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SYSTEMATIC REVIEW

New Guidelines to Designing Interventions that Assess Resetting Thyroid Metabolism with the Integration of Nutrition-Based Exercise Programs

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ABSTRACT

Background: Modifying lifestyle with exercise is generally used to manage preventative medical conditions but is not utilized to manage acquired thyroid disease. Few literature reviews have documented physical activity (PA) in successfully resolving thyroid conditions (hyperthyroidism, hypothyroidism, and autoimmune thyroid disease [AITD]).
Purpose: We aimed to investigate whether PA or specified exercises can alter thyroid hormone activity to resolve disease conditions in patients with thyroid disease.
Methods: Electronic databases were searched for clinical trials investigating the relationship between PA and thyroid disease. Clinical outcomes included the improvement of thyroid hormones or antibodies, health-related quality of life (HRQoL), or resolution of thyroid conditions.
Results: Seven studies evaluated thyroid biomarkers or HRQoL in patients with thyroid conditions. Of the five studies that evaluated exercise programs on thyroid biomarkers, significant improvements were observed in TSH in three studies, T4 in three studies , and T3 in two studies. One study that evaluated AITD biomarkers demonstrated significant improvements in c-reactive protein, thyroid peroxidase, thyroglobulin, TBARs, and OPG concentrations. Other significant improvements included reductions in HOMA-IR in one study, systolic blood pressure in one study, heart rate in two studies, anthropometric measurements in two studies, and increases in VO_2max in three studies. Endurance, aerobic-resistance, and structured training positively affected patients with thyroid conditions. While medium-intensity exercise training and long-term durations (6mos) demonstrated statistical improvements. Two studies reported medication reduction and resolution of thyroid conditions, while two studies assessing HRQOL observed significant improvements across multiple domains.
Conclusion: Endurance, aerobic-resistance, and structured training improved various thyroid biomarkers, HRQoL domains, and may contribute to resolving thyroid disease. Nutrition-based exercise programs should be designed to target the metabolic impacts of thyroid conditions. Further research should use comprehensive guidelines to test the reliability of such results.

Epidemiology

Thyroid medication is the conventional therapeutic approach for treating thyroid disorders. There are over 20 million (6%) Americans diagnosed with thyroid diseases, resulting in more than 90 million (27%) written prescriptions annually.[1] Despite pharmaceutical treatment, the prevalence of thyroid conditions continues to rise, with significant increases reported over the last 5 years.[2] Since medication alone appears insufficient in suppressing rising prevalence, there is a growing demand to explore other factors influencing thyroid health. Lifestyle habits, such as dietary patterns,[3,4] physical activity (PA) levels,[3,5] and increased stress[4,5] have emerged as plausible contributors to thyroid disorders. Taking these factors into account, the authors of this review conducted a rapid search. Two studies[6,7] were discovered claiming resolution of thyroid diseases with exercise programs: 1) subclinical hypothyroidism (SH);[6] and 2) Graves' disease (GD).[7] These findings were perplexing given that 90% of SH cases are Hashimoto's thyroiditis (HT) cases,[8] and that HT and GD are the result of chronic destructive auto-immune cells.[4,9–13] However, thyroid pathophysiology is frequently linked with comorbidities including type 2 diabetes mellitus (T2DM) and cardiovascular complications[10,14] that are recognized to be amenable to lifestyle modification, such as exercise. In light of these contrasting theories, it was decided to perform a systematic review to evaluate if analogous lifestyle interventions may yield positive outcomes in the management or resolution of thyroid conditions.

Understanding Thyroid Autoimmunity

Autoimmune thyroid disease (AITD) is characterized as a loss of immune self-tolerance, involving lymphocytes,

monocytes, and neutrophils.[11,12,15] Lymphocytes include auto-antibody producing bone-marrow-derived (B) cells and thymus-derived (T) cells, with clusters of differentiation ($CD4^+$ and $CD8^+$) surface antigens expressed on T cells.[11,12,15] Monocytes act as antigen-presenting cells (APCs), presenting peptides onto MHC class I and II molecules.[12] High-stress or intense physical activity can increase leukocyte counts, leading to the mobilization of cytotoxic natural killer (NK) cells, T and B cells, and the elevation of cytokines including interferon-gamma (IFN-γ), interleukin 6 (IL-6), IL-10, IL-17, and tumor necrosis factor-alpha (TNF-α).[5,16,17]

Recent findings indicate that auto-reactive B cells play a significant role in the development of AITD.[11,12] These B cells secrete $CD19^+$IL-10 (B10) cytokines and can convert to memory B cells, sustaining the adaptive immune response.[11,12] In HT and GD, auto-reactive B10 cells infiltrate the thyroid along with $CD4^+$ Th and $CD8^+$ cytotoxic T cells, driving the production of IL-6 and IL-17 proinflammatory cytokines, and autoantibodies targeting thyroglobulin (Tg) and thyroid peroxidase (TPO).[4,11] Chronic mild stress and activation by T helper (Th) cells further enhance B cell activity, impacting thyroid-stimulating hormone receptor (TSHR) interactions.[4,12]

Autoimmune thyroid disease is associated with increased Th17 and Treg cells that express forkhead box P3 (FoxP3) transcription factor.[11,15,18] T helper 17 cells are influenced by IL-6 and transforming growth factor-beta (TGF-β), which drive their differentiation through the retinoic acid-related orphan receptor C (ROR-C).[11,15,18] B cells, particularly B10 cells, contribute to the release of IL-17 from Th17 cells, while Treg cells maintain self-tolerance and express FoxP3.[4,11,17] Elevated levels of IL-6 and FoxP3, along with interactions between Tg and TPO, further affect Th17/Treg ratios, impacting AITD development.[11–13] In AITD, Th17 and Treg cells expressing FoxP3 are linked to increased levels of glucocorticoid-induced tumor-necrosis-factor-receptor (GITR) proteins.[11–13] Cortisol, a key glucocorticoid affected by stress and exercise, plays a major role in the biochemical changes associated with AITD.[4,5,16] The GITR ligand (GITRL), mainly expressed by APCs, influences the Th17/Treg ratio, with higher levels of $CD4^+GITR^+$ and $CD4^+FoxP3^+$ cells observed in AITD patients.[11,18] TGF-β promotes the development of Treg cells from naive T cells, though IL-6 can revert them back to Th17 cells, highlighting the impact of glucocorticoids on immune regulation in AITD.[13,16]

IL-6 is produced by skeletal muscle during exercise and by the adrenal glands during stress, influencing immune responses.[5,16] Activation of the sympathetic nervous system (SNS) and catecholamine neurotransmitters from the brainstem and adrenomedullary system stimulate IL-6 secretion and modulate Th cell regulation.[4,5,16] IL-6 acts through β2-adrenergic receptors (β2-AR)on Th antigen-presenting cells and impacts various cytokines and thyroid-releasing hormone (TRH).[4,5] Furthermore, glucocorticoids, influenced by stress, reduce TSH secretion, modify Th1 and Th2 activity, and regulate autoantibody production and leukocyte behavior in AITD.[4,5,17]

The next section highlights the impact of PA on both non-autoimmune and autoimmune thyroid functions.

Impact of PA on Thyroid Functions: FItTeD Insights

Frequency and Intensity on Hormonal Responses

The impact of PA on thyroid function is modulated by '*FItTeD'* factors: frequency (*F*), intensity (*It*) level, type (*Te*), and duration (*D*).[19–22] Beginning with physical exertion, PA triggers a surge in heart rate (HR),[23–24] instigating a cascade of augmented endocrine responses, and as PA '*frequency*'[25]or '*intensity*' [6,7,19–21, 25–32] increases, hypothalamic-pituitary-adrenal (HPA) axis responses become heightened.[4,5,16,17,25] Several studies have elucidated the effects of both exercise[5–7,16, 19,21,25–32] and psychological stress[5,16,17] on the production of TRH, TSH, TSHR, triiodothyronine (T3), and thyroxine (T4).[4–7,19,21,25–32] Iodothyronine deiodinase type 1 (DIO1), DIO2, and DIO3 protein coding gene catalyzation processes are also affected by increased levels of catecholamines,[5] cortisol,[5] and cytokines.[5,33] As well, DIO1, DIO2, and DIO3 convert T4 to T3 or T4 to reverse (R) T3 within the thyroid gland, liver, central nervous system (CNS), and gastrointestinal tract,[5,25,28,32,33] while DIO2 enzymes are particularly subject to the regulation of muscle activation.[25,32] This ensures the production of T3 is essential for preserving active muscle functions and prevention of fatigue.[7,25,28,32] However, deiodinase processes facilitating TSH activity can be negatively affected by elevated proinflammatory cytokines,[5,33] and cellular membrane activity, thereby reducing T3 action on muscle and mitochondrial respiratory functions causing fatigue, which is often observed in AITD patients.[7,25,28,32] This may indicate that frequent, high-intensity PA can persistently activate the HPA axis, resulting in chronic elevation of stress hormones eliciting adverse effects on the immune system influencing deiodinase enzymes, thereby inhibiting thyroid hormone production.

Activity Type and Endocrine-HPA Axis

The physiological functions of muscle are potentiated by PA[25,32] and different '*types*' of movement can impact several metabolic responses.[22,25,32,34–37] PA also

regulates maximal oxygen consumption (VO_2max).[7,22,23,26,27,32,34] As such, endurance and aerobic type activities with intensity levels above moderate levels (60-70%), alters immune activity,[16,27] improves inflammatory biomarkers,[27] and increases IL-6 activity; whereas, elevated IL-6 causes heightened cortisol and HPA axis stimulation.[13,16] Studies have observed elevated cortisol levels in highly trained runners,[5,16] as increased levels of chemokines and integrins are freely available in circulation[16] after muscle contraction from various types of activity. Particularly aerobic activities using large muscle groups or high-intensity interval training impact metabolic efficiency.[38] While fitness productivity improves VO_2max,[22,23,32,34,36,37] when individuals reach a level of 100%, both steady-state and high-intensity exercise suppresses T4 to T3 conversion and elevates cortisol and reverse T3.[38] Maximal oxygen consumption is usually identified to be primarily influenced by intensity and duration.[16] However, when performing aerobic-type exercises, such as cycling,[16] running,[16] endurance training,[5,16] and high intensity interval training[38] cortisol levels increase affecting VO_2max by modulating energy availability, cytokine migration,[16] and muscle efficiency. This information suggests that types of activities with intensity levels above 65% can positively influence cytokine activity, inducing cortisol levels via IL-6 and altering VO_2max. However, if a level of 100% VO_2max is reached a chronic stress state may ensue potentially triggering an autoimmune response.

Different types of PA can impact the transcription of glucose transporter type-4 (GLUT4) mRNA and modulation of metabolic responses to insulin.[5,25,32] However, which particular types (resistance, aerobic, endurance) of exercise that have the strongest influence is not clear.[16] Cortisol is considered a major factor for individuals with insulin resistance (IR), which also has a direct influence on muscle responses[17] and concomitant hypothyroid status.[39] As such, researchers recognize both sedentary activity present with reduction in insulin sensitivity, low levels of T3, and high levels on reverse T3, reducing GLUT4 gene transcription.[39] Skeletal muscle contraction is imperative for glucose uptake, therefore the types of PA can determine muscular glucose metabolism. Resistance and endurance training alter TSH activity,[5] thus leading to thyroid disorders, a common risk factor for T2DM.[39] This may be due to corticotropin release-inhibiting factor, as it is reported to be located within the TRH peptide, which is regulated by hypothalamic neuropeptide Y (NPY) stimulation.[17,33] When glucose levels are optimal, reverse T3 synthesis is blunted.[5] This is corroborated by a report of decreased blood glucose concentrations augmenting cortisol response and suppression of lymphocyte and cytokine activity.[16] Blunted RT3 levels may be due to sympathoadrenal activity secretion of catecholamines and cortisol initiating glucose mobilization in response to PA, as aerobic and resistance training activity types may have a beneficial influence on thyroid disorders.[5,39] Glucocorticoids antagonize anabolic actions promoting the development of metabolic conditions[17] further altering energy expenditure metabolism by stimulation of NPY.[17] Furthermore, when NPY levels are elevated, insulin levels are decreased and adrenal systems are inhibited.[17]

PA Duration-Induced Changes in Energy Utilization

The '*duration*' of PA directly contributes to heat generation and intracellular utilization of energy substrate turnover. Some studies report secretion of catecholamines via sympathoadrenal activity,[5] initiating mobilization of energy stores including the oxidative[5,25,32,39] and glycolytic pathways,[5,13,32,34] stimulating pituitary,[5] endocrine,[5] and glucocorticoid[17] activity.[5] Immune[16] and HPA[5] responses are influenced by longer periods of PA, while decreased carbohydrate availability affects the HPA processes.[17] This undertaking facilitates the mobilization of all energy stores, such as carbohydrate, protein, and fat substrates; and alters plasma insulin[5,13,39] to support the influx of water and electrolyte intracellular processes.[5] The body responds to prolonged periods of energy demands by decreasing TSH,[5] ultimately stimulating thyroid hormones to initiate lipolysis supporting the rate of oxidative substrate utilization.[22,25,32,34] These processes impact intracellular calcium (Ca^{2+}),[32] the functionality of the sodium-potassium (Na^+/K^+) adenosine triphosphatase (ATPase) pump,[22,24,25,32] and mitochondrial density impacting ATP production rate[25,32] particularly during the degradation of adipocytes. The reduction of adipocytes results in cytokine (IL-6 and IL-10) release, thereby decreasing inflammation.[16] Research has demonstrated a positive correlation between TSHR, TPO, and Tg antibodies (Abs) and increased visceral (brown) and subconscious (white) adipose tissue,[40] which can be connected to chronic HPA hyperactivation.[17] These Abs, integral to the pathophysiology of autoimmune thyroid disease and non-autoimmune thyroid conditions, coincide with elevated TPO and Tg Ab biomarkers,[10,26,27,41,42] and exhibiting increased circulating levels of IL-6, TNF-α, and adipokines.[17] The expression of thyroid receptors on adipocytes[40] upregulated during adipogenesis in fat deposits,[40] underscores the interplay between thyroid signaling and adipose tissue dynamics. Additionally,

DIO2 enzymes contribute to the intracellular generation of T3 within adipocytes,[32] and when movement-induced muscle activation occurs, the concomitant activation of adipocytes transpires.[32] Indeed glucocorticoid activity through chronic stress, PA levels, and other environmental factors have a strong effect on neuro-immune-endocrine metabolic outcomes perpetuating susceptibility to autoimmune and HPA regulated diseases.[17] Thyroid conditions may be further potentiated by PA frequency, intensity, type, and duration.

Objective

The objective of this systematic review is to critically evaluate and summarize the existing literature on the relationship between exercise and all thyroid conditions. The authors of this study sought to critically examine clinical outcomes, such as whether PA or specified exercises can improve or resolve thyroid disease for the prevention and management of thyroid conditions, and reduction of medications. Sub-objectives include: 1) the assessment of how exercise affects health-related quality of life (HRQoL) in patients with thyroid disease; 2) if energy substrate utilization or nutrition was considered among studies; and 3) if a structured intervention framework should be followed by exercise protocol programs that measure thyroid biomarker outcomes.

Methods

Eligibility Criteria

Eligibility criteria included clinical trials investigating PA and its effect on patients with thyroid disease (subclinical hyperthyroidism or hypothyroidism [SH], GD, or HT) referencing the following primary outcome measures: thyroid hormones (TSH, T3, and T4), thyroid antibodies (TPO, Tg, TSHR), and studies that investigated HRQoL on thyroid patients. Age, gender, disability, or autoimmunity status, exercise frequency, PA intensity, types of exercises (resistance training, yoga, or otherwise), PA duration, skeletal muscle performance, and the effects of PA on VO_2max, anthropometrics (AM), or cardiovascular mechanisms in thyroid patients were not excluding factors.

Exclusions were studies that investigated patients with thyroid cancer, those exposed to radiation therapy, or those with thyroidectomy. Systematic reviews, narrative reviews, case reports, exploratory findings, and animal studies were also excluded. Furthermore, medication studies were an exclusion factor. If the study aimed to assess the potential improvement in exercise capacity through thyroid medication while maintaining disease control rather than seeking to resolve or improve thyroid disease states to reduce medication dependency through PA, the study was omitted. The authors (LC and JH) searched for trials.

Information Sources

A computerized systematic literature review was conducted using relevant electronic online databases, PubMed and Google Scholar, from February 22nd, 2021, to April 11th, 2021. A second search was conducted from March 31st, 2023, to April 11th, 2023. A third search was performed from August 1st, 2023, to October 13th, 2023. The authors searched PubMed, ResearchGate, Google Scholar, and Google search engine (SE). The returns were reviewed to identify studies that warrant inclusion.

Search Strategy

The overview of this rudimentary analysis was conducted per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist. The search strategy was limited to open-access English studies and only clinical trials. Search terms and results are viewable in Table 1.

Table 1. Search Terms and Results

Study ID	Search Term	Results	Kept	Database
Bousquet-Santos et al[30] Herring et al[51] Werneck et al[36]	no:repeats "ncbi" allintitle:"exercise" OR "physical activity" OR "resistance training" OR "exercise training" OR "interval training" OR "endurance" AND "thyroid" OR "deiodinase" OR "TPO" OR "thyroglobulin" OR "hyperthyroid" OR "hypothyroid"	65	3	PubMed
Cutovic et al[7]	"exercise" "graves disease" ncbi -animal, -mice, -mouse, -rodent, -rat,	1,580	1	Google Scholar
Adamopoulos et al[29] Hackney et al[21]	no:repeats "ncbi" allintitle:"exercise" OR "physical activity" OR "resistance training" OR "exercise training" OR "interval training" OR "high intensity" AND "thyroid"	76	2	Google Search Engine
Almas et al[42]	Physical activity [Title/Abstract] AND hypothyroidism[Title/Abstract]	8	1	PubMed
Caraccio et al[43] Werneck et al[41]	Exercise[Title/Abstract] AND hypothyroidism[Title/Abstract]	11	2	PubMed
Berahman et al[60] Ciloglu et al[20] Hackney & Dobridge[50] Harber et al[59] Kahaly et al[37] Kilic[35] Loucks & Callister[56] Mohammadi Sefat et al[39] Neto et al[54] Opstad et al[57] Rawal et al[44] Wesche & Wiersinga[52] Xiang et al[27]	"exercise thyroid"	122	13	PubMed
Altaye et al[19] Bansal et al[6] Byeon et al[55] Da Silva et al[58] Di Blasio et al[49] Garces-Arteaga et al[26] Karmisholt et al[23] Kęska et al[53] Klasson et al[47] Kouidrat et al[61] Lankhaara et al[45] Lankhaara et al[46] Roa Dueñas et al[48]				Google Search Engine

Selection Process

The research team retained clinically relevant articles with exercise as a treatment arm for attempting to treat or improve patients with thyroid disease. Selected exercise interventions included those with the following key MeSH terms either in the title or the abstract: "exercise, physical activity, resistance training, strength training, running, steady state, cardio, walking, cycling, dancing, martial arts, yoga, stretching, balance, and flexibility, AND thyroid, thyroid hormones, hashimoto's, graves' disease, hypothyroidism, hyperthyroidism, T4, thyroxine, T3, triiodothyronine, thyroid antibodies, thyroglobulin, thyroid peroxidase, thyroid stimulating hormone, deiodinase, and quality of life, OR intensity, low intensity, high intensity, and interval training." No supplemental searches were needed.

Data Collection and Extraction

After the initial search, studies were independently screened by two authors for essential inclusion and exclusion criteria, and data were extracted using standardized data-collection tables. All articles were assessed to determine if they met the inclusion-exclusion for PA thyroid-related articles, and studies with protocols that did not align with these criteria were removed.

Data Items

Tables were created emphasizing: basic study characteristics (Table 2), study intervention characteristics (Table 3), comparison of study sample and mean (Table 4), biomarkers and disease factors across trials (Table 5), *FItTeD* characteristics (Table 6), which includes biomarkers in relation to intensity, frequency, and duration; types of exercise intervention components (Table 7), skeletal muscle fiber aspects related to thyroid diseases (Table 8), and the proposed intervention (Table 9) for future studies.

Study Risk of Bias Assessment and Reporting

The authors of this study reviewed the abstracts of the remaining papers, appraised them for the best evidence, and assessed them for bias. The two authors, which were the appraisers and reviewers assessed the risk of bias by using the Joanna Briggs Institute critical appraisal tools (JBI, 2017).

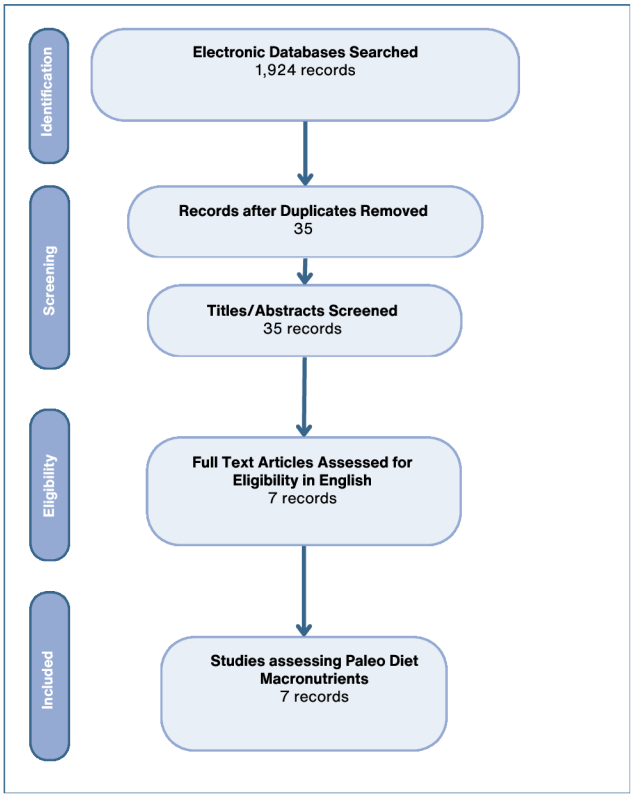
Effect Measures and Studied Outcomes

Clinical outcomes of importance included the resolution of or any improvements in the status of patients with thyroid disease. Primary outcomes included improved thyroid biomarkers (TSH, T3, T4, TPO, Tg, or TSHR), cardiorespiratory kinetics, such as HR and VO_2max, and HRQoL. Secondary outcomes included improvement of glucose and insulin utilization (glucose and homeostatic model assessment-insulin resistance [HOMA-IR]), inflammatory biomarkers, AM, and lipid biomarkers.

Synthesis Methods and Certainty

The analysis models used were basic statistical methods analyzing midranges and mean calculations for age, gender, sample size, and study length, as well as *FItTeD* using Social Science Statistics, MedCalc, and ClinCalc calculators. Ratios were used to measure the relationship between thyroid physiology components (TSH, T3, T4, TPO, Tg, HRQoL, VO_2max, HR, AM, T2DM biomarkers) and exercise intervention components (aerobic and other combined training approaches). Reporting included the documentation of the mean, standard deviation (SD), 95% confidence intervals (CI), relationship (*r*), and P value (*P*) across included trials. P values were rounded (i.e. *P*=.031 rounded to *P*=.03), with the exception of *P*=.049 or *P*=.051 to maintain significance values. If the P value was reported in the examined studies as 0 or less than 0 (i.e. *P*<.00005), then the authors of this study reported the values as < .001 in accordance with AMA reporting standards.

Figure 1. Flow Chart



A total of 1 924 studies were identified in the initial search, of which thirty-five were eligible after screening titles and abstracts. Seven studies were included. The authors excluded one trial that supplemented zinc to determine the effect of exercise on thyroid hormones and testosterone levels in sedentary men[35] and another trial that tested kinetics as the primary outcome measure and not thyroid hormones or Abs.[36] Four trials aimed to establish if PA could help improve recovery of physical performance and body composition in patients with hyperthyroidism[23,30,37] and hypothyroidism[43] during medical treatment were also excluded, as the focus was not on reducing thyroid disease or medication through exercise. Instead, they utilized medication to develop improved PA metabolism. Another study had similar investigations, exposing thyroid patients to one month of yoga, but the patients were also exposed to radioactive iodine treatment.[44] Additionally, five survey-based cross-sectional studies were omitted, including two that used data from the National Survey on Injuries and Physical Activity in the Netherlands (IPAN),[45,46] one that used data from the U.S. National Health and Nutrition Examination Survey (NHANES),[47] one that used data from the Rotterdam Study based in the Netherlands,[48] and one that used data from the Mugello Study, a survey on nonagenarians living in the Mugello area in Italy.[49]

We further excluded sixteen trials due to study populations being normal, healthy adults without thyroid disorders or not being diagnosed with thyroid disease. Of these studies, five studies investigated primary exercise related to thyroid biomarkers in healthy trained athletes,[20,21,50–52] two evaluated exercise on thyroid function in healthy PA non-athletic patients,[53,54] two studied normal healthy women,[55,56] one examined thyroid function during prolonged exercise healthy military cadets,[57] one evaluated whether single-to-multi-joint or multi-to-single-joint exercises had influences on thyroid hormones in healthy subjects,[58] another investigated thyroid status during exercise in anorexia nervosa patients,[59] a prospective ongoing randomized trial studied failing myocardium and thyroid hormones in patients with ventricular assist devices,[29] a randomized trial evaluated water-based rhythmic exercise training on glucose homeostasis and thyroid hormones in postmenopausal women with metabolic syndrome,[60] a longitudinal design investigated obese patients with normal thyroid levels,[61] and one examined exercise influences on thyroid outcome measures in adolescents with intellectual disabilities but without clear identification of thyroid disease status.[19] The characteristics of the remaining included studies are listed in Tables 2 and 3.

Table 2. Basic Study Characteristics

Study	Setting	Location	Type
Almas[42]	Patients were referred to Juiz de Fora Federal University	Clinical setting	PS
Bansal[6]	Patients were recruited from Bastar area (tribal area) of Chhattisgarh	Care Center	CT
Cutovic[7]	Patients were referred by endocrinologists to the Institute for Prevention, Treatment, and Rehabilitation of Thyroid Dysfunctions in Zlatibor, Serbia	Rehabilitation center	RC-C
Garces-Arteaga[26]	Patients were referred to Servicio Medico Universidad del Valle Hospital	Hospital	CT
Mohammadi Sefat[39]	Patients were voluntarily selected from the Children's Hospital	Hospital	RCT
Werneck[41]	Patients were recruited in the Endocrinology Service of Hospital and Maternity Terezinha de Jesus, School of Medical Sciences and Health of Juiz de Fora, Brazil.	Hospital	C-CS-T Phase 1 RCT Phase 2
Xiang[27]	Patients were recruited from Department of Endocrinology Wuhan General Hospital of Guangzhou Command	Hospital	CT

Abbreviations: PS, preliminary study; CT, controlled trial; C-CS-T, controlled cross-sectional trial; RC-C, randomized case control trial; RCT, randomized controlled trial.

Table 3. Study Intervention Characteristics

Study	Treatment Arm	L	Measures	Outcome
Almas[42]	Endurance training (treadmill and cycle) (*n*=9) No exercise training (*n*=9)	12 wks	TSH, T4, TPO, cardiac structure and function, MRT, AM, and RHR	Significant increases in PA level, and decreases in MRT, HR, SBP, and fT4
Bansal[6]	Jogging or sports-type exercises (*n*=10) Non exercise training (*n*=10)	3 mos	TSH, T3, and T4	Significant decrease in TSH and increases in T3 and T4.
Cutovic[7]	Daily walking, strengthening, stretching (*n*=62) Resting, walking, and leisure activities (*n*=62)	3 wks	TSH, T3, T4, fT4, VO_2max, body wt, RHR, duration of fatigue, relapse rate, and S-L exercise test	Decreased TSH, increased T4, improved VO_2max, and reduced fatigue and the need for thyroid medication
Garces-Arteaga[26]	Aerobic circuit and resistance training (*n*=17) No comparison	12 wks	HRQoL, and VO_2max	Significant improvement in HRQoL and cardiorespiratory fitness
Mohammadi Sefat[39]	Aerobic-resistance training, (*n*=10) No exercise training (*n*=10)	8 wks	BMI, HDL, LDL, TC, TG, TSH, T4, glucose, HOMA-IR, and AM	Significant improvements in glucose, HOMA-IR, and AM
Werneck[41]	Aerobic activities (bike and treadmill) (*n*=10) No exercise training (*n*=10)	16 wks	HRQoL	Remarkable improvements in HRQoL.
Xiang[27]	Walking (*n*=62, HT) Walking (*n*=28)	6 mos	OPG, T4, T3, TSH, Tg, TPO, LDL, HDL, DBP, SBP, CRP, TBARS, TG, VO_2max, nitrates	Significant decreases in OPG, TBARS, TPO and Tg Abs, Lp (a), and CRP. Non-significant improvements in fT3 and VO_2max

Abbreviations: L = study length; wks, weeks; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; fT3, free triiodothyronine; fT4, free thyroxine; TPO, thyroid peroxidase; Tg, thyroglobulin; TBARS, thiobarbituric acid reactive substances; LDL low density lipoprotein; HDL, high density lipoprotein; TC, total cholesterol; TG, triglycerides; DBP, diastolic blood pressure; SBP, systolic blood pressure; CRP, C-reactive protein; Lp (a), lipoprotein a; OPG, osteoprotegerin; BMI, body mass index; RHR, resting heart rate; HOMA-IR, homeostatic model assessment of insulin resistance; MRT, mean response time; HRQoL, health-related quality of life; VO_2max, maximal oxygen consumption; PA, physical activity; Abs, antibodies; AM, anthropometrics.

Changes in Thyroid Function Tests Following PA

Studies I and II: Improvements in HRQoL

Werneck et al,[41] included an RCT evaluating HRQoL in fifty-five female subjects with and without SH after endurance training, utilized the BeckmanCoulter®, Access2®, USA a chemiluminescent immunometric assay to measure TSH, thyroid hormones, and TPO Abs. Initial baseline assessments during the phase 1 trial revealed significant differences between the experimental (E) and the control (C) groups.[41] A vast majority (n = 22, 41%) of participants in the SH group showed positive for TPO Abs above 35 UI/mL. Researchers also observed a median of 5.58 mU/L (5.16-7.53) for TSH in the experimental group.[41] A Medical Outcomes Study 36- Item Short-Form Survey (SF-36), a validated peer-reviewed screening tool, was used to assess HRQoL.[41] The functional capacity domain of the survey exhibited significantly lower scores for the experimental group (E: mean 77.0, SD 23.0 -vs- C: mean 88.8, SD 14.6; P=.02), accompanied by an increased prevalence of signs and symptoms (E: mean 3.5, SD 1.6 -vs- C: mean 2.5, SD 1.0; P=.02), and diminished levels of PA (E: mean 7.1, SD 0.9 -vs- C: mean 8.3, SD 1.3; P=.001).[41] Post-intervention, there were no significant differences between groups.[41] However, the experimental group exhibited significant improvements in multiple HRQoL domains from baseline to the end-of-trial timepoints, including functional capacity (mean 73.0, SD 26.4 to mean 86.5, SD 9.4; P=.049), general health (mean 68.1, SD 17.4 to mean 83.0, SD 13.9; P=.01), emotional aspects (mean 43.3, SD 49.8 to mean 90.0, SD 22.5; P=.01), physical component (mean 68.5, SD 25.7 to mean 83.4, SD 6.6; P=.04), and mental component (mean 59.0, SD 30.6 to mean 81.0, SD 14.4; P=.02).[41] The study did not observe significant differences in TSH (P=.85), and did not report post-intervention values for TPO or TSH to contribute to the current evaluation.[41]

The Garces-Artega et al[26] trial aimed to examine the influence of a medium-impact exercise program on HRQoL and cardiorespiratory fitness in Columbian females with SH. All subjects with SH were positive for both Tg and TPO Abs, and were sedentary. Their validated assessment screening tool to assess HRQoL was the Medical Outcomes Study 12- Item Short-Form Survey (SF-12).[26] Garces-Artega et al[26] and colleagues reported significant improvements in the mental health domain, the mental component summary, and the vitality domain by 7 points (mean 7, SD 11, 95% CI 1-12; mean 7, SD 9, 95% CI 2-11; and mean 7, SD 12, 95% CI 2-11) and social functioning domain by 10 points (mean 10, SD 10, 95% CI 4-15) in the experimental group.[26] Notably, the general health domain demonstrated a significant effect by 6 points (mean 6, SD 11, 95% CI 1-11) in the experimental group.[26] Participants in the experimental group exhibited improved cardiorespiratory fitness, as evidenced by the Rockport walk test (P<.01) and a 28% increase in VO_2max (P<.001).[26] It is pertinent to acknowledge that the Garces-Artega et al[26] study reported elevated TSH levels at a mean of 2.90 (SD 1.56) mIU/L for their participants.[26] This observation may be based on their local reference ranges, as SH is typically diagnosed when TSH levels exceed 4.0 mIU/L or its equivalent mass of 4.5µg.[62,63] Interestingly, the researchers decided not to report end-of-trial TSH values. Withal, clinical symptoms impacting HRQoL may not always align precisely with the aforementioned diagnostic cutoffs. A prevailing trend in clinical settings suggests that individuals with thyroid function tests surpassing 2 mIU/L TSH values often experience substantial negative impacts on HRQoL.[64]

Studies III, IV, and V: Changes in Hypothyroidism Biomarkers

Almas et al[42] aimed to evaluate the effect of endurance training on heart rate (HR) kinetics in female patients with SH. They diagnosed SH via TSH levels exceeding 0.35–4.94 mUI/L reference range.[42] Patients in both groups were positive with TPO Abs (P=0.637) and remained unchanged post-intervention. No other information was furnished on the topic of Abs. Following the intervention, significant increases were observed in PA level (mean 7.3, SD 0.7 to mean 8, SD 0.9; moment or time (t) P=.001, group (g) P=.03, and interaction (i) P=.005), and decreases were observed in FT4 concentration (mean 12.31, SD 1.51 to mean 11.93, SD 1.17; i: P=.04) and TSH (E: mean 7.7, SD 3.1 to mean 5.6, SD 3.2 -vs- C: mean 6.9, SD 3.3 to mean 5.4, SD 2.2; t: P<.001) in the experimental group.[42] Additionally, statistically significant reductions were observed in the experiential group for mean response time (mean 39.6, SD 10 to mean 28.9, SD 8.4; t: P=.004, g: P=.01, and i: P=.001), stable HR (E: mean 116.5, SD 13.1 to mean 111.9, SD 12.5 -vs- C: mean 124.6, SD 15.5 to mean 119.9, SD 10.9; t: P=.02), and SBP (E: mean 115.6, SD 7.9 to mean 107.8, SD 8.7 -vs- C: mean 110.2, SD 11.4 to mean 104.2, SD 10.3; t: P=.006).[42] Diastolic blood pressure nearly reached significance (t: P=.057). Adjustment for body mass index (BMI) and age remained significant for PA level (P=.04) and mean response time (P=.005), while FT4 did not exhibit sustained significance.[42] However, the researcher claims the decrease was not due to endurance training, but rather time itself, and HR or cardiac morphology were not altered by exercise

training.[42] Furthermore, Almas et al[42] notated clinical significance was still observed for HR in the experimental group resulting in a lower response rate than the control group,[42] which may indicate that SH does not impair the response to training.[42] While the non-significant interaction between *t* and *g* may suggest that changes were not directly attributable to endurance training,[42] it's essential to acknowledge inter-and intra-assay variability.[42] These assays show us that while endurance training might not be the sole reason for the changes in FT4 levels, over time, results may have a clinical effect on the decrease of FT4.[42]

Bansal et al[6] sought to determine if medium-intensity PA affected thyroid function in male patients undergoing treatment for SH. Post-intervention, they documented significant decreases in TSH (mean 2.51, SD 0.24 to mean 0.61, SD 0.42; *P*<.001) and significant increases in T3 and T4 levels (mean 1.30, SD 0.28 to mean 2.33, SD 1.03; *P*=.007 and mean 8.09, SD 0.45 to mean 11.34, SD 1.98; *P*<.001).[6] Inter-group comparisons revealed there was a significant decrease in TSH (E: mean 0.61, SD 0.42 -vs- C: mean 2.34, SD 1.42; *P*=.002) and a significant increase in T3 and T4 levels (E: mean 2.33, SD 1.03 -vs- C: mean 1.11, SD 0.32; *P*=.002 and E: mean 11.34, SD 1.98 -vs- C: mean 8.77, SD 0.82; *P*=.001) in the experimental group.[6] The study also reported a decrease in mean weight;[6] however, statistical differences in weight changes were not documented,[6] making it challenging to assess the relationship between thyroid function and PA on weight in the current study. Notably, the authors concluded exercise can concomitantly decrease the dose of medication.[6]

Mohammadi Sefat et al[39] aimed to explore the effect of concurrent aerobic-resistance training on primary thyroid biomarkers in adolescent girls with SH.[39] Although there were no substantial improvements in thyroid biomarkers in this study, both groups exhibited increases in TSH and T4 on laboratory results,[39] which holds relevance in clinical practice. Interestingly, TSH trended upward, deviating from the normal range,[39] away from the typical therapeutic goal, and the experimental group exhibited a greater increase (E: mean 4.12, SD 1.9 to mean 6.38, SD 5.2 -vs- C: mean 4.94, SD 2.51 to mean 5.28, SD 2.3).[39] Changes in T4 trended to the normal range in both groups, with the control group observing the most significant change (E: mean 6.96, SD 1.1 to mean 7.62, SD 0.7 -vs C: mean 6.34, SD 1.27 to mean 7.51, SD 2.8).[39] While the experimental group saw a non-significant increase in T4, a trajectory toward the normal reference range aligns with the conventional goal for attempting to resolve hypothyroidism with medication. The experimental group exhibited significant reductions in weight (mean 57.9, SD 5.09 to mean 57.22, SD 5.1; *P*=.002), BMI (mean 26.02, SD 2.2 to mean 25.69, SD 2.3; *P*=.001), fat percentage (mean 24.05, SD 1.3 to mean 23.06, SD 1.4; *P*=.001), glucose (mean 81.70, SD 7 to mean 77.40, SD 5.3; *P*=.04), and HOMA-IR (mean 2.95, SD 0.5 to mean 2.30, SD 0.9; *P*=.03) within groups.[39] Between-group comparisons observed significant differences in weight, BMI, and fat percentage (*P*=.001), and HOMA-IR (*P*=.02).[39] Insulin and triglycerides nearly reached significance (mean 8.13, SD 1.2 to mean 6.70, SD 2.4; *P*=.05 and mean 101.40, SD 30.8 to mean 89.90, SD 11.4; *P*=.07), indicating non-significant, yet clinically relevant decreases between groups.[39] Additionally, triglycerides nearly reached significance in the control group for within-group comparisons (mean 85.80, SD 31.4 to mean 103.80, SD 32.5; *P*=.06).[39] Although T2DM markers were not the primary focus of this study, it is essential to acknowledge the correlation between T3 and GLUT4 as a prominent factor in thyroid disease patients.[14] The GLUT4 gene, predominantly expressed in muscle,[25,32] plays a pivotal role in thyroid disease, with individuals experiencing challenges in overexpressing or under-expressing this gene.[14] Such expression is markedly influenced by the availability of T3.[25,32] Consequently, PA for thyroid patients may prove challenging. The positive correlation between GLUT4 and T3 implies that the non-statistically significant improvement of T4[39] could suggest improvements in GLUT4 gene expression. Notably, improvements in glucose and HOMA-IR biomarkers also allude to improvements in GLUT4 gene expression.[39] Given the inverse correlation between GLUT4 and TSH,[14] this observation could explain the inverse trends observed in TSH biomarkers. No thyroid Abs were discussed.

Study VI: Improvements in HT Biomarkers

Xiang et al[27] sought to investigate correlations between thyroid hormones and osteoprotegerin (OPG) in Chinese female patients with and without HT before and after exercise training.[27] The OPG glycoprotein is a TNF family member, crucial in regulating bone metabolism, but to our knowledge is not a usual biomarker assessed in thyroid studies. The inclusion of this study lies in the association of HT patients with bone-related issues, higher concentrations of OPG, the production of OPG in adipose tissue, and the extended exploration of the effects of exercise on both thyroid hormones and Abs.[27] Both TPO and Tg Abs were used to diagnose HT.[27]

Prior to the initiation of exercise, OPG concentrations exhibited a significant increase (mean 3.0, SD 0.81;

P<.001), followed by a significant decrease after 6-months of exercise (mean 2.40, SD 0.61; *P*<.001) in the experimental group.[27] Baseline concentrations were significantly higher in HT patients: TPO-Ab (*P*<.001), Tg-Ab (*P*<.001), C-reactive protein (CRP) (*P*<.001), thiobarbituric acid reactive substances (TBARS) (*P*<.001), lipoprotein (a) (*P*=.046), and OPG (*P*<.001). Between-group comparisons revealed significant differences were also observed in TPO Abs (E: mean 692, SD 217 to mean 623, SD 196; *P*<.01 -vs- C: mean 4, SD 2 to mean 5, SD 2; *P*<.01), Tg Abs (E: mean 483, SD 206 to mean 415, SD 224; *P*<.01 -vs- C: mean 22, SD 6 to mean 20, SD 6; *P*<.01), and lipoprotein (a) (E: mean 321 [172; 654] to 260 [156; 623]; *P*<.05 -vs- C: mean 152 [0; 263] to 132 [0; 255]; *P*<.05) in the experimental group.[27] OPG correlations were exclusively identified with thyroid hormones and not with thyroid Abs.[27] However, significant differences in thyroid hormones were not evident between groups.[27] While not statically significant, improvements were observed in T3 (E: mean 5.85, SD 2.55 to mean 6.02, SD 2.34 -vs- C: mean 6.47, SD 2.42 to mean 6.33, SD 2.80) during between-group comparisons.[27] In addition, a significant increase of 15.2% in VO_2max was observed in the experimental group for within-group comparisons (mean 27.9, SD 3.9 to mean 33.3, SD 4.2; *P*<.044).[6]

A significant decrease in CRP by 20.8% (E: mean 1.54, SD 0.35 to mean 1.22, SD 0.35; *P*<.01 -vs- C: mean 1.28, SD 0.35 to mean 1.26, SD 0.42) and TBARS by 25.3% (E: mean 1.68, SD 0.42 -vs- C: mean 1.48, SD 0.60; *P*<.01) was observed in the experimental group during between-group comparisons.[27] The absolute changes in OPG concentrations exhibited significant correlations to CRP ($r = -0.503$, P<.001) and TBARS ($r = -0.370$, *P*=.004) were shown.[27] TBARS, indicative of lipid peroxidation, examines the amount of oxidative stress and inflammation associated with adipocyte degradation. Observing the reduction in CRP and TBARS suggests diminishing oxidative stress and inflammation. Considering the expression of thyroid receptors on adipocytes undergoing adipogenesis[40] and the correlation of thyroid Abs with visceral and subcutaneous adipose tissue,[40] a positive association emerges between the reduction of thyroid Abs and inflammation biomarkers (CRP and TBARS). This suggests that improvements in OPG, although not directly correlated, may harbor an indirect relationship with thyroid Abs. Furthermore, the inclusion of a HT experimental group comprising of euthyroid women elucidates the close ranges of thyroid hormones (T3 and T4) in both the experimental and the control groups at baseline (T3: E = 5.85 -vs- C = 6.47 and T4: E = 15.31 -vs- C = 16.29).[27] However, the TPO and Tg Abs exhibited very statistically significant differences between groups at baseline (TPO: E = 692 -vs- C = 4; *P*<.001 and Tg: E = 483 -vs- C = 22; *P*<.001).[27] Hence, the significant difference within the experimental group post-intervention reveals the impact PA can have on thyroid Abs due to adipocyte degradation for energy utilization.

Study VII: Improvements in GD Biomarkers

Cutovic et al[7] aimed to evaluate the short- and long-term effects of structured exercises on patients with GD.[7] Following the intervention, the researchers observed a 9% increase in TSH for the *t* and *i* components, nearly reaching significance (*t*: *P*=.07 and *i*: *P*=.07), with a significant increase for the *g* component (E: mean 3.2, SD 0.7 to mean 3.5, SD 0.6 -vs- C: mean 2.9, SD 0.7 to mean 2.9, SD 0.6; *g*: *P*<.001).[7] A significant decrease in *g*, *t*, and *i* was also observed for T4 (E: mean 117.4, SD 15.3 to mean 105.7, SD 14.1 -vs- C: mean 119.1, SD 16.1 to mean 115.3, SD 14.1; *g*: *P*<.001, *t*: *P*<.001, *i*: *P*=.04) and for resting HR (RHR) (E: mean 80.9, SD 3.9 to mean 75.8, SD 3.8 -vs- C: mean 81.1, SD 4.7 to mean 81, SD 4.5; *g*: *P*<.001, *t*: *P*<.001, *i*: *P*<.001).[7] A significant increase in VO_2max was also observed in the experimental group (mean 23.6, SD 6.1 to mean 39.6 SD 7.8; *P*<.001).[7] In addition, a significant inverse correlation between TSH and T4 ($r = -0.55$; *P*<.001 to $r = -0.51$; *P*<.001) from admission to discharge was further observed in the experimental group, while a similar TSH and T4 inverse correlation was also identified in the control group ($r = -0.53$ and $r = -0.39$; *P*<.001.[7] At discharge, none in the experimental group reported fatigue compared to baseline disclosures of fatigue on the Fisher's exact test (34%; *P*<.001) (% = fatigue rate, where mild = 5%, moderate = 24%, and severe = 71%), and the study reported improved mitochondrial function.[7]

The most substantial finding was the percentage variation (% = variation rate) in medication discontinuation within the first six months between the experimental and control groups (E: 84% -vs- C:18%; *P*<.001), reflecting a shorter mean time to discontinuation (mean 5.0, SD 1.4 months -vs- mean 9.0, SD 2.5 months, *P*<.001), and lower 12-month relapse rate following medication withdrawal (E: 29% -vs- C: 72%, *P*<.001).[8] However, it is imperative to acknowledge the challenging nature of evaluating the relapse rate as TSHR Ab (also known as thyroid stimulating immunoglobulin [TSI]) levels, a crucial parameter, are not reported in the study. The researcher hypothesized that secretion of stress hormones (catecholamines and circulating cortisol) by

exercise may have led to a Th2-mediated shift toward humoral immunity.[7] This shift may have improved the blocking of the Ab and ensuing predominant production of the TSHR.[7] Cutovic et al.[7] further mention the IL-10/IL-12 ratio as a plausible upregulation pathway for Th2, as it is speculated that pregnant individuals with GD experiencing a blunting in this pathway post-pregnancy resulting in remission.

Amalgam of Individual Studies

Intervention Length

Among the seven trials assessed in this study, three implemented interventions lasting for twelve weeks,[6,26,42] with the remaining trials having durations of three, eight, sixteen, and twenty-four weeks, respectively (Table 3). The mean duration for interventions across these trials was calculated to be approximately thirteen weeks (mean 13). Refer to Table 3.

Sample Sizes

The mean starting and ending sample sizes across the seven trials calculated to 44.1 and 43.6, respectively, indicating a completion rate of nearly 100% (completion rate = 98.71%). The ratio of the intervention sample size (mean *n*=25) was approximately 1.19 times larger than the placebo sample size (mean *n*=21). No adverse events were reported in included trials, and the dropout rate was 1.29%. The mean age of participants across all studies was 35 years, and the mean gender distribution was 21% male and 79% female. Please refer to Table 4.

Table 4. Comparison of Study Sample and Mean

Study	Population	Sample Size				Mean		
		Start	End	Intervention	Placebo	Age	m%	f%
Hypothyroidism								
Almas[42]	SH	18	18	9	9	Md 42	0%	100%
Bansal[6]	SH on Rx	20	20	10	10	x 34	100%	0%
Garces-Arteaga[26]	SH	17	17	17	-	x 43	0%	100%
Mohammadi Sefat[39]	SH	20	20	10	10	x 12	0%	100%
Werneck[42]	SH	20	20	10	10	Md 41	0%	100%
Hashimoto's Thyroiditis								
Xiang[27]	HT	90	86	59	27	46	0%	100%
Graves' Disease								
Cutovic[7]	GD on Rx	124	124	62	62	x 28	50%	50%
Mean	**SH 75%**	**44**	**44**	**25**	**21**	**35**	**21%**	**79%**

Abbreviations: m%, male percentage; f%, female percentage.Age medians and means were rounded in accordance with AMA standards.

Thyroid Marker Clinical Significance Comparison

The tabulated data presents scores corresponding to each assessed outcome measure, denoting either statistically significant or non-significant favorable changes, no data provided, or lack of improvement in the data analyzed by the authors of this study. Among the five studies evaluated for TSH and T4, three observed significant improvements.[6,7,42] A total of three studies investigated VO_2max (3:3),[7,26,27] and two studies examined HR (2:2)[7,42] and HRQoL (2:2),[26,41] all demonstrating statistically significant improvements. Conversely, T3 exhibited significant improvements in one of three studies,[6] and a similar trend was observed for AM (2:5).[6,31] TPO and Tg were subjects of evaluation in two studies[27,42] although TPO Abs were measured in four studies,[26,27,41,42] only one study[27] furnished relevant statistical data. This limited data availability poses challenges for authors to draw definitive conclusions regarding Abs outcomes. Refer to Table 5.

Table 5. Biomarkers and Disease Factors Across Trials

Study	TSH	T3	T4	TPO	Tg	HRQoL		HR	AM	T2DM
Almas[42]	<<	-	>> x~	•	•	-	-	<<	x	-
Bansal[6]	<<* << †	>>* >> †	>>* >> †	-	-	-	-	-	<	-
Cutovic[7]	>>* > †	x	<<	-	-	-	>>	<<	x	-
Garces-Arteaga[26]	-	-	-	-	-	>>	>	-	-	-
Mohammadi Sefat[39]	x	-	x	-	-	-	-	-	<<	<<
Werneck[41]	-	-	-	-	-	>>	-	-	-	-
Xiang[27]	x	x	x	<<	<<	-	>> †	-	x	-
TS Assessing Outcomes	5	3	5	2	2	2	3	2	5	1
TS Favorable Results	3	1	3	1	1	2	3	2	2	1

Abbreviations: TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine, TPO, thyroid peroxidase; Tg, thyroglobulin; VO_2max, maximal oxygen consumption rate; HRQoL, health-related quality of life; HR, heart rate; AM, anthropometrics biomarkers; T2DM, type 2 diabetes mellitus biomarkers; TS = total studies.

< = non-significant reduction, decrease, or improvement; yet favorable
> = non-significant increase or improvement, yet favorable
<< = significant reduction, decrease, or improvement
>> = significant increase or improvement
x = no difference, no change, or no improvement
- = study did not evaluate
• = studied, but did not provide data
* = within group
† = between groups
~ = adjusted

FItTeD Comparison of Interventions

In this study, the authors analyzed the mean value for *FItTeD* (frequency, intensity, type, and duration) characteristics across the included studies. The mean frequency of exercise sessions per week was four days, with four out of six (4:6) studies recommending at least three days of PA per week.[26,41,42] After midrange calculations and adjusting for thyroid disease type, hypothyroid patients across studies had a mean frequency of four days per week, while hyperthyroid patients had a mean frequency of five days per week.

Regarding exercise intensity levels in the included

studies, the mean value was calculated at 64%, classified as moderate-intensity (low-intensity = <50%, moderate-intensity ranging from 50-70%, and high-intensity = >70%), and the midrange was also moderate-intensity for five of seven (5:7) studies (60-70%). This suggests that moderate-intensity exercise is a common focus in research related to the effects of PA on the production, secretion, and action of thyroid hormones. It's crucial to highlight that one study began patients at an intensity midrange of 45%, equivalent to low-intensity, and had the longest duration of 75 minutes (1hr and 15 mins).[39] However, this trial did not specify the frequency of exercise,[39] potentially contributing to the absence of significant changes observed in thyroid hormone biomarkers. Nevertheless, non-significant improvements in TSH and T4 were observed, alongside significant improvements in T2DM.[39] This study was one of two that increased the intensity rate during the intervention.[39] The other trial that increased the intensity rate also observed no significant changes in thyroid biomarkers;[27] however, their patients were already in a euthyroid state.[27] Nonetheless, significant improvements in thyroid Ab levels were reported.[27] While PA undoubtedly influences hormone production,[6,7,19–21,25,26,28–32], it is unclear whether changing intensities directly affects the conversion of T3. Therefore, further investigation is warranted to determine the precise impact of intensity changes on thyroid hormone uptake and metabolism.

The mean daily activity duration was calculated to be 55 minutes,[6,26,27,41] with variations spanning 25-75 minutes. According to CDC guidelines, a minimum of 150 minutes (150/5d = 30 mins/day) of moderate-intensity or 75 minutes (75/5d = 15 mins/day) of high-intensity aerobic activity per week is recommended, distributable across different days. When considering midranges for duration, most trials reported a recommended exercise duration of 60 minutes. Refer to Table 6 for tabulated data outlining frequency, intensity, and duration.

In the sole study exploring hyperthyroidism, the authors utilized the combination of strength, stretching, and walking types of exercise as a primary intervention.[7] Among studies assessing hypothyroidism orr HT, aerobic activity types were a common component. While running or jogging it was mentioned in the majority of these trials (5:6),[6,27,39,41,42] three studies emphasized walking,[26,27,41] two included cycling,[41,42] and one incorporated circuit training.[26] Only two mentioned doing strength or resistance exercises in combination with aerobic training.[26,39] Additionally, most of the hypothyroid studies (4:6) recommended warm-up and cool-down routines.[26,39,41,42] Refer to Table 7 for the "types" of exercises implemented across the seven studies reviewed. The consistency of these exercise protocols across studies are outlined in Table 6, FItTeD Characteristics.

Reporting Biases

The authors of this current review did find reporting bias. The reporting varies between studies, with some documenting incomplete reporting of thyroid biomarkers along with other necessary biomarkers, including not reporting all required data such as T3 and T4 concentrations,[27] TSHR Ab concentrations,[7] and weight.[6] These inconsistencies may lead to challenges in interpreting data. Future studies should adhere to comprehensive reporting standards to mitigate reporting bias, testing for and providing all thyroid biomarker information, regardless of its relevance.

Discussion

Key Findings: Summary of Studies I-VII

In this study, we critically investigated the impact of PA activity on the various thyroid conditions for improvements and/or potential resolution. Our results demonstrate that the supposition of exercise being used as an adjunct therapy for AITD is only highlighted by two trials.[6,7] Thyroid disease was claimed to resolve with exercise according to Bansal[6] and colleagues.

Table 6. *FItTeD* Characteristics

Study	P S <	P S >	2 S <	2 S >	It	> It	D (min/d)	> D (min/d)	F (x/wk)	> F (x/wk)
Almas[42]	TSH	T4	HR	-	70-85% mHR	-	50	-	3	-
Bansa[6]	TSH	T3, T4	AM	-	70%	-	60	-	daily	-
Cutovi[7]	T4	TSH	HR	VO_2max	70% mHR	-	45-60	-	5	-
Garces-Arteaga[26]	-	HRQoL	-	VO_2max	55-80% VO_2max	-	60	-	3	-
Mohammadi Sefat[39]	-	-	T2DM,AM	-	40-50% mR60–70% HRR	60-65% mR70–80% HRR	75	-	ND	-
Werneck[41]	-	HRQoL	-	-	65-75% mHR	ND	60	-	3	-
Xiang[27]	TPO, Tg	-	-	VO_2max	60% mHR	70-75% mHR	25-30	40-45	3-4	4-6
Mean	-	-	-	-	**64%**	**68%**	**55**	**42.5**	**4**	**5**

Abbreviations: P, primary biomarkers; 2, secondary biomarkers; S, significant; F, frequency; It, intensity; D, duration; HR, heart rate; HHR, heart rate reserve; AM, anthropometrics; VO_2max, maximal oxygen consumption; mHR, maximal heart rate; mR, maximum repetitions; wk, week; x, how many times; min, minutes; d, day; > = Increase from starting point; < = Decrease; - = no data

Table 7. Types of Exercise Intervention Components

Study	Exercise Category					Aerobic Component				SteadyState
	Endurance	Strength, Resistance, Weights	Flexibility Stretching	Warm Up	Cool Down	Walk	Jog, Run, Treadmill	Cycle	Circuit	
Hypethyroid										
Cutovic[7]		x	x	x	x	x				
Hypothyroid										
Almas[42]	x			x	x		x	x		x
Bansal[6]							x			
Garces-Arteaga[26]		x		x	x	x			x	
Mohammadi Sefat[39]	x	x		x	x		x			
Werneck[41]				x	x	x	x	x		x
Xiang[27]						x	x			x

NOTE: This table describes types of exercise interventions in hyperthyroid studies -vs- hyperthyroid studies. **Abbreviation:** x = interventions that were used in each study

After achieving thyroid hormone equilibrium through medication, PA could emerge as a supplementary modality capable of further improving thyroid hormone biomarkers with the ability to discontinue such medication.[6,7] Cutovic et al[7] further reported a high percentage (84%) of resolution of thyroid conditions among their subjects demonstrating discontinuation of medication without relapse.[7]

Among the seven studies reviewed, three observed significant improvements in TSH and T4,[6,7,42] three demonstrated improvements in VO_2max,[7,26,27] two studies observed improvements in HR,[7,42] while another two showed substantial improvements in HRQoL (2:2).[26,41] In contrast, T3 exhibited significant improvements in only one study,[6] anthropometrics were only shown to be improved in two studies,[6,39] and TPO and Tg Abs were only improved in one study.[27] No studies address stress-related origins for disease manifestation. These findings suggest the potential for exercise to have an impact on the outcomes if studies consider sympathoadrenal and neuro-immune-endocrine pathway variables. Nonetheless, the relatively small number of studies included and a limited amount of evidence makes it difficult to draw broad conclusions.

Considering Stress-Induced Endocrine-Immune Responses During Exercise

Cardiovascular Functions

Throughout the duration of exercise, all cardiovascular functions increase exponentially, affecting HR[23,24] and metabolism, thereby elevating T3, thus regulating HR and the volume of blood flow within the circulatory system.[24,37] Thyroid disorders can disrupt these cardiac functions, while inducing abnormal contractility. Patients afflicted with hyperthyroidism encounter heightened cardiac activity and arterial dilation, exposing them to risks, such as high SBP, tachycardia, atrial fibrillation, and palpitations,[24,37] along with elevated levels of FoxP3,[11] IL-6, and IL-8.[13] In contrast, hypothyroid patients undergo decreased cardiac activity and arterial constriction, leading to risks such as bradycardia, elevated low-density lipoproteins (LDL), diminished LDL receptors, increased homocysteine levels, and lowered pulse rate and pressure,[24,37] and altered Th-17 activity and elevated FoxP3, IL-17 and IL-6.[11] In addition, alterations in thyroid hormones can alter cardiac epinephrine catecholamine content, as there is clear evidence of increased β2-AR in the heart.[13] It is well-known that stressful life events can alter cardiac function.[4,13] This is supported by redeployment of stress-induced leukocytes on vascular reservoirs that usher exercise-induced cardiovascular mechanisms.[16] Furthermore, sprint interval training improves cardiorespiratory capacity and performance, thereby attenuating the cycling of deactivating T3 coding genes during circulatory processes.[28] This reduction in DIO3 activity contributes to the mitigation of oxidative stress, facilitating the restoration of cardiac activity through the diminution of left ventricular mass,[28] through positive feedback. In our review, a comprehensive analysis demonstrated that participants had improvements in HR in both hypo-[42] and hyperthyroid (GD)[8] patients and SBP for hypothyroid patients.[42]

T3 Metabolism and VO_2max Function

Throughout exercise, the body compensates for the increased demands of oxygen by elevating T3, which magnifies VO_2max kinetics, oxygen deficit, and CO_2 release[26,29,31,36] resulting in respiratory burst.[16] Subsequent increases in hormone response element binding,[23] synthesis of Na^+/K^+ ATPase pump proteins,[24] mitochondrial ATP production rate, and stimulation of red blood cells initiate erythropoietin to synthesize genes expeditiously.[24,35] Ultimately, improved VO_2max increases thyroid hormone signaling and hormone receptor α-1 expression,[28,29] leading to improvements in immune function.[16] This may be due to the tightly regulated SNS or parasympathetic system during stress response.[17] Consequently, patients who

have impaired VO_2max function experience exercise intolerance[23,37] due to inadequate cardiovascular suppor[26] and poor muscle cellular respiration,[23,24] as they utilize increased anaerobic metabolism for energy substrate supply during fitness by employing ATP, phosphocreatine, and anaerobic glycolysis.[36] Low T3 profoundly impacts muscle contractility and mitochondria mechanisms, therefore hypothyroid patients present with a delay in VO_2max recovery and impaired VO_2max response.[28] Conversely, exercise intolerance in patients with hyperthyroidism is caused by mitochondria oxidative dysfunction,[26] and these patients experience fatigue as one of their leading symptoms.[7] After a comprehensive analysis, the Garces-Artega[26] study found a 28% increase in VO_2max for hypothyroid patients,[26] Xiang et al[27] saw a 15.2% increase in VO_2max for Hashimoto's patients, and Cutovic et al[7] observed a significant increase in VO_2max, decreased fatigue levels from baseline original values, and improved mitochondrial function in hyperthyroid (GD) patients.

Designing Nutrition-Based Exercise Programs to Fit the Needs of Thyroid Patients

Part I: Considerations for Future Trial Designs

During our search, five of the seven included studies focused on exercise programs for hypothyroid disease states,[6,26,39,41,42] while the sixth study addressed hyperthyroidism (GD)[7] and the seventh investigated Hashimoto's thyroiditis,[27] indicating a need for further research in autoimmune variations of thyroid disease. Of all (excluded and included) studies, there are very few focusing on PA effects and not on medication effects for resolution of thyroid conditions. Given the limited number of studies in our analysis and the paucity of comprehensive data in the reported studies, the existing evidence is insufficient to determine if large numbers of patients with thyroid disease can experience alleviation of symptoms or the resolution of thyroid disease. In the following sections, we discuss favorable and unfavorable trends among the seven studies reviewed and the need for comprehensive holistic intervention guidelines. We also outline the necessity for properly designing nutrition-based exercise programs to fit the demands of thyroid patients through a nested sub-review.

The Need for Comprehensive Research Guidelines

Favorable trends for improvement in thyroid, cardiovascular, inflammatory markers were found across the seven studies aiming to improve thyroid conditions through PA.[6,7,26,27,39,41,42] Previous trials have demonstrated that resistance training improves muscle fibers, thereby enhancing muscle performance, muscle recovery, body composition, lean mass, strength, HRQoL, and endurance in patients with thyroid disease.[30,23,37,43] However, the studies evaluated in the current review are small in number, and do not yield enough data to conclude exercise as an isolated method for managing thyroid conditions. It was noticed that the studies also exhibit inconsistencies in biomarker utilization: 1) there is variability in the selection of biomarkers tested, with some including thyroid Abs and cytokine markers, while others did not; 2) certain biomarkers for diagnostic purposes were not reported in the intervention or baseline data; 3) reporting biases were evident, with some biomarker results omitted, which are crucial for comprehensive analysis. Moreover, while not the primary focus of this study, none of the included studies analyzed energy substrate utilization within their exercise programs. One study integrated nutrition into exercise training protocols,[26] and another briefly noted an increase in the muscle carbohydrate oxidation capacity.[39] Accordingly, 30-60 g/hr of carbohydrate consumption is usually adequate to reduce immune functions and dull the cortisol response[16] in athletes. Finally, none of the studies touched upon stress as a primary factor for disease pathology, knowing exercise is a stress-inducing activity. Therefore, clear guidelines for designing future trials are essential to establish a robust framework for interpreting trial results conclusively.

Proposed Design for Future Interventions

Based on the key activities of the currently assessed studies, we propose the development of a multi-phase single-center trial where all patients are recruited from clinical environments; where-also translational research is practical to bridge the gap between these discoveries and their application in private practice clinical settings. The following is a proposal of intervention basics suggesting a standardized trial length, minimum sample size, standardized biomarker utilization, and stress-examinations as an integral component. It is important to note that the purpose of this study is not to design an entire trial, but to set guidelines for those planning to design future trials. Therefore, details such as specific methods for collecting biomarkers or validated data from clients, facility locations, and other anomalies are beyond our scope and will not be elaborated upon in this review.

Trial Length

The trial length should be approximately thirteen weeks, the mean of all included studies calculated in the results section (refer to Amalgam of Individual Studies: Intervention Length) of the current review. A

minimum of twelve weeks is required to accumulate accurate data for metabolic adaptations to exercise.

Target Sample Size

Power calculations were based on BP to determine sample size at 140 mmHg (SD 11) with an 8% decrease and 80% power, type 1 error rate of 5%. Thirty-two subjects was the calculated total sample size. The mean of all included studies calculated in the results section (refer to Amalgam of Individual Studies: Sample Sizes) was forty-four with an uneven gender distribution (m = 21% and f = 79%). Previous power calculations have suggested sample sizes of 15 with 80% power.[26] However Cutovic used a sample size of 62 with 80% power with SD of 8. Therefore, a starting sample of at least forty-four adults should be an appropriate starting point. Male gender disparity was evident, therefore studies should focus on an even gender distribution between groups to garner comprehensive data.

Standardized Biomarker Utilization

To improve quality and compatibility of research outcomes, it is crucial to establish a standardized set of biomarkers that are consistently measured across all trials. This will ensure a comprehensive assessment of the interventions and allow for meaningful comparisons between studies facilitating accurate tracking of changes, reduction of variability, and enhancing reliability of findings. Thereby, stronger evidence will be provided for clinical guidelines and policy making. It should be further noted that all baseline data should be reported in post-intervention data. This will aid in mitigating reporting bias. These biomarkers should include: HRQoL using the Medical Outcomes Study Short-Form Survey;[26,41] TSH, FT4, FT3, and RT3; AM using calipers, measuring tape, and weight scale;[39,42] HOMA-IR, glucose, fasting insulin;[39] CRP,[27] TPO,[27] Tg,[27] IL-6, and IL-10; HR, SBP, DBP, and VO_2max;[6,7,22,23,26,27,32,37] and nitrates,[27] cortisol, and lipids (TC, TG, LDL, HDL).[27,39] Establishing such standards will help to identify key biomarkers relevant to thyroid, cardiovascular, and immune system health. Tests should be performed at baseline, with a 6-week follow-up, and at the 13-week trial end date.

Stress-Examinations as an Integral Component

Incorporating stress testing through trauma or lifestyle questionnaires is essential for trials that aim to use exercise as a treatment modality for AITD. Stress has a well-documented impact on the endocrine and immune systems,[4,11–13,16,18] influencing the progression and severity of thyroid conditions.[4,5,18] Additionally, during stress, physiological adaptations regulate energy substrate resources.[17] By assessing participants' stress levels and histories of trauma, researchers can better understand the interplay between stress, immune function, the HPA axis, and protein and genetic components in thyroid health. This information is crucial for tailoring exercise interventions to individual needs, ensuring that the potential benefits of physical activity are maximized while considering the unique stress-related factors that may affect each patient. Therefore, integrating these assessments into trial protocols will provide a more comprehensive approach to managing and potentially resolving autoimmune thyroid diseases through lifestyle modifications.

Part II: Integration of Energy Substrate Analysis for Skeletal Muscle Functions

Thyroid conditions including AITD significantly impact skeletal muscle metabolism. While PA has been shown to improve various thyroid disease biomarkers, information pertaining to the role of nutrition in facilitating exercise-induced thyroid functions remains sparse. Optimal management of thyroid conditions requires a holistic approach that addresses PA supported by proper energy substrates. Nonetheless, current research focuses on isolated PA interventions for thyroid health, while leaving out considerations for muscle fiber types, growth and repair, shifting, and adipocyte functions for thyroid-specific patients. Emerging evidence suggests that muscles contain a large number of immune cells trafficking certain leukocytes into vascular circulation.[16] As such, skeletal muscle is reported to generate IL-6,[16] the key player as-so it appears in AITD, leading to exacerbation of IL-10 and IL-1 receptors,[16] and produce IL-7 via muscle contraction.[16] Therefore, tailored nutrition-based strategies supporting exercise programs considering skeletal muscle functions may offer synergetic benefits.

Muscle Fiber Types

The contraction and relaxation of different types of muscle fibers (MF) and their energy substrate preferences are closely regulated by thyroid hormone.[22,32,34] Therefore, designing exercise protocols that consider the different MF types can help optimize the training outcomes for these patients. For example, slow-twitch (type 1) MF, stimulated by slow neuron innervation, is highly sensitive to thyroid hormone activity.[32,34] These MFs rely on oxidative metabolism for energy production, indicating strong fatigue resistance[7] and less cellular ATP production due to increased mitochondrial density.[25,32] Therefore, exercise protocols that aim to improve the function of type 1 MF should focus on endurance training, such as long-distance running or cycling, and should be fueled by fats, carbohydrates, and proteins. On the other

hand, fast-twitch (type 2 [isoforms 2A, 2X, and 2B]) MF, which relies on glycolytic metabolism, exhibits the need for more glycogen and phosphocreatine, and is essential for short-burst activities,[25,32] may benefit more from resistance training or high-intensity interval training; and should rely heavily on carbohydrates and proteins due to demands for ATP.[32]

Muscle Growth and Repair in Patients with Hypothyroidism

Exercise protocols can be designed to promote muscle growth and repair in patients with thyroid disease with muscle weakness or atrophy,[32] as research has proven that T3 is required for normal myogenesis and repair from injuries generating increased satellite cell regeneration sites.[25,32] Resistance training, for example, has been shown to increase muscle mass and strength in patients with hypothyroidism.[26,39] Similarly, aerobic exercise can improve muscle function and endurance, benefiting patients with hypothyroidism who experience fatigue or exercise intolerance.[6,27,39]

Muscle Fiber Type Shifting

It is documented that thyroid hormone plays a pivotal role in the continuous shifting of myosin heavy chain-1 (MyHC-1) (type 1) MF towards type 2A, 2X, and 2B MF.[25,32,34] Customizing exercise protocols to facilitate MF type shifting is a viable approach for patients with thyroid disease exhibiting altered muscle fiber composition.[6,7,26,27,36,39,42] Although reductions of MFs in hypothyroid patients are associated with the inability of thyroid hormone receptor α-1 expression to shift MyHC-1 MF to type 2 MF,[32] while simultaneously promoting type 2 MF shifting to MyHC-1, hyperthyroidism is associated with a shift towards type 2 MF. Therefore, nutrition-based exercise programs should be specifically designed to help shift muscle fiber types toward a more balanced composition.

Adipocyte Activity

Upon movement-induced muscle activation, a concomitant activation of adipocytes ensues, leading to the degradation of adipocytes.[32] As the onset of PA exertion occurs, the UCP1 promotes mitochondrial uncoupling in subcutaneous and visceral adipose tissue[32] to utilize oxidative substrates. This cascade also triggers the reduction of inflammation markers.[27] In the study by Xiang et al,[27] post-exercise, a significant decrease in inflammation and thyroid Abs biomarkers was observed from following a steady-state routine. Hashimoto's, a form of hypothyroidism, undergoes shifts to MyHC-1 MF due to the inhibition of thyroid hormone receptor α-1 expression,[32] as previously mentioned. Nutrition-based exercise programs tailored for patients with thyroid autoimmunity should emphasize PA routines designed to engage oxidative metabolism.

Part III: The Complexities of Energy Expenditure and Nutrition During Physical Activity

The regulation of T3 and T4 mediated by the DIO2 and DIO3 genes,[32] hold dominance over the positive (*hypo* state [slowed metabolism]) and negative (*hyper* state [increased metabolism]) states of estimated energy needs (EEN), thereby impacting metabolic rates.[32] This regulatory process can lead to metabolic complications, where energy substrates (carbohydrates, proteins, and fats) are converted very slowly resulting in hypometabolism, or rapidly, causing hypermetabolism. To address these complexities, daily nutrition-based exercise programs should be structured to facilitate substrate utilization aligned with the MF type shifting promoted by the thyroid disease. For instance, carbohydrate intake ranges should be adjusted to a minimum of 105-120g p/d to prevent T3 decline in patients with hypothyroidism, and average 30-60 g/hr for higher performance subjects to blunt the cortisol response.[16]

In designing trials to evaluate the impact of exercise on patients with thyroid disease, nutrition-based structured exercise programs should be evaluated for their potential to improve symptoms leading to disease amelioration, enhanced HRQoL, or attempts to resolve the condition. If extremely stressful events can lead to auto-reactive B cell activity[4,11–13] researchers may assume that in autoimmunity the immune system is memorizing the persistent incessant action on the fight-or-flight response. Considering EEN during trial phases is critical to prevent diminishing HRQoL due to

Table 8. Muscle Fiber in Relation to Thyroid Diseases

Thyroid Disease	Muscle Fiber Type	Rate of Fatigue	Twitch Type	ATP Need	SubstrateUtilization	Example	Exercise
Hypo shifts to ➡	Type MyHC-1	Resistant	Slow	More	• Oxidative	• CalfAb	• Long Distance Endurance
Hyper shifts to ➡	Type 2A	Low	Fast	Mediocre	• Oxidative • Glycolytic	• Quadriceps • Hamstrings	• Short DistancePowerful BurstsSprinting
Hyper shifts to ➡	Type 2X	High	Fast	Mediocre	• Glycolytic	• TricepBicep	• Resistance Strength Training
Hyper shifts to ➡	Type 2B	High	Fast	High	• Glycolytic	• TricepBicepAb	• Resistance Strength Training

a. Hypothyroid disease shifts to oxidative metabolism, with slow twitch type, and is fatigue resistant. Therefore, endurance or exercises that utilize power bursts are recommended for this population.
b. Hyperthyroid disease shifts to glycolytic metabolism, with fast twitch type, and has a high rate of fatigue. Therefore, resistance and strength training exercises are better suited for this population.

inadequate energy intake leading to malnutrition, fatigue, and decreased physical and cognitive function, which can negatively impact AITD participants' HRQoL.[6,7,23] Nutrients involved in cerebral processes regulating the SNS and adrenal systems are amino acids (glutamine and choline) for neuro transmissions, healthy fats for neuron repair, selenium and iodine for deiodinase H_2O_2 conversions, iron for nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) processes, tyrosine for thyroglobulin synthesis, vitamin B3 for the NADPH/NADP pentose phosphate pathway, vitamin D for cellular DNA repair, glutathione and selenium for the glutathione cycle, vitamin C and B vitamins for mitochondrial support to improve energy synthesis, and electrolytes facilitate cellular membrane movement. By providing sufficient energy and dietary needs to participants', researchers ensure subjects meet energy and nutrient requirements. Hence, primary investigators can increase the likelihood of successful study outcomes.[23]

Intervention Design Recommendation Based on Results Syntheses

The following table is the proposed intervention design for considering the *FItTeD* comparison component of nutrition-based exercise programs. Increases in intensity are highly recommended throughout trials and complete reporting of all biomarkers should be mandatory.

Table 9. 12-13 Week Intervention Proposal

Experimental Groups Hashimoto's Thyroiditis				Control Group
F	**It**	**Te**	**D**	**FItTeD**
4x/wk	Moderate-intensity	EnduranceAerobic Components: Run/jog, cycle, dancing, walking, skating, sports, circuit training, resistance training, martial arts	1 hr	No Training/Leisure Activities
Measure TSH, T3, T4, TPO, Tg, and medication reduction with relapse rate				
Experimental Groups for Graves' Disease				**Control Group**
F	**It**	**Te**	**D**	**FItTeD**
5x/wk	Moderate-intensity	Strength and FlexibilityLoad Bearing Components:Resistance training, body resistance exercises, walking, stretching, yoga, tai chi, water exercises	1 hr	No Training/Leisure Activities
Measure TSH, T3, T4, TPO, Tg, TSHR, and medication reduction with relapse rate				

Abbreviations: F, frequency; It, intensity; Te, type; D, duration.Representation of a 12-13 week trial to accumulate accurate data for metabolic adaptations. Target sample size minimum 44 participants with standardized Biomarker utilization for quality comparisons and mitigation of bias. Stress examinations, such as trauma questionnaires are an integral component. Muscle fiber type shifting should be considered, therefore Te represents specific exercises for specific thyroid diagnosis. Energy expenditure and nutrition should be analyzed exposing groups to minimal requirements for optimal performance.a. Hypothyroid disease shifts to oxidative metabolism, therefore dietary substrates should satisfy this pathway. b. Hyperthyroid disease shifts to glycolytic metabolism, therefore dietary substrates should satisfy this pathway.

Limitations

A significant limitation of this systematic review is the availability of reported data. While the literature search was conducted comprehensively, a limited number of studies met our criteria. This can impact the study's validity, as the included trials may have a selection bias, leading to an incomplete representation of the available evidence. In addition, differences in exercise frequency, intensity, type and duration can significantly alter study outcomes making it difficult to determine which aspect of PA is most beneficial.

The studies that assessed HRQoL[26,41] had limited availability of information on primary thyroid biomarkers, such as TSH, T4, T3, TPO, Tg, and TSHR Ab levels, and it can be stated about the studies that assessed primary thyroid biomarkers,[6,7,27,39,42] as they also neglected to report on HRQoL. Interestingly, there was a common deficit of testing and reporting for lipid, anthropometrics, and T2DM biomarkers.[6,7,26,27,41,42] This was confusing as cardiometabolic biomarkers play a significant role in determining thyroid health outcomes. Additionally, all but one study failed to elaborate on the primary connections between metabolic, cardiovascular, respiratory, and muscular functions during the analysis of symptoms while investigating exercise training programs.[6,7,26,27,41,42] This makes it difficult to determine the impact of exercise on the relationship between thyroid hormone function and HRQoL outcomes and may limit the generalizability and credibility of the findings.

Conclusion

This review found that stress is a key player in AITD. Exercise programs may have the potential to benefit or worsen individuals with thyroid diseases, as these conditions are found to be strongly stress-induced. Glucocorticoids have a powerful influence on the regulation of immune lymphocyte activity, particularly B and T cells, which drive proinflammatory cytokines IL-6 and IL17. Fox3P and GITR levels are increased in individuals with thyroid disorders, and cortisol affected by stress and exercise are critical regulators of biochemical changes. Exercise can potentiate or reduce immune activity through FITeD (frequency, intensity, type, and duration) factors. Cytokines present in muscle may further influence GLUT4 proteins altering energy expenditure metabolism. HPA processes further influence energy substrates during prolonged periods of PA. Therefore, depending on the type of thyroid condition, certain exercises appear to have a beneficial influence due to MF type shifting. Although exercise has a significant impact on HRQoL, results on TPO, Tg, and TSHR Abs are inconclusive, as there is limited evidence to prove exercise effects on antibody status. Nonetheless, there were notable improvements in and thyroid hormone levels. Moderate intensity was found to be the mean intensity level of all included studies, while the mean duration was found to be 4 days per week of PA. Of the studies

reviewed, none tested for cortisol, and there were inconsistencies in functional testing methods across trials. This brings to light the need for tailored interventions specifically designed to with guidelines for testing thyroid disease populations. Such guidelines included a minimal trial length of 12-13 weeks to accumulate accurate data for metabolic responses to exercise interventions, targeted sample sizes with more than 44 subjects, standardized biomarker utilization, and stress examinations as an integral component. Furthermore, trials should consider the following factors: (1) interventions for hyperthyroidism should implement moderate-intensity, strength and flexibility-stretching type exercises; (2) interventions for hypothyroidism should implement endurance type exercises, aerobic style, moderate-intensity with a consistent steady-state exercise routine; (3) patients should be continually monitored for cardiovascular risk, fatigue, and poor muscle recovery; (4) medication should be monitored regularly and assessed for proper reduction; and (5) the feasibility of compliance and modification of lifestyle habits during translational research should be evaluated as a primary objective for healthcare providers that implement therapeutic thyroid interventions to their patients.

In conclusion, it was discovered that endurance, aerobic-resistance, and structured training, independent of medication, positively improved various thyroid biomarkers and HRQoL domains. Meanwhile medium-intensity exercise training and long-term durations (6mos) also demonstrated statistical improvements. However, although two studies claim resolution of thyroid conditions, five only saw small improvements. Thus, there is not enough recorded evidence to conclude. Adhering to new guidelines for future research protocols is essential to ensure comprehensive data collection and yield clear and concise results, better facilitating enhanced nutrition-based exercise programs.

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