Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i1.4040

IDENTIFICATION OF THYROID ABNORMALITIES AMONG HEPATITIS B & C PATIENTS AND ITS INVOLVEMENT WITH INTERFERON THERAPY

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Abstract

The liver infections are the major cause of increasing mortality rate throughout the world. Liver cirrhosis and hepatocellular carcinoma (HCC) cause an estimated 783,000 and 619,000 deaths per year respectively. Thyroid dysfunction (TD) represents an extrahepatic manifestation of chronic hepatitis C (CHC). Moreover, the currently approved treatment of CHC is often associated with TD. However, it remains debatable if TD is mainly virus or treatment related. The aim of this study was to assess the incidence of TD and to identify its predictors in treated and untreated CHC-infected patients. Aim of current work was to explore the effect of interferon therapy on the thyroid profile of viral hepatic patients. A total of 150(are those patients who received therapy and 50 is the control group which is given below) HBV and HCV patients who were receiving peg interferon therapy were assessed for the thyroid profile against 50 patients of untreated viral hepatic control group. Thyroid profile was relatively higher in younger patients (20-30 years) as compared to control group. A higher level of thyroid hormone was observed in age group of 20 to 30 (30.71%) among the exploratory and control group. Female patients show slight elevation in thyroid profile in contrast to male patients. The observed value of certain thyroid hormones was hyperthyroidism is about 28% in HCV patients, followed by hypothyroidism 24% and similarly euthyroidism developed in 48% of patients while in

HBV patients the hyperthyroidism was noted 35%, hypothyroidism was 21% and euthyroidism was observed 44% the current result how that hypothyroidism in HBV is about 21% and HCV is 24%,hyper thyroidism in HBV is 35% and HCV is about 28%.,euthyroidism in HBV is noted 44% and HCV 48%.Our study suggests that the thyroid profile values in different age wise distribution T3 and T4 value were noted high in group 15-25 Years, T4 and TSH values are raised in group 26-35 followed by group 36-45 and 46-55 Years. While T4 value was raised in 56-65 Year group.

Keyword: Interferon, HCV, HBV

I. INTRODUCTION

The liver infections are the major cause of increasing mortality rate throughout the world. The World Health Organization is estimate that in 2002, deaths ratio due to liver cirrhosis and hepatic cancer is about 783,000 and 619,000 respectively (Hanafiah *et al*., 2013). Primary hepatic cancers occurring worldwide among, <85% cases major histologic type disease are hepatocellular carcinoma (HCC). Hepatic Cirrhosis precedes most cases of hepatocellular carcinoma (Mandac *et al.*,2006). Hepatocellular carcinoma developing risk are associated with viral Hepatitis B and C are compared with cirrhosis other cases (Lavanchy *et al.*,2011*)*. The major causes of liver cirrohsis is alcohol abuse in many parts of the world, in the presence of Hepatitis B&C viral infections synergistic affects with some evidence. Appear to be local or regional importance which is the other factors (Wilkins *et al*., 2010). Viral Hepatitis B are transmitted parenteral route, clear, in apparent percutaneous, per mucosal introduction to contaminated blood and other body liquids. Hazard factors for contamination incorporate transfusion of unscreened blood products, sexual relations, Re-utilizing or sharing of syringes between infusion medicate clients, medicinal services proficient, renal dialysis and long haul family or private non-sexual contact with a HBsAg-positive person (Wasley *et al.*,2006).

HCV viruses are belong to Flaviviridae family. The HCV virions are made of a single stranded positive RNA genome (Chevaliez *et al.*,2007). The blood and blood product are the main source of transmission of hepatitis C virus, use of unsterilized sharp instrument or needle stick injuries and tattooing (Lavanchy *et al.*,2011).Pakistan is second one nation after Egypt where pervasiveness of hepatitis C is uncertainly high. By and by around 10 million individuals in Pakistan are contaminated with Hepatitis C disease (Waheed *et al.*,2012).Liver assumes a sole job in the metabolism of thyroid hormones, as it is the most significant organ in the fringe transformation of tetraiodothyronine (T4) to triiodothyronine (T3) by sort iodinase coming about to 5' deiodination of T4 (Sorvillo *et al.*,2003). Thyroid dysfunction may likewise appear as damaging thyrotoxicosis, Graves' thyrotoxicosis and hypothyroidism. These neurotic conditions may happen in a similar patient because of various immunological impacts of IFN-α treatment on the thyroid organ (Costelloe *et al.*,2010). Interferon-alpha therapy were a prominent risk factor for the development of thyroid dysfunctions (Antonelli *et al.*,2009). Thyroid diseases inside Chronic hepatitis C are displayed in various modalities: progressively regular are higher estimations of hostile to TPO antibodies and against TG titres in serum of 15–42% and essential hypothyroidism in 4.5–13%, while commonness of essential hyperthyreosis and threatening thyroid issue are fundamentally lower (Zhang *et al.*,2015).Thyroid dysfunction (TD) is one of the basic symptom of interferon-based antiviral treatment for CHC, which may prompt portion decrease or stopping of treatment.

Although conventional interferon no more used in developed countries but it still is use in Pakistan because of cost-effectiveness (Friedrich *et al.*,2009).The recently standard dual therapy pegylated interferon and ribavirin are affectively recommended for hepatitis C virus. IFN-α based antiviral treatment, normal IFN-α or pegylated interferon alpha, in mix with ribavirin or alone treatment is recognized just like an exceptionally powerful treatment for patients with interminable hepatitis C. This treatment brings about a continued virologic reaction (SVR) in 40–half of patients with genotype 1, and around 80% in those contaminated with genotype 2 and 3 (Ghany *et al.*, 2009).

II. MATERIALS AND METHODS

A case-control study was designed to investigate the effect of interferon therapy on the thyroid profile of HCV and HBV patients. The study was carried out in the department of medicine of PIMS hospital Islamabad from January 2020 to July 2020**. A** total of 200 viral hepatic patients were included in the study. Patients visiting the internal medicine unit of PIMS hospital Islamabad were asked for informed consent. All the relevant information such age, date of diagnosis, type and duration of therapy were recorded on the pre-designed proforma. The patients (150) who were receiving interferon therapy were assessed for the thyroid profile against the patients (74) who were not receiving interferon therapy. Blood samples were collected from both groups. Thyroid profiles were determined as follows.

The blood sample was collected randomly collected in phlebotomy section of the main clinical laboratory attached to emergency outpatient department. The consent was taken from all patients before the sample collection. The blood sample was collected in gel tube of red top containing clumps activators. The sample was then permitted to clot in vertical position for 30 minutes. The samples were centrifuged at 3000 RPM for 20 minutes to separate the serum from the whole blood. Samples were transferred to a pathology Laboratory and processed the sample on the spot. The procedure for TFTS was performing on purely Automated Immunoassay Analyzer Cobas e411 Dependent on Electro Chemilumine scence (ELC) innovation.

Statistical Analysis. The data was analyzed using Microsoft excel sheet and through SPSS4 ONE way ANOVA.

III. RESULTS

A total of 300 individuals were included in this study. The samples were collected from Hepatitis infected patients who are treated by Interferon. The individual was classified into two groups. Exploratory class and control classification. Among a total of 300 patients confirmed viral disease HBV and HCV and getting anti-viral therapy were tested against 73 viral positive control patients. In the same time in both classes the effect of anti-viral therapy on thyroid physiology were monitored.

3.1 Total cases of HCV and HBV

Out of total cases (300) there were 150 cases of HCV treated and 150 were HBV Treated patients included in this study as shown in **Fig: 3.1**

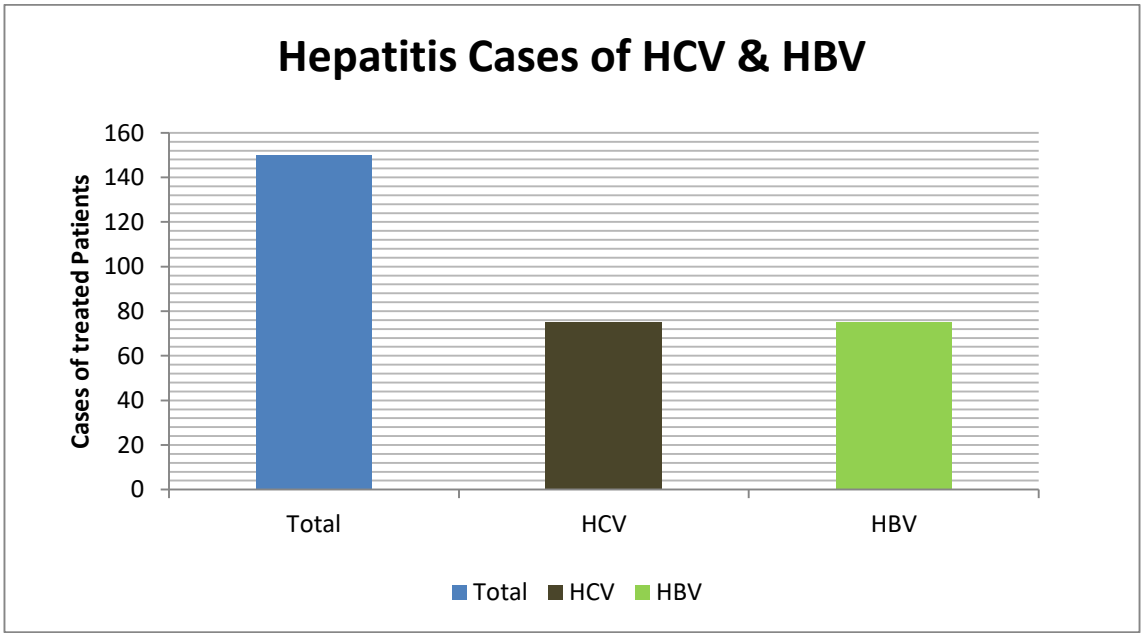
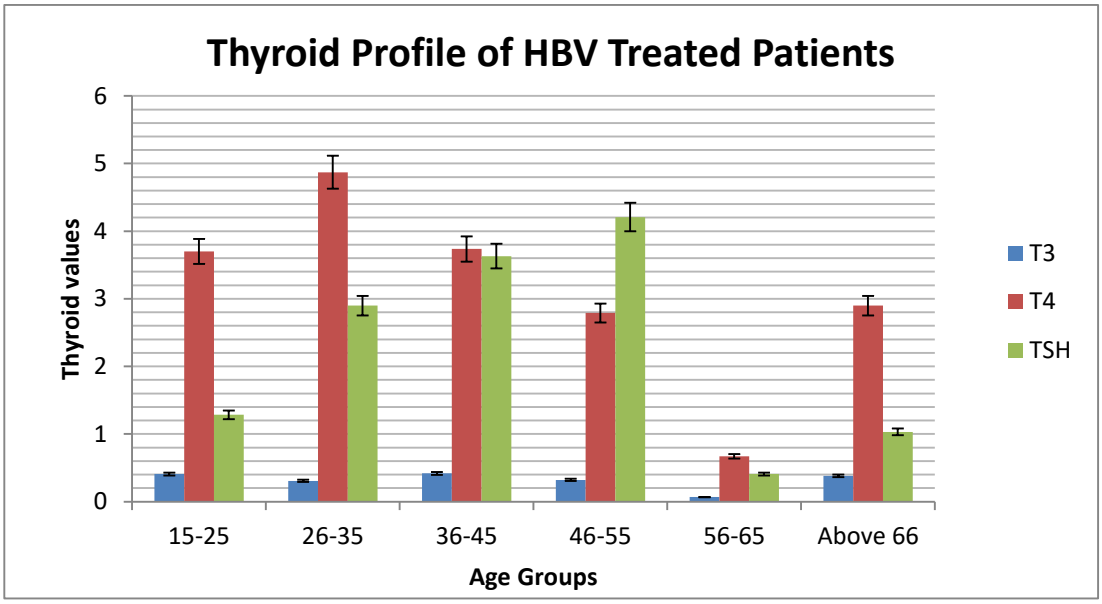


Figure 3.1 Frequencies of HCV and HBV interferon treated patients.



3.2 Thyroid Profile interferon treated of HBV Patients

The thyroid profile of HBV treated patients shows that the age group 26-35 Years followed by 36-45 Years and 46-55 Years having high thyroid values and were identified as hyperthyroidism and the age group 56-65 Years have lowest thyroid values which was identifed as hypothyroidism as shwon in **fig:3.2**

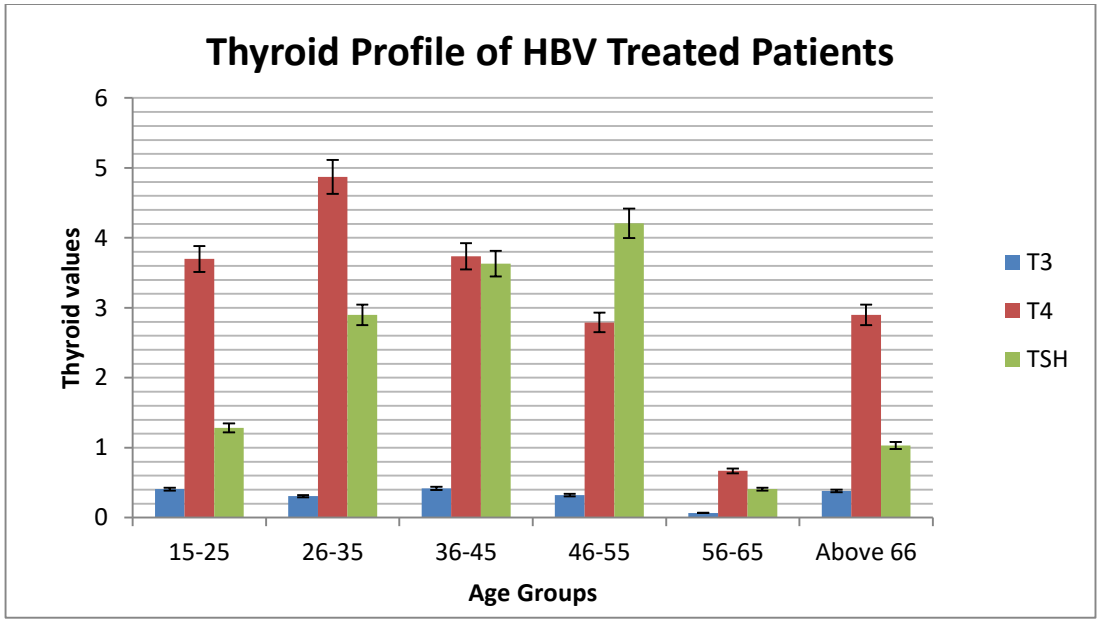


Figure 3.3: Thyroid profile of HBV patients receiving interferon therapy

IV. DISCUSSION

The viral hepatitis (HBV and HCV) is one of the leading causes of chronic liver infection and may result hepatocellular carcinoma and cirrhosis. According to World Health Organization (WHO) the mortality rate of hepatocellular carcinoma and cirrhosis is 783,000 and 619,000 respectively (Hanafiah *et al*., 2013). Owing to diverse sources like from blood transfusion, mother to baby, contaminated syringes the Hepatitis is spread and which infect 3 to 4 million people. Due to follow the standard SOP,s the rate of Hepatitis is decreased . In US the most blood born infection is HCV. The related infection is also involved directly or indirectly these infections are skin problems, kidney diseases, lymphoma, cryoglobuliemia etc. Our recent report concluded that the percentage of HCV infection is high than HBV. The total 300 sample are taken in which 74% are HCV infected person

and 73% are the HBV infected person. 275 people are on the viral therapy.Braira W *et al.,* (2012) suggested that interferon may alter the function of thyroid gland in the range of 3.9%-27.2%. The previous results also suggest that HCV infected female are more prone to hypothyroidism. In other study recommended that the recurrence rate of hypothyroidism is least in those patients who were getting anti-viral therapy Lambda/RBV and alfa/RBV (Fredlund *et al.,* 2015). while in contrast with our study the effect of anti-viral therapy (interferon and ribavirin) is highly remarkable on the physiology of thyroid hormones. Among the total no of HCV patients the percent value of hyperthyroidism is 28%, followed by hypothyroidism 24% and similarly euthyroidism developed in 48% of patients while in HBV patients the hyperthyroidism was noted 35%, hypothyroidism was 21% and euthyroidism was observed 44%. Another study conducted by Corssmit *et al.*(1995) in Brazil. They study IFNa induced cortisol release, probably by activating the hypothalamic-pituitary-adrenal axis. Because cortisol inhibits TSH release, this could at least in part explain our finding of decreased TSH concentrations after IFNa administration. They cannot exclude an cause of rhIFNa regarding intra thyroidal thyroid hormone metabolism because they are not aware of studies on the metabolic effects of IFNa on thyrocytes. IFNa induced a decrease in T and an increase in rT, values, similar to the changes found in NTI. This combination of changes in T, and rT, levels cannot be explained by the decrease in plasma TSH concentrations. These reciprocal alterations in T, and rT, could be related to altered membrane transport of thyroid hormones or to decreased 5'-deiododehydrogenase I activity in the liver, causing a reduction in both T, production and rT, clearance. The above study is closely related with our investigation. In our study the level of T3 and TSH are raised in about 19 patient which are concluded to hyperthyroidism. In the study of Roti., *et al.* (1996) suggested that thyrotoxicosis in 3 patients is induced by interferon alpha treatment. The effect of interferon on other thyroid hormones is also observed in one patient that has lower TSH level in blood although their FT4 level is normal and FT3 level is mildly increased, and TPO-Ab formation is also observed. Some patients were treated with corticosteroid drugs so the hormonal level back to normal. Some patients developed both hyperthyroidism and TSR-Ab. The formation of this antibody inhibits the releasing of TSH that result hypothyroidism. In our studies, hyperthyroidism was observed in patients who received r-IFN-alpha treatment either as the first manifestation of thyroid dysfunction or following transient thyrotoxicosis some hyperthyroid patients required L-thyroxin treatment, whereas others spontaneously became euthyroid.According to Hsieh *et al.(*2000) Study is carried out in Taiwan in which a total of 150 chronic Hepatitis C in these patients 28(18.7%) alpha interferon induced thyroid disorder was observed. In our finding, thyroid disorders including hyperthyroidism (4.7%), sub-clinical hyperthyroidism (7.3%), subclinical hypothyroidism (4.0%) and destructive thyroiditis (2.7%) was observed. This statistical variation shows that interferon may play a major role in the disorder of thyroid gland and may be one of the leading causes of hyperthyroidism. The reason why we did not find hyperthyroidism induced by IFN-a therapy because of or may be due to ethnic differences. The thyroid function comes back to normal after the cessation of anti-viral therapy (26 of 28 patients, 92.9%) except in two patients who developed persistent hyperthyroidism and also received anti-thyroid treatment. The papillary carcinoma is also observed in even patient but their link were not associated with anti-viral therapy. Custro *et al.* (1997) reported that the probability of thyroid autoimmunity is seven times greater in chronic Hepatitis C patients. A conspicuous prevalence of thyroid-Ab was observed in women patient the ratio of seropositive was about is one out of four. The old healthy women are more prone to the development of thyroid autoimmunity. Beside our study the development of thyroid antibodies in untreated women having chronic hepatitis c at higher risk as compares to men patients. While age group has no significant value in the role of thyroid-Ab in severity of liver disorders. The role of autoimmune development against thyroid gland in chronic Hepatitis C patients is still unknown. The development of thyroid antibody and viral antibody may be due to the similarity of amino acid sequence in both organ and condition. This hypothesis may be leading to the development of autoantibodies against both thyrocytes and hepatocytes (Tran A, *et al.,* 1993). The thyroid tissue abnormality may be due to virus cytopathic effects. The interferon production induced by viruses may take part in the pathogenesis of thyroid abnormalities in untreated viral infected patients. Maguid *et al.* (2016) reported that HCV

infected patients is also evaluated for thyroid dysfunction. In about 18.69% patients observed who developed thyroid abnormality. The hypothyroidism is more observed in women rather than hyperthyroidism. This condition is more common in women than in men. Another study carried out by Tran *et al. (*2005) in Australia, overall 272 HCV patients evaluated for thyroid abnormality. Among these patients, 6.7% patients have developed hypothyroidism while hyperthyroidism is observed in about 16.6% patients. Again another study held by Pavan *et al. (*2011) reported that the thyroid function in 293 patients is found normal. However in 19% of patients developed thyroid dysfunction post anti-viral therapy. Among these patients 17.2 % individuals were found to be hyperthyroidism while only 1.8% patients having hypothyroidism, while destructive thyroiditis in some patients have been also observed. So the ratio of hyperthyroidism due to interferon is more common as compare to other thyroid dysfunctions. It has been also reported that in about 4.4% patients developed auto immune thyroiditis, the women are relatively more prone to such developed this type of antibody formation. This may also due to the genus X chromosomes however the exact mechanism of auto antibody formation is not clearly understood. A total of 461 patients were included in this study all patients having thyroid gland disorders. The thyroid abnormality 58(12.6%) is observed at the end of the treatment. The development of thyroid gland abnormality is observed mainly in Women but their actual mechanism is not clearly understood (Kee *et al.,* 2006). In contrast to our study incredible outcomes was observed in the abnormality of thyroid gland in women is about 100 (71.42 %) as compare to men is about 40(28.58%). In our study most of the patients having hyperthyroidism but their sign and symptoms does not appear and they are symptomless rather than these patients having (42%) other sign and symptoms that not correlate with hyperthyroidism. However some common symptoms observed these are 39% patients having cold sensitivity, fatigue observed in 18% of patients, 15% have constipation, 17% dry skin, 19% patients having weight gain, hypertension is observed in 9%of patients, other bones complication such as pain, stiffness and carpal tunnel syndrome is observed in 29% patients, some gynecological complication is also have been observed in women especially irregularities in menstrual cycle is about 16%.In our study Among the 200 individuals the pathological changes in thyroid gland is observed in about 88%, some homeostasis changes in the function of pancreases that regulate the secretion of insulin which control the level of glucose, these alterations is observed in 14% patients. A total of 300 thyroid patients were also evaluated for their effect on other vital organ of the body. The thyroid disorder and diabetes were observed in about 3% patients. About 6% patients having both thyroid disorder and hypertension and about 1% patients having other cardiovascular diseases that are closely related to thyroid disorder.

V. CONCLUSIONS

Chronic hepatitis infected patients is relatively more susceptible to thyroid disorder as induced by anti-viral therapy, especially Interferon alpha 2b. The most observed thyroid disorder is hyperthyroidism rather than other thyroid abnormalities such as hypothyroidism, destructive thyroiditis etc. The observed value of certain thyroid hormones is hyperthyroidism is about 34% in HCV patients, followed by hypothyroidism 29% and similarly euthyroidism developed in 54% of patients while in HBV patients the hyperthyroidism was noted 37%, hypothyroidism was 23% and euthyroidism was observed 48%. Age and gender factor had an incredible effect on the thyroid physiology the age group of 25 to 35(30.71%) are more susceptible to thyroid dysfunction. Similarly, the level of thyroid hormone was relatively more elevated in women viral infected patients 100 (71.42%), while least value of thyroid hormone is observed in men patients 40(28.58%). Our study suggests that the thyroid profile values in different age wise distribution T4 value was noted high in group 15-25 Years, T4 and TSH values are raised in group 26-35 followed by group 36-45 and 46-55 Years. While T4 value was raised in 56-65 Year group.

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