

During systemic chemotherapy it is difficult to analyse the effects of individual chemotherapeutic agents on the thyroid function because most chemotherapeutic protocols involve multiple agents including corticosteroids. In our review, primary thyroid dysfunction during systemic multi-agent chemotherapy was not identified. However, this can be due to a lack of power of the included studies.

The literature regarding thyroid function during systemic chemotherapy in adult patients is limited.

In one study, none the 20 adult patients with Hodgkin lymphoma developed thyroid dysfunction during chemotherapy consisting of mechlorethamine, vinblastine, procarbazine and prednisolone (Stuart et al., 1990). However, after a median follow-up of 35 months 44% of patients developed subclinical hypothyroidism.

In one study, analysing thyroid function in adult patients with testicular carcinoma 10% (two of 20 patients) developed subclinical hypothyroidism after treatment with chemotherapy consisting of cisplatin, bleomycin, vinblastine, etoposide and dactinomycin (Sutcliffe et al., 1981b). The mean level of TSH was positively associated with the cumulative dose of cisplatin and vinblastine. However, this study only evaluated thyroid function after and not during treatment with systemic chemotherapy. Based on these studies (Sutcliffe et al., 1981b; Sklar et al., 2000b) and the results of our reviewed studies primary thyroid dysfunction during systemic multi-agent chemotherapy seems to be rare.

In a study with adult ALL patients treated with monotherapy L-asparaginase a transient reduction in TBG levels was seen (Garnick and Larsen, 1979). In the studies of Ferster et al. and Heidemann et al., in which patients were treated with multi-agent chemotherapy including L-asparaginase, the transient decline in thyroid hormones was also accompanied by a decline in TBG levels also suggesting TBG deficiency (Ferster et al., 1992; Heidemann et al., 1981).

Because we were interested in thyroid dysfunction during systemic antineoplastic therapy and not radiotherapy induced thyroid dysfunction, we excluded radiotherapy studies. Unfortunately, this strategy limited inclusion of studies regarding new drugs, such as checkpoint inhibitors, because children with resistant or progressive cancer were mostly treated with radiotherapy.

However, checkpoint inhibitors have revolutionary changed adult cancer treatment and are expected to be used more frequently in future childhood cancer patients. Endocrine immune related adverse events are common in adult patients. Primary hypothyroidism is seen in 6–15% of patients depending on the type of checkpoint inhibitors. Checkpoint induced (mild) thyroiditis is seen in up to 10% of patients. Central hypothyroidism can also occur due to checkpoint induced hypophysitis, which is seen in 1–10% of patients depending on the type of checkpoint inhibitors (Abdel-Rahman et al., 2016; Haanen et al., 2022; Husebye et al., 2022; Ferrari et al., 2018b). The first experiences with checkpoint inhibitors in childhood cancer patients show similar prevalence of thyroid dysfunction and hypophysitis (Merchant et al., 2016b).

The clinical relevance of aberrant thyroid function during childhood cancer is unclear. In the study of van Santen et al. no significant changes

were found between complaints and thyroid hormone parameters (Van Santen et al., 2005). Also, in the study of Heidemann et al. no obvious clinical symptoms of hypothyroidism were observed (Heidemann et al., 1981). The other reviewed studies did not provide any information on clinical functioning of patients. Thyroid hormone treatment was indicated in only two of the 20 patients (10%) diagnosed with TKI induced subclinical hypothyroidism (Walia et al., 2020). Because of the important role of thyroid hormone in the growth and development of children, therapy-induced primary thyroid disorders should be considered being clinically relevant.

In contrast to primary thyroid disorders, ESS is seen as an adaptive state in critical ill patients and is postulated to be protective by preventing excessive tissue catabolism in the acute setting. However, the clinical effects of chemotherapy-induced ESS, especially if these effects are prolonged (e.g., for a period of one- or two-years during leukemia treatment), are still unknown (Clement et al., 2016; de Vries et al., 2015). The fact that systemic chemotherapy-induced thyroid dysfunction is transient in the reviewed studies is reassuring.

It remains difficult to extrapolate our findings to individual childhood cancer patients being treated with systemic antineoplastics drugs because of the continuous development of new treatment protocols in oncology. However, with upcoming new therapies, such as checkpoint inhibitors it is important to understand the effects of current systemic antineoplastic therapy on thyroid hormone parameters. Especially because treatment with checkpoint inhibitors will often be combined with other systemic antineoplastic therapy (Park and Cheung, 2017).

12. Limitations of the included studies

The six included studies were heterogeneous regarding childhood cancer, systemic antineoplastic therapy and definitions of thyroid dysfunction. Because of this heterogeneity, pooling of the results was not possible. Also, the quality of the studies varied, on many occasions due to a lack of reporting. In 50% of the studies, selection bias could not be ruled out. This may have led to an overestimation of the prevalence of thyroid dysfunction if patient with a higher risk of thyroid function were included in the study or to an underestimation when patients with a lower risk were selected. In addition, if important information is missing (as the exact treatment patients received or prior thyroid dysfunction) it is difficult to interpret the results correctly and extrapolate them to individual patients. This was the case in almost all included studies.

Finally, only one study performed a multivariable risk assessment, so knowledge regarding patients who are at highest risk remains limited. Furthermore, in this study, confounding could not be ruled out which could lead to an over- or underestimation of the real effect of the risk factors.

13. Conclusions

The exact prevalence, risk factors and clinical consequences of thyroid dysfunction during antineoplastic therapy for childhood cancer remains unclear. Before definitive conclusions can be made, high quality studies with a sufficient number of patients are needed. Future trials should preferably be prospective cohort studies that longitudinally assesses the prevalence and risk factors for thyroid dysfunction and include valid outcome definitions. In addition, to distinguish ESS from central hypothyroidism, rT3 and risk factors (e.g., cranial radiotherapy, supra(sellar) tumors) for central hypothyroidism should be noted.

CRediT authorship contribution statement

Stephanie van der Leij identified the studies meeting the inclusion criteria. She performed the data extraction and 'Risk of bias's assessment of the included studies. She analysed the data and interpreted the results. She wrote and revised the manuscript, Chantal Lebbink wrote the protocol. She identified the studies meeting the inclusion criteria. She performed the data extraction and 'Risk of bias' assessment of the included studies. She analysed the data and interpreted the results. She wrote and revised the manuscript, Eef Lentjes, Wim Tissing and Marry van den Heuvel-Eibrink critically reviewed the protocol. They contributed to the interpretation of results and critically reviewed the manuscript, Annemarie Verrijn Stuart contributed to the interpretation of the results and critically reviewed the manuscript, Elvira van Dalen designed the study and critically reviewed the protocol. She developed the search strategy. She acted as third-party arbitrator where needed. She contributed to the interpretation of the results. She critically reviewed the manuscript, Hanneke van Santen designed the study and critically reviewed the protocol. She contributed to the interpretation of the results. She critically reviewed the manuscript, All authors approved the final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.103958.

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