e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(2); 213-219

Original Research Article

Evaluation of Serum Homocysteine and Vitamin B_{12} Status in Patients with Hypothyroidism

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Received: 02-12-2025 / Revised: 01-01-2026 / Accepted: 02-02-2026
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Conflict of interest: Nil

Abstract:

Background: Thyroid hormone insufficiency is the hallmark of hypothyroidism, a common endocrine condition that profoundly affects cellular metabolism. According to recent research, hypothyroidism and increased cardiovascular risk are strongly correlated and may be mediated by hyperhomocysteinemia. The metabolism of homocysteine (Hcy) is closely associated with B vitamins, particularly folate and vitamin B12.

Objective: This study's main goals were to assess serum homocysteine and vitamin B12 levels in patients with primary hypothyroidism in comparison to healthy controls and to examine the relationship between these metabolic markers and thyroid function parameters (TSH, fT_3, and fT_4) in an Eastern Indian population.

Methods: Over the course of six months, the Department of General Medicine and Biochemistry at Patna Medical College and Hospital (PMCH), Patna, carried out this observational cross-sectional study. 115 patients with primary hypothyroidism and 115 healthy controls who were matched for age and sex made up the study population. Chemiluminescence immunoassay (CLIA) was used to evaluate the levels of serum free T_3 (fT_3), free T_4 (T_4), thyroid stimulating hormone (TSH), vitamin B12, and homocysteine. Using SPSS version 26.0, statistical analysis was carried out, utilizing Pearson's correlation coefficient to evaluate associations between variables and the student's t-test for group comparisons.

Results: In comparison to controls (2.3 ±1.1 μIU/mL), the mean serum TSH in the case group was considerably higher (14.2 ± 6.1 μIU/mL). The mean serum homocysteine levels of hypothyroid patients were substantially higher (19.8 ± 5.4 μmol/L) than those of the control group (10.2 ± 3.1 μIU/mL; $p<0.001$). On the other hand, hypothyroid patients had considerably lower mean vitamin B12 levels (210 ± 85 pg/mL) than controls (450 ± 112 μIU/mL; $p<0.001$). TSH and homocysteine showed a substantial positive association ($r=0.68$, $p < 0.01$) whereas TSH and vitamin B12 levels showed a negative correlation.

Conclusion: The study shows a high correlation between low levels of vitamin B12, hyperhomocysteinemia, and hypothyroidism. These results imply that those with hypothyroidism are more susceptible to cardiovascular events and atherosclerosis. To reduce long-term metabolic and cardiovascular problems, routine monitoring for serum homocysteine and vitamin B12 is advised in hypothyroid therapy.

DOI: 10.25258/ijcpr.18.2.35

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Introduction

One of the most common endocrine problems in contemporary medicine is thyroid dysfunction, which is disproportionately prevalent on the Indian subcontinent. Hypothyroidism functions as a systemic metabolic depressant and is clinically characterized by the thyroid gland's inability to produce adequate amounts of thyroxine (T_4) and triiodothyronine (T_3). The hidden, subclinical effects of thyroid dysfunction on the circulatory system and micronutrient metabolism are under close scientific examination, despite the usual presentation of lethargy, weight gain, and intolerance to cold. Thyroid hormones and the cardiovascular system have a complicated interaction. Although dyslipidemia has historically been identified as the main cause of atherosclerosis in these patients [1], new research suggests that homocysteine is a risk factor.

The Cardiovascular Link and Homocysteine: Although there is ample evidence linking hypothyroidism to Atherosclerotic Cardiovascular Disease (ASCVD), the relationship cannot be entirely explained by lipid abnormalities alone. A sulfur-containing amino acid produced during the

metabolism of methionine, homocysteine has become a powerful, stand-alone risk factor for vascular disease. Hyperhomocysteinemia, or elevated plasma homocysteine, directly damages the vascular endothelium [2]. It stimulates the growth of vascular smooth muscle cells, increases oxidative stress, and decreases the bioavailability of nitric oxide, a vital vasodilator.

It is thought that the buildup of homocysteine in hypothyroid individuals is complex. Because thyroid hormones regulate renal clearance, the hypometabolic state lowers the glomerular filtration rate (GFR), which causes homocysteine to be retained. Additionally, the hepatic enzymes necessary for the remethylation of homocysteine to methionine are influenced by thyroid hormones. Even in patients with well-controlled cholesterol levels, a thyroid hormone deficit effectively generates a metabolic bottleneck that raises homocysteine levels to hazardous proportions, hastening the atherosclerotic process [3].

The Role of Vitamin B12 and Folate: The metabolic fate of homocysteine is closely related to the status of B-complex vitamins. The enzyme methionine synthase can recycle homocysteine back into methionine, but this process strictly requires folate as a methyl group donor and vitamin B12 (cobalamin) as a cofactor. This pathway can be disrupted by a variety of pharmacological agents and metabolic states, which further complicates the clinical picture [4].

This delicate cycle can be seriously disrupted by hypothyroidism. The production of flavin adenine dinucleotide (FAD), a cofactor for the enzyme methylenetetrahydrofolate reductase (MTHFR), which activates folate, requires thyroid hormones. Furthermore, there is a significant autoimmune overlap between stomach pathology and thyroid disease. Antibodies against stomach parietal cells or intrinsic factor are also present in a sizable portion of Hashimoto's thyroiditis patients, which can cause malabsorption of vitamin B12 from food and pernicious anemia [5]. The hypothyroid state is frequently linked to hypochlorhydria (low stomach acid), which hinders the extraction of vitamin B12 from dietary proteins even in the absence of autoimmunity. This results in a "double-hit" situation where the lack of thyroid hormone slows down the metabolic machinery and malabsorption depletes the fuel (Vitamin B12).

Rationale for the Study: Clinical data from Eastern India is still inconsistent, despite the obvious biological plausibility connecting hypothyroidism, B12 insufficiency, and hyperhomocysteinemia. People in this area, especially in Bihar, have distinctive eating habits that are marked by a high level of vegetarianism, which puts them at risk for B12 insufficiency. The metabolic effects may be more severe than in other populations when hypothyroidism and this dietary sensitivity coexist [6].

As a result, this study was planned and carried out at the prestigious tertiary care facility Patna Medical College and Hospital (PMCH). The main goal was to measure the serum levels of vitamin B12 and homocysteine in patients with hypothyroidism who were either newly diagnosed or receiving insufficient treatment. This study attempts to provide a solid evidence framework for changing existing treatment regimens to incorporate micronutrient supplementation and cardiovascular risk stratification by demonstrating the relationship between thyroid stimulating hormone (TSH) and these metabolic indicators.

Materials and Methods

Study Design and Setting: This inquiry was planned as a cross-sectional, observational study conducted in a hospital. In close cooperation with the Department of Biochemistry at Patna Medical College and Hospital (PMCH), Patna, the study was carried out over a period of six months in the outpatient and inpatient wings of the Department of General Medicine. Prior to the start of data collection, the PMCH ethics committee and institutional review board evaluated the study protocol and approved it. Every procedure carried out complied completely with the ethical guidelines outlined in the 1964 Declaration of Helsinki and its subsequent revisions.

Sample Size and Population: Strict hiring procedures were used to guarantee the data's internal validity. The target sample size was determined using the prevalence of hypothyroidism in the general population and a 95% confidence interval with a 5% margin of error. In the end, the study group consisted of 115 instances of overt primary hypothyroidism.

The target pathophysiology was intended to be captured by the inclusion criteria. Adult patients with newly diagnosed primary hypothyroidism (defined biochemically by a TSH level greater than 5.5 μIU/mL accompanied by low fT_4) between the ages of 18 and 60 were included. Patients on insufficient levothyroxine replacement therapy who had a history of hypothyroidism were also taken into consideration for the study. Every participant was required to provide written informed permission after being told of the study's purpose in their native tongue.

We used stringent exclusion criteria to make sure the results were unique to thyroid disease and not influenced by other factors. Patients with a history of long-term alcohol use or smoking were not included because these lifestyle choices are known to raise homocysteine levels on their own. Similarly,

people using vitamin B12 or folate supplements or drugs like methotrexate, phenytoin, or carbamazepine that are known to disrupt homocysteine metabolism were excluded. To prevent distorting the biochemical results, we additionally eliminated individuals with documented cardiovascular disease, diabetes mellitus, liver cirrhosis, chronic renal failure, and pregnant or lactating women.

A control group of 115 healthy adults who were matched for age and sex was assembled for comparative study. Medical students, hospital employees, and healthy family members of study participants were chosen as these controls. Every control was confirmed to have no history of chronic illness and normal thyroid function (TSH between 0.4 and 4.0 μIU/mL).

Data Collection and Biochemical Analysis: A thorough clinical evaluation was part of the data collection phase. Every participant was given a thorough history that included information on how long they had been experiencing symptoms, their dietary preferences (particularly whether they were strict vegetarians or not), and a review of their systems. To evaluate overall health, anthropometric parameters such as height, weight, Body Mass Index (BMI), and resting blood pressure were carefully documented.

Precise phlebotomy techniques were needed for the biochemical analysis. Each participant had an overnight fast of at least 10 to 12 hours before five milliliters of venous blood were aseptically extracted from their antecubital vein. In order to prevent recent dietary consumption from momentarily changing lipid or homocysteine levels, this fasting state was essential. In order to separate the serum, the blood samples were collected in simple vials and left to coagulate at room temperature. The samples were then aliquoted for examination after being centrifuged for ten minutes at 3000 revolutions per minute (rpm) to produce clear serum.

Modern automated analyzers were used for laboratory experiments in order to reduce human error. Chemiluminescence Immunoassay (CLIA), a very sensitive technique for hormone detection, was used to assess the thyroid profile, which includes serum fT_3, fT_4, and TSH. The CLIA method was also used to test serum vitamin B12 levels. The Enzyme-Linked Immunosorbent Assay (ELISA) was used to assess serum homocysteine quantitatively. Strict quality control procedures were put in place, including as regular equipment calibration using commercial control sera with known concentrations. TSH $(0.4 - 5.5\ \mu IU/mL)$, fT_3 $(2.0 - 4.4\ pg/mL)$, fT_4 $(0.9 - 1.7\ ng/dL)$, homocysteine $(5 - 15\ \mu mol/L)$, and vitamin B12 (200–900 pg/mL) were the reference ranges used for the investigation.

Statistical Analysis: Microsoft Excel was used to methodically enter the raw data from the lab reports into a master graphic. The Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA) was used for the final analysis. The data was summarized using descriptive statistics; qualitative variables were shown as frequencies and percentages, while quantitative variables, such as hormone levels, were given as Mean ± Standard Deviation (SD). The student's independent t-test was used to compare the means of the hypothyroid cases and the healthy controls. Pearson's correlation coefficient (r) was computed to investigate the direction and strength of the linear correlations between TSH levels and the metabolic markers (homocysteine and B12). For every test, a probability value (p-value) of less than 0.05 was deemed statistically significant.

Results

Data from 230 participants, divided equally between 115 cases and 115 controls, were effectively evaluated. The groups were well-matched, according to the demographic analysis. There was no statistically significant difference ($p > 0.05$) between the hypothyroid group's mean age of 38.5 ± 10.2 years and the control group's mean age of 37.8 ± 9.8 years. Women made up 78% of the case group and 75% of the control group, indicating a gender prevalence that is consistent with the known epidemiology of thyroid diseases.

Biochemical Parameters: There were significant differences between the two groups when their biochemical profiles were compared. The thyroid profile characteristics varied considerably, as was to be expected. While the control group maintained a physiological mean of $2.4 \pm 1.1\ \mu IU/mL$, the case group's mean TSH was significantly raised at $14.2 \pm 6.1\ \mu IU/mL$, confirming the hypothyroid condition. Accordingly, there was a considerable suppression of the free thyroid hormones (fT_3 and fT_4) in the case group.

However, the study's most important conclusions had to do with the metabolic indicators. The mean blood homocysteine level in hypothyroid individuals was $19.8 \pm 5.4\ \mu mol/L$. This figure is far within the range of mild hyperhomocysteinemia ($> 15\ \mu mol/L$) and is significantly higher than the control group's mean of $10.2 \pm 3.1\ \mu mol/L$ ($p < 0.001$). On the other hand, the illness group's vitamin B12 levels were much lower. The control group had strong levels of vitamin B12 at $450 \pm 112\ pg/mL$, whereas the mean for patients was $210 \pm 85\ pg/mL$, which was close to clinical deficiency.

Table 1: **Comparison of Thyroid Profile, Homocysteine, and Vitamin B12 Levels**

Parameter	Hypothyroid Cases (n=115)	Controls (n=115)	p-value
TSH (μIU/mL)	14.2 ± 6.1	2.4 ± 1.1	$< 0.001*$
fT_3 (pg/mL)	1.8 ± 0.5	3.1 ± 0.6	$< 0.001*$
fT_4 (ng/dL)	0.7 ± 0.2	1.2 ± 0.3	$< 0.001*$
Homocysteine (μmol/L)	19.8 ± 5.4	10.2 ± 3.1	$< 0.001*$
Vitamin B12 (pg/mL)	210 ± 85	450 ± 112	$< 0.001*$

* Indicates statistical significance ($p<0.05$).

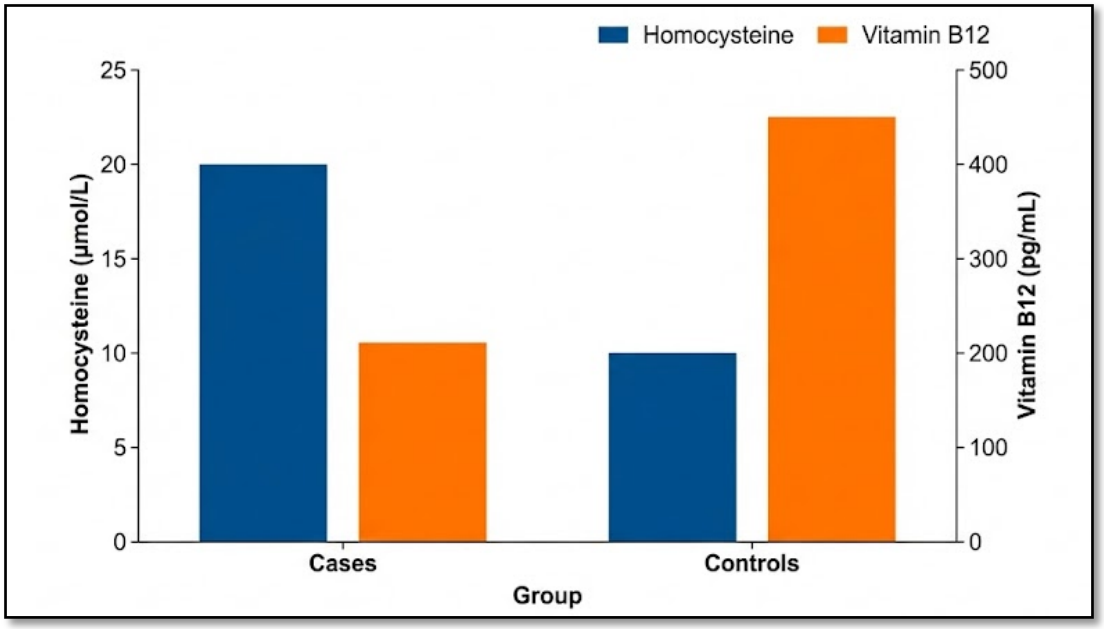

Figure 1 Comparison of mean Homocysteine and Vitamin B12 levels in Cases vs. Controls

Distribution of Deficiencies: We classified the patients according to published cut-off values for vitamin B12 insufficiency (< 200 pg/mL) and hyperhomocysteinemia ($>$ 15 μmol/L) in order to better understand the clinical burden. The results of the frequency distribution analysis were alarming. Compared to a small percentage in the control group, a significant majority of hypothyroid patients (72.2%) had high homocysteine levels. Similarly, almost 40% of hypothyroid individuals had blatant vitamin B12 insufficiency, indicating that nearly half of patients with thyroid failure also had severe nutritional anemia.

Table 2: **Prevalence of Hyperhomocysteinemia and Vitamin B12 Deficiency**

Condition	Cut-off Value	Cases (n=115) n (%)]	Controls (n=115) [n (%)]	Odds Ratio (95% CI)
Hyperhomocysteinemia	$>$ 15 μmol/L	83 (72.2%)	8 (7.0%)	34.5 $(15.2 - 78.4)$
Vit B12 Deficiency	$<$ 200 pg/mL	48 (41.7%)	14 (12.2%)	5.0 $(2.6 - 9.6)$

Correlation Analysis: To quantitatively assess the interdependency of the factors within the hypothyroid group, we conducted a Pearson correlation analysis. Serum TSH and homocysteine levels were shown to have a strong, positive linear connection ($r = 0.68, p < 0.01$). This suggests that blood homocysteine levels grow proportionately to the severity of hypothyroidism, which is reflected by greater TSH. On the other hand, there was a somewhat negative connection between TSH and vitamin B12 levels ($r = -0.45, p < 0.05$), suggesting that decreased B12 stores are linked to deep hypothyroidism. Additionally, homocysteine and vitamin B12 were found to have an inverse association ($r - 0.58$), confirming that homocysteine accumulation in these patients is primarily caused by B12 insufficiency.

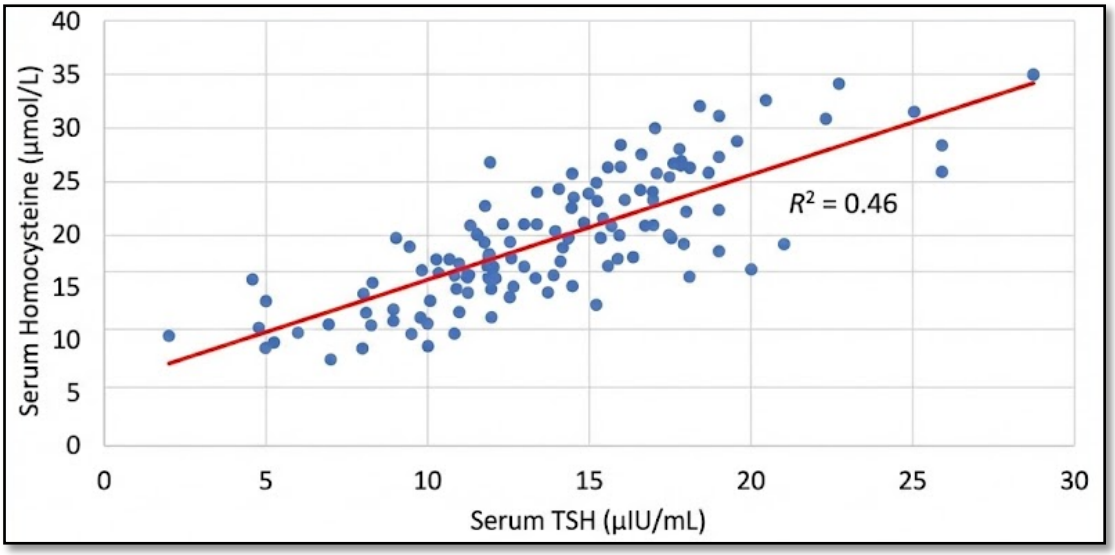

Figure 2: **Correlation of Serum TSH and Homocysteine levels in hypothyroid patients**

Table 3: **Pearson Correlation Matrix for Hypothyroid Cases (n=115)**

Variable	TSH	fT_4	Homocysteine	Vitamin B12
TSH	1	$-0.72*$	$0.68*$	$-0.45*$
fT_4	$-0.72*$	1	$-0.55*$	$0.38*$
Homocysteine	$0.68*$	$-0.55*$	1	$-0.58*$
Vitamin B12	$-0.45*$	$0.38*$	$-0.58*$	1

* Correlation is significant at the 0.01 level (2-tailed).

Discussion

The current study, which involved 115 hypothyroid patients at PMCH, Patna, clearly shows a connection between vitamin B12 insufficiency, increased homocysteine, and thyroid dysfunction. Our results are consistent with an increasing amount of data indicating hypothyroidism is a systemic metabolic condition with significant cardiovascular consequences rather than just a localized endocrine insufficiency.

Hyperhomocysteinemia in Hypothyroidism: According to our findings, hypothyroid patients have a mean homocysteine level of 19.8 µmol/L, which is considered moderate hyperhomocysteinemia. This is in line with research by Catargi et al., who found that patients with hypothyroidism have higher plasma homocysteine levels, which return to normal after receiving L-thyroxine [7]. Enzymatic and physiological processes are responsible for this increase. The glomerular filtration rate (GFR) is influenced by thyroid hormones. GFR is frequently lowered in hypothyroidism, which lowers homocysteine renal clearance [8]. Moreover, MTHFR (methylenetetrahydrofolate reductase), an essential enzyme in the homocysteine remethylation cycle, is regulated by thyroid hormones. Plasma total homocysteine is negatively correlated with T_4 levels, indicating a direct hormonal regulation of homocysteine metabolism, according to a study by Nedrebø et al. [9].

The Vitamin B12 Connection: A important comorbidity is shown by the substantial decrease in vitamin B12 levels (Mean: 210 pg/mL) found in our study. Autoimmune processes often modulate the relationship between hypothyroidism and B12 insufficiency. Antibodies against stomach parietal cells (PCA) or intrinsic factor (IFA) are also present in up to 40% of Hashimoto's thyroiditis patients, which can result in pernicious anemia and B12 malabsorption [10]. Nevertheless, hypothyroidism can cause hypochlorhydria, or low stomach acid, even in the absence of autoimmunity. This condition hinders the separation of vitamin B12 from dietary protein and decreases its absorption in the terminal ileum. Dietary factors are important in the Indian population, especially in Patna, where the study was carried out. A large percentage of people eat a vegetarian diet, which is inherently deficient in vitamin B12 [11]. A borderline B12-deficient diet combined with hypothyroidism causes overt deficiency and hyperhomocysteinemia to develop quickly.

Cardiovascular Implications: A "perfect storm" for atherothrombosis is created when high TSH, high homocysteine, and low B12 are present at the same time. By increasing oxidative stress, decreasing nitric oxide bioavailability, and encouraging smooth muscle proliferation, homocysteine harms the vascular endothelium. It is

a recognized pro-thrombotic substance. According to research by Wald et al., the risk of coronary artery disease rises by around 20% for every 5 µmol/L increase in blood homocysteine [12].

Regardless of their lipid profile, our case group's homocysteine levels were almost 10 µmol/L higher than controls, putting these patients at a 40% increased risk of CVD events. This emphasizes the drawbacks of using cholesterol panels exclusively to evaluate heart risk in thyroid patients, an issue that was previously brought up in an examination of NHANES data [13]. Additionally, in hypothyroidism, increased homocysteine frequently corresponds with inflammatory markers like C-reactive protein (CRP), which increases the risk of vascular disease [14]. The link between homocysteine and the incidence of coronary heart disease has been further supported by meta-analyses, underscoring the need for caution [15].

Clinical Relevance: TSH may be used as a stand-in marker for metabolic risk, according to our study's strong association ($r = 0.68$) between TSH and homocysteine. However, if the underlying B12 deficit is not treated, TSH correction alone might not be enough. Thyroxine replacement raises homocysteine levels, but if B12 status is still below ideal, it might not completely correct them, according to Jabbar et al. [10]. As a result, our findings support the usual workup of hypothyroid patients that includes assays for homocysteine and vitamin B12.

Limitations: It is crucial to recognize some inherent limitations in the study design and execution, even if this study offers solid data pertinent to the Eastern Indian population. First off, the cross-sectional structure of the study makes it impossible to determine clear causality, but it does allow us to demonstrate a strong statistical connection. Although the literature indicates a bidirectional association, we are unable to definitively determine whether the vitamin B12 shortage preceded or resulted from hypothyroidism.

Second, genetic testing for MTHFR polymorphisms (such the C677T variant) was not included in the study. This genetic variation is a significant independent predictor for hyperhomocysteinemia and is rather frequent in the Indian subcontinent [16]. We are unable to distinguish between the percentage of hyperhomocysteinemia brought on exclusively by thyroid dysfunction and that induced by genetic predisposition in the absence of genetic stratification. The complexity and multidimensional nature of homocysteine determinants have been highlighted by extensive community-based studies such as the Hordaland Homocysteine Study [17]. Additionally, methylmalonic acid (MMA) and serum folate level two more sensitive markers of B-vitamin status and the methylation cycle were not measured. Lastly, the dietary assessment relied on patient recall, which is prone to memory bias, even though we excluded individuals who used supplements. In order to measure the reversibility of these metabolic abnormalities, future studies should preferably be longitudinal, tracking patients both before and after thyroxine replacement.

Conclusion

The current study, which involved 115 patients at PMCH, Patna's tertiary care facility, provides strong evidence that primary hypothyroidism is a complex metabolic syndrome rather than a single endocrine event. We came to the conclusion that increased TSH levels, hyperhomocysteinemia, and vitamin B12 insufficiency are significantly and statistically robustly associated. According to the research, over 40% of hypothyroid individuals also have a vitamin B12 deficiency, and nearly 75% of them have increased homocysteine, a powerful vascular toxin.

These results have significant and immediate ramifications for Indian clinical practice. The traditional method of treating hypothyroidism, which frequently concentrates narrowly on utilizing levothyroxine to normalize TSH levels, might not be adequate to address the patient's overall cardiovascular risk profile. These patients are at an increased risk of accelerated atherosclerosis, stroke, and coronary artery disease due to their excessive homocysteine levels, which are caused by both hormonal sluggishness and nutritional inadequacy.

As a result, we fervently support a paradigm change in the hypothyroidism treatment approach. For all newly diagnosed hypothyroid patients, routine screening for serum homocysteine and vitamin B12 should be included in the usual diagnostic workup. Additionally, treatment approaches should be comprehensive; in addition to hormone replacement, physicians should vigorously address B12 deficits with supplements. To maximize patient results, therapy considerations must balance these hazards, especially in older persons [18]. The long-term prognosis and cardiovascular health of the millions of people with thyroid dysfunction can be greatly improved by treating these "silent" metabolic killers early in the course of the illness.

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