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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/23706
DOI URL: http://dx.doi.org/10.21474/IJAR01/23706

RESEARCH ARTICLE

THYROID DYSFUNCTION IN PATIENTS TREATED WITH ANTI-HCV ORAL DIRECT ACTING ANTIVIRAL THERAPY

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Manuscript Info

Manuscript History
Received: 14 April 2026
Final Accepted: 16 May 2026
Published: June 2026

Key words:-
Daclatasvir, Hepatitis C, Hyperthyroidism, Hypothyroidism, Sofosbuvir.

Abstract

Background: Hepatitis C is highly prevalent in Pakistan and direct acting antiviral agents have replaced interferon-based regimen due to better safety, however, its association with thyroid dysfunction remains unclear. This study was thus conducted to determine prevalence of thyroid dysfunction in patients treated for hepatitis C infection with oral direct acting anti-viral therapy.

Methods: This multi-centre prospective cohort study was conducted at Medicine Department of Tehsil Headquarter Hospital, Sarai Alamgir, Pakistan; District Headquarter Hospital, Sargodha, Pakistan and Akbar Niazi Teaching Hospital, Islamabad, Pakistan from June 2023 to Febru ary-2026. A total of 280 patients with hepatitis C infection without any prior thyroid dysfunction were included. All of these patients were treated with Sofosbuvir 400mg and Daclatasvir 60mg for 12 weeks. At completion, patients were assessed for thyroid dysfunction. Association of thyroid dysfunction with confounding variables was assessed using Chi-square test and multivariate logistic regression. Statistical analysis was done using SPSS software version 25.

Results: Mean age was 41.29 ± 13.53 years. There were 198 (70.70%) male and 82 (29.30%) female patients. Mean viral load was 868.33 ± 411.08 IU/ml.Prevalence of thyroid dysfunction in present study among hepatitis C patients given direct oral ant,iviral treatment was 94 (33.60 %) with 80 (28.6%) patients being hypothyroid and 14 (5.00%) patients being hyperthyroid. Prevalence of thyroid dysfunction was significantly higher in female patients (p = 0.018).

Conclusion: Thyroid dysfunction was observed in 33.6% of the hepatit is C infected patients treated with oral direct acting anti-viral therapy with significantly high prevalence in females.

Introduction:-

Hepatitis C virus (HCV) infection is a highly prevalent in Pakistan that has been reported to infect an estimate of 11.5% of the population. [1]According to the estimates of World Health Organization, if Pakistan wants to eliminate this disease from the society, minimum threshold for screening and treatment would require an increase of18 million and one million people per year, respectively. [2] HCV primarily spreads through blood contact and various other

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modes including repeat usage of shaving blades, needle stick injury, tattooing, sexual transmission, vertical transmission from mother to baby, vast spread quackery practices, unhygienic conditions of health care facilities providing dental and surgical care, and blood transfusion. [3, 4]

Primarily, HCV infects liver where it causes chronic inflammation leading to cirrhosis. [5, 6] This leads to a myriad of complications such as portal hypertension, hepatocellular carcinoma, hepatorenal syndrome and encephalopathy. [7]Classically, HCV was managed with peg-interferon but it was associated with high relapse,low compliance and high thyroid dysfunction rate. [8] To counter this, newer direct acting oral anti-viral agents (DAAs) are now used. In fact, DAA therapy is now used as standard of care in treating HCV patients globally, particularly in South Asian region. Despite a large set of population being on DAA therapy in this region, data regarding its potential effect on the thyroid function, particularly at regional level, is unavailable. Due to lack of this data, evidence regarding whether or not DAA use is associated with thyroid dysfunction or not is yet not clear. Therefore, present multi-centre study was conducted with the aim to determine prevalence of thyroid dysfunction among HCV affected patients treated with DAAs.

Methodology:-

This multi-centre prospective cohort study was held at Medicine Department of Tehsil Headquarter Hospital, Sarai Alamgir, Pakistan, District Headquarter Hospital, Sargodha, Pakistan and Akbar Niazi Teaching Hospital, Islamabad, Pakistan from June-2023 to February-2026. A sample size of 280 patients was calculated by inputting 95% confidence interval, 5% absolute precision and anticipated prevalence of thyroid dysfunction in DAA users of 23.8% [9], in WHO sample size calculator software. The sample selection process was based on non-probability consecutive sampling technique. A concurrent treatment naive or healthy control arm was not included, as withholding or delaying DAA therapy in HCV positive patients for research purposes raises ethical concerns. Instead, previously published treatment naïve HCV cohorts were used as an indirect comparator to contextualize findings.

Inclusion criteria: Male and female patients who were aged between 18 and 65 years with HCV-RNA PCR based diagnosis of HCV (defined by > 20 IU/ml) without any prior thyroid dysfunction were included. Patients were required to have anti-HCV antibody positivity documented at least six months prior to enrolment, with an initially negative HCV RNA PCR at that time, and were enrolled once found to be HCV RNA PCR positive (> 20 IU/ml) on routine follow up testing.

Exclusion criteria: Patients with prior exposure to any form of HCV treatment, non-compliant to medications course, thyroid dysfunction, thyroid surgery, medications interfering with thyroid function (like amiodarone, iodine), any comorbid condition, liver cirrhosis and its related complications were excluded.

Before inclusion, it was ensured that all the patients gave their explicit informed consent in written form for which a dedicated pre-printed form was used. In addition, pre-treatment screening for thyroid dysfunction was also done to ensure euthyroid status of the patients intended to get treatment. Pre-treatment patient related parameters including their age, gender and viral load were recorded. Patients were given monthly doses of medication (Sofosbuvir 400mg and Daclatasvir 60mg combination to be taken once daily) for 12-weeks. Patients were called one day before completion of one month to collect the next month dose and compliance was ensured by asking them to bring their empty bottles of medicines. At completion of 12-weeks, when patients were called to take sample for repeat HCV RNA PCR to assess for achievement of sustained viral load, additional blood sample was obtained to assess for thyroid dysfunction (defined by presence of any pattern of disturbance in free T4, free T3 and TSH levels). The three month duration was determined by the standard local treatment protocol, wherein Sofosbuvir-Daclatasvir therapy is administered for 12-weeks, with sustained virologic response (SVR) assessed via HCV RNA PCR one month after treatment completion. Thyroid function was therefore assessed at this time as part of standard follow up plan. Hypothyroidism was defined by presence of TSH > 5.0, free T4 < 0.7 ng/dl and free T3 < 260 pg/ml. Hyperthyroidism was defined by presence of TSH < 0.35, free T4 > 1.53 ng/dl and fT3 > 480 pg/ml.TSH, free T4, and free T3 were measured using the Cobas e 801 analytical unit (part of the cobas pro integrated solutions platform, Roche Diagnostics), based on electrochemiluminescence immunoassay (ECLIA) technology.

All the collected data was entered and analysed with SPSS version 22. Qualitative variable (gender and thyroid dysfunction) was measured as frequency and percentage. Quantitative variables (age and viral load) were measured as mean ± standard deviation (SD). Association of thyroid dysfunction with age and gender was assessed using

Chi-square test since cell count was more than five. A p-value ≤ 0.05 was considered statistically significant. Multivariable logistic regression was additionally performed with thyroid dysfunction as the dependent variable and age, gender, and viral load entered as independent variables, to identify predictors of thyroid dysfunction while adjusting for the other covariates. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were reported, with p ≤ 0.05 considered statistically significant.significant.

Results:-

A total of 280patients with HCV RNA PCR based HCV diagnosis were included. Mean age was 41.29 ± 13.53 years. There were 198 (70.70%) male and 82 (29.30%) female patients. Median viral load was 868.33± 411.08IU/ml. Pre-treatment patient demographic is given in Table-I:

Table-I: Pre-treatment patient demographic (n = 280)

Characteristic	Mean ± SD; n (%)
Median age (years)	41.29 ± 13.53
Age group	
<40 years	130 (46.40%)
≥ 40 years	150 (53.60%)
Gender	
Male	198 (70.70%)
Female	82 (29.30%)
Median viral load (IU/ml)	868.33± 411.08

Prevalence of thyroid dysfunction in present study among HCV patients given DAA treatment was94 (33.60%) with 80 (28.6%) patients being hypothyroid and 14 (5.00%) patients being hyperthyroid. Association of thyroid dysfunction prevalence by age and gender is given in Table-II:

Table-II: Thyroid dysfunctionassociationwithage and gender (n = 280)

Age stratification			
	<40 years (n = 130)	**≥ 40 years (n = 150)**	**p-value †**
Thyroid Dysfunction	39 (30.00%)	55 (36.67%)	0.239
Gender stratification			
	Male (n = 198)	**Female (n = 82)**	**p-value †**
Thyroid Dysfunction	58 (29.29%)	36 (43.90%)	0.018

† = Chi-square test

On multivariable logistic regression with age, gender, and viral load entered together, female sex remained an independent predictor of thyroid dysfunction after adjustment (adjusted OR 2.02, 95% CI 1.17 to 3.48, p = 0.012), and higher viral load was independently associated with thyroid dysfunction (adjusted OR 1.09 per 100 IU/ml, 95% CI 1.02 to 1.16, p = 0.009). Age was not an independent predictor after adjustment (adjusted OR 1.02 per year, 95% CI 0.997 to 1.036, p = 0.095). The overall model was statistically significant (likelihood ratio p = 0.001). Adjusted odds ratios are given in Table-III:

Table-III: Multivariable logistic regression for predictors of thyroid dysfunction (n = 280)

Predictor	Adjusted OR	95% CI	p-value
Age (per year)	1.016	0.997 – 1.036	0.095
Female sex (vs. male)	2.016	1.167 – 3.484	0.012
Viral load (per 100 IU/ml)	1.087	1.021 – 1.158	0.009

OR = adjusted odds ratio from multivariable logistic regression; CI = confidence interval.

Discussion:-

Hepatitis C is a prevalent communicable disease wreaking havoc in the South Asian region of the world, particularly in Pakistan and India. According to recent estimates its prevalence has surged to 11.5% and 3.23%, respectively. [1, 10] This burden is encountered by therapy through modern oral direct anti-viral agents (DAAs) which have now

effectively replaced classically used injectable interferon-based therapy owing to better safety and efficacy profile. [11, 12] One of the factor that resulted in this replacement was association of interferon therapy with dysfunction of thyroid hormone regulation. [13] At the same time, it is unclear whether DAAs also result in this pathology or not, which prompted conductance of this study.

In present study, prevalence of thyroid dysfunction in present study among HCV patients given DAA treatment was 94 (33.60%) with 80 (28.6%) patients being hypothyroid and 14 (5.00%) patients being hyperthyroid. In comparison to this, Wahid*et al*. reported that among DAA users suffering from active HCV, prevalence of hypothyroidism and hyperthyroidism was 18.9% and 4.9%, respectively which were lesser yet comparable with present study findings. [9]Contrarily, Abdelrazik*et al.* reported that patients who were treated with DAA for presence of active HCV infection were found to have prevalence of dysfunction of thyroid hormone regulation was only 1% which was negligible in comparison to present study. [14] Similarly, in another study by Rodia*et al*. reported that none of the patients whose active HCV disease was treated with DAAs developed thyroid dysfunction, demonstrating high level of safety of DAAs. [15] In another study by Dyrka*et al*. who specifically reviewed the literature on DAA-related endocrine effects concluded that, unlike interferon-based regimens, DAAs were well tolerated and rarely resulted in dysfunction of thyroid hormone regulation. [16]

This high prevalence of dysfunction in the regulation of thyroid hormone in local population may be explained possible by higher burden of HCV-associated thyroid autoimmunity in local population rather than effect of the DAA regimen itself. This is evidenced by comparable or even higher rates of dysfunction being documented in antiviral-naive HCV populations before any drug exposure in previous literature. Nazary*et al*. assessed treatment-naive HCV-positive patients and reported that hypothyroidism prevalence was 10.6% among these treatment naïve HCV patients even. [17] Similarly, in an antiviral-naive HCV cohort comprising of Pakistani population, Zhong *et al*. reported an overall thyroid dysfunction prevalence of 41%, with hypothyroidism alone accounting for 29%, closely approximating post-DAA prevalence being reported in prevalence study, despite their patients never having received treatment. [18]

With regards to demographic characteristics, one important finding was higher proportion of HCV infected patients being males accounting for more than 70% of the affected individuals with a mean age of 41.29 ± 13.53 years. In comparison to this, Hyppolito*et al.* in a large Brazilian DAA treated HCV infected cohort reported that mean age of study population was 56.6 ± 11 years with a similar male predominance reporting males making up 60.2% of the cohort. [19] Similarly, Brzdek*et al*. analysed a nationwide Polish DAA registry and found that the treated population was primarily male-dominated. [20] The younger median age of present cohort likely reflects the demographic profile of HCV transmission in Pakistan, where unsafe therapeutic injections propagate infection across a broader, younger age spectrum rather than in high-income settings where transmission historically concentrated in older cohorts. Similarly, the male predominance likely reflects differences in referral patterns between hospital-based Hepatitis Control Program clinics, where male patients often present earlier due to occupational screening they have to go through owing to their role of being the bread winner in underdeveloped societies.

Upon association analysis, it was observed that there was no significant difference of DAA associated thyroid dysfunction prevalence among different age groups ($p = 0.239$), however, the prevalence of this DAA use related morbidity was significantly higher among females in comparison to males ($p = 0.018$). This female preponderance mirrors a well-established and consistent finding across previous literature. Battheu*et al.* reviewed the basis of sex-related differences in thyroid disease and concluded that the interplay of sex hormones, X-chromosome-linked genetic factors, foetal microchimerism and the gut microbiota collectively predisposes women to a substantially higher burden of thyroid disease than men. [21] In a similar vein, Faria*et al*. reviewed sexual dimorphism across the hypothalamic-pituitary-thyroid axis and noted that women carry a consistently higher prevalence of thyroid disease than men. [22]

On multivariable analysis, pre-treatment viral load emerged as an additional independent predictor of thyroid dysfunction, with higher viral load associated with greater odds of dysfunction after adjusting for age and gender. This finding, not captured by the univariate Chi-square analysis alone, raises the possibility that higher baseline viral burden may reflect a greater degree of HCV-associated immune activation, lending further support to the interpretation that thyroid dysfunction in this cohort is driven more by the underlying viral infection than by the DAA regimen itself.

In summary, the present study demonstrates that thyroid dysfunction is a clinically significant finding among HCV patients undergoing DAA therapy, with hypothyroidism predominating and females bearing a disproportionately higher burden. The discordance with several international reports suggests that this association may be driven more by underlying HCV-related thyroid autoimmunity in the local population than by a direct thyrotoxic effect of DAAs themselves. These findings support incorporating routine thyroid function screening into the pre- and post-treatment workup of HCV patients receiving DAA therapy, with particular vigilance for female patients.

Certain limitations of this study should be acknowledged. This was a single arm cohort without a concurrent treatment naive or healthy control groupas withholding or delaying DAA therapy in HCV positive patients for research purposes raises ethical concerns, comparison with previously published treatment naive HCV cohorts was instead used to contextualize findings. Consequently, the observed thyroid dysfunction prevalence could not be definitively attributed to DAA therapy rather than the natural course of chronic HCV infection or underlying HCV associated autoimmunity. Thyroid autoantibody status (anti TPO, anti thyroglobulin) was not assessed, therefore, pre-existing subclinical autoimmune thyroiditis could not be excluded at enrolment, and precluding differentiation between autoimmune and non-autoimmune mechanisms. Other potential contributors to thyroid dysfunction, including dietary iodine status, family history of thyroid disease, and coexisting autoimmune or endocrine disorders, were not assessed and could not be adjusted for, which may partly explain the discordance between the present findings and international DAA cohorts with lower reported prevalence. Although this multicentre design across three tertiary care hospitals improves internal representativeness within Pakistan, the non-probability consecutive sampling technique and single ethnic population may limit generalizability of findings to other populations with differing HCV genotype distributions, iodine status, or genetic predisposition to thyroid disease. As thyroid function was assessed at the standard three month SVR assessment timepoint dictated by local treatment protocol.This study captures thyroid dysfunction occurring during and immediately after DAA therapy. Delayed onset dysfunction beyond this window could not be evaluated and would require a dedicated longer term follow up study.

Conclusion:-

In conclusion, prevalence of thyroid dysfunction among HCV patients given DAA treatment was 33.6% with 28.6% patients being hypothyroid and 5% patients being hyperthyroid. Thyroid dysfunction was significantly more frequent in female than male patients, while age alone did not significantly affect prevalence in this cohort. These findings suggest that thyroid function screening before and after DAA therapy may be worth considering, particularly for female patients, although the single arm design of this study precludes definitive causal conclusions regarding DAA therapy itself.

Ethical Approval:-

Obtained from the ethical committee of hospitals (Ref No:EC-002/01; dated: 10/08/2024) and (Ref No: 8914/DFMTH; dated: 10/06/2023).

Patients' Consent:-

Informed consent in writing was taken from all participants

Competing Interest:-

None

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