Thyroid Research

REVIEW

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Thyroid function abnormalities in individuals with sickle cell disease: a meta-analysis

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Abstract

Background There has been an increasing comprehension and recognition of endocrine dysfunction among both pediatric and adult patients with sickle cell disease (SCD). Thyroid disorders can have significant clinical consequences, including growth retardation and impaired cognitive function. However, there is a disparity in the available data concerning the magnitude and spectrum of thyroid abnormalities in this population. This review aimed to provide a systematic summary and analyses on the status of thyroid function abnormalities in individuals with SCD.

Methods Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a comprehensive search was conducted across Medline/PubMed, Google Scholar, World Health Organization Virtual Health Library Regional Portal, and ScienceDirect. Pooled prevalence and standardized mean difference (SMD) estimates with 95% confidence intervals (CIs) were calculated using Comprehensive Meta-Analysis Software version 3.3.

Results Nineteen studies met the inclusion criteria and were incorporated into the analyses. Serum thyroid-stimulating hormone (TSH) levels were significantly higher in SCD patients compared to controls (SMD = 1.184; 95% CI, 0.269–2.099; $p = 0.011$). While non-significant, there was a trend towards lower levels of triiodothyronine (T3), thyroxin (T4), free T3, and free T4 in the SCD group (T3: SMD = -1.746; 95% CI, -3.561–0.070; $p = 0.059$; T4: SMD = -1.365; 95% CI, -3.030–0.300; $p = 0.108$; free T3: SMD = -0.384; 95% CI, -1.128–0.356; $p = 0.311$; free T4: SMD = -1.205; 95% CI, -2.522–0.111; $p = 0.073$). The pooled prevalence of hypothyroidism and subclinical hypothyroidism among SCD patients was found to be 4.9% and 8.7%, respectively.

Conclusion Individuals with SCD exhibit a tendency towards elevated TSH levels compared to the general population, with a subset potentially developing thyroid abnormalities, particularly subclinical hypothyroidism. Although not highly prevalent in the SCD population, monitoring thyroid function remains essential due to the potential for progression to overt hypothyroidism and its associated adverse health outcomes.

Keywords Sickle cell disease, Thyroid, Hypothyroidism, Meta-analysis

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Introduction

Sickle cell disease (SCD) is one of the most common inherited autosomal recessive hemoglobin disorders, characterized by the production of hemoglobin S (HbS), an abnormal form of hemoglobin resulting from a single point mutation in the β-globin gene [1–2]. This is caused by a point mutation in the β-globin gene in which the 17th nucleotide is changed from thymine to adenine and the sixth amino acid in the β-globin chain becomes valine instead of glutamic acid [1]. The homozygous inheritance of the mutated beta S-globin chains (HbSS) is the most common form that refers to conditions characterized by the production of sickle hemoglobin, triggering a cascade of pathophysiological events, including red blood cell sickling, vaso-occlusion, hemolysis, oxidative stress, hypercoagulability, and chronic inflammation [2–3]. These processes contribute to the diverse clinical manifestations of SCD, such as pain crises, organ damage, and increased susceptibility to infections [1–3]. The global burden of SCD is substantial, with an estimated 312,000 infants born with the disease annually, and over 200,000 of these births occurring in Africa [4].

While the primary pathophysiology of SCD is centered on abnormal hemoglobin production and its consequences, growing evidence suggests a significant interplay between SCD and endocrine dysfunction [5–7]. The endocrine complications in SCD patients have garnered increasing attention due to its potential impact on growth, development, and overall health [5–7]. Timely diagnosis and treatment of these complications in patients with SCD can be delayed as a result of concentration of clinical attention on the primary hematological problems and painful crisis associated with SCD [5]. Among these various endocrine abnormalities observed in SCD, thyroid dysfunction has been described in SCD patients [5–7].

Thyroid hormones play a crucial role in regulating metabolism, energy expenditure, and growth [8–10]. Disruptions in thyroid function, particularly hypothyroidism, can have significant clinical implications, including fatigue, weight gain, cold intolerance, subfertility, impaired cognitive function, and cardiovascular complications [8–10]. However, there is a disparity in the available data concerning the extent and magnitude of thyroid abnormalities in people with SCD, as well as the factors associated with them, which require a systematic summary and analyses for better accuracy. This review aimed to provide a comprehensive overview of the current evidence and identify areas where further research is needed to improve the care of individuals with SCD.

Methods

Search approach and studies inclusion criteria

The methodology for this review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11] (Additional file 1). To gather relevant literature, we conducted a systematic literature search using the electronic databases of MEDLINE (via PubMed), World Health Organization Virtual health library Regional Portal, Google Scholar, and ScienceDirect. There were no restrictions applied to the search in terms of sex, race, geographical area, or publication date.

The search terms used were based on combining Mesh terms and keywords to ensure no possible relevant articles were missed. Furthermore, to identify additional studies for inclusion in this review, we conducted a manual search by carefully screening the reference lists of the studies already included. The search terms used were ((anemia, sickle cell[MeSH Terms]) OR (((hemoglobin S disease[Text Word]) OR (hemoglobin S disorder[Text Word])) OR (sickle cell[Text Word]))) AND ((((thyroid[MeSH Terms]) OR (hypothyroidism[MeSH Terms])) OR (thyroid function tests[MeSH Terms])) OR (thyroid[Text Word] OR thyroid hormone[Text Word] OR thyroid function[Text Word] OR Thyroid Dysfunction[Text Word] OR hypothyroidism[Text Word] OR hyperthyroidism[Text Word] OR TSH[Text Word] OR T3[Text Word] OR FT3[Text Word] OR T4[Text Word] OR FT4[Text Word] OR triiodothyronine[Text Word] OR thyroxin[Text Word] OR thyrotropin[Text Word])). The publications that were found were uploaded to Rayyan software (QCRI, Doha, Qatar; http://rayyan.qcri.org) to expedite initial screening of titles and abstracts and remove duplicate entries [12].

Inclusion and exclusion criteria

The selection process involved a two-step approach. Initially, we screened the titles and abstracts of all identified articles to identify potentially relevant studies. Subsequently, we conducted a comprehensive full-text review of these selected studies to assess their eligibility based on the predefined inclusion criteria.

The inclusion criteria for the articles in this review included cross-sectional, case-control, or cohort studies that provided explicit data on the number of patients with SCD both with and without thyroid abnormalities. In addition, we included studies that explicitly reported the number of SCD patients with and without thyroid abnormalities. Additionally, we included studies that provided data on thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free T3, and free T4 levels in both SCD patients and healthy control groups. Furthermore, we summarized data on any underlying contributing factors for developing thyroid abnormalities

among SCD patients, if available. We excluded case reports, editorials, reviews, abstracts, non-English publications, and studies that did not provide sufficient data on the variables of interest.

Quality assessment and data extraction

We conducted quality assessment of the included studies using the Newcastle– Ottawa scale [13].This tool provides a systematic framework for evaluating the methodological quality of observational studies based on key criteria, including the selection of study groups, comparability between groups, and the ascertainment of exposure and outcome measures [13]. For the comparability domain, we evaluated if studies accounted for sickle cell genotype (HbSS) and age. Studies received one star if they reported and analyzed results stratified by HbSS genotype or specifically focused on HbSS patients, and an additional star if they demonstrated comparable age distributions between groups with and without thyroid dysfunction. For outcome assessment, stars were awarded to studies showed that they used validated laboratory methods for thyroid function evaluation. Data were extracted from each study by three independent reviewers, and any discrepancies among them were resolved by discussion and consensus to ensure accuracy and consistency in data synthesis.

• statistical analysis

The statistical analyses were carried out by using the Comprehensive Meta-Analysis Software version 3.3 (Biostat, Engle-wood, NJ, USA; http://www.Meta-Analysis.com). Heterogeneity among studies was evaluated using the I^2 statistic, which quantifies the percentage of variation in effect estimates attributable to heterogeneity rather than chance. In cases where significant heterogeneity was identified ($I^2 > 50\%$), random-effects models were utilized to calculate the pooled summary prevalence and standardized mean difference (SMD). Publication bias, a potential source of bias due to the tendency for studies with statistically significant results to be published more often, was assessed through Begg and Egger's tests, as well as visual inspection of funnel plots [14–16]. When publication bias was detected, the Duval and Tweedie trim-and-fill method was applied to adjust for potentially missing studies and obtain a more accurate pooled estimate [17]. Furthermore, we used subgroup analyses by the age groups and meta-regression for examining the effect of continuous variables (sample size and publication year) to explore the reasons for heterogeneity between studies. The chi-square test was used to assess the differences between the categorical subgroups and the significance level was set at 0.05.

Results

Studies characteristics

The schematic flow of the study identification and selection process is presented in Fig. 1. Initially, the search yielded a total of 438 records. After removing duplicate data, 225 studies were included for the title and abstract screening. 174 were excluded due to irrelevance. Full texts of the remaining 48 records were screened with a subsequent exclusion of 29 records as shown in Fig. 1. Lastly, a total of 19 studies published from 1995 to 2023 met the eligibility criteria and were further included for evidence synthesis [18–36]. The main features of the included studies, including risk of bias assessment, are presented in (Additional file 2: Table S1).

TSH hormone levels

Among the included studies, 11 provided sufficient data to calculate the SMD in TSH levels between patients with SCD and healthy controls. The pooled effect size demonstrated that individuals with SCD exhibited significantly higher serum TSH levels compared to controls, with an SMD of 1.184 (95% confidence interval [CI], 0.269 to 2.099 $p=0.011$) (Fig. 2). No evidence of publication bias was detected on examination of the funnel plot and from the results of Begg's test ($p=0.11$) and Egger's test ($p=0.14$).

T3 and T4 hormones levels

There were five studies with sufficient data to calculate the SMD of both T3 and T4 estimates between patients with SCD and their controls. Although, the pooled effect size showed that both serum T3 and T4 levels in SCD patients were lower than their controls, there were no statistically significant differences detected between the two groups. The analysis of T3 levels showed that the pooled SMD = -1.746 (95% CI, -3.561 to 0.070; $p=0.059$) (Fig. 3), with no evidence of publication bias detected on visual examination of the funnel plot and from the results of Begg's test ($p=0.23$) and Egger's test ($p=0.58$). Regarding the T4 levels, the analysis showed that the pooled SMD = -1.365 (95% CI, -3.030 to 0.300; $p=0.108$) (Fig. 3), with no evidence of publication bias detected on visual examination of the funnel plot and from the results of Begg's test ($p=0.40$) and Egger's test ($p=0.13$).

Free T3 and free T4 hormones levels

There were four studies and seven studies with sufficient data to calculate the SMD of free T3 and free T4 estimates, respectively. Although the pooled effect size showed that both serum T3 and T4 levels in SCD patients were lower than their controls, there were no statistical significant differences detected between the two groups. The analysis of the free T3 levels showed that the pooled SMD = -0.384 (95% CI, -1.128 to 0.356; $p=0.311$) (Fig. 4),

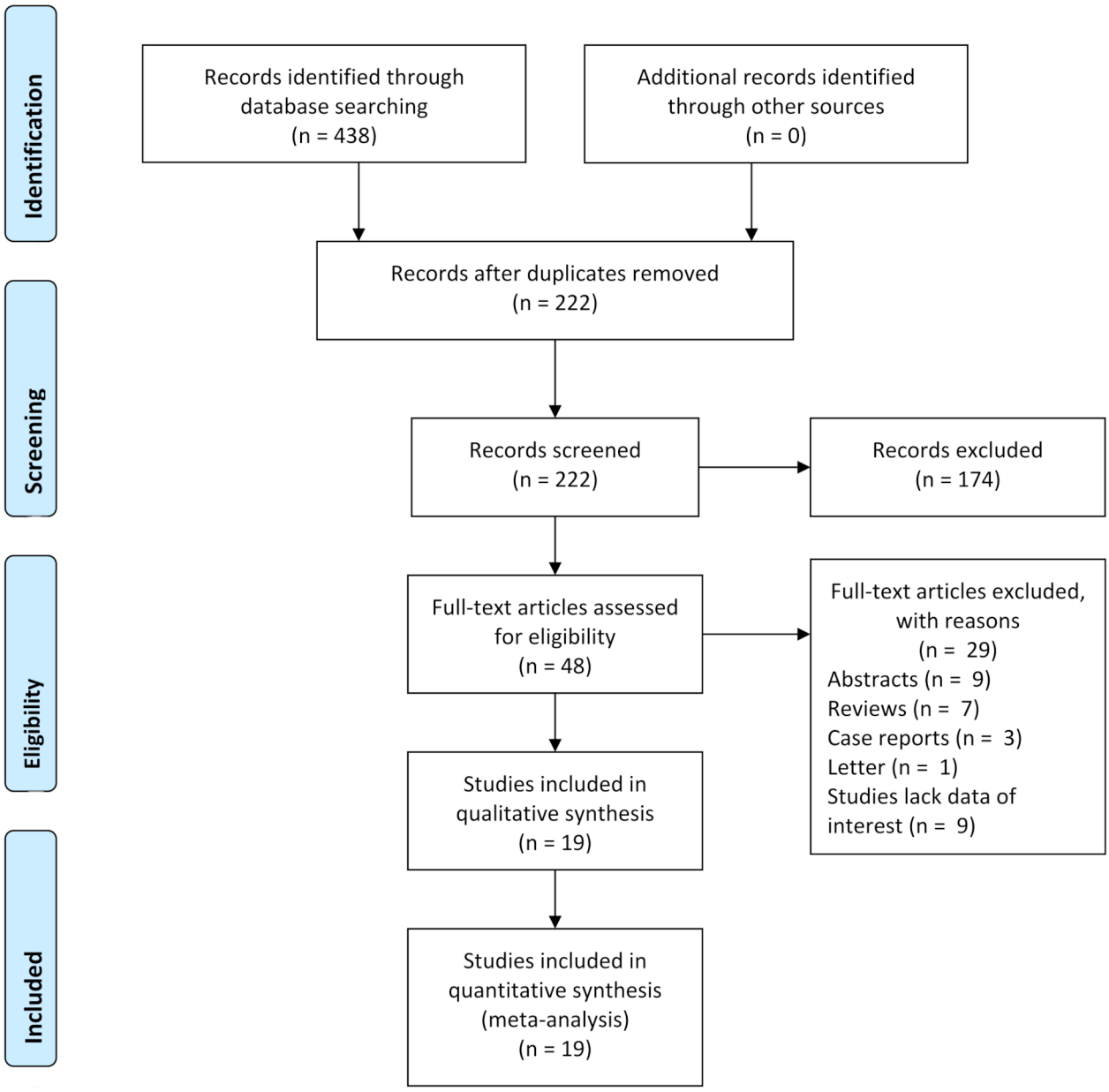

Fig. 1 Flow chart for studies selection process

with no evidence of publication bias was detected on visual examination of the funnel plot and from the results of Begg's test (p=0.15) and Egger's test (p=0.16). Regarding the free T4 levels, the analysis showed that the pooled SMD = -1.205 (95% CI, -2.522 to 0.111; p=0.073) (Fig. 4). The publication bias test was significant for the Begg's test (p=0.03) but not for the Egger's test (p=0.56). However, the Duval and Tweedie trim-and-fill method showed that no potential studies are missing and the adjusted estimate was similar to the original findings.

Prevalence of hypothyroidism and subclinical hypothyroidism among SCD patients

The meta-analysis for the included studies showed that the overall prevalence of hypothyroidism among SCD patients was 4.9% (95% 2.0–11.5%) (Fig. 5). The publication bias test was significant for the Egger's test (p=0.003) but not for the Begg's test (p=0.053). However, upon applying the Duval and Tweedie trim-and-fill method to account for potential missing studies, no missing studies were identified, and the adjusted prevalence estimate remained similar to the initial finding.

Of the included studies, only four provided sufficient data to estimate the pooled prevalence of subclinical

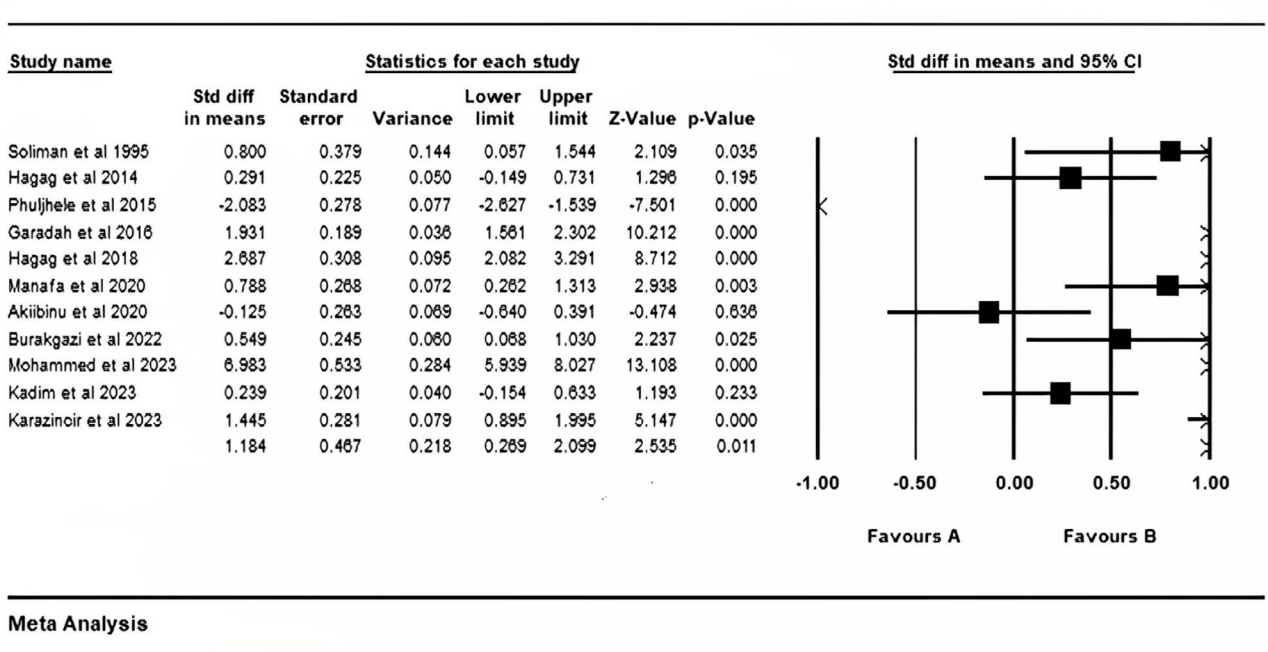

Fig. 2 Pooled SMD of TSH estimates between patients with SCD and their controls

hypothyroidism among SCD patients. All of these studies were conducted on children. The overall prevalence of subclinical hypothyroidism among SCD patients was found to be 8.7% (95% CI, 3.8–18.6%) (Fig. 6). While the Egger's test for publication bias was significant ($p=0.007$), the Begg's test was not ($p=0.56$). However, the trim-and-fill analysis confirmed the absence of missing studies and yielded an adjusted estimate consistent with the original finding.

Moderators of heterogeneity

Due to the limited number of studies, only hypothyroidism and TSH levels were further analyzed to examine potential moderators of heterogeneity. Subgroup analysis revealed a significant difference in the prevalence of hypothyroidism across age groups ($X^2 = 14.64$, $p<0.001$). The lowest pooled prevalence was observed in children with SCD, at 3.70% (95% CI 1.20% – 10.7%). In contrast, the pooled prevalence was higher among adults with SCD (9.80%, 95% CI 5.00% – 18.3%) and in studies that included both adults and children (7.20%, 95% CI 1.50–28.4%).

For TSH levels, the sub-group analysis showed that the pooled analysis of children-based studies did not show a significant difference between SCD patients and healthy controls (SMD=0.295, 95% CI, −0.809 to 1.398; $p=0.601$). In contrast, the pooled analysis of studies conducted on adults (SMD=3.174, 95% CI, 0.744 to 5.605; $p=0.010$) and studies conducted on all age groups (SMD=2.712, 95% CI, 1.035 to 4.389; $p=0.002$) showed a significant difference between SCD patients and healthy controls.

Furthermore, meta-regression analyses were conducted to analyze whether continuous variables (sample size and publication year) affected the heterogeneity in this meta-analysis. For hypothyroidism, the results showed that sample size ($r=-0.013$, $p<0.001$) had a moderating effect on the outcome, while publication year ($r=0.081$, $p=0.230$) did not (Fig. 7). Regarding TSH levels, the meta-regression results showed that neither sample size (r = -0.002, $p=0.919$) nor publication year ($r=0.059$, $p=0.348$) had a moderating effect on the outcome (Fig. 8).

Discussion

This review examined the spectrum of thyroid function abnormalities present in patients with SCD. The meta-analysis revealed significantly higher serum TSH levels in SCD patients compared to controls, particularly in older age groups. In addition, the meta-analysis revealed a trend toward lower serum levels of T3, T4, free T3, and free T4 in SCD patients compared to controls, although these differences did not reach statistical significance. While the meta-analysis identified a subset of SCD patients with thyroid dysfunction, the prevalence of both overt and subclinical hypothyroidism was relatively low compared to other endocrine complications frequently observed in this population. Previous studies

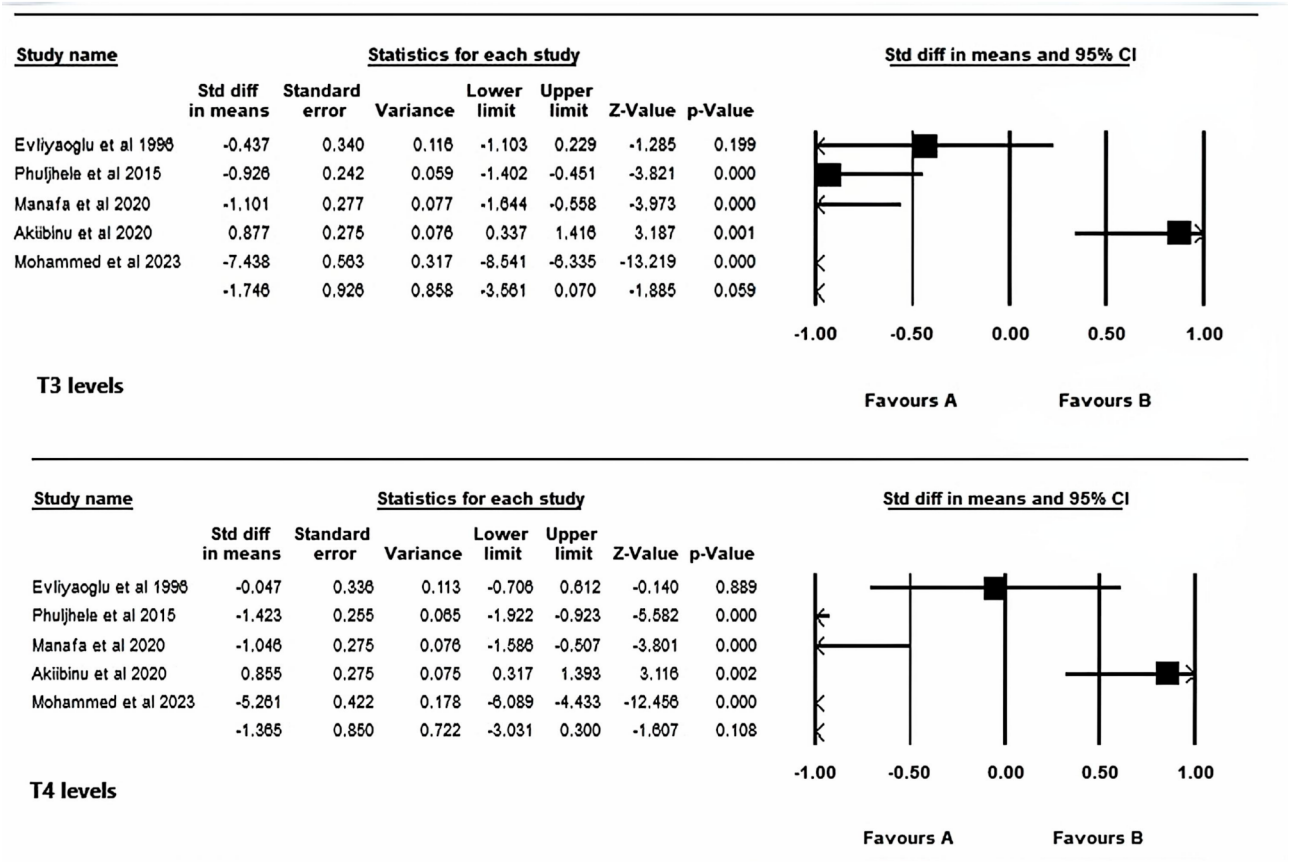

Fig. 3 Pooled SMD of T3 and T4 estimates between patients with SCD and their controls

have reported a higher occurrence of metabolic bone diseases, hypogonadism, growth impairment, and diabetes mellitus in individuals with SCD [37].

The observed findings of thyroid hormonal levels among SCD patients in this meta-analysis suggest a complex interplay of factors, with subclinical hypothyroidism being a likely explanation. In subclinical hypothyroidism, while T3 and T4 levels typically remain within the normal range, a slight decrease in T3 and T4 or a shift towards the lower end of the normal range may be observed. Conversely, TSH levels are characteristically elevated as the body attempts to compensate for the subtle reduction in thyroid hormone levels [8–10].

The occurrence of thyroid abnormalities among patients with SCD may be attributed to the nature of SCD. The sickling endothelial dysfunction, oxidative stress, chronic inflammation, and vaso-occlusive nature of the disease can compromise blood flow to the thyroid gland, leading to impaired microcirculation [1–4]. Several studies have presented findings on reduced thyroid gland volume in SCD patients compared to healthy controls, suggesting a potential structural alteration in the thyroid gland of individuals with SCD [20–21, 26]. This phenomenon and this has been attributed to thyroid microcirculation dysfunction and chronic inflammation [20–21, 26].

Furthermore, iron overload resulting from repeated blood transfusions and subsequent iron deposition in the thyroid gland may contribute to thyroid dysfunction in SCD, causing cellular damage and provoking primary thyroid failure [5]. Several studies have suggested a link between iron overload and thyroid abnormalities, with autopsy reports revealing significant iron deposition in the thyroid glands of some patients [5, 28]. Yassin et al. reported a higher prevalence of hypothyroidism in SCD patients with hepatic iron overload, while Fung et al. identified transfusion duration as a significant predictor of hypothyroidism development [22, 38]. However, other studies, such as those by Özen et al. and Elalfy et al., did not find a significant correlation between serum ferritin levels (a marker of iron overload) and thyroid function tests, highlighting the need for further investigation into the complex relationship between iron overload and thyroid dysfunction in SCD [21, 28].

Although research specifically investigating medication interference with thyroid function in SCD patients

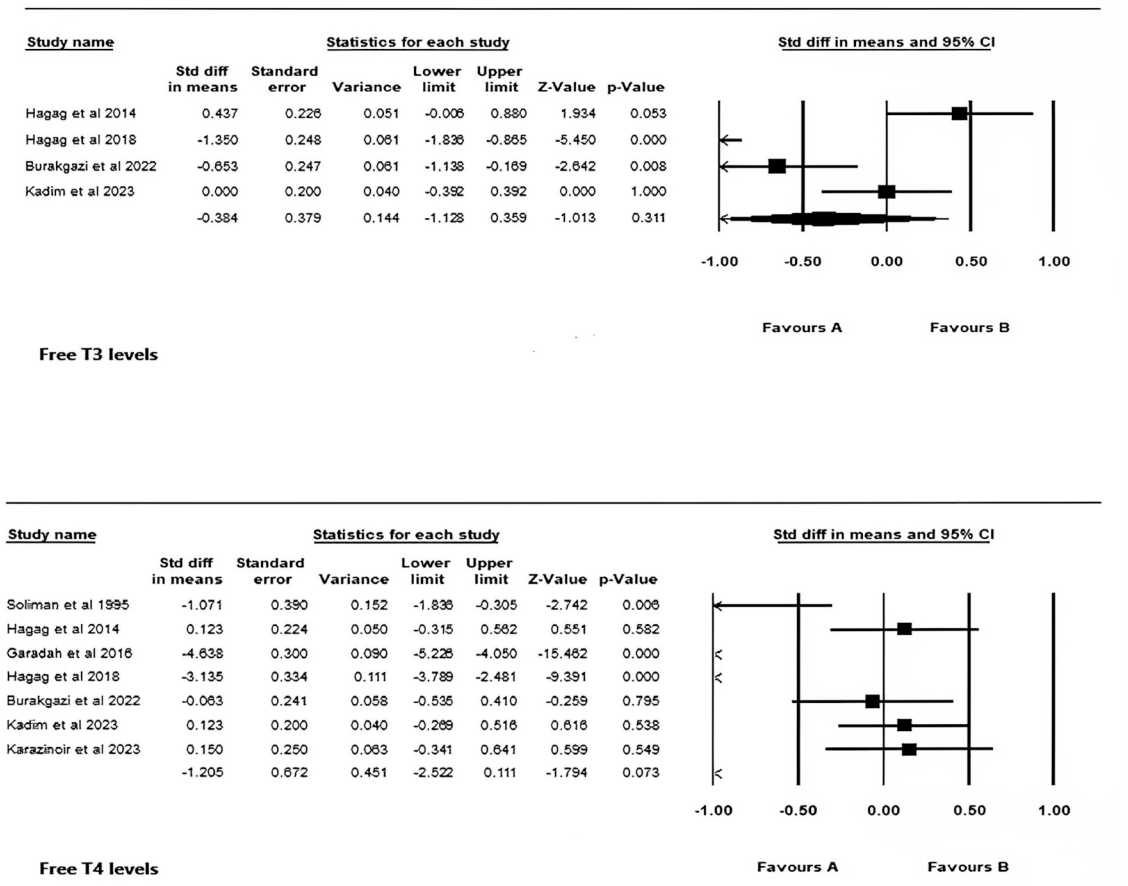

Fig. 4 Pooled SMD of free T3 and free T4 estimates between patients with SCD and their controls

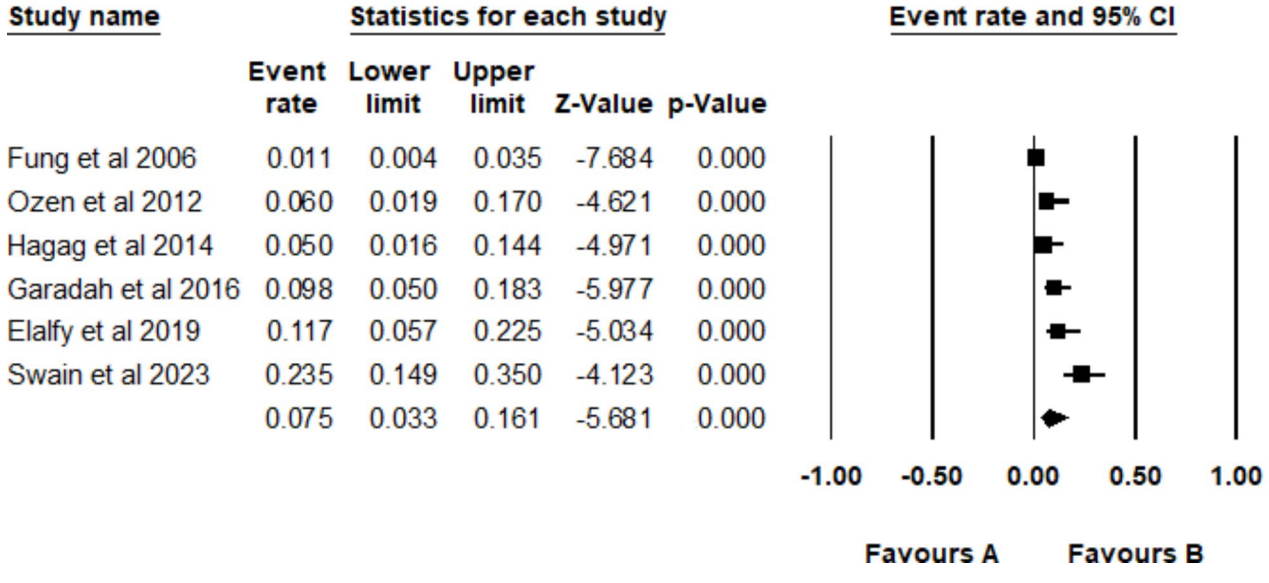

Fig. 5 Pooled prevalence of hypothyroidism among patients with SCD

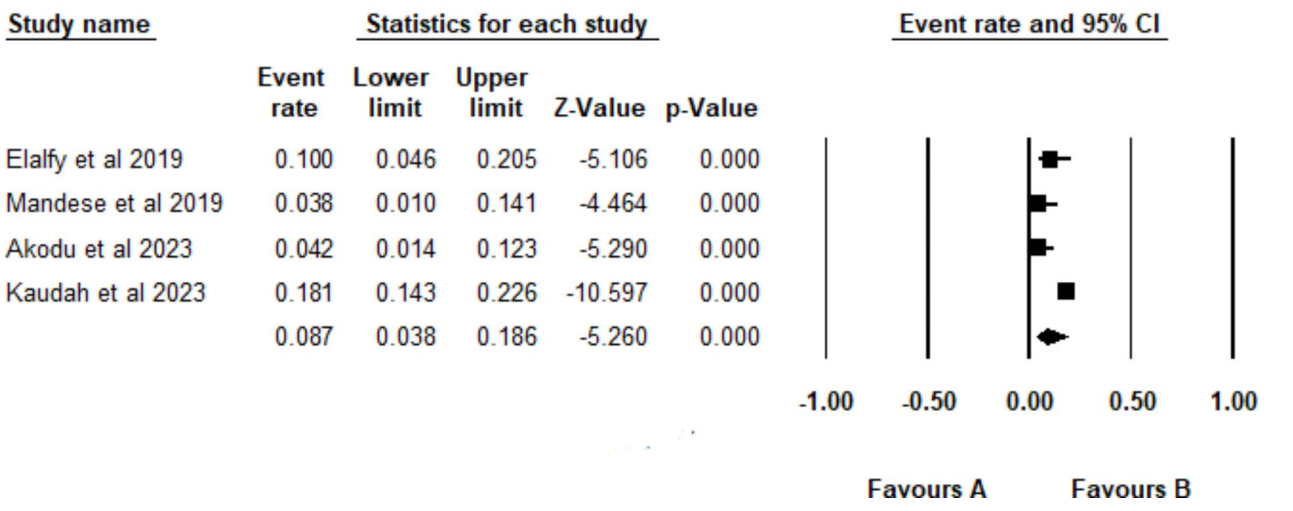

Fig. 6 Pooled prevalence of subclinical hypothyroidism among patients with SCD

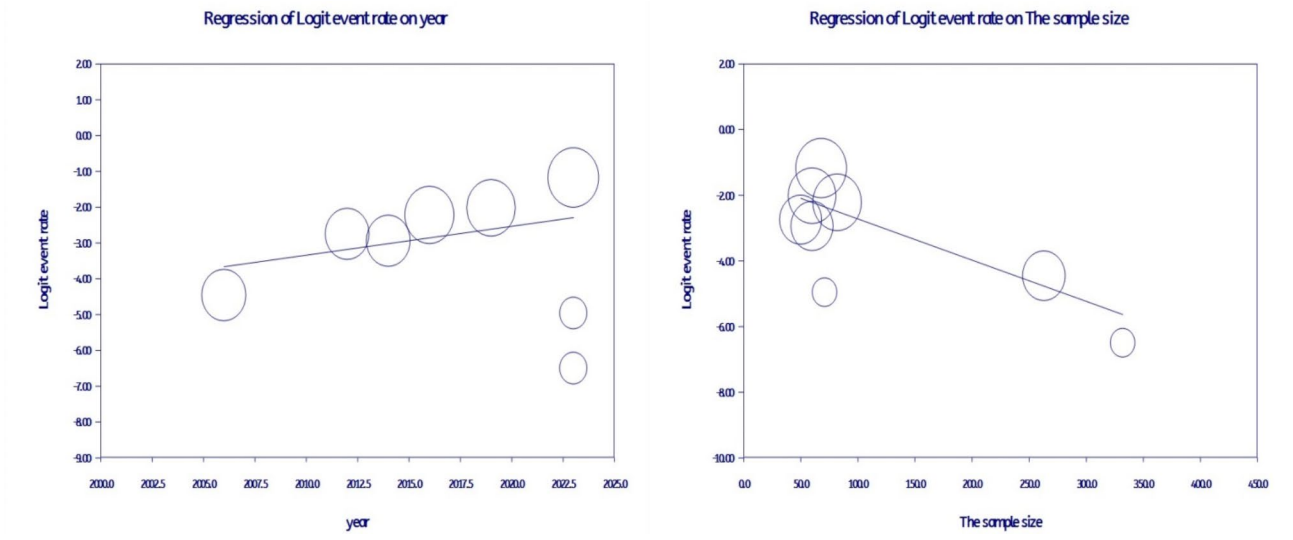

Fig. 7 Meta-regression scatter plots showing the correlation between prevalence of hypothyroidism, sample size, and publication year: **(a)** regression of sample size on prevalence; **(b)** regression of publication year on prevalence

is scarce, some medications commonly used for SCD management, such as opioids for pain control, have been associated with endocrine disruptions, including potential alterations in the hypothalamic-pituitary-thyroid axis [39–40]. These alterations could lead to changes in TSH and thyroid hormone levels [39–40]. However, the evidence supporting these medication interactions is not definitive, and their clinical significance necessitate further investigation [41].

Additionally, existing research has described an association between deficiencies in trace elements and impaired thyroid hormone synthesis and metabolism and demonstrated reduced serum concentrations of zinc and selenium in individuals with hypothyroidism compared to healthy controls [42–43]. Given the established prevalence of zinc and selenium deficiencies among SCD patients, this observation can present another plausible explanation for susceptibility to thyroid dysfunction within this population [44–46].

There are several implications to the findings of this review. From a clinical perspective, the overlap between certain symptoms of hypothyroidism and those commonly observed in SCD itself, such as reduced growth velocity, short stature, delayed puberty, fatigue, and mood changes, highlights the importance of considering and proactively evaluating thyroid dysfunction and its potential complications in all SCD patients presenting with these clinical manifestations. While SCD-related factors like chronic anemia, hypoxia, increased energy expenditure, nutritional deficiencies, and recurrent infections

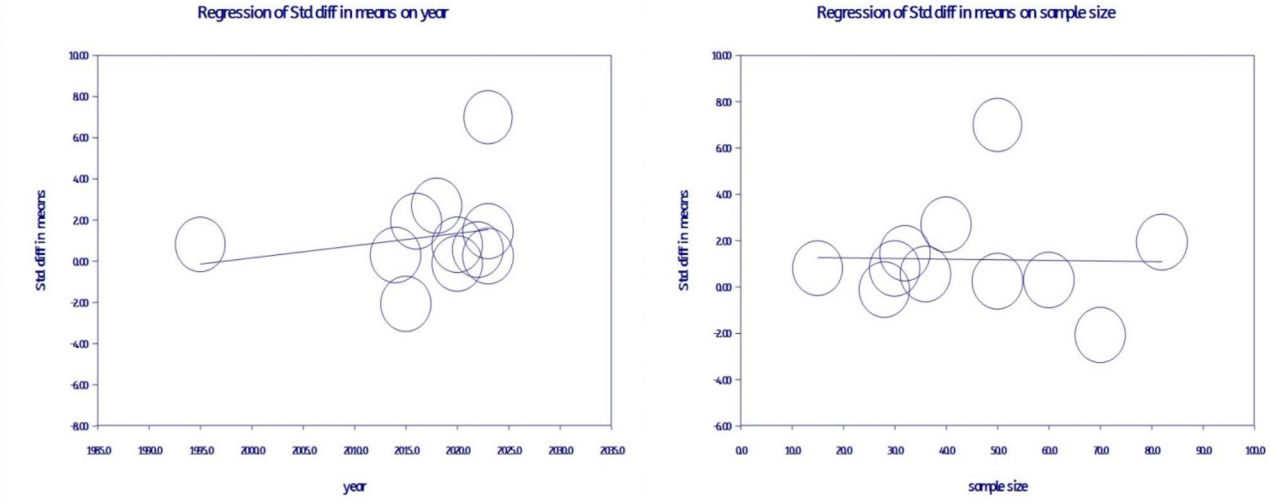

Fig. 8 Meta-regression scatter plots showing the correlation between TSH levels, sample size, and publication year: **(a)** regression of sample size on prevalence; **(b)** regression of publication year on prevalence

can contribute to growth impairment, the presence of thyroid abnormalities warrants attention. While this meta-analysis suggests that thyroid abnormalities may not be highly prevalent in individuals with SCD, maintaining regular monitoring of thyroid function remains crucial, particularly in older age groups. Even a small subset of the SCD population may develop overt hypothyroidism, potentially impacting their overall health and well-being. Timely identification and management of thyroid-related concerns can mitigate complications and improve quality of life. The findings also highlight the need for further research to refine our understanding of the mechanisms and factors influencing thyroid function in SCD and to develop more targeted prevention and treatment strategies.

The findings of this review need to be considered in the context of some limitations. The potential influence of clinical factors such as patients' genotype, SCD severity, ferritin levels, and treatment regimens, and varying compliance to treatment was not fully explored and require further investigation. Data limitations within the included studies precluded analyses of these potential risk factors. Additionally, the inclusion of only English-language publications may have limited representativeness.

Conclusion

This review showed that patients with SCD tend to have higher levels of TSH than the general population, particularly in older age groups. A subset of SCD patients may potentially develop thyroid abnormalities, primarily subclinical hypothyroidism. While these abnormalities are not widespread among SCD patients, monitoring thyroid function remains crucial due to the risk of developing overt hypothyroidism. This vigilance is essential for improving quality of life and clinical outcomes in this population. Further research is warranted to elucidate the mechanisms and contributing factors underlying thyroid dysfunction in individuals with SCD.

Abbreviations

SCD	Sickle cell disease
TSH	Thyroid stimulating hormone
T3	Triiodothyronine
T4	Thyroxin
SMD	Standardized mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13044-024-00220-9.

Additional file 1: PRISMA checklist.

Additional file 2: Table S1. Baseline characteristics of the studies included in the review.

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Author contributions

SM conceptualized the research idea. SM, SF, and OA undertook database search and articles screening. HA, MM, and KA undertook quality assessment and data extraction. SM undertook data analysis. SM, HA, MM, SF, KA, OA, and IA interpreted the results and drafted the manuscript. All authors All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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