

HYPERHOMOCYSTEINEMIA IN PATIENTS WITH HYPOTHYROIDISM

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Abstract

Objective: To determine the frequency of hyperhomocysteinemia in patients with hypothyroidism. Methods: A cross-sectional study was carried out in six months duration (September 15, 2024 to March 14, 2025) at the Department of Medicine, Bilawal Medical College (BMC) Hospital. A total of 138 patients between the ages of 20 and 60 years old who had a diagnosis of hypothyroidism (≥ 6 weeks) with complaints of fatigue, weakness, or dizziness participated in the study. Patients with other endocrinopathies or complicating medical treatments were not included. Hyperhomocysteinemia was defined as serum homocysteine $>20 \mu\text{mol/L}$. Demographic details, clinical features, and biochemistry were noted. Data were analyzed using SPSS. Univariate analyses were conducted using Chi-square and Fisher's exact test for categorical variables, $p \leq 0.05$ was considered significant statistically. Results: In 138 patients of hypothyroid, hyperhomocysteinemia was present in 88 (63.77%) cases. There were significant associations between hyperhomocysteinemia and sex ($p=0.032$), residence ($p=0.041$), hypertension ($p=0.019$), smoking history ($p=0.044$), obesity ($p = 0.021$), hyperlipidemia ($P = 0.033$), NAFLD ($p = 0.025$), and vitamin D deficiency ($p = 0.015$). There was no association between diabetes and low platelet count and they were not identified as either a risk factor or protective factor, but there may be an impact if prevalence is high. The mean levels of TSH, FT_4 , FT_3 , BMI and homocysteine were indicative of biochemical hypothyroidism and metabolic dysfunction. Conclusion: Hyperhomocysteinemia is a frequent metabolic disturbance in hypothyroid individuals associated significantly with several modifiable risk factors. Regularly screening for serum homocysteine in hypothyroid patients, particularly those with metabolic co-morbidities should be considered, in order to minimize the risk of cardiovascular complications.

INTRODUCTION

Thyroid hormones are critical hormones that mediate the general growth, development and metabolism in human body [1]. The thyroid gland is a small butterfly-shaped endocrine organ that weighs

15–20 g and comprises two lobes connected by an isthmus [2]. Iodine insufficiency is still the most widespread reason for hypothyroidism worldwide resulting in synthesis disturbance of hormone [3].

In addition to their key role in metabolism, thyroid hormones have effects on many other physiological systems such as cardiovascular system [4]. Disruption of these hormones can disrupt lipid metabolism and blood pressure and may have a role in the evolution of atherosclerotic cardiovascular disease [5]. In reality, the patients with untreated or uncontrolled hypothyroidism have an elevated prevalence of coronary artery disease, while appropriate and timely treatment with thyroid hormone replacement can exert a cardioprotective effect [6, 7].

Hypothyroidism is a common endocrine disorder, the consequences of which can persist for life if not diagnosed and treated appropriately [8]. It is not only metabolic regulation that the thyroid hormones modulate they also play a crucial role in the maintenance of cellular energy as well as in normal function of many organ systems. Thus, it is not surprising that thyroid dysfunction has been associated with many possible clinical scenarios and warranted extensive study on its systemic consequences [9, 10].

An area that could be of particular interest is the association between hypothyroidism and homocysteine concentration [11]. Homocysteine is an amino acid formed in the course of methionine metabolism and its elevated blood concentrations, called hyperhomocysteinemia, are well known as a risk factor for cardiovascular diseases [12]. A number of studies have found that patients with hypothyroidism may have elevated plasma total homocysteine (tHcy), indicating the potential existence of an independent association between them [13, 14].

Nevertheless, the relation between thyroid hormones and increased homocysteine levels is still controversial. Other reports point to an undeniable atherogenic lipid profile and hyperhomocysteinemia in hypothyroid patients, which may be some determinant of higher coronary artery disease risk [15]. Although in general the prevalence of hyperhomocysteinemia has been estimated to be around 32% [16], the investigation like Butt SA et al. May be even higher rates up to 64% in hypothyroid people, Slissenko, 78 Bio Perspectives Questions still remain about firmness and stability of this link [17]. According to relatively controversially having no specific local data, in this study we aimed to

investigate the prevalence of hyperhomocysteinemia in hypothyroid patients. The investigation of this association is key for early recognition and management of those patients at risk. Hence, the aim of this study was to assess the prevalence of hyperhomocysteinemia in hypothyroid patients attending BMC Hospital and whether their thyroid status is an independent determinant for serum homocysteine level.

PATIENTS AND METHODS:

A six-month cross-sectional study was carried out at the Department of Medicine, Bilawal Medical College (BMC) Hospital, spanning from September 15, 2024, to March 14, 2025. The research was initiated after obtaining ethical approval from the College of Physicians and Surgeons Pakistan (CPSP), and written informed consent was collected from all participants.

Inclusion and Exclusion Criteria: Patients were eligible to participate if they were diagnosed with hypothyroidism for at least six weeks, aged between 20 to 60 years, of either gender, and had been experiencing symptoms such as fatigue, weakness, or dizziness for at least four weeks. All subjects were selected from those presenting to BMC Hospital.

On the other hand, individuals were excluded if they had a known diagnosis of hyperthyroidism, were receiving corticosteroids, immunosuppressants, vitamin B12, folic acid, pyrazinamide, thiazide diuretics, lipid-lowering drugs, or antioxidant therapy. Patients with chronic liver diseases (such as viral hepatitis), chronic kidney disease, or those who were pregnant or breastfeeding were also not included in the study.

Sample Size and Sampling Technique:

The sample size was calculated based on a previously reported minimum prevalence of hyperhomocysteinemia in hypothyroid patients (64%), with a margin of error (d) of 8%, resulting in a total of 138 participants. A non-probability consecutive sampling technique was used to recruit eligible patients.

Diagnostic Criteria and Data Collection:

Patients were classified as hypothyroid based on both clinical symptoms tiredness, excessive sleepiness, and unexplained weight gain and abnormal thyroid

hormone levels on biochemical testing. The diagnostic thresholds used were:

TSH > 4.50 μ IU/mL

Free T4 (FT4) between 0.8-1.8 ng/dL

Free T3 (FT3) between 1.4-4.4 pg/mL

Hyperhomocysteinemia was defined as a serum homocysteine level greater than 20 μ mol/L.

Eligible participants underwent blood sampling for serum homocysteine levels. A 2cc venous blood sample was drawn by the principal investigator using a sterile 5cc syringe and immediately sent to the laboratory for analysis. All samples were evaluated by a senior pathologist with over five years of laboratory experience. Data collection was done using a structured proforma, and all expenses related to the study were covered by the researcher personally.

Assessment of Variables and Definitions

Several clinical and demographic variables were recorded to evaluate potential effect modifiers, including age, gender, residence (urban or rural), confirmed through patient history, educational level, marital status, duration of hypothyroidism, comorbid conditions, such as hypertension, diabetes mellitus, obesity, smoking, hyperlipidemia, low platelet count, nafld, vitamin d deficiency, and hyperhomocysteinemia

The definitions and diagnostic criteria used for these variables were:

Hypertension: Blood pressure $\geq$ 140/90 mmHg at presentation

Diabetes Mellitus: Random blood glucose $\geq$ 200 mg/dL or being on anti-diabetic therapy

Smoking: Active smokers had a history of using $\geq$ 5 cigarettes/day for $\geq$ 3 years; ex-smokers were those who had smoked over 100 cigarettes in their lifetime but had quit for at least 28 days

Obesity: Body Mass Index (BMI) $\geq$ 27.5 kg/m²

Hyperlipidemia: Elevated lipid levels defined as:

Total cholesterol $\geq$ 200 mg/dL, Triglycerides $\geq$ 150 mg/dL, LDL $\geq$ 100 mg/dL, HDL <40 mg/dL

Thrombocytopenia: Platelet count <150,000/ μ L

Non-Alcoholic Fatty Liver Disease (NAFLD): Diagnosed via ultrasound findings (e.g., bright liver, blurred hepatic vessels) with no history of alcohol use or steatogenic drug intake

Vitamin D deficiency: Serum levels <20 ng/mL

Marital status was classified into married and non-married (including single, divorced, or separated

individuals). Education levels were grouped as illiterate: unable to read or write, primary: 1-5 years of education, middle: 6-8 years, secondary: 9-10 years, higher education: more than 11 years, including college and professional degrees.

The collected patient data was processed and analyzed using SPSS software. Descriptive statistics, such as frequencies and percentages, were computed for categorical variables including gender, type of residence (urban or rural), level of education, marital status, presence of hypertension, diabetes mellitus, smoking habits, obesity, hyperlipidemia, thrombocytopenia, nonalcoholic fatty liver disease (NAFLD), vitamin D deficiency, and elevated homocysteine levels. For numerical variables like age and duration of illness, the mean and standard deviation (SD) were calculated.

To assess potential confounding factors, stratification was performed based on age, gender, residence, education level, marital status, disease duration, and comorbidities such as hypertension, diabetes, smoking, obesity, hyperlipidemia, low platelet count, NAFLD, and vitamin D deficiency. This helped identify their influence on the outcome and control for effect modifiers. After stratification, the chi-square test or Fisher's exact test (as appropriate) was used to analyze the association between categorical variables. A p-value of $\leq$ 0.05 was considered statistically significant, with a 95% confidence interval applied throughout the analysis.

RESULTS:

Descriptive Statistics:

A total of 138 patients with hypothyroidism were included. The mean age was 40.3 ± 11.0 years, and the mean duration of disease was 28.9 ± 13.7 weeks.

Frequency of Hyperhomocysteinemia:

Out of 138 patients:

88 patients (63.77%) had hyperhomocysteinemia (homocysteine > 20 μ mol/L).

50 patients (36.23%) did not have hyperhomocysteinemia.

Table 01: Demographic and Clinical Profile

Variable	Category	Frequency	Percentage (%)
Gender	Male	66	47.8
	Female	72	52.2
Residence	Urban	70	50.7
	Rural	68	49.3
Marital Status	Married	93	67.4
	Non-Married	45	32.6
Hypertension	Yes	48	34.8
	No	90	65.2
Diabetes Mellitus	Yes	41	29.7
	No	97	70.3
Obesity	Yes	55	39.9
	No	83	60.1
Hyperlipidemia	Yes	53	38.4
	No	85	61.6
Smoking Status	Smoker	38	27.5
	Ex-Smoker	36	26.1
	Non-Smoker	64	46.4
Low Platelet Count	Yes	34	24.6
	No	104	75.4
NAFLD	Yes	45	32.6
	No	93	67.4
Vitamin D Deficiency	Yes	58	42.0
	No	80	58.0

Table 02: The mean $\pm$ standard deviation values for biochemical and anthropometric parameters

Variable	Mean $\pm$ SD
TSH (μ IU/mL)	8.5 $\pm$ 2.5
FT4 (ng/dL)	0.9 $\pm$ 0.15
FT3 (pg/mL)	2.2 $\pm$ 0.4
BMI (kg/m ²)	28.3 $\pm$ 3.5
Homocysteine (μ mol/L)	22.5 $\pm$ 4.5

Table 03: Post-Stratification Analysis of Hyperhomocysteinemia (n=138)

Variable	Categories	P-Value
Gender	Male / Female	0.032*
Residence	Urban / Rural	0.041*
Marital Status	Married / Non-Married	0.5709
Educational Status	Illiterate / Primary / Middle / Secondary / Higher	0.3538
Hypertension	Yes / No	0.019*
Diabetes Mellitus	Yes / No	0.2897
Smoking Status	Smoker / Ex-Smoker / Non-Smoker	0.044*
Obesity	Yes / No	0.021*
Hyperlipidemia	Yes / No	0.033*
Low Platelet Count	Yes / No	0.3066
NAFLD	Yes / No	0.025*
Vitamin D Deficiency	Yes / No	0.015*

*Statistically significant

Interpretation: A statistically significant association ($p \leq 0.05$) was observed between hyperhomocysteinemia and gender, residence, hypertension, smoking, obesity, hyperlipidemia, NAFLD and vitamin D deficiency

No significant association was found with marital status, educational status, diabetes mellitus and low platelet count

DISCUSSION:

The current study showed that 63.77% patients with hypothyroidism were found to have high levels of homocysteine, indicating that hyperhomocysteinemia is common metabolic dysfunction in such patient group. This result corroborates findings obtained from several other studies carried out in various populations that

showed hyperhomocysteinemia was observed in 50-70% of the population with hypothyroidism, and there may be a uniform and high degree of overlap between both conditions.

Thyroid hormones are involved in the metabolism of homocysteine regulation by controlling enzymes (i.e., methionine synthase, cystathionine β -synthase) related to the clearance of homocystein. In hypothyroidism, the decreased levels of thyroid hormone reduced the activity in both remethylation and transsulfuration pathways leading to homocysteine accumulation in plasma. Similarly, decreased thyroid function could reduce renal clearance and lead to an increased concentration of homocysteine.

This investigation also identified an agreement between hyperhomocysteinemia and the following variables:

Gender: It was more common in females; hormones may have an impact on folate and vitamin B metabolism, which influences homocysteine level indirectly.

Residence (Urban vs. Rural): People in the urban area were affected more compared to those in rural, this is due to sedentary life style and dietary habit as well as environmental stress.

Obesity and Hyperlipidemia: Both obesity and hyperlipidemia have been associated with aggravation of endothelial dysfunction and inflammation, thereby generating a vicious cycle that further increases homocysteine levels.

Hypertension and Smoking - Both of these are classic risk factors for your heart. Smoking induces oxidative stress and hypertension is a reported complication of high homocysteine, all bringing an emphasis on finding the levels of these data.

Vitamin D Deficiency, and NAFLD: These results are especially interesting. Vitamin D is a regulator of immune function and inflammation. Its deficiency might result in a disturbed metabolism whereas NAFLD suggest hepatic involvement in altered homocysteine metabolism.

All of these relationships support the concept that hyperhomocysteinemia is not just an isolated abnormality but rather a multifactorial metabolic condition which has been affected by thyroid function impairment as well as other co-morbidities.

Comparison with Previous Studies:

An increased level of homocysteine in hypothyroid patients as compared to healthy controls has been reported by Kharb et al [18] on newly detected hypothyroids. Similarly, the study of Lentz SR [19] considers homocysteine as a potential risk enhancer of cardiovascular events in patients with endocrine pathologies. In a separate study in Pakistan, by Ahmed et al., 2019 [20], also reported the prevalence of about 65%, comparable with the present study making this more relevant to local population.

However, several reports have indicated that subclinical hypothyroidism does not markedly affect homocysteine levels and demonstrate that the degree

of thyroid failure effect blood measurements and the duration of disease directs its impact on human [21-23].

Furthermore, our results suggest that regular homocysteine screening is recommended in patients with hypothyroidism with risk factors such as obesity, smoking and vitamins deficiency. Recognition and treatment in the form of folic acid, vitamin B12, and lifestyle intervention might help to reduce cardiovascular risk burden in these patients.

Furthermore, clinicians should pay attention to the associated metabolic syndromes that serve as a smoke-screen but also accelerate the development of vascular complications. Inclusion of homocysteine as a risk factor in protocols for managing hypothyroidism may result in better preventive care.

Study Limitations: This was a cross-sectional study in a single center, patients did not have an evaluation of the nutritional status (B12, folate) which can affect homocysteine levels. Diet and genetic polymorphism (e.g., MTHFR mutation) were not evaluated.

CONCLUSION:

The prevalence of hyperhomocysteinemia in patients with hypothyroidism was found to be 63.77% in the present study. Elevated homocysteine levels were found to be associated with several clinical factors, including sex, residence, and hypertension, smoking status, obesity and hyperlipidemia as well as having a diagnosis of NAFLD or vitamin D deficiency. The findings emphasize the need for regular homocysteine estimation in hypothyroid patients, especially when associated with metabolic disease. Earlier recognition and treatment may contribute in mitigating the long-term cardiovascular risk among these high-risk patients. The latter will need to be confirmed in larger multicenter longitudinal studies that allow assessment of causality and impact over time. The beneficial effect of reducing homocysteine levels should be explored in the future studies with respect to cardiovascular outcome in hypothyroidism. Assessment of micronutrient status, dietary intake and genetic markers may offer more in-depth knowledge for an individualized intervention.

AUTHOR'S CONTRIBUTION:

Collection and acquisition of data & grammatical corrections	Dr. Sufyan Malik
Concept & design of study & proof read	Dr. Muzaffar Shaikh
Drafting the article and finalizing the manuscript	Dr. Iqra Kalhoro
Revising critically and make it suitable for final format	Dr. Kuldeep Kumar Poorani
Acquisition of data and grammatical review	Dr. Muhammad Iqbal Shah
Drafting the article and finalizing the manuscript	Dr. Farman Ali
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