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EFFECT OF FOLIC ACID PLUS LEVOTHYROXINE ON SERUM HOMOCYSTEINE LEVELS IN HYPOTHYROIDISM

General Medicine

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ABSTRACT

Background- Hypothyroidism is one of the most common disorders involving the thyroid gland, mainly resulting from iodine deficiency which remains a common cause worldwide .Treatment is with levothyroxine replacement, starting from low dose initially; followed by gradually increasing the dose to maintain TSH within the reference range .Homocysteine is an amino acid produced when proteins are broken down.A high level of homocysteine in the blood increases the risk of atherogenesis thus causing ischemic injury. Rise in serum homocysteine level may be associated with higher prevalence of cardiovascular diseases in hypothyroidism. This study is conducted to assess if Levothyroxine and folic acid supplements given prophyllactically can reduce serum homocysteine level. **Objectives Of The Study-** 1)To study the homocysteine levels in hypothyroid patients .2) To study the effect of coadministration of folic acid with levothyroxine on serum homocysteine levels. **Methods-** 60 patients with hypothyroidism attending outpatient clinic and inpatient at Al Ameen hospital were enrolled for the study from March 2021 to Sept 2022. Results - Out of 60 patients with hypothyroidism, levels of homocysteine were observed to fall in 43 (72%) patients after levothyroxine and folic acid therapy , 11 (18%) patients had no change in homocysteine levels, 6 (10%) patients had elevation in homocysteine levels . Interpretation- There was elevated levels of serum homocysteine among hypothyroid patients. There was a statistically significant reduction in homocysteine levels 2 months after combination therapy of levothyroxine and folic acid. **Conclusion-** Hypothyroid patients are at an increased rsik of atherogenic complications as reflected by higher homocysteine levels. Treatment of hypothyrioid patients with levothyroxine and folic acid showed significant fall in homocysteine levels. This combination therapy prophyllactically can help prevent atherogenic complications among hypothyroid patients .

KEYWORDS

Serum Homocysteine, Hypothyroidism, Folic Acid, Levothyroxine

INTRODUCTION

The thyroid gland is an endocrine gland present in the neck , which consists of 2 lobes connected by the central isthmus . The thyroid gland secretes 3 hormones namely triiodothyronine (T3) , thyroxine (T4) and the calcitonin. While calcitonin is of no apparent physiological significance in humans [1], the thyroid hormones act via the receptors α and β, and play an important role in cell differentiation and organogenesis during development and help maintain thermogenic and metabolic homeostasis in the adult. Secretion of the two thyroid hormones is regulated by thyroid-stimulating hormone (TSH), which is secreted from the anterior pituitary gland. TSH is regulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus [2].

Hypothyroidism is one of the most common disorders involving the thyroid gland, mainly resulting from iodine deficiency which remains a common cause worldwide. However autoimmune diseases such as Hashimoto's thyroiditis, iatrogenic causes (surgical treatment of thyrotoxicosis) or thyroid failure following I131 account for over 90% of cases except in areas where iodine deficiency is endemic [1,2] . In vast majority of cases, hypothyroidism results from an intrinsic disorder of thyroid gland (primary hypothyroidism) where in the TSH is elevated and T4 is low.

Secondary hypothyroidism is rare and is caused by failure of TSH secretion in an individual with hypothalamic or anterior pituitary disease. Treatment is with levothyroxine replacement, starting from low dose initially followed by gradually increasing the dose to maintain TSH within the reference range.

Homocysteine is an amino acid produced when proteins are broken down. It is an analogue of the amino acid cysteine, differing by an additional methylene bridge. A high level of homocysteine in the blood increases the risk of endothelial cell injury, which in turn results in an inflammatory reaction by the circulating immune cells such as monocytes, which in turn may lead to atherogenesis thus causing ischemic injury. Thus hyperhomocysteinemia has been associated with heart attacks, strokes, recurrent abortions and neural tube defects however its cause has not been studied in detail.

Patients with hypothyroidism are at an increased risk of cardiovascular diseases and other atherogenic complications , however its correlation with the homocysteine levels has been poorly understood . Moreover the effect of coadministration of levothyroxine and folic acid on serum homocysteine levels in hypothyroid patients has not been established in detail.

Rise in serum homocysteine level may be associated with higher prevalence of cardiovascular diseases in hypothyroidism. Levothyroxine can partly diminish serum homocysteine level. Folic acid participates in homocysteine metabolic cycle in the human body. Thus an effort has been made to study the effect of concomitant administration of folic acid and levothyroxine on serum homocysteine level in hypothyroid patients .

Objectives of the study

- To study the homocysteine levels in hypothyroid patients on levothyroxine.
- To study the effect of coadministration of folic acid with levothyroxine on serum homocysteine levels .

METHODOLOGY

The study was carried out at Al Ameen Medical College and Hospital From March 2021 to June 2022.

Prior approval for the study protocol was obtained from institutional ethical committee. After explaining the need for relevant investigations, and their role in the further management, patients were included in the study. Informed written consent was obtained from patient or a responsible attendant before including the patient in the study.

The study group consisted of 60 patients of both sexes with hypothyroidism attending the outpatient clinic as well as those admitted in medical wards in the age group between 20-75 years .

All newly diagnosed and old cases of hypothyroidism, irrespective of duration of hypothyroidism were taken into the study. The exclusion criteria were all cases of

- pregnant women
- age less than 20 years and more than 75 years.
- patients with malignancy
- patients with hepatic , renal or bone disorders .
- patients with known atherogenic complications or on treatment that affects the TSH and homocysteine levels .

A detailed history and clinical examination with vitals was recorded for all patients.Case record form with follow up chart was maintained . All the baseline investigations including Free T3 , Free T4 ,TSH and Serum homocysteine (preferably in fasting) were recorded in the fasting state .

Hypothyroidism, among those with no prior history of hypothyroidism, was diagnosed if the TSH levels were more than the normal range for the laboratory (here Normal range - 0.35-4.94 µIU/ml) and/or reduced Free T3 (normal range -1.71-3.71 pg/ml) and/or Free T4 levels (normal range- 0.93-1.70 ng/dl) .

Patient was then started on folic acid 5 mg per oral , once a day along with the levothyroxine as advised .

Patient was advised for follow up after a period of 6-8 weeks and blood investigations i.e Free T3, Free T4 , TSH and Serum Homocysteine (Normal range 5-15 µmol/L) were repeated in fasting state and the data was recorded .

All the data collected was maintained in Excel sheet and statistical analysis was done using the various tools and variables .

RESULTS

l Among the study group of 60 patients with hypothyroidism , 72% of patients with hypothyroidism had reduction in serum homocysteine levels , 18% of patients had no change in the homocysteine levels and 10 % had an increase in serum homocysteine levels .

Table 1 - Comparison of outcome of homocysteine levels among hypothyroid patients after 2 months of follow up

S.homocysteine	Baseline		After 2 Months		Wilcoxon Signed Ranks Test	P value
	Mean	Std./Deviation	Mean	Std. Deviation		
S. Homocysteine	17.10	8.678	15.45	7.464	5.373	0.0001
Statistically significant						

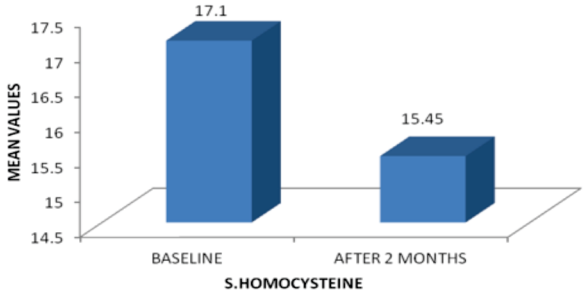

Figure 1- Graph showing Comparison of mean Serum Homocysteine levels at baseline and 2 months after follow up with levothyroxine and folic acid among the study group .

- Among the study group of 60 patients with hypothyroidism , the mean level of Serum homocysteine at baseline was 17.10 and the levels showed a significant reduction after 2 months of treatment with levothyroxine and folic acid and was found to be 15.45 .

Table 2 : Comparison of Serum Homocysteine levels at baseline and 2 months after follow up with levothyroxine and folic acid among the study group .

S. Homocysteine	Baseline		After 2 Months		Wilcoxon Signed Ranks Test	P value
	Mean	Std. Deviation	Mean	Std. Deviation		
S. Homocysteine	17.10	8.678	15.45	7.464	5.373	0.0001
Statistically significant						

DISCUSSION

Hypothyroidism affects between 4% and 10% of the population, and the prevalence of subclinical hypothyroidism is reported to be as high as 10% in various studies.[3]The effects of thyroid dysfunction on the cardiovascular system have been well documented for >2 centuries. [4]

This is a prospective study of 60 hypothyroid patients at a tertiary care hospital in Karnataka . In this study , an effort is made to compare the levels of serum homocysteine among hypothyroid patients and the effect of co-administration of folic acid with levothyroxine on serum homocysteine , which in turn reflects the increased cardiovascular and atherosclerotic complications among hypothyroid patients and the need to reduce homocysteine levels in such patients.

Dr. Ziaee et al.'s manuscript published in your valuable journal about serum homocysteine level entitled “Effects of folic acid plus levothyroxine on serum homocysteine level in hypothyroidism”. In this clinical trial study the efficacy of concomitant administration of folic acid and levothyroxine versus single levothyroxine prescription on serum homocysteine level was compared with hypothyroid patients. The authors concluded that “levothyroxine can decrease serum homocysteine level partly; still its combination with folic acid empowers the effect. Combination therapy declines serum homocysteine level more successfully (5)”.

In our study of patients in the age group of 20-75 years , majority of the patients i.e 46.6% were in the age group of 30-49 years with mean age of around 43.9 years.

Out of the total 60 patients with hypothyroidism ,there was higher incidence of hypothyroidism among females with 56.7 % as compared to 43.3% being males .Molham Ali Al-Habori et al [6] conducted a study in Kuwait which included 50 patients with hypothyroidism, the age distribution was between 25 to 64 years of age and mean age was 39.2 years and all were females. B.G Nedrobo et al[7] included 109 patients ,of which 64 were hyperthyroid and 45 were hypothyroid, mean age in this study was around 64 years and 79% were females .

In a study conducted by Dariusz kajdaniuk et al[8] The mean age of patients studied was 39 years out of 163 patients included 110 patients were females.

CONCLUSION

Hypothyroid patients are associated with

- Elevated Serum Homocysteine level (45%)
- Increased risk of cardiovascular and atherosclerotic complications.

There was statistically significant Reduction of serum homocysteine levels after co administration of levothyroxine and folic acid among hypothyroid patients .

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