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FREQUENCY OF THYROID DYSFUNCTION DURING INTERFERON AND RIBAVIRIN THERAPY IN CHRONIC HEPATITIS C INFECTION

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Abstract

OBJECTIVE

To determine the frequency of thyroid dysfunction during interferon and ribavirin therapy in chronic hepatitis C infection.

METHODOLOGY

This cross-sectional research executed at Department of Medicine, JPMC, Karachi from 2nd December 2024 to 2nd April 2026. The sample of 160 patients aged 20 to 60 years on combined IFN-α and ribavirin therapy for 12 to 24 weeks were enrolled by consecutive sampling. Serum TSH and FT4 were assayed by automated chemiluminescent immunoassay. Statistical findings were expressed as mean ± SD or frequency, with chi-square applied at $p \leq 0.05$.

RESULTS

The mean age of participants was 41.38 ± 8.33 years, with 92 male participants (57.5%) and 68 female participants (42.5%). Thyroid dysfunction was identified in 20 patients (12.5%). Mean serum TSH was significantly higher in patients with thyroid dysfunction at 5.65 ± 3.49 μIU/mL compared with 2.15 ± 1.00 μIU/mL in unaffected patients ($p = 0.001$).

CONCLUSION

Thyroid dysfunction was documented in a clinically significant number of patients with chronic HCV in Pakistan treated with combination therapy with IFN-α and ribavirin. Only the serum TSH level was significantly different between the patients affected and patients unaffected, and age, FT4, duration of disease, duration of treatment, and sex were not significantly associated.

INTRODUCTION

Hepatitis C virus (HCV) infection remains a major global cause of chronic liver disease, accounting for an estimated 56 million infections worldwide, and continues to drive substantial morbidity, mortality, and pressure on hepatology services [1,2]. Pakistan harbours one of the heaviest national burdens of HCV in the region, sustained by unsafe therapeutic injections, recycled needles, unsterilised dental and surgical instruments, and inadequate screening of donor blood [3,4,5]. This is because a chronic hepatitis B virus (HBV) infection leads to progressive hepatic fibrosis, cirrhosis, and hepatocellular carcinoma, creating an increasing need for liver-specific healthcare in already limited health care systems [6].

Despite the dramatic changes in the global therapeutic picture brought about by direct antivirals in many low-resource contexts worldwide, such as specialised liver clinics in Pakistan, the use of interferon alpha (IFN-α) plus ribavirin is still in use due to drug access issues,

limited payers, and specific genotype considerations [6]. The most extensively documented extrahepatic complications associated with interferon-based regimens are haematological cytopenias, dermatological reactions, neuropsychiatric and endocrine disorders, but the most clinically relevant is thyroid disease [7,8]. Identification of these complications early is important for understanding drug tolerance, dose adjustments and the chances of a successful antiviral treatment. Thyroid dysfunction (TD) during HCV treatment is a combination of host immune genetic predisposition, HCV effects on thyrocytes, and direct immunomodulation of thyrocytes by HCV-derived cytokines, such as IFN-α [9,10]. It stimulates expression of major histocompatibility complex molecules on follicular cells; its effect on T helper responses is toward a type 1 cytokine profile and can unmask or accelerate latent thyroid autoimmunity, leading to Hashimoto's thyroiditis, Graves' disease, or, in some patients, a destructive non-autoimmune thyroiditis [11,12]. Experimental studies have also demonstrated that the HCV envelope protein E2 directly binds to thyrocytes and elicits a chemokine and heat shock protein (HSP) response that is interferon exposure independent, suggesting a role for HCV in thyroid injury that is independent of interferon exposure [13]. Reported frequencies of thyroid dysfunction during interferon-based therapy vary widely across populations, with cohort estimates extending from low single digits to more than one quarter of treated patients, the variability reflecting differences in case definition, treatment duration, and baseline thyroid autoimmunity [9,12]. In a contemporary cohort of patients receiving combined pegylated interferon and ribavirin, Hwang and colleagues documented incident thyroid dysfunction in approximately twelve percent of patients, with female sex and pretreatment thyroid autoantibody positivity emerging as the strongest predictors [14]. Subclinical hypothyroidism is the predominant biochemical pattern reported in most series, although overt presentations of either hyper or hypothyroidism remain sufficiently common to justify systematic surveillance during therapy.

Despite the substantial Pakistani burden of chronic HCV and the continued local use of interferon-based regimens, contemporary data on the frequency and pattern of thyroid dysfunction during such therapy in our population remain limited. Routine thyroid surveillance during antiviral therapy is inconsistent across tertiary care liver clinics, and the available local evidence is dominated by small or older single centre reports. Generating local, methodologically robust frequency data is essential to inform screening protocols, anticipate complications, and protect treatment adherence in patients who remain on IFN-α and ribavirin. The present study was therefore designed to determine the frequency of thyroid dysfunction during interferon and ribavirin therapy in chronic hepatitis C infection in a tertiary care setting.

METHODOLOGY

This cross-sectional study was conducted following formal approval ERC of JPMC, with written informed consent obtained from every participant after a detailed explanation of the study aim and procedures. Patients of either gender, aged 20 to 60 years, with a documented diagnosis of chronic HCV infection confirmed by PCR within the preceding six months and an HCV RNA level >10,000 IU/mL were included in the study. Patients receiving conventional interferon-alpha (IFN-α) at a dose of 3 million units subcutaneously three times weekly together with ribavirin 1000–1200 mg/day orally according to body weight for 12 to 24 weeks were recruited through non-probability consecutive sampling. Genotype testing was available, the dominant local distribution was genotype 3 followed by genotype 1, consistent with published Pakistani data. Combined IFN-α and ribavirin therapy continued to be used at the institution during the study period because of restricted access to direct-acting antivirals and payer limitations. During the study period, all eligible patients attending the liver clinic for interferon-based therapy were consecutively screened and recruited according to

the predefined inclusion criteria. Patients with known thyroidal disease, those who were critically ill or pregnant, and those with a history of congestive cardiac failure, myocardial infarction, chronic obstructive pulmonary disease (COPD), or chronic renal failure were excluded, along with any individual declining participation. Thyroid dysfunction encompassed any biochemical thyroid abnormality identified between 12 and 24 weeks of combined therapy. Euthyroid status was defined as a serum thyroid stimulating hormone (TSH) level of 0.27–4.20 µIU/mL together with a free thyroxine (FT4) level of 0.93–1.70 ng/dL. Clinical hypothyroidism corresponded to a TSH above 4.20 µIU/L with FT4 below 0.93 ng/dL; clinical hyperthyroidism to a TSH below 0.27 µIU/mL with FT4 above 1.70 ng/dL. Subclinical hypothyroidism to a TSH above 4.20 µIU/mL with a normal FT4; and subclinical hyperthyroidism to a TSH below 0.27 µIU/mL with a normal FT4. Anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were not assessed because of resource constraints. Furthermore, the present study was designed primarily to estimate the frequency of thyroid dysfunction rather than to investigate immunological predictors or mechanistic associations. The required sample size of 160 patients was determined W.H.O calculator, taking an anticipated frequency of thyroid dysfunction of 11.8%[22], a 95% C.I, and 5% of precision. Data were collected by the principal investigator, a postgraduate medical officer with three years of clinical experience, on a structured proforma capturing demographic details, duration of disease, duration of antiviral therapy, and relevant comorbidities. Venous blood samples of 5 mL were collected aseptically after an 18-hour fast from all participants, and serum TSH and FT4 levels were measured by automated chemiluminescent immunoassay in the hospital biochemistry laboratory. All blood samples were analysed, and the results recorded on the proforma and interpreted using the operational definitions set above to classify each patient as euthyroid, clinically hypothyroid, clinically hyperthyroid, subclinically hypothyroid or subclinically hyperthyroid.

RESULTS

A total of 160 patients with chronic HCV receiving combined IFN-α and ribavirin therapy were enrolled. The mean age of the cohort was 41.38 ± 8.33 years, with 92 male participants (57.5%) and 68 female participants (42.5%). The mean duration of HCV disease was 18.49 ± 6.41 months and the mean duration of antiviral therapy at the time of evaluation was 16.33 ± 4.06 weeks. Baseline biochemical thyroid indices showed a mean serum TSH of 2.59 ± 1.92 µIU/mL and a mean FT4 of 1.28 ± 0.30 ng/dL, consistent with euthyroid status in most of the sample. The complete set of demographic and clinical characteristics is summarised in **Table I.**

Table I: Baseline and Clinical Characteristics of Patients with Chronic Hepatitis C Infection (n=160)

Mean ± Standard Deviation		**95% Confidence Interval**
Age in years = **41.38 ± 8.33**		40.07—42.68
TSH µIU/mL = **2.59 ± 1.92**		2.29—2.89
FT4 ng/dL= **1.28 ± 0.30**		1.23—1.32
Duration of Disease in Months= **18.49 ± 6.41**		17.49—19.49
Duration of Treatment in Weeks = **16.33 ± 4.06**		15.69—16.96
Frequency %		
Gender	Male	92 (57.5)
	Female	68 (42.5)
Thyroid Dysfunction		20 (12.5)

Thyroid dysfunction was identified in 20 of 160 patients, yielding an overall frequency of 12.5% (Table I). On comparison of demographic and clinical variables between patients with and without thyroid dysfunction, the only statistically significant difference was in serum TSH concentration, which was substantially higher in patients with thyroid dysfunction at 5.65 ± 3.49 µIU/mL compared with 2.15 ± 1.00 µIU/mL in those without dysfunction (p = 0.001). Mean age (41.15 ± 7.63 vs 41.41 ± 8.45 years, p = 0.898), FT4 (1.19 ± 0.66 vs 1.29 ± 0.21 ng/dL, p = 0.179), duration of disease (18.08 ± 5.99 vs 18.55 ± 6.49 months, p = 0.762), and duration of antiviral therapy (15.40 ± 4.16 vs 16.46 ± 4.04 weeks, p = 0.278) did not differ significantly between groups. Although female participants showed a numerically higher proportion of thyroid dysfunction at 10 of 68 (14.7%) compared with 10 of 92 (10.9%) among males, this difference did not reach statistical significance (p = 0.468). The stratified findings are presented in **Table II**

Table II: Comparison of Demographic and Clinical Characteristics with Thyroid Dysfunction (n=160)

Demographic and Clinical Characteristics		Thyroid Dysfunction		95% Confidence Interval	P-Value
		Yes (n=20)	No (n=140)		
Age in years		41.15 ± 7.63	41.41 ± 8.45	-4.203–3.689	0.898
TSH µIU/mL		5.65 ± 3.49	2.15 ± 1.00	2.781–4.230	0.001*
FT4 ng/dL		1.19 ± 0.66	1.29 ± 0.21	-0.241– -0.045	0.179
Duration of Disease in Months		18.08 ± 5.99	18.55 ± 6.49	-3.504–2.571	0.762
Duration of Treatment in Weeks		15.40 ± 4.16	16.46 ± 4.04	-2.974–0.859	0.278
Gender	Male	10 (10.9)	82 (89.1)	0.277–1.809	0.468
	Female	10 (14.7)	58 (85.3)		

DISCUSSION

In Pakistan, the ongoing use of IFN-α and ribavirin in selected tertiary care centres maintains interest in the extrahepatic adverse effects of these drugs [3-5], and the problem of chronic HCV infection continues to be a large public health burden. Thyroid disease has become one of the most common endocrine side effects and could interfere with drug tolerability and adherence to treatment [7,8]. Thus, the therapy may reveal the presence of a predisposition to develop autoimmunity, a phenomenon induced by the cytokine activity in immunomodulation, and the virus itself is directly involved in targeting thyrocytes through the E2 envelope protein during viral exposure during antiviral therapy [9,11,13]. The present study quantitatively estimated the occurrence of thyroid dysfunction in the combined IFN-alpha and ribavirin therapy in a tertiary care Pakistani population.

The prevalence of thyroid dysfunction in the current sample of 160 patients was 12.5%, with a mean age of 41.38 ± 8.33 years and a slight male predominance of 57.5%. These rates are comparable to those reported by Hwang et al, in their contemporary Korean cohort, who reported incident thyroid dysfunction in 11.8% of patients receiving combined pegylated IFN-α and ribavirin [14]. In a similar population, Nadeem and Aslam observed 18.69%, which was higher than our study with female preponderance among the affected patients [15]. The Egyptian series of Hamza et al. reported that pegylated IFN-α and ribavirin therapy caused dysfunction in 12% of patients at 24 weeks of treatment [16], a rate that is near the one we reported. This convergence confirms the view that interferon therapy is safe in terms of its endocrine effects in a variety of populations.

The overall frequency of thyroid dysfunction reported in the present study is like those previously reported in international and regional studies that examined interferon therapy in chronic HCV infection [17]. Mandac and co-

workers had previously outlined a spectrum of response to IFN-α therapy: destructive thyroiditis, Hashimoto's thyroiditis, and Graves' disease, all of which might have subclinical biochemical features prior to any apparent phase [11]. Our results continue to support the need for biochemical monitoring in the 12-to-24-week treatment period based on the protocol.

Patients with dysfunction had significantly higher levels of serum TSH (5.65 ± 3.49 μIU/mL) than patients without dysfunction (2.15 ± 1.00 μIU/mL) (p=0.001), and most of the patients with dysfunction had serum FT4 levels within the reference ranges. This biochemical profile is indicative of thyroid dysfunction over time while on interferon therapy and is the prevailing biochemical pattern reported by Carella et al. in their seminal clinical review of IFN-α-related thyroid disease [20]. The Mechanism involves upregulation of MHC class I on thyroid follicular cells induced by interferon, polarisation towards type 1 cytokine responses and subsequent immune-mediated cytotoxic damage. Possibly by chemokine activation and heat shock protein induction in thyrocytes, HCV E2 protein also may play a role. [10,11,13,23].

Although numerically higher among affected females (14.7% vs. 10.9% for males), female gender was not significant in our cohort (p = 0.468). This finding contradicts to the Taiwanese registry reported by Chang and colleagues, who found female gender, hyperlipidaemia, and goitre history as independent risk factors [18] and the meta-analysis by Tran and colleagues that reported that female gender was a risk factor among those developing thyroid disease on IFN-α [19]. This discrepancy may have been related to the limited number of patients and lack of pretreatment thyroid autoantibody results, and our own results do not contradict the known susceptibility of females noted in larger series [14,18].

The strengths of the study are the clearly defined treatment window (12-24 weeks), the standardised proforma based assessment of biochemical thyroid status using validated cut-offs for TSH and FT4, and the prospective consecutive recruitment. The cross-sectional design does not allow for incidence estimation and description of the treatment's trajectory beyond the treatment window. Mechanistic interpretation was limited because of the lack of data for antithyroid autoantibody titres, thyroid ultrasonography and viral genotype [12,21]. Single-centre recruitment limits generalisability, and the modest absolute number of affected patients reduces statistical power to detect smaller subgroup effects.

The present findings reinforce that thyroid dysfunction occurs in approximately one in eight Pakistani patients receiving combined IFN-α and ribavirin therapy for chronic HCV, predominantly as biochemical subclinical disease. The principal differentiator between affected and unaffected patients was a clinically meaningful elevation of serum TSH, consistent with the international literature [17,20,21]. These data add a locally generated, methodologically standardised dataset to the wider evidence base on extrahepatic complications of antiviral therapy in chronic HCV [2,7]. Anti-thyroid autoantibody titres, thyroid ultrasonography, and viral genotype data were not evaluated, which limited mechanistic interpretation of thyroid dysfunction among the study participants.

CONCLUSION

Thyroid dysfunction was documented in a clinically significant number of patients with chronic HCV in Pakistan treated with combination therapy with IFN-α and ribavirin. Only the serum TSH level was significantly different between the patients affected and patients unaffected, and age, FT4, duration of disease, duration of treatment, and sex were not significantly associated.

REFERENCES

Manns MP, Buti M, Gane E, Pawlotsky JM, Razavi H, Terrault N, et al. Hepatitis C virus infection. Nat Rev Dis Primers. 2017;3:17006.

Polaris Observatory HCV Collaborators. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. Lancet Gastroenterol Hepatol. 2022;7(5):396–415.

Mahmud S, Al Kanaani Z, Abu-Raddad LJ. Characterization of the hepatitis C virus epidemic in Pakistan. BMC Infect Dis. 2019;19(1):809.

Al Kanaani Z, Mahmud S, Kouyoumjian SP, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Pakistan: systematic review and meta-analyses. R Soc Open Sci. 2018;5(4):180257.

Umer M, Iqbal M. Hepatitis C virus prevalence and genotype distribution in Pakistan: Comprehensive review of recent data. World J Gastroenterol. 2016;22(4):1684–1700.

Spearman CW, Dusheiko GM, Hellard M, Sonderup M. Hepatitis C. Lancet. 2019;394(10207):1451–1466.

Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. Ther Adv Infect Dis. 2016;3(1):3–14.

Ferri C, Ramos-Casals M, Zignego AL, Arcaini L, Roccatello D, Antonelli A, et al. International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement. Autoimmun Rev. 2016;15(12):1145–1160.

Pastore F, Martocchia A, Stefanelli M, Prunas P, Giordano S, Toussan L, et al. Hepatitis C virus infection and thyroid autoimmune disorders: A model of interactions between the host and the environment. World J Hepatol. 2016;8(2):83–91.

Tomer Y, Menconi F. Interferon induced thyroiditis. Best Pract Res Clin Endocrinol Metab. 2009;23(6):703–712.

Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology. 2006;43(4):661–672.

Antonelli A, Ferrari SM, Ragusa F, Elia G, Paparo SR, Ruffilli I, et al. Graves' disease: epidemiology, genetic and environmental risk factors and viruses. *Best* Pract Res Clin Endocrinol Metab. 2020;34(1):101387.

Hammerstad SS, Stefan M, Blackard J, Owen RP, Lee HJ, Concepcion E, et al. Hepatitis C virus E2 protein induces upregulation of IL-8 pathways and production of heat shock proteins in human thyroid cells. J Clin Endocrinol Metab. 2017;102(2):689–697.

Hwang Y, Kim W, Kwon SY, Yu HM, Kim JH, Choe WH. Incidence of and risk factors for thyroid dysfunction during peginterferon α and ribavirin treatment in patients with chronic hepatitis C. Korean J Intern Med. 2015;30(6):792–800.

Nadeem A, Aslam M. Association of interferon-alpha and ribavirin-induced thyroid dysfunction with severity of disease and response to treatment in Pakistani Asian patients of chronic hepatitis C. Hepat Res Treat. 2012;2012:864315.

Hamza I, Eid Y, El-Sayed M, Marzaban R, Abdul-Kareem S. Thyroid dysfunction in chronic hepatitis C patients treated with the combined pegylated interferon-ribavirin therapy. J Interferon Cytokine Res. 2016;36(7):442–448.

Andrade LJ, Atta AM, D'Almeida Junior A, Paraná R. Thyroid dysfunctions during interferon alpha treatment of single and combination therapy in hepatitis C virus-infected patients: a systematic review based analysis. PLoS One. 2013;8(2):e55364.

Chang YK, Tseng YT, Chen KH, Chen KT. Long-term outcomes and risk factors of thyroid dysfunction during pegylated interferon and ribavirin treatment in patients with chronic hepatitis C infection in Taiwan. BMC Endocr Disord. 2019;19(1):36.

Tran HA, Reeves GE, Gibson R, Attia JR. Development of thyroid diseases in the treatment of chronic hepatitis C with alpha-interferon may be a good prognosticator in achieving a sustained virological response: a meta-analysis. J Gastroenterol Hepatol. 2009;24(7):1163–1168.

Carella C, Mazziotti G, Amato G, Braverman LE, Roti E. Clinical review 169: Interferon-alpha-related thyroid disease: pathophysiological, epidemiological, and clinical aspects. J Clin Endocrinol Metab. 2004;89(8):3656–3661.

Lim AK. Hepatitis C virus infection: clinical manifestations beyond the liver. Clin Liver Dis. 2017;21(3):449–466.

Dalgard O, Bjero K, Hellum K, Myrvang B, Bjøro T, Haug E, et al. Thyroid dysfunction during treatment of chronic hepatitis C with interferon alpha: no association with either interferon dosage or efficacy of therapy. J Intern Med. 2002 May;251(5):400-6.

Antonelli A, Ferrari SM, Ragusa F, Elia G, Mazzi V, Ruffilli I, et al. Thyroid disorders during interferon-alpha therapy in chronic hepatitis C virus infection: an update. Endocrine. 2022;75(2):323–335. doi:10.1007/s12020-021-02927-3.