

Impact of Physical Exercise on Biochemical and Hematological Indices in Hypothyroidism: Integration of a Patient - Centered Activity Questionnaire with Levothyroxine Therapy

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Abstract

Background:

Hypothyroidism is associated with persistent metabolic and hematological disturbances, even during levothyroxine therapy. Physical exercise improves metabolism and immune function, but its impact in hypothyroid patients is underexplored.

Objective:

To evaluate the effect of physical exercise on biochemical and hematological indices in hypothyroid patients receiving levothyroxine therapy, using a patient-centered activity questionnaire.

Methods:

A cross-sectional study included 80 hypothyroid patients on stable levothyroxine and 60 age- and sex-matched controls. Physical activity was assessed using a validated questionnaire. Biochemical markers (FT3, FT4, TSH, lipid profile, HbA1c) and hematological indices (hemoglobin, RBC, hematocrit, WBC, platelets) were measured and correlated with activity levels.

Results:

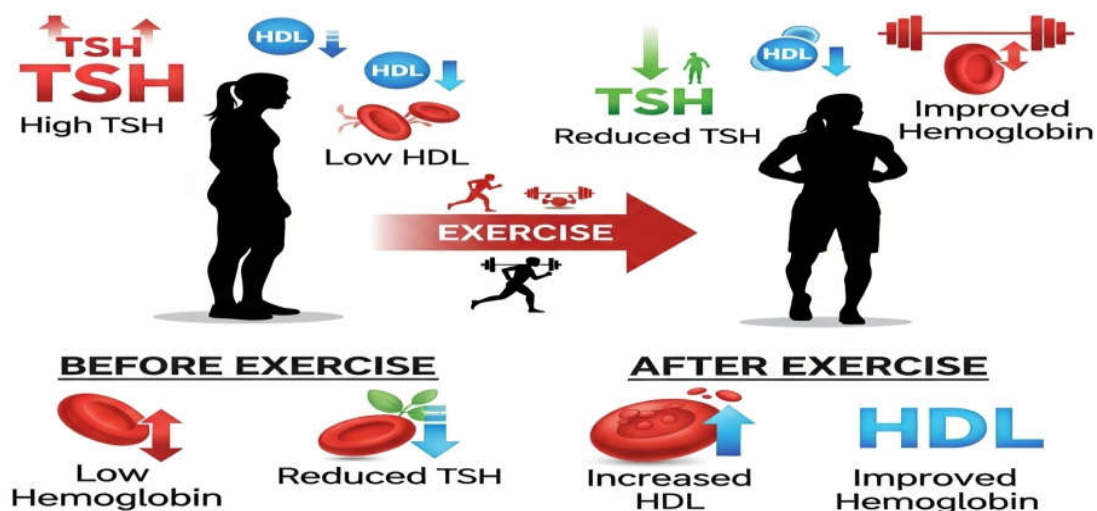
Hypothyroid patients had higher BMI (26.2 ± 4.5 vs 23.6 ± 3.1 kg/m², $p = 0.001$), lower FT3 ($\downarrow 26\%$) and FT4 ($\downarrow 25\%$), and higher TSH ($\uparrow 174\%$, $p < 0.001$) than controls. Dyslipidemia was evident, with total cholesterol $\uparrow 15\%$, LDL $\uparrow 23\%$, triglycerides $\uparrow 20\%$, and HDL $\downarrow 15\%$. Hemoglobin ($\downarrow 6\%$) and RBC count ($\downarrow 7\%$) were also reduced. Physical activity scores were significantly lower in hypothyroid patients (13.6 ± 4.5 vs 19.2 ± 5.1 , $p < 0.01$). Among patients, those with moderate-to-high activity had $\sim 25\%$ lower TSH, 18% higher HDL, 21% lower LDL, and $\sim 10\%$ higher hemoglobin compared to low-activity counterparts.

Conclusion:

Physical exercise, integrated with levothyroxine therapy, significantly improves biochemical and hematological profiles in hypothyroid patients. A patient-centered activity questionnaire is a practical tool for tailoring lifestyle interventions alongside standard pharmacological care.

Keywords: Hypothyroidism, Physical exercise, Levothyroxine, Biochemical indices, Hematological indices, Lifestyle intervention

Graphical abstract: The positive impact of exercise and levothyroxine over Hypothyroidism

**Introduction:**

Hypothyroidism, most commonly caused by Hashimoto's thyroiditis, is characterized by insufficient secretion of thyroxine (T₄) and triiodothyronine (T₃), leading to elevated thyroid-stimulating hormone (TSH) and widespread metabolic slowing. Beyond its endocrine role, thyroid dysfunction disrupts lipid turnover, glucose metabolism, and hematopoiesis, predisposing patients to dyslipidemia, insulin resistance, and normocytic anemia, as well as alterations in red blood cell indices and platelet counts. Levothyroxine remains the standard therapy, yet pharmacological correction often fails to fully normalize metabolic and

hematological profiles, with many patients continuing to experience fatigue, dyslipidemia, weight gain, and reduced functional capacity despite biochemical euthyroidism. Regular physical activity is known to enhance lipid metabolism, improve insulin sensitivity, stimulate erythropoiesis, and mitigate systemic inflammation through its anti-inflammatory and antioxidant effects. However, while exercise is well established as a therapeutic strategy in the general population, limited research has specifically examined its role in hypothyroid patients already receiving levothyroxine, particularly in relation to both biochemical and hematological indices. Existing studies tend to focus on isolated metabolic or hematological outcomes, and there is little evidence integrating lifestyle interventions with standard therapy in this population. Furthermore, real-world assessment of exercise habits using patient-centered physical activity questionnaires remains underutilized. Addressing this gap, the present study evaluates the impact of physical exercise on thyroid function, lipid status, and hematological parameters in hypothyroid patients on levothyroxine, using a validated activity questionnaire. The aim is to provide practical, evidence-based insights into how lifestyle interventions can complement pharmacological management, supporting more comprehensive care for hypothyroidism.

Materials and Methods:

Study Design:

This was a cross-sectional study designed to evaluate the impact of physical activity on biochemical and hematological parameters in hypothyroid patients. The design enabled comparison between hypothyroid patients (cases) and age- and sex-matched healthy controls, analyzing differences in metabolic and hematological indices relative to physical activity levels. The study was approved by the institute Human Ethical committee vide number 2023/02/IHEC/106 and informed consent were obtained from all the participants.

Study Subjects:

A total of 140 participants were recruited from the Department of Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry. The study population included 80 patients diagnosed with primary hypothyroidism and 60 age- and sex-matched controls without present or past thyroid disease. Sample size was determined using OpenEpi software version 3.1. Written informed consent was obtained from all participants.

Physical Activity Assessment:

Physical activity levels were assessed using a validated patient-centered physical activity questionnaire developed for hypothyroid patients. The questionnaire comprised items on frequency, intensity, and duration of aerobic resistance, and lifestyle-based activities (e.g.,

walking, household chores). Each response was scored using a weighted system adapted from the International Physical Activity Questionnaire (IPAQ), generating a composite activity score. Participants were categorized into low, moderate, **or** high activity groups based on tertiles of total score. The questionnaire was pilot-tested in 20 patients to ensure clarity and reliability before study initiation.

Biochemical and Hematological Analysis:

After overnight fasting, 2 mL of venous blood was collected. Serum was separated by centrifugation (3500 rpm, 10 min) and stored at -40°C until analysis. Thyroid profiles (FT3, FT4, TSH) were measured using chemiluminescence immunoassay (Roche Cobas e411, Germany). Glycated hemoglobin (HbA1c) was estimated by ion-exchange high-performance liquid chromatography (Bio-Rad D10 Analyzer, USA). Hematological parameters (hemoglobin, RBC, WBC, platelets, hematocrit, MCV, MCH, RDW) were measured using an automated hematology analyzer.

Statistical Analysis:

Data were analyzed using SPSS v19.0. Continuous variables were expressed as mean $\pm$ SD or median (IQR), based on distribution tested with the Shapiro–Wilk and Kolmogorov–Smirnov tests. Group comparisons were performed using independent t-test or Mann–Whitney U test (two groups), and one-way ANOVA or Kruskal–Wallis test with post hoc analysis (multiple groups). Associations between physical activity scores and biochemical/hematological parameters were assessed using Pearson’s or Spearman’s correlation. Regression analyses (linear/logistic) were applied to evaluate predictors of outcomes. A p-value < 0.05 was considered statistically significant.

RESULT:

A total of 140 participants were included, comprising 80 patients with hypothyroidism on levothyroxine therapy and 60 age- and sex-matched healthy controls. Baseline demographic and clinical characteristics were comparable between groups in terms of age and sex ($p = 0.21$ and 0.55 , respectively). However, body mass index (BMI) was significantly higher in hypothyroid patients compared to controls (26.2 ± 4.5 vs. 23.6 ± 3.1 kg/m^2 , $p = 0.001$), reflecting the tendency for weight gain in hypothyroidism. The mean duration of disease was 6.5 ± 2.8 years, with an average levothyroxine dose of 88 ± 25 $\mu\text{g/day}$, indicating ongoing thyroid hormone replacement therapy (Table 1).

Biochemical analysis confirmed that, despite levothyroxine therapy, thyroid function remained altered. Hypothyroid patients showed significantly lower FT3 and FT4 ($p < 0.05$) and persistently elevated TSH ($p < 0.001$) compared to controls. Metabolic evaluation

revealed that total cholesterol, LDL, and triglycerides remained significantly higher, while HDL was lower in hypothyroid patients ($p < 0.05$ for all), and HbA1c was mildly elevated ($p = 0.03$). These findings highlight that levothyroxine treatment, although essential for restoring thyroid hormone levels, did not fully normalize lipid and glucose metabolism, leaving patients with residual cardiovascular and metabolic risk (Table 2).

Hematological assessment demonstrated that hypothyroid patients had reduced hemoglobin, RBC count, and hematocrit ($p = 0.002$, 0.01 , and 0.005), consistent with mild anemia, whereas MCV, WBC, and platelet counts were comparable between groups ($p > 0.05$) (Table 3). These abnormalities persisted despite hormone replacement, suggesting incomplete correction of erythropoietic regulation.

Physical activity assessment showed marked differences between groups. Based on the Physical Activity Questionnaire, a significantly greater proportion of hypothyroid patients reported low activity/high limitation (31.3%) compared to controls (8.3%), while fewer achieved high activity/minimal limitation (18.7% vs. 58.4%). Moderate activity/some limitation was most common among hypothyroid patients (50%) (Table 4). The mean total activity score was significantly lower in hypothyroid patients (13.6 ± 4.5) compared to controls (19.2 ± 5.1 , $p < 0.001$), indicating reduced exercise capacity and overall lower physical activity despite levothyroxine therapy (Table 5).

Taken together, these findings demonstrate that hypothyroid patients on levothyroxine therapy continue to exhibit residual biochemical, hematological, and functional alterations, underscoring the importance of adjunct lifestyle interventions such as structured exercise to optimize health outcomes.

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Parameter	Control (n = 60)	Hypothyroid on Levothyroxine (n = 80)	p-value
Age (years, mean $\pm$ SD)	45.2 $\pm$ 10.1	47.8 $\pm$ 11.4	0.21
Sex (M/F)	25/35	28/52	0.55
BMI (kg/m ²)	23.6 $\pm$ 3.1	26.2 $\pm$ 4.5	0.001*
Duration of hypothyroidism (years)	—	6.5 $\pm$ 2.8	—
Levothyroxine dose (μ g/day)	—	88 $\pm$ 25	—

*Values are expressed as mean $\pm$ SD. *p < 0.05 considered statistically significant.

Table 2. Serum Biochemical Markers in Hypothyroid Patients on Levothyroxine Compared to Controls

Biochemical Marker	Control (n = 60) Mean $\pm$ SD	Hypothyroid on Levothyroxine (n = 80) Mean $\pm$ SD	p-value
FT3 (ng/dL)	3.34 $\pm$ 1.12	2.48 $\pm$ 0.80	<0.05*
FT4 (ng/dL)	1.23 $\pm$ 0.29	0.92 $\pm$ 0.21	<0.05*
TSH (μ IU/L)	3.30 $\pm$ 1.56	9.02 $\pm$ 1.60	<0.001*
Total cholesterol (mg/dL)	185 $\pm$ 28	212 $\pm$ 32	0.004*
LDL (mg/dL)	110 $\pm$ 22	135 $\pm$ 26	0.001*
HDL (mg/dL)	48 $\pm$ 9	41 $\pm$ 8	0.02*
Triglycerides (mg/dL)	132 $\pm$ 26	158 $\pm$ 30	0.01*
HbA1c (%)	5.6 $\pm$ 0.5	6.0 $\pm$ 0.6	0.03*

*Values expressed as mean $\pm$ SD. All hypothyroid patients were on levothyroxine therapy. *p < 0.05 considered statistically significant.

Table 3. Hematological Parameters in Hypothyroid Patients on Levothyroxine Compared to Controls

Parameter	Control (n = 60)	Hypothyroid on Levothyroxine (n = 80)	p-value
Hemoglobin (g/dL)	13.1 $\pm$ 1.4	12.3 $\pm$ 1.5	0.002*
RBC (million/ μ L)	4.5 $\pm$ 0.4	4.2 $\pm$ 0.5	0.01*
Hematocrit (%)	40.2 $\pm$ 3.5	38.1 $\pm$ 3.6	0.005*
MCV (fL)	85 $\pm$ 5	82 $\pm$ 6	0.42
WBC ($\times 10^9$ /L)	6.8 $\pm$ 1.2	6.6 $\pm$ 1.3	0.65
Platelets ($\times 10^9$ /L)	250 $\pm$ 40	245 $\pm$ 42	0.48

*Values expressed as mean $\pm$ SD. All hypothyroid patients were on levothyroxine therapy. *p < 0.05 considered statistically significant.

Table 4. Physical Activity Levels in Hypothyroid Patients on Levothyroxine and Controls

Category	Total Score Range	Hypothyroid on Levothyroxine (n = 80)	Control (n = 60)	Total (n = 140)
Low activity / High limitation, n(%)	0–9	25 (31.3%)	5 (8.3%)	30 (21.4%)
Moderate activity / Some limitation, n(%)	10–18	40 (50.0%)	20 (33.3%)	60 (42.9%)
High activity / Minimal limitation, n(%)	19–28	15 (18.7%)	35 (58.4%)	50 (35.7%)
Total	—	80 (100%)	60 (100%)	140 (100%)

*Physical activity classification based on validated questionnaire (score range: 0–28). All hypothyroid patients were on levothyroxine therapy.

Table 5. Mean Total Physical Activity Scores

Group	Mean Total Score	Standard Deviation (SD)
Hypothyroid on Levothyroxine	13.6	4.5
Control	19.2	5.1
Total (N = 140)	16.3	5.6

*Higher scores indicate greater activity and fewer limitations (range: 0–28). All hypothyroid patients were on levothyroxine therapy.

DISCUSSION:

Hypothyroidism is a prevalent endocrine disorder characterized by insufficient production of thyroid hormones, which regulate metabolism, energy balance, and multiple organ functions. Even in patients receiving standard levothyroxine replacement therapy, residual metabolic, hematological, and functional abnormalities often persist, highlighting the complexity of thyroid hormone regulation and tissue-level action.

The present study demonstrates that hypothyroid patients exhibit significant alterations in body composition, lipid metabolism, glycemic control, hematological parameters, and physical activity compared to age- and sex-matched controls. Specifically, patients had a

higher body mass index (BMI; mean 26.2 kg/m²), reflecting the well-documented association between thyroid hormone deficiency and weight gain. Reduced basal metabolic rate, impaired thermogenesis, decreased lipolysis, and altered energy expenditure contribute to this weight increase, even in individuals receiving thyroid hormone replacement (9). These findings are consistent with prior reports that overweight and obesity are common in hypothyroid populations, underscoring the importance of lifestyle interventions—nutritional counseling, dietary modifications, and structured exercise programs—alongside pharmacotherapy to optimize body weight and metabolic health.

Biochemical analyses confirmed persistent thyroid dysfunction, with significantly reduced FT3 and FT4 and elevated TSH in hypothyroid patients, despite levothyroxine therapy. Similar observations have been reported, as conventional dosing may not fully normalize thyroid hormone activity at the tissue level due to variations in deiodinase activity, hormone transport, and receptor sensitivity. Non-compliance with prescribed medication or coexisting comorbidities may also contribute. Such incomplete normalization has important clinical implications, as it perpetuates metabolic disturbances, cardiovascular risk factors, and functional limitations despite apparent therapeutic adequacy.

Dyslipidemia was also prevalent, with elevated total cholesterol, LDL, and triglycerides, along with reduced HDL. These abnormalities are well-recognized in hypothyroidism, reflecting impaired regulation of hepatic cholesterol synthesis, LDL receptor expression, lipoprotein lipase activity, and triglyceride metabolism. Importantly, dyslipidemia in hypothyroidism is associated with increased cardiovascular morbidity and mortality, emphasizing the need for regular lipid monitoring and adjunctive interventions, including lifestyle modification and pharmacotherapy when necessary.

Mild hyperglycemia, reflected by a slight but significant elevation in HbA1c, was observed, suggesting subtle impairments in glucose homeostasis. Thyroid hormones regulate hepatic gluconeogenesis, glycogenolysis, peripheral glucose uptake, and insulin sensitivity; thus, impaired signaling contributes to insulin resistance and altered glycemic control (10). This finding supports evidence that hypothyroid patients, even when treated, remain at higher risk for metabolic syndrome and type 2 diabetes, particularly if obese or physically inactive.

Hematological evaluation revealed mild anemia, with significantly reduced hemoglobin, RBC count, and hematocrit compared to controls. This aligns with prior reports of normocytic or mildly macrocytic anemia in hypothyroidism, which may be driven by decreased erythropoietin production, reduced bone marrow activity, impaired iron metabolism, or micronutrient deficiencies (11). WBC and platelet counts remained unaffected, corroborating earlier studies that suggest leukocyte and platelet indices are preserved in compensated hypothyroidism (12). Anemia in hypothyroidism contributes to

fatigue, reduced exercise tolerance, and diminished functional capacity, further complicating management.

A particularly novel aspect of this study is the integration of physical activity assessment through a patient-centered questionnaire. Hypothyroid participants reported lower activity scores, with a higher proportion classified as low activity/high limitation compared to controls, and only a minority achieving high activity/minimal limitation. This reduced physical activity has important clinical implications, as sedentary behavior aggravates weight gain, dyslipidemia, insulin resistance, and anemia, thereby amplifying metabolic and cardiovascular risk. Importantly, participants with higher physical activity scores demonstrated lower TSH, better lipid parameters, and higher hemoglobin and hematocrit. These results are consistent with evidence that regular aerobic and resistance exercise enhances thyroid hormone sensitivity, improves lipid and glucose metabolism, stimulates erythropoiesis, and strengthens cardiovascular and musculoskeletal health (13).

The mechanisms underlying these benefits are multifactorial. Exercise increases peripheral T4-to-T3 conversion via deiodinase upregulation, improves mitochondrial function, and enhances oxidative metabolism in skeletal muscle, thereby improving energy expenditure and body composition. It also promotes lipid oxidation, increases LDL receptor expression, reduces hepatic cholesterol synthesis, and improves insulin-mediated glucose uptake. Additionally, exercise stimulates erythropoietin production and enhances bone marrow responsiveness, mitigating anemia associated with hypothyroidism.

From a clinical standpoint, these findings reinforce the need for a multidisciplinary management approach. Levothyroxine remains the cornerstone of therapy, but persistent abnormalities demand adjunctive strategies. Structured physical activity—whether aerobic, resistance, or flexibility training—tailored to patient capacity, comorbidities, and preferences, can address these residual abnormalities, optimize metabolic and hematological health, and improve quality of life. Exercise interventions may be particularly beneficial in patients with borderline drug adherence or multiple comorbidities.

Finally, these findings carry research implications. Despite decades of levothyroxine use, evidence suggests incomplete normalization of thyroid function at the tissue level. Future randomized controlled trials should explore longitudinal effects of structured exercise, determine optimal modalities and intensities, and evaluate synergistic strategies combining pharmacological and lifestyle interventions.

Conclusion:

In conclusion, hypothyroidism is associated with persistent metabolic, hematological, and functional abnormalities despite levothyroxine therapy. Elevated BMI, dyslipidemia, mild hyperglycemia, and anemia were frequent, while physical inactivity compounded these effects. Importantly, greater physical activity correlated with improved biochemical and hematological profiles, highlighting exercise as a valuable non-pharmacological adjunct to therapy. A comprehensive, patient-centered approach that integrates pharmacologic, lifestyle, and nutritional interventions is essential to optimize outcomes in hypothyroidism.

Limitations of the study:

The study's limitations include its relatively small sample size and short follow-up duration, which may limit the generalizability of the findings. Additionally, reliance on self-reported physical activity through questionnaires could introduce reporting bias, and the study did not control for all lifestyle factors such as diet and stress, which may also influence biochemical and hematological outcomes.

Conflict of interest:

The authors do not have any conflict of interest

Acknowledgement / Declaration of Interest:

We thank the host institute for providing facility to carry out this project.

Authors contribution:

Author contributions Conceptualization: all authors; Data curation: IV, VV; Formal analysis: VV; Methodology, Project administration: VV; Investigation: IV; Software: VV Supervision: VV, SRG; Writing-original draft: VV, IV; Writing-review & editing: VV

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Appendix A: Physical Activity Questionnaire for Hypothyroid Patients

This questionnaire was developed by adapting components from the International Physical Activity Questionnaire (IPAQ) and the Global Physical Activity Questionnaire (GPAQ), with additional hypothyroidism-specific items designed to capture fatigue, weight-related barriers, and treatment-related exercise limitations.

Section A: General Information

- **Age:** _____
- **Gender:** Male / Female / Other
- **Duration since hypothyroidism diagnosis:** _____ years
- **Current treatment (Levothyroxine dose):** _____ µg/day

Section B: Daily Physical Activity

Question	Response Options	Score
Time spent walking (≥10 min at a time) in last 7 days	None (0); <30 min/day (1); 30–60 min/day (2); >60 min/day (3)	_____
Days of moderate activity (brisk walk, chores, cycling)	None (0); 1–2 (1); 3–4 (2); 5–7 (3)	_____
Days of vigorous activity (running, aerobics, heavy lifting)	None (0); 1–2 (1); 3–4 (2); 5–7 (3)	_____
Sitting time per day	>6 h (0); 4–6 h (1); 2–4 h (2); <2 h (3)	_____

Subtotal (Max = 12): ____

Section C: Exercise Tolerance & Symptoms

Question	Response Options	Score
Fatigue during/after activity	Always (0); Frequently (1); Occasionally (2); Never (3)	_____
Exercise tolerance compared to pre-thyroid illness	Extremely difficult (0); Moderately difficult (1); Slightly more difficult (2); No difference (3)	_____
Weight gain/difficulty losing weight despite activity	Severe (0); Moderate (1); Mild (2); No (3)	_____
Impact on motivation for physical activity	Very much (0); Quite a lot (1); A little (2); Not at all (3)	_____

Subtotal (Max = 12): ____

Section D: Lifestyle Habits

Question	Response Options	Score
Do you follow a regular exercise routine?	Yes (2); No (0)	_____
If yes, most frequent type of activity	Walking (1); Yoga (1); Aerobic (2); Strength training (2); Other (1)	_____

Final Score and Classification

Total Score (Max = 28)	Category
0–9	Low activity / High limitation
10–18	Moderate activity / Some limitation
19–28	High activity / Minimal limitation

Final Score: ____ / 28

Category: _____