

Study on Ischemia Modified Albumin (IMA) and high sensitive C-Reactive Protein (hs-CRP) in subjects with hypothyroidism

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Abstract

Introduction: Thyroid diseases are the commonest endocrine disorders worldwide. According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases. Hypothyroidism patients are more prone for cardiovascular abnormalities. In our study we have studied the marker of ischemia, Ischemia Modified Albumin & marker of inflammation hs CRP in hypothyroidism patients.

Objectives:

1. To estimate the thyroid hormone levels (T3, T4, TSH) in hypothyroidism patients compared with normal subjects
2. To estimate levels of IMA & hs CRP in hypothyroidism patients compared with normal subjects

Materials and Method: The study group includes 61 hypothyroidism patients and 61 age & sex matched healthy controls. hs-CRP was measured by immunoturbidimetric method using fully automated analyzer, IMA was measured by Albumin Cobalt Binding method & thyroid hormones are measured by ECLIA method. Statistical analysis was done using SPSS 16 version software.

Results: In our study we have found that there is statistically significant (p value < 0.05) increase in hs-CRP & IMA levels in hypothyroidism patients compared to controls.

Conclusion: The levels of IMA - a marker of ischemia & hs-CRP - a marker of inflammation were increased in patients with hypothyroidism. This indicates that the altered thyroid hormones have strong impact on the imbalances between the production of oxidants and their elimination by antioxidant systems in the circulation. The consequences of this imbalance cause lipid abnormality in the body which indicates that the hypothyroid patients are more prone for ischemic changes in the cardiac tissue leading to atherosclerosis & myocardial infarction. Therefore, estimation of these novel markers such as IMA & hs-CRP levels in hypothyroid patients might be useful as early markers to detect the future cardiac ischemic diseases.

Keywords: Hypothyroidism, IMA, hs-CRP

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Introduction

Thyroid diseases are the commonest endocrine disorders worldwide. According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases.⁽¹⁾

Thyroid hormones are the most important humoral factors involved in setting the basal metabolic rate on a long-term basis in target tissues such as liver, heart, kidney and brain. Hypothyroidism, or under activity of thyroid gland, results from either reduced secretion of thyroxine (T4) and triiodothyronine (T3) that may be correlated with increased secretion of thyroid stimulating hormone (TSH) from pituitary.⁽²⁾

In hypothyroidism, a diastolic hypertension is observed which is due to increased systemic vascular resistance, leading to increased arterial stiffness which in turn causes the endothelial dysfunction and altered coagulability.⁽³⁾ All these effects are due to altered thyroid hormone levels which causes increased oxidative stress and ischemic changes in heart. In such incidences there is an increased release of ischemia and inflammatory mediators like ischemia modified

albumin (IMA) and high sensitive C- reactive protein (hs-CRP) into the circulation.

IMA has been regarded as new and emerging marker of ischemia and oxidative stress.⁽⁴⁾ C-reactive protein is regarded as a classic acute phase reactant and an important sensitive marker of low grade inflammation. Several studies have shown that increased concentrations of hs-CRP to be associated with atherosclerosis and coronary artery disease. Although thyroid hormones play an important role in cardiovascular hemodynamics, the association between altered levels thyroid hormones and low grade inflammation is still unclear.⁽⁵⁾

Release of currently used cardiac ischemia markers into circulation is believed to require tissue necrosis. Whereas few recent studies showed that cardiac ischemia can be assessed much before or even in absence of cell death has become very important in the present situation.⁽⁶⁾ Thus present study was undertaken, to establish role of IMA and hs-CRP in early diagnosis of ischemic changes in cardiac tissue. This may help in preventing the chances of irreversible infarction in patients with altered levels of thyroid hormones.

Objectives

1. To estimate the thyroid hormone levels (T3, T4, TSH) in hypothyroidism patients compared with normal subjects
2. To estimate levels of IMA & hs CRP in hypothyroidism patients compared with normal subjects

Materials and Method

This study was conducted in Department of Biochemistry in collaboration with Department Of Medicine, K.R. Hospital, MMC&RI, Mysore.

The ethical clearance was obtained from the institutional ethical committee. An informed consent was taken from all the study subjects before the collection of sample.

The study subjects were selected based on following inclusion and exclusion criteria.

Inclusion criteria: Clinically diagnosed cases of hypothyroidism in the age group of 18 to 60 years of both sexes were selected as cases.

Healthy volunteers in the age group of 18 to 60 years were selected as control group.

Exclusion criteria:

- Chronic smokers and alcoholic subjects.
- H/o Cardiovascular disease
- H/o Chronic kidney and liver disease
- H/o Peripheral vascular disease and stroke
- H/o Diabetes mellitus.

Sample size: Sample size was calculated with 5% alpha error and 20% beta error, considering the prevalence of the thyroid dysfunction at 2% in the population. Based on the calculation, the study group included 61 cases & 61 controls.

Group 1: Cases - 61 patients were selected for the study who are diagnosed to have hypothyroidism were considered as cases & they belong to the age group of 18-60 years.

A detailed history was taken pertaining to the duration of disease, treatment taken for hypothyroidism, personal history of diabetes, hypertension, cardiac events, smoking and alcohol intake.

Group 2: Controls – 61 age & sex matched healthy subjects who came for routine health check-up to the Department of Medicine, K.R. Hospital, MMC&RI, Mysore, were considered as controls.

Collection of Blood Samples: Blood sample was collected in the 5ml red vacutainer which is devoid of any anticoagulants. The collected blood was subjected to centrifugation at 3000 rpm for 5-7 minutes. The clear serum obtained after centrifugation was used for the following biochemical investigations:

- Ischemia Modified Albumin (IMA) was measured by Albumin Cobalt Binding method⁽⁷⁾ using

spectrophotometry and values were taken in absorption unit.

- hs-CRP was measured by immuno turbidimetry method using autoanalyser. Reference value: less than 1mg/L

The AHA and CDC has defined risk groups with hs-CRP as follows:⁽⁸⁾

- Low risk: < 1.0 mg/L
- Average risk: 1.0 to 3.0 mg/L
- High risk: > 3.0 mg/L
- Thyroid profile - TSH, total T₄, and total T₃ were measured by Electrochemiluminescence method by using immuno assay analyser.

Reference range:

TSH 0.4 – 4.72 μ IU/mL

T4 4.5 – 12.5 μ g/dL

T3 81 – 178ng/dL

Statistical analysis: Data collected was entered in MS Excel 2010 and analysed using SPSS version 18. Descriptive statistics like percentage, mean and standard deviation are applied for the analysis. Inferential statistical tests like student t test were applied to compare the means between two groups. The differences were interpreted at 5% levels of significance; Data is presented as graphs and tables as relevant.

Results

Table 1 reveals that, in control group total number of male was 21 and female was 40, whereas in cases total number of male and female is 7 and 54 respectively. So in our study population hypothyroidism is found to be more common in females when compared to males.

Table 2 shows that there was an increase in TSH (>6.5 μ IU/ml) values in cases when compared to control subjects, which is indicative of hypothyroidism and those cases were recruited for the study.

Table 3 reveals the comparison of IMA values among controls and cases. Mean value of IMA among the control group was 0.44 \pm 0.37 whereas in cases it was 0.79 \pm 0.66. This shows that hypothyroid patients have increased IMA values when compared to control group which is statistically significant with p value 0.0005.

Table 4 shows comparison of hs-CRP values among controls and cases. hs-CRP values among controls was 0.70 \pm 0.738mg/L where as in cases it was 1.85 \pm 2.804mg/L. This indicates that hypothyroid patients have increased hs-CRP values when compared to control group which is statistically significant with p value 0.0028.

Table 1: Baseline characteristics of study groups

| | Controls | | Cases | |
|--------------------|----------|--------|-------|--------|
| | Male | Female | Male | Female |
| Mean age (Years) | 21 | 30 | 39 | 36 |
| Sex (Total number) | 21 | 40 | 07 | 54 |

Table 2: Thyroid profile values in controls and cases

| Parameters | Controls (Mean±SD) | Cases (Mean±SD) |
|-------------|--------------------|-----------------|
| T3(ng/dl) | 129.17±34.65 | 96.85±14.68 |
| T4(µg/dl) | 9.98±3.0 | 7.3±1.35 |
| TSH(µIu/ml) | 2.49±0.99 | 7.64±8.63 |

Table 3: Comparison of IMA values between controls and cases

| Parameter | Control (Mean±SD) | Cases (Mean±SD) | t value | p value |
|-----------------|-------------------|-----------------|---------|---------|
| IMA (OD values) | 0.44±0.37 | 0.79±0.66 | 3.58 | 0.0005* |

*statistically significant p value

Table 4: Comparison of hs-CRP between controls and cases

| Parameter | Control (Mean±SD) | Cases (Mean±SD) | t value | p value |
|----------------|-------------------|-----------------|---------|---------|
| hs - CRP(mg/L) | 0.70±0.738 | 1.85±2.804 | 3.0977 | 0.0028* |

*statistically significant p value

Discussion

Hypothyroidism is a common metabolic disorder in the general population. It is associated with increased morbidity from cardiovascular disorder.

In our study hypothyroidism was found more in females when compared to male cases as revealed in table no 1. It was also found that, the mean age group of hypothyroidism cases in females was 36 years. This is because the activity of the estrogen is more in reproductive age when compared to perimenopausal or menopausal age. The estradiol has a role in pathophysiology of hypothyroidism and it has an antagonistic action for the activity of T3, T4 by competing with T3, T4 for their binding receptor proteins. Hence there might be decreased activity of T3, T4 in the circulation which may lead to hypothyroidism. The similar findings were also observed in other studies such as Ghanshyam et al.⁽⁹⁾

The cardiovascular system is an important target of thyroid hormone action and is sensitive to slight variations in circulating thyroid hormone levels. In our study, all the study subjects recruited as cases showed hypothyroidism.

These altered thyroid hormone levels may directly act on the heart by impairing the systolic and diastolic functions, or indirectly it may increase cardiovascular risk by altering peripheral vascular resistance. These altered thyroid hormone levels may also change the levels of serum lipid and coagulation profile. These direct and indirect effects of hypothyroidism on heart may lead to increased oxidative stress and ischemia changes in heart. In such incidences the estimation of the markers of ischemia and inflammatory mediators

like IMA and hs- CRP can be useful in assessing the atherosclerotic changes in the heart.

In our study the IMA values were increased in cases when compared to controls as shown in Table 3. This increased IMA value may be because of increased oxidative stress. This oxidative stress may be due to imbalance between production of oxidants and their elimination by antioxidant system in the body.⁽¹⁰⁾ Our observations are in concordance with other studies done by Choudary et al⁽¹¹⁾ and Ma SG et al.⁽¹²⁾ Therefore IMA is found to be very useful for the detection of oxidative stress in thyroid disorder.

An inflammatory marker such as hs-CRP was also estimated in our study. Table 4 showed that there is an increase in hs-CRP values in cases when compared to normal subjects. Whenever there is inflammation there is an increased activity of IL1, IL6 & TNF-α which induces release of CRP into the circulation from liver.⁽¹³⁾ Once CRP is released, this may directly promote atherosclerosis and endothelial dysfunction by attenuating the release of nitric oxide a key molecule in endothelium that plays a pivotal role in the maintenance of vascular tone.

Several studies have shown that increased CRP in hypothyroidism may also induce ICAM and VCAM. This increase in hs-CRP levels were also observed in other studies done by Mirjam Christ et al,⁽¹⁴⁾ Abhinav Kumar et al,⁽¹⁵⁾ Tuzu et al.⁽¹⁶⁾ In contrary to our study Huston et al⁽¹⁷⁾ has shown that there is no difference in hs-CRP levels between hypothyroid patients and euthyroid individuals.

A study done by Asahi-Machi et al⁽¹⁸⁾ had shown that increased serum CRP might have an important

independent role in increased arterial stiffness and the measurement of serum CRP is a useful predictor for degree of improvement in arterial stiffness.

To summarize, our study confirms that the estimation of IMA and hs-CRP would be helpful in early diagnosis of ischemia changes in cardiac tissue. This may help in preventing the chances of irreversible infarction in patients with altered levels of thyroid hormones.

Conclusion

The concentration levels of IMA - a marker of ischemia & hs-CRP - a marker of inflammation were increased in patients with hypothyroidism. This indicates that the altered thyroid hormones have strong impact on the imbalances between the production of oxidants and their elimination by antioxidants systems in the circulation. The consequences of this imbalance cause lipid abnormality in the body which indicates that the hypothyroid patients are more prone for ischemic changes in the cardiac tissue leading to atherosclerosis & myocardial infarction. Therefore, estimation of these novel markers such as IMA & hs-CRP levels in hypothyroid patients might be useful as early markers to detect the future cardiac ischemic diseases.

Limitations

1. Our study included small sample size.
2. IMA estimation could have been done by more sensitive method
3. Estimation of lipid profile is required as a risk factor of cardiovascular diseases, which was not estimated in our study.
4. We have not compared the IMA values with other markers of oxidative stress such as Malondialdehyde and ischemic markers like CK-MB
5. We have not done Angiography and echocardiography of patients. So further studies are required to compare the IMA and hs-CRP value with Angiography and echocardiography of patients.

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