ASSESSMENT OF THYROID PARAMETERS IN ALCOHOLIC LIVER DISEASE

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ABSTRACT

Normal level of thyroid hormone is important for normal hepatic function as it maintains the metabolism of bilirubin by playing a role in the enzymatic activity of glucuronyl transferase and by regulating the level of ligandin. The liver in turn glucuronidates and sulphates the thyroid hormone, excretes into bile and regulates their systemic endocrine effects. Therefore, hepatic dysfunction is commonly observed in patients with thyroid disease. Mean levels of Gamma-glutamyl transferase are increased in alcoholic cirrhosis with alcohol abuse of < 10 years duration. In this study thyroid function tests and liver function tests were performed on the 200 subjects, of which 100 subjects were patients with Alcoholic Liver Disease, 100 were healthy controls and it was found that the serum tri-iodothyronine and free tri-iodothyronine levels were decreased and levels of Thyroid stimulating hormone were increased in patients with Alcoholic Liver Disease as compared to controls.

KEYWORDS: ALD, Thyroid hormones, Deiodinase, Gamma-glutamyl transferase.

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INTRODUCTION

Alcoholic liver disease is a term that encompasses the liver manifestations of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis with liver fibrosis or cirrhosis. Of all chronic heavy drinkers, only 15–20% develop hepatitis or cirrhosis, which can occur concomitantly or in succession. 80% of alcohol passes through the liver to be detoxified. Additionally, the liver has tremendous capacity to regenerate and even when 75% of hepatocytes are dead, it continues to function as normal. Alcoholism causes development of large fatty globules the liver and can begin to occur after a few days of heavy drinking. Alcohol is metabolized by alcohol dehydrogenase (ADH) into acetaldehyde, then further metabolized by aldehyde dehydrogenase (ALDH) into acetic acid, which is finally oxidized into carbon dioxide (CO₂) and water (H₂O). Gamma-glutamyl transferase (GGT) is an enzyme that transfers gamma-glutamyl functional groups. It is found in many tissues, the most notable one being the liver. GGT plays a key role in the gamma-glutamyl cycle, a pathway for the synthesis and degradation of glutathione. Isolated elevation or disproportionate elevation compared to other liver enzymes (such as ALP or ALT) can indicate alcohol abuse or alcoholic liver disease. Alcohol might increase GGT production by inducing hepatic microsomal production, or it might cause the leakage of GGT from hepatocytes.GGT is a sensitive and highly specific test of liver cell injury in suspected alcoholics and is superior to transaminase determination. GGT remains the best of simple lab screening test and depending on population studied the sensitivity is in the order of 50% and specificity about 85%. There are three homologous iodothyronine deiodinases which catalyse these reactions. Type I deiodinase is located in liver, kidney, and thyroid. Liver has an important role in thyroid hormone transport and metabolism. These hormones are required for the normal growth, development and function of nearly all tissues, with major effects on oxygen consumption and metabolic rate. Thyroid hormone synthesis and secretion is regulated by a negative feedback system that involves the hypothalamus, pituitary, and the thyroid gland. The free, unbound component of thyroid hormone within plasma is in equilibrium with the protein bound hormone and accounts for it’s biological activities. Thyroid hormones (TH) are known to stimulate basal metabolic rate for over a century. Subsequent studies showed that THs induced energy expenditure in response to increased caloric intake. The active form of TH, 3,3′,5′-triiodo-l-thyronine (T₃), is a critical regulator of cellular and tissue metabolism throughout the body. It controls gene expression in target tissues by binding to its cognate nuclear receptors (TRα and TRβ), which are ligand-inducible transcriptional factors. In the presence of T₃, TH receptors (TRs) bind to TH response elements in the promoters of target genes and form coactivator complexes containing histone acetyltransferase activity to activate transcription. Our main objective is to evaluate the thyroid hormone levels and liver function parameters in patients with liver disease.

MATERIALS AND METHODS

The present study consists of 200 subjects, 100 subjects were patients with alcoholic liver disease 100 were healthy controls. The study was conducted at Goa Medical College and Hospital, Bambolim-Goa during the period of 2013-2014. Ethical clearance was obtained from the institution's ethical committee. 7-8ml of fasting samples were collected in plain bulbs by venepuncture, under aseptic conditions of the 200 subjects. Serum was separated by centrifuging blood samples at 3000 rpm in clinical centrifuge for 10 minutes. Serum was used to perform thyroid function tests and liver function tests on the above mentioned 200 subjects. All tests were performed on Ci2000 autoanalyser. ARCHITECT Total T₃ (tri-iodothyronine) assay is a two step immunoassay to determine the presence of Total T₃ in human serum and plasma using CMIA (Chemiluminescent Microparticle ImmunoAssay) technology with flexible assay protocols, referred to as chemiflex. The sample and anti T₃ coated paramagnetic microparticles are combined. T₃ present in the sample binds to the anti-T₃ coated microparticles. After washing, T₃ acridinium-labeled conjugate is added. Pre-trigger and trigger solutions are then added to the reaction mixture, the resulting chemiluminescent reaction is measured as relative light units (RLUs). Reagent contains microparticles 1 or 4 bottles (6.6ml/27.0ml) anti-T₃ coated particles in MES buffer with sheep IgG Stabilizers and 1 or 4 bottles (5.9ml/26.3ml) T₃ acridinium-labeled conjugate in citrate buffer with NaCl and triton X-100 stabilizers. Antimicrobial agent is used as preservative. Calibrator range is 0.0-8.0ng/ml. Expected value of TT₃ is 0.58-1.59 ng/mL. The sample and anti T₄ coated paramagnetic microparticles are combined. T₄ present in the sample binds to the anti-T₄ coated microparticles. After washing, T₄ acridinium-labeled conjugate is added. Pre-trigger and trigger solutions are then added to the reaction mixture, the resulting chemiluminescent reaction is measured as RLUs. Reagent contains microparticles 1 or 4 bottles of anti-T₄ coated particles in TRIS buffer. Calibrator range is 0.0-24.0 µg/dL. Expected value of TT₄ is 4.87-11.72 µg/dL. The ARCHITECT TSH assay is a two step immunoassay to determine the presence of thyroid stimulating hormone (TSH) in human serum and plasma using CMIA technology with flexible assay protocols. The sample and anti-β TSH antibody coated paramagnetic microparticles and TSH Assay Diluent are combined. TSH present in the sample binds to the anti-TSH coated microparticles. After washing, anti-α TSH acridinium labeled conjugate is added. Pre-trigger and trigger solutions are then added to the reaction mixture, the resulting chemiluminescent reaction is measured as RLUs. Reagent contains microparticles 1 or 4 bottles of anti-α TSH coated particles in TRIS buffer. Expected value of TT₄ is 0.58-1.59 µg/dL. Expected value of TT₄ is 0.58-1.59 ng/mL. The ARCHITECT Free T₃ assay is a two step immunoassay to determine the presence of free (unbound) T₃ in human serum and plasma using CMIA technology. The sample and anti T₃ coated paramagnetic microparticles are combined. Free T₃
Aspartate Aminotransferase (AST) present in the sample catalyzes the transfer of the amino group from L-alanine to α-ketoglutarate, forming pyruvate and L-glutamate. Pyruvate in the presence of NADH and lactate dehydrogenase (LD) is reduced to L-lactate. In this reaction, NADH is oxidized to NAD. The reaction is monitored by measuring the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD. Expected values are 0-55 U/L in adult serum. Alkaline Phosphatase (ALP) present in the sample catalyzes the hydrolysis of colourless p-nitrophenyl phosphate (p-NPP) to give p-nitrophenyl and inorganic phosphate. The rate of increase in absorbance at 404 nm is directly proportional to the alkaline phosphatase activity in the sample. Expected values are 40-150 U/L in adult serum. \(^{20}\) Alkaline phosphatase (ALP) present in the sample catalyzes the hydrolysis of colourless p-nitrophenyl phosphate (p-NPP) to give p-nitrophenyl and inorganic phosphate. The rate of increase in absorbance at 404 nm is directly proportional to the alkaline phosphatase activity in the sample. Expected values are 40-150 U/L in adult serum. \(^{20}\) Total protein polypeptides containing at least two peptide bonds react with biuret reagent in alkaline solution, cupric ion forms a coordination complex with protein nitrogen with very little difference between albumin and globulin on a protein-nitrogen basis. Expected values are 6.4 to 8.3 g/dL in adult serum. The Albumin BCG procedure is based on the binding of bromcresol green specifically with albumin to produce a coloured complex. The absorbance of the complex at 628 nm is directly proportional to the albumin concentration in the sample. Expected values are 3.5 to 5.2 gm/dl in adult serum. \(^{21}\) Gamma Glutamyl Transferase (GGT) catalyzes the transfer of amino group between L-glutamyl-3-carboxy-4-nitroanilide and Glycylglycine to form L-glutamylglycylglycine and 5-amino-2-nitrobenzoate. The rate of formation of 5-amino-2-nitrobenzoate is measured as an increase in absorbance which is proportional to the GGT activity in the sample. Expected values are 10-50 U/L in adult serum. \(^{21}\)
The present study consists of 200 subjects, 100 subjects were patients with alcoholic liver disease and 100 were healthy controls. In this study, patients with alcoholic liver disease were evaluated for thyroid function tests and it was found that the serum T3 and FT3 levels were decreased and levels of TSH were increased as compared to controls. The mean serum T3 level in patients with ALD was 0.41±0.082 and in control group was 0.96±0.27. This difference was statistically significant (p value <0.001). The mean serum FT3 level in patients with ALD was 1.35±0.41 and in control group was 2.29±0.62. The mean serum TSH level in patients with ALD was 4.28±2.21 and in control group was 2.29±1.33. This difference was statistically significant (p value <0.001).

**DISCUSSION**

Thyroid hormones are essential for normal organ growth, development, function and regulation of the basal metabolic rate of all cells and therefore, its alteration can affect the entire metabolism. Most affected organs include liver and heart. So, it alters the liver enzymes like ALP, AST, ALT, GGT and cardiac enzymes like CPK, LDH and AST. These biochemical changes, usually mild, are also reversible with adequate thyroid replacement therapy. The findings of our study is in corroboration with findings of the study by Yadav A. et al. and Pandey R. et al. Malik and Hodgson et al who mentioned that thyroid hormones T3 and T4 regulate BMR of hepatocytes and modulate all the organ functions. The liver, muscle and kidney in turn metabolizes thyroid hormones and
Among patients with alcohol-induced liver cirrhosis, low T-hormones maintain the metabolism glucuronyltransferase and by regulating Israel et al. may have thyroiditis, hyperthyroidism or hypothyroidism functions. (ii) Some patients with chronic liver diseases through autoimmune mechanisms. (iii) Alterations of hormone excess or direct toxic effects and subclinical damage secondary to the systemic effect of thyroid therapy of thyroid or liver disease. (iv) Liver or thyroid disorders related to the thyroid hormone metabolism or tests secondary to liver disease. and normal TSH values have been observed. In patients with alcoholic liver disease Israel et al. reported an inverse correlation between serum T3 concentrations and the severity of liver dysfunction as well as a progressive T3 increase suggesting that T3 concentrations in patients with alcoholic liver disease may be considered as helpful prognostic indicator. The low total and free T3 levels may be regarded as an adaptive hypothyroid state that serves to reduce the basal metabolic rate within hepatocytes and preserve liver function and total body protein stores. Indeed, a recent study in cirrhotic patients showed that the onset of hypothyroidism from intrinsic thyroid disease of various aetiologies during cirrhosis resulted in biochemical improvement in liver function.

**CONCLUSION**

Hepatic dysfunction is commonly observed in patients with thyroid disease. The mean T3 and FT3 levels were decreased in patients with alcoholic liver disease has compared to controls probably because type I deiodinase which is the major enzyme in liver carries out 5’ deiodination of T4 to form T3. Type II 5’ deiodinase is important for providing the T3 required to stimulate the pituitary to synthesize and secrete TSH.

**CONFLICT OF INTEREST**

Conflict of interest declared none.