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The Influence of Nutrition and Exercise on Untreated Subclinical Hypothyroidism: A Systematic Review

Ernährung und körperliche Aktivität bei einer unbehandelten subklinischen Hypothyreose

REVIEW

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Summary

› **Problems:** Hypothyroidism is associated with increased cardiovascular events and a reduced quality of life. The goal of this systematic review is to identify additive treatment strategies besides hormone replacement through diet and exercise intervention and to point out research gaps.

› **Methods:** A comprehensive literature search was conducted in four databases (PubMed, Scopus, Science direct and SportDiscus) using defined MeSH words by two independent researchers. Literature from year 1990 onwards was considered.

› **Results:** To investigate the effects of diet and exercise on thyroid function, three randomized controlled trials and one comparative study with a total of 356 subjects (nutrition) and four randomized controlled trials with a total of 189 subjects (exercise) are identified. The nutrition-related studies show that nutritional interventions can reduce perceived symptoms in subclinical hypothyroidism. An effect on thyroid hormone serum levels has been demonstrated by an intake of selenium and phytoestrogens. Exercise-related studies show improvement in quality of life and symptoms through exercise in subclinical hypothyroidism. Changes in thyroid hormone serum levels could not be shown.

› **Discussion:** Due to the heterogeneous parameters recorded in the included studies, no clear conclusion can be drawn. Nevertheless, first findings show that nutrition and exercise have an effect on the symptoms of hypothyroidism. Both measures can reduce the development of comorbidities in subclinical hypothyroidism and improve quality of life. Studies combining both dietary intervention and exercise have not yet been conducted.

KEY WORDS:
Endocrine disorders, Thyroid Hormones, Diet, Physical Activity, Quality of Life

Zusammenfassung

› **Problemstellung:** Eine Hypothyreose wird mit vermehrten kardiovaskulären Ereignissen und einer verminderten Lebensqualität in Verbindung gebracht. Ziel dieser systematischen Übersichtsarbeit ist es, durch Ernährung und Bewegung alternative Behandlungsstrategien zu identifizieren und Forschungslücken aufzuzeigen.

› **Methoden:** Es wurde eine umfassende Literaturrecherche in vier Datenbanken (PubMed, Scopus, Science direct und SportDiscus) unter Verwendung definierter MeSH-Wörter von zwei unabhängigen Forschern durchgeführt. Berücksichtigt wurde Literatur ab dem Jahr 1990.

› **Ergebnisse:** Zur Untersuchung der Auswirkungen von Ernährung und Bewegung auf die Schilddrüsenfunktion wurden drei randomisierte kontrollierte Studien und eine vergleichende Studie mit insgesamt 356 Probanden (Ernährung) und vier randomisierte kontrollierte Studien mit insgesamt 189 Probanden (Bewegung) identifiziert. Die ernährungsbezogenen Studien zeigen, dass Ernährungsinterventionen die wahrgenommenen Symptome bei einer subklinischen Hypothyreose verringern können. Ein Einfluss auf die Schilddrüsenhormon-Serumspiegel wurde durch die Einnahme von Selen und Phytoöstrogenen nachgewiesen. Studien zum Thema Bewegung zeigen eine Verbesserung der Lebensqualität und der Symptome bei einer subklinischen Hypothyreose. Veränderungen des Schilddrüsenhormon-Serumspiegels konnten nicht nachgewiesen werden.

› **Diskussion:** Aufgrund der heterogenen Parameter, die in den eingeschlossenen Studien erfasst wurden, kann keine eindeutige Schlussfolgerung gezogen werden. Dennoch zeigen erste Ergebnisse, dass Ernährung und Bewegung einen Einfluss auf die Symptome der Hypothyreose haben. Beide Ansätze zeigen das Potential die Entwicklung von Komorbiditäten bei einer subklinischer Hypothyreose zu verringern und die Lebensqualität der Patienten zu verbessern. Studien, die eine Ernährungsintervention und körperlicher Aktivität kombiniert haben, gibt es bislang noch nicht.

SCHLÜSSELWÖRTER:
Hormonelle Störungen, Schilddrüsenhormone, Ernährungsintervention, Sport, Lebensqualität

Introduction

Hypothyroidism is the pathological condition of thyroid hormone deficiency. If left untreated, it can result in serious adverse health effects. Diagnostically, two forms of hypothyroidism can be differentiated: The overt hypothyroidism and the subclinical hypothyroidism (sHT). Overt hypothyroidism is characterized by THS levels above the reference range (most commonly used 0.4-4.0 mIU/L) and free thyroxine levels below the reference range (8). sHT, which may be a sign of early thyroid failure, is defined as TSH concentrations above the reference range but free thyroxine still within the normal range (8, 11). In overt hypothyroidism, levothyroxine monotherapy is usually the treatment of choice. But if treatment with levothyroxine does not lead to an improvement of symptoms, a levothyroxine and liothyronine ›

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Table 1

PICOST eligibility criteria for the nutrition-related studies.

PARAMETER	INCLUSION CRITERIA	EXCLUSION CRITERIA
Population	Untreated subclinical hypothyroidism	Treatment with levothyroxine or liothyronine; Thyroid cancer; pregnancy; Overt hypothyroidism
Intervention	Diet intervention (including supplement intervention)	Concurrent treatment with levothyroxine or liothyronine
Comparator	No intervention, western diet, no comparison	/
Outcome	Effect of diet intervention on thyroid hormones or concomitant features	No information about thyroid hormones or concomitant features
Study design	Experimental or observational study with original primary data; English or German language	Study Protocol or other papers without original data; Not in English or German language
Timing	Literature from year 1990 up to May 2022	Literature published before year 1990

combination therapy can be used (8). Treatment of sHT with levothyroxine at TSH levels > 10 mU/l is generally recommended because the risk of developing overt hypothyroidism is increased (12). For TSH levels between 5 and 9 mU/l, treatment depends on the clinical situation of the patient, such as age, symptoms and cardiovascular risk factors (11). Nevertheless, over 50% of patients treated with levothyroxine report symptoms despite normalization of TSH levels (14, 28, 37, 43). At the current time, there are no alternative/additive treatment strategies besides hormone replacement therapy (8, 16).

The synthesis of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) requires the trace elements iodine (13), copper (21) and iron (47). Furthermore, selenium (47) and zinc (39) are needed for the conversion of T4 to T3. In patients suffering from autoimmune thyroid disease (also known as Hashimoto's disease), the most common cause of hypothyroidism (8), deficiencies in minerals such as iodine, iron, zinc, copper, magnesium, potassium, and vitamins A, C, D, and B can often be observed (20). Furthermore, Kalicanin et al. (2020) identified differences in nutritional patterns between patients with autoimmune thyroid disease and healthy individuals. Animal fat, processed meat and nuts were shown to be consumed more frequently by patients suffering from Hashimoto's disease. Red meat, non-alcoholic beverages, whole grains, plant oil, olive oil, liquor, oily fish and fruits are ingested significantly more often by healthy individuals. It was suggested that a number of dietary recommendations might be of help for the management of hypothyroid patients (19).

In addition, physical activity also appears to influence thyroid function. Some studies reported changes in thyroid hormones as a result of endurance training in euthyroid subjects (4, 17, 27, 40, 45). Likewise, athletes partly show altered thyroid hormone levels. For example, reduced T3 levels were found in long-distance runners (18). Physical activity also seems to have positive effects on thyroid function in hypothyroid patients who are adjusted with levothyroxine (6).

The subclinical form is the most prevalent form of hypothyroidism. Only a small minority of patients with sHT have symptoms. However, the evidence that levothyroxine improves symptoms in these patients is weak (34). Therefore, this review considers sHT patients who are not treated with levothyroxine. The aim of this review is to identify the influences of diet and exercise on thyroid function in patients suffering from sHT and to identify influences on possible concomitant conditions of (subclinical) hypothyroidism such as an unfavorable lipid profile, insulin resistance, increased body weight and impairments in quality of life. For this purpose, the available literature will be presented, and research gaps identified. To determine whether dietary and exercise adjustments could be additive treatments to hormone therapy, only patients not treated with levothyroxine or liothyronine will be considered in this review.

Materials and Methods

Search Strategy and Data Sources

This systematic review was conducted following the PRISMA recommendations and the reporting of meta-analysis guidelines (26). A comprehensive literature search was performed on PubMed, Scopus, Science direct, and SportDiscus to identify effects of nutrition and exercise in untreated hypothyroidism. Literature from year 1990 up to May 2022 was considered. This review included randomized controlled trials, clinical trials, clinical studies, comparative studies, and observational studies that were available in English and German and conducted in humans. The search strategy was intentionally defined broadly to avoid additional limitations on study selection for the specific topic of this review.

Nutrition-Related Studies

The following PICO (Patients, Interventions, Comparators and Outcomes) components were selected to identify the nutrition-related studies: (P) subjects with untreated subclinical hypothyroidism, no age limitation; (I) diet intervention (including supplement intervention); (C) no intervention, no (subclinical) hypothyroidism, western diet, no comparison; (O) effect of diet intervention on thyroid hormones or concomitant features. Search strategies used the following Boolean expression: („diet" OR "nutrition" OR „nutritional therapy" OR „diet therapy") AND („hypothyroidism" OR „subclinical hypothyroidism" OR "Hypothyreose").

Exercise-Related Studies

The following PICO components were selected to identify the exercise-related studies: (P) subjects with untreated subclinical hypothyroidism, no age limitation; (I) exercise intervention; (C) no intervention, no hypothyroidism, no comparison; (O) effects of exercise intervention on thyroid hormones or concomitant features. Search strategies used the following Boolean expression: („hypothyroidism" OR „subclinical hypothyroidism" OR „Hypothyreose") AND („fitness" OR „physical activity" OR „physical exercise" OR „training" OR „Fitnesstraining" OR „workout").

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the selection of nutrition-related studies, are described in table 1. The inclusion and exclusion criteria for the selection of exercise-related studies, are described in table 2.

Data Extraction and Quality Assessment

Based on the above criteria (table1 and table 2), two reviewers (Lars Hanke and Leena Wedde) independently screened the titles and abstracts and selected the eligible articles. After duplicates were removed and abstracts screened, potentially

eligible full-text articles were downloaded and independently reviewed by the authors. In case of disagreement another reviewer (Eduard Isenmann) was consulted, if necessary, to resolve disputes about the quality assessment. Data of the year of publication, age and sex of the patients, type of intervention and the results were recorded. As a result of the heterogeneity of study designs and assessment methods used in the included studies, a statistical meta-analysis was not performed.

Results

Study Selection and Characteristics

The following describes the selection of both the nutrition-related articles and the exercise-related articles for the Systematic Review. The selection strategy is identical in both fields.

Nutrition-Related Studies

Through databases research a total of 3226 articles were identified. After title screening and duplicate removal, 108 articles remained. Subsequently abstracts were screened. 85 additional articles were removed because the inclusion criteria were not met. 23 articles remained in the analysis. Then, 19 of these articles were excluded after full-text screening because they also did not meet the inclusion criteria. As a result, a total of 4 articles fulfilled the eligibility criteria and were finally included in the systematic review (Fig. 1). The selected articles were published from year 2010-2020.

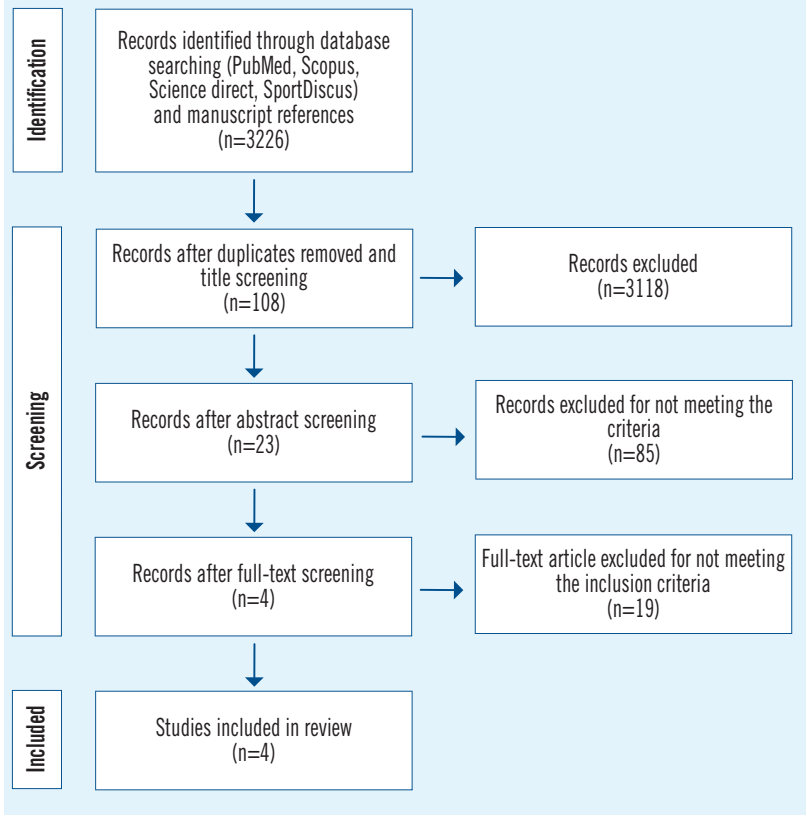

Figure 1

PRISMA flow diagram of the nutrition-related studies.

Exercise-Related Studies

Through databases research a total of 2312 articles were identified. After title screening and duplicate removal, 35 articles remained. Subsequently abstracts were screened. 20 additional articles were removed because the inclusion criteria were not met. 15 articles remained in the analysis. Then, 11 of these articles were excluded after full-text screening because they also did not meet the inclusion criteria. As a result, a total of 4 articles fulfilled the eligibility criteria and were finally included in the systematic review (Fig. 2). The selected articles were published from year 2009-2019.

Data Extraction

Nutrition-Related Studies

Table 3 (see supplemental material online) shows the main characteristics and results of the included nutrition-related studies that evaluate the effects of diet and supplement intervention on thyroid function, hypothyroidism related symptoms and related conditions. All participants of the experimental (EG) and the control groups (CG) have an untreated sHT. However, the interventions differ widely:

Akasheh et al. (2019) investigate the influence of alternate day fasting (ADF) and calorie restriction (CR) on the weight loss efficacy in adults with sHT. Both methods lead to a significant body weight reduction, relative to controls. The reduction in body fat between ADF and CR was comparable, but insulin resistance was reduced more by ADF. Changes in fT4 and THS could not be observed (2). Van der Gaag et al. (2020) conducted a nutrition intervention with children suffering from sHT. The intervention required subjects to consume a selection of foods rich in selenium, vitamin A, iron, omega-3 fatty acids, and iodine, as these nutrients are essential for healthy thyroid function. They could identify a significant reduction of fatigue in the EG and a non-significant reduction of TSH in the EG and the CG (42). The remaining two studies did not examine dietary patterns, but rather influences of dietary supplements on thyroid function and concomitant features of hypothyroidism. Sathyapalan et al. (2011) administered 30 g of soy protein with 16 mg of phytoestrogens for 8 weeks to adult patients with untreated sHT. Through this intervention, 10% of participants developed an overt hypothyroidism. Nevertheless systolic and diastolic blood pressure, insulin resistance and hsCRP decreased (38). Pirola et al. (2016) investigated the effect of selenium supplementation on thyroid function in adults with untreated sHT. By taking 83 mcg of selenium for a period of 4 months, 17.2% of the EG achieved euthyroid status. This was comparable to only 3.1% of the CG (33).

Exercise-Related Studies

Table 4 (see supplemental material online) shows the main characteristics and results of the included exercise-related studies that evaluate the effects of aerobic and resistance training on thyroid function, hypothyroidism related symptoms and related conditions. All participants of the EG have an untreated sHT. However, in some cases healthy participant were used as a control. The training interventions differ greatly:

Xiang et al. (2009) examined the influences of 6 months walking/jogging training on thyroid function and concomitant features of hypothyroidism. They used sHT patients in the EG and a healthy CG. It was shown that triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), C-reactive protein (CRP), antithyroid peroxidase (TOP-Ab) and antithyroglobulin (Tg-Ab) were significantly higher in the ›

Table 2

PICOST eligibility criteria for the exercise-related studies.

PARAMETER	INCLUSION CRITERIA	EXCLUSION CRITERIA
Population	Untreated subclinical hypothyroidism	Treatment with levothyroxine or liothyronine; Thyroid cancer; pregnancy; Overt hypothyroidism
Intervention	Exercise intervention	Concurrent treatment with levothyroxine or liothyronine
Comparator	No intervention; no comparison	/
Outcome	Effect of exercise intervention on thyroid hormones or concomitant features	No information about thyroid hormones or concomitant features
Study design	Experimental or observational study with original primary data;	Study Protocol or other papers without original data; Not in English or German language
	English or German language	
Timing	Literature from year 1990 up to May 2022	Literature published before year 1990

sHT group than in the healthy CG. In addition, aerobic training significantly reduced TC, LDL, TG, and CRP in the sHT group but not in the CG and there was an increase of $\dot{V}O_2$max in both groups. Nevertheless, there were no changes in terms of thyroid function, TPO-Ab and TG-Ab (46). Ahn et al. (2019) conducted a combined strength and endurance training program for a period of 12 weeks. They also examined patients with sHT and used healthy participants as CG. Each training session consisted of strength exercises with a resistance band and an endurance workout on the bicycle ergometer. The intervention demonstrated reductions in body fat, systolic blood pressure (BP), LDL, and carotid artery intima-media thickness (IMT) in both groups. No changes in waist-hip ratio (WHR), TC, TG, HDL, T3, T4, fT4, and TSH were observed. Furthermore there were no changes in insulin, glucose, aspartate transaminase, alanine transaminase and HOMA insulin resistance (HOMA-IR) between groups (1).

Werneck et al. (2018) conducted a cross-sectional (phase 1) and a longitudinal (phase 2) study. In the first phase, they compared quality of life (QoL) among participants with untreated sHT and a healthy control group. For this purpose, they used the SF-36 questionnaire. It was shown that the sHT group was less physically active and had significantly lower scores in the "functional capacity" dimension than the healthy CG. Similarly, except for the category "social aspects", the scores of the other dimensions were also lower in the sHT group, but not significantly. In the second phase, the sHT group was divided into an intervention group (EG) and a passive CG. The EG performed a 16-week endurance training using a treadmill and a bicycle ergometer. Before and after intervention, the SF-16 was used in both groups. As a result the scores of "functional capacity", "general health", "emotional aspects", "psychological component" and "physical component" increased in the EG (44).

Garces-Arteaga et al. (2013) conducted a 12-week aerobic circuit training program with patients that suffer from sHT. There was no CG. Before and after the intervention, the SF-12 was performed to determine QoL and the $\dot{V}O_2$max was determined. After intervention subjects showed (not significant) improvements in the "vitality" domain, the "social functional" domain, the "mental health" domain and the "mental component summary". Significant improvements were noted in the "general health" domain and an increase of $\dot{V}O_2$max was noted (15).

Discussion

At the current time, hormone replacement (in particular levothyroxine monotherapy) is the only form of treatment for hypothyroidism (8). The trace elements iodine (13), copper (21), iron (47), selenium (47) and zinc (39) are needed for healthy thyroid function. In patients with Hashimoto's disease, deficiencies of iodine, iron, zinc, copper, magnesium, potassium and vitamins A, C, D and B are common (20). For this reason, nutritional behavior seems to be of particular importance in maintaining or establishing healthy thyroid function. In addition, there are large numbers of studies that demonstrated effects of physical activity on thyroid function in euthyroid subjects (3, 5, 9, 10, 22, 29, 30, 31, 32, 36). Therefore, it is a plausible assumption that nutrition and exercise interventions can positively influence thyroid function in patients suffering from hypothyroidism and its unfavorable concomitant conditions.

Nutrition-Related Studies

Regarding the nutrition-specific studies, there were 4 studies found that met the inclusion criteria (2, 33, 38, 42). However, the methodological approach and the measuring methods were very heterogeneous. Two studies examined dietary patterns (2, 42), while the other two investigated the influences of individual nutrients (33, 38). Influences on thyroid function in untreated sHT patients could only be shown by the studies of Sathyapalan et al. (2016) and Pirola et al. (2016). Accordingly, the intake of phytoestrogens in soy proteins can lead to an increase in TSH and a reduction in fT4 and consequently to a deterioration of thyroid function (38) and the intake of selenium can induce a reduction in TSH (33), suggesting improvement in symptoms. The studies by Akasheh et al. (2019) and van der Gaag et al. (2020), who conducted nutritional interventions, were unable to detect changes in thyroid function but showed positive influences on unfavorable concomitant conditions of hypothyroidism. Thus, it was shown that caloric restriction as well as alternate day fasting in untreated sHT leads to a decrease in body fat and reduced insulin resistance. The latter even more due to alternate day fasting (2). Also, a diet rich in nutrients associated with improved thyroid function has been shown to reduce fatigue in untreated sHT patients (33). In addition to the strong distinctions between intervention types, different intervention lengths were selected-either 2 (38), 4 (33), or 6 months (2, 42). Furthermore the studies showed strong age differences. Across studies, the age range of participants varies from 7 to 65 years (table 3, see supplemental material online). For this reason, it is not possible to compare the studies with each other suitable. The literature shows that while the targeted use of supplements such as selenium (33) can influence thyroid function, dietary changes cannot. However, an influence of different diets (e.g. ketogenic diet, gluten free diet) on thyroid function could be demonstrated in euthyroid individuals (7, 23, 24, 35). According to a meta-analysis, all patients with Hashimoto's disease should be screened for celiac disease because the coexistence of these two diseases is more common (35). It has been shown that a gluten-free diet can reduce the antibodies TPO-Ab and TG-Ab in patients with Hashimoto's disease and normal TSH levels (23). For this reason, a reduction of gluten seems to have the potential to be beneficial for the majority of patients as well. Nevertheless, studies examining effects of these diets on thy-

roid function in patients suffering from sHT are lacking. In addition, there also appear to exist substances that negatively affect thyroid function, such as foods that contain high levels of phytoestrogens, like soy protein (38). Identification of such foods could help to provide specific dietary recommendations to sHT patients.

Exercise-Related Studies

Regarding the exercise-specific studies, 4 studies were identified that met the inclusion criteria (1, 15, 44, 46). As in nutrition-specific studies, there were strong methodological differences. Two studies used pure endurance training (44, 46), one included a circuit training (15), another had a combined strength and endurance training (1), and one study included a cross-sectional survey (44). This might have a different impact on the study outcomes. In addition, heterogeneous parameters were recorded in all identified studies, which impairs comparison of the studies. Xiang et al. (2009) and Ahn et al. (2019) identified physiological parameters such as body fat, waist-to-hip ratio, and various blood markers. They demonstrated that the TC, TG, LDL, CRP, TPO-AB, and TG-AB were significantly higher in untreated sHT patients compared to the healthy control group. In addition, the TC, LDL, TG, CRP and FMD could be reduced by 6 months of endurance training (46). Similarly, body fat, systolic BP, LDL and IMT could be reduced by a combination of resistance and endurance training (1). Changes in thyroid hormones were not shown in any of the studies (1, 46). Werneck et al (2018) and Garces-Arteaga et al. (2013) examined patient quality of life through a survey (SF-36 and SF-12 respectively). It could be shown that untreated sHT patients are less physically active than the healthy control group. However, 4 months of endurance training and 3 month of circuit training improved almost all domains (15,31). However, the domains "vitality", "mental health", the "functional domain" and the "mental component summary" improved non-significantly (15).

In addition to different measurement parameters, the lack of a control group involving patients with sHT (rather than healthy participants) (1, 44, 46) is a limitation of the studies. A control group consisting of inactive sHT patients would better clarify the effects of the interventions. One study did not use a control group (15), making interpretation of the results difficult. In addition, endurance-based training was performed in all studies. Only one study included light strength training in addition to endurance training (1). For this reason, no conclusions can be drawn about the influences of other forms of exercise like strength training or high-intensity endurance exercise.

Another important point is that thyroid hormones decrease during very intense exercise. This can be explained as a metabolic response to decreased availability of thyroid hormones (41). Therefore, it can be concluded that an increase in thyroid hormone concentration, for example by the intake of levothyroxine, could increase physical performance. First indications for this are already provided by a study of Maintenti et al. (2009), who could prove an increase of the submaximal cardiopulmonary performance by a levothyroxine-induced normalization of TSH in untreated sHT (25). Whether targeted exercise or nutritional interventions have the potential (alone or as an addition to hormone replacement) to raise thyroid hormone concentrations and concomitantly increase exercise performance is not clear.

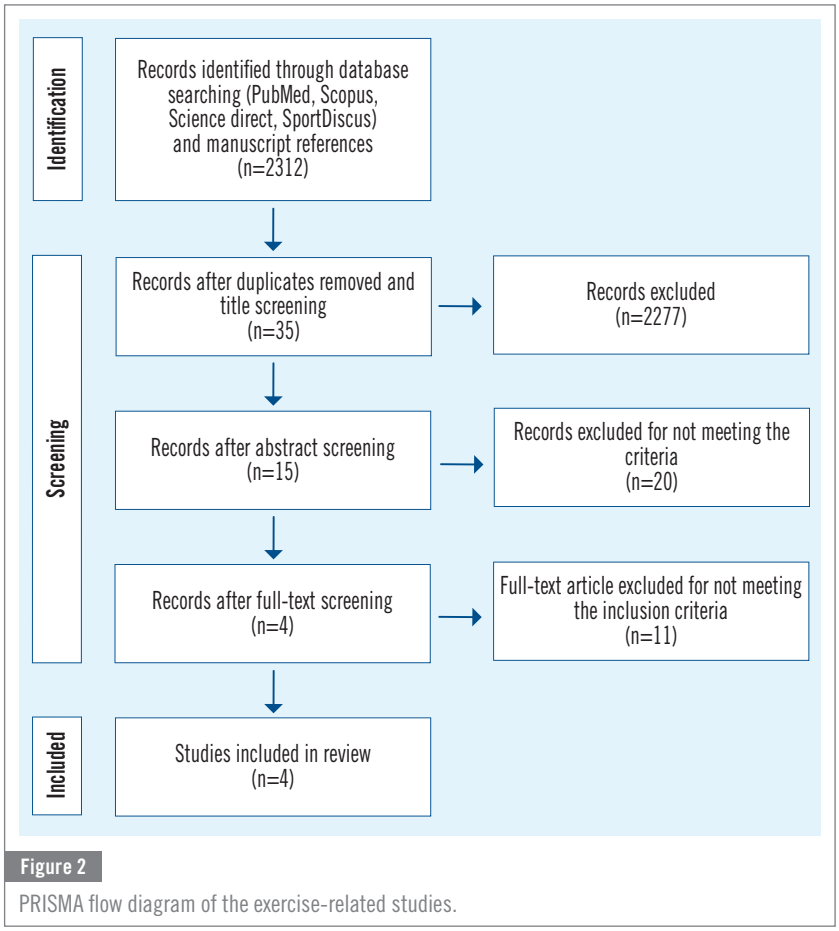

Figure 2

PRISMA flow diagram of the exercise-related studies.

Indications for Future Studies

The aim of this review is to present the current state of research on the influence of diet and exercise on thyroid function in untreated sHT patients. The number of studies identified is very small. Furthermore, a comparison of the studies is hardly possible due to heterogeneous study designs. Likewise, qualitative weaknesses of the studies can be identified in part (e.g., small samples, no or suboptimal control groups). Future studies should work with randomized and comparable samples. In addition, influences of many diets, such as gluten-free, vegan, vegetarian, or the targeted intake of trace elements or vitamins have not been investigated in untreated sHT. Furthermore, besides endurance training, no other forms of physical activity, such as strength training, have been considered. This could be an issue for future research.

Conclusion

At the current time, the administration of levothyroxine and/or liothyronine is the only treatment option for hypothyroidism. This review aimed to identify whether nutritional or exercise interventions may represent possible treatment options in untreated sHT. It could be shown that the quality of life and unfavorable concomitant conditions, such as elevated LDL, triglycerides, insulin resistance and body fat of patients with sHT can be beneficially influenced by changes in diet and exercise behavior. According to current research, changes in thyroid function in patients with untreated sHT can only be achieved by the intake of selenium (reduction of TSH) or the targeted intake of phytoestrogens through soy protein (increase of TSH). For this reason, first restults indicated that moderate consumption of soy protein, a diet rich in trace elements and vitamins associated with healthy thyroid function-especially ›

selenium-and regular, moderate exercise-especially endurance training-seem to have a beneficial effect on the complaints of patients suffering from hypothyroidism. However, such a change in lifestyle seems inferior to classical hormone replacement according to current research. It should be emphasized that due to the widely varying methods and small number of studies, further influences on thyroid function by dietary patterns, dietary supplements, or other forms of physical activity (e.g., weight training) have not yet been identified. In addition to the potential of exercise interventions and dietary strategies, negative side effects such as possible endocrine disruptors should be considered. Further research is needed in these fields.

Conflict of Interest

The authors have no conflict of interest.

Authors' Contributions

Lars Hanke, Leena Wedde and Eduard Isenmann conceived and designed the systematic review. Lars Hanke and Leena Wedde independently reviewed abstracts and papers and disagreements were resolved by consensus of Lars Hanke, Leena Wedde and Eduard Isenmann. Lars Hanke revised the draft of the manuscript, which was critically reviewed by all authors for important aspects of content. Stefan Geisler, Patrick Diel and Eduard Isenmann revised the manuscript and contributed with intellectual ideas. All authors have read and agreed to the published version of the manuscript.

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