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Research Article

Prevalence of Anemia in Hypothyroidism: Systematic Review and Meta-Analysis

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Abstract

Objective: To evaluate the prevalence rate of different types of anemia in hypothyroidism patients.

Methods: Eight databases were searched systematically for any original study measuring the prevalence rate of anemia in hypothyroidism. In addition, manual search with different methods was performed to retrieve all possible studies. Three independent reviewers scanned retrieved references for possible inclusion.

Results: A total of eight studies were finally included in the meta-analysis of this systematic review. The pooled overall prevalence rate of anemia among hypothyroid patients was 33.77% with 95% CI (21.53 to 52.95). Regarding different types of anemias, the highest prevalence rate was for normocytic anemia [PR (95%) = 46.27 (34.46 to 62.14)] followed by microcytic [PR (95%) = 24.36 (14.68 to 40.44)] and macrocytic anemias [PR (95%) = 16.36 (11.66 to 22.96)], respectively. Regarding different types of hypothyroidism, the prevalence of anemia in overt hypothyroidism was 24.79% (95% CI = 11.01 to 55.81) and 24.47% (95% CI = 13.41 to 44.67) for subclinical hypothyroidism.

Conclusions: The high prevalence of anemia in patients with hypothyroidism suggests screening for hypothyroidism during the differential diagnosis of cases presenting with anemia.

Keywords: *Anemia; Hypothyroidism; Prevalence; Screening; Meta-Analysis*

Introduction

Hypothyroidism constitutes a global health concern among clinical society. The disease varies in symptoms and signs according to the age of patients and ranges from asymptomatic to life-threatening illness mostly due to multiple organ dysfunction as thyroid hormones are required for several metabolic activities [1]. Based on thyroxin and thyroid-stimulating hormone (TSH) level, hypothyroidism can be categorized into two pathologic subtypes. Subclinical hypothyroidism is characterized by low TSH and normal thyroxin production in addition to no or few clinical symptoms; therefore, the diagnosis of subclinical hypothyroidism is problematic. Meanwhile, overt hypothyroidism is associated with a decrease in both TSH and thyroxin levels with apparent clinical manifestations [2,3]. Different etiologies are responsible for hypothyroidism affection. Hashimoto's hypothyroid followed by idiopathic hypothyroidism were the common causes of hypothyroidism reported by Hunter., *et al* [4]. Moreover, the disease can be transmitted in-utero. Despite there is no specific clinical features for congenital newborn affection after delivery and may reach up to 3 months due to maternal thyroxin reservoir which passes to the newborn through placenta, various clinical signs can be beneficial for diagnosis of congenital hypothyroidism during

first week of life such as visible icterus, large tongue, abnormal muscle tone and cold skin [5]. Thyroid hormones provide an essential component in the normal process of erythropoiesis. Therefore, dysfunction of thyroid hormones results in anemia in those patients. The most common type of anemia in hypothyroidism patients is normocytic normochromic; however different types of anemia were observed such as macrocytic and microcytic anemia [6]. The prevalence of anemia was found to be higher in overt type rather than subclinical type [7]. In contrast, subclinical hypothyroidism patients have more frequency of anemia compared to overt hypothyroidism patients; however, the overt population has low hemoglobin and hematocrit values [8]. There is no meta-analysis discussing the prevalence of anemia in hypothyroidism. Therefore, we aim to study the prevalence of anemia in hypothyroidism patients and to demonstrate the common type of anemia in overt and subclinical cases.

Methods

Search strategy and study selection

The study was conducted following the accepted methodology recommendations of PRISMA's checklist for systematic review and meta-analysis [9]. We conducted a systematic electronic database search for suitable studies from inception till April 2019 in eight databases including Popline, WHO health library (GHL), System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), The New York Academy of Medicine (NYAM) using the following search term: Anemia and hypothyroidism. A manual search was conducted by searching for relevant publications from references of included articles, relevant papers in PubMed. We also hand searched using each keyword to avoid missing any relevant publications. Three independent reviewers scanned the titles and abstracts against our inclusion and exclusion criteria to select potential articles. We included all relevant original publications reporting anemia in hypothyroidism patients. There were no restrictions on study design, country, language or publication date. Papers were excluded if any of the following exclusion criteria were met: i) *in vitro* or animal studies; ii) data duplication, overlapping or unreliably extracted or incomplete data; iii) abstract only articles, reviews, thesis, books, conference papers or articles without available full texts (editorials, author response, letters, and comments) along with any previous systematic reviews, meta-analyses and literature reviews on our topic of interest. Three reviewers independently performed an initial eligibility assessment on the retrieved titles and abstracts. Full texts of eligible articles were then retrieved and reviewed for inclusion in the systematic review and were further screened for inclusion in the meta-analysis. In both steps of the screening, inclusion or exclusion of a study by all three reviewers was considered conclusive. Controversies during the process were resolved by discussion and consensus. When necessary, disagreements and discrepancies were resolved by consensus with senior reviewers.

Data extraction

Based on a pilot review and extraction, a data extraction form was developed by two authors, using Microsoft Excel file. Three reviewers independently extracted data from included studies using the excel sheet. Data rechecking was carried out by at least two different authors and re-checked by the third reviewer for accuracy. All the disagreements and discrepancies were resolved by discussion and consensus. Papers published by the same research group and studying the same factors were checked for potential duplicate data based on the year of patient recruitment and the hospital where the patients were recruited and confirmation from study authors.

Quality assessment

Three independent reviewers evaluated the risk of bias in included studies. Methodological quality assessment was done using the National Institute of Health (NIH) quality assessment tool to determine the quality of the included studies. Any discrepancy between the reviewers was solved by consensus.

Statistical analysis

Meta-analyses were performed using meta-package in R 3.4.4 when there was more than one study [10]. Dichotomous variables were pooled to compute pooled prevalence rate (PR). A fixed-effect model was used when there is no evidence of heterogeneity between

studies, otherwise, a random-effects model was chosen. Heterogeneity between studies was evaluated using the Q statistic and I^2 test which describes the percentage of variability in the effect estimates that is because of heterogeneity beyond sampling error [11,12]. To evaluate the presence of publication bias, Begg's funnel plot [13] and Egger's regression test [14,15] will be performed when there were ten or more studies in the analysis. The publication bias will be considered significant when the p-value was < 0.1. If the publication bias was found, the trim and fill method of Duvall and Tweedie was performed by adding studies that appeared to be missing [16,17] to enhance the symmetry [18].

Results

Search results

A total of 1650 studies were initially retrieved. When duplicated studies were removed, 1366 studies remained for further selection and investigation. After a thorough screening of titles, abstracts, and keywords, 263 articles were selected for further full-text screening. Following the full-text screening, 257 articles were excluded based on the pre-specified exclusion criteria with only six remained. Manual search resulted in the identification of two more relevant studies. Eventually, a total of eight studies were included in the meta-analysis of this systematic review. A flow chart illustrating the systematic review process of identifying and selecting studies based on the widely accepted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines is presented in figure 1 [19].

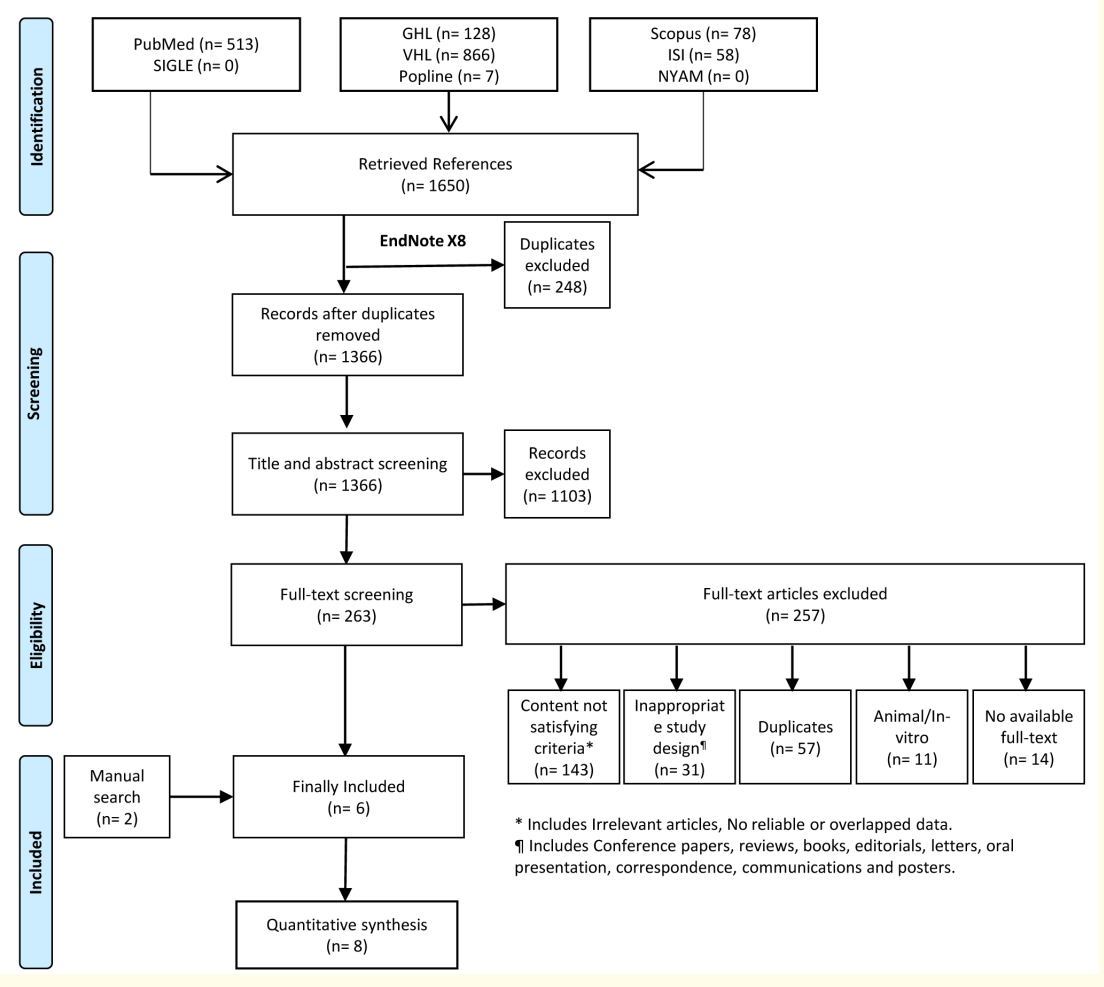

Figure 1: *PRISMA flow diagram.*

Characteristics and quality of included studies

Eight studies were finally included in the qualitative synthesis of the study with variable study designs including; four cohorts [7,20-22], three cross-sectional studies [6,8,23] and one clinical trial [24]. Additionally, sample sizes ranged from only 17 to as high as 604 with ages of included subjects varying significantly between children, adolescents, and adults. Moreover, subclinical and overt hypothyroidism was the dominant type among the included studies, whereas anemia types were varying even within the same study. The quality of five of the included studies was fair while three of them were poor in quality (Table 1).

Reference ID	Study design	Sample size (N)	Age Mean (SD)	Gender (male) (N)	Type of hypothyroidism	Type of anemia	Quality rating
Mehmet/2012/ Turkey [6]	Cross-sectional	200	44.7 (1.8)	27	subclinical and overt	Macrocytic, normocytic and microcytic	Poor
Anand/2017/ India [7]	Prospective cohort	383	(18 - >70)#	93	subclinical and overt	Macrocytic, normocytic and microcytic	Fair
Jahromi/2010/ Iran [24]	Clinical trial	70	45.3 (13.7)	14	NR	Macrocytic, normocytic and microcytic	Poor
Bensalah/2016/ UK [20]	Retrospective cohort	604	NR	NR	subclinical and overt	NR	Fair
Refaat/2014/KSA [23]	Cross-sectional	108	NR	NR	subclinical and overt	Normocytic and microcytic	Poor
Chu/1981/USA [21]	Retrospective cohort	17	NR	8	NR	NR	Fair
Dawson/1970/ USA [22]	Retrospective cohort	96	NR	NR	NR	NR	Fair
Patel/2019/India [8]	Cross-sectional	472	39.1 (1)	99	subclinical and overt	Macrocytic, normocytic and microcytic	Fair

Table 1: *Basic characteristics and quality of the included studies.*

N: Number; #: Range; NR: Not Reported.

Prevalence of anemia in hypothyroidism

A total of 1950 patients from eight studies were included in the meta-analysis. The pooled overall prevalence rate of anemia among hypothyroid patients was 33.77% with 95% CI (21.53 to 52.95). The lowest prevalence rate reported from all studies was 5.96% [20] while the highest one was 62.14% [7]. Moreover, there was statistically significant heterogeneity in the results with $I^2 = 98\%$ and $P < 0.001$ (Figure 2). Assessment of risk of bias and funnel plot wasn't possible due to the small number of studies (less than ten).

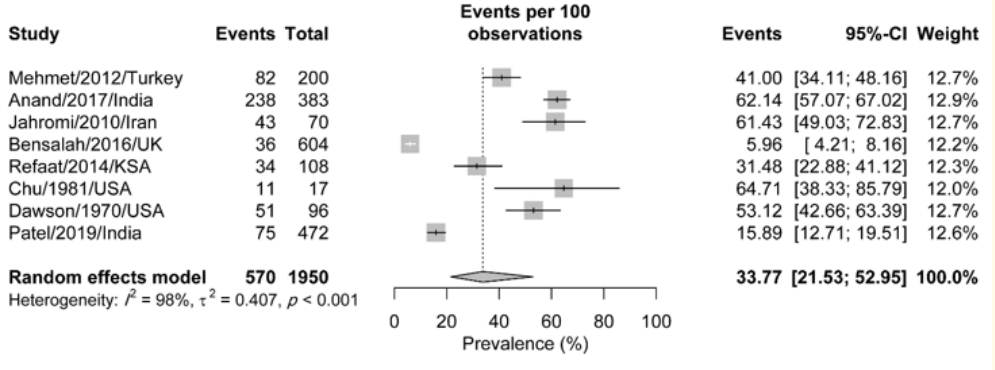

Figure 2: *The overall prevalence of anemia in hypothyroidism.*

In the same context, further subgroup analysis was done for both anemia and hypothyroidism types. The highest prevalence rate was for normocytic anemia [PR (95%) = 46.27 (34.46 to 62.14)] followed by microcytic [PR (95%) = 24.36 (14.68 to 40.44)] and macrocytic anemias [PR (95%) = 16.36 (11.66 to 22.96)], respectively. The difference in prevalence rate among different types of anemia was statistically significant (Chi^2 = 21.07; df = 2; P< 0.001) (Figure 3). However, there was no similar significant difference among different hypothyroidism types (Chi^2 < 0.001; df = 1; P < 0.980). The prevalence of anemia in overt hypothyroidism was 24.79% (95% CI = 11.01 to 55.81) and 24.47% (95% CI = 13.41 to 44.67) for subclinical hypothyroidism (Figure 4).

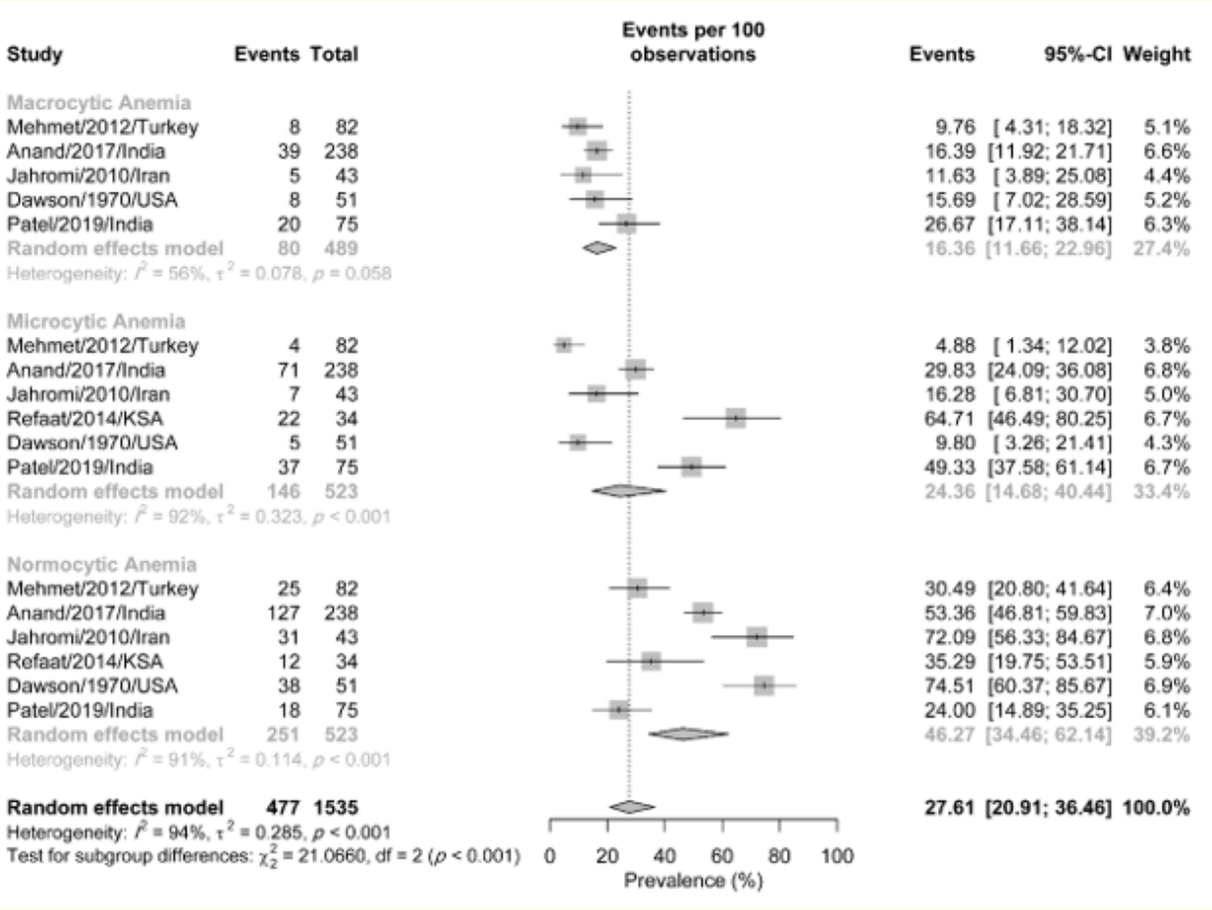

Figure 3: *Prevalence of anemia in hypothyroidism (sorted by anemia type).*

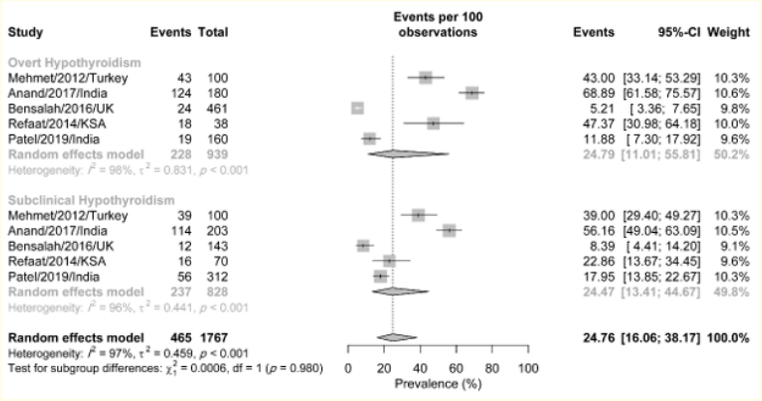

Figure 4: *Prevalence of anemia in hypothyroidism (sorted by hypothyroidism type).*

Discussion

Multiple etiologies lie behind the occurrence of anemia in many patients, including the elders, including, nutritional deficiencies and chronic diseases [25,26]. However, the underlying cause in approximately one-third of cases remains unexplained [26]. Noteworthy, anemia has been documented to occur in a large portion of patients with hypothyroidism, ranging from 23% to 60% [7,23,27,28]. It has been reported that anemia is the first presenting sign in patients with hypothyroidism [29]. Even though a considerable number of patients present with recurring anemia or persistent anemia that is unresponsive to treatment, most of these patients get better with levothyroxine, where a significant increase in hemoglobin level is noticeable [30,31]. That being said, with the lack of systematic reviews and meta-analyses to study the association between anemia and hypothyroidism, no conclusions can be drawn out about the indication of screening for thyroid function disturbance in patients presenting with anemia. Therefore, we conducted this investigation in order to assess the current literature and to determine the association between anemia and hypothyroidism.

Our analysis revealed an overall estimated pooled prevalence rate of anemia of 33.77% in patients with hypothyroidism. The study of Rabet-Bensalah., *et al.* [20] estimated the lowest reported prevalence rate of anemia in patients with hypothyroidism. On the other hand, the study of Anand., *et al.* [7] reported the highest prevalence rate in the literature of 62.14%. Based on the data of the World Health Organization (WHO), anemia has an estimated prevalence of 24.8% throughout the world [32]. The pooled rate in our study is higher than that reported by WHO, therefore, we can conclude that hypothyroidism can be considered as a risk factor for anemia, overall. However, the current evidence is insufficient and of poor quality. So, more studies are warranted to further elaborate such association.

Unfortunately, we encountered a significantly considerable heterogeneity in the analysis. The wide variation in laboratory definition of anemia among analyzed studies could be one of the factors attributing to the resulting substantial heterogeneity. This is also one of the limitations encountered in the literature, leading to a wide variation in prevalence rates of anemia among hypothyroidism patients. The majority of studies used the same laboratory definition of anemia (Hb below 12 g/dL for females and 13 g/dL for males) [6-8,20,24]. However, Chu., *et al.* [21] used the criteria of Hb level below the third percentile as the defining criteria of anemia among children and adolescents. On the other hand, other authors used a Hb level below 14 gm% for males and 12 gm% for females [22] and Hb below 11 regardless of gender as the criteria to define anemia [23].

In hypothyroidism, a drop in baseline metabolic rate with a reduction in baseline cellular oxygen consumption may result in a reduced secretion of erythropoietin with subsequent reduction in Hb concentration and, eventually, causing anemias either normocytic normochromic, microcytic, or macrocytic anemia, depending on presenting comorbidities [33,34]. In further subgroup analysis, our results showed that prevalence of normocytic normochromic anemia among patients with hypothyroidism was significantly higher than the other two types of anemias. On the other hand, microcytic anemia had the second rank, while macrocytic anemia had the lowest prevalence rate. This goes in line with what has been reported by other studies in literature [7,23,27,28]. They included hypothyroid patients who were untreated and also non-pregnant, so that they can control for such confounding factors, and they found that normocytic anemia was the most common type of anemia presenting in those patients. This can occur directly or indirectly through inhibition of erythroid colony development as a result of the lack of thyroid hormones and diminution of erythropoietin hormone level, with further reduction in oxygen transfer to tissues [35].

Some authors have reported that macrocytic anemia was the most prevalent type among hypothyroid patients [36], while others revealed that microcytic anemia was the most presenting type [8]. Noteworthy, it is important to thoroughly investigate the cause of anemia of either type and properly manage it accordingly. Cinemre., *et al.* [37] pointed out the importance of addressing hypothyroidism (subclinical type) in patients presenting with iron-deficiency anemia- unresponsive to treatment. They found that in hypothyroidism patients who were treated with oral iron supplementations that Hb levels had a mean decrease of 0.4 gm/dl only, while those on iron plus levothyroxine a mean reduction in Hb level of 1.9 gm/dl was noted.

From the perspective of the type of hypothyroidism, relatively similar prevalence rates of anemia in our study were noted between subclinical hypothyroidism and overt hypothyroidism. The pooled rates in each type of hypothyroidism are comparably similar to that reported by WHO as regards the worldwide population (24.80%) [32]. This points out that the frequency of anemia in subclinical and overt hypothyroidism is relatively similar to that of the general population. Moreover, this finding reveals that the risk of anemia in hypothyroidism still requires further investigation, an increase in prevalence rates of anemia could have been confounded by other co-existing comorbidities. Herein, we declare that the prevalence of anemia in hypothyroidism, overall, is relatively higher than the general population as declared by the WHO; however, the prevalence of anemia among each type of hypothyroidism is not higher but is relatively similar to that of the general population. Moreover, we point out that current literature provides insufficient evidence regarding the risk of anemia in patients with subclinical and overt hypothyroidism.

To the best of our knowledge, this is the first meta-analysis to pool the prevalence rates of anemia among patients with hypothyroidism in the literature. However, we have encountered several major limitations. First, the low quality of evidence (fair or poor) of our included studies is a major limiting factor of the generalizability of our findings. Second, the lack of a standardized laboratory definition of anemia would be the factor resulting in the variability of prevalence rates of anemia among reported studies. Third, the majority of included studies left the exclusion criteria ambiguous in terms of previous use of anemia treatment or thyroxine medications which would significantly impact the interpretation of our findings [6,8,20-22]. Fourth, the sample size of most reports was small. Finally, thyroid hormone levels were measured once only at baseline; patients who had subclinical hypothyroidism and developed overt hypothyroidism over time, or those reverted to euthyroidism may have been misclassified.

Conclusion

The high prevalence of anemia in patients with hypothyroidism suggests screening for hypothyroidism during the differential diagnosis of cases presenting with anemia. Normocytic anemia is the most common type in hypothyroidism. We strongly recommend that physicians should investigate for hypothyroidism when patients present with anemia that is either of unknown etiology or unresponsive to treatment. However, current evidence is insufficient and more studies are warranted to assess the association between anemia and hypothyroidism.

Conflict of Interest

The authors declare no conflict of interest and that no funding was received.

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