Abstract:

Chronic hepatitis C is a major health problem associated with high mortality and morbidity. It is the most common chronic hepatitis leading to chronic liver disease and hepatocellular carcinoma. One of the standard treatment used for hepatitis C is interferon therapy which can lead to thyroid dysfunction i.e. hyperthyroidism and hypothyroidism. Objective: To assess the frequency of hypothyroidism in chronic hepatitis C patients treated with standard interferon therapy.

Methods: This descriptive case series study was carried out at Outpatient Department of Medicine, King Edward Medical University/ Mayo Hospital Lahore for 06 months from January to June 2017. After ethical approval of the study, 200 patients of ages 15 to 65 years with both genders having chronic hepatitis C on Polymerase chain reaction (PCR) & normal thyroid functions test were taken by Non-probability, purposive sampling technique. Informed written consent was taken from all the patients. Serum thyroid stimulating hormone level (TSH) was sent to Centre for Nuclear Medicine (CENUM), Mayo Hospital Lahore before and after the completion of three months of interferon therapy and hypothyroidism was considered as TSH > 4.0 mIU/L (normal range: 0.2 - 4.0 mIU/L).

Results: The mean age of the patients was 36.29 ± 8.5 years. Out of total 200 patients, 123 (61.5%) were males and 77 (38.5%) were females. At baselines mean TSH of the patients was 3.16 ± 2.57 mIU/L. After 3 months of therapy 163 patients (81.5%) were euthyroid and 37 patients (18.5%) were having thyroid dysfunction. Among patients with thyroid dysfunction 29 (14.5%) were hypothyroid. Among hypothyroid patients 8 (27.6%) were males and 21 (72.4%) were females. The difference was statistically significant (P=0.0003).

Conclusions: we concluded that large number of chronic hepatitis C patients develops hypothyroidism after getting standard interferon therapy and females are at more prone to develop hypothyroidism as compared to males.

Key Words: Chronic Hepatitis C, Hypothyroidism, Standard interferon therapy.
5.3% in general population as concluded by WHO & Pakistan Medical Association jointly [8]. Hepatitis C virus is associated with many autoimmune disorders. Cutaneous manifestations include lichen planus, porphyria cutanea tarda (PCT) and vasculitic skin rashes in cryoglobulinaemia. Rheumatological associations include arthropathy, polyarteritis nodosa & Sjogren's syndrome. Hematological disorders include decrease platelets & white blood cells. Neurological manifestations include mononeuritis of cranial or peripheral nerves. A number of reversible thyroid diseases have been associated with Anti-Nuclear Antibodies positive chronic viral hepatitis treated with interferons alpha (INF Alpha) [1, 9]. IFN alpha is the standard treatment of chronic hepatitis C [10]. Main side effect are nausea, flu-like symptoms, cytopenias, elevated liver enzymes and psychiatric illness. It can also cause hyperthyroidism or hypothyroidism [11, 12]. Hypothyroidism is defined as endocrine disorder resulting from thyroid hormone deficiency. It results due to autoimmune destruction of thyroid gland by interferons [13]. Multiple international studies have focused thyroid dysfunction (hypothyroidism, hyperthyroidism, and autoimmune thyroditis) in HCV patients on interferon therapy in last few years. Vezali et al., (2009) studied prospective cohort of chronic HCV patients receiving interferon therapy as outpatients (n=61) in Athens, Greece. 13 (21.3%) treated patients had thyroid dysfunction, out of which 11 (18%) were hypothyroid [14]. Thyroid dysfunction due to interferon therapy was also studied by Yan et al. where they found 11.5% cases & out of them 6.4% were hypothyroid [15]. Similarly it was also studied by Bini et al. where they found to be 10.7% as a whole of which 8% were hypothyroid [16]. Ward et al. carried out a similar study on hepatitis C patients taking interferons in USA showing that thyroid dysfunction was present in 3 to 14% of all treated patients. He also concluded that female gender, preexisting subclinical, overt or autoimmune thyroid disease are the predisposing factors for developing autoimmune thyroid dysfunction [17]. Foldes et al. studied 138 patients with viral hepatitis treated with INF-alpha. Thyroid dysfunction was seen in 30 (21.7%) patients with 12 (8.7%) patients having hypothyroidism [18]. Similarly Kee et al. found the frequency of thyroid dysfunction as 12.6% and 2% patients developed persistent disease thereafter[19]. Nadeem et al., (2010) concluded that most patients tolerated therapy well however developed thyroid dysfunction. So hypothyroidism is an independent risk factor for treatment cessation [19]. A number of studies had been done at international level on pegylated interferon therapy but in Pakistan standard interferon therapy is more common used [20] and not many studies have been conducted with this therapy. As data is lacking in our country regarding this issue so we decided to do this study to see how often standard interferon therapy causes hypothyroidism.

Methods:
This was a descriptive case series study, done at Outpatient Department of Medicine, Mayo Hospital Lahore for 6 months i.e. January to June 2017. After ethical approval of the study, 200 patients of age 15 to 65 year with both genders having hepatitis C confirmed on polymerase chain reaction (PCR) having normal thyroid function test, were taken by Non-probability, purposive sampling & was calculated with 95% confidence level, 6% margin of error and taking expected hypothyroidism percentage in hepatitis C patients on standard interferon therapy as 18%. Informed Written consent was taken. Demographic data like name, age and gender were noted. All patients received conventional interferon therapy i.e. Interferon alpha 2b given in the form of subcutaneous injections at a dose of 3 million international units three times in a week. Thyroid stimulating hormone (TSH) was carried out under aseptic measures as 3 cc blood taken with sterilized disposable syringe and was sent to center for nuclear medicine laboratory (CENUM), Mayo hospital Lahore before & after the completion of
interferon therapy and hypothyroidism was labeled to patients having TSH levels more than 4.0 mIU/L (Normal =0.20-4.00mIU/L). All data was collected on a predesigned proforma. All the collected data was entered into computer based program SPSS version 15 and analyzed accordingly. The variables of study were age, gender and hypothyroidism. Numerical variable like age was presented by calculating as mean and standard deviation. Qualitative data like gender and status of patient regarding the presence and absence of hypothyroidism were presented by calculating frequency and percentage.

**Results:**

In our study the mean age of the patients was 36.29±8.5 years. There were 123 (61.5%) males and 77 (38.5%) females. At baselines mean TSH of the patients was 3.16 ± 2.57 mIU/L. The mean TSH of the patients after 3 months of therapy was was 1.72 ± 1.54 mIU/L (Table 1). Out of 200 patients, 37 patients (18.5%) were having thyroid dysfunction at 3 months of therapy whereas 163 patients (81.5%) were not having any thyroid dysfunction (euthyroid). In 37 thyroid dysfunction patients 29 (14.5%) were hypothyroid and 8 patients (4%) were hyperthyroid (Table 2). Out of 29 hypothyroid patients, 8 (27.59%) patients were males and 21 (72.41%) patients were females (Table 4) (Figure 1).

<table>
<thead>
<tr>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
<th>Std. Deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
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<tbody>
<tr>
<td>1.72</td>
<td>1.17</td>
<td>1.00</td>
<td>1.54</td>
<td>0.05</td>
<td>6.80</td>
</tr>
</tbody>
</table>

**Table 1:** TSH level at 3 months of therapy

<table>
<thead>
<tr>
<th>Thyroid status</th>
<th>Frequency</th>
<th>%</th>
<th>Cumulative percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroid</td>
<td>29</td>
<td>14.5</td>
<td>96.0</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>8</td>
<td>4.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>163</td>
<td>81.5</td>
<td>81.5</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2:** Distribution of patients by thyroid status

<table>
<thead>
<tr>
<th>Patients</th>
<th>Frequency</th>
<th>%</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroid</td>
<td>29</td>
<td>14.5</td>
<td>14.5</td>
</tr>
<tr>
<td>Not hypothyroid</td>
<td>171</td>
<td>85.5</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3:** Distribution of patients by hypothyroid vs. non hypothyroid status

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>8</td>
<td>27.59</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>72.41</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 4:** Gender wise distribution of Hypothyroid Patients
Hypothyroidism in HCV patients on Interferon Therapy

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Figure 1: Patients Percentage Comparison of Hypothyroid and Not Hypothyroid

Discussion:
The objective of our study was to determine the frequency of hypothyroidism in chronic hepatitis C patients after getting standard interferon therapy. According to our results this incidence was 14.5% with significantly higher rate in female patients. Hepatitis C is the most common cause of chronic viral hepatitis worldwide [1]. In United States the prevalence of chronic hepatitis C is 1.6% [3]. Globally it leads to 366000 deaths per year [5]. In Pakistan hepatitis C is the most common viral hepatitis affecting over 10 million people [6].

Chronic hepatitis C can lead to reversible thyroid dysfunction. Interferon alpha is the standard treatment of chronic hepatitis C [9] that can cause hyperthyroidism or hypothyroidism [9] due to autoimmune destruction of the gland [12]. Multiple international studies have focused thyroid dysfunction (hypothyroidism and hyperthyroidism) in HCV patients on interferon therapy in last few years.

Vezali et al., studied prospective cohort of chronic HCV patients receiving interferon therapy as outpatients (n=61) in a Greece Hepatology Unit, of Elena Venizelou Hospital, Athens. Out of the 61 treated, 11 (18%) developed hypothyroidism [14]. Yan et al., studied interferon induced hypothyroidism where it was found 11.5% [15]. Bini et al., studied interferon induced hypothyroidism in HCV patients which was found to be 10.7% as a whole [16]. Ward et al. carried out a similar study on hepatitis C patients taking interferon in USA showing that thyroid dysfunction was present in 3 to 14% of all treated patients. He also concluded that female gender, preexisting subclinical, overt or autoimmune thyroid disease are the predisposing factors for developing autoimmune thyroid dysfunction [17].

Foldes et al. studied 138 patients with viral hepatitis treated with INF-alpha. Thyroid dysfunction was seen in 30 (21.7%) patients with 12 (8.7%) patients having hypothyroidism [15]. Similarly Kee et al. found the frequency of thyroid dysfunction as 12.6% and 2% patients developed persistent disease thereafter [19]. Nadeem et al., concluded that most patients tolerated therapy well however developed thyroid dysfunction. So hypothyroidism is an independent risk factor for treatment cessation [20].

The mean age of the patients in our study was 36.29 ± 8.5 years which is comparable with that of Vezali et al., [14] and Yan et al., [15]. We had 123 (61.5%) males and 77 (38.5%) females in our study while Vezali et al had a comparable number of 33 (54.1%) males and 28 (45.9%) females [14]. It is also comparable with the study by Yan et al [15] but not with Bini et al (2004) [13].The mean TSH level of the patients 1.74 ± 1.62 mIU/L in our study is comparable to Vezali et al. mean TSH of 1.62 ± 0.92 mIU/L [11]. Thyroid dysfunction in our study was 18.5% as compared to Vezali et al i.e. 13 (21.3%) [14]. Similarly in Foldes et al it was 21.7% [18].

Another study by Kee KM et al. is also comparable with our results [19]. In our study thyroid dysfunction was found in 26 (70.3%) females. Similarly by Vezali et al.,found 9 (69.2%) were female which is comparable with our study [14]. Yan et al.,study found 47 (69.1%) females which is also comparable with our results [15]. In our study 29(14.5%) patients were hypothyroid while by Vezali et al., hypothyroidism was found in 11(18%) [14].
hypothyroidism was found in 38(6.4%) which is also comparable with our study [15]. In another study by Bini et al., 18(8%) patients had hypothyroidism. These results are also comparable with our study [16]. In another study by Foldes et al. 12 (8.7%) patients were hypothyroid which is again comparable with our study [18].

**Conclusion:** Hence we concluded that large number of chronic hepatitis C patients develops hypothyroidism after getting standard interferon therapy and females are at more prone to develop hypothyroidism as compared to males. Therefore all chronic hepatitis C patients should be followed after standard interferon therapy for hypothyroidism to prevent future complications.

**References:**

2b and ribavirin therapy in men with chronic hepatitis C. Arch Intern Med;164:2371-6.


