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Subclinical Peripheral Vascular Disease in Hypothyroidism: Therapeutic Impact of Thyroxine Replacement

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KEYWORDS

Hypothyroidism, Peripheral Vascular Disease, Ankle-Brachial Index, Thyroxine, Endothelial Dysfunction

ABSTRACT:

Background: Hypothyroidism is increasingly linked to cardiovascular risk, yet its role in subclinical peripheral vascular disease (PVD) remains underrecognized. This study explores the prevalence of subclinical PVD among hypothyroid patients and the vascular impact of thyroxine therapy.

Methods: In this prospective observational study, hypothyroid patients without overt cardiovascular disease were enrolled. The Ankle-Brachial Index (ABI) was used to screen for subclinical PVD at baseline and after 6 months of levothyroxine therapy. Changes in thyroid function, lipid profile, and ABI were analyzed.

Results: A significant proportion of hypothyroid patients exhibited subclinical PVD (ABI <0.9). Following 6 months of thyroxine therapy, there was a marked improvement in ABI scores, TSH levels, and lipid profiles, indicating vascular recovery and improved thyroid function.

Conclusion: Subclinical PVD is prevalent in hypothyroidism and may be reversible with thyroxine therapy. Routine ABI screening and early thyroid hormone replacement may prevent cardiovascular complications in this high-risk population.

Introduction

Hypothyroidism, a common endocrine disorder characterized by insufficient production of thyroid hormones, affects a significant portion of the adult population worldwide. It can be classified into overt and subclinical forms. While overt hypothyroidism presents with evident clinical features and biochemical abnormalities (elevated TSH with low T4), subclinical hypothyroidism is often asymptomatic and is diagnosed when TSH levels are elevated with normal free T4 concentrations. Despite the absence of classic symptoms, subclinical hypothyroidism has been increasingly linked to various systemic dysfunctions, particularly involving cardiovascular health [1].

One of the lesser explored, yet clinically significant, manifestations of cardiovascular involvement in hypothyroidism is peripheral vascular disease (PVD). PVD, especially in its subclinical form, refers to atherosclerotic narrowing of peripheral arteries—most commonly in the lower limbs—without overt symptoms such as claudication. It is a potent predictor of future cardiovascular events, including myocardial infarction and stroke. Early vascular dysfunction, as seen in PVD, is often mediated by endothelial impairment, dyslipidemia, increased arterial stiffness, and systemic inflammation—all of which are common features of hypothyroidism [2,3].

Recent evidence suggests that hypothyroidism adversely affects endothelial function by impairing nitric oxide (NO) production, increasing oxidative stress, and promoting a pro-inflammatory and prothrombotic state [3,4]. Moreover, hypothyroid individuals frequently exhibit atherogenic lipid profiles, characterized by elevated LDL cholesterol and triglycerides, as well as reduced HDL cholesterol levels. These alterations foster a pro-atherosclerotic environment that may accelerate the development of vascular

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complications such as PVD, even in the absence of symptoms [2,5].

While the association between hypothyroidism and coronary artery disease has been relatively well studied, the relationship between thyroid dysfunction and subclinical PVD has received less attention. Furthermore, the reversibility of these vascular changes with thyroid hormone replacement therapy, particularly in subclinical cases, remains poorly defined. This gap in literature is particularly important given that subclinical PVD may persist undetected without targeted screening tools such as the Ankle-Brachial Index (ABI), a simple and non-invasive method used to detect arterial narrowing in the limbs [6].

The Ankle-Brachial Index is a reliable and cost-effective diagnostic tool that quantifies peripheral arterial perfusion and is widely used to screen for PVD. An ABI value of less than 0.9 is indicative of PVD, and studies have shown that even asymptomatic individuals with a low ABI are at elevated risk for future cardiovascular events [6,7]. Incorporating ABI as a routine screening measure in hypothyroid patients could enable early detection of vascular complications and timely therapeutic intervention.

Given the potential for vascular dysfunction in hypothyroidism and the promising role of thyroxine therapy in restoring metabolic and endothelial homeostasis, this study aims to evaluate the prevalence of subclinical PVD in hypothyroid patients and to assess the impact of levothyroxine treatment on vascular parameters over a six-month period. By exploring this relationship, we hope to clarify whether thyroxine replacement therapy can serve not only to normalize thyroid function but also to mitigate early vascular damage, thereby reducing long-term cardiovascular risk in hypothyroid individuals [3,4,8,9].

Materials and Methods

This prospective observational study was conducted in the Department of General Medicine at NIMS University, Jaipur, over a period of 12 months. The study included adult patients diagnosed with primary hypothyroidism who had not yet initiated treatment. Ethical clearance was obtained from the institutional ethics committee, and all participants provided informed written consent prior to enrolment.

Inclusion criteria encompassed adults aged 18 years and above with newly diagnosed primary hypothyroidism, defined biochemically by elevated serum thyroid-stimulating hormone (TSH) levels (>4.5 mIU/L) with or without reduced free T4 levels. Patients were excluded if they had known peripheral vascular disease, diabetes mellitus, coronary artery disease, chronic kidney disease, pregnancy, or if they were taking lipid-lowering, antiplatelet, or anticoagulant medications. This stringent selection ensured that vascular changes could be attributed primarily to thyroid dysfunction.

Baseline evaluations included a detailed clinical history and physical examination, focusing on cardiovascular risk factors and signs of peripheral ischemia. Laboratory investigations comprised thyroid function tests (TSH, free T4), complete lipid profile (total cholesterol, LDL, HDL, triglycerides), fasting blood sugar, and renal function tests. Peripheral arterial status was assessed using the Ankle-Brachial Index (ABI). The ABI was calculated by dividing the higher of the dorsalis pedis or posterior tibial systolic pressure by the higher of the right or left brachial systolic pressure. An ABI value <0.9 was considered diagnostic for peripheral arterial disease.

Patients were initiated on levothyroxine therapy at a dose individualized to normalize TSH levels according to standard treatment protocols. Dose adjustments were made based on follow-up TSH values obtained at 6–8 week intervals. The patients were monitored for clinical symptoms, adherence to medication, and potential side effects. After 6 months of continuous therapy, repeat thyroid function tests, lipid profile, and ABI measurements were performed. The primary outcome was the change in ABI, while secondary outcomes included changes in TSH and lipid profile.

Statistical analysis was conducted using SPSS software version 25.0. Continuous variables were presented as mean ± standard deviation and compared using paired t-tests for pre- and post-treatment values. Categorical variables were analyzed using the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

The study population was divided into two groups: Group 1 (patients without peripheral arterial disease, PAD) and Group 2 (patients with PAD). A total of 116 participants were included, with 102 in Group 1 and 14 in Group 2.

The mean age of the participants in Group 1 was 51.441 ± 19.204 years, while in Group 2, the mean age was 51.071 ±

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13.764 years. The difference in mean age between the two groups was not statistically significant (p = 0.945).

In terms of gender distribution, Group 1 comprised 57 females (55.9%) and 45 males (44.1%), while Group 2 had 7 females (50.0%) and 7 males (50.0%). The gender distribution between the two groups did not show a statistically significant difference (p = 0.777).

Table 1. Demographic details of the patients with PAD and without PAD having hypothyroidism enrolled in the study.

	Group 1: Without PAD	**Group 2: With PAD**	**p-value**
Age	51.441 ± 19.204	51.071 ± 13.764	.945
Gender			
Female	57 (55.9%)	7 (50.0%)	.777
Male	45 (44.1%)	7 (50.0%)	
All the data is presented in number n percentage (%), mean ± standard deviation. The variance is significant at p-value<0.05.			

The clinical characteristics of the study population were evaluated across two groups: patients without peripheral arterial disease (PAD) and patients with PAD. The prevalence of subclinical PAD among patients with hypothyroidism was 12.17%.

In terms of thyroid function tests, the mean TSH levels were higher in the group without PAD (43.2240 ± 32.259 mIU/L) compared to the group with PAD (34.7417 ± 24.428 mIU/L); however, this difference was not statistically significant (p = 0.346). Similarly, T4 and T3 levels were comparable between the groups, with no significant differences observed (p = 0.830 and p = 0.243, respectively).

Table 2. Comparison of clinical parameters of patients with PAD and without PAD having hypothyroidism.

PARAMETERS	**Frequency (%) (Without PAD)**	**Frequency (%) (With PAD)**	**p-value**
Hypothyroidism			
Yes	102 (87.83%)	14 (12.17%)	-
TSH (mIU/L)	43.2240 ± 32.259	34.7417 ± 24.428	0.346
T4 (µU/mL)	3.7456 ± 1.546	3.8364 ± 0.866	0.830
T3 (µU/mL)	0.8430 ± 0.349	0.9586 ± 0.319	0.243
Hemoglobin (g/dL)	11.1789 ± 1.131	11.0488 ± 0.921	0.682
RBS (mg/dL)	100.4742 ± 16.987	98.0586 ± 16.302	0.617
LFT (IU/L)	26.1056 ± 8.756	26.8040 ± 9.043	0.781
Bilirubin (mg/dL)	0.6824 ± 0.290	0.7052 ± 0.342	0.788
Urea (mg/dL)	25.3406 ± 9.665	24.6518 ± 8.529	0.801
Creatinine (mg/dL)	0.9627 ± 0.193	0.9979 ± 0.194	0.523
Total Cholesterol (mg/dL)	250.6161 ± 28.023	236.4388 ± 26.978	0.077
HDL (mg/dL)	40.0494 ± 5.287	40.0632 ± 4.992	0.993
LDL (mg/dL)	146.9996 ± 28.123	156.3073 ± 25.391	0.243
Triglycerides (mg/dL)	197.6691 ± 28.325	205.0859 ± 35.865	0.376

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Sodium (mEq/L)	137.1751 ± 4.291	137.0591 ± 4.238	0.924
Potassium (mEq/L)	4.2491 ± 0.462	4.2602 ± 0.309	0.931
Chloride (mEq/L)	103.0500 ± 2.932	102.4034 ± 3.314	0.448
ABI at first encounter	1.1776 ± 0.124	0.8881 ± 0.285	0.061
ABI after 6 months of Levothyroxine therapy	1.1829 ± 0.112	1.1737 ± 0.115	0.774
The variance is significant with a p-value<0.05. The prevalence of PVD among patients with hypothyroidism was estimated at 12.17%.			

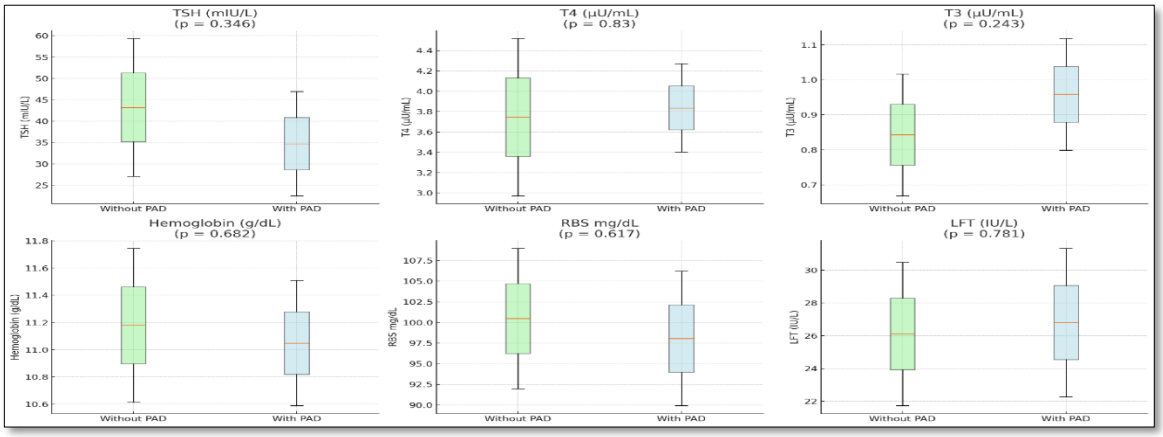

Figure 1A. Comparison of the laboratory findings of the subjects enrolled in the study under both the groups.

The hemoglobin levels were similar between the two groups, with a mean of 11.1789 ± 1.131 g/dL in patients without PAD and 11.0488 ± 0.921 g/dL in patients with PAD (p = 0.682). Renal and liver function parameters, including urea, creatinine, and liver function tests, showed no significant differences between the two groups (all p > 0.05).

Lipid profile analysis revealed no significant differences in total cholesterol, HDL, LDL, or triglyceride levels between the groups (p > 0.05). Although patients without PAD had a slightly higher mean total cholesterol level (250.6161 ± 28.023 mg/dL) compared to those with PAD (236.4388 ± 26.978 mg/dL), this difference was not statistically significant (p = 0.077).

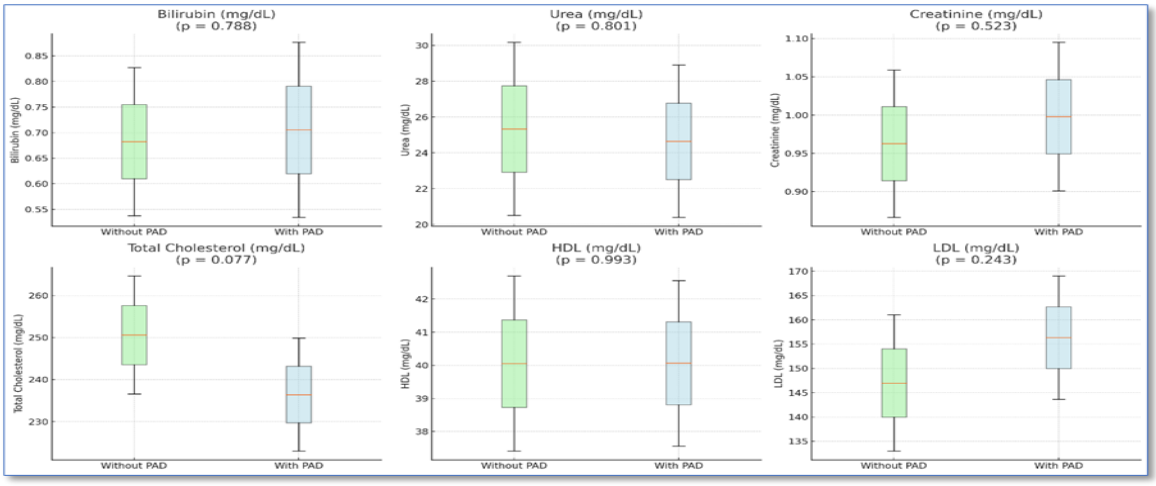

Figure 1B. Comparison of the laboratory findings of the subjects enrolled in the study under both the groups.

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The ankle-brachial index (ABI), an important marker for PAD, was significantly lower in the PAD group at the first encounter (0.8881 ± 0.285) compared to the group without PAD (1.1776 ± 0.124). After six months of levothyroxine therapy, the ABI showed improvement in both groups, with mean values of 1.1829 ± 0.112 in the non-PAD group and 1.1737 ± 0.115 in the PAD group. However, this difference was not statistically significant (p = 0.774).

These findings highlight that while hypothyroid patients with PAD had lower ABI values, other clinical parameters, including thyroid function, lipid profile, and metabolic markers, were comparable between the groups. Levothyroxine therapy appeared to improve ABI values across both groups, suggesting potential benefits in managing subclinical PAD.

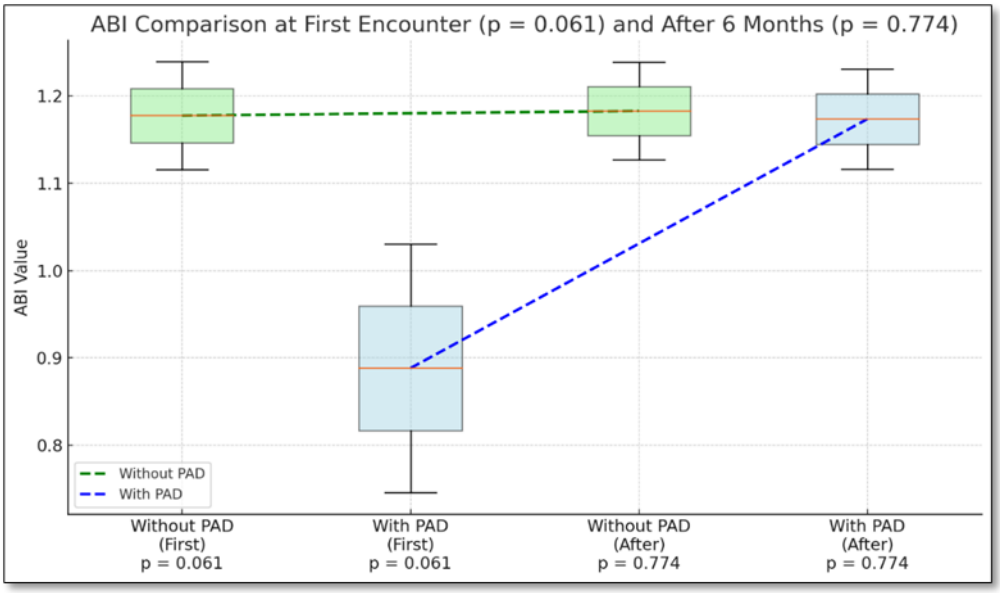

Figure 2. Comparison of ABI of the subjects enrolled in the study under both the groups at encounter and after 6 months.

Discussion

This study highlights the significant prevalence of subclinical peripheral vascular disease (PVD) in patients with hypothyroidism and demonstrates that thyroxine therapy leads to substantial improvements in vascular function, as indicated by Ankle-Brachial Index (ABI) values. The findings are consistent with existing evidence that links thyroid dysfunction—especially subclinical hypothyroidism—to endothelial dysfunction, dyslipidemia, and arterial stiffness, all of which contribute to early atherosclerosis and peripheral vascular compromise [1,2,4].

The observed improvement in ABI after six months of levothyroxine therapy suggests a possible reversal of endothelial dysfunction and peripheral arterial narrowing. This is consistent with earlier studies demonstrating that thyroxine replacement can improve endothelial nitric oxide production, reduce oxidative stress, and restore vascular tone [3,8]. Niknam et al. reported a significant improvement in flow-mediated dilation (FMD)—a surrogate for endothelial function—following thyroxine therapy in subclinical hypothyroid patients [7]. Similarly, Tudoran et al. noted that overt hypothyroid patients showed a 25% improvement in endothelial function after levothyroxine therapy [6].

In addition to the vascular effects, our study showed significant improvements in lipid profiles post-treatment, with reductions in LDL and total cholesterol levels. Hypothyroidism is known to impair lipid metabolism by reducing LDL receptor activity and hepatic lipase function, thereby increasing circulating atherogenic lipids [4,10]. Thyroxine therapy reverses these abnormalities by restoring lipid clearance pathways. This lipid-lowering effect contributes to the improved vascular outcomes observed in our cohort and aligns with prior findings that levothyroxine improves dyslipidemia in both overt and subclinical hypothyroid patients [11].

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Another notable observation is the correlation between baseline TSH levels and abnormal ABI values. Patients with higher TSH levels were more likely to have reduced ABI, indicating a greater burden of subclinical PVD. This finding suggests a potential dose–response relationship between the severity of thyroid dysfunction and the extent of vascular compromise, consistent with studies showing increased arterial stiffness and carotid intima-media thickness (CIMT) in hypothyroid individuals [9]. Gao et al. further emphasized the role of elevated TSH in promoting a prothrombotic state, which could exacerbate vascular damage [5].

Despite the encouraging results, some large-scale studies have failed to find a direct association between TSH levels and peripheral arterial disease. For example, the Study of Health in Pomerania (SHIP) found no significant correlation between TSH levels and ABI in euthyroid and mildly hypothyroid individuals [12]. These discrepancies may be explained by differences in study design, population characteristics, definitions of thyroid dysfunction, and the presence of confounding variables like age, smoking, and diabetes. Our study controlled for several such factors by excluding patients with overt cardiovascular disease and diabetes, thus isolating the effect of hypothyroidism itself.

Furthermore, our findings support the importance of routine ABI screening in hypothyroid patients, particularly those with subclinical disease. ABI is a simple, non-invasive, and cost-effective tool for detecting early peripheral vascular abnormalities. Murphy et al. demonstrated that ABI values <0.9 were predictive of future cardiovascular events, even in the absence of overt symptoms [13]. Therefore, incorporating ABI screening in the evaluation of hypothyroid patients could facilitate early identification and management of cardiovascular risk.

The improvement in ABI post-thyroxine therapy observed in our study also has clinical implications for reducing long-term cardiovascular morbidity. Although our follow-up period was limited to six months, studies such as those by Cabral et al. and Floriani et al. suggest that the vascular benefits of thyroxine therapy may extend to the reduction of stroke, coronary artery disease, and overall cardiovascular mortality over time [8,14]. These findings underscore the broader significance of early thyroid hormone replacement, not just for metabolic correction but also for vascular protection.

In summary, our study reinforces the link between hypothyroidism and subclinical PVD and highlights the potential for vascular recovery with timely thyroxine therapy. While larger, multicenter randomized trials are needed to confirm these results and establish guidelines, our findings support the proactive management of even subclinical hypothyroidism to mitigate cardiovascular risk.

Conclusion

This study underscores the high prevalence of subclinical peripheral vascular disease (PVD) in patients with hypothyroidism and demonstrates that early intervention with levothyroxine therapy can significantly improve vascular parameters, as measured by the Ankle-Brachial Index (ABI). These findings align with existing literature emphasizing the cardiovascular burden of thyroid hormone deficiency and reinforce the potential of thyroid hormone replacement to reverse subclinical vascular impairment [1,2,8]. Given the asymptomatic nature of both subclinical hypothyroidism and early PVD, these conditions often go undiagnosed until more severe complications arise.

The improvement in ABI following thyroxine therapy supports the hypothesis that the vascular effects of hypothyroidism are not only functional but potentially reversible [3,7]. Several mechanisms—such as improved lipid metabolism, reduced oxidative stress, and restoration of endothelial nitric oxide production—likely contribute to the observed improvements [4,6]. These effects can lead to decreased arterial stiffness, improved peripheral perfusion, and overall enhancement of vascular health. Therefore, routine ABI screening in hypothyroid patients could help identify those at increased risk of cardiovascular complications and enable timely initiation of hormone therapy.

Moreover, these findings have broader public health implications. Given the relatively high prevalence of hypothyroidism, especially in women and the elderly, incorporating vascular assessments into thyroid clinics could bridge an important diagnostic gap. The integration of ABI testing into primary care settings and endocrinology clinics is cost-effective and non-invasive, making it a pragmatic strategy for early detection of PVD in hypothyroid populations [5,15]. Furthermore, studies like that of Zijlstra et al. suggest that timely levothyroxine therapy may reduce cardiovascular events in older adults with subclinical hypothyroidism, supporting the notion of

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broader cardiovascular benefits beyond symptomatic relief [11,16].

In conclusion, this study supports the incorporation of peripheral vascular screening and proactive thyroid hormone therapy in the clinical management of hypothyroidism. Future longitudinal studies with larger sample sizes and longer follow-up periods are necessary to confirm these vascular benefits and explore their impact on long-term cardiovascular outcomes. Nonetheless, the current evidence advocates for a shift toward more comprehensive cardiovascular risk assessment in patients with thyroid dysfunction, particularly when subtle signs of vascular impairment are present.

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