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A STUDY OF ASSOCIATION OF SERUM FERRITIN WITH HYPOTHYROIDISM AND EFFEECT OF THYROID HORMONE REPLACEMENT THERAPY

Medicine

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ABSTRACT

Background: Ferritin is an iron storage protein found in almost all of the body tissues. Serum ferritin levels also have been reported to be altered in patients with thyroid disease. Thus, changes in the serum concentrations of ferritin reflect thyroid function.
Conclusion: Hypothyroidism is associated with low serum ferritin levels. The estimation of serum ferritin may help in understanding the etiopathogenesis, diagnosis, and monitoring of hypothyroid patients.

KEYWORDS

Ferritin, hypothyroidism, thyroid

INTRODUCTION

Thyroid disorder is one of the most common endocrinal disorder. It may affect at any stage of life but more commonly encountered in the mid age and adulthood. Thyroid hormones influence nearly all major metabolic pathways. Their most obvious and well known action is the increase in basal expenditure obtained by action on protein, carbohydrate and lipid metabolism. It also influence iron metabolism and erythropoiesis. Worldwide Thyroid diseases are common and In India too, there is a significant burden of thyroid disease. According to projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid disease. Common thyroid diseases are hypothyroidism, hyperthyroidism, Thyroid goiter, hashimoto's thyroiditis and thyroid cancer. Early diagnosis and treatment remain the cornerstone of management.

Hypothyroidism is a disorder characterized by a varied symptoms and/or signs related to decreased metabolism and/or increased glycosaminoglycans (GAG) deposition in soft tissue (myxedematous features) due to decreased production/action of thyroid harmones and/or thyroid stimulating harmone (TS) exces. Symptoms related to decreased metabolism are lethargy, fatigue, fatigue, bradycardia, cold intolerance, and “aches and pain” and are primarily due to thyroxine (T_4) deficiency. Symptoms related to increased GAG deposition are periorbital puffiness, hoarseness of voice, nonpitting edema, and macroglossia and are predominantly due to excess of thyroid stimulating harmone (TSH). This common disorder occurs in 2 to 15% of the population more common in women than in men. The causes of hypothyroidism are classified as primary and secondary hypothyroidism. The causes of primary hypothyroidism are classified as endogenous or exogenous. Endogenous disorders are conditions that develop within the patient such as autoimmune thyroid gland dysfunction, inborn errors, and developmental abnormities. Exogenous disorders are condition that originates outside the patients such as iodine deficiency or excess, drug effects, and post surgical hypothyroidism or hypothyroidism following radioactive iodine treatment.

Ferritin is an iron storage protein found in almost all the body tissues. It is involved in iron sequestration with some antioxidant properties. High TSH, as observed in clinical hypothyroidism, is known to induce inflammatory cytokines and to decrease the concentration of antioxidants in the body. This may be an additional reason for decrease in ferritin levels, which exhibits antioxidant properties, in the patients.

Iron forms an important part of the mechanism that transports thyroid hormone into the cells and lack of it can lead to pooling of thyroid hormone leading to metabolically hypothyroid picture even in presence of normal FT3 levels, producing a thyroxine resistance like situation .

T3 may have a role to up regulate hepatic ferritin gene expression which may in part contribute to low serum ferritin in hypothyroidism.(2,56,85) Though molecular mechanism to explain regulation of ferritin post transcriptionally at the level of mRNA by T3 but still it is not clear.

Estimation of serum ferritin is simple, reliable, economic, and sensitive and can be used as a marker of thyroid hormone action.

Present study is an attempt to find out correlation if any between serum ferritin and hypothyroidism and also changes of serum ferritin level if any after correction of the disorders with levothyroxine therapy.

AIMS & OBJECTIVES

General objective of this study is to assess whether serum ferritin can be a biomarker of thyroid dysfunction.

Specific Objectives:

1.To establish association of serum ferritin level with serum FT3, FT4 and TSH level in control group as well as in study group.
2.To detect whether any change occurs in serum ferritin level with Levothyroxine Therapy in the study group.

MATERIALS AND METHODS

Study Site: Study conducted at deptt of Medicine All India Institute of Medical Science, Patna.
Study Type: Observational Prospective cohort and case control study
Participants

Case : Fifty Patient with clinical feature of hypothyroid and confirmed by Lab estimation TSH, FT3 ,FT4 were selected for the study. Out of these 14 patients were male and 36 were female of age group in between 12 to 70 year. After taking written consent from the patient

Control: For control of the study normal person was selected from MOPD of which 14 are male and 36 are female of same age and sex matched with study group between age 12 to 70 years.

Patient visiting medicine outpatient door (MOPD), Department of Medicine, AIIMS, Patna with the suspicious of hypothyroidism will be selected for study group and for control of the study the normal person of the same age and sex matched individual will be selected after taking written consent from the case and control.

Exclusion Criteria

1. Extremes of age (below 12 years and above 70 years
2. Other endocrinopathies (like- Diabetes Mellitus, Addison disease and etc.)
3. Chronic Renal Disease

4. Anemia
5.Chronic Infections
6.Patients taking Iron supplement
7.Subclinical Hypothyroidism
8.Recent Blood Transfusion

Study Procedure :
After selecting Study group and control and after taking consent, underwent medical history and assessment and general physical examination and then 6 ml of ml blood will be taken in vial for estimation of FT3, FT4, TSH and Ferritin and estimated by Enzyme Linked Immune Sorbent Assay (ELISA) method Urea will be assayed from serum by urease method and creatinine will be done by Jafe's Method. All the above parameters will estimated in study group before commencement of Levothyroxine Therapy and after six months (at least) of therapy.

ELISA Of Serum Sample For Estimation Of Serum Level Of Free Thyroxin (Ft4):

ELISA KIT: Accu Bind, Mono Bind Inc., USA

Test Principle: Competitive Enzyme Immunoassay.

ELISA Of Serum Sample For Estimation Of Serum Level Of Free Thyroxin (FT3):

ELISA KIT: Accu Bind, Mono Bind Inc., USA

Test Principle: Competitive Enzyme Immunoassay.

The essential reagents required for a solid phase enzyme immune assay inclued immobilized antibody, enzyme – antigen conjugate and native antigen. Upon, mixing immobilized antibody, enzyme-antigen conjugate and a serum containing the native free antigen, a competitive reaction results between the native free antigen and the enzyme-antigen conjugate for alimited number of insolubulized binding sites.

ELISA Of Serum Sample For Estimation Of Serum Level Of Thyroid Stimulating Hormone (TSH).

ELISA KIT : Aspen Laboratories Pvt. Ltd.

Test Principle:
This assay is based upon the sandwich method. Micro wells are pre-coated with anti-TSH. The enzyme conjugate is formed by labeling anti-TSH with horseradish peroxidase. Then a complex is generated between the solid phase, the TSH within the sample and enzyme-linked antibodies by immunological reaction. This complex catalyzes the substrates, resulting in a chromogenic reaction. The color intensity is proportional to the amount of TSH.

ELISA Of Serum Sample For Estimation Of Serum Level Of Feritin:

ELISA KIT: Accubind, Monobind INC, USA

Test Principle:
Upon mixing monoclonal biotinylated antibody, and a serum containing the native antigen, forming an antibody – antigen complex, simultaneously the biotin attached to the antibody binds to the streptavidin coated on the micro wells resulting in immobilization of the complex.

Estimation Of Urea From Serum:

Kit: ERBA (ERBA Diagnostics Mannheim Gmbh)

Method: GLDH (Glutamate Dehydrogenase) – Urease Method,

Estimation Of Creatinine From Serum:
Kit: ERBA (ERBA Diagnostics Manheim Gmbh)

Method: Modified Jaffe's Method

RESULTS AND ANALYSIS
The present study on serum ferritin level was carried out in 50 hypothyroid (36 female and 14 male) and 50 (36 female and 14 male) age and sex matched normal controls. Hypothyroid cases are detected by estimation of TSH, FT4, and FT3 by ELISA method, urea, creatinine, and done for exclusion of cases. Serum ferritin level estimated before and after thyroid hormone therapy by ELISA method (used Accubind kit).

Results are expressed mean ±SD; chi-square test has been used to find the homogeneity of sex distribution between apparently healthy controls and hypothyroid cases. Student T-test has been used to find the significance of serum ferritin and T3 or T4 between two groups.

Table 1: Distribution Of Age In Two Groups

CASE			
AGE (YEARS)	**Case**	**Control**	**TOTAL**
≤20 Row % Col %	7 50.0 14.0	7 50.0 14.0	14 100.0 14.0
21-30 Row % Col %	24 52.2 48.0	22 47.8 44.0	46 100.0 46.0
31-40 Row % Col %	10 45.5 20.0	12 54.5 24.0	22 100.0 22.0
41-50 Row % Col %	5 50.0 10.0	5 50.0 10.0	10 100.0 10.0
51-60 Row % Col %	2 40.0 4.0	3 60.0 6.0	5 100.0 5.0
>60 Row % Col %	2 66.7 4.0	1 33.3 2.0	3 100.0 3.0
TOTAL Row % Col %	50 50.0 100.0	50 50.0 100.0	100 100.0 100.0

p=0.9769, Statistically not significant.

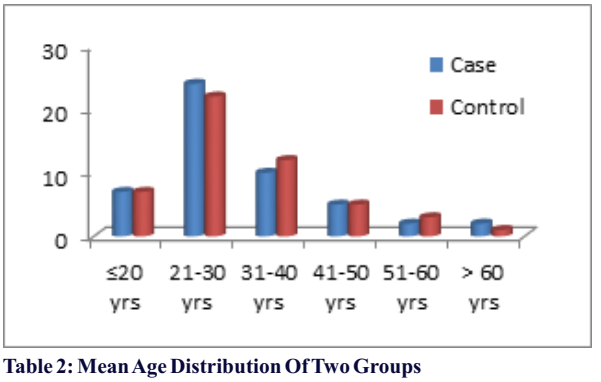


Table 2: Mean Age Distribution Of Two Groups

Group	Number	Mean	SD	Minimum	Maximum	Median	p-value
CASE	50	30.1600	11.7792	17.0000	63.0000	25.0000	0.7438
CONTROL	50	30.9200	11.4068	15.0000	66.0000	26.0000	

p=0.7438, Statistically not significant.

In case, The mean age (mean± s.d.) of patients was 30.1600 ±11.7792 years with range 17.0000 -63.0000 years and the median age was 25.0000 years.

In control, The mean age (mean± s.d.) of patients was 30.9200 ±11.4068 years with range 15.0000 -66.0000 years and the median age was 26.0000 years.

Difference of mean age in case and control was not statistically significant (p=0.7438). Thus age matched case and control was selected in this study.

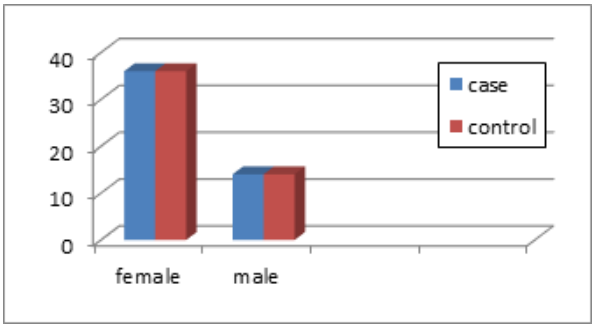
Table 3: Distribution Of Sex In Two Groups

SEX			
Case	**Female**	**Male**	**TOTAL**
Case	36	14	50

Row % Col %	72.0 48.6	28.0 53.8	100.0 50.0
Control Row % Col %	36 72.0 48.6	14 28.0 53.8	50 100.0 50.0
TOTAL Row % Col %	74 74.0 100.0	26 26.0 100.0	100 100.0 100.0

P=0.6484, Statistically not significant.

Association between sex with case and control was not statistically significant (p=0.6484). Thus sex was matched in two groups.



DISCUSSION

This hospital based observational study at Department of Medicine outpatient door of All India Institute Medical Science, Patna, Bihar.

In my study "association of serum ferritin with hypothyroidism and effect of thyroid replacement therapy" has been conducted to determine the association if any between serum ferritin and hypothyroidism and whether ferritin level change after correction of hypothyroidism with levothyroxine therapy of at least six months.

In the present study it has been found that out of 50 subjects in control there was 14 male and 36 female, in case group there was 14 male and 36 female. The sex distribution in between all these groups found to be statistically insignificant (p=0.6484).

In the present study it has been found that the mean age in control group is 30.92 years (SD 11.40), and in case is 30.16 years (SD 11.77). The age distribution in between all these groups have been found to be statistically insignificant (p=0.7438).

Present study shows that the mean serum ferritin level is 18.22 in before treatment and 28.28 after treatment. So it is observed that the mean serum ferritin level in after treatment is greater than before treatment.

Serum ferritin levels also have been reported to be altered in patients with thyroid disease. Recently, it has been reported that the serum level of ferritin is high in hyperthyroidism and low in hypothyroidism, and changes in the serum concentrations reflect thyroid function. Ferritin level is estimated before iron suppliments. Iron is also used by bacteria and cancer cells. Iron works in conjunction with iodine and has stimulatory effect on thyroid peroxidase and deiodinase that convert T4 to T3. Therefore levothyroxine prescription in such cases reverses the deleterious effect of hypothyroidism in iron deficiency. The study results demonstrated that treatment of patients with hypothyroidism and iron-deficiency anemia with a levothyroxine resulted in a favorable outcome. Ferritin as the leading indicator for improvement in anemia and thyroid stimulating hormone as an indicator for hypothyroidism both improved significantly. IT has been suggested those people with thyroid disorder should have routine screening of hematological, biochemical and hormonal profile assay and simultaneously proper management of this metabolic disease.

It is said that ferritin and its formation can protect against iron toxicity, thus causing decrease in oxidative stress. Lowering of ferritin levels accompanies release of free iron which may contribute to increasing oxidative stress thereby may oxidatively damaged thyroid follicular cells and reducing the synthesis of T3.

T3 may have a role to up regulate hepatic ferritin gene expression which may in part contribute to low serum ferritin in hypothyroidism. Though molecular mechanism to explain regulation of ferritin mRNA by T3 is still not clear.

The study done by Takamatasu J et al suggested that serum ferritin measurements were evaluated as a marker of thyroid hormone action on peripheral tissues. Furthermore, a significant interindividual correlation between serum levels of ferritin and T4 or T3 was found in 2 patients with thyrotoxic Graves' disease in whom levels were measured serially throughout the course of therapy. Similarly, serum ferritin levels increased in all 12 hypothyroid patients with Hashimoto's disease when euthyroidism was achieved with L-T4 therapy. Administration of 75 micrograms T3 daily for 1 week to 11 euthyroid subjects resulted in a 23-243% (mean +/-SD, 117 +/- 70%) increases in serum ferritin above basal values. In contrast, in 3 patients with thyroid hormone resistance, the same treatment produced rises in serum ferritin concentrations of only 2%, 5% and 15%.Their data suggest that alterations in thyroid status in a given individual produce changes in serum ferritin levels. Measurement of this protein before and after T3 therapy may prove useful in the diagnosis of thyroid hormone resistance.

CONCLUSION

In the present study, fifty cases of hypothyroid subject were selected to study the serum ferritin level before and after treatment and to find if any association between these two parameters. A total number of fifty age and sex matched healthy individuals were taken as control for this study. All the subjects are 12 to 70 years of age.

The study was conducted in the Department of Medicine AIIMS, Patna. This study has been performed on human subject and it is a Observational study. The present study was carried out with the aim to determine the association if any between serum ferritin and hypothyroidism and effect after thyroid hormone replacement therapy.

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