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ORIGINAL ARTICLE

PEGYLATED INTERFERON ASSOCIATED THYROIDAL DYSFUNCTION AMONG HEPATITIS C PATIENTS

Nida Sajid , Karim Kammeruddin , Muhammad Imran

ABSTRACT

**Background:** Chronic hepatitis C and interferon both have their effect on thyroid gland function including clinical and subclinical thyroidal dysfunction (TD) that form major clinical manifestations of chronic hepatitis c.

**Objective:** To assess Pegylated interferon based therapy related thyroidal dysfunction in chronic hepatitis C patients and to compare it with those who are hepatitis C Sero positive but have not receive interferon based treatment.

**Methods:** A case control study in which, 203 patients of Chronic, compensated hepatitis C(130 females,73 males) were included from Baqai University Hospital Karachi Liver Clinic (b/w Jan 2010–Jun 2014). The participants were checked for thyroid dysfunction at the onset, 17 patients were found to have thyroidal dysfunction in the beginning and were excluded from the total 203 cases, then out of the remaining 186 cases, 101 patients (who were not having TD initially) opted treatment with pegylated interferon/ribavarin (Treated Group) and the rest (85 cases) were taken as control group.

**Results:** Thyroid dysfunction was identified in 7 patients giving a frequency of 6.9%. Out of these 7 patients only one patient was male while the rest were females. The mean age of the patients with thyroid dysfunction was 39.2 ± 7.13 years. Amongst the patients identified with the thyroid dysfunctions, 2 (28.5%) had overt hypothyroidism and 5 (71.4%) had sub-clinical hypothyroidism. The treatment with combination therapy was significant for development of thyroid dysfunction in patients with hepatitis C (p=0.013) as compared to control group in which 85 patients of chronic hepatitis C who have not developed (TD) during the study period.

**Conclusion:** dysfunction after pegylated interferon/ribavarin treatment in chronic hepatitis C is statistically significant with sub-clinical hypothyroidism is the predominant type in the study population.

**KEY WORDS:** Hepatitis C, Interferon, Thyroidal Dysfunction.

INTRODUCTION

The immensity of literature available on the subject of hepatitis C infection is not unwarranted. This specific infection is responsible for the major bulk of cirrhosis, chron-ic liver disease and hepatocellular carcinoma. Affecting 3% of the world population<sup>1</sup>, the global nature of the disease leaves little to imagination. Preventive measures to stop the spread of the infection, early detection of the disease and prompt treatment remain the logical mainstays of management throughout the world.

Pegylated interferon alpha along with ribavarin has been considered to be the cornerstone in the management of hepatitis C infection.<sup>2</sup> As is with every other drug regimen this treatment is not without its side effects. The mode of

action of these drugs is via modulation of the immune system and antiviral properties.<sup>3</sup> Side effects mentioned in the literature are varied with reported unwanted effects on the cardiac system, mental health and on the thyroid gland.<sup>2,4,5</sup>

Inter-relation between hepatitis C infection and thyroid dysfunction has generated a lot of debate in the research community. While interferon has been held responsible for development of thyroid dysfunction by some authors, others have implicated hepatitis C virus infection to be a cause of this clinical entity in its own right.<sup>6</sup> Others have implicated pegylated interferon as the culprit.<sup>7</sup> The former group in their study quoted the prevalence of thyroid dysfunction in untreated patients of hepatitis C to be 12.5%. Those who observed this phenomenon in patients being treated with interferon and ribavarin reported this frequency to be 18.69%.<sup>8</sup>

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The manifestation of thyroid disease in such patients can be both autoimmune or non-autoimmune. One study quoted that patients of hashimotos thyroiditis have increased chances of thyroid dysfunction when getting combination therapy for hepatitis C when compared with those without Haashimotos thyroiditis.<sup>9</sup> Different inferences have been derived with regards to the effect on treatment outcome by thyroid dysfunction occurrence where some label it as beneficial and others saying it does not affect the result of treatment.<sup>10,11</sup>

We therefore decided to conduct an investigation into the frequency of thyroid dysfunction amongst the patients being treated for hepatitis C with interferon and ribavarin combination therapy.

### METHODOLOGY

This prospective observational study was conducted at Department of Medicine, Baqai University Hospital Nazimabad, Karachi, from January 2010 to June 2014. All patients of either gender, minimum 20 years of age but less than 60 years, who were diagnosed with hepatitis C virus infectivity and had not yet started treatment for the same, were included in the study.

All patients had their history taken to rule out prior thyroid hormone derangements and those who were on any thyroid regulation medications were excluded. The patients who were included had their thyroid profile measured that included thyroid stimulating hormone (TSH) and free thyroxine (FT4). TSH was taken as normal between the range 0.4-4.2 µIU/ml & FT4 0.8-2.7ng/dL. Those patients who were shown to have normal thyroid functions were included in the study. Patients were given treatment in the form of combination therapy, however those who declined treatment but kept turning up for follow up were considered as controls and the others as cases.

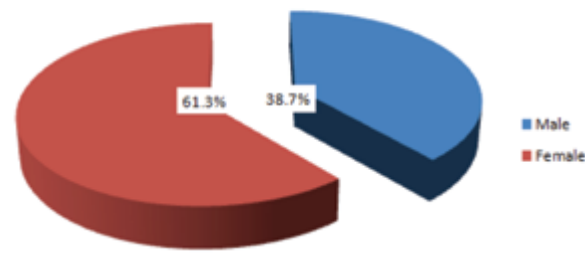
Subclinical hypothyroidism was labeled when the TSH was above the normal range and FT4 was normal. Overt hypothyroidism when the TSH was high but FT4 was below the range. Overt thyrotoxicosis was labeled when the TSH was low, and FT4 above the range.

The findings were noted on a predesigned proforma which included the patient's age, gender, TSH and FT4 levels. The software program SPSS for windows version 13 was used for all statistical analyses. Mean ± SD were used for quantitative variable like age TSH and FT4 levels. Frequency and percentages were used for qualitative data like gender distribution.

### RESULTS

A total one hundred and eighty six were enrolled in the study with a mean age of 42.19 ± 10.48 years. Of these 72(38.7%) were males and 114(61.3%) were females with a male to female ratio 1:1.58 (Figure 1). Out of these, 85 patients refused treatment for hepatitis C, and were therefore taken as the control group while the rest were considered as cases.

**Figure 1. Gender Distribution**



Thyroid dysfunction was identified in 7 of the patients giving a frequency of 6.9%. Out of these 7 patients only one patient is male while the rest are females. The mean age of the patients with thyroid dysfunction was 39.2 ± 7.13 years. Amongst the patients identified with the thyroid dysfunctions, 2 (28.5%) had overt hypothyroidism and 5 (71.4%) had sub-clinical hypothyroidism (Table 1). The treatment with combination therapy was significant for development of thyroid dysfunction in patients with hepa-

**Table 1. Characteristics of Patients with Thyroid Dysfunction**

Characteristics of Patients with Thyroid Dysfunction	
Age (mean ± SD)	35.24 ± 13
Gender	
• Male	01 (14.3%)
• Female	06 (85.7%)
Thyroid dysfunction	
• Overt hypothyroidism	02 (28.5%)
• Subclinical hypothyroidism	05 (71.4%)

### DISCUSSION

The chronic nature of hepatitis C virus is the main reason behind the pathological inflections it confers on its sufferers. Though the symptomatology may be acute leading to an early detection, this occurs only in 15% of the cases.<sup>12</sup> This implies that 85% of the affected, will have chronic initially asymptomatic disease that will lead to scarring and fibrosis of the liver causing a myriad of diseases. Though the main route of spread is blood to blood contact via transfusions and unsterile equipment, vertical transmission occurs in 5% of the cases putting the children of the 'asymptomatic' mother at risk with a lifelong affliction.<sup>13</sup>

Therefore since the identification of the virus in 1989<sup>14</sup>, effective treatment has been researched. Combination therapy with interferon and ribavarin is the current standard.<sup>15</sup> With regards to the factors influencing outcomes of the treatment, treatment outcome is dependent on multiple influences. First is the genotype of the virus, amongst the three genotypes, type 2 and three have a better prognosis with cure rates of upto 50%.<sup>16</sup> Other effect modifiers include age, viral load, gender, compliance, duration of diseases etc.

The debate about the association between hepatitis C infection and thyroid disease is a multifaceted one. One of the primary issues is, which is the primary responsible entity responsible in the development of thyroid dysfunction? The virus infection itself or the subsequent treatment? Both have been implicated in researches,<sup>6,7</sup> and it seems both entities have to be kept in mind while managing a patient during the course of treatment. As Shao et al<sup>6</sup> reported that the thyroid peroxidase antibody is the factor responsible behind the development of thyroid dysfunction in the untreated patients and Friedrich-Rust et al<sup>7</sup> nominated the direct destruction of the gland as the mechanism in patients on treatment for the infection.

There also has been controversy regarding which interferon therapy, the classic or the pegylated, has more degree of thyroid dysfunction with some authors implicating the

classic variety of the drug and others finding no difference.<sup>17,18</sup> In this study we observed that the frequency of thyroid dysfunction in the patients being treated with pegylated interferon and ribavarin to be 6.9%. None of the patients who never received any treatment for hepatitis C developed thyroid dysfunction. The frequency of thyroid dysfunction in this study is lower than that reported by Jamil et al<sup>17</sup>, who placed it at 12%. However they reported a frequency of 7% when using classic interferon and this frequency is comparable to the findings of this study. Barut and colleagues<sup>15</sup>, found this frequency to be around 16% which is again higher than this study's finding. These findings may suggest that the association of thyroid dysfunction with the treatment for hepatitis C may be governed by multiple factors and not alone due to the drugs used.

### CONCLUSION

There is a definitive association between the treatment of Hepatitis C with interferon and ribavarin and development of thyroid dysfunction. This however may be multifactorial and further investigation may be needed to assess effect modifiers. However, in light of current investigations it is imperative that the patients on therapy for hepatitis C must be actively screened for thyroid dysfunction and managed accordingly.

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