Original Research Article

International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 27-02-2020; Accepted: 22-03-2020; Published: 29-03-2020
www.medicalsciencejournal.com
Volume 6; Issue 3; 2020; Page No. 148-152

Evaluation of hs-CRP and lipid profile in patients diagnosed with the hypothyroid condition

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Abstract

Thyroid disorders are known to influence lipid metabolism and other CV risk factors predominantly. Dyslipidaemia is a well-recognized association of thyroid dysfunction which should be considered in the process of evaluating and treating dyslipidemic patients. Hence based on above findings the present study was planned for Evaluation of hs-CRP and lipid profile in Patients Diagnosed with the hypothyroid Condition.

The present study was planned in Department of General Medicine, Indira Gandhi Institute of Medical sciences, Patna, Bihar. In the present study 30 cases of the newly detected hypothyroid adults were enrolled in the Group A. The 30 cases of control were also enrolled in Group B for comparative evaluation.

The data generated from the present study concludes that hypothyroidism is associated with dyslipidemia and low-grade inflammation. Subclinical hypothyroidism was found to be more common than clinical hypothyroidism. The mild and inconsistent changes which were observed in the biochemical parameters in hypothyroidism may be due to the preponderance of subclinical hypothyroid cases in this study. However, dyslipidemia and inflammatory markers were found to be increased in the cases that helped in prediction and evaluation of patients at risk of cardiovascular disease.

Keywords: hs-CRP, thyroid stimulating hormones, clinical hypothyroidism, subclinical hypothyroidism, etc

Introduction

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. In the United States and other areas of adequate iodine intake, autoimmune thyroid disease (Hashimoto disease) is the most common cause of hypothyroidism; worldwide, iodine deficiency remains the foremost cause.

Third-generation thyroid-stimulating hormone (TSH) assays are generally the most sensitive screening tool for primary hypothyroidism. If TSH levels are above the reference range, the next step is to measure free thyroxine (T4) or the free thyroxine index (FTI), which serves as a surrogate of the free hormone level. Routine measurement of triiodothyronine (T3) is not recommended. Biotin, a popular health supplement, may interfere with immunoassays of many hormones, resulting in values that are falsely elevated or suppressed, including for thyroid levels. To avoid misleading test results, the American Thyroid Association recommends cessation of biotin consumption at least 2 days prior to thyroid testing.

Hypothyroidism, also called underactive thyroid or low thyroid, is a disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. It can cause a number of symptoms, such as poor ability to tolerate cold, a feeling of tiredness, constipation, depression, and weight gain. Occasionally there may be swelling of the front part of the neck due to goiter. Untreated cases of hypothyroidism during pregnancy can lead to delays in growth and intellectual development in the baby or congenital iodine deficiency syndrome [1].

Worldwide, too little iodine in the diet is the most common cause of hypothyroidism. Hashimoto's thyroiditis is the most common cause of hypothyroidism in countries with sufficient dietary iodine. Less common causes include previous treatment with radioactive iodine, injury to the hypothalamus or the anterior pituitary gland, certain medications, a lack of a functioning thyroid at birth, or previous thyroid surgery. The diagnosis of hypothyroidism, when suspected, can be confirmed with blood tests measuring thyroid-stimulating hormone (TSH) and thyroxine levels [2].

Salt iodization has prevented hypothyroidism in many populations. Thyroid hormone replacement with levothyroxine treats hypothyroidism. Medical professionals adjust the dose according to symptoms and normalization of the thyroxine and TSH levels. Thyroid medication is safe in pregnancy. Although an adequate amount of dietary iodine is important, too much may worsen specific forms of hypothyroidism [2].

Worldwide about one billion people are estimated to be iodine-deficient; however, it is unknown how often this results in hypothyroidism. In the United States, hypothyroidism occurs in 0.3–0.4% of people. Subclinical hypothyroidism, a milder form of hypothyroidism characterized by normal thyroxine levels and an elevated TSH level, is thought to occur in 4.3–8.5% of people in the United States. Hypothyroidism is more common in women than in men [3]. People over the age of 60 are more commonly affected. Dogs are also known to develop hypothyroidism, as are cats and horses, albeit more rarely. The word "hypothyroidism" is from Greek hypo- meaning reduced, thyreos for shield, and eidos for form [3].

Hypothyroidism is caused by inadequate function of the gland itself (primary hypothyroidism), inadequate stimulation by thyroid-stimulating hormone from the pituitary gland (secondary hypothyroidism), or inadequate release of thyrotropin-releasing hormone from the brain's hypothalamus (tertiary hypothyroidism). Primary

hypothyroidism is about a thousand-fold more common than central hypothyroidism [4].

Iodine deficiency is the most common cause of primary hypothyroidism and endemic goiter worldwide. In areas of the world with sufficient dietary iodine, hypothyroidism is most commonly caused by the autoimmune disease Hashimoto's thyroiditis (chronic autoimmune thyroiditis). Hashimoto's may be associated with a goiter. It is characterized by infiltration of the thyroid gland with T lymphocytes and autoantibodies against specific thyroid antigens such as thyroid peroxidase, thyroglobulin and the TSH receptor [5].

After women give birth, about 5% develop postpartum thyroiditis which can occur up to nine months afterwards. This is characterized by a short period of hyperthyroidism followed by a period of hypothyroidism; 20–40% remain permanently hypothyroid. Autoimmune thyroiditis is associated with other immune-mediated diseases such as diabetes mellitus type 1, pernicious anemia, myasthenia gravis, celiac disease, rheumatoid arthritis and systemic lupus erythematosus. It may occur as part of autoimmune polyendocrine syndrome (type 1 and type 2) [5].

Thyroid hormone is required for the normal functioning of numerous tissues in the body. In healthy individuals, the thyroid gland predominantly secretes thyroxine (T4), which is converted into triiodothyronine (T3) in other organs by the selenium-dependent enzyme iodothyronine deiodinase. Triiodothyronine binds to the thyroid hormone receptor in the nucleus of cells, where it stimulates the turning on of particular genes and the production of specific proteins. Additionally, the hormone binds to integrin αvβ3 on the cell membrane, thereby stimulating the sodium–hydrogen antiporter and processes such as formation of blood vessels and cell growth. In blood, almost all thyroid hormone (99.97%) is bound to plasma proteins such as thyroxine-binding globulin; only the free unbound thyroid hormone is biologically active. Overexpression of deiodinase can thus lead to consumptive hypothyroidism [6].

The thyroid gland is the only source of thyroid hormone in the body; the process requires iodine and the amino acid tyrosine. Iodine in the bloodstream is taken up by the gland and incorporated into thyroglobulin molecules. The process is controlled by the thyroid-stimulating hormone (TSH, thyrotropin), which is secreted by the pituitary. Not enough iodine, or not enough TSH, can result in decreased production of thyroid hormones.

The hypothalamic–pituitary–thyroid axis plays a key role in maintaining thyroid hormone levels within normal limits. Production of TSH by the anterior pituitary gland is stimulated in turn by thyrotropin-releasing hormone (TRH), released from the hypothalamus. Production of TSH and TRH is decreased by thyroxine by a negative feedback process. Not enough TRH, which is uncommon, can lead to not enough TSH and thereby to not enough thyroid hormone production [4].

Pregnancy leads to marked changes in thyroid hormone physiology. The gland is increased in size by 10%, thyroxine production is increased by 50%, and iodine requirements are increased. Many women have normal thyroid function but have immunological evidence of thyroid autoimmunity (as evidenced by autoantibodies) or are iodine deficient, and develop evidence of hypothyroidism before or after giving birth [7].

Laboratory testing of thyroid stimulating hormone levels in the blood is considered the best initial test for hypothyroidism; a second TSH level is often obtained several weeks later for confirmation. Levels may be abnormal in the context of other illnesses, and TSH testing in hospitalized people is discouraged unless thyroid dysfunction is strongly suspected. An elevated TSH level indicates that the thyroid gland is not producing enough thyroid hormone, and free T4 levels are then often obtained. Measuring T3 is discouraged by the AACE in the assessment for hypothyroidism. There are a number of symptom rating scales for hypothyroidism; they provide a degree of objectivity but have limited use for diagnosis [5].

Many cases of hypothyroidism are associated with mild elevations in creatine kinase and liver enzymes in the blood. They typically return to normal when hypothyroidism has been fully treated [7]. Levels of cholesterol, low-density lipoprotein and lipoprotein (a) can be elevated; the impact of subclinical hypothyroidism on lipid parameters is less well-defined.

Very severe hypothyroidism and myxedema coma are characteristically associated with low sodium levels in the blood together with elevations in antidiuretic hormone, as well as acute worsening of kidney function due to a number of causes. In most causes, however, it is unclear if the relationship is causal [8].

A diagnosis of hypothyroidism without any lumps or masses felt within the thyroid gland does not require thyroid imaging; however, if the thyroid feels abnormal, diagnostic imaging is then recommended. The presence of antibodies against thyroid peroxidase (TPO) makes it more likely that thyroid nodules are caused by autoimmune thyroiditis, but if there is any doubt, a needle biopsy may be required.

Screening for hypothyroidism is performed in the newborn period in many countries, generally using TSH. This has led to the early identification of many cases and thus the prevention of developmental delay. It is the most widely used newborn screening test worldwide. While TSH-based screening will identify the most common causes, the addition of T4 testing is required to pick up the rarer central causes of neonatal hypothyroidism. If T4 determination is included in the screening done at birth, this will identify cases of congenital hypothyroidism of central origin in 1:16,000 to 1:160,000 children. Considering that these children usually have other pituitary hormone deficiencies, early identification of these cases may prevent complications [4].

In adults, widespread screening of the general population is a matter of debate. Some organizations (such as the United States Preventive Services Task Force) state that evidence is insufficient to support routine screening, while others (such as the American Thyroid Association) recommend either intermittent testing above a certain age in all sexes or only in women. Targeted screening may be appropriate in a number of situations where hypothyroidism is common: other autoimmune diseases, a strong family history of thyroid disease, those who have received radioiodine or other radiation therapy to the neck, those who have previously undergone thyroid surgery, those with an abnormal thyroid examination, those with psychiatric disorders, people taking amiodarone or lithium, and those with a number of health conditions (such as certain heart and skin conditions). Yearly thyroid function tests are recommended in people with Down syndrome, as they are at higher risk of thyroid disease [9].

CRP is used mainly as an inflammation marker. Apart from liver failure, there are few known factors that interfere with CRP production. Interferon alpha inhibits CRP production from liver cells which may explain the relatively low levels of CRP found during viral infections compared to bacterial infections [10]

Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments. ELISA, immunoturbidimetry, nephelometry, rapid immunodiffusion, and visual agglutination are all methods used to measure CRP. A high-sensitivity CRP (hs-CRP) test measures low levels of CRP using laser nephelometry. The test gives results in 25 minutes with a sensitivity down to 0.04 mg/L. The risk of developing cardiovascular disease is quantified as follows [11]: low: hs-CRP level under 1.0 mg/L; average: between 1.0 and 3.0 mg/L; high: above 3.0 mg/L

Normal levels increase with aging. Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns (>200 mg/L). CRP cut-off levels indicating bacterial from non-bacterial illness can vary due to co-morbidities such as malaria, HIV and malnutrition and the stage of disease presentation [12]. CRP is a more sensitive and accurate reflection of the acute phase response than the ESR (Erythrocyte Sedimentation Rate). ESR may be normal while CRP is elevated. CRP returns to normal more quickly than ESR in response to therapy.

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Methodology

The present study was planned in Department of General Medicine, Indira Gandhi Institute of Medical sciences, Patna, Bihar. In the present study 30 cases of the newly detected hypothyroid adults were enrolled in the Group A. The 30 cases of control were also enrolled in Group B for comparative evaluation.

A fasting blood sample was taken and serum separated after centrifugation and stored at -80 C. This was later analysed for lipid profile parameters which included total cholesterol, triglycerides, HDL and LDL. These were done on automated analyser Olympus AU400 by colorimetric method. HDL and LDL were estimated by the direct assay method. Apart from this fasting blood sample was taken in a sodium fluoride-potassium oxalate vial for estimation of sugar and plasma stored after centrifugation at -80 C. Lp(a) was done by ELISA (DRG International Inc., USA). ELISA was done for hsCRP estimation (Diagnostics Biochem Canada Inc.). Insulin levels were measured on Elecsys 2010 (Roche diagnostics) by the principle of electro-chemiluminescence. Insulin resistance was calculated using HOMA-IR.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Newly detected hypothyroid cases between age group of 20 - 60 years.

Exclusion criteria: Medical/ Surgical illness like Cardio vascular disorders, Diabetes Mellitus, kidney failure, Liver disorders and other major chronic illnesses. Hypothyroid adults with any other medications or treatments.

Results & Discussion

Hypothyroidism is defined as peripheral thyroid hormones T3 and T4 within their reference ranges with the presence of elevated thyroid stimulating hormone (TSH) [13]. There may be few or no associated symptoms suggestive of hypothyroidism. SCH was described in early 1970's after Hypothyroidism estimation became routine. It is a more common problem than overt hypothyroidism with a prevalence of 3–8 % in the adult population. This prevalence increases with age and is more common in women [14]. Many studies have been conducted worldwide to see if SCH progresses to overt hypothyroidism [15, 16]. The cardiovascular mortality, endothelial dysfunction, underlying inflammation, neuromuscular and psychiatric disturbances, adverse fetal effects in a pregnant subclinical hypothyroid female, association with metabolic syndrome are all debatable aspects as many different studies have given contradictory results [17].

Studies in the past have evaluated that the presence of dyslipidemia may not be neglected in patients, more specifically in moderate SCH having TSH >10 mIU/L, but the results were contradictory [18, 19]. Since the presence of dyslipidemia may suggest future progression of cardiovascular risks, the role of inflammatory markers may be important in SCH patients because without inflammation cholesterol cannot be trapped [20, 21]. High-sensitive C-reactive protein (Hs-CRP), a diagnostic tool for assessment of cardiovascular disease, is a marker of low-grade inflammation, which may lead to atherosclerosis [22]. Estimation of Hs-CRP may be valuable since it is an effective marker for heart diseases rather than low-density lipoprotein (LDL) cholesterol alone [23].

CRP is a critical component of the immune system, a complex set of proteins that our bodies make when faced with a major infection or trauma. CRP was discovered nearly 70 years ago by scientists exploring the human inflammatory response. CRP is a member of the pentraxin protein family, which is so named because these proteins possess five identical subunits. CRP, which is elaborated dramatically during acute inflammation, augments the immune response to certain antigens, activates complement, and increases the monocytic production of tissue factors [24]. CRP binds to phosphoryl choline on bacterial surfaces, acting as an opsonin and playing a pivotal role in host defence. Interestingly, CRP also appears to bind low-density lipoprotein cholesterol (LDL-C) in vitro, which suggests a direct interaction with the atherogenic lipids [25].

Table 1: Basic Details

Parameters	Group A	Group B
Cases of	**Hypothyroid adults**	**Control Patients**
No. of Cases	30	30
Age		
20 – 30 years	1	2
30 – 40 years	6	9
40 – 50 years	16	11
50 – 60 years	7	8
BMI (Kg/cm2)	22.4 – 31.5	20.4 – 28.6

Table 2: Biochemical Parameters

Parameters	Group A	Group B
Cases of	**Hypothyroid adults**	**Control Patients**
No. of Cases	30	30
Thyroid Stimulating Hormone µIU/ml	8.5 – 17.5	1.8 – 3.6
Free T3 pg/ml	0.8 – 2.9	1.5 – 2.6
Free T4 pg/ml	0.5 – 1.3	0.7 – 0.8
High sensitive c- reactive protein (hs -CRP)	2.2 – 6.9	1.2 – 3.3
Total Cholesterol (mg/dl)	143.5 – 219.8	154.6 – 211.6
High Density Lipids (mg/dl)	34.5 – 53.9	48.7 – 61.2
Low Density Lipids (mg/dl)	108.6 – 176.8	101.2 – 162.7
Triglycerides (mg/dl)	102.4 – 215.6	124.5 – 178.9

An elevated TSH in an individual patient, thus, means that the circulating thyroid hormone concentrations are insufficient, with a few rare exceptions (TSH-secreting tumors, thyroid hormone resistance syndromes). Subclinical hypothyroidism represents mild thyroid failure and is a clinically important disorder that has adverse clinical consequences and that should be treated in most, if not all, case [26].

The etiologies of subclinical and overt hypothyroidism are identical. Chronic autoimmune thyroiditis (Hashimoto's disease) accounts for the majority of cases. Approximately 54% of patients with subclinical hypothyroidism have Hashimoto's disease with high serum concentrations of antithyroid microsomal or antithyroid peroxidase antibodies [27].

Subclinical hypothyroidism may increase the risk of coronary heart disease (CHD) by adversely affecting cardiovascular risk factors. Despite some conflicting results many studies have found that subjects with subclinical hypothyroidism have higher total cholesterol and low-density lipoprotein/cholesterol levels than euthyroid subjects. A cross-sectional study showed that subjects with subclinical hypothyroidism have increased C-reactive protein values. Subclinical hypothyroidism also has been associated with increased risk for atherosclerosis. Another important concern is the progression of subclinical hypothyroidism to overt hypothyroidism during its natural history. Risk is high if the TSH is more than 10 mIU/L or thyroid peroxidase antibody is positive. In the Whickham survey the annual risk of women developing hypothyroidism was 4.3% per year if both an elevated serum TSH and anti-thyroid antibodies were found, 2.6% with elevated TSH alone, and 2.1% per year with positive anti-thyroid antibodies alone [28].

In a recent prospective study on the spontaneous course of patients with subclinical hypothyroidism by Gerold Huber and team they concluded that risk factors for progression to overt hypothyroidism were base line TSH >12mIU/L, decreased thyroid reserve and presence of thyroid peroxidase antibody [29].

Subclinical hypothyroidism is much more common than overt hypothyroidism Therefore, early diagnosis and treatment may prevent the onset of overt hypothyroidism and its associated effects. Subclinical hypothyroidism may be associated with increased risk of coronary artery disease (CAD), peripheral vascular disease, diastolic dysfunction and various biochemical abnormalities including increased LDL-C levels, increased total cholesterol and serum triglyceride values. Inflammation and oxidation of lipoproteins play an important role in the progression and complications of atherosclerosis. High sensitive CRP is a known cardiovascular biomarker. It is associated with high risk of myocardial infarction, acute coronary syndromes, diastolic dysfunction. In subclinical hypothyroidism, several metabolic and organ function indices will show only marginal alterations in view of minor thyroid hormone secretion impairment. Nonetheless, such changes may become clinically relevant when they affect target organs over a period of several years. So here is an attempt to find out the correlation between marker of inflammation, hsCRP and subclinical hypothyroidism, so that treatment of subclinical hypothyroidism may prevent cardiovascular disease.

Conclusion

The data generated from the present study concludes that hypothyroidism is associated with dyslipidemia and low grade inflammation. Subclinical hypothyroidism was found to be more common than clinical hypothyroidism. The mild and inconsistent changes which were observed in the biochemical parameters in hypothyroidism may be due to the preponderance of subclinical hypothyroid cases in this study. However, dyslipidemia and inflammatory markers were found to be increased in the cases that helped in prediction and evaluation of patients at risk of cardiovascular disease.

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