Journal of Diabetes and Metabolism
ISSN: 2155-6156

Rahman et al., J Diabetes Metab 2017, 8:7
DOI: 10.4172/2155-6156.1000750

Research Article Open Access

Sub-Clinical Thyroid Disorders in Patients With Hepatitis C Before and After Conventional Treatment

Attiya Sabeen Rahman[1*], **Muhammad Amir**[2], **Adnan Aziz**[3], **Muhammad A Siddiqui**[4], **Qaiser Jamal**[1] and **Mehwish Riaz**[5]

[1]*Department of Medicine, Karachi Medical and Dental College and Abbasi Shaheed Hospital, Karachi, Pakistan*

[2]*Department of Medicine, Jinnah Post Graduate Medical Centre, Karachi, Pakistan*

[3]*Department of Surgery, Civil Hospital and Dow University of Health Sciences, Karachi Pakistan*

[4]*Professional Faculties, University of Calgary, Calgary, Canada*

[5]*Department of Community Medicine, Foundation University Medical College, Islamabad, Pakistan*

[*]**Corresponding authors:** Dr Attiya Sabeen Rahman, Department of Medicine, Karachi Medical and Dental College and Abbasi Shaheed Hospital, Karachi, Pakistan, Tel: 00923212425076; E-mail: nervousystem.asr@gmail.com

Received date: July 09, 2017; **Accepted date:** July 22, 2017; **Published date:** July 27, 2017

Abstract

Objective: Thyroid dysfunction represents one of the commonest endocrine manifestations of chronic hepatitis C infection, exaggerated by interferon based treatment. The purpose of this study was to assess the frequency of hepatitis C virus and sub-clinical thyroid disorder in patients with hepatitis C before and after treatment.

Methods: This is an observational, cross sectional analysis conducted in Lyari general hospital and Abbasi Shaheed hospital from January 2009 to December 2015. Patients with a positive rt-PCR and genotype 3 were included in the study. After a positive rt-PCR, patients were screened by thyroid stimulating hormone before starting the treatment. All patients were given therapy of conventional interferons (3 million units thrice weekly) and ribavirin (800 mg per day in two divided doses) for a period of 6 months. Patient with normal TSH level was included and patients with a co-existing hepatitis B or D were excluded from the study. After 6 months of therapy all patients had a repeat rt-PCR to see the end treatment response to therapy and a thyroid stimulating hormone to screen for thyroid disorders.

Results: A total of 129,430 patients have visited the medical outpatient department of which, 4069 were HCV RNA PCR positive. The prevalence of unrecognized hepatitis C Virus was 13.4% in the study population. The prevalence of sub-clinical thyroid disorders was 9%. Of which 6.5% had sub-clinical hypothyroidism and 2.5% had overt or subclinical hyperthyroidism. A total of 2196 patients were included in the analysis. Mean age was 36.22 ±10.01 years range from 16 to 63 years. Among all 36.9% were male and 5.1% were known diabetics. On the whole 14.8% were non-responders, 80.9% achieved an end treatment response and 4.3% lost to follow up. We observed an association between the post treatment TSH level and the ETR of HCV (p=0.015). A statistically significant difference (p<0.001; 95% CI -3.008-1.577) was observed in the thyroid stimulating hormone at the baseline and following the conventional interferon and ribavirin therapy for a period of 6 months. 388 (17.6%) patients had abnormal thyroid function tests after conventional interferon treatment. These 388 patients were further followed up for 6 months.

Conclusion: In conclusion, this study results shows 13.4% prevalence of HCV in Karachi and the prevalence of sub-clinical thyroid disorders was 9%, of which 6.5% and 2.5% had overt hypothyroidism and hyperthyroidism respectively.

Keywords: Hepatitis C; Thyroid disorders; Thyroid stimulating hormone; Rt-PCR; End treatment response and prevalence

Introduction

The overall global burden of hepatitis C (HCV) is 2.2% [1,2]. The disease is becoming a major health problem of developing countries. Pakistan has the second highest prevalence rate of hepatitis C ranging from 4.5% to 8%. 1 Studies in Pakistan on small targeted groups including blood donors, health professionals, drug abusers and chronic liver disease patients indicate that the prevalence of hepatitis C is as high as 40% [1,3]. However, literature is still inadequate to clearly reflect the overall brunt of the illness.

Thyroid dysfunction represents one of the commonest endocrine manifestations of chronic hepatitis C infection, exaggerated by interferon based treatment [4]. Changes in thyroid function are common side-effects occurring during antiviral therapy with interferon-alpha (IFN-α). In this way, the spectrum of thyroid diseases range from the production of isolated anti-thyroid antibodies to dysfunctions such as hypothyroidism, Graves' disease (GD), and destructive thyroiditis [4,5]. IFN-α therapy for HCV may induce thyroid changes or dysfunction in 2.5% to 20% of treated patients. These adverse effects impair and interfere the treatment of HCV [4,6].

Almost all side-effects of IFN-α treatment are due to its effects on the immune system, it has an immune modulatory mechanism that also causes thyroiditis by direct thyrotoxicity [4]. Ribavirin is a

nucleoside analogue with broad spectrum anti- viral activity against several RNA and DNA viruses, and it is suggested that it may stimulate the immune system alone or along with IFN-α to cause thyroid disease via an autoimmune phenomena [4]. Ribavirin can also enhance non-virus-induced immune response, suggesting that this drug could trigger autoimmune phenomena in predisposed patients [4]. Thyroid dysfunction is more prevalent in patients treated with IFN-α and ribavirin combination therapy (12.1%) than in patients treated with IFN-αalone (6.6%) [4,7].

The other side effects of IFN-α are influenza like symptoms, fever, headache, chills and muscle aches and pains, hair loss, weakness, fatigability, anorexia and weight loss may occur later. Suicidal tendencies, depression and irritability have also been reported. Neuro-retinitis is rare but very serious complication and its occurrence calls for immediate discontinuation of therapy [6]. Hematological side effects like anemia, neutropenia and thrombocytopenia are common and needs dose adjustment of the drugs plus supportive therapy [8]. Recent data suggests that IFN-alpha has direct toxic effects on the thyroid gland [9]. Ribavirin may stimulate the immune system alone or synergistically with IFN-alpha to cause thyroid disease via an autoimmune mechanism. Patients who develop an IFN-induced thyroid disease are perhaps genetically susceptible [10].

Several studies have reported the development of thyroid disorders in patients treated with interferon and ribavirin, there is a paucity of literature describing the prevalence of thyroid dysfunction during interferon-alpha and ribavirin combination therapy. Therefore, we conducted a prospective study to determine the prevalence of sub-clinical thyroid disorders before and after 6 months of conventional interferon- alpha therapy in combination with ribavirin.

Methods

This is an observational prospective cross sectional study conducted in the Lyari general hospital and Abbasi Shaheed hospital from January 2009 to December 2015. A favourable ethical opinion was obtained from Abbasi Shaheed hospital ethical committee for the study. Patients were enrolled in the study after written informed consent. All patients having deranged liver function tests were screened for hepatitis C antibody by ELISA method. Patients with positive antibody then had a real time polymerase chain reaction (rt-PCR) for HCVRNA and genotyping.

Patients with a positive rt-PCR and genotype 3 were then included in the study. After a positive rt-PCR, patients were screened by thyroid stimulating hormone (TSH) before starting the treatment. TSH and LFTs were performed using Abbott Total Lab Automation (architect c Systems & Aeroset Systems). Specifically: TSH (kit ref. no: Abbott B7K620). Total bilirubin (kit ref.no: Abbott 8G62). Direct bilirubin: (kit ref.no:Abbott 8G63). Gamma GT: (kit **ref.no**: 7D65). ALT: (kit ref: 7D56) ALP:(kit ref: 7D55-21 & 7D55-31). Aspartate: (kit ref.no:7D81).

Patients who had an abnormal TSH were not included; they were referred to an endocrinologist for the normalization of their thyroid levels prior to HCV treatment. Patients with a normal thyroid levels were put on the therapy of conventional interferons (3 million units thrice weekly) and ribavirin (800 mg per day in two divided doses) for a period of 6 months. Patients with a co-existing hepatitis B or D were excluded from the study. After 6 months of therapy all patients had a repeat rt-PCR to see the end treatment response to therapy and a thyroid stimulating hormone to screen for thyroid disorders. Primary outcome measures were unrecognized or subclinical thyroid disorders before and after conventional interferon treatment and secondary outcome measures were age, gender, end treatment response of HCV and prevalence of HCV.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 22.0 (SPSS Statistics Inc., Chicago, US). Mean, standard deviation, frequencies and percentages were calculated. Cross tabulation was performed to determine if there is a relationship between subgroups. The chi-square test for categorical data and paired t-test was used to compare differences between two groups and pre and post values.

Results

A total of 129,430 patients have visited the medical outpatient department of which, 4069 were HCV RNA PCR positive (Figure 1). The prevalence of unrecognized hepatitis C Virus was 13.4% in the study population. A total of 367 patients had thyroid disorders that were than referred to the endocrinologist and were excluded. The prevalence of sub-clinical thyroid disorders was 9%. 265 (6.5%) had sub-clinical hypothyroidism and 102 (2.5%) had overt or subclinical hyperthyroidism.

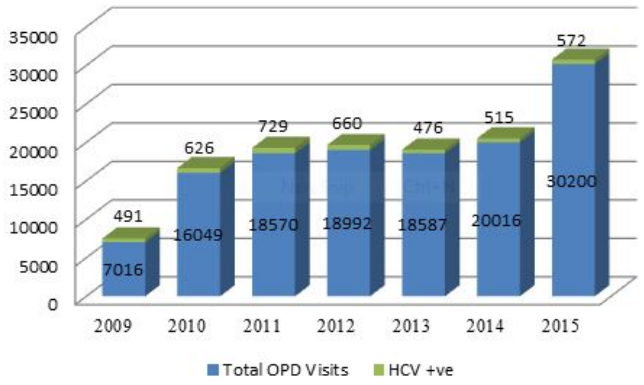

Figure 1: Frequencies of hepatitis C between 2009-2015.

A total of 3702 meet criteria for conventional treatment of interferon and ribavirin therapy. Out of 3702 patients, 802 patients refused and 2900 were agreed to participate in the study. Of which, 2196 patients started treatment of interferon and ribavirin therapy. However, 346 patients were referred to other parts of the province as this facility was far and inconvenient to them and 358 patients did not complete the treatment (Figure 2).

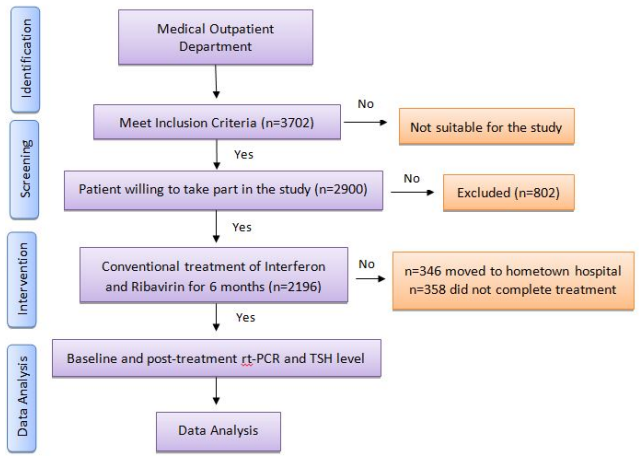

Figure 2: Flow diagram showing steps of the study.

Mean age was 36.22 ± 10.01 years range from 16 to 63 years. Among all 810 (36.9%) were male and 1386 (63.1%) were female participants. Overall, 112 (5.1%) were known diabetics, 154 (7%) newly diagnosed and 1930 (87.9%) were non-diabetics participants. On the whole 326 (14.8%) were non-responders, 1776 (80.9%) achieved an end treatment response and 94 (4.3%) lost to follow up.

Among all study participants 30.1% male and 50.7% females who achieved an end treatment response. While 5.1% male and 9.7% females were non-responders. Probability associated with the chi square statistic p=0.761 indicating there is no relationship between male and female and end treatment response of HCV. Conversely, statistically significant (p=0.003) association was observed between whether or not the existence of diabetes and end treatment response of HCV (Table 1). A total of 1808 (82.3%) patients had normal post treatment TSH level, among these 264 (12%) were non-responders to conventional interferon therapy. We observed an association between the post treatment TSH level and the ETR of HCV (p=0.015).

	PCR Positive	PCR Negative	Defaulters	Total	P-Value
Gender					0.761
Male	112 (5.1)	662 (30.1)	36 (1.6)	810 (36.9)	
Female	214 (9.7)	1114 (50.7)	58 (2.6)	1386 (63.1)	
Diabetes					0.003
Diabetics	4 (0.2)	108 (4.9)	0	112 (5.1)	
Newly Diagnosed DM	34 (1.5)	120 (5.5)	0	154 (7)	
Non-Diabetics	288 (13.1)	1548 (70.5)	94 (4.3)	1930 (87.9)	
TSH after Therapy					0.015
<0.4 IU/ml	42 (1.9)	180 (8.2)	0	222 (10.1)	
0.4-4.5 IU/ml	264 (12)	1450(66)	94 (4.3)	1808 (82.3)	
>4.5 IU/ml	20 (0.9)	146 (6.6)	0	166 (7.6)	

Table 1: End treatment response of HCV-n (%).

A statistically significant difference (p<0.001; 95% CI -3.008-1.577) was observed in the thyroid stimulating hormone at the baseline and following the conventional interferon and ribavirin therapy for a period of 6 months.388 (17.6%) patients had abnormal thyroid function tests after conventional interferon treatment. These 388 patients were further followed up for 6 months. 92 (23.7%) were lost to follow-up. 296 were further followed up for next 6 months and TSH were repeated. Only 4 (1.3%) had an abnormal thyroid function, who were than referred to an endocrinologist. The rest of 292 (98.6%) become euthyroid without any therapy.

Discussion

In our study, criteria defined for labelling sub clinical thyroid disorder was abnormal levels of Thyroid Stimulating Hormone (reference range 0.45-4.5 µU per mL). 388 patients (17.6%) our study population developed abnormal thyroid function tests after 6 months of conventional interferon and ribavirin treatment. Our results are consistent with other researches done in recent years showing frequency of 10.77% by Andrade LJ et al. [4], 18% in 139 patients with genotype 1 HCV by Zhang et al. [11], 18% in 100 patients by Masood et al. [12] 15% in 100 patients by Mehmood et al. [8], 22% in 557 ELISA positive HCV patients by Saeed et al. [13]. Mean age of our study population was 36.22 ± 10.01 years corresponding with 35.3 ± 7.8 years [12] and 37.22 ± 1.09 years 13.63% of our study population was female in similar to 77% [12] and 73 % [8].

Most frequent thyroid abnormality reported in our study is hyperthyroidism i.e., 10% whereas hypothyroidism was found in 7.6% patients. Our results are contrary to other studies regarding frequency of hyperthyroidism which is greater than hypothyroidism. This is in accordance with three Japanese [14-16] and one Italian study [17], where the majority of patients developed hyperthyroidism and in contrast with studies done previously nationally and internationally in

which hypothyroidism was most common manifestation [8,12,18,19]. The differentiation of hyper- and hypothyroidism observed indifferent areas could be explained by variations in dietary iodine intake of study population.

Similar to our study 82% patients had normal post treatment TSH level was concluded by Masood et al. [12]. Novel approach of our study was to follow up patients after 6 months of completion of therapy. 1.3% had an abnormal thyroid function, who were than referred to an endocrinologist and 98.6% become euthyroid without any therapy this follow up was missing in previous studies [12]. Thus this study confirms previous findings that reversibility of thyroid dysfunction after completion of interferon and ribavirin therapy in hepatitis C virus patients [20,21]. Statistically significant (p-0.003) association was observed between the existence of diabetes and end treatment response of HCV because a positive association between chronic HCV infection and DM has been consistently demonstrated across different ethnicities and geographic regions, in both developed and developing countries [22].

Conclusion

Changes in thyroid function are common side-effects occurring during antiviral therapy in patients with hepatitis C. In conclusion, this study results shows13.4% prevalence of HCV in Karachi and the prevalence of sub-clinical thyroid disorders was 9%, of which 6.5% and 2.5% had overt hypothyroidism and hyperthyroidism respectively.

References

1. Jiwani N, Gul R (2011) A silent storm: Hepatitis C in Pakistan. J Pak Med Stud 1: 89-91.
2. Alter MJ (2007) Epidemiology of hepatitis C virus infection. World J Gastroenterol 13: 2436-2441.
3. Abbas Z, Jeswani NL, Kakepoto GN, Islam M, Mehdi K, et al. (2008) Prevalence and mode of spread of hepatitis B and C in rural Sindh, Pakistan. J trop Gastroenterol 29: 210-216.
4. Andrade LJO, Atta AM, Atta MLBS, Mangabeira CNK, Parana R (2011) Thyroid disorders in patients with chronic hepatitis C using interferon-alpha and ribavirin therapy. Braz J Infect Dis 15: 377-381.
5. Tomer Y, Menconi F (2009) Interferon induced thyroiditis. Best Pract Res Clin Endocrinol Metab 23: 703-712.
6. Antonelli A, Ferri C, Fallahi P (2009) Hepatitis C: thyroid dysfunction in patients with hepatitis C on IFN-alpha therapy. Nat Rev Gastroenterol Hepatol 6: 633-635.
7. Koh LK, Greenspan FS, Yeo PP (1997) Interferon-alpha induced thyroid dysfunction: three clinical presentations and a review of the literature. Thyroid 7: 891-896.
8. Mehmood MA, Qureshi MA, Taseer IH (2015) Thyroid dysfunction; during combined peg-interferon alpha-2a and ribavirin therapy in patients with chronic hepatitis C. Professional Med J 22:196-190.
9. Nadeem A, Hussain MM, Aslam M, Hussain T (2010) Interferon-alpha induced and ribavirin induced thyroid dysfunction in patients with chronic hepatitis C. J Hepat Mon 10: 132-140.
10. Prummel MF, Laurberg P (2003) Interferon-alpha and autoimmune thyroid disease. Thyroid 13: 547-551.
11. Zhang RW, Shao CP, Huo N, Li MR, Xi HL, et al. (2015) Thyroid dysfunction in Chinese hepatitis C patients: Prevalence and correlation with TPOAb and CXCL10. WJG. 21: 9765-9773.
12. Masood N, Ghori R, Memon A, Memon S, Memon KI, et al. (2008) Frequency of thyroid disorders during interferon and ribavirin therapy in chronic hepatitis C infection. J Coll Physicians Surg Pak 18: 347-351.
13. Saeed MA, Sadiq M, Zulfiqar A, Irfan J, Jalali S (2009) Thyroid disorders in hepatitis C virus infected untreated patients. J Rawalpindi Med College 13: 60-62.
14. Okanoue T, Sakamoto S, Itoh Y, Minami M, Yasui K, et al. (1996) Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol 25: 283-291.
15. Watanabe U, Hashimoto E, Hisamitsu T, Obata H, Hayashi N (1994) The risk factor for development of thyroid disease during interferon-alpha therapy for chronic hepatitis C. Am J Gastroenterol 89: 399-403.
16. Kakizaki S, Takagi H, Murakami M, Takayama H, Mori M (1999) HLA antigens in patients with interferon-alpha-induced autoimmune thyroid disorders in chronic hepatitis C. J Hepatol 30: 794-780.
17. Fattovich G, Giustina G, Favarato S, Ruol A (1996) A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 24: 38-47.
18. Dalgard O, Bjoro K, Hellum K, Myrvang B, Bjoro T, et al. (2002) Thyroid dysfunction during treatment of chronic hepatitis C with interferon alpha: no association with either interferon dosage or efficacy of therapy. J Intern Med 251: 400-406.
19. Andrade LJ, Atta AM, D'Almeida Junior A, Paraná R (2008) Thyroid dysfunction in hepatitis C individuals treated with interferon-alpha and ribavirin- a review. Braz J Infect Dis 12: 144-148.
20. Nagane Y, Utsugisawa K, Kizawa H, Kondoh R, Terayama Y (2005) Hypothyroid myopathy caused by interferon-alpha therapy for chronic hepatitis C. Rinsho Shinkeigaku.45:441-444.
21. Indolfi G, Stagi G, Bartolini E, Salti R, de Martino M, et al. (2008) Thyroid function and anti-thyroid autoantibodies in untreated children with vertically acquired chronic hepatitis C virus infection. Clin Endocrinol (Oxf) 68:117-121.
22. Hammerstad SS, Grock SF, Lee HJ, Hasham A, Sundaram N, et al. (2015) Diabetes and hepatitis C: a two-way association. Frontiers Endocrinol 6: 134.